

Cognitive development and risk for psychopathology in 22q11.2 Deletion Syndrome

Sinéad Margaret Morrison



Thesis submitted in fulfilment of the requirements for the
degree of Doctor of Philosophy

September 2019

Acknowledgments

I would first like to acknowledge the amazing families that have taken part in this research and been so welcoming to me arriving at their houses with a large suitcase of assessments! This research would not be possible without them. I am grateful to 22q11.2 Deletion Syndrome support groups Max Appeal! and 22crew for supporting the study.

I would like to thank my supervisors Marianne van den Bree and Michael Owen for their guidance and support throughout the PhD. I would like to thank the funders of this PhD, the Medical Research Council's Centre for Neuropsychiatric Genetics and Genomics. Furthermore, thank you to the Cardiff University Division of Psychological Medicine and Clinical Neurosciences (DPMCN) Core Technical Team for genotyping samples.

Thank you to the amazing ECHO/IMAGINE/DEFINE staff and students that have made this team a dream to work with over my PhD. Particularly Hayley Moss for seeing ECHO from inception to the success it has been over the last 9 years, Sam and Adam for endless patience and encouragement and Hayley Moulding for being a fierce inspiration. For brightening every day in the office, Nicola, Sinéad, Sarah Law, Matt, Pip, Molly, Sam B, Rachael, Ali, Chris and Jo.

To everyone I went on a visit with and drove here, there and everywhere, chatting, singing and ranking service stations across the UK; Stephen, Ciara, Nadia, Rachel, Alice, Poppy, Kezzie, Amy, Charl, Lauren, Meg, Lucy, Sam, Hannah, Chloe, Umayya, Emily.

To all the amazing people I met through my time here in Cardiff, who also became amazing friends; Ceci, Africa, Teia, Caer, Freya, Zoe, Hester, Amy, Carmen, Rhys, Frankie - thank you for supporting me through the rollercoaster that is a PhD.

To my lunch and life buddy Jasmine, we've gone through this whole journey together, through laughter, tears, and more laughter and you made this experience the best it could possibly be.

To the Gladys girls et al, Grace, Kat, Jenny, Sophie, Jade, Bex, Emma and Sarah, your messages of support and encouragement have seen me over the finishing line.

To my long-distance coven Gina, Emily, and Rochelle, thank you for being an endless source of strength and love that I can always turn to.

To my mum Helen for walks and talks filled with wisdom and joy, my dad Richard for sage advice and my sister Louise for always cheering me on.

Thank you to my best friend Will for showing me that life is to be grabbed with both hands, and that fear should never stand in the way. You inspire me every day.

Last but not least I would like to thank my partner and hero Simon for all the listening to, believing in, and being there for me throughout. You knew I could do it when I wasn't sure. You are truly excellent.

Contributions

I was responsible for co-ordinating the third wave of data collection in the Cardiff University Experiences of Children with Copy Number Variants (ECHO) study. I contacted and recruited families through phone and email and organised visits all over the United Kingdom. I personally visited and assessed 50 children with 22q11.2 Deletion Syndrome (22q11.2DS) and their sibling without deletion (if applicable). At least one other colleague attended each visit to assist with data collection. One of us would generally conduct the neurocognitive assessments, and the other the psychiatric assessments.

I scored and consensus-scored completed psychiatric interviews and neurocognitive tests. I extracted and cleaned cognitive and psychiatric data. I carried out all literature reviews and summarised all background information in this thesis. I conducted all the analysis and interpreted and wrote up the results and discussions.

I carried out the work for this thesis with the guidance of my supervisors, Professor Marianne van den Bree and Professor Sir Michael Owen.

I collaborated with researchers at two European sites to add data from individuals with 22q11.2DS to Chapter 3, resulting in a large multi-site sample. I cleaned and analysed all data and wrote up the results. A manuscript resulting from this work was commented on by my supervisors along with Professor Ann Swillen, Prof Therese van Amelsvoort, Dr Samuel Chawner, Dr Claudia Vingerhoets, Dr Elfi Vergaelen, Professor David Linden and Professor Stefanie Linden. These comments were incorporated into this thesis.

Publications based on this thesis

Sinead Morrison, Samuel Chawner, Therese van Amelsvoort, Ann Swillen, Claudia Vingerhoets, Elfi Vergaelen, David Linden, Stefanie Linden, Michael Owen and Marianne van den Bree. **Cognitive deficits in childhood, adolescence and adulthood in 22q11.2 Deletion Syndrome and association with psychopathology.** (Under review)

Publications to which I have contributed

Robbie Davies, Ania Fiksinski, Elemi Breetvelt, Nigel M. Williams, Stephen R. Hooper, Thomas Monfeuga, Anne S. Bassett, Michael J. Owen, Raquel E. Gur, Bernice E. Morrow, Donna M. McDonald-McGinn, Ann Swillen, Eva W. C. Chow, Marianne van den Bree, Samuel Chawner, Sinead Morrison, Beverly S. Emanuel, Joris R Vermeesch, Stephen T. Warren, Therese van Amelsvoort, Celso Arango, Marco Armando, Linda E. Campbell, Joseph F. Cubells, Stephan Eliez, Sixto Garcia-Minaur, Doron Gothelf, Wendy R. Kates, Kieran C. Murphy, Clodagh M. Murphy, Declan G. Murphy, Nicole Philip, Gabriela M. Repetto, Vandana Shashi, Tony Simon, Damià H. Suñer, Stefano Vicari, International 22q11.2 Brain and Behavior Consortium, Carrie E. Bearden, Jacob Vorstman. **Using common genetic variation to examine phenotypic expression and risk prediction in 22q11.2 Deletion Syndrome.** (Under review)

Thesis Summary

22q11.2 Deletion Syndrome (22q11.2DS) is one of the strongest known genetic risk factors for schizophrenia and is a valuable model for understanding cognitive trajectories which may be associated with vulnerability for later psychosis. This thesis examined cognition and psychopathology over development in 22q11.2DS through cross-sectional and longitudinal approaches.

First, in a large multi-site cross-sectional sample, I investigated whether the presence of Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD) or anxiety disorder was associated with cognitive performance in children and adolescents with 22q11.2DS. In adults, I examined whether cognition was associated with presence of psychotic disorder. Psychopathology was associated with cognitive profile of individuals with 22q11.2DS in an age- and domain-specific manner. I also found that magnitude of cognitive impairment differed by developmental stage (child, adolescent or adult) in 22q11.2DS and the pattern differed by domain.

Next, I longitudinally examined the trajectories of a range of cognitive domains over three timepoints in children and adolescents with 22q11.2DS as compared to a control group of siblings without the deletion. There was no evidence for cognitive deterioration, but mostly initial impairment which remained stable over time, or additional lags in some domains whereby individuals with 22q11.2DS were not progressing at the same rate as controls.

Lastly, I compared the prevalence of prodromal psychotic symptoms in adolescents aged 15 years old with 22q11.2DS to control siblings, and whether longitudinal cognitive trajectories differed in individuals with 22q11.2DS and prodromal symptoms compared to those without. I found higher rates of prodromal symptoms in 22q11.2DS compared to controls, and that individuals with 22q11.2DS and prodromal positive psychotic symptoms displayed different antecedent cognitive development to those without psychotic symptoms in the form of initial deficits or lags over time.

This thesis extends knowledge of cognitive development in 22q11.2DS and how this relates to psychopathology in both clinical and high-risk stages.

Table of Contents

1	Introduction	1
1.1	Cognition	1
1.2	Psychopathology	1
1.2.1	Neurodevelopmental disorders	2
1.2.2	Intellectual Disability	3
1.2.3	Autism Spectrum Disorder	3
1.2.4	Attention Deficit Hyperactivity Disorder	4
1.2.5	Psychotic disorders	4
1.2.6	Schizophrenia as a neurodevelopmental disorder	5
1.2.7	Subthreshold psychotic experiences	6
1.2.8	Co-morbidity	7
1.3	The relationship between cognitive and psychiatric phenotypes	8
1.3.1	The relationship between ADHD and cognitive functioning	9
1.3.2	The relationship between ASD and cognition functioning	9
1.3.3	The relationship between psychotic disorders, psychotic experiences and cognitive functioning	10
1.3.4	Previous approaches to examining the relationship between cognition and psychopathology	11
1.3.5	Genetic first approach	12
1.4	22q11.2 Deletion Syndrome	12
1.4.1	Genetic structure	12
1.4.2	Phenotype	14
1.4.3	Inheritance	15
1.4.4	Diagnosis	15
1.5	Psychopathology in 22q11.2DS	16
1.5.1	Psychotic disorders in 22q11.2DS	16
1.5.2	Subthreshold psychotic symptoms in 22q11.2DS	16
1.5.3	ADHD	18
1.5.4	ASD	18
1.5.5	Other psychopathology	19
1.6	Cognition in 22q11.2DS	19
1.7	Relationship between cognition and psychopathology in 22q11.2DS	20
1.7.1	Relationship between ASD and ADHD and cognition in 22q11.2DS	20
1.7.2	Relationship between psychotic disorders and subthreshold psychotic experiences and cognition in 22q11.2DS	21
1.7.3	Summary	21
1.8	Aims of the thesis	23
1.8.1	Aim 1 – Cross-sectional investigation of cognition and psychopathology at different developmental stages in 22q11.2DS	24
1.8.2	Aim 2 – Characterise neurocognitive phenotype of 22q11.2DS longitudinally	24
1.8.3	Aim 3 – Presence of prodromal psychotic symptoms in 22q11.2DS and association with cognitive trajectories	25
1.8.4	Implications	25
2	General Methodology	27
2.1	Chapter overview	27
2.2	The Experiences of CHildren with cOpy number variants (ECHO) study	27
2.3	Cognitive Assessments	28

2.3.1	Wechsler Abbreviated Scale of Intelligence (WASI)	29
2.3.2	Wisconsin Card Sorting Test (WCST).....	30
2.3.3	Cambridge Neuropsychological Test Automated Battery (CANTAB).....	31
2.4	Psychiatric Assessments.....	33
2.4.1	Child and Adolescent Psychiatric Assessment (CAPA)	33
2.4.2	Structured Interview for Prodromal Symptoms (SIPS)	34
2.4.3	Assessment of Autism Spectrum Disorder (ASD).....	37
2.5	Recruitment.....	37
2.6	Sample characteristics	38
2.7	Retention rates.....	41
2.7.1	Individuals with 22q11.2DS.....	41
2.7.2	Control siblings.....	42
2.8	Attrition	42
3	<i>Cognitive deficits in childhood, adolescence and adulthood in 22q11.2 Deletion Syndrome and association with psychopathology.....</i>	57
3.1	Chapter overview	57
3.2	Introduction	57
3.2.1	The psychiatric and cognitive phenotype of 22q11.2DS	57
3.2.2	The relationship between cognition and psychopathology in 22q11.2DS	58
3.2.3	Cognition over the lifespan in 22q11.2DS.....	59
3.3	Aims	60
3.3.1	Aim 1: Associations of cognition and psychopathology in the three developmental stages in 22q11.2DS.....	61
3.3.2	Aim 2: Comparing cognitive performance across the three developmental stages in 22q11.2DS	61
3.4	Methods.....	61
3.4.1	Participants	61
3.4.2	Cognitive assessments	67
3.4.3	Psychiatric assessments.....	67
3.5	Analysis	68
3.5.1	Differences in 22q11.2DS compared to controls.....	68
3.5.2	Aim 1: Associations of cognition and psychopathology in the three developmental stages in 22q11.2DS.....	69
3.5.3	Aim 2: Comparing cognitive performance across the three developmental stages in 22q11.2DS	70
3.5.4	Gender.....	71
3.5.5	Site differences.....	71
3.5.6	Statistical correction	71
3.6	Results.....	71
3.6.1	Differences in 22q11.2DS compared to controls	71
3.6.2	Aim 1: Associations of cognition and psychopathology in the three developmental stages in 22q11.2DS.....	74
3.6.3	Aim 2: Comparing cognitive performance across developmental stages in 22q11.2DS	80
3.7	Discussion.....	84
3.7.1	Aim 1: Associations of cognition and psychopathology in the three developmental stages in 22q11.2DS.....	84
3.7.2	Aim 2: Comparing cognitive performance across developmental stages in 22q11.2DS	89

3.7.3	Limitations	90
3.7.4	Conclusions	92
3.7.5	Future work	93
4	<i>Longitudinal developmental cognitive trajectories in 22q11.2 Deletion Syndrome compared to controls</i>	94
4.1	Chapter overview	94
4.2	Introduction	94
4.2.1	Longitudinal studies in 22q11.2DS	94
4.2.2	Aims	99
4.3	Methods	100
4.3.1	Participants	100
4.3.2	Cognitive assessments	101
4.3.3	Statistical analyses	102
4.3.4	Statistical correction	105
4.4	Results	106
4.4.1	Aim 1: developmental trajectories of cognition in 22q11.2DS compared to controls	108
4.4.2	Aim 2: cognitive deterioration in 22q11.2DS compared to controls	115
4.5	Discussion	116
4.5.1	Aim 1: developmental trajectories of cognition in 22q11.2DS compared to controls	116
4.5.2	Aim 2: cognitive deterioration in 22q11.2DS compared to controls	119
4.5.3	Strengths and Limitations	120
4.5.4	Conclusions	122
4.5.5	Future work	123
5	<i>Prodromal psychotic symptoms in 22q11.2 Deletion Syndrome and association with cognitive trajectories</i>	124
5.1	Chapter overview	124
5.2	Introduction	124
5.2.1	Prevalence of psychotic symptoms in 22q11.2DS	124
5.2.2	Cognitive associations with prodromal symptoms	134
5.2.3	Longitudinal studies examining the relationship between cognition and psychosis in the general population	134
5.2.4	Longitudinal studies examining the relationship between cognition and psychosis in 22q11.2DS	135
5.2.5	Aims	138
5.3	Methods	138
5.3.1	Participants	139
5.3.2	Assessment of prodromal psychotic symptoms	140
5.3.3	Cognitive assessments	142
5.3.4	Statistical Analyses	143
5.3.5	Statistical correction	146
5.4	Results	146
5.4.1	Aim 1: prevalence and severity of prodromal psychotic symptoms in individuals with 22q11.2DS compared to controls	146
5.4.2	Aim 2: longitudinal cognitive trajectories in individuals with 22q11.2DS and prodromal symptoms compared to those without prodromal symptoms	153
5.5	Discussion	169
5.5.1	Aim 1: prevalence and severity of prodromal psychotic symptoms in individuals with 22q11.2DS compared to controls	169

5.5.2	Aim 2: longitudinal cognitive trajectories in individuals with 22q11.2DS and prodromal symptoms compared to those without prodromal symptoms	173
5.5.3	Strengths and Limitations	176
5.5.4	Conclusions	177
5.5.5	Future work.....	178
6	General discussion.....	180
6.1	Overview	180
6.2	Bringing results together.....	182
6.2.1	Converging cross-sectional and longitudinal findings	182
6.2.2	Attention as a transdiagnostic deficit	183
6.2.3	Cognitive trajectories	186
6.3	Implications.....	186
6.3.1	Dimensional measures of psychopathology	186
6.3.2	Control groups and reliable change	187
6.3.3	Schizophrenia risk and brain development	187
6.4	Strengths and Limitations	189
6.4.1	Sample size	189
6.4.2	Ascertainment bias	190
6.4.3	Controlling for IQ.....	190
6.4.4	Specificity of findings	191
6.5	Future directions	192
6.5.1	Early development	192
6.5.2	Later development	192
6.5.3	Environmental factors.....	193
6.5.4	Dimensional measures of psychopathology	194
6.5.5	Care and outcomes for individuals with 22q11.2DS.....	195
6.6	Conclusions	196
7.	References	197

Glossary of abbreviations

22q11.2DS	22q11.2 Deletion Syndrome
A'	A prime
ADHD	Attention Deficit Hyperactivity Disorder
ADI-R	Autism Diagnostic Interview-Revised
ANOVA	Analysis of Variance
APS	Attenuated Positive Symptom Prodromal Syndrome
ASD	Autism Spectrum Disorder
BIPS	Brief Intermittent Psychotic Symptom Prodromal Syndrome
bp	Base pairs
CAARMS	Comprehensive Assessment of At-Risk Mental States
CANTAB	Cambridge Neuropsychological Test Automated Battery
CAPA	Child and Adolescent Psychiatric Assessment
CNV	Copy Number Variation
COPS	Criteria of Prodromal Syndromes
DD	Developmental Delay
DEFINE study	Defining Endophenotypes From Integrated Neuroscience
df	Degrees of Freedom
DNA	Deoxyribonucleic Acid
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders (4th Edition) – Text Revision
DSM-5	Diagnostic Statistical Manual of Mental Disorders (5 th Edition)
ECHO study	Experiences of CHildren with cOpy number variants study
ESQ	Epilepsy Screening Questionnaire
FDR	False Discovery Rate
FEP	First Episode of Psychosis
FSIQ	Full Scale IQ
GAF	Global Assessment of Functioning
GCM	Generic Cognitive Model
GRD	Genetic Risk and Deterioration Prodromal Syndrome

IBBC	International 22q11.2DS Brain and Behaviour Consortium
ID	Intellectual Disability
IID	Idiopathic Intellectual Disability
IQ	Intelligence Quotient
kb	Kilobase
KSADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version
LCR	Low Copy Repeat
Mb	Mega base pairs
MINDDS	Maximising Impact of research in NeuroDevelopmental DisorderS
MINI	Mini International Neuropsychiatric Interview
MTS	Match To Sample
NHS	National Health Service
OCD	Obsessive Compulsive Disorder
ODD	Oppositional Defiant Disorder
PANSS	Positive and Negative Syndrome Scale
PAS-ADD	Psychiatric Assessment Schedule for Adults with Developmental Disabilities
PD	Parkinson's Disease
PIQ	Performance IQ
PQ-16	Prodromal Questionnaire
RCI	Reliable Change Indices
RDoC	Research Domain Criteria
RTI	Reaction Time
RVP	Rapid Visual Information Processing
SCID	Structured Clinical Interview for DSM-IV
SCQ	Social Communication Questionnaire
SD	Standard Deviation
SE	Standard Error
SIPS	Structured Interview for Prodromal Symptoms
SOC	Stockings of Cambridge

SPD	Schizotypal Personality Disorder
SWM	Spatial Working Memory
T1	Time 1
T2	Time 2
T3	Time 3
VIQ	Verbal IQ
WAIS	Wechsler Adult Intelligence Scale
WASI	Wechsler Abbreviated Scale of Intelligence
WISC	Wechsler Intelligence Scale for Children
WCST	Wisconsin Card Sorting Test
WHO	World Health Organization

1 Introduction

1.1 Cognition

Cognition is comprised of mental faculties that allow us to interact with the world successfully, such as attention, memory and problem solving (Deary et al., 2010). Cognitive impairment is associated with life outcomes such as academic achievement (Johnson et al., 2006), job performance (Gottfredson, 1997) and even mortality (Batty et al., 2007). Cognition develops over the lifespan, and the way in which it develops can give us insight into brain mechanisms (Deary et al., 2010) which could be influenced by environmental factors such as socioeconomic status, peer environment and culture (Foulkes and Blakemore, 2018) and contributions from genetic variation (Davies et al., 2011). Cognitive ability is often assessed by measuring the Intelligence Quotient (IQ), which is an overall compound score of someone's cognitive function relative to the general population. However, IQ scores have been criticised as limited in assessing specific cognitive abilities, such as attention or memory (Ardila, 1999). Therefore, neuropsychological tests have been developed which hone in on particular domains, enabling us to profile an individual's strengths and weaknesses in a variety of areas. Although IQ is often correlated with neuropsychological domains, it does not fully explain performance on them (Mohn et al., 2014).

1.2 Psychopathology

Emotional and behavioural difficulties that significantly interfere with an individual's functioning can reflect exposure to a variety of possible genetic and environmental risk factors, and may lead to a diagnosis of specific psychopathological symptoms or syndromes (Rutter et al., 2006). Individuals may present with, and seek help for, problems at different ages, and there appears to be some identifiable patterns in the temporal onset of different types of psychopathology, which will be discussed below (Rutter et al., 2006). Often there are indicators in childhood for later psychopathology, which has led to a recognition of the importance of a developmental perspective when assessing an individual (Rutter et al.,

2006). Studying trajectories of psychopathology may also provide an insight into brain mechanisms (Kates et al., 2018).

The Diagnostic Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association (2013)) is a widely-used tool for classifying mental disorders in order to aid diagnosis and treatment. In this section I will briefly detail the criteria for the various disorders that will be referred to throughout this thesis. The DSM-5 is not without its critics; it has been accused of medicalisation of behaviours which would not have reached a diagnostic level in previous DSM editions and over-involvement of drug companies leading to 'pharmaceuticalisation' (Pickersgill, 2014). Furthermore, it has been criticised as having a weak basis in biological findings relating to psychopathology, leading to the inception of newer initiatives such as Research Domain Criteria (RDoC) to address this (Insel et al., 2010). RDoC aims to construct a more dimensional framework to understand mental disorders, such as identifying commonalities in perceptual and cognitive functioning that cut across traditional categories of mental disorders. RDoC is being developed and honed, and work is ongoing to incorporate this approach into research but for the remainder of this thesis I will generally refer to the established DSM-5 definitions of mental disorders that are relevant to the research questions.

1.2.1 Neurodevelopmental disorders

Neurodevelopmental disorders are a collection of conditions that have their "onset in the developmental period" (DSM-5; American Psychiatric Association (2013)). They are hypothesised to result from disruption of development of the central nervous system, manifesting as childhood difficulties in cognitive and motor functioning. These difficulties generally persist over the lifespan, potentially with some reduction of symptoms over time (Thapar and Rutter, 2015). The neurodevelopmental disorders according to DSM-5 include Intellectual Disability (ID), Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD).

1.2.2 Intellectual Disability

Intellectual disability (ID), as defined by DSM-5, includes difficulties in intellectual functioning, such as planning and reasoning, which affect the person's daily life. These difficulties must be evident in the developmental period (i.e. in childhood or adolescence), unlike cognitive deficits that originate later in life due to, for example, traumatic brain injury or neurodegenerative disorder. ID should be assessed both clinically and through standardised intelligence tests. Standardised IQ tests have a population mean of 100 and standard deviation of 15, and it is expected that individuals with ID will score around 2 standard deviations below the population mean, around 65-75, with some margin for error. However, standardised IQ tests are subject to sociocultural biases, may move away over time from the historical reference group that the tests were standardised against and therefore show an inflation in scores (the Flynn effect), and may be influenced by language or motor difficulties, as some of the tests rely on verbal skills or movement, for example arranging wooden blocks in a pattern by a time limit (American Psychiatric Association, 2013). Therefore, it is useful to identify a neuropsychological profile that assesses the individual's ability in multiple domains rather than reducing the description of performance to a single number.

Clinically, there must also be evidence of conceptual (academic), social and practical difficulties that affect daily life to reach diagnosis. Therefore, even if an individual has an IQ above 70, if they show clinically significant impairments in the aforementioned domains that are comparable to others with a lower IQ they may benefit from a diagnosis of ID. It is by combining both criteria that a reliable assessment can be made. With all this information, clinicians can make a judgement on whether the severity of the ID is mild, moderate, severe or profound.

1.2.3 Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is characterised by persistent deficits in social communication and interaction, and restricted, repetitive patterns of behaviour, interests or activities which cause clinically significant impairment (American Psychiatric Association,

2013). The prevalence is estimated at around 1% in the general population (Elsabbagh et al., 2012). Diagnosis of ASD is often made at around 4-5 years old, despite parents often first experiencing concern over their child's development around 12-18 months (Zwaigenbaum et al., 2009). The diagnosis is thought to be fairly stable over time, although a minority, around 15%, no longer meet diagnostic criteria at follow up (Woolfenden et al., 2012). It has been reported that symptoms may worsen around times of change such as adolescence (Le Couteur and Szatmari, 2015). Additionally, some children may have subthreshold ASD symptoms that reach threshold after increasing academic and social demands (Le Couteur and Szatmari, 2015).

1.2.4 Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is characterised by persistent symptoms of inattention, such as difficulty organising tasks and activities, being forgetful and easily distracted, and symptoms of hyperactivity-impulsivity, such as fidgeting or talking excessively, and interrupting others (American Psychiatric Association (2013)). These symptoms must be pervasive across different settings, and to meet diagnosis must interfere with functioning in daily life. Individuals may meet criteria for predominantly inattentive or hyperactive presentation, or combined. 2-6% of the general population are thought to meet criteria for ADHD (Polanczyk et al., 2007). Referral for diagnosis for ADHD is typically in middle childhood but longitudinal studies have shown that signs are often present from much earlier, for example hyperactivity and aggression at pre-school age (Sonuga-Barke and Halperin, 2010) and symptoms often persist over the lifespan into adulthood (Biederman et al., 2012).

1.2.5 Psychotic disorders

Psychotic disorders such as schizophrenia typically emerge in late adolescence to early adulthood (American Psychiatric Association, 2013). They are generally characterised by two main categories of symptoms; positive symptoms, described as experiences which "add to or distort" consciousness such as delusions, hallucinations, disorganized thinking or speech,

disorganised behaviour; and negative symptoms, described as experiences which may “take away” from consciousness such as diminished emotional expression and avolition, which is a lack of motivation to complete goal-directed activities (American Psychiatric Association, 2013). To reach a diagnosis of schizophrenia, one must experience two or more of the above symptoms, at least one of which should be delusions, hallucinations or disorganized thinking or speech with the onset at least six months prior with active symptoms for at least a month of that time (or less if recognised and treated). The symptoms must affect functioning in daily life. Cognitive symptoms are also common in schizophrenia, such as deficits in executive functioning. If the person is experiencing symptoms of schizophrenia that are impairing but they do not meet the full criteria, for example in duration or frequency of symptoms, they may be diagnosed with Other Schizophrenia Spectrum and Psychotic Disorder. Schizoaffective disorder is characterised by the presence of delusions or hallucinations during a period of depressed or manic mood.

According to a recent meta-analysis, the lifetime prevalence of psychotic disorders is approximately one in 150 individuals, around 0.7% (Moreno-Kustner et al., 2018). Despite the classification of schizophrenia as a low prevalence disorder (Baxter et al., 2013), it ranks in the top 15 causes of disability worldwide (Vos et al., 2017) and carries a great economic burden, with costs estimated to range from 0.02% to 1.65% of gross domestic product (GDP) worldwide (Chong et al., 2016). It is proposed that policymakers may underestimate the economic and social burden of schizophrenia, resulting in insufficient allocation of resources and inadequate delivery of health care services (Chong et al., 2016). Early intervention, although initially costly, has been proposed to be cost-effective in the long term as a longer duration of untreated psychosis results in a greater likelihood of inpatient care and therefore higher treatment costs (Fusar-Poli et al., 2013). Furthermore, engaging the individual in treatment early can reduce the trauma of a first episode of psychosis (FEP) and therefore the human cost to the person and their family (Fusar-Poli et al., 2013).

1.2.6 Schizophrenia as a neurodevelopmental disorder

Although it is not classified as such in the DSM-5, schizophrenia has been proposed to display characteristics of a neurodevelopmental disorder, as there are observable indicators

of disrupted development which can potentially be measured in early childhood prior to the onset of psychosis such as cognitive, motor and social impairments (Howes and Murray, 2014). Additionally, there are links between pre- and perinatal insults and later schizophrenia, demonstrating that early development can influence the likelihood of schizophrenia (Howes and Murray, 2014). Furthermore, brain abnormalities identified at FEP suggest that the changes in the brain have already occurred (Owen et al, 2011). However, it has also been argued that schizophrenia does not fully fit into the category of neurodevelopmental disorder as it tends to follow a pattern of remissions and relapses, as opposed to disorders such as ASD and ADHD which generally follow a steadier course for a long period of time, with lessening in adulthood (Thapar and Rutter, 2015). Despite this, the support for the neurodevelopmental hypothesis of schizophrenia from a wide range of fields, such as neuroimaging, developmental and epidemiological studies has meant it has informed research directions (Owen et al., 2011).

1.2.7 Subthreshold psychotic experiences

Psychosis has been proposed to exist on a continuum from absence of symptoms, to presence of subthreshold psychotic symptoms, to psychosis meeting criteria for a schizophrenia diagnosis (DeRosse and Karlsgodt, 2015). These subthreshold psychotic symptoms have also been referred to as psychotic experiences, psychosis proneness, schizotypy or at-risk mental states (van Os et al., 2009). The proposal of a continuum has been criticised by some for being impractical in clinical practice as it could result in overmedicalisation of symptoms, and isn't useful for where dichotomous decisions are often needed, such as whether to prescribe medication (Lawrie et al., 2010). It is important to note that both categorical and continuous approaches to psychosis have advantages and may both contribute towards understanding (DeRosse and Karlsgodt, 2015).

It has been proposed that such subthreshold psychotic phenomena may be part of a "prodromal" phase of schizophrenia; that is, a state of changes in experience and functioning before psychosis (Woodberry et al., 2016). This may manifest as unusual thinking, such as a sense that things are odd or different or belief in mind control; suspiciousness, such as feeling unsafe or believing others intend to harm you; grandiose

ideas, such as believing you are particularly gifted or chosen for a special role; perceptual abnormalities, such as hallucinations, which could affect any of the senses but most commonly take the form of hearing or seeing things that are not there; and disorganised communication, being unable to get one's point across and stay on track (Woodberry et al., 2016). In the prodromal phase the person generally retains scepticism over these experiences, unlike psychosis where the person believes the experiences to be true, and the extent to which they find the experiences distressing may depend on the onset, frequency, duration and interference with their daily routine (Johns and van Os, 2001).

This prodromal phase has been hypothesised to occur in the majority of individuals who are later diagnosed with a psychotic disorder (Hafner et al., 2003). This suggests that if we could intervene in the prodromal phase this could prevent conversion to psychosis, with great benefits both economically and to the affected person (Fusar-Poli et al., 2013). However, it must be noted that currently in the UK, only around 4% of individuals had accessed prodromal services prior to FEP, suggesting that these services are not yet well established or that the prodromal phase is less common than previously thought (Ajnakina et al., 2017).

In recognition of the prodromal phase, "Attenuated Psychosis Syndrome" has been included in DSM-5. It has been argued that prodromal symptoms may reflect multifinality (Woodberry et al., 2016), that is, that they may relate to other non-psychotic disorders such as anxiety and depression (Woods et al., 2009). A meta-analysis reported conversion rates from the prodromal phase to a psychotic disorder of 36% after 3 years (Fusar-Poli et al., 2012a), so although there is a clear connection between the prodrome and psychosis, symptoms in most individuals appear to remit or remain under the threshold for psychosis within a 3-year window. One possibility is that their symptoms, although appearing prodromal, were unrelated to psychosis. Even if there is no conversion to psychotic disorder, it could be argued that prodromal symptoms that have motivated an individual to seek help still deserve to receive treatment and so the addition of "Attenuated Psychosis Syndrome" as a diagnosis may facilitate this (Fusar-Poli et al., 2013).

1.2.8 Co-morbidity

Co-morbidity refers to the presence of two or more separate disorders in the same individual (Thapar and Rutter, 2015). It is common for individuals with one diagnosis, for example of ASD, to have one or more other diagnoses such as ADHD or Oppositional Defiant Disorder (Leyfer et al., 2006, Joshi et al., 2010). This could represent shared genetic or environmental factors across disorders (Thapar and Rutter, 2015). Sequential comorbidity refers to when one disorder consistently appears to manifest after another, which could suggest some common mechanism across disorders which may have different temporal onsets (Thapar and Rutter, 2015). This is important as successful treatment of the predisposing disorder could then potentially prevent or ameliorate the secondary disorder. For example, it has been reported that children and adolescents with ADHD may be more likely to develop schizophrenia in adulthood (Dalsgaard et al., 2014). However, this phenomenon does not represent the majority of these disorders, and there are likely psychosocial factors playing an important role (Thapar and Rutter, 2015). For example, individuals with ADHD may be more likely to be exposed to negative life events such as bullying that could raise the risk for psychopathology later in life, but more research is needed on this (Thapar and Rutter, 2015)

1.3 The relationship between cognitive and psychiatric phenotypes

It has been proposed that the prevalence of psychiatric disorders is higher in individuals with cognitive impairments and that the same neurodevelopmental event could have produced both outcomes (Vorstman et al., 2006). A common feature associated with neurodevelopmental disorders is aberrant cognitive development (Doherty and Owen, 2014). A neurodevelopmental continuum has been proposed, whereby greatest cognitive impairment can be seen in ID, followed by ASD, ADHD, schizophrenia, and finally bipolar disorder showing the least cognitive impairment (Owen and O'Donovan, 2017). Furthermore, it has been suggested that the degree of cognitive impairment may align to the extent of genetic insult (Owen and O'Donovan, 2017). For example, ID would be associated with the greatest number of pathogenic genetic changes and the most severe cognitive impairment, followed by the other disorders. The fact that the common feature of cognition underlies these disorders points to a shared biological pathway (Thapar and

Rutter, 2015) and warrants further investigation. However, it should be recognised that there must also be distinct biological processes at play, with evidence from the effectiveness of medication that individuals with ASD for example would not benefit from stimulant medication that is effective for those with ADHD (Thapar and Rutter, 2015).

1.3.1 The relationship between ADHD and cognitive functioning

In early onset disorders such as ADHD it has been proposed that cognitive deficits may underlie behavioural and emotional problems (de Sonneville et al., 2018). Executive functioning deficits are thought to be prevalent in ADHD, in domains such as working memory, inhibition, attention and planning (Sonuga-Barke et al., 2010). However, there is heterogeneity and, rather than these deficits affecting everyone, there may be subgroups of individuals with strengths and weaknesses in particular cognitive domains (Sonuga-Barke et al., 2010). It has been suggested that individuals who show greater persistence of ADHD symptoms from childhood to adolescence have greater deficits in executive functioning, which could suggest that different trajectories of ADHD are associated with different impairments in cognitive function (Halperin et al., 2008).

1.3.2 The relationship between ASD and cognition functioning

It has been proposed that elucidating the cognitive phenotype of ASD can help understand underlying brain functioning (Le Couteur and Szatmari, 2015) and that aberrant cognition in ASD contributes to behavioural expression (Jones et al., 2018, de Sonneville et al., 2018). As in ADHD, individuals with ASD show impairments on executive functioning tasks (Demetriou et al., 2018). Interestingly, a meta-analysis found that there does not seem to be a specific pattern of impairment but rather a broad-ranging deficit across all tasks (Demetriou et al., 2018). It is proposed that this reflects a global impairment across brain networks, rather than deficits in specific brain regions (Demetriou et al., 2018). It has also been demonstrated that individuals with autism have impairments in theory of mind, which is the ability to understand the intentions of others and make subsequent predictions about their behaviour (Jones et al., 2018). Additionally, it has been suggested that theory of mind is

associated with behavioural ASD symptoms whereas executive functioning is not (Jones et al., 2018), so the role of executive functioning in ASD is still under debate. Nonetheless, it has been proposed that better cognitive ability predicted better long-term outcome in individuals with ASD suggesting this is an important area of study (Levy and Perry, 2011).

1.3.3 The relationship between psychotic disorders, psychotic experiences and cognitive functioning

In terms of later onset disorders, cognitive deficits have been recognised since the earliest accounts of schizophrenia (Weinberger and Levitt, 2011). It is estimated that four out of every five individuals with schizophrenia have cognitive impairments relative to the general population, and almost all do when compared to their own pre-morbid functioning (Saperstein and Kurtz, 2013). These impairments are often apparent in domains of attention, executive functioning and memory when an individual presents with their FEP (Meshulam-Gately et al., 2009) but it is unclear whether cognitive functioning is stable thereafter or declines further (Bozikas and Andreou, 2011).

A meta-analysis found that cognitive deficits may also be present in the prodromal phase of psychosis (Fusar-Poli et al., 2012b) but to a lesser extent than during FEP (Broome et al., 2009). The magnitude of impairments in the prodromal phase may differ by cognitive domain, with visual and verbal memory most affected, followed by domains such as working memory and attention, whereas processing speed may not differ between high-risk individuals and controls (Fusar-Poli et al., 2012b). Baseline performance in some domains was found to predict conversion to psychosis within 19 months, demonstrating the prognostic power of cognitive deficits (Fusar-Poli et al., 2012b). It has been suggested that this should be included in calculating an individual's risk of transition to psychosis (Riecher-Rossler et al., 2009).

Furthermore, poorer cognitive functioning in individuals with psychotic disorders has been associated with worse outcomes, such as likelihood of relapse, severity of symptoms, social and occupational functioning and treatment resistance (Fusar-Poli et al., 2012b), cementing the importance of cognition as a focus for research. Meta-analyses have concluded that

cognitive remediation may improve cognition, symptoms and functioning in both early stages (Revell et al., 2015) as well as chronic schizophrenia (Wykes et al., 2011), suggesting that cognition could be a viable target for interventions which could also confer benefits for the positive and negative psychotic symptoms.

1.3.4 Previous approaches to examining the relationship between cognition and psychopathology

It is clear that cognitive deficits are prevalent in a number of disorders with proposed neurodevelopmental origins, such as ADHD, ASD and schizophrenia. Furthermore, it appears that the magnitude of cognitive deficit may be related to severity of psychiatric presentation, making cognition a key target for research (Etkin et al., 2013). Studies of cognitive profiles in psychiatric disorders have often focused on one disorder and have been examined by different research groups with different instruments and criteria. There is a need for examination in a more homogeneous sample, where there is less background variation, with the same cognitive and psychiatric assessments. Furthermore, it is important not to assume that cognition or psychopathology is static over the lifespan but adopt a developmental lens by measuring ability in different age groups or longitudinally where possible.

Previous studies have identified cognitive impairments prior to the onset of psychotic symptoms in various ways. Older studies that have looked retrospectively at functioning of participants who were later diagnosed with schizophrenia, for example school performance (Bilder et al., 2006), have been criticised as this is a proxy of intelligence rather than a direct measure and is not time or domain specific (Reichenberg et al., 2010). Prospective longitudinal population studies such as Reichenberg et al. (2010) have been very useful in clarifying trajectories of cognitive development in those who will develop psychosis. However, as over 1000 people had to be followed from age 7 onwards to capture 35 that developed schizophrenia by age 32, this is a costly and lengthy undertaking.

1.3.5 Genetic first approach

One approach that can address these issues is following a group of individuals where a high proportion will develop the disorder (Chawner et al., 2019b), such as a “genetic first” approach. This identifies a genetic risk factor that increases likelihood of the outcome and follows individuals prospectively, meaning fewer participants overall are needed to achieve adequate power. Additionally, as these participants share the risk factor, they will be relatively genetically homogeneous compared to the general population, boosting the signal-to-noise ratio in identifying mechanisms of the disorder (Tang et al., 2017b). This magnifying effect can illuminate pathways to disease that may also apply to the general population (Gur et al., 2017).

One such group is individuals with 22q11.2 Deletion Syndrome (22q11.2DS), which is caused by a deletion of a small piece of genetic material from chromosome 22 (more detail provided in section 1.4.1). At least 60% of individuals with this deletion meet criteria for at least one psychiatric diagnosis at any given age (Jonas et al., 2014). ADHD and ASD are commonly reported, and most strikingly, ~29-40% are diagnosed with a psychotic disorder including schizophrenia in adulthood (Schneider et al., 2014a, Monks et al., 2014). This makes the syndrome one of the strongest genetic risk factors for schizophrenia, after having a monozygotic twin or two parents with schizophrenia (Tang et al., 2015). Therefore, 22q11.2DS represents a valuable model for understanding psychosis risk and following individuals with the deletion longitudinally could inform us about factors that may precipitate the onset of psychosis, such as cognitive functioning (Tang et al., 2017b).

1.4 22q11.2 Deletion Syndrome

1.4.1 Genetic structure

22q11.2DS is a heterozygous microdeletion syndrome whereby a section of one of chromosomes 22 is missing, or deleted. The estimated prevalence is 1:3000 to 1:6000 live births (McDonald-McGinn et al., 2015). The deletion is thought to occur through the

mechanism of non-allelic homologous recombination, whereby certain sections of the genome are more susceptible because they are very similar (Low Copy Repeat or LCR sections) and so during meiosis the LCRs can misalign, resulting in deletions or duplications of sections of DNA (Deoxyribonucleic Acid; Babcock et al. (2003)). If the deletion or duplication comprises greater than 1000 base pairs (bp; this can also be referred to as 1 kilobase (kb)) this is known as Copy Number Variation (CNV) (Lee and Scherer, 2010). CNV are present in every individual and have been hypothesised to contribute to evolution of the human genome through increased genetic diversity (Iafrate et al., 2004, Perry, 2009). However, several CNV have been classed as pathogenic due to their association with neurodevelopmental and psychiatric disorders (Chawner et al., 2019a), of which 22q11.2DS is the most common deletion syndrome.

There are variable deletion sizes in 22q11.2DS that are thought to produce similar outcomes, if they span the 'critical region' (McDonald-McGinn et al., 2015). This region is LCRA-LCRB (around 1.5Mb or mega base pairs, representing 1,000,000 bp; see Figure 1-1). However, usually the deletion spans 3Mb from LCRA-LCRD (85% of individuals affected; Shaikh et al. (2000)). Atypical deletions such as LCRB-LCRD also occur but have reduced penetrance (McDonald-McGinn et al., 2015) and therefore are not the focus of this thesis. Similarly, distal deletions such as LCRD-LCRF have been identified but have been reported to result in a different phenotype to deletions in the critical region (Ben-Shachar et al., 2008). It is estimated that 46 protein-coding genes are affected in the typical 3Mb deletion (Guna et al., 2015). The functions of some of these genes have been hypothesised to relate to symptoms present in 22q11.2DS, but much is still unknown about the interactions and influences of specific genes (McDonald-McGinn et al., 2015).

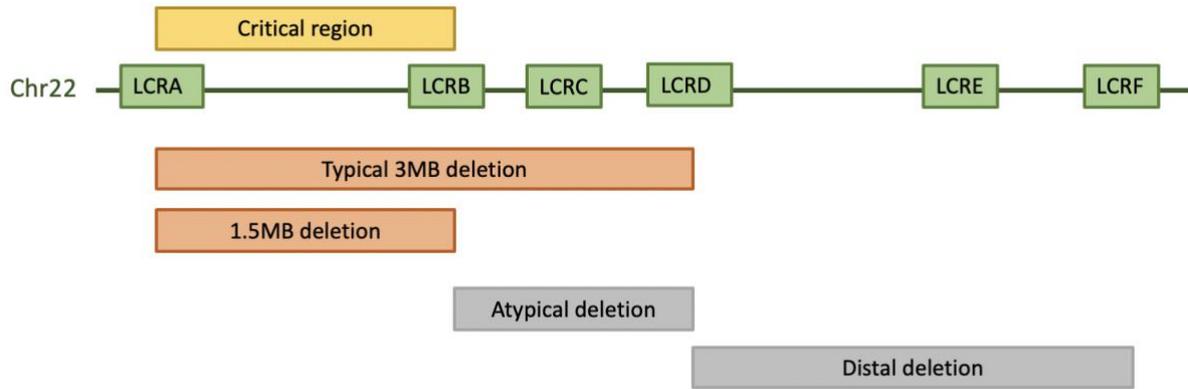


Figure 1-1. Low Copy Repeat (LCR) breakpoints of deletions on Chromosome 22 (Chr22).

1.4.2 Phenotype

22q11.2DS affects multiple body systems from fetal development throughout the lifetime. Apart from the aforementioned high prevalence of psychiatric disorders, common physical features that affect around 75% of individuals with 22q11.2DS are congenital heart defects, palatal abnormalities and immunodeficiency (McDonald-McGinn et al., 2015), often resulting in the need for surgery, problems with speech and feeding, and recurrent infections, respectively. Individuals may display characteristic facial features such as hooded eyelids, but these are generally quite subtle (McDonald-McGinn et al., 2015). The cognitive and psychiatric phenotype of 22q11.2DS will be covered in more detail in later sections. Overall, there are approximately 180 possible symptoms associated with 22q11.2DS with varying levels of penetrance, resulting in a diverse phenotypic expression (Shprintzen, 2008). The remarkable variation in clinical presentation is still not well understood, but could relate to a number of factors, such as variation in the remainder of the genome, variation on the intact 22q11.2, environmental influences and/or stochastic effects (McDonald-McGinn et al., 2015).

Due to the multitude of symptoms 22q11.2DS has had many different names over the years based on symptom clusters (such as DiGeorge, velocardiofacial syndrome, conotruncal anomaly face syndrome). However, once it was discovered that all these syndromes had the same underlying chromosomal deletion it was decided to establish a unifying name reflecting the genetic nomenclature, therefore 22q11.2DS (McDonald-McGinn and Sullivan,

2011). This is important in avoiding confusion for families that may be researching their child's symptoms and hopefully reduce the diagnostic odyssey (McDonald-McGinn et al., 2015).

1.4.3 Inheritance

22q11.2DS is most often a de novo event, meaning it is not inherited from either parent (90-95%; McDonald-McGinn et al. (2001)). The low rate of inheritance of the deletion is thought to be due to negative effects it has on mortality and reproductive fitness (Rees et al., 2011). However, it is hypothesised that as mortality rates are continuing to improve in 22q11.2DS, most likely due to improved cardiac interventions and outcomes, the prevalence of inherited 22q11.2DS may increase (McDonald-McGinn et al., 2001). Maternal age does not appear to be associated with likelihood of de novo 22q11.2DS (Delio et al., 2013). It appears that individuals who inherit 22q11.2DS may have more severe cognitive impairments, but it is difficult to tease apart the underlying environmental and genetic factors (Swillen et al., 1999).

1.4.4 Diagnosis

When an individual receives their diagnosis of 22q11.2DS often depends on the symptoms they experience. The presence of congenital heart defects, which are often associated with genetic conditions, often prompts diagnostic testing in the prenatal or neonatal period. If this is not present, other symptoms such as developmental delay, characteristic syndromic facial features and physical problems such as scoliosis in childhood may prompt testing (McDonald-McGinn et al., 2015). Parents who have a child with 22q11.2DS may discover they also have the deletion, even though they may have experienced minimal symptoms (McDonald-McGinn et al., 2001). Because 22q11.2DS is often diagnosed early in life, it provides the opportunity to study risk factors for disorders with a later onset, such as schizophrenia (Feinstein et al., 2002). This thesis will focus on the aspects of brain development which are proposed to be affected by presence of 22q11.2DS; psychopathology and cognition.

1.5 Psychopathology in 22q11.2DS

As mentioned earlier, 22q11.2DS is associated with a range of psychiatric disorders, with at least 60% of individuals reaching criteria for at least one psychiatric diagnosis at any given age (Jonas et al., 2014). A large study of more than 1400 participants across 15 sites that are part of the International 22q11.2DS Brain and Behaviour Consortium (IBBC) reported rates of a range of disorders in individuals with 22q11.2DS, from 6-70 years old (Schneider et al., 2014a). The findings from this study will be referred to in the following sections breaking down rates of psychopathology in 22q11.2DS.

1.5.1 Psychotic disorders in 22q11.2DS

~29-40% of adults with 22q11.2DS have been reported to meet criteria for a psychotic disorder including schizophrenia (Schneider et al., 2014a, Monks et al., 2014). Generally the presentation of psychotic disorder is thought to be very similar to that of idiopathic schizophrenia, with no difference in age of onset or content of symptoms (Bassett et al., 2003, Monks et al., 2014), however a higher global level of functioning was reported in 22q11.2DS individuals with schizophrenia (Monks et al., 2014) and lower level of substance abuse (Bassett et al., 2003) compared to individuals with schizophrenia without the deletion. The comparable age of onset suggests that similar aberrant neurodevelopmental processes are acting in idiopathic and 22q11.2DS schizophrenia (Tang et al., 2017b). In general, the similarities demonstrate that 22q11.2DS is a valuable model for investigating schizophrenia (Gur et al., 2017).

1.5.2 Subthreshold psychotic symptoms in 22q11.2DS

Rates of subthreshold psychotic symptoms in 22q11.2DS vary across studies, likely due to differences in definition, instrument used to determine presence of symptoms and age of participants. Estimates of prodromal positive symptoms vary from 14-52% which is generally much higher than control groups, where reported rates range from around 0-12%

(Baker and Skuse, 2005, Debbane et al., 2006, Feinstein et al., 2002, Vorstman et al., 2006, Chawner et al., 2019b, Antshel et al., 2017, Stoddard et al., 2010, Tang et al., 2014b). A higher prevalence of schizotypal traits has also been found in individuals with 22q11.2DS compared to controls (84% vs 12%; Baker and Skuse (2005)), and prodromal symptom levels in 22q11.2DS have been found to be similar to individuals with schizotypal personality disorder (Shapiro et al., 2011).

Lesser studied are prodromal negative symptoms, despite the fact that these are thought to impact more on daily-life functioning (Schneider et al., 2012). Nonetheless, a great proportion of individuals with 22q11.2DS have been reported to experience negative prodromal symptoms -74-85%; Schneider et al. (2012), Stoddard et al. (2010), Schneider et al. (2019), disorganised symptoms -55%; Stoddard et al. (2010) and general prodromal symptoms - 60%; Stoddard et al. (2010).

However, it is important to mention that the proposed high rate of negative symptoms in 22q11.2DS may reflect comorbidity with other psychopathology such as anxiety, ADHD or ID (Tang et al., 2014b). For example, the negative symptom of reduced ideational richness that relates to rigid and concrete thinking and struggling to interpret nuances of conversation, is associated with impaired reading ability in 22q11.2DS (Tang et al., 2014b). However, in the general population there is often comorbidity between prodromal symptoms/psychosis and other disorders, but if the symptoms are not accounted for fully by other disorders and are sufficiently impairing and distressing they should not be dismissed (Woods et al., 2009).

Longitudinal studies following children with 22q11.2DS suggest that the prevalence of subthreshold psychotic symptoms increases as the children enter adolescence and therefore nearer the risk period for psychotic disorder (Chawner et al., 2019b, Antshel et al., 2017). However, it is also apparent that the symptoms can fluctuate and may persist, remit or emerge at follow-up (Tang et al., 2017a).

The content of psychosis features in 22q11.2DS has also been proposed to be similar to that of age- and sex-matched individuals without the deletion who were classified as “psychosis spectrum” (Tang et al., 2017b). The main differences reported were reduced tolerance of

stress and ideational richness in individuals with 22q11.2DS (Tang et al., 2017b). Overall, combined with the studies comparing schizophrenia between individual with and without the deletion (Monks et al., 2014, Bassett et al., 2003) it appears that the presentation of psychotic disorder as well as risk states is similar and therefore researching 22q11.2DS is a promising approach to investigate psychosis risk which could generalise to wider populations.

1.5.3 ADHD

The large cross-sectional IBBC study reported that 37% of children (6-12 years) met criteria for ADHD, as did 24% of adolescents (13-17 years) and 16% of adults (18 years; Schneider et al. (2014a)). This appears to follow a similar trajectory to the general population in terms of a decrease in prevalence in adulthood (Dopfner et al., 2015). However, a longitudinal study found that ADHD persisted from childhood to adulthood in 22q11.2DS in 29% of individuals (Kates et al., 2018) which is reportedly higher than the ADHD persistence rate of 15% in the general population (Faraone et al., 2006). It should also be noted that the clinical presentation of ADHD in 22q11.2DS differs from idiopathic ADHD in that it is predominantly the inattentive subtype, which is not explained by intellectual impairment (Niarchou et al., 2015).

1.5.4 ASD

ASD has been reported in 13% of children, 27% of adolescents and 16% of adults with 22q11.2DS (Schneider et al., 2014a). The higher rate in adolescents than children differs from findings in the general population and could reflect methodological differences in the multi-site IBBC study (Schneider et al., 2014a). Potentially cohorts that focused on adolescents with 22q11.2DS used different measurement instruments that may be more sensitive to ASD than the cohorts focused on children (Schneider et al., 2014a). Alternatively, it has been proposed that measuring ASD symptoms in young people with 22q11.2DS may be indexing pre-psychotic traits, especially social deficits, which would peak in adolescence (Eliez, 2007). However, a longitudinal study did not find an association

between autistic features in individuals with 22q11.2DS in childhood and risk of developing psychotic disorders or symptoms (Fiksinski et al., 2018) which suggests that both psychiatric conditions may be pleiotropic phenotypes of 22q11.2DS; that is, both conditions are linked to the 22q11.2 deletion but are not related to each other.

1.5.5 Other psychopathology

Anxiety disorders are thought to be common over the lifespan in 22q11.2DS, especially in children and adolescents (35% of individuals; Schneider et al. (2014a)), which is higher than in the general population (Kates et al., 2018). The prevalence of oppositional defiant disorder (ODD) at around 14% in childhood and adolescence in 22q11.2DS (Schneider et al., 2014a) is at the higher end of what is estimated for the general population (2-16% depending on methodology; Christenson et al. (2016)), but is similar to rates of 13.9% reported in idiopathic intellectual disability (Dekker and Koot, 2003). Conduct disorder was not reported in any of the 496 children and adolescents assessed (Schneider et al., 2014a).

Mood disorders such as depression and bipolar disorder increase in prevalence throughout the lifespan, reaching around 20% in adults over 36 years (Schneider et al., 2014a), which is comparable to the general population (Kates et al., 2018). Substance related disorders were found to affect a low prevalence of individuals with 22q11.2DS, peaking around 6% in young adults (26-35 years old; Schneider et al. (2014a)). As the prevalence of psychiatric disorders appears to vary over the lifespan in 22q11.2DS, it is important to take a developmental perspective that reflects the dynamic development of the brain (Kates et al., 2018).

1.6 Cognition in 22q11.2DS

Cognitive impairments affect nearly everyone with 22q11.2DS to some degree (Gothelf et al., 2013, De Smedt et al., 2007, Campbell et al., 2010). The spread of IQ in individuals with 22q11.2DS follows a normal distribution, as in the general population, but is shifted around 30 points to the left, with a mean of approximately 70 (Niarchou et al., 2014). Previous studies have estimated that around 30-50% of individuals with 22q11.2DS would meet

criteria for mild ID, classically with an IQ of ~53-69 (Swillen et al., 1997, Niklasson et al., 2009, Niarchou et al., 2014). Some individuals have an average IQ with minimal impairments. Severe ID appears to be rare at around 5% (Swillen et al., 1997).

IQ has been found to correlate weakly with tests probing specific cognitive domains in 22q11.2DS (Niarchou et al., 2014) so it is key to use a range of measures in this population, as by understanding these fine-grained deficits and their patterns with other traits we may gain greater understanding of the affected neurobiology behind the syndrome (Gur et al., 2014). Deficits in executive functioning, working memory, attention and processing speed have been reported in children with 22q11.2DS (Niarchou et al., 2014). The magnitude of these deficits has been found to exceed those in individuals with idiopathic developmental delay, suggesting a neurocognitive profile specific to 22q11.2DS (Gur et al., 2014).

It is important to investigate whether cognitive deficits in 22q11.2DS are stable over development, or if they are worse at certain developmental time points, as looking at cognition across the life span in a group at high-risk for psychopathology can provide important insights into mechanisms that may underlie both (Gur et al., 2014). So far, there is an inconsistent literature on the stability of cognitive abilities over time in individuals with 22q11.2DS, with some studies proposing a decline in cognitive abilities in individuals with 22q11.2DS (Duijff et al., 2013) but others finding no evidence for decline (Chawner et al., 2017). This may reflect methodological differences such as inclusion of a control group, the age of participants and the use of different assessments at different time points. For example, without including a control group, fluctuations in cognition in 22q11.2DS may be interpreted as abnormal when they are within a comparable range (Chawner et al., 2017).

1.7 Relationship between cognition and psychopathology in 22q11.2DS

1.7.1 Relationship between ASD and ADHD and cognition in 22q11.2DS

In terms of the relationship between cognition and ASD and ADHD in 22q11.2DS, studies have produced mixed results, with some suggesting that cognitive deficits and

psychopathology constitute distinct pleiotropic outcomes of the deletion (Green et al., 2009, Niarchou et al., 2014), but others reporting that cognition may mediate psychopathology (de Sonnevile et al., 2018), or inversely that psychopathology may mediate cognitive functioning (Sanders et al., 2017, Niklasson and Gillberg, 2010). It has furthermore been suggested that age may play a role in these complex relationships between cognitive deficits and psychopathology (de Sonnevile et al., 2018), but to date no studies have looked at potential differences in these relationships at different developmental stages.

1.7.2 Relationship between psychotic disorders and subthreshold psychotic experiences and cognition in 22q11.2DS

Presence of schizophrenia in 22q11.2DS has been associated with greater cognitive deficits (van Amelsvoort et al., 2004, Chow et al., 2006, Weinberger et al., 2016, Fiksinski et al., 2018), concurring with studies of idiopathic schizophrenia (Gold et al., 2017). However, most individuals with 22q11.2DS and schizophrenia were taking neuroactive medication such as antipsychotics, which may affect cognitive functioning (Weinberger et al., 2016). Therefore, it is beneficial to have a pre-medication measure of cognition. Longitudinal studies following adolescents with 22q11.2DS into adulthood found that IQ (particularly verbal IQ) was lower in those with, than those without, psychotic disorder (Gothelf et al., 2013, Vorstman et al., 2015). There is also evidence from longitudinal studies that cognitive deficits may predict presence of subthreshold psychotic experiences (Antshel et al., 2017, Chawner et al., 2019b) but this is less well characterised and needs more research attention.

1.7.3 Summary

There is indication that neurodevelopmental psychopathology such as ADHD, ASD and psychotic disorders are associated with cognitive deficits but there is a need for replication of these findings, taking a developmental perspective to investigate this over the lifespan in 22q11.2DS.

There are mixed findings on cognitive trajectories in 22q11.2DS. Previous studies have suggested evidence for a cognitive decline across childhood and adolescence in 22q11.2DS but suffer from methodological flaws such as lack of a control group and different assessments at different timepoints, meaning interpretation of change over time is difficult. Longitudinal studies are necessary to disentangle different models of cognitive development, but most studies have been restricted to two timepoints and a fairly narrow age range. High rates of subthreshold psychotic experiences have been reported in adolescents with 22q11.2DS, but the content and stability of these experiences have not been much investigated.

Competing models have been proposed which could contribute towards explaining the developmental origins of mental health difficulties, in particular schizophrenia, in 22q11.2DS (see Figure 1-2). As discussed in section 1.7.2, in adulthood individuals with 22q11.2DS and schizophrenia demonstrate cognitive deficits compared to those without schizophrenia (van Amelsvoort et al., 2004, Weinberger et al., 2016, Fiksinski et al., 2018). However, it is unclear at what point in development these differences can be observed. As discussed in section 1.2.6, it has been hypothesised that there may be signs of disrupted neurodevelopment in early childhood prior to the onset of psychotic symptoms in adulthood, such as cognitive deficits (Howes and Murray, 2014). These deficits may remain stable over time, such that the difference between those with and without later schizophrenia is at the same magnitude throughout development, as in a deficit model.

Alternatively, there may be no discernible differences in cognition in childhood between individuals with 22q11.2DS with or without schizophrenia in adulthood, but rather differences may become more apparent as individuals age over adolescence and approach adulthood where there is increased risk of developing psychosis. This would follow a lag model, whereby the cognitive scores of the group which will develop schizophrenia do not progress at the same rate as those without schizophrenia, and therefore the difference between groups widens over time. This could be indicative of biological processes associated with schizophrenia such as increased synaptic pruning, whereby there is excessive elimination of synapses which affects adolescent neurodevelopment (Sekar et al., 2016). Identified environmental risk factors for schizophrenia such as bullying and

victimisation may also increase through adolescence and increase risk (Varese et al., 2012). A third model proposes that there may be an absolute loss of cognitive abilities in adolescence relative to previous performance, a deterioration model (Duijff et al., 2012). It could be possible that individuals could show differing developmental trajectories in different cognitive domains, or that there could be combinations of the models, for example an early deficit and a lag over adolescence. This framework will be used throughout the thesis to formulate and test hypotheses.

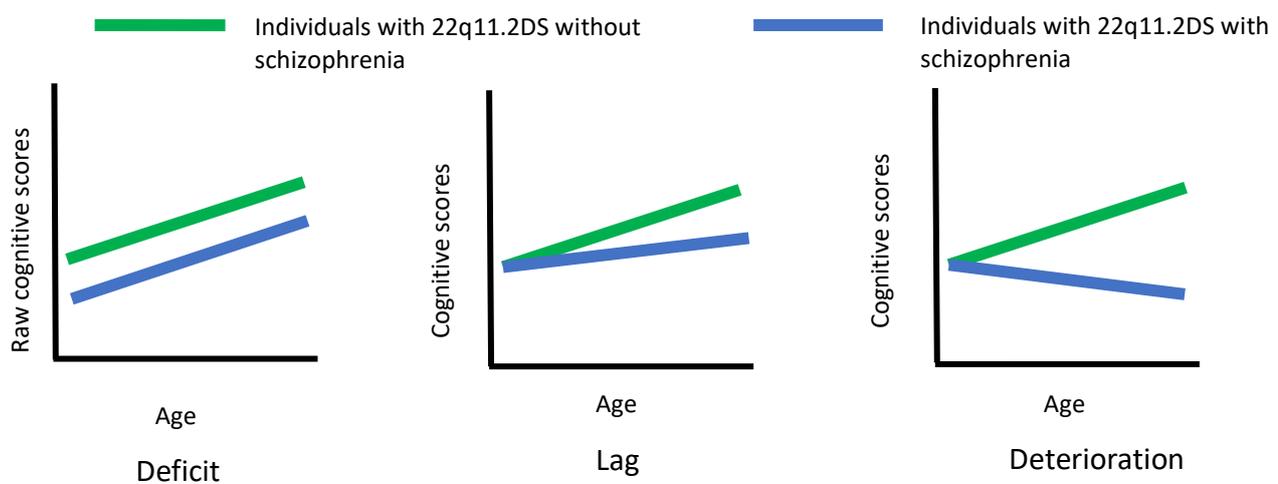


Figure 1-2. Competing models of cognitive development in childhood and adolescence prior to schizophrenia in adulthood in 22q11.2DS (22q11.2 Deletion Syndrome).

1.8 Aims of the thesis

As is evident from the literature above, individuals with 22q11.2DS represent a genetic high-risk sample for development of schizophrenia and other psychiatric disorders. The Cardiff University ECHO (Experiences of CHildren with cOPy number variants) study is a large prospective study which has, to date, recruited and assessed in great detail, using well-established psychiatric and cognitive assessments, ~800 individuals with CNV conferring high risk for neurodevelopmental disorder, including 141 with 22q11.2DS. In addition to the child with the CNV, siblings without the CNV (control sibling) were also invited to take part.

1.8.1 Aim 1 – Cross-sectional investigation of cognition and psychopathology at different developmental stages in 22q11.2DS

The ECHO study is part of the 22q11.2DS IBBC, presenting opportunities to collaborate with other member sites at Maastricht University and Katholieke Universiteit (KU) Leuven. In Cardiff our cohort is mainly comprised of children and adolescents, whereas the other sites mainly recruit adults. Some of the same cognitive tests have been administered across these sites as in the ECHO study, presenting an opportunity to collate this data and conduct a multi-site, cross-sectional investigation.

The core questions this chapter will address are:

- Are there associations between cognition and psychopathology in 22q11.2DS; specifically, ADHD, ASD, anxiety disorders and psychotic disorders?
- Does the magnitude of cognitive deficit differ at different stages of development (i.e. across children, adolescents and adults)?

1.8.2 Aim 2 – Characterise neurocognitive phenotype of 22q11.2DS longitudinally

The second aim of this thesis is to longitudinally characterise the complex neurocognitive phenotype of individuals with 22q11.2DS within the ECHO cohort compared to control siblings. As part of the longitudinal programme 89 families with a child with 22q11.2DS have been assessed twice approximately two and a half years later, and 62 of those followed up for a third time (more details in Methods chapter).

Cognitive tests included measures of full scale, verbal and performance IQ, sustained attention, processing speed, planning and working memory. As most previous longitudinal studies of individuals with 22q11.2DS have focussed on IQ to investigate cognition over the lifespan, the ECHO study data provide an opportunity to this address a gap in the literature and allow investigation of specific cognitive trajectories beyond IQ that may further explain risk of psychiatric disorder.

The core questions this chapter will address are:

- What does the group trajectory of cognitive development in 22q11.2DS look like in comparison to control siblings?
- Are there subgroups within 22q11.2DS that follow different trajectories?
- How does taking account of measurement error impact on conclusions?

1.8.3 Aim 3 – Presence of prodromal psychotic symptoms in 22q11.2DS and association with cognitive trajectories

A further target of this thesis is to estimate the prevalence of psychotic phenomena in the ECHO study third wave of data collection (mean age 15.5 years). The Structured Interview for Prodromal Symptoms (SIPS) was administered at the third wave, enabling a sensitive evaluation of prodromal psychotic experiences.

Furthermore, this thesis will compare longitudinal cognitive trajectories between individuals with 22q11.2DS who are identified as experiencing prodromal symptoms of psychosis at the third wave with those who have not reported prodromal symptoms. It will be possible to examine previously reported potential risk factors for prodromal symptoms, such as decline in IQ prior to psychotic symptoms, and test new associations.

The core questions this chapter will address are:

- What is the prevalence of psychotic symptoms in individuals with 22q11.2DS at age 15.5 years compared to control siblings?
- Do individuals with 22q11.2DS and psychotic symptoms show differing cognitive trajectories to those without psychotic symptoms?

1.8.4 Implications

Through convergent longitudinal and cross-sectional methods, I aim to gain insight into the neuropsychiatric development of individuals with 22q11.2DS, and how this may be disrupted. This research may therefore provide an insight to the mechanisms by which these disorders manifest. This research is impactful to families and carers of those with 22q11.2DS, where relatively little is known on what to expect over the lifespan. Furthermore, as I have covered in this introduction, the findings can be applied to the general population to further understanding of the relationship between cognition and psychopathology.

2 General Methodology

2.1 Chapter overview

In this thesis I aim to characterise the complex neurocognitive phenotype of individuals with 22q11.2 Deletion Syndrome (22q11.2DS) and association with psychopathology through cross-sectional and longitudinal investigation. This chapter will outline in more detail the methodology that relates to subsequent experimental chapters.

2.2 The Experiences of CHildren with cOpy number variants (ECHO) study

The ECHO study is a large prospective study which has, to date, recruited and assessed in great detail, using well-established and widely used psychiatric and cognitive assessments, ~800 individuals with Copy Number Variants (CNV) conferring high risk for neurodevelopmental disorder. Subjects were recruited across the United Kingdom and included 141 children and adolescents with 22q11.2DS. This cohort was established in 2010 by Principal Investigators Professor Marianne van den Bree and Professor Sir Michael Owen. In addition to the child with the CNV, siblings without the CNV (control sibling) were also invited to take part. As siblings share approximately half the same DNA and will usually have been raised in the same family environment, a sibling comparison group controls to some extent for shared genetic and environmental influences. When selecting a control group, it has been reported that comparing against siblings enables better detection of true differences with 22q11.2DS than unrelated typically developing individuals (Moberg et al., 2018).

As part of the longitudinal programme families were re-visited approximately every 2.5 years. The minimum age for participation was 6 years old, as the cognitive assessments used are not valid in children younger than 6. To encourage participation, data collection generally took place at the family home to eliminate factors that could dissuade participation such as travel and initial financial burden (before reimbursement of the family takes place), as well as reducing anxiety for the children participating as they were in a

familiar environment. Around 10% of data collection took place at Cardiff University, to enable the family to take part in brain imaging studies at the same time (please see for example Sun et al. (2018) for brain imaging findings in 22q11.2DS including ECHO study data).

Children were recruited primarily from National Health Service (NHS) medical genetics clinics, as well as UK charities, such as Max Appeal!, 22crew and Unique, the ECHO study website, social media outreach and word of mouth. Recruitment of individuals with 22q11.2DS was therefore not biased toward any particular phenotypic characteristics, as they were not recruited from a specific service such as a psychiatry or cardiology clinic (Hooper et al., 2013).

A report confirming the deletion was usually provided by the medical genetics clinic or the child's caregiver. In addition, following cognitive and psychiatric assessment, a biological sample was taken from all participating family members (child with CNV, control sibling and both parents where feasible); this was preferably a blood sample, but saliva was taken if obtaining a blood sample was not possible. The presence or absence of 22q11.2DS was then confirmed by in-house genotyping in the Cardiff University Division for Psychological Medicine and Clinical Neuroscience laboratory using microarray. It was particularly important to confirm control status of siblings as they are not always routinely tested.

Written informed consent was obtained from the parent or caregiver, and children over 16 years, to take part in the study. Children under 16, or those aged 16-18 years who lacked capacity completed an assent form with the opportunity to ask any questions. Study protocols were approved by the relevant NHS Research Ethics and Research and Development Committees.

2.3 Cognitive Assessments

Cognitive assessments are listed in the order they were administered.

2.3.1 Wechsler Abbreviated Scale of Intelligence (WASI)

Intelligence Quotient (IQ) was measured with the WASI (Wechsler, 1999) at all waves of assessment. It is composed of four subtests, two of which measure Verbal IQ (VIQ) and two of which Performance IQ (PIQ). The results from all four subtests generate the Full Scale IQ (FSIQ). Broadly VIQ measures crystallised (existing knowledge) and PIQ measures fluid (thinking on the spot) intelligence (Horn and Cattell, 1966).

The VIQ tests tap into expression of vocabulary and abstract verbal reasoning. PIQ tests tap into spatial processing and non-verbal reasoning. Table 2-1 outlines the four specific subtests participants undertook. Every IQ test was double coded, first by the assessor and then by another member of the team, to ensure agreement. Once the raw score for each subtest was established, these were converted into “T scores”, which are based on the age of the participant. The T scores are then converted to IQ scores using an IQ equivalent table (Wechsler, 1999).

IQ domain	Subtest name	Subtest outline	Raw measure	Possible raw score range
Verbal IQ – expression of vocabulary	Vocabulary	Participants must define increasingly difficult words	Points for words correctly defined	0-72
Verbal IQ – abstract reasoning	Similarities	The participant is read two words and asked to explain how they are similar	Points for similarities correctly identified	0-48
Performance IQ – spatial visualisation	Block Design	Participant must replicate block designs from watching the experimenter create a block design or from a booklet of designs	Points for block formations correctly replicated	0-71
Performance IQ – nonverbal reasoning	Matrix Reasoning	Participant is shown a matrix with a section missing and asked to identify the missing	Points for identifying the correct missing section	0-35

		section from five possible options.		
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Table 2-1. Outline of Wechsler Abbreviated Scale of Intelligence (WASI) IQ domains and subtests.

The WASI was chosen for this study as it can be administered to individuals between the ages of 6-89, negating the need as in previous research to move between child (Wechsler Intelligence Scale for Children; WISC) and adult (Wechsler Adult Intelligence Scale; WAIS) versions of IQ tests once the participant is over 18. This means the trajectory of raw scores over time can be examined, which is essential to distinguish between models of cognitive development (Chawner et al. (2017); see Chapter 4 Section 4.2.1.2 Models of cognitive development for more details).

Additionally, the WASI is relatively quick to administer (~30 minutes for the four subtests) compared to the comprehensive WISC/WAIS which take around an hour with the most recent versions having 10 subtests. The relative brevity of the WASI was particularly attractive given that we also wished to test a number of specific cognitive abilities as well as to assess psychopathology in a group of children of whom many had a number of behavioural and health issues. While the WASI allows a quick assessment of IQ, it is not necessarily suitable for assessing participants on an individual basis to make recommendations about their education or care; a comprehensive assessment such as the WISC-III or WAIS-III should be conducted in these cases (Axelrod, 2002).

Overall, the WASI is a good measure of general intelligence but does not probe into specific cognitive functions, such as attention, in detail. To further understand deficits in learning processes in 22q11.2DS a battery of neuropsychological tasks can be used to provide additional insights to a global measure of intelligence such as IQ (Gur et al., 2014).

2.3.2 Wisconsin Card Sorting Test (WCST)

Executive function is often probed by the WCST (Heaton, 1993), which evaluates cognitive flexibility (Rockers et al., 2009). The WCST is proposed to be sensitive to atypical frontal lobe function and therefore is often used to assess individuals with psychopathology or acquired brain injury (Jones, 2013). Individuals with 22q11.2DS have been reported to experience executive dysfunction (Rockers et al, 2009) and therefore the WCST was included to measure this, over time, compared to controls.

The participant is shown four target cards and then presented with consecutive response cards which they match in turn with one of the target cards, potentially based on similarities in colour, number or form. After ten successful matches of a particular “category” the rule is changed and the participant must deduce the new rule to enable successful matches in a new category (Jones, 2013). If the participant perseveres with multiple incorrect matches after the rule is changed, this is recorded as perseverative errors, an indicator of cognitive set shifting, which is the ability to shift focus between multiple tasks or mental sets (Miyake et al., 2000). The range of perseverative errors is 0-46 errors.

2.3.3 Cambridge Neuropsychological Test Automated Battery (CANTAB)

A battery of five neurocognitive tasks was administered using the CANTAB (CANTAB, 2006). These tasks assess multiple cognitive domains and are largely non-verbal, language-independent and culture-free (Levaux et al., 2007). Computerised testing such as the CANTAB may also be perceived as more motivating due to its game-like quality (Levaux et al., 2007) and require less interaction with the assessment administrator, which could reduce test anxiety in the individual (Ozonoff, 1995).

Given the high risk of schizophrenia in 22q11.2DS, cognitive areas were chosen that have been identified as core deficits in schizophrenia (Kern et al., 2004); spatial working memory, planning, processing speed, visual search and sustained attention (see Table 2-2 for full task details). These specific CANTAB tasks have been validated to be sensitive to deficits in individuals with schizophrenia (Barnett et al., 2010).

Neurocognitive function	Test name	Task outline	Raw measure	Possible raw score range
Spatial working memory	Spatial Working Memory (SWM)	Participant is shown a number of coloured boxes, each of which will in turn contain a target. The participant must search boxes to find the target, and when one is found, remember that that box will not contain a target in future and search the other boxes to find the other targets. The task increases in difficulty as more boxes are presented.	Between errors; the number of times the participant returned to a box where a target had already previously been found.	0-∞ errors
Planning	Stockings of Cambridge (SOC)	Participant is shown a display of coloured balls held in stockings on top row and must attempt to copy this display on bottom row. At first it is only necessary to make one move to copy the display, but gradually more moves are needed requiring more planning steps.	Minimum moves; number of occasions when the participant completed a test problem in the minimum number of moves.	0-12 moves
Processing speed	Five Choice Reaction Time (RTI)	Participants must respond as fast as possible to a stimulus in one of five locations.	Reaction time (ms).	0-∞ ms
Visual search	Match To Sample (MTS)	Participant must identify the matching pattern to a centrally displayed target pattern after a brief delay.	Total correct; number of correct responses.	0-48 correct responses

Sustained attention	Rapid Visual Information Processing (RVP)	Participants must respond to a target sequence of numbers over a few minutes of a continuous pseudo-random presentation of digits.	A' (A prime); probability of correct responses.	0-1
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Table 2-2. Outline of Cambridge Neuropsychological Test Automated Battery (CANTAB) tasks.

2.4 Psychiatric Assessments

Semi-structured interviews were conducted to assess presence of psychiatric symptoms and diagnoses, including subthreshold psychotic experiences. Interviews were carried out and diagnosed by a trained researcher, then double diagnosed by another member of the team. Interviews were audio-taped, and any unclear decisions were discussed in consensus meetings led by a child and adolescent psychiatrist.

2.4.1 Child and Adolescent Psychiatric Assessment (CAPA)

The CAPA (Angold et al., 1995) is a well-established and widely used semi-structured interview with the primary carer, focussing on psychopathology in the last 3 months. The CAPA has previously been successfully administered in 22q11.2DS research (Baker and Skuse, 2005). It assesses the presence and severity of psychotic experiences, psychotic disorders, mood disorders, anxiety disorders, tic disorders, trichotillomania, conduct disorder, oppositional defiant disorder and attention deficit hyperactivity disorder according to DSM-IV-TR (American Psychiatric Association, 2000).

Following the recommendations of Baker and Skuse (2005), the individual with 22q11.2DS and their sibling(s) were also directly interviewed where possible with child-appropriate psychosis, anxiety and depression sections of the CAPA. Presence of psychotic disorders, psychotic experiences, anxiety disorders and mood disorders could be established from this.

2.4.2 Structured Interview for Prodromal Symptoms (SIPS)

As psychosis risk is thought to increase over time in 22q11.2DS (Tang and Gur, 2018) the SIPS (McGlashan et al., 2001), a more detailed interview of psychotic phenomena, was added to the assessment battery at the start of the third wave of data collection. The SIPS has been administered successfully in previous 22q11.2DS research (Stoddard et al., 2010, Antshel et al., 2017, Tang et al., 2014b); however it is not recommended for children under 12 years old (Miller et al., 2003) and therefore these younger participants were interviewed solely with the child CAPA to obtain a measure of psychotic experiences.

The SIPS is intended to be a direct assessment of symptoms that may precede clinical schizophrenia and has been proposed to be more effective in measuring such symptoms than interviews of general psychopathology (Stoddard et al., 2010). The SIPS has excellent inter-rater reliability and, in the general population, predicts conversion to psychosis at a rate of 1 in 3 people reporting prodromal symptoms at 3 years from first assessment (Tang et al., 2014b). In 22q11.2DS, the rate of conversion from a prodromal syndrome identified by the SIPS to psychosis has been reported to be 27.3% after 32 months (Schneider et al., 2016).

The SIPS comprises 19 items, grouped into 5 positive, 6 negative, 4 disorganised and 4 general symptoms as follows:

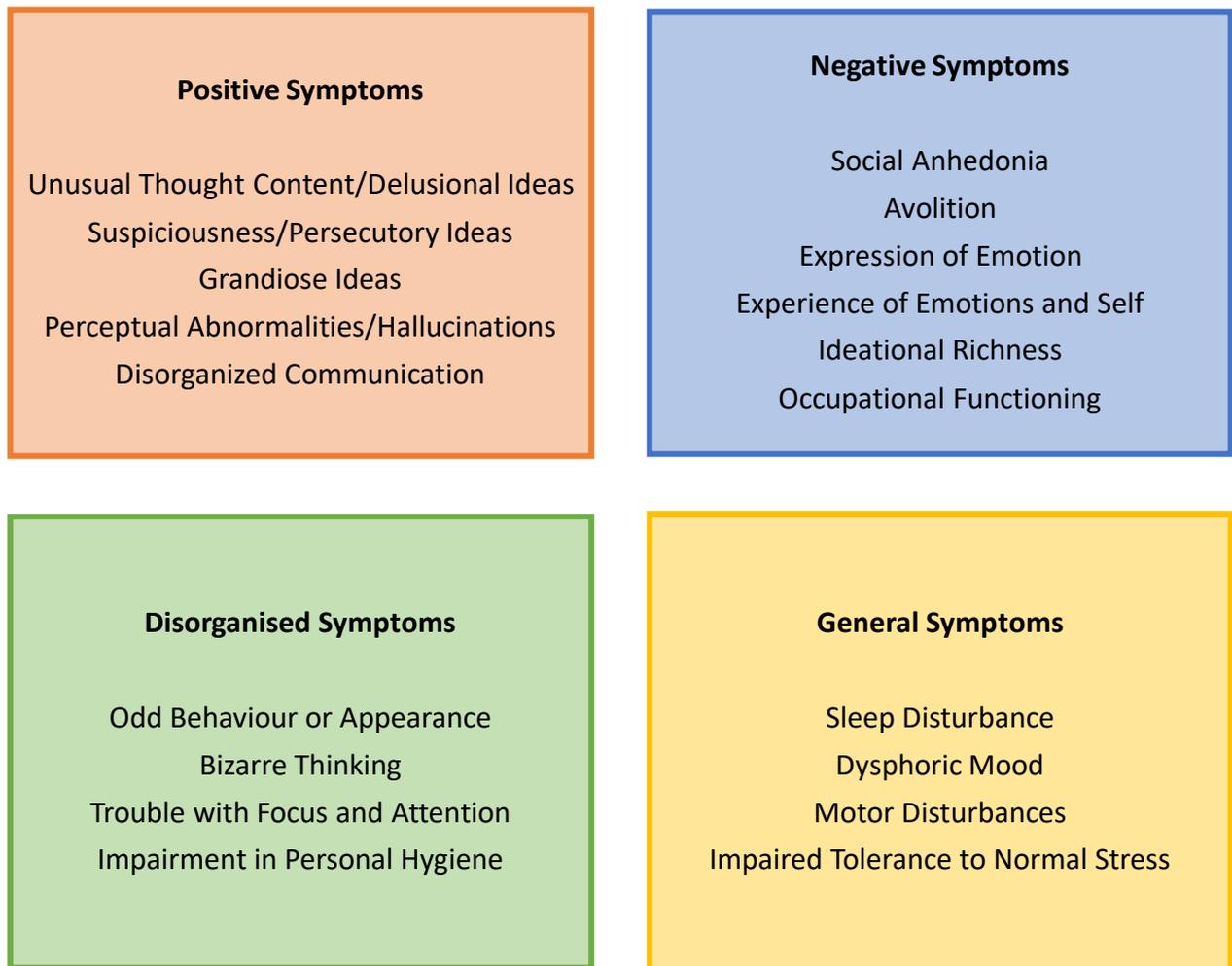


Figure 2-1. Positive, negative, disorganised and general prodromal psychotic symptoms assessed by the Structured Interview for Prodromal Symptoms (SIPS).

On each item the individual can score from 0 to 6 (see Table 2-3). A score of 0-2 is thought to be non-prodromal, 3 to 5 prodromal and 6 psychotic (Miller et al., 2002). Essentially for a reported symptom to score as psychotic (6), the individual must have total conviction regarding the externally generated “real” nature of the symptom and a lack of insight regarding the sense that the experience is in fact a symptom (Miller et al., 2003).

0	1	2	3	4	5	6
Absent	Questionably Present	Mild	Moderate	Moderately Severe	Severe but not Psychotic	Severe and Psychotic

Table 2-3. Scoring system for the Structured Interview for Prodromal Symptoms (SIPS).

Prodromal syndromes can also be defined by applying the Criteria of Prodromal Syndromes (COPS) after assessment. Three prodromal syndromes have been identified that are linked to high risk of developing schizophrenia (Yung et al., 1998, Yung and McGorry, 1996):

- Brief Intermittent Psychotic Symptom (BIPS) Prodromal Syndrome is applied if the individual scores a 6 (severe and psychotic) on any of the positive symptoms and these have been present at least several minutes a day at least once per month in the last three months.
- Attenuated Positive Symptom (APS) Prodromal Syndrome is applied if the individual scores a 3-5 (moderate to severe but not psychotic) on any of the positive symptoms and these have been experienced at least once a week in the last month. The symptoms must also have begun in the past year or currently rate at least one point higher than 12 months ago. As there is only one assessment of the SIPS it was not possible to assess whether symptoms were one point higher, so it could only be applied that symptoms had begun in the past year.
- Genetic Risk and Deterioration (GRD) Prodromal Syndrome is applied if the individual meets criteria for Schizotypal Personality Disorder (experiencing cognitive or perceptual distortions that affect social relationships; American Psychiatric Association (2013)) and has a first degree relative with psychotic disorder. Furthermore, they must demonstrate a 30% drop in a score of Global Assessment of Functioning (GAF) compared to 12 months ago. Again, we did not have a GAF measurement from a previous timepoint so could not assess these criteria.

Following Tang et al. (2014b), the questions relating to positive symptoms, which mainly cover subjective experiences, were administered with the child, and the questions relating to negative, disorganised and general symptoms were administered with the parent/caregiver, as they have been reported to rate these behavioural expressions related to psychosis more reliably (Tang et al., 2014b).

When scoring the SIPS, raters are advised to refrain from attributing symptoms to other psychopathology; prodromal symptoms can overlap with other disorders (see Chapter 1, section 1.2.7) but the SIPS is intended to be a phenomenological and dimensional measure which does not mutually exclude symptoms (Miller et al., 2003). For example, a question in the disorganised symptom section of the SIPS probes “Trouble with Focus and Attention”, which should be rated regardless of whether the individual would reach criteria for a diagnosis of ADHD which could also explain such a symptom (Tang et al., 2014b).

2.4.3 Assessment of Autism Spectrum Disorder (ASD)

Presence of ASD traits was screened using the Social Communication Questionnaire (SCQ; Rutter (2003)), which was completed by the primary caregiver. This is a questionnaire which was developed to align to the gold-standard Autism Diagnostic Interview-Revised (ADI-R; Lord et al. (1994)) and the two measures correlate highly (Berument et al., 1999, Charman et al., 2007), although it has been proposed that the SCQ does not perform as well as the ADI-R when discriminating ASD from intellectual disability (ID; Berument et al. (1999)). Total scores can range from 0 to 39; a score of 15 or over is indicative of probable ASD. This criterion has been applied in previous 22q11.2DS studies but as it is a screener will henceforth be identified as “probable ASD” (Niarchou et al., 2014, Vorstman et al., 2013). We did not regard ASD and ADHD as mutually exclusive diagnoses as in DSM-IV.

2.5 Recruitment

The following flow chart demonstrates the recruitment of participants into the ECHO study (Figure 2-2). Some control siblings entered the study at later waves as they were too young (under 6 years old) to take part at the first wave of data collection (n=16). Some participants did not complete all assessments at each wave; for example, some families took part via Skype at the first wave and so cognitive assessment would not be available at this wave (n=4). Some families were not ready to be reassessed as 2 years had not elapsed since their previous assessment. Subsequent results chapters will present relevant numbers of individuals in each analysis.

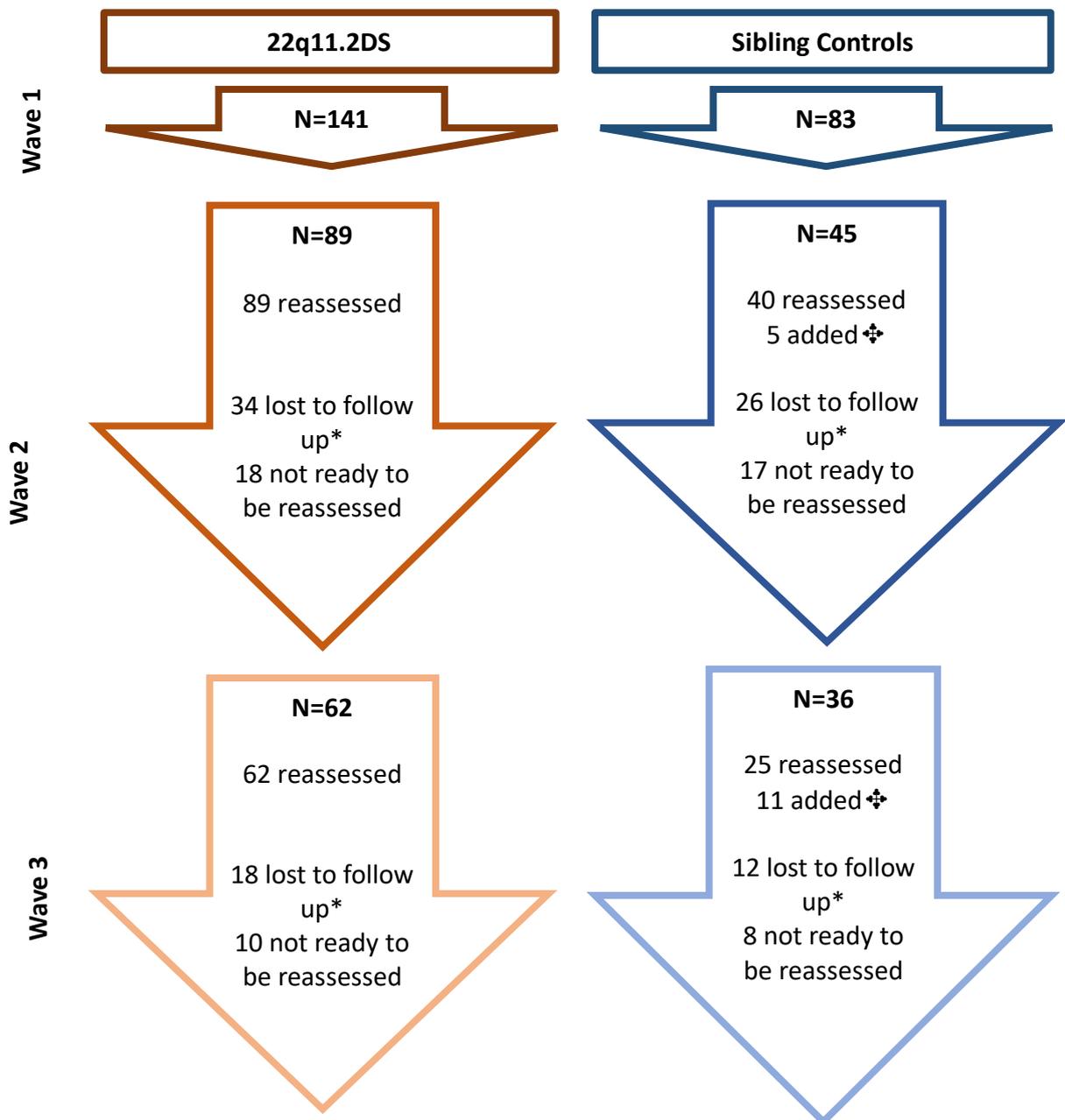


Figure 2-2. Flow chart of recruitment into the Experiences of CHildren with cOpy number variants (ECHO) study. ❖Siblings that entered the study at later waves once they were old enough to take part. *Families were lost to follow up for a number of reasons; uncontactable, child ill, deceased, withdrawn.

2.6 Sample characteristics

Baseline characteristics of the 141 individuals with 22q11.2DS are presented in Table 2-4.

	n (of 141)	%
Family Characteristics		
Family Ethnic Background		
European	126	89%
Non-European	2	1%
Mixed	6	4%
Unknown	7	5%
Highest Maternal educational qualification		
Low (O-Level/GCSEs)	43	30%
Middle (A-Levels/Highers/Vocational training)	46	33%
High (University degree and/or other higher postgraduate qualification)	40	28%
Unknown	12	9%
Family income		
≤19,999	31	22%
20,000 - 39,999	33	23%
40,000 - 59,999	29	21%
≥60,000	29	21%
Unknown	19	13%
Child with 22q11.2DS Characteristics		
Sex		
Male	76	54%
Female	65	46%
Origin of deletion		
De novo	115	82%
Inherited	13	9%

Unknown	13	9%
Deletion type		
~3Mb A-D	104	74%
~2Mb A-C	0	0%
~1.5Mb A-B	6	4%
Unknown	31	22%
Heart condition		
Yes	79	56%
No	56	40%
Unknown	6	4%
Epilepsy diagnosis		
Yes	11	8%
No	99	70%
Unknown	31	22%
Neuroactive medication		
Melatonin (sleep)	7	5%
Sodium Valproate (epilepsy)	2	1%
Aripiprazole (anti-psychotic)	1	1%
Melatonin and levothyroxine (sleep/hypothyroidism)	1	1%
None	111	79%
Unknown	19	13%

Table 2-4. Sample characteristics of individuals with 22q11.2DS (22q11.2 Deletion Syndrome) at baseline data collection.

For 22% of the sample it was not possible to obtain a biological sample and information on deletion size was not available. In the individuals with known deletion size, the majority had the 3Mb 22q11.2 deletion spanning LCRA-D as reported in the literature (Shaikh et al.,

2000). Six individuals were identified as having the 1.5Mb proximal 22q11.2 deletion, which still spans the critical region of LCRA-B (for more details see Chapter 1, section 1.4.1: Genetic structure). The phenotype of the 3Mb and 1.5Mb deletions is not thought to differ (Karayiorgou et al., 1995, Rozas et al., 2019) so these participants were included in further analysis.

Two individuals were identified as having distal LCRD-E deletions and one an atypical LCRB-D deletion (i.e. outside the critical region). Distal and atypical deletions have been reported to be less penetrant than deletions that span the critical region (McDonald-McGinn et al., 2015, Ben-Shachar et al., 2008) and therefore these individuals were excluded from further analysis.

Epilepsy diagnosis was assessed through the Epilepsy Screening Questionnaire (ESQ; (Eaton et al., 2019, Ottman et al., 2010)). The ESQ assesses lifetime diagnoses of epilepsy but was introduced later into the study, so this data was not collected on participants who only took part in one wave (n=31); those who took part at multiple waves would have completed the ESQ at one of those later times and therefore epilepsy diagnosis data was available for them (n=110).

The most common neuroactive medication was melatonin for sleep disturbance. Previous findings from the ECHO study have reported that sleep problems are common in 22q11.2DS, affecting 60% of individuals (Moulding et al., 2019). One individual who was taking aripiprazole (an anti-psychotic) at baseline at age 16 had previously been diagnosed with a psychotic disorder. Generally, rates of neuroactive medication treatment in 22q11.2DS were low, as previously reported (Tang et al., 2014a, Kates et al., 2018).

2.7 Retention rates

2.7.1 Individuals with 22q11.2DS

141 individuals with 22q11.2DS took part in the study at the first wave. Participants were eligible to be re-visited if 2 years had elapsed since the previous visit. 123 were eligible to be

re-visited and 89 were seen, with a retention rate of 72%. 79 participants were eligible to be visited a third time and 62 were, with a retention rate of 78%.

2.7.2 Control siblings

83 control siblings took part in the study at the first wave. 66 participants were eligible to be re-visited and 40 were seen, with a retention rate of 61%. 37 participants were eligible to be re-visited a second time and 25 were, with a retention rate of 68%.

The longer a follow-up period extends in a longitudinal study, the greater the likelihood of drop-out (Gustavson et al., 2012). Factors contributing to drop-out include change of contact details, illness or death of participant and withdrawal. In the current study the retention rates actually improved slightly between later recruitment waves, with retention from Wave 2 to Wave 3 (78%) being better than those from Wave 1 to Wave 2 (72%). This could be due to families having high commitment to the study being more likely to consistently participate, whereas others may be more likely to drop out early on (Lugtig, 2014). Retention rates were slightly lower for siblings; this was usually a result of an older sibling turning 18 and leaving the family home, or the increasing pressures of schoolwork at an older age meaning it was not feasible for them to participate. Generally, retention rates of 61-78% would be regarded as good (Gustavson et al., 2012).

2.8 Attrition

Attrition in longitudinal studies can pose problems for the generalisability of the findings if participants with certain characteristics are more likely to drop out (Pérez, 2007). Generally it is hypothesised that individuals with lower socioeconomic status and greater psychopathology may be more likely to drop out of mental health research (Pérez, 2007). This could lead to an underestimation of the rates of such psychopathology and contributing factors (Pérez, 2007).

Individuals with 22q11.2DS who took part at all three waves or dropped out of the study after one or two waves (due to becoming uncontactable, ill, deceased or withdrawing from

the study) were compared on baseline variables (see Table 2-5). Participants who were not eligible to be revisited because less than 2 years had elapsed since their last visit (n=28) are not included in the following analyses.

	Dropped out after Wave 1	Dropped out after Wave 2	Took part in all Waves	p-value
Age at Wave 1 (n)	33	18	62	
Mean (sd)	10.27 (2.96)	10.28 (2.18)	9.86 (2.51)	0.719✚
Sex (n male)	15/33	8/18	38/62	
%	45%	44%	61%	0.228●
Origin of deletion (n inherited)	2/27	3/17	5/62	
%	7%	18%	8%	0.448●
Wave 1 FSIQ (n)	31	18	53	
Mean (sd)	78.23 (12.15)	77.0 (14.40)	75.96 (11.83)	0.721✚
Any DSM-IV Psychiatric Disorder at Wave 1 (n)	21/33	12/18	32/62	
%	64%	67%	52%	0.367●
Psychotic Experiences at Wave 1 (n)	5/33	2/18	1/62	
%	15%	11%	2%	0.038●
SCQ score at Wave 1 (n)	33	18	62	
Mean (sd)	9.42 (8.82)	13.06 (8.32)	11.39 (7.98)	0.301✚
Heart condition (n)	14/29	13/18	35/62	
%	48%	72%	48%	0.272●
Medication (n)	2/26	0/16	4/59	
%	8%	0%	8%	0.541●
Family Ethnic Background (n)	29	18	61	
European	93%	97%	94%	
Non-European	3%	0%	0%	
Mixed	3%	3%	6%	
Highest Maternal educational qualification (n)	28	16	61	

Low	43%	50%	28%	0.150●
Middle	21%	38%	43%	
High	38%	13%	30%	
Family income (n)	27	18	55	
≤19,999	30%	44%	18%	0.225●
20,000 - 39,999	26%	22%	31%	
40,000 - 59,999	15%	6%	27%	
≥60,000	30%	28%	24%	

Table 2-5. Comparison of participants that dropped out after one or two waves or took part in all three waves on baseline variables. ♦Continuous variables were compared with ANOVA.

● Categorical variables were compared with chi-square.

There were no differences on any baseline variables between those who took part at all waves or who dropped out after the first or second wave, except for in rate of psychotic experiences ($p=0.038$). Psychotic experiences at baseline were highest in individuals who dropped out after one wave (15%), then after a second wave (11%) and lowest in those who took part at all three waves (2%). It is possible that symptoms may have worsened in these participants such that they were unable to take part in the study; furthermore, individuals seeking treatment for mental health problems have been reported to be more likely to drop out of research (Pérez, 2007). Parents may have been worried that interviewing the child about psychotic symptoms for the study could aggravate such symptoms or the feeling that they are “different”. Alternatively, the child may have been unwilling to participate because they were already having to detail their psychotic symptoms in clinical services, an experience which they do not enjoy or want to repeat (Pérez, 2007). Therefore, the longitudinal analysis may underestimate the prevalence of psychotic experiences at the most recent timepoint. This will be considered alongside the findings of later chapters.

3 Cognitive deficits in childhood, adolescence and adulthood in 22q11.2 Deletion Syndrome and association with psychopathology

3.1 Chapter overview

22q11.2 Deletion Syndrome (22q11.2DS) is associated with high risk of psychopathology such as Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD) and psychotic disorders. Similarly, cognitive impairments are highly penetrant. This chapter will examine associations between cognition and psychopathology in 22q11.2DS, and the stability of cognitive impairments at different developmental stages. First, I will discuss previous research on this, then report findings from a large, multi-site cross-sectional study of children, adolescents and adults with 22q11.2DS.

3.2 Introduction

3.2.1 The psychiatric and cognitive phenotype of 22q11.2DS

22q11.2 Deletion Syndrome (22q11.2DS) is associated with a range of psychopathology, with over half of individuals reaching criteria for at least one psychiatric diagnosis across the lifespan (Baker and Vorstman, 2012, Niarchou et al., 2014). Most strikingly, in adult samples, 29-42% are diagnosed with a psychotic disorder including schizophrenia (Schneider et al., 2014a, Monks et al., 2014). Several studies have established a high prevalence of childhood psychopathology manifesting as ADHD, ASD and anxiety disorders (Niarchou et al., 2014, Schneider et al., 2014a, Baker and Skuse, 2005). Prevalence of psychiatric disorders appears to follow different trajectories over the lifespan, such as the rate of anxiety disorders remaining relatively stable across developmental stages (Gothelf et al., 2013), whereas the rate of ADHD diagnosis declines, with 33-43% individuals no longer reaching diagnostic criteria at follow up in adolescence (Antshel et al., 2010, Chawner et al., 2019b). Therefore,

it is important to take a developmental perspective when considering psychiatric disorders in 22q11.2DS, which reflects the dynamic development of the brain.

22q11.2DS is highly penetrant for a broad range of cognitive impairments (Gothelf et al., 2013, Hooper et al., 2013, Campbell et al., 2010). It is important to investigate whether cognitive deficits in 22q11.2DS are stable over development, or if they are worse at certain developmental time points, as looking at cognition across the life span in a high-risk group for psychopathology can provide important insights into underlying mechanisms (Gur et al., 2014).

3.2.2 The relationship between cognition and psychopathology in 22q11.2DS

Studies investigating associations between cognition and psychopathology in young people with 22q11.2DS have produced mixed results. Some previous research has suggested that cognitive deficits and psychopathology constitute distinct pleiotropic outcomes of the deletion (Green et al., 2009, Niarchou et al., 2014). Other research has suggested that cognition may mediate psychopathology, for example, that deficits in executive functioning may index vulnerability to ASD or ADHD in children with 22q11.2DS (de Sonnevile et al., 2018). Conversely, reverse causation has been proposed, with the finding that presence of anxiety symptoms may mediate the relationship between 22q11.2DS and working memory capacity, with greater anxiety linked to less efficient cognitive performance (Sanders et al., 2017). Other research has reported that the presence of ASD or ADHD may predict poorer executive functioning ability in 22q11.2DS (Niklasson and Gillberg, 2010). It has furthermore been suggested that age may play a role in these complex relationships between cognitive deficits and psychopathology (de Sonnevile et al., 2018) but this has not yet been examined.

In adults with 22q11.2DS, research on the relationship between cognition and psychopathology has largely focused on associations with psychotic disorders. Individuals with 22q11.2DS and schizophrenia have been reported to display greater deficits on measures of executive function such as working memory and sustained attention than individuals with 22q11.2DS without schizophrenia (van Amelsvoort et al., 2004, Weinberger

et al., 2016, Fiksinski et al., 2018), conforming to studies of schizophrenia in individuals without a genetic syndrome (Gold et al., 2017). Additionally, longitudinal studies following adolescents with 22q11.2DS into adulthood found that IQ (particularly verbal IQ) was lower in those with psychotic disorders than those without psychotic disorder (Gothelf et al., 2013, Vorstman et al., 2015). A cross-sectional study of adults found deficits in verbal learning between adults with 22q11.2DS and schizophrenia compared to those without schizophrenia, but did not find this difference on attentional measures, suggesting that attentional dysfunction may be a general feature of 22q11.2DS over and above the influence of psychosis (Chow et al., 2006). Despite this, inattention symptoms have been proposed to have an important role in psychosis in 22q11.2DS (Niarchou et al., 2018). Therefore, there is still debate as to which cognitive functions are associated with psychotic disorders in 22q11.2DS.

3.2.3 Cognition over the lifespan in 22q11.2DS

The literature on cognitive trajectories from childhood to adulthood in 22q11.2DS is also inconsistent. Some studies have reported evidence of cognitive decline as individuals get older, with studies focussing on IQ reporting negative associations with age both cross-sectionally (Green et al., 2009) and longitudinally (Duijff et al., 2013). Other longitudinal studies comparing children with the deletion with a control sample of typically developing siblings assessed with the same measures have not found evidence of decline in IQ or a range of neurocognitive functions that have been associated with psychiatric disorder, including processing speed, sustained attention and working memory (Chawner et al., 2017, Hooper et al., 2013), although there may be developmental lags in specific domains (i.e., children with 22q11.2DS lag behind controls without the deletion). Furthermore, it has been reported that longitudinal cognitive profiles were similar between children with 22q11.2DS and IQ- and age-matched children with idiopathic intellectual disabilities (IID; (Van Den Heuvel et al., 2018)). Examining impairments in specific cognitive domains such as attention may provide insights into neurobiological processes (Gur et al., 2014) and these functions may be more sensitive both to cognitive decline and to remediation strategies than a global measure of intelligence like IQ (Antshel et al., 2017).

The majority of the studies of specific cognitive domains in 22q11.2DS have focussed on children and adolescents despite evidence that many cognitive functions continue to mature through early adulthood (Foulkes and Blakemore, 2018, Maeder et al., 2016). Our understanding of cognitive function in adults with the deletion thus remains limited (Swillen, 2016, Jonas et al., 2014, Moberg et al., 2018). One study found that adults with 22q11.2DS exhibited deficits in visuo-perceptual, planning, abstract and social thinking compared to age-, gender- and IQ-matched controls, which further reinforces the importance of considering specific cognitive domains beyond a sole focus on IQ (Henry et al., 2002). When examining change over a wider age range up to 26 years, one study found that overall working memory trajectory in 22q11.2DS differed from typically developing controls whereas other domains such as inhibition followed the same developmental course (Maeder et al., 2016). It was therefore proposed that individuals with 22q11.2DS may reach a “developmental plateau” in working memory ability before controls, but this was only observable because of the inclusion of older adolescents and adults (Maeder et al., 2016). However, another study with a similar age range investigating working memory abilities found that individuals with 22q11.2DS caught up with controls by age 25 (Antshel et al., 2017).

A recent meta-analysis of cognitive functioning in 22q11.2DS compared to controls reported that in paediatric samples there was evidence for greater cognitive impairment in older children, but in adulthood there was an improvement in cognitive abilities over time (Moberg et al., 2018), highlighting the importance of looking over a wide age range to understand better the continuing development of cognitive functions in 22q11.2DS. Furthermore, it is a general methodological limitation of previous research that different studies with relatively small numbers of participants have used different cognitive testing batteries, limiting comparisons that can be made across samples (Moberg et al., 2018). There is a need for testing a range of cognitive domains in a large sample where all participants have completed the same battery (Weinberger et al., 2016).

3.3 Aims

3.3.1 Aim 1: Associations of cognition and psychopathology in the three developmental stages in 22q11.2DS

The first aim of this chapter is to examine associations between cognitive performance and psychopathology. Specifically, in young individuals with 22q11.2DS I investigated whether associations with cognitive performance and the presence of ASD, ADHD or anxiety disorders differed for children and adolescents. In adults, I examined the association of cognition with the presence of a psychotic disorder. Based on the majority of previous research, I hypothesised that presence of a psychiatric disorder would be associated with greater cognitive deficits.

3.3.2 Aim 2: Comparing cognitive performance across the three developmental stages in 22q11.2DS

The second aim was to assess whether cognitive functioning differed across the three developmental stages in 22q11.2DS (childhood, adolescence and adulthood) compared to typically developing individuals. I hypothesised that there would be greater cognitive impairments in older individuals compared to younger individuals, based on previous research.

3.4 Methods

3.4.1 Participants

342 participants (236 individuals with 22q11.2DS and 106 controls) were recruited from three sites across Europe; Table 3-1 provides a description of the sample. Cardiff University recruited children and adolescents with 22q11.2DS and their typically developing control siblings through the Experiences of Children with cOpy number variants (ECHO) study, and adults with 22q11.2DS through the Defining Endophenotypes From Integrated Neuroscience (DEFINE) study. KU Leuven recruited adolescents and adults with 22q11.2DS and Maastricht University recruited adults with 22q11.2DS and adult community controls.

Participants were ascertained through similar recruitment methods, which was not on the basis of psychiatric presentation but largely through medical genetics services after receiving a diagnosis of 22q11.2DS (see Table 3-1). Children were defined as 6-9.9 years old, adolescents as 10-17.9 years old and adults 18+ following World Health Organization guidelines (World Health Organization, 2017). Mean ages were comparable in 22q11.2DS and control groups within the adolescent and adult developmental stages; however, in the child stage the 22q11.2DS group were on average a few months younger (see Table 3-2). Gender distributions were comparable in the child and adolescent developmental stages but there were significantly more female participants in the adult stage (see Table 3-2).

Site

	Cardiff			Leuven			Maastricht			Total
	<i>n</i>	<i>Ascertainment</i>	<i>Exclusion</i>	<i>n</i>	<i>Ascertainment</i>	<i>Exclusion</i>	<i>n</i>	<i>Ascertainment</i>	<i>Exclusion</i>	<i>n</i>
<i>Children (6-10 years)</i>	22q11.2DS	60	Medical genetics clinics, charities, social media	None	-	-	-	-	-	60
	Control siblings	23	Sibling of individual with 22q11.2DS	No diagnosis of 22q11.2DS	-	-	-	-	-	23
<i>Adolescents (10-18 years)</i>	22q11.2DS	61	Medical genetics clinics, charities, social media	None	5	Medical genetics service	None	-	-	66
	Control siblings	35	Sibling of individual with 22q11.2DS	No diagnosis of 22q11.2DS	-	-	-	-	-	35

Adults (18+ years)	22q11.2DS	18	Medical genetics clinics, charities, social media	None	28	Medical genetics service	None	64	Family associations, academic psychiatry outpatient clinic (automatically referred after diagnosis of 22q11.2DS, independently from any psychiatric problems)	None	110
(18+ years)	Community controls	-	-	-	-	-	-	48	Advertisement on internet	18-60 years of age, not using psychotropic medication, no history of psychiatric illness, no first degree relative with 22q11.2DS	48

Table 3-1. Site specific sample sizes of individuals with 22q11.2DS (22q11.2 Deletion Syndrome) and controls, ascertainment methods and exclusion criteria.

		<i>n</i>	<i>Age; mean (SD)</i>	<i>t (df)</i>	<i>p</i>	<i>Effect size; Cohen's d</i>	<i>Females; n (%)</i>	<i>χ² (df)</i>	<i>p</i>	<i>Effect size; Cramér's V</i>
<i>Children (6-10 years)</i>	22q11.2DS	60	8.15 (0.90)	2.32 (81)	0.023*	0.57	29 (48%)	0	1	0
	Control siblings	23	8.73 (1.05)				11 (48%)			
<i>Adolescents (10-18 years)</i>	22q11.2DS	66	12.5 (1.93)	1.12 (99)	0.267	0.23	33 (50%)	0.04 (1)	0.841	0.02
	Control siblings	35	12.08 (1.61)				16 (46%)			
<i>Adults (18+ years)</i>	22q11.2DS	110	30.49 (10.33)	1.98 (126.84)	0.05	0.30	74 (67%)	5.57 (1)	0.018*	0.19
	Community controls	48	27.67 (7.12)				22 (46%)			

Table 3-2. Age and gender distributions in 22q11.2DS (22q11.2 Deletion Syndrome) and controls across developmental stages.

54 participants (1 child, 3 adolescents and 50 adults) were taking neuroactive and/or thyroid medication at the time of testing (Table 3-3).

Neuroactive and thyroid medication	n (adults)
Quetiapine	3
Quetiapine and Aripiprazole	1
Aripiprazole	3*
Risperidone	3
Alprazolam and Sulpiride	1
Lithium carbonate, Atomoxetine and Olanzapine	1
Aripiprazole, Sodium valproate and Levothyroxine	1
Lorazepam, Aripiprazole, Quetiapine and Clozapine	1
Clozapine	2
Haloperidol	1
Fluoxetine and Antipsychotic Not specified	1
Mirtazapine and Olanzapine	1
Sertraline	2
Paroxetine, Zolpidem and Risperidone	1
Levetiracetam	1
Escitalopram and Bupropion	1
Escitalopram, Prothipendyl and Bromazepam	1
Escitalopram	1
Paroxetine	4
Methylphenidate	2
Oxazepam	1
Alprazolam and Venlafaxine	1
Unknown antiepileptic	1
Citalopram and Levothyroxine	1
Citalopram and Quetiapine	1
Diazepam, Amytriptyline, Paroxetine	1
Clomipramine and Quetiapine	1
Propranolol	1
Fluoxetine, Topiramate, Acetazolamide, Aripiprazole and Levothyroxine	1
Fluoxetine and Gabapentin	1
Citalopram and Risperidone	1
Gabapentin	1
Sodium valproate	2•
Levothyroxine	7†

Table 3-3. Medication use.

* n includes 1 adolescent

- n includes 2 adolescents

- † n includes 1 child

3.4.2 Cognitive assessments

A battery of three neurocognitive tasks comparable across sites was administered using Cambridge Neuropsychological Test Automated Battery (CANTAB) software CANTAB (2006); see Chapter 2 for full task details). Processing speed was measured through speed on the Five Choice Reaction Time (RTI) task, where the participant must respond as fast as possible to a stimulus in one of five locations. Sustained attention was measured through the probability of correct responses on the Rapid Visual Information Processing (RVP) task, where participants must respond to a target sequence of digits over a few minutes of a continuous pseudo-random presentation of digits. Spatial working memory was assessed as the number of errors on the Spatial Working Memory (SWM) task, where participants must remember where previous targets were in space. CANTAB raw scores were transformed into age-standardised z-scores based on normative data.

Full scale IQ (FSIQ), Verbal IQ (VIQ) and Performance IQ (PIQ) were assessed at each site with Wechsler scales in validated local language versions (WASI; Wechsler (2011) at Cardiff University and shortened WAIS-III; Wechsler (1997) for adults at the Leuven and Maastricht sites and WISC-III; Wechsler (1991) for adolescents at the Leuven site). IQ scores were calculated by standardising raw scores for age based on normative data. Not all participants completed all cognitive tasks, due to cognitive or behavioural issues or time constraints, but all completed at least one; this is detailed in Table 3-4.

3.4.3 Psychiatric assessments

3.4.3.1 Children and adolescents

The same psychiatric assessments were completed for children and adolescents recruited by the Cardiff site (see Chapter 2 for full assessment details). Psychopathology was established in line with DSM-IV criteria. Presence of psychotic experiences and disorders, ADHD and anxiety disorder was ascertained from the Child and Adolescent Psychiatric Assessment

(CAPA; (Angold et al., 1995)), a semi-structured interview with the primary caregiver. For children age 12+ self-report of psychotic experiences and disorders and anxiety disorder was also ascertained using the child CAPA. Presence of ASD traits was screened using the Social Communication Questionnaire (SCQ; Rutter (2003)) which was completed by the primary caregiver. We did not regard ASD and ADHD as mutually exclusive diagnoses as in DSM-IV.

3.4.3.2 Adults

At the Maastricht site, presence of prodromal psychotic symptoms was assessed by the Prodromal Questionnaire (PQ-16; (Ising et al., 2012)) and presence of psychotic disorder in adulthood was assessed by the Mini International Neuropsychiatric Interview (MINI; Sheehan et al. (1998)). The Leuven site used the Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung et al. (2005)) to detect prodromal psychotic symptoms and the Structured Clinical Interview for DSM-IV (SCID; (First, 2002)) and the MINI to assess presence of psychotic disorder. Cardiff used the Structured Interview for Prodromal Symptoms (SIPS; McGlashan et al. (2001)) to ascertain presence of prodromal symptoms and the Psychiatric Assessment Schedule for Adults with Developmental Disabilities (PAS-ADD; (Moss et al., 1993)) for psychotic disorder.

Instruments were comparable across sites and provided DSM-IV diagnoses of psychiatric disorders including schizophrenia, schizoaffective disorder and psychotic disorder.

Diagnoses at each of the three sites were made during consensus meetings led by a psychiatrist. All three centres that have contributed data to this paper are part of the IBBC, which used careful evaluation procedures to ensure phenotypic harmonization across sites (described in more detail in Gur et al. (2017)).

3.5 Analysis

3.5.1 Differences in 22q11.2DS compared to controls

Data analysis was conducted using R version 3.5.0. Mean neurocognitive z-scores and IQ scores were compared between individuals with 22q11.2DS and the control sample in the

separate developmental stages. Children and adolescents were compared against sibling controls with linear mixed models with deletion status as the fixed effect and family relatedness as a random effect. Adults were compared against (unrelated) community controls with t-tests (with correction for unequal variance if applicable). Mean FSIQ, VIQ and PIQ scores were compared between sibling and community controls with t-tests to investigate whether these different groups of typically developing individuals performed differently.

Within each developmental stage the mean score for the control sample (typically developing siblings for the children and adolescents and community controls for the adults) was subtracted from the score of each individual with 22q11.2DS for each cognitive measure. This produced a difference score for each individual with 22q11.2DS on each measure. A difference of 0 would therefore represent no difference between the individual with 22q11.2DS and the control mean and a negative difference would represent an impairment on that measure in the individual with 22q11.2DS compared to the mean control performance. This enabled the analysis to take into account control performance while comparing performance across age groups (i.e., it enabled us to focus on variation in cognitive performance that can be attributed to the 22q11.2 deletion).

3.5.2 Aim 1: Associations of cognition and psychopathology in the three developmental stages in 22q11.2DS

3.5.2.1 Children and adolescents

No children or adolescents met criteria for psychotic disorder at the time of assessment. One adolescent had been diagnosed with a psychotic disorder in the past which was currently managed with antipsychotic medication. Two other adolescents and one child were taking medication which could have affected cognitive performance (see Table 3-3), so sensitivity analyses were run for each analysis these four participants were included in. 2/60 children and 8/64 adolescents with 22q11.2DS reported subthreshold psychotic phenomena. As the number of children with psychotic experiences was small, comparisons in cognition between those with and without psychotic disorder/experiences would not

have been reliable. However, psychotic experiences were included as a covariate in analyses to establish whether this altered results.

To establish whether prevalence of probable ASD, ADHD or anxiety disorder differed in children and adolescents with 22q11.2DS compared to their typically developing siblings generalised linear mixed models were conducted, with prevalence of disorder as the outcome, deletion status as the fixed effect and family relatedness as a random effect. Odds ratios were estimated, i.e. the odds that the disorder occurred given diagnosis of 22q11.2DS. When there were no symptoms present in controls, p-values were estimated with Fisher's Exact test, but these should be interpreted with caution. Odds ratios could not be reliably estimated if there were no symptoms present in controls.

To investigate whether childhood psychopathology was associated with greater cognitive impairment in childhood or adolescence 2x2 ANOVAs were conducted to test for interaction effects (i.e., child vs adolescent x diagnosis present or absent) and main effects of psychopathology (i.e., diagnosis present or absent).

3.5.2.2 Adults

To compare performance on cognitive measures between adults with psychotic disorder and those without, independent t-tests were performed either with or without a correction for unequal variance, as applicable.

3.5.3 Aim 2: Comparing cognitive performance across the three developmental stages in 22q11.2DS

To compare performance on cognitive measures across the three developmental stages, one-way ANOVAs were performed on the difference scores for each cognitive measure. If a significant overall group difference (p-value <0.05) was found, Tukey HSD post hoc tests were conducted to establish which developmental stages differed from each other.

3.5.4 Gender

All analyses were also ran controlling for gender as a covariate, as it has been previously reported that there may be gender differences in cognitive performance (Niklasson and Gillberg, 2010)

3.5.5 Site differences

Analyses were also ran controlling for site as a covariate to account for potential variation arising from, for example, different assessments of psychopathology.

3.5.6 Statistical correction

The Benjamini-Hochberg method for controlling False Discovery Rate (FDR) was used to correct for multiple comparisons (Benjamini and Hochberg, 1995). This method ranks p-values in a cluster of tests, then divides the rank by the number of tests in the cluster, then multiplying by an acceptable FDR (in this case, 10%, following Crawford et al. (2018)) to produce a Benjamini-Hochberg critical value. The highest p-value that is below the Benjamini-Hochberg critical value survives FDR correction, as with all p-values below that one.

3.6 Results

3.6.1 Differences in 22q11.2DS compared to controls

Individuals with 22q11.2DS in every developmental stage showed impairment on all neurocognitive and IQ scores compared to controls except for adolescents in processing speed (Table 3-4). All comparisons survived FDR correction. There was no difference between sibling and community controls on FSIQ ($p=0.322$), VIQ ($p=0.841$) or PIQ ($p=0.318$).

Children and adolescents with 22q11.2DS had higher rates of probable ASD, ADHD and anxiety disorders compared to their typically developing siblings (Table 3-5).

	<i>Child</i>							<i>Adolescent</i>							<i>Adult</i>						
	<i>22q11.2DS</i>		<i>Control</i>		<i>t</i> (df)	<i>p</i>	Effect size; Cohen's <i>d</i>	<i>22q11.2DS</i>		<i>Control</i>		<i>t</i> (df)	<i>p</i>	Effect size; Cohen's <i>d</i>	<i>22q11.2DS</i>		<i>Control</i>		<i>t</i> (df)	<i>p</i>	Effect size; Cohen's <i>d</i>
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)				<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)				<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)			
<i>Neurocognitive z scores</i>																					
<i>Processing speed</i>	55	-0.64 (2.19)	22	0.58 (0.77)	2.51 (11)	0.029	1.52	60	0.02 (1.66)	34	0.55 (0.75)	1.75 (14)	0.101	0.94	99	0.49 (1.44)	48	1.02 (0.45)	3.32 (130.48)	0.001	0.43
<i>Sustained attention</i>	49	-2.93 (2.36)	20	-0.68 (1.20)	4.20 (10)	0.002	2.66	56	-1.77 (4.24)	34	-0.08 (1.22)	5.60 (14)	<0.001	2.99	86	-1.70 (1.12)	48	0.52 (0.81)	13.17 (123.79)	<0.001	2.16
<i>Working memory</i>	60	-0.89 (1.02)	23	0.21 (0.88)	4.26 (12)	0.001	2.46	65	-1.21 (0.84)	36	-0.50 (1.03)	4.18 (16)	<0.001	2.09	106	-0.41 (0.89)	48	1.20 (0.32)	16.45 (146.53)	<0.001	2.12
<i>IQ test scores</i>																					
<i>Full-scale IQ</i>	58	79.71 (10.05)	22	114.50 (16.29)	11.67 (11)	<0.001	7.04	65	72.90 (13.35)	35	104.49 (11.45)	14.13 (15)	<0.001	7.30	104	73.47 (11.98)	48	111.42 (16.87)	14.04 (69.72)	<0.001	2.77
<i>Verbal IQ</i>	58	81.40 (12.33)	22	116.05 (14.00)	11.36 (11)	<0.001	6.85	65	74.71 (13.80)	35	104.09 (10.26)	13.10 (15)	<0.001	6.76	102	72.97 (14.53)	48	108.10 (16.67)	13.17 (148)	<0.001	2.3
<i>Performance IQ</i>	60	81.52 (9.29)	22	109.73 (17.52)	9.46 (11)	<0.001	5.70	65	75.12 (13.06)	35	104.17 (14.17)	12.43 (15)	<0.001	6.42	102	72.26 (15.68)	48	110.08 (21.65)	10.84 (71.04)	<0.001	2.13

Table 3-4. Differences in cognitive performance between individuals with 22q11.2DS and typically developing controls for the three developmental stages.

	<i>Child</i>				<i>Adolescent</i>			
	<i>22q11.2DS n/total (%)</i>	<i>Control n/total (%)</i>	<i>Odds Ratio (95% Confidence Interval)</i>	<i>p</i>	<i>22q11.2DS n/total (%)</i>	<i>Control n/total (%)</i>	<i>Odds Ratio (95% Confidence Interval)</i>	<i>p</i>
<i>Probable ASD diagnosis</i>	17/58 (29%)	1/22 (5%)	8.71 (1.08 to 69.98)	0.032*	24/63 (38%)	1/34 (3%)	20.30 (2.61 to 158.28)	0.004*
<i>ADHD diagnosis</i>	28/59 (47%)	1/19 (5%)	16.26 (2.04 to 129.80)	0.012*	20/63 (32%)	1/35 (3%)	15.81 (2.02 to 123.84)	0.009*
<i>Anxiety disorder diagnosis</i>	19/60 (32%)	0/19 (0%)	-	0.004*	15/64 (23%)	2/35 (6%)	5.05 (1.08 to 23.56)	<0.001*

Table 3-5. Prevalence of probable ASD, ADHD and anxiety disorder in children and adolescents with 22q11.2DS and typically developing control siblings.

3.6.2 Aim 1: Associations of cognition and psychopathology in the three developmental stages in 22q11.2DS

3.6.2.1 Probable ASD

Interaction effects between probable ASD status and developmental stage were present on all neurocognitive measures (Table 3-6). Adolescents with probable ASD appeared to display a greater deficit in these domains compared to adolescents without ASD, but this did not appear to be the case for children (Figure 3-1). There were no interaction effects between probable ASD status and developmental stage on IQ measures (Table 3-6). There were no main effects of probable ASD on IQ measures. All comparisons survived FDR correction.

3.6.2.2 ADHD

There were no interaction effects between ADHD status and developmental stage on neurocognitive or IQ measures (Table 3-6). There was a main effect of ADHD on sustained attention such that those with ADHD displayed greater impairment regardless of developmental stage (Figure 3-2). This survived FDR correction. There were no associations between ADHD and processing speed, working memory or IQ measures.

3.6.2.3 Anxiety Disorder

There were no interaction effects between anxiety disorder status and developmental stage or main effects of anxiety disorder status on neurocognitive or IQ measures (Table 3-6).

Sensitivity analyses excluding four participants taking medication which could have affected cognitive performance did not affect results. Furthermore, analyses including presence of subthreshold psychotic experiences as a covariate did not alter results.

	Probable ASD						ADHD						Anxiety Disorder					
	Main effect on measure			Interaction with developmental stage			Main effect on measure			Interaction with developmental stage			Main effect on measure			Interaction with developmental stage		
	F (df)	p	Effect size; η^2	F (df)	p	Effect size; η^2	F (df)	p	Effect size; η^2	F (df)	p	Effect size; η^2	F (df)	p	Effect size; η^2	F (df)	p	Effect size; η^2
Neuro-cognitive scores																		
Processing speed	0.59 (1, 107)	0.443	0.01	5.45 (1, 107)	0.021	0.05	2.13 (1, 107)	0.147	0.019	1.89 (1, 107)	0.172	0.02	0.01 (1, 109)	0.916	0	0.44 (1, 109)	0.507	0
Sustained attention	2.11 (1, 98)	0.149	0.02	5.42 (1, 98)	0.022	0.05	8.85 (1, 98)	0.004	0.082	1.61 (1, 98)	0.207	0.02	0.02 (1, 100)	0.891	0	0.03 (1, 100)	0.86	0
Working memory	0.18 (1, 116)	0.669	0	8 (1, 116)	0.006	0.06	2.39 (1, 117)	0.125	0.019	0.03 (1, 117)	0.865	0	2.29 (1, 119)	0.133	0.02	0.76 (1, 119)	0.385	0.01
IQ test scores																		
Full-scale IQ	0.53 (1, 114)	0.468	0.01	0.54 (1, 114)	0.463	0.01	0 (1, 115)	0.954	0	2.75 (1, 115)	0.1	0.02	0.55 (1, 117)	0.46	0.01	0.01 (1, 117)	0.905	0
Verbal IQ	1.82 (1, 114)	0.18	0.02	0.13 (1, 114)	0.723	0	0.08 (1, 115)	0.78	0.001	2.46 (1, 115)	0.12	0.02	1.46 (1, 117)	0.229	0.01	0 (1, 117)	0.971	0

Performance IQ	0 (1, 116)	0.957	0	1.3 (1, 116)	0.257	0.01	0.28 (1, 117)	0.598	0.002	2.17 (1, 117)	0.143	0.02	0.02 (1, 119)	0.891	0	0.19 (1, 119)	0.665	0
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Table 3-6. Association of cognition and psychopathology in children and adolescents with 22q11.2DS (22q11.2 Deletion Syndrome) relative to typically developing controls. ASD, Autism Spectrum Disorder; ADHD, Attention Deficit Hyperactivity Disorder. η^2 = Partial Eta Squared.

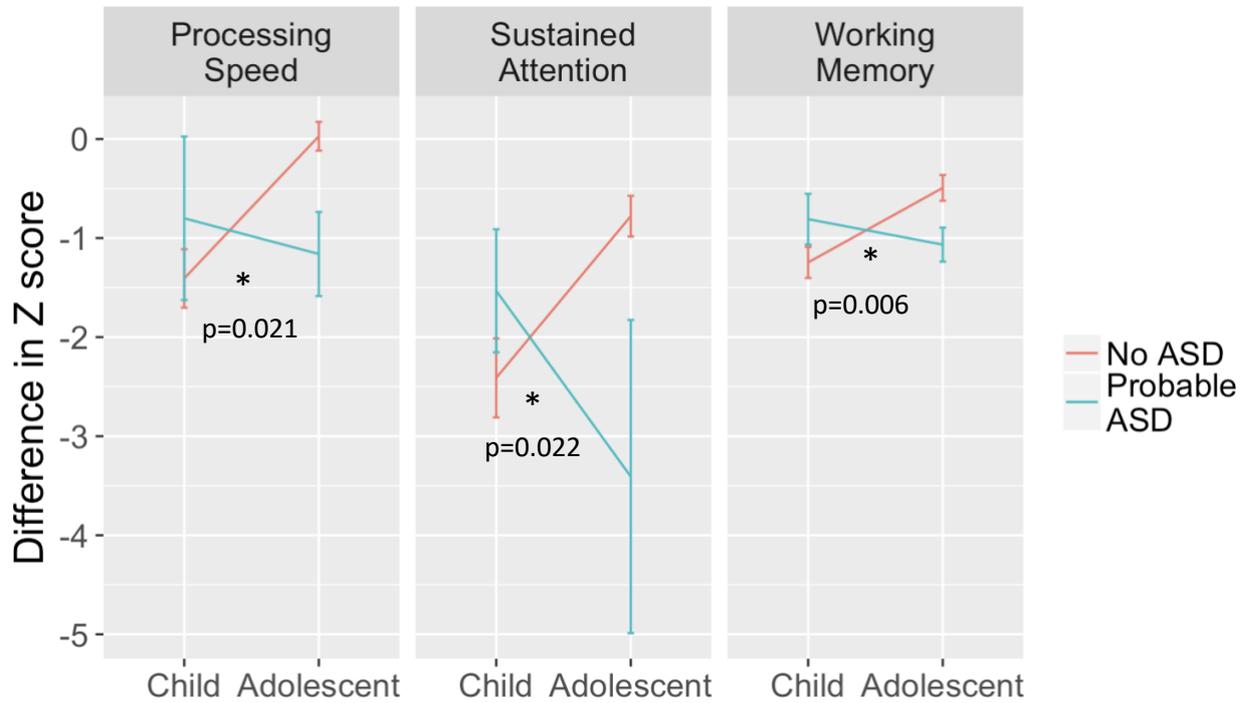


Figure 3-1. Association of probable ASD (Autism Spectrum Disorder) with neurocognitive performance in children and adolescents with 22q11.2DS (22q11.2 Deletion Syndrome) relative to typically developing controls.

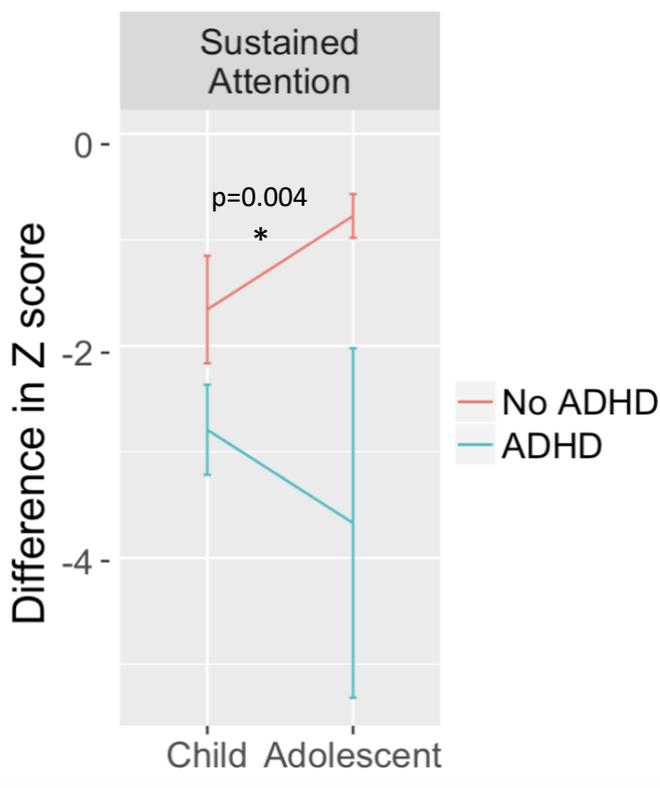


Figure 3-2. Association of ADHD (Attention Deficit Hyperactivity Disorder) with sustained attention in children and adolescents with 22q11.2DS (22q11.2 Deletion Syndrome) relative to typically developing controls.

3.6.2.4 Adults

16% of the adult sample (n=18) were categorised as having a psychotic disorder; 14 of these had a schizophrenia diagnosis, three a diagnosis of psychotic disorder not otherwise specified (NOS), and one a diagnosis of schizoaffective disorder. None of the control group were diagnosed with a psychotic disorder.

7% of adults without psychotic disorder (n=6) met criteria for prodromal psychotic symptoms. As this was a small number of adults, it was not appropriate to categorise these as a separate group, and so they were classified as adults without psychotic disorder. A sensitivity analysis including presence of prodromal symptoms as a covariate did not change results.

Individuals with a psychotic disorder displayed greater impairment in sustained attention and all IQ measures (Table 3-7; Figure 3-3; Figure 3-4). Conversely, presence of a psychotic disorder was not associated with processing speed or working memory. All comparisons survived FDR correction.

	<i>Psychotic disorder</i>		
	<i>t (df)</i>	<i>p</i>	<i>Effect size; Cohen's d</i>
Neurocognitive scores			
<i>Processing speed</i>	0.61 (97)	0.54	0.17
<i>Sustained attention</i>	3.13 (12.67)	0.008*	1.29
<i>Working memory</i>	0.26 (104)	0.797	0.07
IQ test scores			
<i>Full-scale IQ</i>	2.43 (102)	0.017*	0.66
<i>Verbal IQ</i>	2.64 (100)	0.010*	0.74
<i>Performance IQ</i>	2.03 (100)	0.045*	0.57

Table 3-7. Association of cognition and psychotic disorder in adults with 22q11.2DS (22q11.2 Deletion Syndrome) relative to typically developing controls

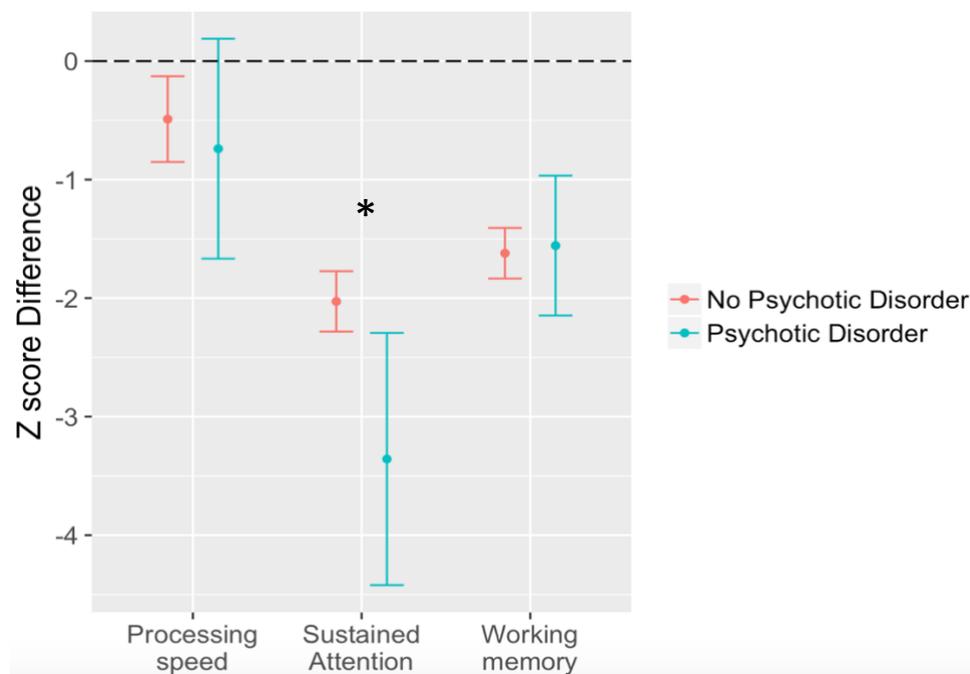


Figure 3-3. Association of psychotic disorder with neurocognitive performance in adults with 22q11.2DS (22q11.2 Deletion Syndrome) relative to typically developing controls.

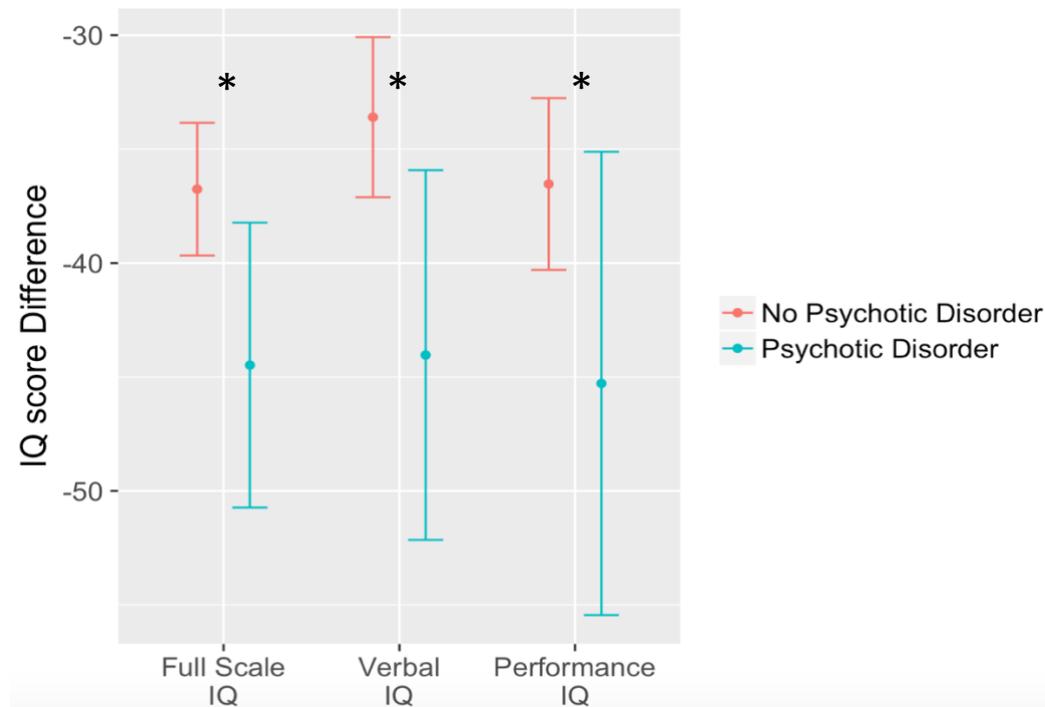


Figure 3-4. Association of psychotic disorder with IQ in adults with 22q11.2DS (22q11.2 Deletion Syndrome) relative to typically developing controls.

50 adult participants were taking medication which could have affected cognitive performance. Analyses were repeated controlling for medication as a covariate, and results were unchanged.

3.6.3 Aim 2: Comparing cognitive performance across developmental stages in 22q11.2DS

Working memory performance differed across the developmental stages (Table 3-8). Post hoc tests revealed that adults with 22q11.2DS showed more impairment on this task than children and adolescents. Processing speed differed according to developmental stage with children displaying greater deficits than adults. Impairment in sustained attention appeared to be similar across developmental stages (Figure 3-5).

There were differences across developmental stages on all measures of IQ (Table 3-8). Post hoc tests revealed that adults showed greater impairment than adolescents on all measures, and that adults also performed worse than children on PIQ (Figure 3-6). All comparisons survived FDR correction.

	ANOVA		Tukey HSD post-hoc tests			
	<i>F (df)</i>	<i>p</i>	<i>Effect size; η²</i>	<i>Child & Adolescent</i>	<i>Child & Adult</i>	<i>Adolescent & Adult</i>
Neurocognitive scores						
<i>Processing speed</i>	3.32 (2, 211)	0.038*	0.031	0.080	0.045*	0.999
<i>Sustained attention</i>	0.82 (2, 188)	0.443	0.009	-	-	-
<i>Working memory</i>	20.39 (2, 228)	<0.001*	0.152	0.051†	0.002*	<0.001*
IQ test scores						
<i>Full-scale IQ</i>	5.74 (2, 224)	0.004*	0.049	0.20	0.644	0.003*
<i>Verbal IQ</i>	3.81 (2, 222)	0.024*	0.033	0.089	0.975	0.025*
<i>Performance IQ</i>	13.02 (2, 224)	<0.001*	0.104	0.936	<0.001*	<0.001*

Table 3-8. Comparison of associations between developmental stage and cognitive impairment between the three developmental groups. Tukey HSD post-hoc tests were conducted if there was a significant difference between groups on ANOVA. † when controlling for site as a covariate, this difference was significant ($p=0.028$).

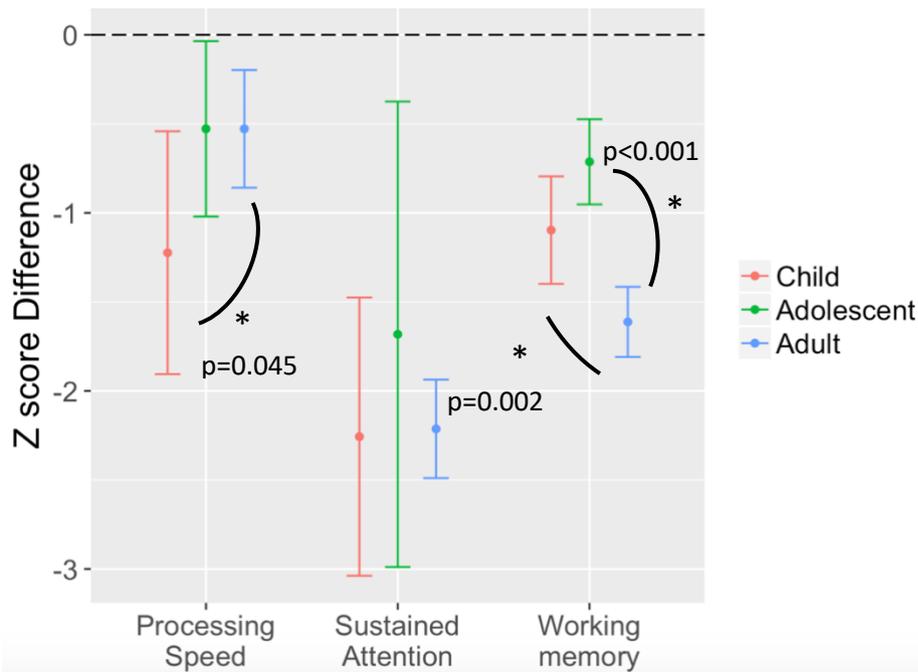


Figure 3-5. Neurocognitive performance across developmental stages in individuals with 22q11.2DS relative to typically developing controls.

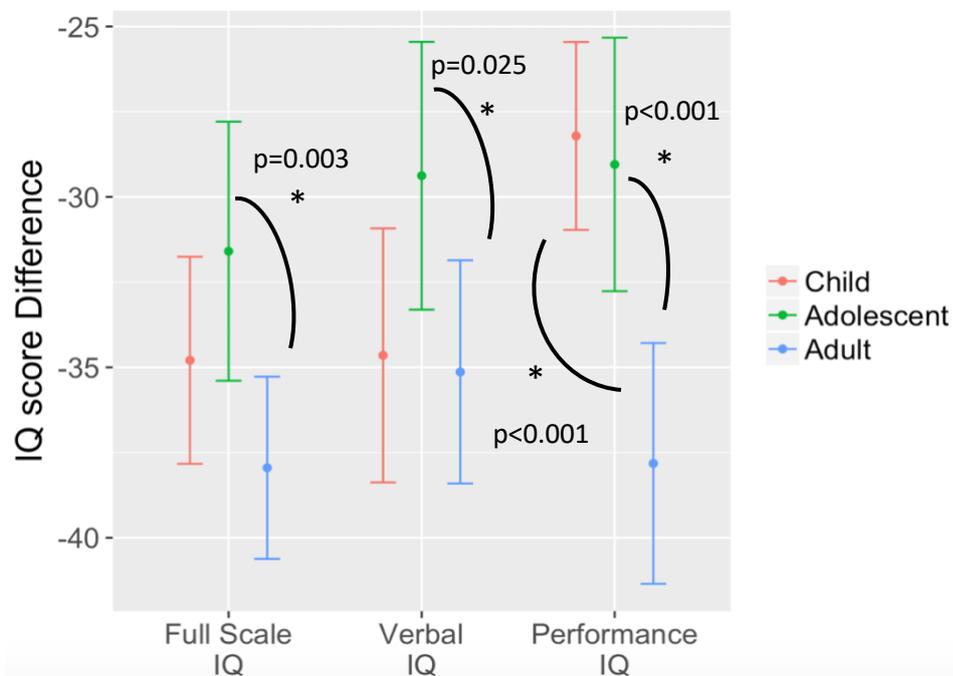


Figure 3-6. IQ performance across developmental stages in individuals with 22q11.2DS relative to typically developing controls.

54 participants were taking medication which could have affected cognitive performance, so analyses were repeated controlling for medication as a covariate. Results were unchanged.

Controlling for gender in analyses did not change any associations. When controlling for site in analyses, results were unchanged except adolescents with 22q11.2DS displayed less impairment on working memory than children when there was previously no difference.

3.7 Discussion

To date, this is the largest study in 22q11.2DS where all participants have completed the same testing battery in the specific cognitive domains of processing speed, sustained attention and working memory, in addition to standard IQ assessments. Furthermore, typically developing individuals (siblings and community controls) were included to account for natural variation in cognition over development. Rates of psychiatric disorders in the current study were comparable to a large previous multi-site study of individuals with 22q11.2DS (Schneider et al., 2014a).

3.7.1 Aim 1: Associations of cognition and psychopathology in the three developmental stages in 22q11.2DS

Presence of psychopathology had developmental and domain specific associations with the cognitive profile, broadly supporting the first hypothesis that psychopathology would be associated with greater cognitive deficits in 22q11.2DS, however, there were also differences between disorders which will be further discussed. The presence of probable ASD, ADHD and psychotic disorder at different developmental stages were all associated with impairments in sustained attention, suggesting a transdiagnostic deficit. It has been previously hypothesised that deficits in attention may be ubiquitous across conventional diagnostic boundaries (Baker and Vorstman, 2012).

3.7.1.1 Associations between cognition and probable ASD

Presence of probable ASD was found to interact with developmental stage such that adolescents with probable ASD experienced greater impairment than children with probable ASD in processing speed, sustained attention and working memory. Previous research in 22q11.2DS did not find a relationship between probable ASD and cognition (Niarchou et al., 2014), but this study considered children and adolescents as one group, whereas in the current study the increased sample size facilitated comparison between the developmental stages of children and adolescents, yielding a more finely-tuned picture of the relationship between ASD and cognition.

These results could imply that cognitive impairment associated with ASD emerges in adolescence and is not present in early childhood. This indicates that there may be a sensitive period for acquiring certain cognitive domains in ASD, whereby individuals with ASD acquire skills well in childhood but this does not continue into adolescence, a theory which is in line with a longitudinal study of young people with idiopathic autism (Sigman and McGovern, 2005). This study found that language and cognitive skills were gained in childhood in individuals with autism, but these gains did not continue into adolescence as expected in typically developing individuals (Sigman and McGovern, 2005).

As a cross-sectional design was employed in the current investigation, it is unclear whether the findings indicate a developmental lag, where the gap between children and adolescents with ASD increases with age compared to those without ASD, or whether adolescents with ASD are performing worse at a later time point than at baseline, which would index cognitive deterioration. Longitudinal research is vital to make this distinction.

It could also be possible that increasing perceived social and academic demands on individuals with ASD during adolescence result in greater difficulty reaching equivalent mental age to controls than in childhood (Sigman and McGovern, 2005). Alternatively, it has been proposed that measuring ASD symptoms in young people with 22q11.2DS may be indexing pre-psychotic traits, especially social deficits that are measured by the SCQ (Eliez, 2007). As the presence of such prodromal symptoms has been associated with poorer cognitive functioning in 22q11.2DS (Antshel et al., 2017, Maeder et al., 2016), an alternative

explanation for the association in this study of probable ASD with cognitive deficits in adolescence could be that those categorised with probable ASD are actually manifesting prodromal psychotic symptoms. However, including the presence of subthreshold psychotic experiences as a covariate did not change results. Furthermore, a longitudinal study did not find an association between autistic features in individuals with 22q11.2DS in childhood and their risk of developing psychotic disorders or symptoms (Fiksinski et al., 2017) which suggests that both psychiatric conditions may be pleiotropic phenotypes of 22q11.2DS.

However, as the presence of probable ASD was determined by the SCQ which is a screening questionnaire and does not provide a formal research diagnosis, caution must be taken in interpreting these findings. This is a questionnaire which was developed to align to the gold-standard Autism Diagnostic Interview-Revised (ADI-R; Lord et al. (1994)) and the two measures correlate highly (Berument et al. (1999); Charman et al. (2007)). However, it is thought that it does not perform as well as the ADI-R when discriminating ASD from intellectual disability (ID; Berument et al. (1999)) so it is possible that the SCQ may be indexing more than ASD only. However, there was no association of IQ with meeting the cut-off for ASD on the SCQ, which suggests the SCQ was not just indexing ID. Furthermore, this criterion has been applied in previous 22q11.2DS research (Niarchou et al., 2014, Vorstman et al., 2013). Above all, the finding that children who meet clinical cut-off for social communicative deficits may have different cognitive trajectories is informative.

The finding that ASD was associated with impairments in all neurocognitive domains is supported by findings of a meta-analysis of cognitive impairments in idiopathic ASD which found that there were consistent deficits across multiple executive functioning domains at a similar effect size (Demetriou et al., 2018). This supports the idea of a global under- or over-connectivity between executive function related brain networks rather than deficits in specific brain regions in ASD (Aoki et al., 2013) and suggests that these findings may be applicable to 22q11.2DS.

3.7.1.2 Associations between cognition and ADHD

Presence of ADHD in childhood or adolescence was associated with a greater deficit on the sustained attention task but no other cognitive measure, which is in agreement with previous findings in 22q11.2DS (de Sonnevile et al., 2018). As processing speed and working memory were not associated with presence of ADHD, this lends support to the hypothesis that there may be a specific neurobiological pathway which leads to attention deficits which affect cognition and behaviour (de Sonnevile et al., 2018).

The results of the current study differ somewhat from studies of children with idiopathic ADHD which have found evidence of impairments in domains such as working memory and inhibitory control as well as attention (Sonuga-Barke et al., 2010). A possible contributing factor towards the difference in findings between the 22q11.2DS and idiopathic populations could be that the clinical presentation of ADHD in 22q11.2DS differs from idiopathic ADHD in that it is predominantly the inattentive subtype (Niarchou et al., 2015); therefore, it could be more likely that individuals with the inattentive subtype (as in 22q11.2DS) struggle more with attention than other cognitive processes, whereas in the idiopathic ADHD population where the picture is more mixed the hyperactivity and impulsivity symptoms may be more associated with other or additional cognitive impairment.

Additionally, research on idiopathic ADHD populations has highlighted that children with ADHD made more errors on a sustained attention task and also showed reduced skin conductance in response to errors made compared to typically developing controls (O'Connell et al., 2004). They suggested that individuals with ADHD may evaluate errors differently than typically developing individuals (O'Connell et al., 2004). Unfortunately in the current study it was not possible to investigate specifically whether the individuals with 22q11.2DS and ADHD made more errors than those without ADHD as the sustained attention measure collected in the current study gave an overall indicator of performance, the likelihood of responding correctly (A'), and it was not possible to break this down into amount or type of errors made.

3.7.1.3 Associations between cognition and anxiety

Presence of anxiety disorder was not associated with cognitive deficits, as previously reported (Niarchou et al., 2014). Other research which found a relationship between anxiety and working memory impairments (Sanders et al., 2017) controlled for ADHD as a covariate in the analysis, which may explain different findings. However, it could be argued that controlling for comorbid psychopathology would not be a realistic representation of 22q11.2DS, as the phenotype is naturally variable and complex.

3.7.1.4 Associations between cognition and psychotic disorder

Adults with 22q11.2DS and psychotic disorder appeared to show greater deficits in attention as has been previously reported (van Amelsvoort et al., 2004). Furthermore, the fact that the same magnitude of impairment in attention was present in the sample from a young age and was associated with psychosis supports the hypothesis that attention deficits are a core feature of psychotic disorders, both in the high-risk and clinical stages (Niarchou et al., 2018). There were greater deficits in IQ compared to those with no psychotic disorder, which is in line with previous research suggesting that a decline in IQ precedes the emergence of psychotic disorder (Gothelf et al., 2013, Vorstman et al., 2015). However, as this study is cross-sectional it cannot be determined if the cognitive impairments precede or result from the onset of psychosis.

We did not find deficits in working memory or processing speed which have been previously reported in individuals with 22q11.2DS and psychotic disorder (van Amelsvoort et al., 2004). It could be that in our sample these deficits were general features of 22q11.2DS and not associated with psychosis (Chow et al., 2006). Furthermore, in previous studies attention and working memory have been combined into a broader “executive function” domain which was reported as the most striking impairment in individuals with 22q11.2DS and psychosis (Weinberger et al., 2016); however, as we have shown, there may be differences even within this broad executive function domain, with deficits in attention possibly driving the association with psychotic disorder.

3.7.2 Aim 2: Comparing cognitive performance across developmental stages in 22q11.2DS

Cognitive impairments were present across childhood, adolescence and adulthood in 22q11.2DS compared to typically developing controls, but magnitude of impairment differed by developmental stage and the pattern differed by domain. I hypothesised that adults would display greater deficits than younger individuals, which was the case for working memory and IQ but was not observed in the processing speed and sustained attention domains. Children with 22q11.2DS displayed a greater deficit in processing speed compared to adults. This supports previous longitudinal research showing that there is developmental maturation in the processing speed domain through adolescence (Chawner et al., 2017), which this research suggests is maintained in adulthood. The deficit in sustained attention was present at the same magnitude across all developmental stages, suggesting that this is pervasive over time in 22q11.2DS (Niarchou et al., 2018).

Adults displayed the greatest deficits in working memory which supports previous research which proposed that adults with 22q11.2DS reach a “developmental plateau” in working memory ability before controls, and so may not experience ongoing age-appropriate increases in this domain (Maeder et al., 2016). That study however did not extend beyond the age of 26, whereas our wide age range up to 60 years old provides insights into the relative strengths and weaknesses in adults with 22q11.2DS more generally, suggesting that some domains such as processing speed may “catch-up”, and others such as working memory may be targets for remediation (Mariano et al., 2015). Executive performance has been found to be associated with adaptive functioning in adults with 22q11.2DS with or without schizophrenia, lending support to the idea that remediation in executive performance may also benefit functional outcome (Fiksinski et al., 2018).

There were greater IQ impairments in adults with 22q11.2DS compared to younger individuals, as has been previously reported (Green et al., 2009) which may be related to presence of psychotic disorder (see above in discussion). There were no differences between children and adolescents with 22q11.2DS on IQ measures which contradicts previous work that IQ deficits are larger in adolescents with 22q11.2DS than children

(Gothelf et al., 2013). The reason for this discrepancy with previous findings may be a result of including a control group, as previous longitudinal work found that when taking into account control performance, there was no strong evidence for a 'cognitive decline' over childhood specific to 22q11.2DS (Chawner et al., 2017).

3.7.3 Limitations

The study was multi-site which facilitated a large sample size; furthermore, combining data from different sites may reduce bias from individual sites (Smelror et al., 2018). However, as the majority of the child and adolescent participants were recruited from Cardiff University, and the majority of adults from the other sites, it could be hypothesised that differences between adults and the child and adolescent group may be attributable to site specific characteristics which influenced cognitive performance. However, adding site as a covariate to the analyses did generally not alter results significantly. Furthermore, it is a strength that we have included adults, as there is far less research on older individuals than paediatric 22q11.2DS samples (Moberg et al., 2018).

Longitudinal studies have found that rates of psychopathology such as ADHD and psychotic symptoms in 22q11.2DS have variable trajectories and may remit or persist over time (Kates et al., 2018, Tang et al., 2017a). The cross-sectional design of the current study was unable to capture this variation in the same individuals over time and therefore associations reported between cognition and psychopathology may differ if measured longitudinally.

Furthermore, comorbidity of psychopathology in 22q11.2DS may affect associations between psychopathology and cognition. Comorbidity is a common feature of 22q11.2DS (Kates et al., 2018, Yi et al., 2015). It could be argued that for the analysis of a specific trait, possible overlap at the item level with another trait should be taken into account. This would however, complicate the interpretation of findings at the trait level and also mean that the real-life complex clinical presentation of these young people would no longer be adequately captured.

Children with 22q11.2DS were younger on average than child controls, however as the standardised cognitive scores took age into account we would not expect this to impact interpretation of results. Furthermore, although there were significantly more females in adult individuals with 22q11.2DS than controls running all analyses with gender as a covariate did not change results. As some participants were unable to complete the assessments, it's possible that our findings may not represent those individuals with the greatest cognitive deficits (Chawner et al., 2019b).

In the current study psychopathology was defined categorically (i.e. as presence or absence of ADHD) rather than dimensionally (i.e. symptom count). This may reduce sensitivity of findings, e.g. individuals that may be subthreshold for ADHD but still have high levels of symptoms would be categorised as ADHD absent but may have a different cognitive profile to those with no symptoms at all. This should be considered when interpreting these findings. Despite this, both categorical and dimensional approaches can help us understand the complex interaction between mental health and cognition.

Previous research has found that IQ contributes to performance on specific cognitive abilities (Mohn et al., 2014); therefore, it could be the case that variation in IQ accounts for the association e.g. between sustained attention impairment and presence of psychotic disorders. However, I was cautious of removing the effects of IQ from analyses, as lower IQ is inherently linked to 22q11.2DS and so removing this variation may not be representative of individuals with 22q11.2DS (Dennis et al., 2009). Furthermore, a previous study including a subset of 22q11.2DS individuals from the current study did not find strong correlations between IQ and specific cognitive functions such as attention, working memory and processing speed (Niarchou et al., 2014), suggesting that specific cognitive impairments may have distinct associations with psychopathology despite the contribution of IQ. However, it is possible that if controlling for IQ results presented in this chapter may have differed.

Different versions of cognitive tests were used in older and younger individuals, such as IQ tests, which is a general issue in the field (Gothelf et al., 2013). Therefore, it was important for us to include comparison groups, to control for version differences. However, the recruitment of adult sibling controls is fraught with difficulty and therefore our adult control

sample consisted of individuals from the community. This may introduce bias as our comparisons for child and adolescence groups consisted of family controls. A meta-analysis reported that comparing the cognitive performance of individuals with 22q11.2DS to community controls produced smaller effect sizes than comparing against control siblings (Moberg et al., 2018). However, this did not appear to be the case in the current study, with effect sizes of a similar magnitude across developmental stages.

This study made the most of the fact that several studies had used the same measures. In future studies, best practice would be for prospective assessment with the same control recruitment strategy at several sites. Despite this, in rare syndromes such as 22q11.2DS, it is best practice to collaborate and data from different sites has been pooled in many previous studies (Vorstman et al., 2015, D'Angelo et al., 2016).

3.7.4 Conclusions

The findings of the current study support the view that it is essential to consider developmental period (childhood, adolescence, adulthood) when investigating cognitive domains in individuals with 22q11.2DS as observations generated when examining one developmental stage may not apply to others. Furthermore, research linking cognition and psychopathology in 22q11.2DS, and indeed other genetic syndromes, should account for developmental stages in their samples, as grouping children and adolescents together in analyses could mask potential associations. This study also shows that it is important to investigate cognitive ability beyond IQ as presence of ASD and ADHD was not associated with IQ, but was with specific neurocognitive functions, where the underlying mechanisms are more easily interpretable than the general measure of IQ.

The finding that attention deficits are prevalent across ASD, ADHD and psychotic disorders supports the theory that going beyond diagnoses and recognising symptom domains such as “attention-executive deficits” may be a beneficial alternative in understanding the complex 22q11.2DS phenotype (Baker and Vorstman, 2012).

An especially important aim for future research is the inclusion of more adults and older individuals with 22q11.2DS where there has been less research than on paediatric populations. It is also important to include comparison or control groups, which could take the form of sibling, IQ-matched peers or typically developing peers, as this aids interpretation of cognitive findings.

There is a need for increased awareness of clinicians of critical periods or windows more amenable to intervention which have been highlighted in this study, such as in children with probable ASD, before greater impairment is present in adolescence. Encouragingly, cognitive remediation has been found to be feasible and effective in adolescents with 22q11.2DS (Mariano et al., 2015), and may be especially successful at these periods.

3.7.5 Future work

Future studies of individuals with 22q11.2DS should include dimensional measures of psychopathology that capture symptoms that cut across traditional diagnostic categories taking into account symptom levels to enable a more sensitive understanding of the relationship between cognition and psychopathology.

A deeper analysis of the cognitive datasets collected in this study could enable greater understanding of the specific difficulties that individuals with 22q11.2DS experience, for example within the sustained attention task clarifying between the amount of stimuli missed as opposed to incorrectly responded to would provide greater insights into the mechanisms underlying impairment on that task.

More comparison groups would enable the specificity of results to 22q11.2DS, for example inclusion of children with idiopathic ADHD and ASD would help delineate the cognitive deficits which are generally associated with ADHD/ASD and those which may be specific to 22q11.2DS + ADHD/ASD. Additionally, looking further within individuals with 22q11.2DS and cognition in those with differing levels of hyperactive or inattentive ADHD symptoms, or repetitive or social communication ASD symptoms would provide insights into how symptoms are associated with cognition.

4 Longitudinal developmental cognitive trajectories in 22q11.2 Deletion Syndrome compared to controls

4.1 Chapter overview

22q11.2 Deletion Syndrome (22q11.2DS) is one of the strongest known genetic risk factors for schizophrenia and is a valuable model for understanding trajectories of cognitive development which may be associated with vulnerability for later psychosis development. Previous studies have suggested evidence for a cognitive decline in IQ across childhood and adolescence in 22q11.2DS, but it is unclear if this represents a deterioration in previously acquired ability or may be accounted for by a deficit present early in development or a lag that widens over time. This chapter will examine the developmental trajectories of a range of cognitive domains over three timepoints in children and adolescents with 22q11.2DS as compared to a control group of siblings without the deletion.

4.2 Introduction

In Chapter 3 I showed that cognitive impairments were present across childhood, adolescence and adulthood in 22q11.2DS compared to typically developing controls, but magnitude of impairment differed by developmental stage and the pattern differed by domain. IQ and working memory were more impaired in adults with 22q11.2DS compared to children and adolescents, and processing speed was improved in adults compared to children with 22q11.2DS. Due to the cross-sectional nature of this research, it was unclear what the underlying mechanisms could be behind increased impairment in older individuals. Longitudinal research is essential in delineating the course of cognitive development.

4.2.1 Longitudinal studies in 22q11.2DS

4.2.1.1 Cognitive decline

Longitudinal studies of cognition in individuals with 22q11.2DS are relatively rare and have suffered some methodological issues. A study of 69 children from age 5.5-9.5 years reported a decline in IQ over three timepoints of assessment (Duijff et al., 2012). Similarly, in a large collaborative study of 829 individuals with 22q11.2DS from 8-24 years old, it appeared that on average across the group there was a lower IQ at subsequent timepoints than at the initial timepoint (Vorstman et al., 2015). However, as measures such as IQ are standardised to age, a decrease over time does not necessarily represent a deterioration in ability; in fact, it could be indexing a lag whereby individuals raw scores increase but not at the rate expected by the standardisation process (Reichenberg et al., 2010).

Therefore, despite an apparent decline in cognition, there may be multiple underlying processes at work. The only way to distinguish which of these processes may be at play is to examine the unstandardized (raw) scores that contribute to the overall IQ score; however, many previous longitudinal studies of 22q11.2DS have used different versions of IQ tests at different timepoints and have therefore been unable to do this (Vorstman et al., 2015, Duijff et al., 2012). Studies that have used the same tests at multiple timepoints can examine raw scores and therefore distinguish between models of cognitive development (Chawner et al., 2017, Maeder et al., 2016); these will be discussed in more detail after outlining such models.

4.2.1.2 Models of cognitive development

Various models have been proposed to define how cognition in an affected group, such as individuals with 22q11.2DS, develops in comparison to a control group, such as typically developing individuals. Figure 4-1 presents a schematic diagram of such models. It could be that there is a cognitive deficit that emerges early and remains stable over the lifespan, a lag where the gap in scores widens over time, a deterioration where previous ability is lost, or a maturation where scores “catch up” to a typically developing control population (Chawner et al., 2017, Reichenberg et al., 2010).

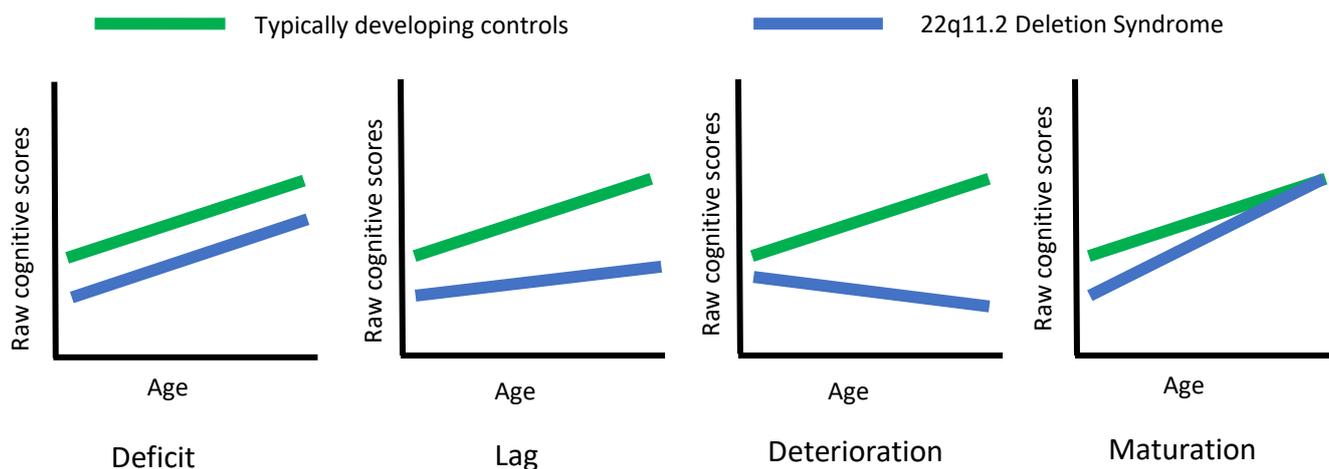


Figure 4-1. Different models of cognitive development. We would expect individuals with 22q11.2DS to display a deficit compared to typically developing controls from a young age, and subsequently follow one of the above trajectories.

4.2.1.3 Going beyond IQ

Much research on cognition in 22q11.2DS has focussed on IQ (Duijff et al., 2012, Vorstman et al., 2015), but it is important to consider the trajectory of other neurocognitive functions that have been identified as core impairments in schizophrenia such as processing speed, sustained attention and working memory (Reichenberg et al., 2010) as 22q11.2DS is such a high risk group for schizophrenia development (Gur et al., 2017). It has been argued that examining impairments in specific cognitive domains such as these may provide insights into neurobiological processes (Gur et al., 2014) and that these functions may be more amenable to remediation than IQ as they can be specifically targeted (Antshel et al., 2017).

4.2.1.4 The Experiences of Children with cOpy Number Variants (ECHO) Study

The ECHO study has consistently assessed participants, both individuals with 22q11.2DS and their typically developing siblings, with the same measures in order to capture true cognitive change. The first wave of data collection found impairments in a range of cognitive measures in 22q11.2DS compared to controls at 10 years old and demonstrated that these were distinct deficits in different domains (Niarchou et al., 2014).

After another wave of data collection at around 12.5 years old (Chawner et al., 2017) longitudinal analysis was able to distinguish between models of cognitive development, and found that the impairments in most cognitive domains assessed (e.g., verbal IQ, sustained attention and working memory) were present from early in development in 22q11.2DS and subsequently remained stable (i.e., developmental deficit, see Figure 4-1). The domain of processing speed, however, showed developmental maturation, with children with 22q11.2DS initially showing a deficit but performing at the same level as controls at older ages (Chawner et al., 2017). The current research aims to extend knowledge of cognitive development into adolescents of around 15 years old, where not much is yet known, and which represents a period of increased risk for psychotic disorders (Tang and Gur, 2018).

4.2.1.5 Other longitudinal studies of cognitive development in 22q11.2DS

Similarly to (Chawner et al., 2017), when comparing cognitive performance in individuals with 22q11.2DS to typically developing controls, Hooper et al. (2013) found that most domains (IQ, working memory and processing speed) were relatively stable over two timepoints in 10-14 year olds with 22q11.2DS compared to typically developing controls, except sustained attention where individuals with 22q11.2DS did not appear to show appropriate age-related progression. This would suggest developmental deficits in most domains with a developmental lag in attention, but as this study measured standardised scores over time and not raw scores, it is difficult to conclude which developmental model would fit best. However, it refutes the idea of a decline or deterioration in cognitive functioning in 22q11.2DS.

Most previous studies have also spanned a narrow age range (Duijff et al., 2012, Hooper et al., 2013), which has restricted the range of interpretation of trajectories, especially in older individuals with 22q11.2DS. One study with four timepoints focussed on development of executive function in 22q11.2DS found that working memory trajectory differed from controls whereas other domains such as inhibition and vocabulary followed the same developmental course as controls (Maeder et al., 2016). Raw scores were used, and it was therefore proposed that individuals with 22q11.2DS may reach a “developmental plateau”

in working memory ability before controls, but this was only observable due to the inclusion of older adolescents, with a wide age range from 6-26 years (Maeder et al., 2016).

Another study with four timepoints and an age range from around 9-22 years found that trajectories of IQ in 22q11.2DS were marginally different from siblings ($p=0.05$) and community controls ($p=0.04$), suggesting developmental lags, but again as different test versions had been used at different points raw scores were not compared, therefore limiting conclusions (Antshel et al., 2017). The trajectories of working memory and sustained attention were also different in 22q11.2DS to both control groups, also implying developmental lags in these areas (Antshel et al., 2017).

4.2.1.6 Cognitive deterioration

Although in general previous research has not found evidence for cognitive deterioration when averaging over the whole sample of 22q11.2DS, it is important to determine whether specific individuals experience cognitive deterioration, constituting a subset of the entire sample (Duijff et al., 2012). It is possible to examine this by comparing raw scores over time, as it is expected that as the child ages they will score higher on the test; therefore, scoring lower on retest indicates a deterioration (Duijff et al., 2012). Although Duijff et al. (2012) used different IQ tests at different ages, a smaller group of 29 children had completed the same IQ test at two timepoints, and they found that around a third of those children scored lower on retest than the first test.

However, they had not compared against a control group, which is important as, even in typically developing children, considerable variability in cognitive function over time has been documented (Foulkes and Blakemore, 2018, Ramsden et al., 2011). (Chawner et al., 2017) found that an equivalent subset of typically developing control participants exhibited cognitive deterioration suggesting that this fluctuation in 22q11.2DS is within the normal range and should not be interpreted as abnormal. Furthermore, Van Den Heuvel et al. (2018) found that a comparable proportion of individuals with 22q11.2DS and Idiopathic Intellectual Disability (IID) experienced a decline in cognitive functioning over two

timepoints, age range 6-15 years, suggesting again that this is not a phenomenon specific to 22q11.2DS.

Previous research has also not established how reliable the cognitive deterioration was (Duijff et al., 2012), which is important as small fluctuations in test scores can be related to common issues in cognitive testing, such as measurement error and regression to the mean (Lineweaver and Chelune, 2003). There is a degree of measurement error such that on taking a test multiple times the score will be likely to change from one assessment to another, even if there is no true change (Lineweaver and Chelune, 2003). Regression to the mean may also be at play, which is the statistical likelihood that an individual's test score will be closer to the population mean upon retest (Lineweaver and Chelune, 2003). A boundary of reliable change was developed that takes into account test-retest reliability and standard error of measurement: Reliable Change Indices (RCI; Lineweaver and Chelune (2003)). (Chawner et al., 2017) in the ECHO study again found no evidence for a greater proportion of individuals with 22q11.2DS experiencing deterioration than controls when employing RCI.

It is therefore important to examine cognitive change in 22q11.2DS with raw scores so that developmental trajectories can be delineated, and in reference to a control group ensuring that change is reliable. Furthermore, it is essential to build up our knowledge of cognitive development in a broader age range with multiple timepoints, providing rich data.

4.2.2 Aims

4.2.2.1 Aim 1: developmental trajectories of cognition in 22q11.2DS compared to controls

The first aim was to examine the developmental trajectories of a range of cognitive domains over three timepoints in individuals with 22q11.2DS as compared to a control group of siblings without the deletion. The same test versions have been completed at all timepoints and therefore raw scores could be examined to determine the trajectories of developmental

deficit, lag, deterioration or maturation. Based on previous research (Chawner et al., 2017, Hooper et al., 2013) I hypothesised that most cognitive domains would exhibit a developmental deficit in individuals with 22q11.2DS compared to controls, whereby an impairment is present from early in life and persists at a consistent rate throughout.

4.2.2.2 Aim 2: cognitive deterioration in 22q11.2DS compared to controls

The second aim was to investigate whether there was evidence for a substantial proportion of individuals with 22q11.2DS experiencing cognitive deterioration, in comparison to controls. I hypothesised that although there may be a group of individuals with 22q11.2DS in which scores are decreased from a previous timepoint, there is likely to be a similar sized group of controls meeting criteria for cognitive deterioration as this fluctuation would be expected even in the general population, as in (Chawner et al., 2017).

4.3 Methods

4.3.1 Participants

Detailed recruitment procedure, demographic information, and representativeness of the sample are discussed in Chapter 2. Briefly, the study was structured as an accelerated longitudinal study, where participants were different ages when enrolling into the study and then followed up around every 2.5 years (age at first timepoint ranged from 6-20 years in individuals with 22q11.2DS and 6-18 years in controls). Despite the wide age range, average age was comparable between 22q11.2DS and controls at different timepoints (Figure 4-2).

Some participants were recruited at different points in the study (for example, siblings that were under 6 years old and therefore too young to take part on the first visit may have taken part at the second and third visits; see Chapter 2); Figure 4-2 details the participants with cognitive data at one, two and three timepoints.

	22q11.2DS	Controls
One timepoint	N=141 Mean age 10.31 years old (sd=2.73) 65 (46%) females	N=92 Mean age 10.68 years old (sd=2.68) 46 (50%) females
Two timepoints	N=89 Mean age 12.83 years old (sd=2.44) 38 (43%) females	N=41 Mean age 13.11 years old (sd=2.25) 21 (51%) females
Three timepoints	N=55 Mean age 15.57 years old (sd=2.37) 23 (42%) females	N=21 Mean age 15.99 years old (sd=2.16) 10 (48%) females

Figure 4-2. Number, age and sex of individuals with data at one, two and three timepoints.

There was no difference between 22q11.2DS and controls on age as assessed by t-test at one timepoint (T1; $t=-1.00$, $p=0.318$), second timepoint (T2; $t=0.62$, $p=0.536$) or third timepoint (T3; $t=0.74$, $p=0.465$). Likewise, there was no difference between 22q11.2DS and controls in sex distribution as assessed by chi-square at T1 ($X^2=0.20$, $p=0.654$), T2 ($X^2=0.51$, $p=0.473$) or T3 ($X^2=0.04$, $p=0.844$).

4.3.2 Cognitive assessments

Participants undertook a range of cognitive assessments that are described in detail in Chapter 2; they will be outlined briefly here. First, IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler (2011) yielding a Full scale IQ (FSIQ), Verbal IQ (VIQ) and Performance IQ (PIQ) score. These are age-standardised scores based on normative data. Raw scores were available from the subtests of VIQ and PIQ. VIQ subtest Vocabulary was assessed by number of words correctly defined. VIQ subtest Similarities was assessed by number of correctly identified similarities between two words. PIQ subtest Block Design was assessed through number of block formations correctly replicated. PIQ subtest Matrix Reasoning was assessed through number of correctly identified missing

patterns in a matrix design. The Wisconsin Card Sorting Test (WCST) was administered, obtaining raw and standardised measures of set-shifting ability as assessed by number of perseverative errors.

A battery of neurocognitive tasks was administered using CANTAB software (Cognition, 2006). Processing speed was measured through speed on the Five Choice Reaction Time (RTI) task, where the participant must respond as fast as possible to a stimulus in one of five locations. Sustained attention was measured through the probability of correct responses on the Rapid Visual Information Processing (RVP) task, where participants must respond to a target sequence of digits over a few minutes of a continuous pseudo-random presentation of digits. Planning (SOC) was assessed through number of problems solved using the minimum amount of moves on the Stockings of Cambridge task, a tower-building problem. Spatial working memory was assessed as the number of errors on the Spatial Working Memory (SWM) task, where participants must remember where previous targets were in space. Visual search (MTS) was measured through number of patterns successfully matched on a match-to-sample task. Raw and age-standardised z-scores based on normative data were available, except for visual search (MTS) where only raw scores were available.

Not all participants completed all cognitive tasks, due to cognitive or behavioural issues or time constraints; sample size for each task at each timepoint are presented in Table 4-1.

4.3.3 Statistical analyses

Analysis in general was based upon the relationship between age and cognitive performance. This is more sensitive than a timepoint-based approach where performance would be grouped by timepoint and timepoints compared to each other, meaning much information would be lost. Furthermore, although the age of participation is similar in 22q11.2DS and controls for participation at first, second and third timepoint (see 4.3.1 Participants section) there was a range of ages at these points (from 6-20 years in individuals with 22q11.2DS and 6-18 years in controls) so it is more appropriate to analyse by age.

For the purposes of demonstrating the difference in cognitive functioning between 22q11.2DS and controls however, mean scores for individuals at their first, second and third timepoints are displayed in Table 4-1. Because participants may have been different ages at different timepoints, these scores are age standardised. IQ and WCST are standardised to a mean of 100 and standard deviation of 15; CANTAB results are standardised as z scores, with a mean of 0 and standard deviation of 1. Standardised scores were not available for the CANTAB visual search task (MTS) so this measure was not included in this comparison. Standardised scores at each timepoint were compared between individuals with 22q11.2DS and sibling controls with linear mixed models with deletion status as the fixed effect and family relatedness as a random effect.

4.3.3.1 Aim 1: developmental trajectories of cognition in 22q11.2DS compared to controls

To examine the relationship of age with performance on cognitive tasks in individuals with 22q11.2DS compared to controls over three timepoints, I first examined visually whether raw scores in the various cognitive domains increased over time (see Figures 3-5). If raw scores decreased over time in individuals with 22q11.2DS and increased in controls, this would indicate a developmental deterioration in 22q11.2DS.

To determine which developmental models best fitted the data (see Figure 4-1), linear mixed model analysis was undertaken with the R package *nlme*. This can incorporate individuals with data from varying numbers of timepoints rather than listwise deletion of those with incomplete data (Pineiro et al., 2013). The outcome variable was performance on each cognitive task, run as separate models. The fixed effects in the model were age and deletion status and the interaction between age and deletion status. The random effects were family relatedness and the within-subject repeated measures effect.

If raw scores were increased across time points, a significant interaction between age and deletion status would indicate that the course of cognitive development is different in individuals with 22q11.2DS and controls. A significant negative interaction indicated a developmental lag (divergence in trajectories between 22q11.2DS and controls); a

significant positive interaction indicated a developmental maturation (convergence in trajectories between 22q11.2DS and controls). A non-significant interaction indicated a developmental deficit, whereby there was an initial difference between 22q11.2DS and controls at the earliest measurement, the magnitude of which did not change as participants aged.

Some previous research (Duijff et al., 2012, Antshel et al., 2005) has reported relationships between sex and cognitive performance in 22q11.2DS so sex and the interaction between sex and deletion status was also added into the model as part of a sensitivity analysis.

To enable comparison between the current study of three timepoints and the results of two timepoints (Chawner et al., 2017), a table comparing models fitted between studies is presented (Table 4-3). There are some statistical differences in that (Chawner et al., 2017) solely included individuals with data for both timepoints in their analysis, whereas in the current analysis individuals with any number of timepoints were included to maximise the sample.

4.3.3.2 Aim 2: cognitive deterioration in 22q11.2DS compared to controls

To examine whether there was a substantial subset of individuals experiencing cognitive deterioration compared to controls, a cognitive change score was obtained by subtracting the Time 1 (T1) score from the Time 3 (T3) score. This analysis was limited to participants who took part in both these assessments. For most measures, where a higher score indicates better performance, a difference of 0 would indicate no change, a negative difference a deterioration, and a positive difference an improvement. The exceptions were processing speed (RTI), working memory (SWM) and set-shifting (WCST) measures where lower scores indicate better performance, which was adjusted for by considering a negative difference an improvement and a positive difference a deterioration.

Individuals were coded as experiencing deterioration versus no change/improvement. Fisher's exact test of independence was used to determine whether there was a higher proportion of individuals with 22q11.2DS experiencing cognitive deterioration than controls.

To account for issues that can affect cognitive change scores such as measurement error and regression to the mean (see section 4.2.1.6) Reliable Change Indices (RCI) were generated for each cognitive domain, calculated from the following formula (Lineweaver and Chelune, 2003, Chawner et al., 2017):

$$RCI = \pm 1.96 SE_p$$

Where

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

And

SE_p = standard error of prediction

SD₂ = standard deviation of observed retest

r²₁₂ = test – retest reliability coefficient

Test-retest reliability coefficients and standard deviations can be obtained from the relevant manuals/literature for each measure (WASI; Wechsler (1999), CANTAB; Harrison (2006) and WCST; Heaton (1993)).

Cognitive change scores were then compared against the relevant RCI and if an individual's raw decrease exceeded this boundary they were coded as experiencing deterioration, if not they were coded as no change/improvement. Fisher's exact test of independence was used to determine whether there was a higher proportion of individuals with 22q11.2DS experiencing cognitive deterioration exceeding RCI than controls.

4.3.4 Statistical correction

The Benjamini-Hochberg method for controlling False Discovery Rate (FDR) was used to correct for multiple comparisons (Benjamini and Hochberg, 1995). This method ranks p-values in a cluster of tests, then divides the rank by the number of tests in the cluster, then

multiplying by an acceptable FDR (in this case, 10%, following Crawford et al. (2018)) to produce a Benjamini-Hochberg critical value. The highest p-value that is below the Benjamini-Hochberg critical value survives FDR correction, as with all p-values below that one.

4.4 Results

Time 1 (T1)	22q11.2DS		Control		Difference	t (df)	p	Effect size; Cohen's d
	n	mean (sd)	n	mean (sd)				
IQ								
Full Scale IQ	137	75.76 (11.87)	90	108.29 (14.20)	-32.53	20.17 (86)	<0.001	4.35
Verbal IQ	137	76.96 (13.21)	90	107.29 (14.46)	-30.33	17.28 (86)	<0.001	3.73
Performance IQ	140	78.39 (11.49)	90	107.62 (15.49)	-29.24	18.13 (88)	<0.001	3.87
Set-shifting	130	87.16 (21.17)	81	115.43 (23.84)	-28.27	9.27 (74)	<0.001	2.16
Processing speed	123	-0.44 (2.1)	81	0.29 (1.21)	-0.73	3.06 (73)	0.003	0.72
Sustained attention	109	-2.12 (2.20)	77	-0.41 (1.53)	-1.7	6.45 (63)	<0.001	1.62
Planning	115	-1.16 (1.04)	80	-0.41 (1.02)	-0.7	4.65 (64)	<0.001	1.16
Working memory	135	-1.12 (0.96)	84	-0.18 (0.99)	-0.94	7.27 (82)	<0.001	1.61
Time 2 (T2)								
Time 2 (T2)	22q11.2DS		Control		Difference	t (df)	p	Effect size; Cohen's d
	n	mean (sd)	n	mean (sd)				
IQ								
Full Scale IQ	87	71.70 (12.62)	40	107.83 (12.95)	-36.12	17.28 (40)	<0.001	5.47
Verbal IQ	87	73.05 (12.74)	40	104.35 (12.48)	-31.3	14.78 (40)	<0.001	4.67

Performance IQ	86	74.90 (13.40)	40	109.88 (14.39)	-34.98	15.16 (40)	<0.001	4.79
Set-shifting	79	94.52 (21.01)	39	127.49 (19.54)	-32.97	8.20 (38)	<0.001	2.66
Processing speed	78	-0.27 (1.89)	39	0.59 (0.70)	-0.86	2.76 (37)	0.009	0.91
Sustained attention	72	-2.09 (2.99)	39	0.24 (0.98)	-2.33	5.18 (34)	<0.001	1.78
Planning	73	-1.17 (1.06)	39	0.00 (1.00)	-1.18	6.19 (34)	<0.001	2.12
Working memory	83	-1.31 (1.15)	39	0.08 (0.93)	-1.39	6.64 (38)	<0.001	2.15
Time 3 (T3)								
	22q11.2DS		Control		Difference	t (df)	p	Effect size; Cohen's d
	n	mean (sd)	n	mean (sd)				
IQ								
Full Scale IQ	55	70.16 (12.69)	20	106.95 (15.93)	-36.79	12.29 (19)	<0.001	5.64
Verbal IQ	55	72.45 (14.40)	20	104.75 (17.05)	-32.30	9.27 (19)	<0.001	4.25
Performance IQ	55	72.27 (13.39)	20	107.00 (15.10)	-34.73	11.02 (19)	<0.001	5.05
Set-shifting	52	92.00 (20.31)	19	115.21 (18.76)	-23.21	4.75 (18)	<0.001	2.24
Processing speed	47	-0.18 (1.59)	18	0.59 (0.73)	-0.77	1.95 (15)	0.070	1.01
Sustained attention	47	-0.40 (1.17)	19	0.46 (1.20)	-0.86	3.08 (16)	0.007	1.54
Planning	45	-1.51 (1.06)	19	-0.74 (1.44)	-0.77	2.52 (15)	0.024	1.30
Working memory	49	-1.70 (0.96)	19	-0.14 (1.09)	-1.56	8.41 (16)	<0.001	4.20

Table 4-1. Mean cognitive performance z-scores in 22q11.2DS (22q11.2 Deletion Syndrome) and controls.

Individuals with 22q11.2DS displayed deficits on all cognitive measures compared to controls at each timepoint except in processing speed at T3 ($p=0.070$). Although this difference was not significant, the effect size at T3 (Cohen's $d=1.01$) was higher than at T2 (Cohen's $d=0.91$) and T1 (Cohen's $d=0.72$), suggesting that the smaller sample size at T3 reduced the power of the model to detect the difference between 22q11.2DS and controls. The deficit in IQ and set shifting (perseverative errors) between individuals with 22q11.2DS and controls was around 30 points (2 standard deviations (sd)). The deficit in neurocognitive battery tasks ranged from 0.73sd (processing speed at T1) to 2.33sd (sustained attention at T2).

4.4.1 Aim 1: developmental trajectories of cognition in 22q11.2DS compared to controls

On age standardised measures of IQ, scores appeared to decrease over time, but when examining the subtests contributing to IQ raw scores increased over time in individuals with 22q11.2DS and controls. In all other cognitive domains, raw scores also increased over time, ruling out a group-level developmental deterioration.

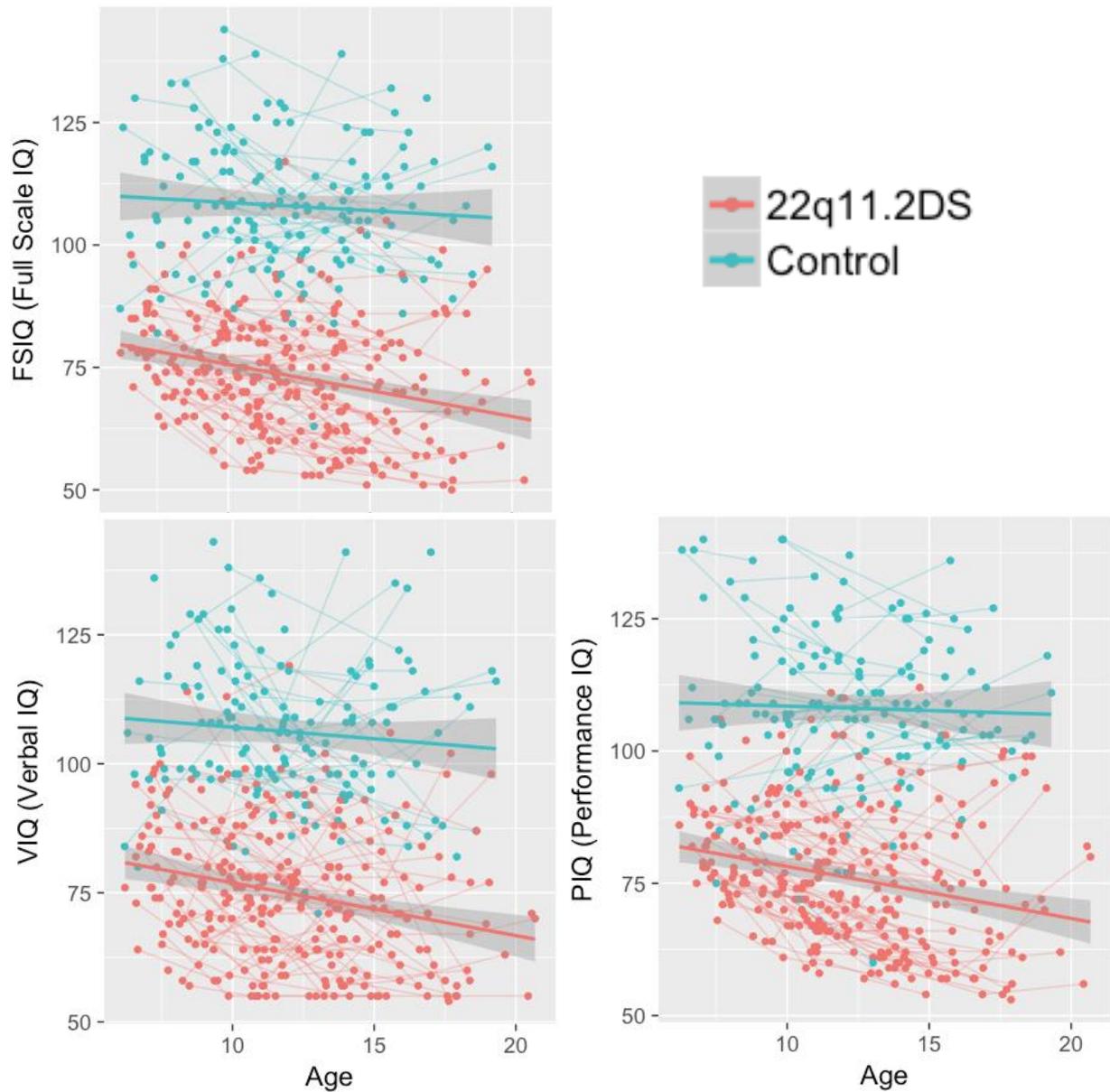


Figure 4-3. Age-standardised FSIQ (Full Scale IQ), VIQ (Verbal IQ) and PIQ (Performance IQ) scores in individuals with 22q11.2DS (22q11.2 Deletion Syndrome; red) compared to control siblings (blue). All graphs have been constructed so that higher values on the y-axis indicate better performance. The fitted linear model is shown with standard error. Repeated measures are joined.

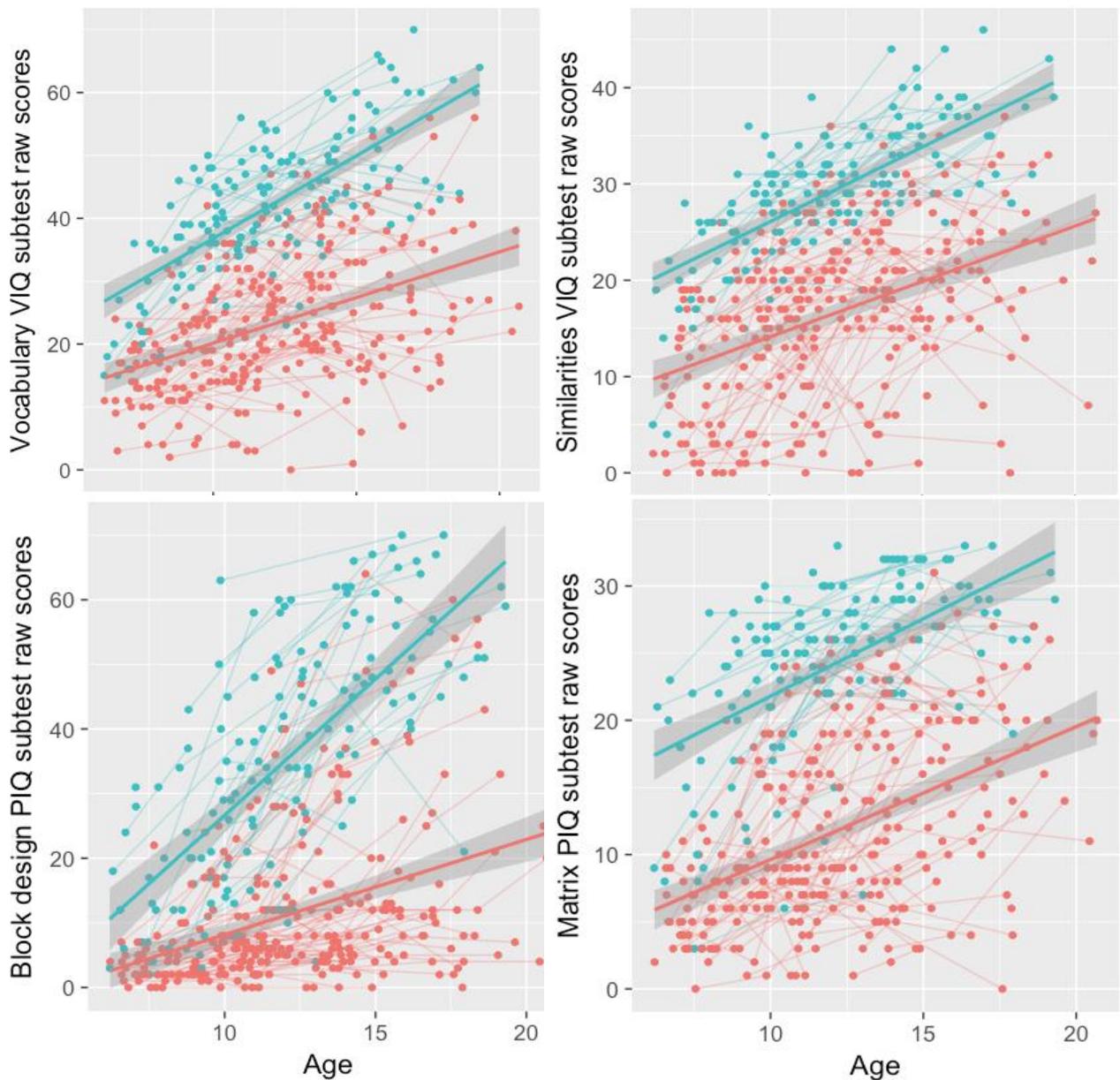


Figure 4-4. Raw scores on IQ subtests Vocabulary (VIQ), Similarities (VIQ), Block Design (PIQ) and Matrix reasoning (PIQ) in individuals with 22q11.2DS (22q11.2 Deletion Syndrome; red) compared to control siblings (blue). All graphs have been constructed so that higher values on the y-axis indicate better performance. The fitted linear model is shown with standard error. Repeated measures are joined.

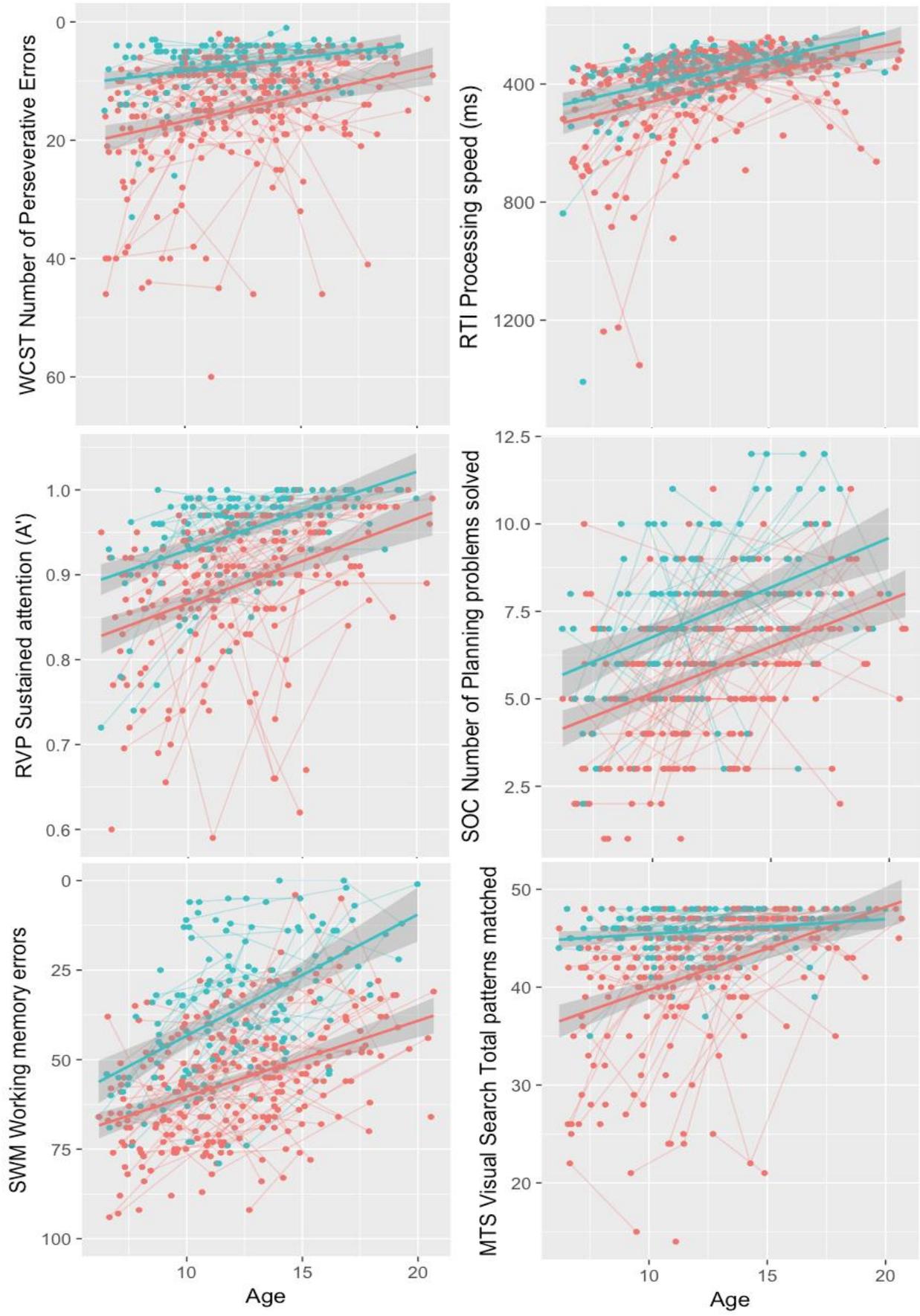


Figure 4-5. Raw scores on set-shifting (number of perseverative errors on WCST), processing speed in milliseconds (ms; RTI), sustained attention (probability of correct responses, A'; RVP), planning (number of problems solved in the minimum amount of moves; SOC), working memory (number of errors; SWM) and visual search (number of patterns matched; MTS) in individuals with 22q11.2DS (22q11.2 Deletion Syndrome; red) compared to control siblings (blue). All graphs have been constructed so that higher values on the y-axis indicate better performance. The fitted linear model is shown with standard error. Repeated measures are joined.

Scores (possible score range)	Interaction between age and deletion; p	Change in 22q11.2DS compared to controls	Raw score performance over time in 22q11.2DS	Model supported
Age standardised IQ scores				
Full Scale IQ	0.046	0.58/year	-	Lag
Verbal IQ	0.543	0.22/year	-	Deficit
Performance IQ	<0.001	1.06/year	-	Lag
IQ subtest raw scores				
Vocabulary	<0.001	Divergence	Increased	Lag
Similarities	0.061	None	Increased	Deficit
Block design	<0.001	Divergence	Increased	Lag
Matrix reasoning	0.388	None	Increased	Deficit
WCST raw scores				
Set-shifting	0.172	None	Increased	Deficit
Neurocognitive battery raw scores				
Processing speed (RTI)	0.805	None	Increased	Deficit
Sustained attention (RVP)	0.541	None	Increased	Deficit
Planning (SOC)	0.907	None	Increased	Deficit
Spatial working memory (SWM)	0.017	Divergence	Increased	Lag

Visual search (MTS)	<0.001	Convergence	Increased	Maturation
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Table 4-2. Results of linear mixed models investigating the trajectories of cognitive domains in 22q11.2DS (22q11.2 Deletion Syndrome) and control siblings.

Cognitive scores appeared to decline over time on the age-standardised PIQ measure at a rate of 1.06 points a year in individuals with 22q11.2DS compared to controls, with a significant interaction between age and deletion status ($p < 0.001$), indicating a developmental lag. When looking at the raw subtest scores, the significant interaction demonstrating a developmental lag in block design ($p < 0.001$) would have been driving this effect; however, it appears that many of the participants with 22q11.2DS scored in the lower range on this subtest, indicating a floor effect (see Discussion). Matrix reasoning ability did not appear to lag over time ($p = 0.388$) but instead represented a stable deficit.

VIQ appeared to follow a developmental deficit model, with similar trajectories in 22q11.2DS and controls after initial impairment at the earliest point of measurement ($p = 0.543$). This was echoed in the similarities subtest ($p = 0.061$). On the vocabulary subtest, however there was evidence for lag ($p < 0.001$), where it appears that this ability was more similar between 22q11.2DS and controls at an earlier age and the gap between groups widened over time. As FSIQ is a composite measure of VIQ and PIQ, the marginally significant interaction ($p = 0.046$) in 22q11.2DS compared to controls is most likely driven by the PIQ result.

Set-shifting ($p = 0.172$), sustained attention ($p = 0.541$) and planning ($p = 0.907$) domains showed evidence of a developmental deficit, whereby those with 22q11.2DS displayed an initial impairment compared to controls but this did not worsen over time. Spatial working memory appeared to show a lag ($p = 0.017$). Visual search showed evidence of developmental maturation in an interaction with a positive slope ($p < 0.001$); however, it could be possible that this finding reflects a ceiling effect in controls (see Discussion). All results survived FDR multiple comparison correction.

The sensitivity analysis including sex and the interaction between sex and deletion status did not alter any interaction effects. There was a relationship between visual search and sex, with males performing better regardless of deletion status (p=0.012).

	(Chawner et al., 2017) model supported over two timepoints	Current study model supported over three timepoints
Age standardised scores		
Full Scale IQ	Deficit	Lag*
Verbal IQ	Deficit	Deficit
Performance IQ	Lag	Lag
IQ subtest raw scores		
Vocabulary	Deficit	Lag*
Similarities	Deficit	Deficit
Block design	Lag	Lag
Matrix reasoning	Deficit	Deficit
WCST raw scores		
Set-shifting	Deficit	Deficit
Neurocognitive battery raw scores		
Processing speed (RTI)	Maturation	Deficit*
Sustained attention (RVP)	Deficit	Deficit
Planning (SOC)	Deficit	Deficit
Spatial working memory (SWM)	Deficit	Lag*
Visual search (MTS)	Deficit	Maturation*

Table 4-3. Comparison between the results of the current study over three timepoints and what was found over two timepoints. Asterisks () denote differences between studies.*

Out of the 13 measures assessed in both studies, 5 (38%) were different between the two- and three-timepoint studies (FSIQ, VIQ subtest vocabulary, processing speed, spatial working memory and visual search).

4.4.2 Aim 2: cognitive deterioration in 22q11.2DS compared to controls

A subset of individuals with 22q11.2DS experienced a decrease in raw scores from T1 to T3 in all cognitive domains (see Table 4-4), which varied from 3.7% of the whole 22q11.2DS group on matrix reasoning to 28.6% on set-shifting. A subset of control individuals also displayed a decrease in raw scores from T1 to T3, from 0% on similarities and block design to 31.6% on planning. The proportion of individuals with 22q11.2DS and controls experiencing a decrease were compared with Fisher’s exact test of independence and found that the proportions of 22q11.2DS and controls showing a decrease were comparable across groups except for the similarities subtest ($p=0.029$) where a greater proportion of the 22q11.2DS group displayed a decrease in raw scores (22.6% in 22q11.2DS compared to 0% in controls). However, this finding did not survive FDR correction for multiple comparisons.

When comparing against RCI, there were much lower proportions of individuals with 22q11.2DS reaching criteria for reliable decrease in scores (from 0% on similarities, block design, matrix reasoning, sustained attention and working memory to 8.7% on processing speed). Controls only exceeded RCI on planning (10.5%) but no other subtest. On cognitive measures where no individuals in either the 22q11.2DS or control group met criteria for reliable decrease in scores, no further statistical testing was undertaken. On measures where there was a proportion of individuals with 22q11.2DS reaching criteria for reliable decrease, there were no differences in proportion of 22q11.2DS or controls experiencing reliable decrease according to Fishers exact test.

Cognitive measure	n (22q11.2DS, Control)	Raw score decrease			RCI decrease		
		22q11.2DS % (n)	Controls % (n)	Fisher’s exact p- value	22q11.2DS % (n)	Controls % (n)	Fisher’s exact p- value
IQ subtest raw scores							
Vocabulary	53, 18	15.1 (8)	5.6 (1)	0.432	1.9 (1)	0 (0)	1
Similarities	53, 18	22.6 (12)	0 (0)	0.029	0 (0)	0 (0)	-
Block design	54, 18	13.0 (7)	0 (0)	0.181	1.9 (1)	0 (0)	1

Matrix reasoning	54,18	3.7 (2)	5.6 (1)	1	0 (0)	0 (0)	-
WCST raw scores							
Set-shifting	49, 18	28.6 (14)	22.2 (4)	0.76	4.1 (2)	0 (0)	1
Neurocognitive battery raw scores							
Processing speed	46, 17	28.3 (13)	23.5 (4)	1	8.7 (4)	0 (0)	0.567
Sustained attention	40, 17	7.5 (3)	17.6 (3)	0.349	0 (0)	0 (0)	-
Planning	41, 19	22.0 (9)	31.6 (6)	0.525	2.4 (1)	10.5 (2)	0.233
Working memory	49, 19	24.5 (12)	21.1 (4)	1	0 (0)	0 (0)	-
Visual search	44, 19	13.6 (6)	15.7 (3)	1	4.5 (2)	0 (0)	1

Table 4-4. Raw cognitive change scores and those exceeding Reliable Change Indices (RCI) in individuals with 22q11.2DS (22q11.2 Deletion Syndrome) compared to controls.

4.5 Discussion

4.5.1 Aim 1: developmental trajectories of cognition in 22q11.2DS compared to controls

This is the only study to examine developmental models of cognition including IQ over three timepoints using raw scores in 22q11.2DS. I found that the previously reported cognitive decline with age in 22q11.2DS (Duijff et al., 2012, Vorstman et al., 2015) was not accounted for by an absolute deterioration in scores over time, as raw scores on a range of cognitive functions increased over time. Especially in age standardised measures of IQ, the fact that older children with 22q11.2DS appeared to have poorer IQ at an older age does not actually indicate a loss of previous ability but instead the mechanics of the standardising process, whereby individuals with 22q11.2DS were not progressing at the same rate as controls over time (developmental lag) or had a stable deficit present from early in development (developmental deficit).

I hypothesised that a deficit model would mainly account for differences in trajectories of cognitive performance between 22q11.2DS and controls based on previous findings (Chawner et al., 2017). This was partially supported by the results, which found that a deficit model fitted verbal IQ, verbal IQ subtest similarities, performance IQ subtest matrix reasoning, set-shifting, processing speed, sustained attention and planning. However, a substantial amount of other areas fitted a lag model (full scale IQ, performance IQ, verbal IQ subtest vocabulary, performance IQ subtest block design and spatial working memory). This differs from the findings of the two timepoint study in this sample (Chawner et al., 2017); see Table 4-3) where full scale IQ, verbal IQ subtest vocabulary and spatial working memory previously followed a deficit model, suggesting that when examining older individuals with 22q11.2DS it is possible to observe a greater divergence from typically developing individuals. This will be further discussed with respect to specific cognitive domains below.

Individuals with 22q11.2DS displayed significant impairments on most cognitive measures compared to controls, in line with previous research (Gothelf et al., 2013, Niarchou et al., 2014). The exception was processing speed at T3, where there was not a significant difference between 22q11.2DS and controls. Similarly, in Chapter 3 I reported that there was less impairment in processing speed in adults (over 18 years) than children (6-10 years) with 22q11.2DS. Due to the cross-sectional nature of that analysis, standardised scores were used, so we were not able to conclude which mechanism underlies the apparent improvement in processing speed. From the findings at T3 and Chapter 3, we might expect a model of maturation; however, a deficit model was the best fit to the data. As individuals with 22q11.2DS at the most recent timepoint were on average 15 years old, the age range may not be sufficiently wide for the individuals with 22q11.2DS to have fully caught up to the control group, but this could be the case at a further timepoint.

Age-standardised PIQ trajectories differed between 22q11.2DS and controls, demonstrating the most change per year in 22q11.2DS compared to controls (1.06 points per year) compared to VIQ (0.22 points per year). When examining the subtests this appeared to be driven by a developmental lag on the block design subtest, as in (Chawner et al., 2017). However, it could be argued that there is a floor effect influencing this trajectory as many younger individuals with 22q11.2DS attained low scores, and therefore there may not have

been a wide enough range on this subtest to measure this domain sensitively. Had there been lower scores possible on this subtest, it is probable that younger individuals with 22q11.2DS especially would have scored in that range, which would alter the trajectory and likely support a deficit model (Chawner et al., 2017).

It is likely that the issue of floor effects has affected other 22q11.2DS studies, but is not often reported except in the previous two-timepoint study on this data (Chawner et al., 2017), probably because raw scores are rarely considered. The other component of PIQ, the matrix reasoning subtest, appeared to present with a stable developmental deficit, as in (Chawner et al., 2017). This further supports why it is essential to consider raw scores in a longitudinal design and not just age-standardised scores, as the overall score will obscure the fact that there may be multiple underlying processes.

The trajectories of age-standardised VIQ were found to be similar in 22q11.2DS and controls after initial impairment, but when examining the VIQ subtests, individuals displayed a lag in vocabulary and deficit in similarities. This suggests that as individuals with 22q11.2DS get older, their vocabulary skills do not progress at the same rate as controls. This differs from the two timepoint results where both VIQ subtests fit a deficit model (Chawner et al., 2017), and the results of Maeder et al. (2016) that vocabulary performance did not lag. However, other studies have reported change in verbal IQ over time in 22q11.2DS and suggested it is related to psychosis development (Vorstman et al., 2015). This will be explored in more detail in Chapter 5.

There was also a developmental lag in working memory, which was not present when looking only across two timepoints (Chawner et al., 2017), suggesting that working memory ability in older individuals with 22q11.2DS does not progress at the same rate as controls. This supports findings from Chapter 3 that there was greater impairment in working memory in adults (over 18 years) than children and adolescents (6-18 years) with 22q11.2DS. As the Chapter 3 analysis was cross-sectional and based on standardised scores, we were not able to conclude which underlying process could pertain to the findings. Although individuals at T3 are on average 15.5 years old, it appears that it may be possible to observe the lag in working memory that was not visible from T1-T2. This result supports

previous studies with larger age ranges that found evidence for lags in working memory compared to controls (Maeder et al., 2016, Antshel et al., 2017). Furthermore, executive performance such as working memory ability has been found to be associated with adaptive functioning in adults with 22q11.2DS with or without schizophrenia, lending support to the idea that remediation in executive performance may also benefit functional outcome (Fiksinski et al., 2018).

Set-shifting, sustained attention and planning ability showed evidence of developmental deficit; present from an early age and remaining stable. This is in line with the findings of (Chawner et al., 2017), suggesting that performance on these tasks is stable on a group level as individuals with 22q11.2DS grow into older adolescence. There appeared to be developmental maturation on the visual search task, however, this could reflect a ceiling effect, as there is a clustering of individuals from the control group around the highest score of 48. Therefore, if higher marks were possible it's likely the control group would have scored in that range, changing the slope of the trajectory. Ceiling effects in controls were previously reported in a study using a modified (simpler) version of the WCST (Rockers et al., 2009), demonstrating the difficulty of selecting tasks which are both challenging for typically developing controls and accessible for individuals with learning problems.

Overall there were no relationships between sex and cognitive performance, except on the visual search task where males performed better. This is largely consistent with (Chawner et al., 2017) who found no effects of sex on cognition. Studies that have reported sex differences in 22q11.2DS on cognitive tasks have generally found that females perform better (Antshel et al., 2005, Duijff et al., 2012). This contrasts with our visual search finding, however previous studies were focussed on IQ, which could explain the different direction as these tasks are not immediately comparable. Furthermore, as the relationship between sex and visual search was present in both 22q11.2DS and control groups it suggests this may be a general effect, reinforcing the importance of also testing a control group to avoid attributing associations solely to 22q11.2DS.

4.5.2 Aim 2: cognitive deterioration in 22q11.2DS compared to controls

As hypothesised, it did not appear that cognitive deterioration affected a large proportion of the group with 22q11.2DS, and overall, it was not more common than in the control group. Raw score change on the similarities VIQ subtest was the exception to this, where there was a greater proportion of individuals with 22q11.2DS achieving a lower score at T3 than T1 than controls. However, it should be noted that as this did not survive multiple comparison correction, it could have been a spurious finding. Additionally, none of the individuals with 22q11.2DS displaying a raw decrease in similarities scores met criteria for reliable change. This indicates that the decrease in similarities from T1 to T3 was small, and when accounting for factors such as measurement error and regression to the mean, this change is no longer meaningful.

There was no evidence for significantly greater cognitive deterioration in individuals with 22q11.2DS compared to controls on any other measures when employing RCI, supporting research that there can be fluctuations over time in cognition in typically developing adolescents, likely related to considerable changes in the brain at this stage in development (Ramsden et al., 2011). The prevalence of these fluctuations appear to manifest at a similar magnitude in 22q11.2DS, supporting previous research in this cohort (Chawner et al., 2017).

4.5.3 Strengths and Limitations

This study is one of the rare longitudinal studies in 22q11.2DS and is unique in having three timepoints of data on 54 individuals with 22q11.2DS, 20 of their typically developing siblings and a range of cognitive measures where raw scores could be examined over time and in relation to indices of reliable change. However, some limitations should be noted.

This study is one of few that have been able to collect data over more than two timepoints, giving us a richer understanding of cognitive processes in 22q11.2DS. However, attrition increases with more timepoints, so it could be hypothesised that individuals with greater cognitive impairment would be more likely to drop out. However, FISQ at baseline did not differ between individuals that dropped out after the first or second visit (see Chapter 2), suggesting that the three timepoint sample is representative of the whole the sample in cognitive functioning.

Despite this, it could be argued that including individuals with varying numbers of timepoints may skew results and it would also be beneficial to solely examine the trajectories of individuals with three complete timepoints. The current study was guided by the fact that previous studies have however taken the approach of including all individuals regardless of amount of timepoints (Maeder et al., 2016, Antshel et al., 2017), however in some studies missing data was imputed (Antshel et al., 2017), but this is not without its problems, as this technique was developed for use in large population samples. The two timepoint study in this sample only included individuals with both timepoints in the analysis (Chawner et al., 2017) but in the current study I aimed to use all the data available to maximum effect.

The study may appear to have a small sample size compared to population based studies, but it is comparable to other studies of cognitive development in 22q11.2DS (Antshel et al., 2017, Maeder et al., 2016, Duijff et al., 2012).

The presence of floor effects on the block design task and ceiling effects on the visual search task makes interpretation of trajectories difficult and should be taken into consideration for new studies in 22q11.2DS to ensure measures are sensitive to the broad range of ability in both a 22q11.2DS and a control group over a wide age span.

It could be argued that since the difference between deterioration and lag models was based on eyeballing the data as opposed to a statistical test, this may not be a stringent enough method of delineating these trajectories. However, when looking at the average trajectory across the group it can be fairly obviously viewed whether the trajectory is in decline as opposed to flat or slightly progressing, and this method has been applied in previous research (Chawner et al., 2017).

In calculating RCI, only test-retest reliability coefficients were available; it may be possible that values would be different for a second retest (as in, the testing at T3). Furthermore, needing a T3 and T1 assessment for this analysis limited the number of participants and therefore generalisability to the whole sample.

It could be argued that the time gap of around 2.5 years between assessments would miss developmentally significant changes; however, it is a similar gap to other studies in 22q11.2DS (Antshel et al., 2017). The variable ages at enrolment in the study mean we cannot make firm claims about specific years of development, but this design enabled us to look over a wider age range.

4.5.4 Conclusions

Deficit and lag models appeared to best explain cognitive development in 22q11.2DS, and there was no evidence for deterioration. Broadly, vigilance measures such as sustained attention, processing speed and visual search tasks appear to be relatively spared in individuals with 22q11.2DS over time, and although there may be an initial impairment in these domains this could remain stable or even catch up with controls. In contrast, performance on tasks associated with retrieving knowledge and maintaining representations, such as working memory and verbal reasoning appear to lag in comparison to controls.

This study highlights the importance of comparing against a control group, as without one it may appear that substantial cognitive deterioration is occurring, which could imply a neurodegenerative mechanism. In fact, it appears that individuals with 22q11.2DS do gain new knowledge over time, and the misconception may arise through an artefact of the IQ standardisation process. This has implications for how we think of measuring change in cognition over time in those with borderline and mild intellectual disability, and how raw scores should be examined in conjunction with reliable change indices to confidently determine when deterioration is happening as opposed to minor fluctuation.

The finding that different cognitive domains progress with different trajectories suggests that there may be different mechanisms that could be related to psychopathology. This will be explored further in Chapter 5.

4.5.5 Future work

To build on these results I would re-analyse the developmental trajectories only including individuals with three timepoints to provide a purely longitudinal consideration of trajectories, and compare this against the current results to validate the current findings.

Future studies with typically developing and 22q11.2DS participants should include measures that have a wide range of responses to avoid floor or ceiling effects, and take into account that floor and ceiling limits will vary over development; for example, the ceiling effect for a typically developing 16 year old will differ from that for a 10 year old. This would ensure that results can be confidently attributed to developmental processes and not artefacts of the tasks.

As the typically developing group in this study was a high IQ group, it would be interesting to include another comparison group of individuals with Idiopathic Intellectual Disability (IID) to establish whether there are 22q11.2DS specific trajectories or deterioration over and above the intellectual disability associated with the deletion, an approach taken by Gur et al. (2014) in a cross-sectional study and (Van Den Heuvel et al., 2018) in a longitudinal study with two timepoints, but has not yet been carried out with three timepoints.

5 Prodromal psychotic symptoms in 22q11.2 Deletion Syndrome and association with cognitive trajectories

5.1 Chapter overview

22q11.2DS (22q11.2 Deletion Syndrome) is associated with high risk of schizophrenia that emerges in late adolescence or early adulthood. High rates of subthreshold psychotic experiences have also been reported in 22q11.2DS throughout adolescence. The neurodevelopmental hypothesis of schizophrenia posits that prior to the onset of psychotic symptoms there are observable indicators of disrupted development, such as cognitive impairments. This chapter will examine rates of prodromal symptoms in individuals with 22q11.2DS around 15 years old and whether there are cognitive trajectories specific to the development of prodromal symptoms.

5.2 Introduction

In Chapter 4 I examined trajectories of cognitive development in individuals with 22q11.2DS compared to control siblings. I did not find evidence for cognitive deterioration in 22q11.2DS, but rather development in most domains followed a deficit model, whereby there was an initial impairment in 22q11.2DS compared to controls that remained at the same magnitude over childhood and adolescence (verbal IQ, similarities verbal IQ subtest, matrix reasoning performance IQ subtest, set-shifting, sustained attention, planning). I also found that some domains followed a lag model, where individuals with 22q11.2DS did not progress at the same rate as controls and therefore the gap between groups widened over time (performance IQ, full scale IQ, vocabulary verbal IQ subtest, block design performance IQ subtest, spatial working memory). In this chapter I aim to examine how cognitive functioning may be associated with development of prodromal symptoms.

5.2.1 Prevalence of psychotic symptoms in 22q11.2DS

As detailed in the Introduction, section 1.5.1, around ~29-40% of adults with 22q11.2DS are diagnosed with a psychotic disorder such as schizophrenia (Schneider et al., 2014a, Monks et al., 2014). In adolescence, it has been reported that many individuals with 22q11.2DS experience psychotic symptoms below the threshold to be diagnosed with a psychotic disorder (Tang and Gur, 2018); however, rates vary across studies, likely due to differences in definition, instrument used to determine presence of symptoms, and age of participants.

Generally previous research has focused on the rate of positive psychotic symptoms in individuals with 22q11.2DS. Positive symptoms were first defined as behaviours that are prevalent in psychosis that are not commonly reported in the general population and therefore represent an addition to consciousness (Jackson, 1887), such as hallucinations and delusions. However, negative symptoms are also a core component of psychotic disorders, so-called as they represent the absence of typical behaviour (Jackson, 1887), such as social withdrawal and lack of motivation. A third dimension of disorganised symptoms has also been hypothesised as necessary for full understanding of psychosis, encompassing symptoms such as bizarre behaviour and inattention (Liddle, 1987); however, the disorganised domain is less well validated (Van Os, 2003). Other symptoms that commonly co-occur with psychosis such as difficulty sleeping and motor co-ordination difficulties are known as general symptoms (McGlashan et al., 2001).

Some studies that assessed individuals with 22q11.2DS with the Structured Interview for Prodromal Symptoms (SIPS; McGlashan et al. (2001)) evaluated rates of negative, disorganised and general symptoms as well as positive symptoms (see section 5.3.2 for specific symptoms assessed). Furthermore, presence of prodromal syndromes can be defined using information from the positive symptom domain of the SIPS as defined by the Criteria of Prodromal Syndromes (COPS), such as Brief Intermittent Psychotic Symptoms (BIPS), Attenuated Positive Symptoms (APS) and Genetic Risk and Deterioration (GRD; see Chapter 2, section 2.4.2 for detailed criteria).

Table 5-1 outlines reported rates of subthreshold psychotic symptoms in individuals with 22q11.2DS.

Study	Assessment	Definition	Mean age in years (SD), range (if reported)	% meeting criteria for psychotic symptoms	Type of controls	% controls meeting criteria for psychotic symptoms	Statistical difference between 22q11.2DS and controls?
Niarchou et al. (2014)¹	CAPA	Subthreshold positive psychotic experiences	10.2 (2.1), 6.6-14.1	10% (8 of 80)	Siblings	8% (3 of 39)	Not tested
Chawner et al. (2019b)¹	CAPA	Subthreshold positive psychotic experiences	12.5 (2.3)	21% (16 of 75)	Siblings	3% (1 of 33)	Yes
Baker and Skuse (2005)	CAPA	Subthreshold positive psychotic experiences	16.4 (2)	48% (12 of 25)	Age and IQ matched	0% (0 of 25)	Not tested
Baker and Skuse (2005)	Junior Schizotypy scale	Schizotypy	16.4 (2)	84% (21 of 25)	Age and IQ matched	12% (3 of 25)	Not tested
Antshel et al. (2010)²	SIPS	Positive prodromal symptoms of psychosis (one or more of the positive symptom items rated mild or above; ≥ 2)	15 (2.1)	20% (14 of 70)	Sibling and community controls	0% (0 of 27) siblings, 4% (1 of 25) community controls	Not tested
Kates et al. (2015)²	SIPS	Positive prodromal symptoms of psychosis (one or more of the positive symptom items rated moderate or above; ≥ 3)	18 (2.2), 14.9-24	16% (12 of 73)	Siblings and community controls	Not reported	Not tested

Antshel et al. (2017)²	SIPS	Positive prodromal symptoms of psychosis (one or more of the positive symptom items rated moderate or above; ≥ 3)	21.2 (2.2)	22% (18 of 82)	Siblings and community controls	Not reported	Not tested
Stoddard et al. (2010)	SIPS	Positive, negative, disorganised and general prodromal symptoms of psychosis (one or more of the symptom domain items rated moderate or above; ≥ 3) and presence of a psychotic or prodromal syndrome as determined by the COPS	15.1 (4.3), 12-22	Positive - 45% (9 of 20) and 2 of these meeting criteria for APS prodromal syndrome Negative – 85% (17 of 20) Disorganised – 55% (11 of 20) General – 60% (12 of 20)	None	-	-
Debbane et al. (2006)	KSADS-PL psychosis module	Positive psychotic symptoms	10-11, 6-19	28% (12 of 43)	None	-	-
Feinstein et al. (2002)	KSADS-PL (only parent interview)	Delusions or hallucinations (positive)	12.31 (3.9), 6-19	14% (4 of 28)	Age and gender matched developmental delay	7% (2 of 29)	No

Vorstman et al. (2006)	KSADS-PL psychosis module	Delusions or hallucinations (positive)	13.7 (2.7), 9-20	27% (16 of 60), 7 of which met criteria for psychotic disorder, 2 of which schizophrenia	None	-	-
Rockers et al. (2009)	SIPS	Presence of a psychotic or prodromal syndrome as determined by the COPS	22 (3.16), 17-27	20% (4 of 20), 3 met criteria for APS and 1 for BIPS prodromal syndromes	Age matched community	12% (2 of 17)	No
Esterberg et al. (2013)	SIPS	Positive, negative, disorganised and general prodromal symptoms of psychosis (mean severity scores)	19.3 (4.1), 14-29	Not reported	Community controls and individuals with Schizotypal Personality Disorder (SPD)	Severity of scores	Community controls show less severe prodromal symptoms in all areas compared to Schizotypal Personality Disorder (SPD) and 22q11.2DS; SPD participants show more severe positive prodromal symptoms than 22q11.2DS.
Schneider et al. (2012)	SIPS	Negative prodromal symptoms (one or more of the negative symptom items rated moderate or above; ≥ 3)	15.4 (2.31), 11-20	83% (39 of 47)	None	-	-

Schneider et al. (2014b)	SIPS	Presence of a psychotic or prodromal syndrome as determined by the COPS	20.5 (6.84), 6-44	22% (13 of 59; 6 met criteria for a psychotic syndrome and 7 met criteria for a prodromal syndrome)	None	-	-
Schneider et al. (2019)	SIPS	Negative symptoms (one or more of the negative symptom items rated moderate or above; ≥ 3)	15.7 (4.7), 8-33	73.9%	None	-	-
Tang et al. (2014b)	SIPS	Psychosis-prone (one or more of the positive symptom items rated moderate or above; ≥ 3 and/or two or more negative or disorganized symptoms rated ≥ 3)	15.2 (4.8)	54% (85 of 157)	None	-	-
Niarchou et al. (2018)	SIPS	Subthreshold psychosis symptoms (one or more of the positive symptom items rated moderate or above; ≥ 3 and/or two or more negative or	13.9 (4.1), 8-23	53% (72 of 137)	None	-	-

		disorganized symptoms rated ≥ 3)					
Maeder et al. (2016)	PANSS	Psychotic symptoms (one or more positive or negative item scored moderate or above; ≥ 4)	12.8 (4.23) at first timepoint, ~55% have 2-4 timepoints mean 3.68 years apart, 6-26	Not reported	Siblings and community controls	Not reported	Not tested

Table 5-1. Studies that have examined the rate of subthreshold psychotic experiences in individuals with 22q11.2DS (22q11.2 Deletion Syndrome). Some, but not all, had available information on control individuals. Varying assessments have been employed; the CAPA (Child and Adolescent Psychiatric Interview (Angold et al., 1995)), the SIPS (Structured Interview for Prodromal Symptoms (McGlashan et al., 2001)), the KSADS-PL (Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (Kaufman et al., 2000)) and the PANSS (Positive and Negative Syndrome Scale (Kay et al., 1987)). COPS is the Criteria for Prodromal Syndromes. APS is Attenuated Positive Symptom Prodromal Syndrome. BIPS is Brief Intermittent Psychotic Symptom Prodromal Syndrome. ¹These studies are the first and second waves of the Experiences of Children with cOpy Number Variants (ECHO) Study at Cardiff University. ²These studies are the second, third and fourth waves of a longitudinal study based in New York.

There is a wide range in the prevalence of psychotic symptoms reported in individuals with 22q11.2DS, with estimates of positive symptoms ranging from 10% to 48% (Niarchou et al., 2014, Baker and Skuse, 2005). Averaging across studies, the rate of positive symptoms is 24.42% at an average age of 15.62 years (Niarchou et al., 2014, Chawner et al., 2019b, Baker and Skuse, 2005, Antshel et al., 2010, Kates et al., 2015, Antshel et al., 2017, Stoddard et al., 2010, Debbane et al., 2006, Feinstein et al., 2002, Vorstman et al., 2006, Rockers et al., 2009, Schneider et al., 2014b).

It has been hypothesised that the rate of positive symptoms may increase as individuals with 22q11.2DS age (Tang and Gur, 2018). To investigate this, I plotted the mean age against the rate of positive psychotic experiences reported in the studies that were averaged across above (see Figure 1). The Pearson correlation coefficient between mean age and reported rate of positive symptoms was weak ($R=0.072$, $p=0.82$). This suggests that overall there may be a fairly constant rate of positive psychotic symptoms around 24% from 10-22 years.

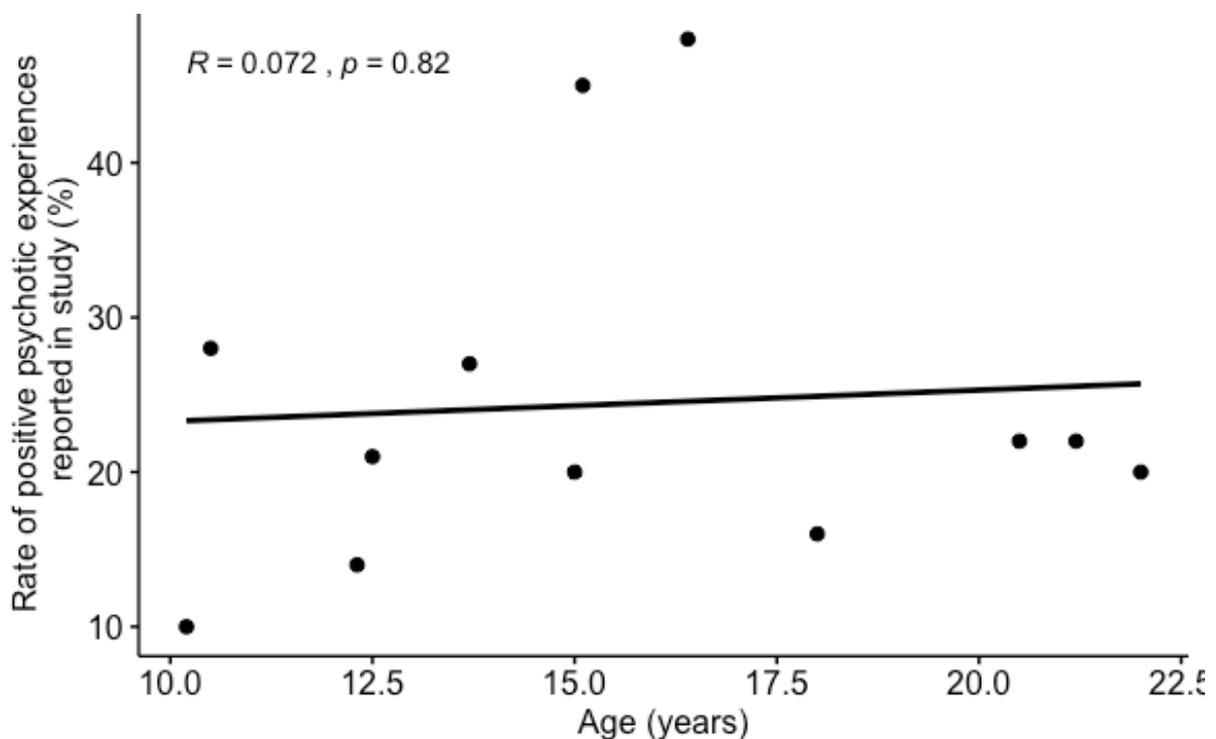


Figure 5-1. Scatter plot of age and rate of psychotic experiences, Pearson correlation coefficient (R) and p value.

However, it should be noted that as the majority of these studies were cross-sectional and conducted with a range of different assessments, Figure 1 should be interpreted with caution. When focussing on the longitudinal studies, in the New York cohort the rate of prodromal symptoms was 20% at the second timepoint at 15 years (Antshel et al., 2010), 16% at the third at 18 years (Kates et al., 2015) and 22% at the fourth at 21 years (Antshel et al., 2017), refuting the concept of a progressive increase in symptoms over time in 22q11.2DS. However, these authors also changed the definition of prodromal symptoms from ≥ 2 on the SIPS at the second timepoint to a stricter ≥ 3 at the third and fourth timepoint, which could also explain why rates were lower at the third than the second timepoint. In the Cardiff cohort, the prevalence of psychotic experiences increased from 10% the first timepoint at around 10 years (Niarchou et al., 2014) to 21% at the second timepoint at around 12.5 years (Chawner et al., 2019b) as assessed by the child CAPA. This could suggest that this period of development may be when psychotic experiences emerge.

The rate of positive psychotic experiences in individuals with 22q11.2DS is generally much higher than in control groups, where reported rates range from around 0-12% with an average of 5.3% (Baker and Skuse, 2005, Rockers et al., 2009, Niarchou et al., 2014, Chawner et al., 2019b, Antshel et al., 2010, Feinstein et al., 2002). However, many studies that tested controls did not report rates of symptoms (Kates et al., 2015, Antshel et al., 2017, Maeder et al., 2016). Some studies that reported rates of psychotic symptoms in controls did not statistically compare rates against 22q11.2DS (Baker and Skuse, 2005, Antshel et al., 2010, Niarchou et al., 2014). In those that did, one reported a difference in rate of psychotic symptoms between 22q11.2DS and controls (Chawner et al., 2019b) but another did not (Feinstein et al., 2002). The rate of prodromal syndromes as defined by the COPS was found to be 10-22% with Attenuated Positive Symptom (APS) Prodromal Syndrome the most common (Stoddard et al., 2010, Rockers et al., 2009, Schneider et al., 2014b).

It is evident that prevalence of negative psychotic symptoms has been less established despite reports that these may impact more on daily-life functioning than positive symptoms in 22q11.2DS (Schneider et al., 2012). Averaging over the three studies that have

investigated this the rate was 80.63% at a mean age of 15.4 years (Schneider et al., 2012, Schneider et al., 2019, Stoddard et al., 2010). Only one study reported on the rate of disorganised (55%) and general (60%) symptoms at 15.1 years old (Stoddard et al., 2010). From these limited studies, it can be hypothesised that negative, disorganised and general prodromal symptoms are more common in 22q11.2DS than positive symptoms around 15 years of age, but further research is needed. Additionally, these studies did not compare against a control group, which is important in establishing the true prevalence of these symptoms.

One study that reported on the severity of psychotic symptoms in positive, negative, general and disorganised domains on the SIPS found that these were rated significantly higher in 22q11.2DS than community controls (Esterberg et al., 2013). In comparison to individuals with Schizotypal Personality Disorder (SPD) however individuals with 22q11.2DS reported less severe positive symptoms, suggesting that there may be distinct symptom profiles in different schizophrenia high-risk groups (Esterberg et al., 2013). Alternatively, ascertainment bias may have played a large role as SPD individuals were identified based on presentation of positive psychotic symptoms but those with 22q11.2DS were recruited solely on basis of deletion and not symptoms (Esterberg et al., 2013).

When investigating severity of positive symptoms in individuals with 22q11.2DS that met criteria for a prodromal syndrome compared to those who did not, Schneider et al. (2014b) found that scores were more severe on grandiose ideas, hallucinations and delusional ideas, but not suspiciousness or disorganised communication, suggesting that specific symptom domains could delineate at-risk individuals with 22q11.2DS. This also suggests that the at-risk cut off is valid for identifying individuals with more intense symptoms. However, individuals with 22q11.2DS identified as having a prodromal syndrome did not differ from non-prodromal individuals on negative symptoms (Schneider et al., 2014b).

The longitudinal course of psychotic experiences in 22q11.2 Deletion Syndrome has been reported to be variable, with waxing and waning in symptoms over time (Tang and Gur, 2018). In a longitudinal study over two timepoints of individuals with 22q11.2DS aged 6-44 (Schneider et al., 2014b), four groups of persistence of psychotic symptoms were identified,

each around 25% of the sample; enduring, emerging, transient, or no symptoms at either timepoint. This demonstrates that there is not one clear pattern of persistence of psychotic experiences in 22q11.2DS over time but likely many different possible trajectories (Tang and Gur, 2018).

5.2.2 Cognitive associations with prodromal symptoms

It has been hypothesised that prior to onset of psychotic symptoms in late adolescence or adulthood, there are observable indicators of disrupted development such as cognitive impairments in childhood (Howes and Murray, 2014). This would support the neurodevelopmental hypothesis of schizophrenia; that is, that it is not necessarily a disorder that emerges in adulthood but that there are processes that are visible throughout early life that index risk of psychosis (Owen et al. (2011); see Chapter 1, section 1.2.6 for further discussion).

As detailed in Chapter 4, there are various models that can characterise cognitive development in an affected group compared to a control group; deficit, lags, maturation and deterioration (see Chapter 4, section 4.2.1.2 for further details). The following sections will explore the findings of longitudinal studies that have examined whether there is evidence of different cognitive trajectories in individuals that experience psychosis or psychotic symptoms compared to those who do not.

5.2.3 Longitudinal studies examining the relationship between cognition and psychosis in the general population

Previous studies in the general population have found evidence for cognitive impairments prior to the onset of schizophrenia. In a study of over 1000 individuals from the general population in Dunedin, New Zealand, where 35 had developed schizophrenia at age 32, cognitive development over 4 timepoints from age 7-13 was measured (Reichenberg et al., 2010). There were deficits in childhood in tasks that measured verbal and visual reasoning in those that later met criteria for schizophrenia compared to controls, and lags over age 7-13 in tasks that measured processing speed, working memory and visual-spatial organisation.

This suggests that both initial and increasing cognitive impairments may precede psychosis (Reichenberg et al., 2010). However, many of the tasks were complex, requiring a number of cognitive processes, for example the digit symbol task used “is a test of psychomotor speed and coordination and attention/concentration”. Therefore, it is difficult to establish what specific cognitive components may be associated with schizophrenia development.

In a study investigating cognitive trajectories in children aged 9-16 years at risk for schizophrenia compared to controls over three timepoints, Dickson et al. (2018) found that deficits were present in verbal reasoning, working memory and tasks measuring inhibition in at-risk children, and a lag in spelling ability. Interestingly, there was also evidence for an initial deficit in visual and verbal memory tasks in at-risk individuals, which showed maturation to catch up to controls. The findings of this study are consistent with previous research of cognitive trajectories preceding schizophrenia (Reichenberg et al., 2010), suggesting that findings may be translatable from the high-risk to the clinical stages (Dickson et al., 2018).

5.2.4 Longitudinal studies examining the relationship between cognition and psychosis in 22q11.2DS

In a large collaborative study of 411 individuals with 22q11.2DS Vorstman et al. (2015) found that there was a measurable decline in IQ from 8-24 years in individuals that would later be diagnosed with psychosis compared to those without, particularly in verbal IQ, which could be observed from 11 years old. They also reported that a low initial IQ at or before adolescence increased the risk of psychosis in 22q11.2DS. However, there were some methodological issues, such as a fairly large proportion of the sample having their last cognitive assessment after their psychiatric assessment (40.9%), making it difficult to determine whether changes in cognition precede psychosis onset, or cognition is impacted by psychosis.

Gothelf et al. (2013) similarly found evidence that a decline in verbal IQ was associated with psychotic disorder when looking over two timepoints from 5-49 years, as well as lower baseline full scale IQ. However, it should be noted that many of the participants from this

study (n=125, Tel Aviv and Geneva cohorts) were included in the Vorstman et al. (2015) study and therefore contributed to those findings, so it is not unexpected that results from both studies are similar. Furthermore, only standardised measures of IQ were available in both studies (Vorstman et al., 2015, Gothelf et al., 2013) and so it is unclear what a decline in verbal IQ represents; there could be a loss of previous ability (deterioration) or a lag whereby individuals raw scores increase but not at the rate expected by the standardisation process (Reichenberg et al., 2010). Studies that can investigate raw score change are needed to delineate models of cognitive development (see Chapter 4, section 4.2.1.2 for further discussion).

Results from the Geneva cohort (Schneider et al., 2014b) in a smaller sample of 59 individuals with 22q11.2DS aged 6-44 years did not support a decline model in IQ over two timepoints but did also find that a lower baseline IQ was associated with positive prodromal symptoms. This study also assessed specific cognitive variables perceptual organisation and processing speed and found that initial deficits in these domains were associated with positive prodromal symptoms but did not find evidence for lags or deterioration (Schneider et al., 2014b).

Also looking beyond IQ, in a recent study that tested participants between 6-27 years with the Wisconsin Card Sorting Test (WCST), 18/75 (24%) of individuals that were diagnosed with psychosis a year later displayed more perseverative errors at baseline (Pontillo et al., 2019). This indicates difficulties in cognitive flexibility, a component of executive functioning, prior to positive symptoms of psychosis, which has also been reported in idiopathic schizophrenia (Remberk et al., 2014). Full scale IQ, verbal IQ and performance IQ were also lower at baseline in individuals reaching criteria for psychosis (Pontillo et al., 2019). However, other measures of executive functioning, response inhibition and verbal fluency were not associated with positive symptoms of psychosis in this sample (Pontillo et al., 2019).

Maeder et al. (2016) also did not find associations between response inhibition and verbal fluency and positive prodromal symptoms in 95 individuals with 22q11.2DS age 6-26 years; however, they found that in individuals displaying negative symptoms, trajectories of

executive functioning measures response inhibition and working memory diverged from those without negative symptoms over time. This supports research in idiopathic schizophrenia that finds that negative symptoms are associated with executive dysfunction (Donohoe et al., 2006, Semkowska et al., 2004). These findings demonstrate that cognitive abilities may be differentially associated with different domains of psychotic symptoms.

However, the previous studies span large age ranges from 6 years well into adulthood, which may obscure developmentally relevant associations between cognition and psychotic symptoms. A longitudinal study based in New York with a narrower age range starting at 12 years of age has reported on its second (15 years; Antshel et al. (2010)), third (18 years; Kates et al. (2015)) and fourth (21 years; Antshel et al. (2017)) waves of data collection on around 75 individuals with 22q11.2DS and found that associations between cognition and psychotic symptoms differ at those different timepoints.

At the second wave (Time 1 (T1) = 12 years and Time 2 (T2) = 15 years) poorer executive functioning at T1 (working memory, inhibition and non-perseverative errors) predicted positive prodromal symptoms at T2 (Antshel et al., 2010). At the third wave, some individuals had been diagnosed with psychosis, and therefore participants experiencing either overt or prodromal psychosis were combined into one category. It appeared that lower full scale IQ at T1 predicted prodromal/overt symptoms of psychosis at T3, but there were no associations with other cognitive measures (Kates et al., 2015). At fourth wave divergent trajectories of reading ability, perseverative errors and emotion recognition were associated with prodromal/overt symptoms of psychosis (Antshel et al., 2017). This could suggest that associations change over time, highlighting the importance of following up with participants in a narrower age range. It could also be the case that attrition and recruitment of new participants changed associations, as well as differing statistical techniques over time that are appropriate to additional waves of data collection.

Over two waves of the Experiences of Children with Copy Number Variants (ECHO) study at Cardiff University, Chawner et al. (2019b) examined what baseline cognitive factors or change in baseline factors would predict psychotic experiences at a second timepoint in 75 individuals aged on average 12.5 years. They found that in those that developed psychotic

experiences, there was a deficit at the first timepoint in working memory that increased between timepoints. Furthermore, change in sustained attention from T1 to T2 was associated with the emergence of psychotic experiences. This research was essential to discovering what may predict psychotic experiences in early adolescence in 22q11.2DS, and leads to the question of what happens at the subsequent timepoint, when psychosis risk may have increased (Tang and Gur, 2018).

5.2.5 Aims

5.2.5.1 Aim 1: prevalence of prodromal psychotic symptoms in individuals with 22q11.2DS compared to controls

The first aim was to examine the prevalence of prodromal psychotic positive, negative, disorganised and general symptoms in adolescents with 22q11.2DS and controls (siblings without the deletion) on average 15 years old in the ECHO study cohort as assessed by the SIPS. Based on previous research, I hypothesised that there would be a higher rate and severity of psychotic phenomena in individuals with 22q11.2DS than controls.

5.2.5.2 Aim 2: longitudinal cognitive trajectories in individuals with 22q11.2DS and prodromal symptoms compared to those without prodromal symptoms

The second aim was to determine whether cognitive trajectories differ in individuals with 22q11.2DS with or without prodromal psychotic positive or negative symptoms. I hypothesised that individuals with psychotic symptoms would display different cognitive development to those without psychotic symptoms in the form of initial deficits or lags over time.

5.3 Methods

5.3.1 Participants

Detailed recruitment procedure, demographic information, and representativeness of the sample are discussed in Chapter 2. Briefly, the study was structured as an accelerated longitudinal study, where participants were of different ages when enrolling into the study and then followed up around every 2.5 years (age at first timepoint ranged from 6-20 years in individuals with 22q11.2DS and 6-18 years in controls).

The SIPS (McGlashan et al., 2001), a detailed interview of psychotic phenomena (see section 5.3.2 for more details), was added to the assessment battery at the start of the third wave of data collection in July 2015 when participants were on average age 15 years, as it is not recommended for younger children (Miller et al., 2003). Three individuals recently completed the SIPS at second wave as they were over 12 years old. Therefore, prodromal symptoms or not as determined by the SIPS was the outcome measure. Cognitive data (see section 5.3.3 for more details) had been collected at each previous timepoint, i.e. from wave 1 to wave 3. Therefore, there were up to three waves of cognitive data per individual with SIPS data at the most recent timepoint.

63 individuals with 22q11.2DS had SIPS data; 51 had completed both positive and negative sections, 5 had only completed the positive section, and 7 had only completed the negative section. As detailed in Chapter 2, section 2.4.2, the positive SIPS was completed with the child, so the reasons for non-completion were that the child refused to participate in the interview (n=3), they did not understand the questions (n=3; see section 5.5.3, Strengths and Limitations for further discussion) or lack of time on the visit (n=1). The negative SIPS was completed with the parent after the general psychopathology interview, the Child and Adolescent Psychiatric Assessment (CAPA), and so if the interviews were not finished on the visit to the family home attempts were made to complete it over the phone after the visit but unfortunately this was not possible in 5 cases.

32 control siblings had SIPS data; 22 completed both positive and negative sections, 5 only completed the positive section, and 5 only completed the negative section. Missing data is due to the child's refusal to participate in the positive SIPS interview (n=2) or lack of time on

the visit (n=8). There were no differences in age or sex between the children with 22q11.2DS and controls with SIPS data (see Table 5-2).

		22q11.2DS	Control	p
Positive SIPS	Age (SD)	15.47 (2.40)	14.30 (3.15)	0.065
	Sex (male, %)	32 (57%)	14 (52%)	0.814
Negative SIPS	Age (SD)	15.63 (2.55)	14.61 (3.54)	0.19
	Sex (male, %)	32 (55%)	13 (48%)	0.643

Table 5-2. Age and sex distributions in individuals with 22q11.2DS (22q11.2 Deletion Syndrome) and controls. Differences in age were tested with t-tests and differences in sex were tested with Fisher’s exact test. SD = Standard Deviation.

5.3.2 Assessment of prodromal psychotic symptoms

Presence of prodromal psychotic symptoms was assessed with the SIPS. A detailed description is available in Chapter 2, section 2.4.2. Briefly the SIPS measures prodromal psychotic phenomena that may precede schizophrenia (Stoddard et al., 2010).

The SIPS comprises 19 items, grouped into 5 positive, 6 negative, 4 disorganised and 4 general symptoms as follows:

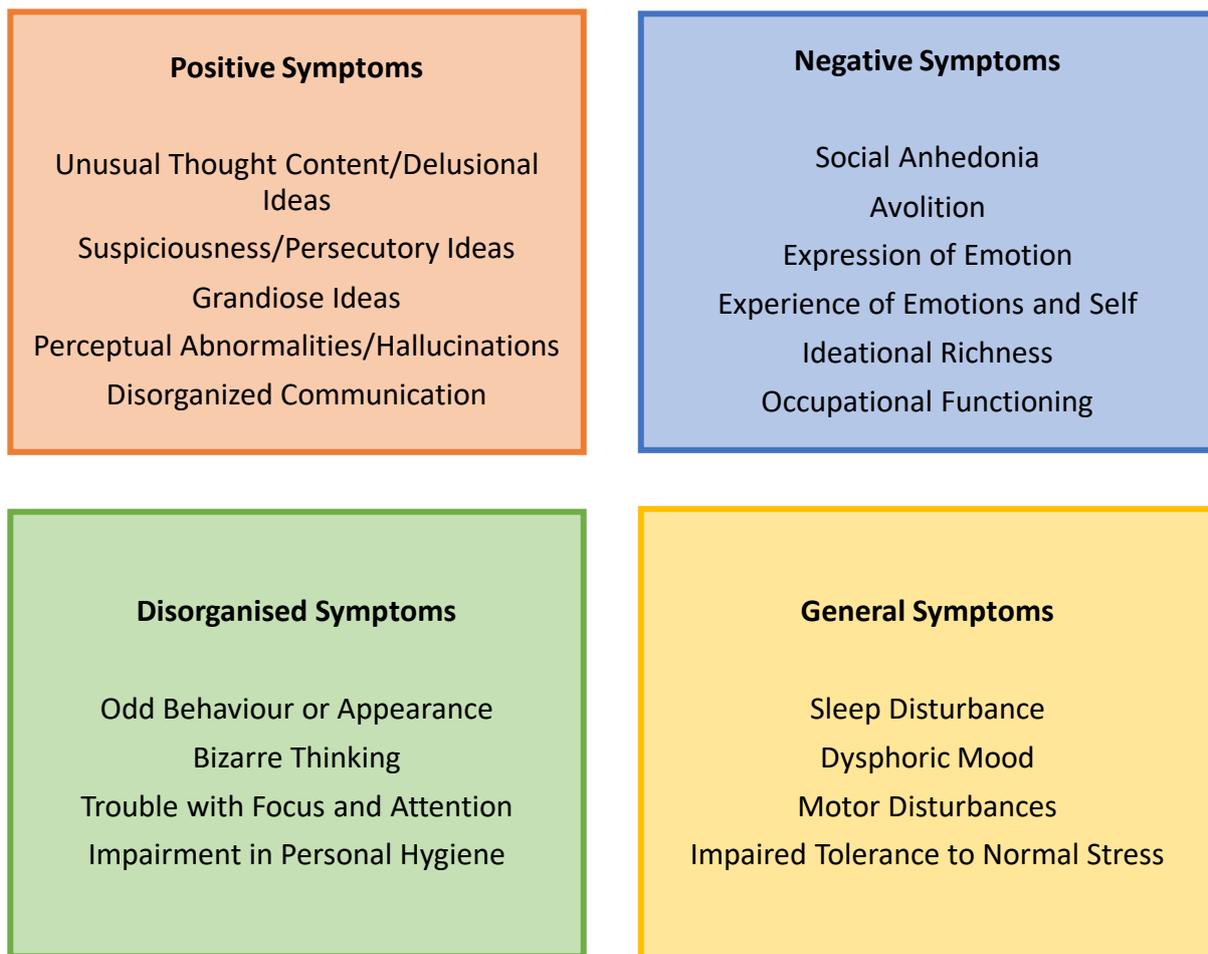


Figure 5-2. Positive, negative, disorganised and general prodromal psychotic symptoms assessed by the Structured Interview for Prodromal Symptoms (SIPS).

On each item the individual can score from 0 to 6. A score of 0-2 is thought to be non-prodromal, 3 to 5 prodromal and 6 psychotic (Miller et al., 2002). Therefore, individuals were categorised as experiencing a prodromal symptom if they scored ≥ 3 . This threshold has been applied in many other 22q11.2DS studies (Kates et al., 2015, Antshel et al., 2017, Stoddard et al., 2010, Schneider et al., 2019, Schneider et al., 2012, Niarchou et al., 2018, Tang et al., 2014b).

If an individual scores ≥ 3 on any of the positive symptoms, they may meet criteria for a prodromal syndrome depending on the frequency and onset of their symptoms. Brief Intermittent Psychotic Symptom (BIPS) Prodromal Syndrome is applied if the individual scores a 6 (severe and psychotic) on any of the positive symptoms and these have been present at least several minutes a day at least once per month in the last three months.

Attenuated Positive Symptom (APS) Prodromal Syndrome is applied if the individual scores a 3-5 (moderate to severe but not psychotic) on any of the positive symptoms and these have been experienced at least once a week in the last month. The symptoms must also have begun in the past year or currently rate at least one point higher than 12 months ago. As there is only one assessment of the SIPS it was not possible to assess whether symptoms were one point higher, so it could only be applied that symptoms had begun in the past year. Genetic Risk and Deterioration (GRD) Prodromal Syndrome is applied if the individual meets criteria for Schizotypal Personality Disorder and has a first degree relative with psychotic disorder. Furthermore, they must demonstrate a 30% drop in a score of Global Assessment of Functioning (GAF) compared to 12 months ago. Again, we did not have a GAF measurement from a previous timepoint so could not assess these criteria.

5.3.3 Cognitive assessments

Participants undertook a range of cognitive assessments at each wave that are described in detail in Chapter 2; they will be outlined briefly here. First, IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler (2011)) yielding a Full scale IQ (FSIQ), Verbal IQ (VIQ) and Performance IQ (PIQ) score. These are age-standardised scores based on normative data. Raw scores were available from the subtests of VIQ and PIQ. VIQ subtest Vocabulary was assessed by number of words correctly defined. VIQ subtest Similarities was assessed by number of correctly identified similarities between two words. PIQ subtest Block Design was assessed through number of block formations correctly replicated. PIQ subtest Matrix Reasoning was assessed through number of correctly identified missing patterns in a matrix design. The Wisconsin Card Sorting Test (WCST) was administered, obtaining raw and standardised measures of set-shifting ability as assessed by number of perseverative errors.

A battery of neurocognitive tasks was administered using CANTAB software (Cognition, 2006). Processing speed was measured through speed on the Five Choice Reaction Time (RTI) task, where the participant must respond as fast as possible to a stimulus in one of five locations. Sustained attention was measured through the probability of correct responses on the Rapid Visual Information Processing (RVP) task, where participants must respond to a

target sequence of digits over a few minutes of a continuous pseudo-random presentation of digits. Planning (SOC) was assessed through number of problems solved using the minimum amount of moves on the Stockings of Cambridge task, a tower-building problem. Spatial working memory was assessed as the number of errors on the Spatial Working Memory (SWM) task, where participants must remember where previous targets were in space. Visual search (MTS) was measured through number of patterns successfully matched on a match-to-sample task.

5.3.4 Statistical Analyses

5.3.4.1 Aim 1: prevalence and severity of prodromal psychotic symptoms in individuals with 22q11.2DS compared to controls

Proportion of individuals with 22q11.2DS or controls scoring ≥ 3 (moderate to psychotic symptom) on any of the symptoms or overall symptom domains was compared with generalised linear mixed models, with prevalence of prodromal symptom as the outcome and deletion status, age and sex as fixed effects and family relatedness as a random effect. Odds ratios were estimated, i.e. the odds that prodromal symptoms would occur given diagnosis of 22q11.2DS. When there were no symptoms present in controls, p-values were estimated with Fisher's Exact test, but these should be interpreted with caution. Odds ratios could not be reliably estimated if there were no symptoms present in controls.

Mean severity of prodromal symptoms was compared across 22q11.2DS and controls with linear mixed models with deletion status, age and sex as fixed effects and family relatedness as a random effect.

To examine the severity of symptoms in individuals with 22q11.2DS and controls that scored at ≥ 3 (prodromal level) compared to those not meeting prodromal level, ANOVA was carried out to test whether severity of symptoms was significantly different across these four groups. If so, pairwise comparisons with Tukey post-hoc tests were conducted to examine whether severity of symptoms was higher in prodromal individuals with 22q11.2DS than

prodromal controls, and whether severity of symptoms was higher in prodromal individuals with 22q11.2DS than non-prodromal individuals with 22q11.2DS.

Persistence of positive psychotic experiences from previous timepoints to the current timepoint was examined through dividing the sample into four groups as in Schneider et al. (2014b); individuals with emerging symptoms (present at the most recent timepoint but not at previous timepoints), transient symptoms (present at previous timepoints but not at the most recent timepoint), enduring symptoms (present at previous and most recent timepoints) and no symptoms (not present at any timepoint).

5.3.4.2 Aim 2: longitudinal cognitive trajectories in individuals with 22q11.2DS and prodromal symptoms compared to those without prodromal symptoms

Positive and negative dimensions of schizophrenia have been the most clinically validated; evidence for other domains such as disorganised are less convincing (Van Os, 2003). Therefore, further analysis will examine the relationship between positive and negative symptom dimensions and cognition.

To examine the relationship of age with performance on cognitive tasks in individuals with 22q11.2DS and prodromal symptoms compared to those without prodromal symptoms over three timepoints, I first examined visually whether raw scores in the various cognitive domains increased over time (see Figures 6-8 for positive prodromal symptoms, Figures 10-12 for negative prodromal symptoms). If raw scores decreased over time in individuals with prodromal symptoms and increased in those without, this would indicate a developmental deterioration.

To determine which cognitive developmental models best fitted the data, linear mixed model analysis was undertaken with the R package *nlme*. This can incorporate individuals with data from varying numbers of timepoints rather than listwise deletion of those with incomplete data (Pinheiro et al., 2013). The outcome variable was performance on each cognitive task, run as separate models. The fixed effects in the model were age and group

(experiencing prodromal symptoms at mean age 15 and a half or not) and the interaction between age and group. The random effect in the model was the within-subject repeated measures effect.

If raw scores were increased across time points, a significant interaction between age and group would indicate that the course of cognitive development is different in individuals with and without prodromal symptoms. Generally, a significant negative interaction indicated a developmental lag (divergence in trajectories between individuals with and without prodromal symptoms); a significant positive interaction indicated a developmental maturation (convergence in trajectories between individuals with and without prodromal symptoms).

To investigate the presence of an early developmental deficit in cognition between those with and without prodromal symptoms, I examined whether there was an overall effect of group (prodromal symptoms or not) on performance on the cognitive test. However, this defaults to the difference between groups on cognition at age 0 (Afshartous and Preston, 2011), which would not make sense as cognition was not measured by us at this age, and indeed would not have much practical relevance. To be able to interpret the difference between groups on cognition at the earliest age of the whole sample, age was centred to the mean age of all participants at the first assessment (10.21 years), as in Dickson et al. (2018). This was done through creating a new Age Centred variable by subtracting 10.21 years from each participant's age (Afshartous and Preston, 2011). This meant that the estimated overall difference between those with and without prodromal symptoms on a cognitive test and the resulting p-value reflects performance at age 10.21 years, a representative early age, rather than 0 years. Centring age does not alter interaction effects, only the main effect of group on cognition.

7 individuals that had SIPS data at Wave 3 had reported a psychotic symptom at Wave 2 (n=6) or Wave 1 and 2 (n=1). None of the individuals that had SIPS data at Wave 2 had previously reported a psychotic symptom at Wave 1. To control for the possible influence of previous psychotic experiences on cognitive trajectories, this was entered into the models

as a covariate, as in Antshel et al. (2017). Findings are reported with and without this covariate.

5.3.5 Statistical correction

The Benjamini-Hochberg method for controlling False Discovery Rate (FDR) was used to correct for multiple comparisons (Benjamini and Hochberg, 1995). This method ranks p-values in a cluster of tests, then divides the rank by the number of tests in the cluster, then multiplying by an acceptable FDR (in this case, 10%, following Crawford et al. (2018)) to produce a Benjamini-Hochberg critical value. The highest p-value that is below the Benjamini-Hochberg critical value survives FDR correction, as with all p-values below that one.

5.4 Results

5.4.1 Aim 1: prevalence and severity of prodromal psychotic symptoms in individuals with 22q11.2DS compared to controls

Table 5-3 displays prevalence and severity of prodromal symptoms in individuals with 22q11.2DS and controls.

Symptom	Number of participants scoring ≥3 (%)		Odds Ratio (95% Confidence Interval)	p	Mean severity of symptom (SD)		p
	22q11.2DS	Controls			22q11.2DS	Controls	
Positive Symptoms	<i>22q11.2DS n=56, Control n=27</i>						
Any positive symptom	15 (26.8)	4 (14.8)	1.71 (0.71 to 4.14)	0.236	3.61 (4.68)	1.44 (2.74)	0.018
Unusual thought content/delusional ideas	5 (8.9)	1 (3.7)	1.79 (0.37 to 8.64)	0.466	0.75 (1.30)	0.30 (0.72)	0.042
Suspiciousness/Persecutory Ideas	2 (3.6)	3 (11.1)	0.20 (0.03 to 105.19)	0.404	0.48 (0.83)	0.48 (1.01)	0.982
Grandiose Ideas	6 (10.7)	0 (0.0)	-	0.17	0.64 (1.43)	0.15 (0.36)	0.039
Perceptual Abnormalities/Hallucinations	14 (25.0)	2 (7.4)	3.03 (0.96 to 9.54)	0.063	1.36 (1.73)	0.41 (1.01)	0.011
Disorganised Communication	1 (1.9)	0 (0.0)	-	1	0.40 (0.80)	0.12 (0.44)	0.114
Negative Symptoms	<i>22q11.2DS n=58, Control n=27</i>						
Any negative symptom	18 (31.0)	0 (0.0)	-	<0.001	3.53 (3.88)	0.33 (0.78)	0.001
Social Anhedonia	6 (10.3)	0 (0.0)	-	0.17	0.64 (1.21)	0.07 (0.27)	0.045
Avolition	11 (19.0)	0 (0.0)	-	0.014†	1.09 (1.41)	0.04 (0.19)	0.001
Expression of Emotion	1 (1.7)	0 (0.0)	-	1	0.24 (0.63)	0.07 (0.27)	0.356
Experience of Emotions and Self	2 (3.4)	0 (0.0)	-	1	0.31 (0.75)	0.11 (0.42)	0.314
Ideational Richness	6 (10.3)	0 (0.0)	-	0.17	1.03 (1.26)	0.04 (0.19)	0.001
Occupational Functioning	2 (3.4)	0 (0.0)	-	1	0.22 (0.92)	0.00 (0.00)	0.169
Disorganised Symptoms	<i>22q11.2DS n=58, Control n=27</i>						

<i>Any disorganised symptom</i>	25 (43.1)	1 (3.7)	12.43 (2.52 to 61.36)	0.025 [†]	2.71 (2.93)	0.41 (0.84)	<0.001
Odd Behaviour or Appearance	6 (10.3)	0 (0.0)	-	0.17	0.36 (0.95)	0.00 (0.00)	0.061
Bizarre Thinking	1 (1.8)	0 (0.0)	-	1	0.18 (0.57)	0.07 (0.38)	0.473
Trouble with Focus and Attention	22 (37.9)	1 (3.7)	11.42 (2.24 to 58.20)	0.193	1.60 (1.56)	0.29 (0.72)	<0.001
Impairment in Personal Hygiene	4 (7.0)	0 (0.0)	-	0.3	0.57 (1.21)	0.04 (0.19)	0.04
<i>General Symptoms</i>	22q11.2DS n= 58, Control n=27						
<i>Any general symptom</i>	15 (25.9)	1 (3.7)	5.20 (1.16 to 23.38)	0.032 [†]	2.97 (4.01)	0.41 (0.93)	0.005
Sleep Disturbance	6 (10.5)	0 (0.0)	-	0.17	0.89 (1.25)	0.15 (0.53)	0.008
Dysphoric Mood	8 (13.8)	1 (3.7)	2.91 (0.62 to 13.52)	0.174	0.72 (1.54)	0.26 (0.71)	0.167
Motor Disturbances	3 (5.2)	0 (0.0)	-	0.548	0.57 (1.03)	0.00 (0.00)	0.064
Impaired Tolerance to Normal Stress	10 (17.2)	0 (0.0)	-	0.027 [†]	0.79 (1.42)	0.00 (0.00)	0.014
<i>All Prodromal Symptoms</i>	Only individuals that had completed all SIPS domains; 22q11.2DS n=51, Control n=21						
<i>Total symptoms</i>	34 (66.7)	4 (19.0)	5.32 (2.10 to 13.48)	<0.001	11.96 (9.74)	2.43 (2.98)	<0.001

Table 5-3. Prevalence and severity of prodromal psychotic symptoms in individuals with 22q11.2DS (22q11.2 Deletion Syndrome) compared to controls. Overall symptom categories are italicised. P-values <0.05 are in bold. † indicates findings that did not survive multiple comparison False Discovery Rate (FDR) correction.

There was a greater proportion of individuals with 22q11.2DS meeting criteria for any prodromal symptom compared to controls (66.7% v 19%, $p < 0.001$). Mean total severity of prodromal symptoms overall was also higher in individuals with 22q11.2DS compared to controls (11.96 v 2.43, $p < 0.001$). The most prevalent symptoms in individuals with 22q11.2DS were trouble with focus and attention (37.9%), perceptual abnormalities/hallucinations (25%) and avolition (19%). Individuals with 22q11.2DS also scored higher than controls in all overall symptom domains (positive, $p = 0.018$; negative, $p = 0.001$; disorganised, $p < 0.001$; general, $p = 0.005$).

There was a greater proportion of individuals with 22q11.2DS scoring ≥ 3 (moderate to psychotic) in all overall symptom domains compared to controls except positive symptoms, $p = 0.236$, i.e., negative symptoms, $p < 0.001$; disorganised symptoms, $p = 0.025$; and general symptoms, $p = 0.032$). However, when controlling for multiple comparisons on tests of proportion, only total symptoms and negative symptoms remained significant. 4/27 (14.8%) controls scored a 3 or above on one of the positive symptoms, compared to 15/56 (26.8%) individuals with 22q11.2DS. This did not reach statistical significance, possibly due to a lack of power resulting from small sample size (see Discussion).

Despite this, individuals with 22q11.2DS generally scored higher on the overall positive symptom domain in comparison to controls (3.61 v 1.44, $p = 0.018$). There was no difference in proportion of individuals with 22q11.2DS scoring moderately or above on individual positive symptoms compared to controls, but there was higher mean severity of scores in 22q11.2DS in delusional ideas ($p = 0.042$), grandiose ideas ($p = 0.039$) and hallucinations ($p = 0.011$). All severity comparisons survived FDR correction.

When comparing the positive symptom profile, prodromal individuals with 22q11.2DS (scoring ≥ 3 on any of the positive symptoms) experienced more severe symptoms in the domains of hallucinations ($p = 0.007$) and grandiosity ($p = 0.035$) than prodromal controls (see Figure 5-3). Conversely, prodromal controls scored higher on the suspiciousness domain than prodromal 22q11.2DS ($p < 0.001$). There was no difference between severity of prodromal 22q11.2DS and controls on delusional ideas ($p = 0.590$) or disorganised communication ($p = 0.969$). Prodromal individuals with 22q11.2DS scored higher than non-

prodromal 22q11.2DS on all positive symptoms (delusional ideas, $p<0.001$; suspiciousness, $p<0.001$; grandiosity, $p<0.001$; hallucinations, $p<0.001$; disorganised communication, $p=0.020$).

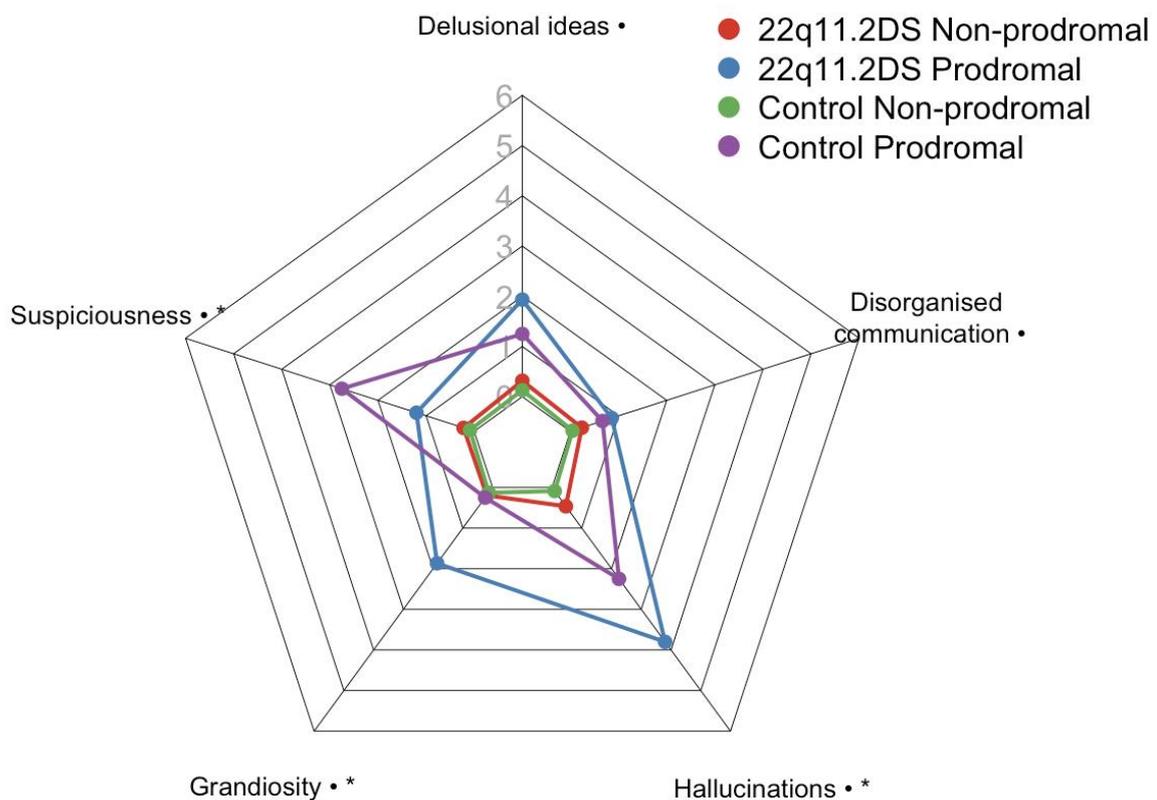


Figure 5-3. Spider plot depicting the distribution of positive symptoms in 22q11.2DS (22q11.2 Deletion Syndrome) and controls with and without prodromal symptoms (scoring ≥ 3 on any positive symptom on the Structured Interview for Prodromal Symptoms (SIPS)). • denotes a significant difference ($p<0.05$) between prodromal and non-prodromal 22q11.2DS. * denotes a significant difference ($p<0.05$) between prodromal 22q11.2DS and prodromal controls.

None of the controls scored at a moderate or higher level on any of the negative symptoms. There was a higher proportion of individuals with 22q11.2DS reaching this threshold compared to controls on the overall negative symptom domain ($p<0.001$) and the individual symptom of avolition ($p=0.014$). There was higher severity of scores in social anhedonia

($p=0.045$), avolition ($p=0.001$) and ideational richness ($p=0.001$) in individuals with 22q11.2DS compared to controls.

A greater proportion of individuals with 22q11.2DS scored moderately or above on the disorganised symptom domain ($p=0.025$). There were higher scores on trouble with focus and attention in 22q11.2DS compared to controls ($p<0.001$) as well as impairment in personal hygiene ($p=0.04$).

There was a greater proportion of individuals with 22q11.2DS scoring ≥ 3 on the general symptom domain ($p=0.032$) and the individual symptom of impaired tolerance to normal stress ($p=0.027$). There was also a higher severity of scores in impaired tolerance to normal stress ($p=0.014$) and sleep disturbance ($p=0.008$).

When applying COPS criteria, 6 of the 15 individuals with positive prodromal symptoms met criteria for a prodromal syndrome (40%); 5 with APS and 1 with BIPS. This represented 10.7% (6/56) of everyone that completed the positive symptom section of the SIPS. None of the 4 controls that reported positive prodromal symptoms met criteria for a prodromal syndrome.

There was no difference in age between those experiencing positive prodromal symptoms with 22q11.2DS (mean 15.3 years) or controls (mean 15.2 years) (t-test, $p=0.955$). There was also no difference in gender between individuals with 22q11.2DS (8/15 males, 53%) experiencing positive prodromal symptoms and controls (1/4, 25%) (Fishers exact test, $p=0.582$). As there were no controls experiencing negative prodromal symptoms and only one experiencing disorganised/general prodromal symptoms, it was not statistically possible to make the same comparisons in age and sex between individuals with 22q11.2DS and controls.

Within individuals with 22q11.2DS, there were generally no differences in age or sex between those with or without prodromal symptoms as examined with t-test and Fishers exact test respectively (see Table 5-4). The exception was the disorganised domain, where

individuals with prodromal symptoms were on average younger than those without prodromal symptoms ($p=0.013$); see Discussion.

		No prodromal symptoms	Prodromal symptoms	p
Positive	Age	15.52	15.3	0.762
	Sex	24 (59%)	8 (53%)	0.768
Negative	Age	15.81	15.54	0.714
	Sex	10 (55%)	22 (56%)	1
Disorganised	Age	16.34	14.69	0.013
	Sex	17 (52%)	15 (60%)	0.599
General	Age	15.73	15.31	0.586
	Sex	24 (56%)	8 (53%)	1

Table 5-4. Age and sex distribution in individuals with 22q11.2DS (22q11.2 Deletion Syndrome) with and without prodromal symptoms.

Figure 5-4 depicts the percentage proportions of different patterns of persistence of positive psychotic experiences across timepoints in individuals that had an assessment of psychotic experiences at the most recent and previous timepoints ($n=55$). As previously discussed 7 individuals had previously reported psychotic experiences. Of these 7, 1 individual had enduring symptoms, that is symptoms were present at their previous and most recent timepoint. 6 individuals had transient symptoms, that is they reported psychotic experiences at previous timepoints but not at the most recent timepoint. 14 individuals reported emerging symptoms at their most recent timepoint, that is they did not report a psychotic experience at a previous timepoint but did at the most recent timepoint. Most individuals did not report a positive psychotic experience at any timepoint ($n=34$).

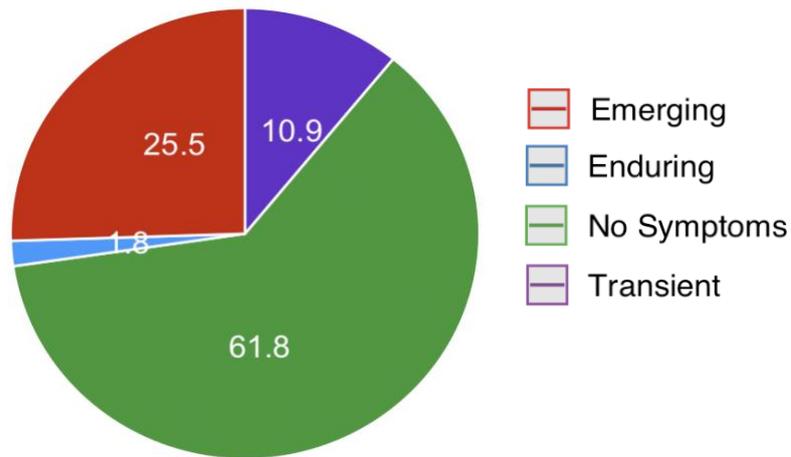


Figure 5-4. Percentage proportions of persistence of positive psychotic experiences from previous timepoints, as assessed by the child-appropriate version of the Child and Adolescent Psychiatric Assessment (CAPA), to most recent timepoint, as assessed by the Structured Interview for Prodromal Symptoms (SIPS).

5.4.2 Aim 2: longitudinal cognitive trajectories in individuals with 22q11.2DS and prodromal symptoms compared to those without prodromal symptoms

5.4.2.1 Positive prodromal symptoms

Figure 5-5 details sample size, age and sex of participants with or without prodromal positive symptoms as assessed by the SIPS at their most recent timepoint that have cognitive data at one, two or three timepoints.

	22q11.2DS with prodromal positive symptoms	22q11.2DS without prodromal positive symptoms
One timepoint	N=15 Mean age 10.40 years old (SD=2.70) 7 (47%) females	N=40 Mean age 10.05 years old (SD=2.22) 17 (43%) females
Two timepoints	N=15 Mean age 12.95 years old (SD=2.88) 7 (47%) females	N=40 Mean age 12.71 years old (SD=2.08) 17 (43%) females
Three timepoints	N=11 Mean age 15.61 years old (SD=2.98) 5 (45%) females	N=36 Mean age 15.76 years old (SD=2.04) 14 (39%) females

Figure 5-5. Sample size, age and sex distribution of individuals with 22q11.2DS (22q11.2 Deletion Syndrome) with and without prodromal positive symptoms as assessed by the Structured Interview for Prodromal Symptoms (SIPS). SD= Standard Deviation.

There was no difference in age between those with and without prodromal positive symptoms as assessed by t-test at first timepoint (T1; $t=0.50$, $p=0.619$), second timepoint (T2; $t=0.34$, $p=0.735$) or third timepoint (T3; $t=0.19$, $p=0.849$). Likewise, there was no difference in sex between those with and without prodromal positive symptoms as assessed by Fishers exact test at T1 ($p=1$), T2 ($p=1$) or T3 ($p=0.737$).

On age standardised measures of IQ, scores appeared to decrease over time in both those with and without positive prodromal symptoms (Figure 5-6), but when examining the subtests contributing to IQ, raw scores increased over time in both groups (Figure 5-7). In all other cognitive domains, raw scores also increased over time, ruling out a developmental deterioration model (Figure 5-8).

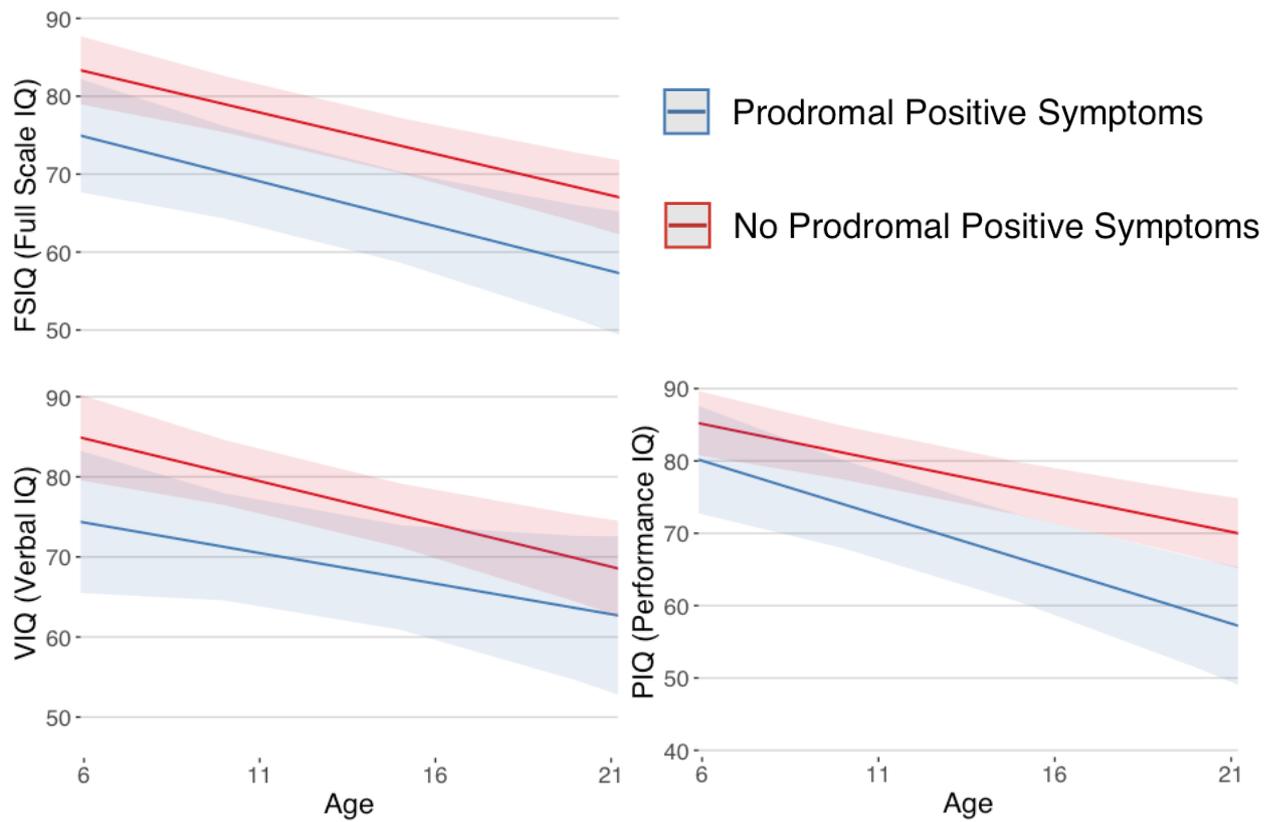


Figure 5-6. Line graphs of predicted values adjusted for repeated measures for age-standardised FSIQ (Full Scale IQ), VIQ (Verbal IQ) and PIQ (Performance IQ) in individuals with 22q11.2DS (22q11.2 Deletion Syndrome) and positive prodromal symptoms (blue) compared to those without positive prodromal symptoms (red). Shaded area is standard error. All graphs have been constructed so that higher values on the y-axis indicate better performance.

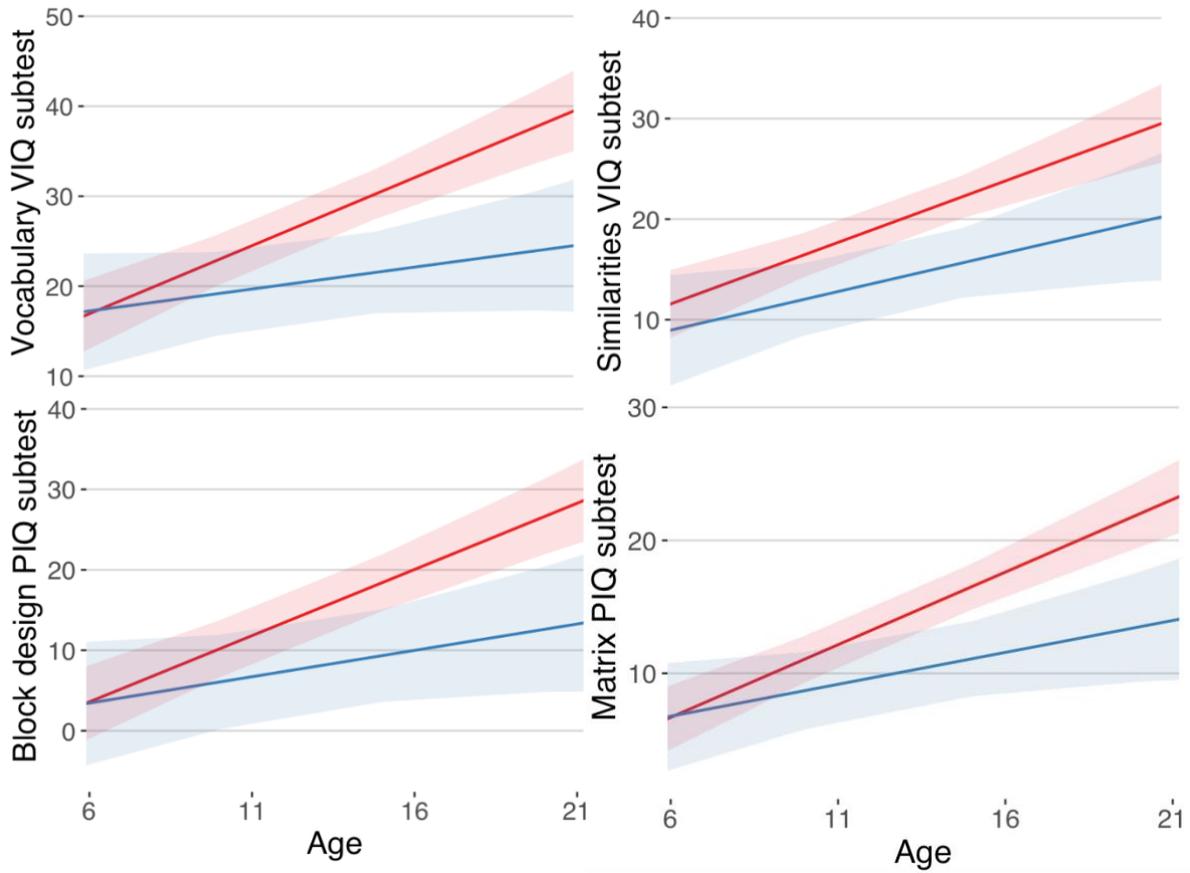


Figure 5-7. Line graphs of predicted values adjusted for repeated measures for raw scores on IQ subtests Vocabulary (VIQ), Similarities (VIQ), Block Design (PIQ) and Matrix Reasoning (PIQ) in individuals with 22q11.2DS (22q11.2 Deletion Syndrome) and positive prodromal symptoms (blue) compared to those without positive prodromal symptoms (red). Shaded area is standard error. All graphs have been constructed so that higher values on the y-axis indicate better performance.

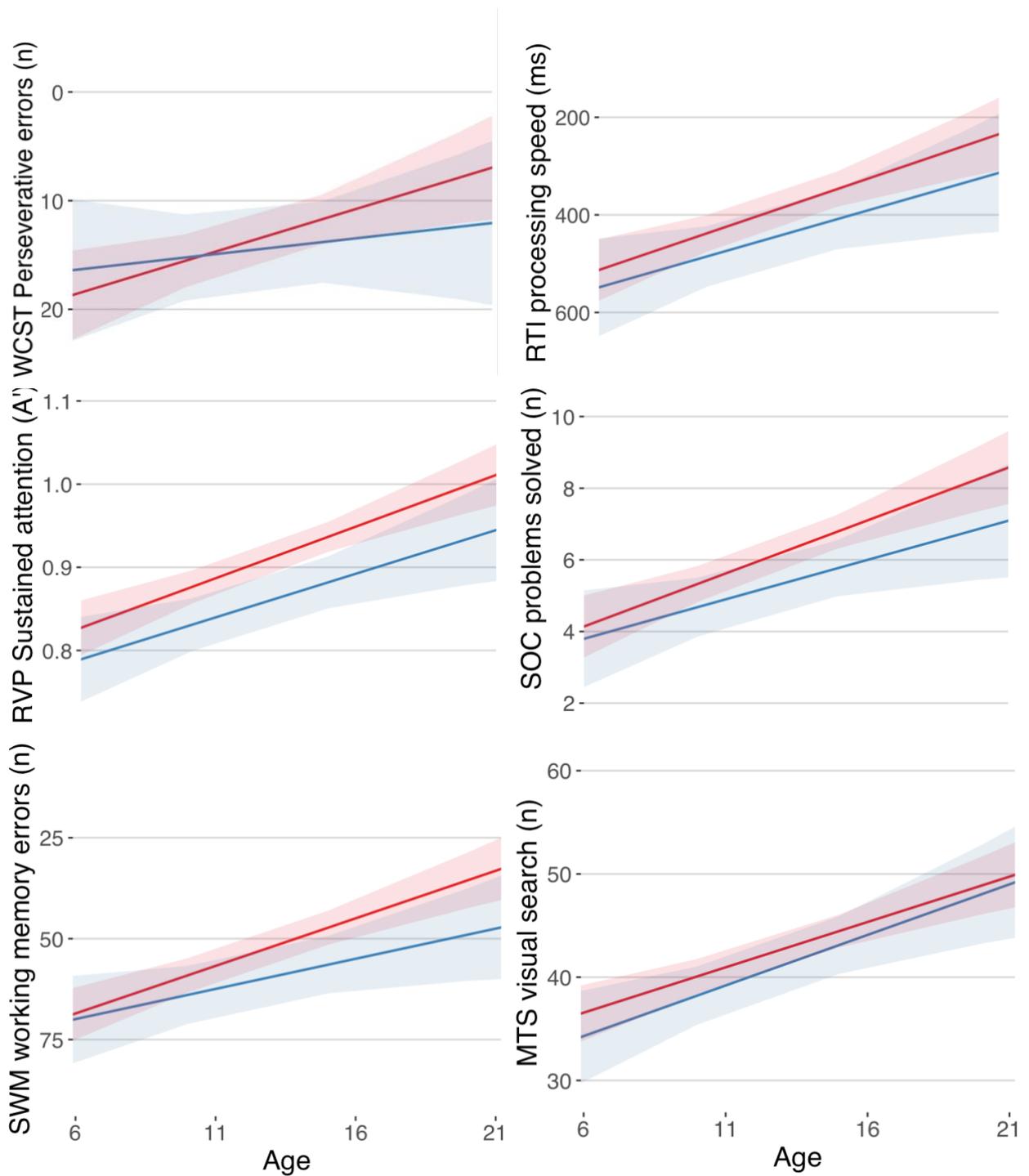


Figure 5-8. Line graphs of predicted values adjusted for repeated measures for raw scores on set-shifting (number of perseverative errors on WCST), processing speed in milliseconds (ms; RTI), sustained attention (probability of correct responses, A'; RVP), planning (number of problems solved in the minimum amount of moves; SOC), working memory (number of errors; SWM) and visual search (number of patterns matched; MTS) in individuals with 22q11.2DS (22q11.2 Deletion Syndrome) and positive prodromal symptoms (blue) compared

to those without positive prodromal symptoms (red). Shaded area is standard error. All graphs have been constructed so that higher values on the y-axis indicate better performance.

Scores (possible score range)	Interaction between age and prodromal symptoms; p	Estimated between group difference in change per 1 year of age (SE)	Main effect of prodromal symptoms at age 10.21; p	Estimated between group difference at age 10.21 (SE)	Model supported
Age standardised IQ scores					
Full Scale IQ (50-160)	0.819	-0.09 (0.38)	0.019	-8.65 (3.56)	Deficit
Verbal IQ (55-156)	0.591	0.29 (0.54)	0.031	-8.82 (4.00)	Deficit
Performance IQ (53-157)	0.201	-0.50 (0.39)	0.05	-7.36 (3.36)	Deficit
IQ subtest raw scores					
Vocabulary (0-72)	0.013	-1.05 (0.42)	0.237	-3.86 (2.75)	Lag
Similarities (0-48)	0.248	-0.45 (0.39)	0.051	-4.28 (2.14)	No difference
Block design (0-71)	0.033	-0.98 (0.45)	0.188	-4.67 (3.61)	Lag
Matrix reasoning (0-35)	0.019	-0.62 (0.26)	0.181	-2.35 (1.73)	Lag
WCST raw scores					
Perseverative errors*	0.334	0.48 (0.49)	0.953	-0.14 (2.36)	No difference

(0-46)					
Neurocognitive battery raw scores					
Processing speed (RTI)* (0-∞)	0.704	2.89 (7.60)	0.202	47.67 (36.89)	No difference
Sustained attention (RVP) (0-1)	0.575	0.00 (0.00)	0.026	-0.04 (0.02)	Deficit
Planning (SOC) (0-12)	0.425	-0.08 (0.10)	0.226	-0.59 (0.48)	No difference
Spatial working memory (SWM)* (0-∞)	0.224	0.94 (0.76)	0.318	4.22 (4.19)	No difference
Visual search (MTS) (0-48)	0.806	0.08 (0.33)	0.317	-1.68 (1.66)	No difference

Table 5-5. Results of linear mixed models investigating the trajectories of cognitive domains in individuals with 22q11.2DS (22q11.2 Deletion Syndrome) with positive prodromal symptoms compared to those without. *Generally, a negative estimated group difference represents poorer performance in individuals with positive prodromal symptoms compared to those without, except for perseverative errors, spatial working memory and processing speed measures where positive differences represent poorer performance (i.e. more errors and slower reaction times).

Table 5-5 presents results from linear mixed models investigating cognitive trajectories in individuals with 22q11.2DS with and without positive prodromal symptoms. Individuals with positive prodromal symptoms demonstrated initial deficits at 10.21 years compared to those without prodromal symptoms in FSIQ (main effect $p=0.019$, 8.65 points lower), VIQ (main effect $p=0.031$, 8.82 points lower) and borderline in PIQ (main effect $p=0.05$, 7.36 points lower).

In terms of IQ subtests, individuals with positive prodromal symptoms lagged over time in vocabulary (interaction $p=0.013$, 1.05 points lower each year), block design (interaction $p=0.033$, 0.98 points lower per year) and matrix reasoning (interaction $p=0.019$, 0.62 points lower per year) and displayed a borderline initial deficit in similarities (main effect $p=0.051$, 4.28 points lower) compared to those without positive prodromal symptoms.

Individuals with positive prodromal symptoms also displayed an initial deficit in sustained attention compared to those without prodromal symptoms (main effect $p=0.026$, 0.04 lower, equating to 4% less likely to correctly respond). There were no differences in cognitive trajectory between those with and without positive prodromal symptoms in perseverative errors, processing speed, planning, spatial working memory or visual search.

When removing previous psychotic experiences as a covariate results were largely unchanged, except for verbal IQ similarities subtest, which displayed a deficit in individuals with prodromal symptoms compared to those without (main effect $p=0.039$, changed from $p=0.051$). All significant findings survived multiple comparison correction.

5.4.2.2 Negative prodromal symptoms

Figure 9 details sample size, age and sex of participants with or without prodromal negative symptoms as assessed by the SIPS at their most recent timepoint that have cognitive data at one, two or three timepoints.

	22q11.2DS with prodromal negative symptoms	22q11.2DS without prodromal negative symptoms
One timepoint	N=18 Mean age 10.67 years old (sd=2.85) 8 (44%) females	N=39 Mean age 9.96 years old (sd=2.32) 18 (46%) females
Two timepoints	N=18 Mean age 13.49 years old (sd=2.88) 8 (44%) females	N=39 Mean age 12.58 years old (sd=2.30) 18 (46%) females
Three timepoints	N=13 Mean age 15.61 years old (sd=2.98) 5 (38%) females	N=35 Mean age 15.76 years old (sd=2.04) 17 (49%) females

Figure 5-9. Sample size, age and sex distribution of individuals with 22q11.2DS (22q11.2 Deletion Syndrome) with and without prodromal negative symptoms as assessed by the Structured Interview for Prodromal Symptoms (SIPS). SD= Standard Deviation.

There was no difference in age between those with and without negative prodromal symptoms as assessed by t-test at one timepoint (T1; $t=1.00$, $p=0.324$), second timepoint (T2; $t=1.28$, $p=0.207$) or third timepoint (T3; $t=0.63$, $p=0.533$). Likewise, there was no difference in sex between those with and without prodromal positive symptoms as assessed by Fishers exact test at T1 ($p=1$), T2 ($p=1$) or T3 ($p=0.746$).

On age standardised measures of IQ, scores appeared to decrease over time in both those with and without negative prodromal symptoms (Figure 10), but when examining the subtests contributing to IQ, raw scores increased over time in both groups (Figure 11). In all other cognitive domains, raw scores also increased over time, ruling out a developmental deterioration model (Figure 12).

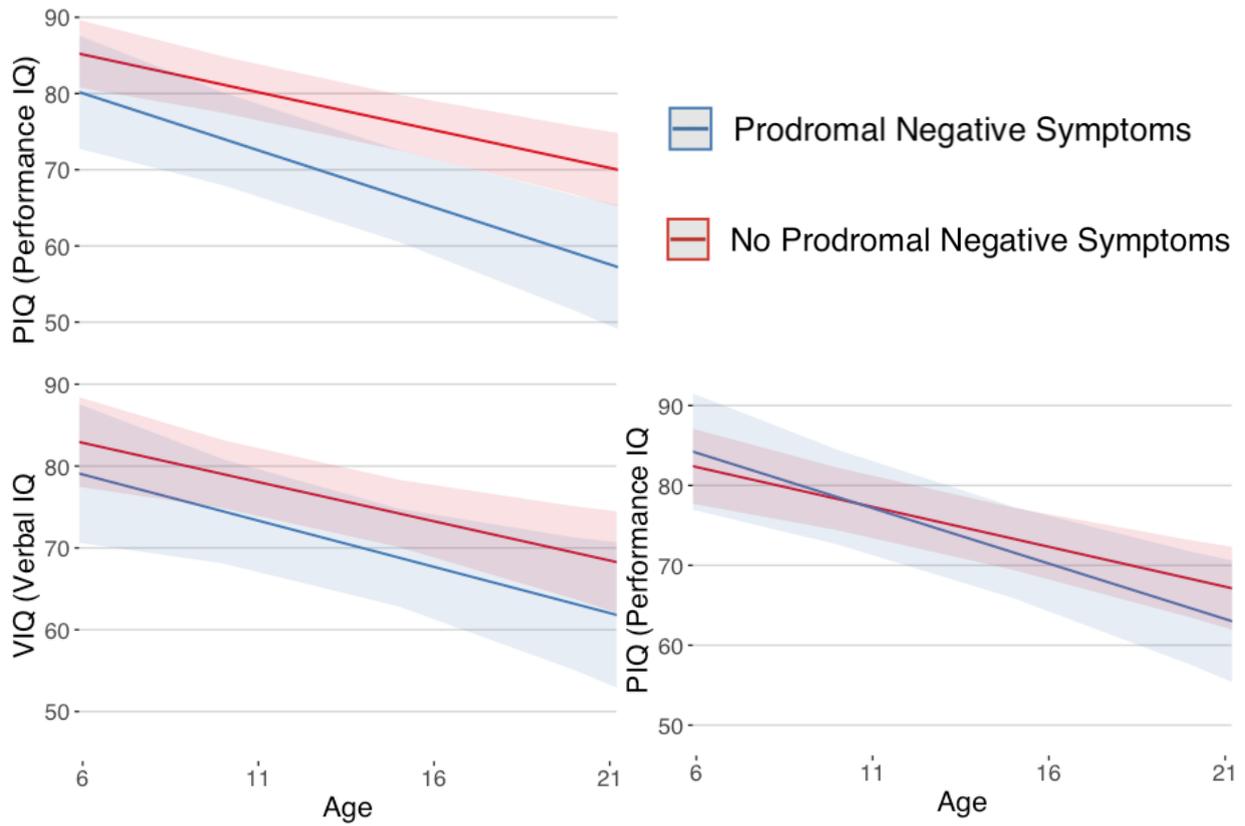


Figure 5-10. Line graphs of predicted values adjusted for repeated measures for age-standardised FSIQ (Full Scale IQ), VIQ (Verbal IQ) and PIQ (Performance IQ) in individuals with 22q11.2DS (22q11.2 Deletion Syndrome) and negative prodromal symptoms (blue) compared to those without negative prodromal symptoms (red). Shaded area is standard error. All graphs have been constructed so that higher values on the y-axis indicate better performance.

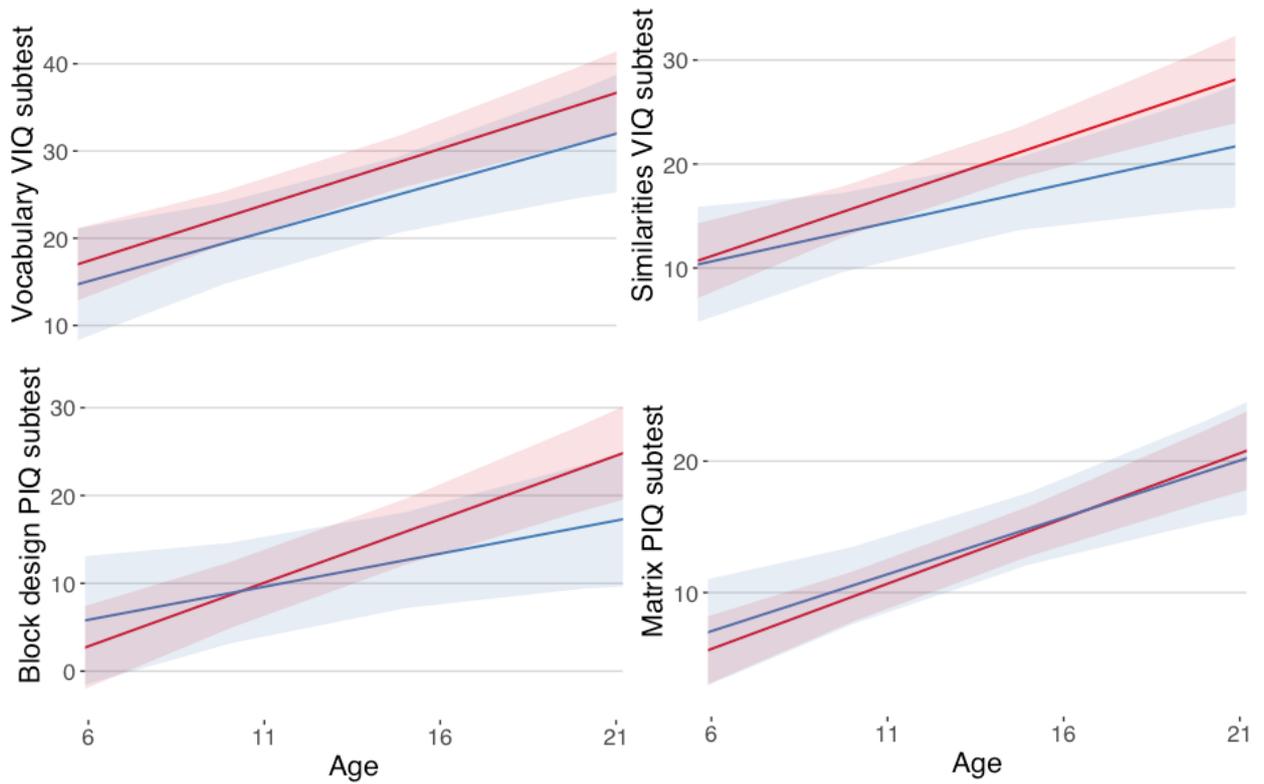


Figure 5-11. Line graphs of predicted values adjusted for repeated measures for raw scores on IQ subtests Vocabulary (VIQ), Similarities (VIQ), Block Design (PIQ) and Matrix reasoning (PIQ) in individuals with 22q11.2DS (22q11.2 Deletion Syndrome) and negative prodromal symptoms (blue) compared to those without negative prodromal symptoms (red). Shaded area is standard error. All graphs have been constructed so that higher values on the y-axis indicate better performance.

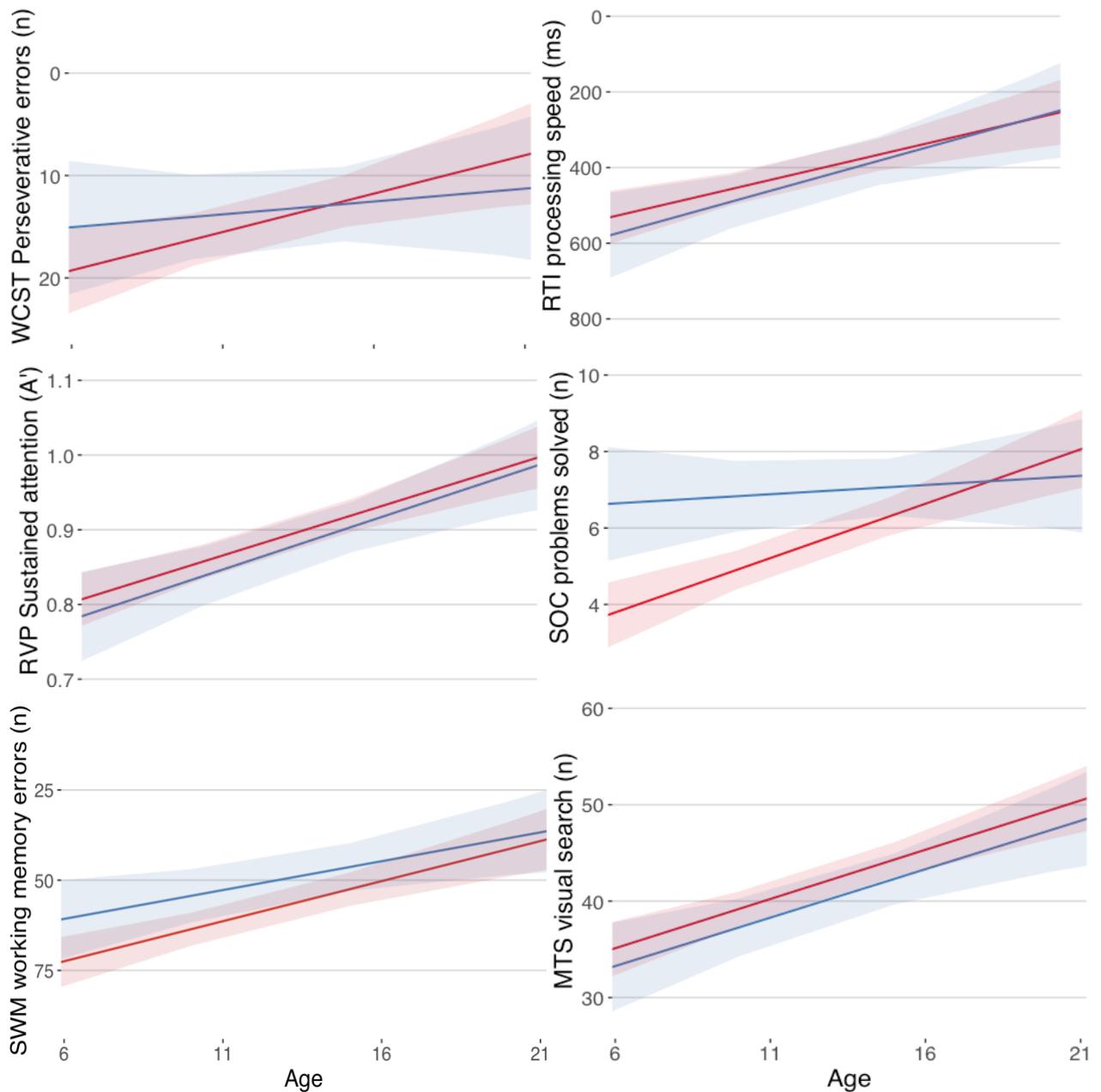


Figure 5-12. Line graphs of predicted values adjusted for repeated measures for raw scores on set-shifting (number of perseverative errors on WCST), processing speed in milliseconds (ms; RTI), sustained attention (probability of correct responses, A'; RVP), planning (number of problems solved in the minimum amount of moves; SOC), working memory (number of errors; SWM) and visual search (number of patterns matched; MTS) in individuals with 22q11.2DS (22q11.2 Deletion Syndrome) and negative prodromal symptoms (blue) compared to those without negative prodromal symptoms (red). Shaded area is standard error. All graphs have been constructed so that higher values on the y-axis indicate better performance.

Scores (possible score range)	Interaction between age and prodromal symptoms; p	Estimated between group difference in change per 1 year of age (SE)	Main effect of prodromal symptoms; p	Estimated between group difference at age 10.21 (SE)	Model supported
Age standardised IQ scores					
Full Scale IQ (50-160)	0.226	-0.46 (0.38)	0.528	-2.44 (3.84)	No difference
Verbal IQ (55-156)	0.51	-0.35 (0.53)	0.326	-4.10 (4.13)	No difference
Performance IQ (53-157)	0.468	-0.28 (0.39)	0.818	-0.92 (3.95)	No difference
IQ subtest raw scores					
Vocabulary (0-72)	0.595	-0.23 (0.43)	0.346	-2.82 (2.96)	No difference
Similarities (0-48)	0.079	-0.68 (0.38)	0.493	-1.61 (2.34)	No difference
Block design (0-71)	0.112	-0.71 (0.44)	0.85	-0.73 (3.85)	No difference
Matrix reasoning (0-35)	0.411	-0.22 (0.26)	0.788	0.51 (1.90)	No difference
WCST raw scores					
Perseverative errors	0.276	0.54 (0.49)	0.418	-2.06 (2.52)	No difference

(0-46)					
Neurocognitive battery raw scores					
Processing speed (RTI) (0-∞)	0.997	-0.03 (7.86)	0.897	5.30 (40.82)	No difference
Sustained attention (RVP) (0-1)	0.762	0.00 (0.00)	0.825	0.00 (0.02)	No difference
Planning (SOC) (0-12)	0.006	-0.29 (0.10)	<0.001	1.92 (0.50)	Maturation
Spatial working memory (SWM) (0-∞)	0.404	0.62 (0.74)	0.038†	-9.12 (4.27)	Deficit
Visual search (MTS) (0-48)	0.473	-0.24 (0.33)	0.728	-0.62 (1.77)	No difference

Table 5-6. Results of linear mixed models investigating the trajectories of cognitive domains in individuals with 22q11.2DS (22q11.2 Deletion Syndrome) with negative prodromal symptoms compared to those without. *Generally, a negative estimated group difference represents poorer performance in individuals with negative prodromal symptoms compared to those without, except for perseverative errors, spatial working memory and processing speed measures where positive differences represent poorer performance (i.e. more errors and slower reaction times). † indicates findings that did not survive multiple comparison False Discovery Rate (FDR) correction.

Table 5-6 presents results from linear mixed models investigating cognitive trajectories of individuals with 22q11.2DS with and without negative prodromal symptoms. There was a maturation effect in planning, where those without negative symptoms initially performed worse but caught up with individuals with negative symptoms over time (interaction $p < 0.001$). There was also an initial deficit in working memory in individuals without negative symptoms compared to those with negative symptoms (main effect $p = 0.038$, 9.12 more errors), but this did not survive multiple comparison correction. There were no differences in any other cognitive trajectories between those with and without negative prodromal symptoms.

Results were largely unchanged when not controlling for previous psychotic experiences, except there was no longer a significant deficit in working memory in those without negative symptoms compared to those with (main effect $p = 0.156$, estimated between group difference 5.54 errors). To investigate this more thoroughly, trajectories were compared between individuals with emerging, transient, enduring, or no psychotic symptoms (see Figure 13).

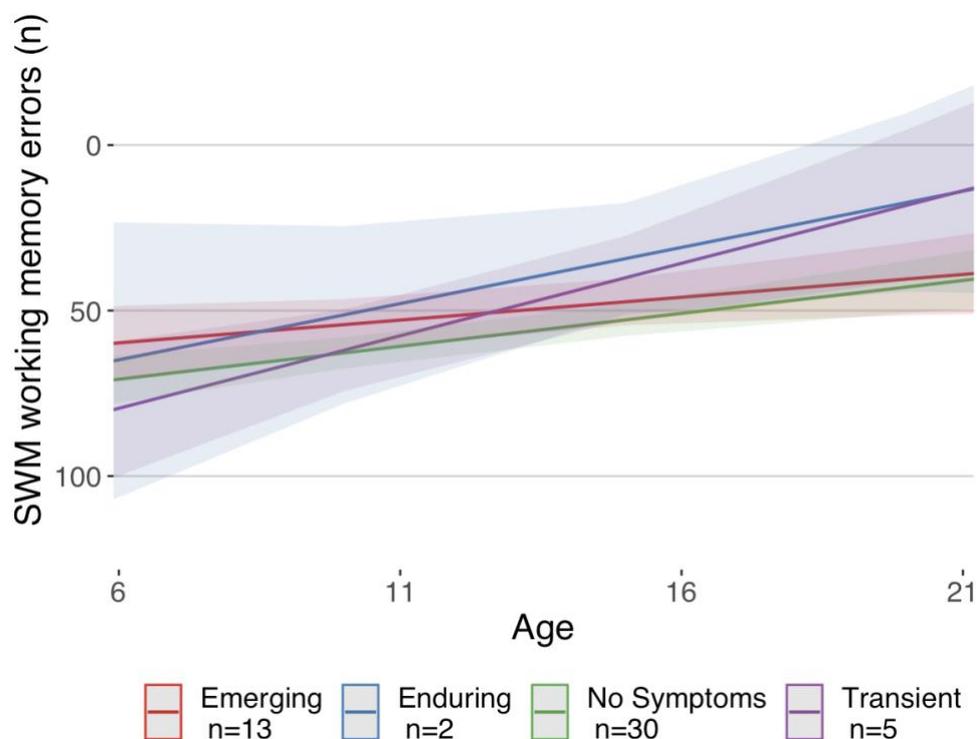


Figure 5-13. Trajectories of individuals with emerging, enduring, transient or no psychotic symptoms on working memory performance (number of errors; SWM).

It can be seen that trajectories appear to differ across groups, although the group numbers are too small for reliable statistical tests. The model with covariate controlled for individuals that had previously reported psychotic symptoms; that is, the 'transient' and 'enduring' groups (n=7). When controlling for these, this would leave the 'emerging' and 'no symptoms' groups, which appear with an initial deficit despite becoming more similar over time. Therefore, without the influence of the transient and enduring groups, the adjusted mean difference at age 10.21 years was larger between those with and without negative symptoms.

5.5 Discussion

5.5.1 Aim 1: prevalence and severity of prodromal psychotic symptoms in individuals with 22q11.2DS compared to controls

This study is the first to investigate the prevalence and severity of positive, negative, disorganised and general prodromal psychotic symptoms as assessed by the SIPS in individuals with 22q11.2DS compared to typically developing controls around 15 years old. As hypothesised, I found that overall there was a greater severity of psychotic symptoms in individuals with 22q11.2DS compared to controls, and that a greater proportion of individuals with 22q11.2DS met criteria for prodromal status (scoring moderate to severe) than controls.

However, I was surprised that there was no difference in proportion of individuals with 22q11.2DS or controls (26 v 14%) meeting threshold for prodromal psychotic positive symptoms, which is unexpected given that the incidence of psychotic disorder is around 30 times higher than in the general population in adulthood (Tang and Gur, 2018). Therefore, one would expect that the rate of psychotic symptoms would be at least 30 times or

possibly higher in 22q11.2DS than in controls, as not all with symptoms go on to develop full psychotic disorder.

Despite this, the proportion of 26% individuals with 22q11.2DS experiencing prodromal positive symptoms is consistent with the average across previous reports of 24.42% at 15.62 years, a very similar age to the current study (Niarchou et al., 2014, Chawner et al., 2019b, Baker and Skuse, 2005, Antshel et al., 2010, Kates et al., 2015, Antshel et al., 2017, Stoddard et al., 2010, Debbane et al., 2006, Feinstein et al., 2002, Vorstman et al., 2006, Rockers et al., 2009, Schneider et al., 2014b). Therefore, an explanation for the lack of difference may be that the rate of psychotic symptoms in controls is higher than expected. However, it is difficult to compare our findings against previous studies of individuals with 22q11.2Ds and controls. Although one previous study has reported similar rates up to 12% (Rockers et al., 2009) most others have not reported the rates of psychotic symptoms in controls (Kates et al., 2015, Antshel et al., 2017, Maeder et al., 2016) or have not statistically tested for a difference between participants with 22q11.2DS and controls (Baker and Skuse, 2005, Antshel et al., 2010). Therefore, we cannot establish to what extent our findings agree with other 22q11.2DS studies.

Additionally, sample sizes are limited in studies of 22q11.2DS, as a consequence of the relative rarity of the condition affecting 1:3000 to 1:6000 live births (McDonald-McGinn et al., 2015) and this is particularly the case for longitudinal studies. As not all children with 22q11.2DS will have a sibling who also takes part, the sample size of the control group will inevitably be smaller. Therefore, although the rate of positive psychotic symptoms was nearly twice as high in 22q11.2DS compared to controls (Odds Ratio = 1.71), there may not be optimum statistical power to detect differences (Feinstein et al., 2002).

Furthermore, reports of positive psychotic symptoms such as hallucinations and delusions in the general population at 15 years have been reported to be as high as 28% (Yung et al., 2009), with other studies reporting 14% in 11 and 12 year olds (Poulton et al., 2000, Horwood et al., 2008). It has been proposed that particular positive symptoms may index greater vulnerability for psychotic disorders, such as hallucinations, whereas others are normal personality variants, such as magical thinking, which is represented within the first

positive symptom on the SIPS of “unusual thought content and delusional ideas” (Yung et al., 2009). In the current study, when comparing severity of symptoms in prodromal individuals with 22q11.2DS and controls, participants with 22q11.2DS scored higher on mean levels of hallucinations as well as grandiosity. Given that 22q11.2DS is related to high risk of schizophrenia this could suggest that these domains are particular markers for psychosis risk, but others such as persecutory ideas, which were higher in controls, or unusual thought content, in which there was no difference with controls, may be more likely to represent aspects of personality (Yung et al., 2009). Schneider et al. (2014b) also reported in 22q11.2DS that severity of hallucinations and grandiosity discriminated non-prodromal individuals from those meeting at risk criteria. Therefore, it could be the case that although the rate of psychotic symptoms is not hugely increased in 22q11.2DS compared to controls, the content or quality of the symptoms is such that it is more likely they will progress onto psychotic disorder.

When comparing the rate of psychotic symptoms across timepoints in the ECHO study, the rate at the current timepoint (26%) is increased from the rate of 10% at the first (Niarchou et al., 2014) and 21% at the second (Chawner et al., 2019b) timepoint. A more detailed assessment was used in the current study (SIPS) than previous timepoints (child CAPA) so rates are not entirely comparable, but tentatively it could be concluded that rates of positive symptoms appear to increase slightly between 12 to 15 years, but the sharpest increase may be between 10 and 12 years (Chawner et al., 2019b). When comparing the mean age of individuals with 22q11.2DS with and without prodromal symptoms, there was no difference, further suggesting that it is not necessarily older individuals that are more likely to experience psychotic symptoms.

The proportion of 31% individuals with 22q11.2DS scoring at a moderate-severe level of negative symptoms in the current study agrees with previous research that these symptoms are more common in 22q11.2DS than positive symptoms (Schneider et al., 2012, Schneider et al., 2019, Stoddard et al., 2010). There was a higher level of prodromal negative symptoms in individuals with 22q11.2DS compared to controls, with no controls meeting criteria for moderate or above negative symptoms. This suggests that negative symptoms can potentially differentiate between 22q11.2DS and controls better than positive

symptoms. It has been previously reported that negative symptoms are more prevalent in individuals with 22q11.2DS than those with Williams Syndrome, which is also associated with developmental disabilities, suggesting a specific severe negative symptom profile in 22q11.2DS that is not explained by Intellectual Disability (ID; Mekori - Domachevsky et al. (2016)). The most prevalent negative symptom in 22q11.2DS in the current study was avolition, or lack of motivation. Previous research has found that this symptom is specifically related to daily-life outcomes in 22q11.2DS and may be a particular predictor of transition to psychosis (Schneider et al., 2012), highlighting the importance of this symptom.

Only one other study (Stoddard et al., 2010) has previously reported rates of disorganised (55%) and general (60%) symptoms in 22q11.2DS. The current study found rates of 43% and 26% respectively. A large proportion of those meeting criteria for disorganised prodromal symptoms scored on the specific symptom of “trouble with focus and attention” (22/25 individuals), which is likely reflective of the high incidence of Attention Deficit Hyperactivity Disorder (ADHD) in 22q11.2DS (Schneider et al., 2014a, Niarchou et al., 2014), which would have overlap with that symptom domain (Weisman et al., 2017). Younger individuals with 22q11.2DS were more likely to meet criteria for disorganised prodromal symptoms, which could reflect that ADHD rates are higher in younger individuals with 22q11.2DS (Schneider et al., 2014a, Chawner et al., 2019b). In regard to the lower rate of general symptoms in this study than previous studies, it could be that methodological differences played a part; the current study had a considerably larger sample size (n=58 with general symptom data versus n=20 in Stoddard et al. (2010)) as well as a younger age range.

Severity of many (10 out of 19) individual prodromal symptoms was higher in 22q11.2DS than controls highlighting the importance of also evaluating these symptoms continuously. Fewer studies have taken this approach but our findings are consistent with Esterberg et al. (2013) who found greater severity of overall positive, negative, disorganised and general symptom domains in 22q11.2DS compared to controls.

40% of individuals with positive prodromal symptoms (6/15) met criteria for a prodromal syndrome, the majority of which was APS (5/6) and 1 BIPS. This is similar to previous studies in 22q11.2DS that found a higher rate of APS than BIPS and no GRD (Rockers et al., 2009,

Stoddard et al., 2010). Furthermore, the rate of 10.7% meeting criteria for a prodromal syndrome across the whole sample aligns with previous findings of 10% (Stoddard et al., 2010).

Psychotic experiences were found to be rather transient in the current study in individuals with 22q11.2DS, with only one of seven individuals that previously experienced psychotic symptoms reporting them at the most recent timepoint. The majority that had previously experienced psychotic symptoms no longer reported them at the most recent timepoint (n=6). Previous research has also reported high levels of transient symptoms in their sample (Schneider et al., 2014b). Different possible trajectories to psychosis in 22q11.2DS have been hypothesised by Tang and Gur (2018); some individuals may consistently display increasingly severe psychotic symptoms, whereas others may follow a more episodic course. This presents an ongoing challenge for predicting risk of psychosis in individuals with 22q11.2DS (Tang and Gur, 2018).

5.5.2 Aim 2: longitudinal cognitive trajectories in individuals with 22q11.2DS and prodromal symptoms compared to those without prodromal symptoms

This study also examined whether individuals with 22q11.2DS at around age 15 years with prodromal psychotic symptoms displayed a different prior longitudinal cognitive trajectory to individuals without prodromal psychotic symptoms. As hypothesised, I found that individuals with 22q11.2DS with positive prodromal symptoms displayed lags and deficits in some cognitive domains compared to those without symptoms. Individuals with positive prodromal symptoms at mean age 15 displayed initial deficits at age 10 in FSIQ, VIQ and borderline in PIQ, which remained constant until age 15. This is consistent with other studies in 22q11.2DS (Vorstman et al., 2015, Gothelf et al., 2013, Pontillo et al., 2019, Kates et al., 2015, Schneider et al., 2014b) and the general population (Dickson et al., 2018, Reichenberg et al., 2010). The deficit was roughly 8 FSIQ points, consistent with previous reports in childhood measures of individuals that went on to develop schizophrenia (Reichenberg et al., 2010, Woodberry et al., 2008).

These findings lend support to the neurodevelopmental hypothesis of schizophrenia development, that cognitive deficits are apparent from early in life before psychotic symptoms, reflecting aberrant brain development (Vorstman et al., 2015). Schneider et al. (2014b) also hypothesised that individuals with a lower IQ from early in development may experience more difficulty coping with environmental pressures, which could confer increased risk for schizophrenia (Beaton and Simon, 2011), but further research into this theory is needed.

A deficit in sustained attention was also associated with positive prodromal symptoms. Sustained attention has been highlighted as an important risk marker for schizophrenia (Michie et al., 2000). It could be that attentional impairments increase risk of psychotic symptoms or that a deficit in both attention and psychotic symptoms are caused by a third unknown factor (Michie et al., 2000). This hypothesised third factor could represent genetic liability for inattention and psychotic symptoms, which is supported by studies finding genetic overlap (pleiotropic genetic effects) between ADHD and schizophrenia in the general population (Demontis et al., 2019, Hamshere et al., 2013).

Alternatively, it has been posited that individuals with attentional impairments may attend atypically to environmental stimuli, possibly resulting in different perceptions of the world and therefore unusual beliefs or perceptual abnormalities (Fletcher and Frith, 2008, Niarchou et al., 2019). The finding of the current study is also supported by Niarchou et al. (2019) who found that ADHD inattention symptoms at time 1 predicted psychotic symptoms at time 2 in 22q11.2DS. As demonstrated in Chapter 3, children and adolescents with 22q11.2DS and ADHD had poorer sustained attention than those without ADHD, demonstrating that the cognitive and psychiatric measures of inattention overlap.

Furthermore, the finding that attention was linked to prodromal symptoms at the third wave supports the results of the two wave ECHO findings in that attention was a predictor of psychotic symptoms, suggesting a consistently important role for this cognitive domain in psychosis risk (Chawner et al., 2019b). Chawner et al. (2019b) did not find links with IQ, but suggested that changes in such a global measure of intelligence may become apparent later in development after changes in specific cognitive domains, which appears to be borne out

in this third wave. Furthermore, predictors of psychotic symptoms have changed over waves in previous longitudinal studies (Antshel et al., 2017, Antshel et al., 2010, Kates et al., 2015), reinforcing the importance of taking a developmental perspective in assessing associations between cognition and psychosis.

There were also lags present in IQ subtests vocabulary, block design and matrix reasoning in those with positive prodromal symptoms compared to without, which suggests that there is slower development in these domains in those with prodromal symptoms. Reichenberg et al. (2010) also found lags on the block design subtest in their sample of children that went on to develop schizophrenia. This suggests two processes that are linked to psychosis risk; that cognitive impairments may precede psychotic symptoms but also that cognitive impairments may increase as the onset of psychotic symptoms approaches, generally in late adolescence (Antshel et al., 2017).

Less studied has been the relationship between negative symptoms of psychosis and cognition in 22q11.2DS, an area highlighted for study (Pontillo et al., 2019). Limited previous research found that there was a lag over ages 6-26 years in working memory in individuals with negative symptoms compared to those without (Maeder et al., 2016). However, the current study found that working memory performance was better in individuals with negative symptoms compared to those without; although this difference was only significant when controlling for previously reported psychotic experiences and did not survive multiple comparison correction.

When comparing working memory trajectories between individuals with and without previous psychotic experiences it appeared that individuals with transient symptoms (no symptoms at the current timepoint, but some previously reported symptoms) initially performed worse than other groups but made the most improvement to perform better than other groups at older age. In contrast, the individuals with emerging symptoms initially performed the best but did not progress much over time. This could suggest that working memory performance is impacted by experiencing psychotic symptoms. However, due to the small sample sizes in the groups, e.g. only 5 individuals in the transient group, further research with larger sample sizes would be needed to investigate this further.

Furthermore, it was also unexpected that planning ability was initially poorer in individuals without negative symptoms, then converged with those with negative symptoms around age 17. It is unclear why this might be the case but demonstrates that this may also be a cognitive domain in which different trajectories can be observed in those with and without prodromal negative symptoms.

5.5.3 Strengths and Limitations

This study provided rich data on the distribution of prodromal psychotic symptoms in a high-risk group for schizophrenia, individuals with 22q11.2DS, compared to typically developing controls. It also prospectively investigated associations between cognition and psychosis risk in 22q11.2DS in a developmentally relevant group around age 15 years, over three time points with a wide range of cognitive tasks. However, some limitations should be noted.

The SIPS was not specifically developed for populations with ID, which can present some challenges when conducting and interpreting it with individuals with 22q11.2DS, as discussed in Tang et al. (2014b). Specifically, some of the questions are quite abstract or complex, and at times it was necessary to re-word questions or divide questions into smaller chunks to enable understanding (Tang et al., 2014b). In this study, in 3 cases it was not possible to administer the positive SIPS to the individual with 22q11.2DS due to lack of comprehension, which may mean these findings are not fully representative of individuals with 22q11.2DS and more severe cognitive deficits. Furthermore, Moss et al. (1996) reported that it may be difficult to detect positive psychotic symptoms except hallucinations in individuals with ID. In the current study hallucinations were the most frequently noted positive symptom at a prodromal level in 22q11.2DS, suggesting that it may have been more difficult to determine the presence of other positive symptoms in individuals with 22q11.2DS compared to controls. This could have led to an underestimate of psychotic symptoms in individuals with 22q11.2DS which would have affected both the comparison of prevalence and severity of psychotic symptoms and analysis of cognitive trajectories.

Additionally, the SIPS was developed to measure change in prodromal symptoms in help-seeking populations, and therefore may be less sensitive to individuals who are experiencing psychotic symptoms but not at a help-seeking level (Zammit et al., 2013). Nonetheless, the SIPS has been globally conducted with individuals with 22q11.2DS at many different co-operating sites within the International Brain and Behaviour in 22q11.2DS Consortium (IBBC), meaning that these findings can be compared to large, multi-site investigations of prodromal symptoms in 22q11.2DS (Gur et al., 2017), as well as other high-risk samples such as individuals with family history of psychosis (Niarchou et al., 2018).

It must also be noted that caution should be taken if applying these results in the context of the high-risk prodromal stage of psychosis development to clinical psychotic disorder. Schneider et al. (2016) found that the rate of conversion from a prodromal syndrome identified by the SIPS to psychosis in individuals with 22q11.2DS was 27.3% after 32 months, indicating that many individuals with a prodromal syndrome do not go on to develop psychosis in this fairly wide timeframe. Therefore, findings here may differ from those in psychosis.

Finally, as detailed in Chapter 2, individuals with psychotic experiences reported at wave 1 or 2 were more likely to drop out of the longitudinal study. It could be hypothesised that these individuals would have been more likely to have psychotic symptoms at later timepoints and therefore estimates of associations between cognition and psychotic symptoms are likely to be conservative; however, as demonstrated psychotic experiences may be fairly transient in 22q11.2DS and so it cannot be certain that those that dropped out would have experienced persistent psychotic experiences that would have influenced findings.

5.5.4 Conclusions

This study found that at age 15 around a quarter of individuals with 22q11.2DS experience positive prodromal symptoms, and 31% negative prodromal symptoms. Furthermore, there appear to be deficits in IQ and attention at around 10 years of age in those that later experience positive prodromal symptoms at age 15. There may also be specific lags in

measures of vocabulary, non-verbal and spatial reasoning over this period. This stage of development is essential for cognitive development and could have consequences for attainment in school, given that the IQ deficit is around 8 points, or half a standard deviation.

These findings support the neurodevelopmental hypothesis of schizophrenia, that there is an early disruption to development that could affect both cognitive and psychosis development. There is no evidence for deterioration in cognition linked to prodromal symptoms, which therefore does not support a neurodegenerative mechanism. Additionally, there is support for increasing cognitive impairment in some domains over adolescence in individuals that later experience psychotic symptoms.

5.5.5 Future work

When compared with other studies, it is apparent how impactful age is on the associations found and that it is important to take a developmental perspective. Therefore, following up this sample at a fourth timepoint to investigate associations between psychosis risk at around age 18 and prospective cognitive trajectories would be invaluable in determining how these mechanisms can change over time.

I discussed how individuals with 22q11.2DS and controls appear to experience similar rates of positive psychotic symptoms but individuals with 22q11.2DS are much more likely to experience psychotic disorder. One explanation for this could be that the content or quality of psychotic symptoms differs between controls and 22q11.2DS in such a way that conversion to psychosis is more likely in 22q11.2DS. To investigate this further qualitative analysis of accounts of psychotic experiences with longitudinal follow up to track who develops psychosis could give an insight into the possible psychotic content that poses a greater risk when experienced.

One domain that I could not examine in the current study but has previously been linked to psychosis is social cognition. Social cognition is defined as mechanisms that underlie social interaction and help us navigate the social world, such as emotion recognition in others and

theory of mind, which refers to understanding what another is thinking, planning or feeling (Norkett et al., 2017). A meta-analysis concluded that social cognition has been impaired in individuals at clinical high risk for schizophrenia in the general population (Lee et al., 2015) but so far there has been limited research in 22q11.2DS of the relationship between social cognition and psychosis, with one cross sectional study finding that theory of mind was a stronger predictor of positive psychotic symptoms than non-social cognitive measures (Jalbrzikowski et al., 2012). Replication of these results and an examination from a longitudinal perspective would be a next step to understand the relationship of social cognition to psychosis in 22q11.2DS.

As discussed in the limitations, understanding on the SIPS may have been a barrier to some individuals with 22q11.2DS taking part and so in the future measures should be developed or adapted to those with learning difficulties to enable detection of psychotic experiences in those with more severe cognitive impairment. Additionally, including a comparison group of individuals with Idiopathic Intellectual Disability (IID) in this analysis could enable understanding of the general prevalence of such symptoms in those with learning difficulties and which maybe specific to 22q11.2DS, which is more strongly linked to psychosis. Furthermore, including comparison groups of individuals at idiopathic high risk for schizophrenia as Niarchou et al. (2018) and Esterberg et al. (2013) have done would enable understanding of 22q11.2DS specific relationships between cognition and psychosis.

6 General discussion

6.1 Overview

High rates of cognitive and psychological difficulties have been reported in 22q11.2 Deletion Syndrome (22q11.2DS). However, it is unclear how these interact and how they may progress over the lifespan. This thesis sought to examine cognition over development in 22q11.2DS and its relation to psychopathology through both cross-sectional and longitudinal methods.

Chapter 3 was a large collaborative effort between the Experiences of Children with cOpy Number Variants (ECHO) study cohort at Cardiff University and predominantly adult cohorts from the Netherlands and Belgium, which resulted in a large sample with a wide age range of participants from 6 to 60 years old. I found that there was a high prevalence of ADHD, ASD and anxiety disorder in children and adolescents with 22q11.2DS, and psychotic disorders in adults, as previously reported (Schneider et al., 2014a), demonstrating that our sample is representative of the wider 22q11.2DS population. Furthermore, IQ was around 30 points lower in 22q11.2DS than in controls, and the specific cognitive domains of working memory, sustained attention and processing speed were approximately 1-2 standard deviations lower in 22q11.2DS than controls, also as previously reported (Gur et al., 2014, Gothelf et al., 2013).

Adolescents with 22q11.2DS who had probable ASD displayed greater impairments in working memory, sustained attention and processing speed than children with 22q11.2DS with probable ASD. There was a greater impairment in sustained attention in children and adolescents with 22q11.2DS and ADHD than those with the deletion but without ADHD. Adults with 22q11.2DS with psychotic disorder displayed greater deficits in sustained attention and IQ than those with the deletion without psychotic disorder. This demonstrated that there may be associations between cognitive and psychiatric functioning in individuals with 22q11.2DS.

When comparing cognitive performance across developmental stages, there were domain-specific patterns. Adults displayed greater deficits in working memory and IQ than children and adolescents. Children had a greater deficit in processing speed than adults. The magnitude of sustained attention was similar across developmental stages.

Chapter 4 examined the difference in cognitive trajectories over three timepoints between adolescents with 22q11.2DS and siblings without the deletion solely within the ECHO study cohort. Importantly, I could examine change in raw scores to distinguish between different models of development, i.e. developmental deficit, lag, deterioration and maturation.

On a group level, raw performance scores increased over time in all domains, suggesting no evidence of deterioration, or loss of previous ability over time. Most domains (verbal IQ, verbal IQ subtest similarities, performance IQ subtest matrix reasoning, set shifting, processing speed, sustained attention and planning) showed evidence of deficits, i.e. a greater impairment in performance in individuals with 22q11.2DS compared to controls that is stable at the same magnitude over time.

As well as initial deficits, other domains showed evidence of lags, where raw scores did not progress over time in individuals with 22q11.2DS at the same rate as controls (spatial working memory, full scale IQ, performance IQ, verbal IQ subtest vocabulary, performance IQ subtest block design). There was evidence of maturation in visual search, a match to sample test, where individuals with 22q11.2DS initially displayed a deficit in this domain but caught up with controls over time.

On an individual level, there was a small subset of adolescents with 22q11.2DS that displayed reliable deterioration in scores from the first to third timepoints, but there was a similar proportion of control adolescents displaying similar deterioration. This suggests that deterioration is not specific to 22q11.2DS but rather is a feature that can be observed in adolescents more generally, most likely due to major changes in the brain during this developmental stage (Ramsden et al., 2011).

Chapter 5 investigated the profile of prodromal psychotic symptoms in adolescents with 22q11.2DS at timepoint 3, where mean age was 15.5 years (SD=2.4) compared to sibling controls and found higher prevalence and severity of overall combined positive, negative, disorganised and general prodromal symptoms in 22q11.2DS. However, there were domain specific patterns, with no difference between 22q11.2DS and controls in prevalence of overall positive symptoms (26% versus 14%, $p=0.236$), likely due to a higher than expected rate of symptoms in controls. The proportion of negative symptoms in 22q11.2DS was higher than controls (31% versus 0%, $p<0.001$), suggesting these symptoms can differentiate effectively between groups.

I also examined whether there was a difference in longitudinal cognitive trajectories between individuals with 22q11.2DS who experienced prodromal positive or negative psychotic symptoms at timepoint 3, when controlling for presence of psychotic experiences at previous timepoints. Those that experienced positive prodromal symptoms at mean age 15.5 displayed deficits in full scale IQ, verbal IQ, performance IQ and sustained attention at timepoint 1 (mean age= 10.2 years) which were stable over time. This group furthermore also showed lags in verbal IQ subtest vocabulary and performance IQ subtests block design and matrix reasoning. This suggests that two processes, stable deficits and increasingly worse performance (lags), may be associated with psychosis development.

Individuals who experienced negative symptoms at mean age 15.5 appeared to perform better at age 10.2 years on working memory and planning cognitive domains. In the case of working memory, when not controlling for psychotic experiences at a previous timepoint, there was no difference between those with and without negative symptoms, suggesting that there are different trajectories in those with transient, enduring or emerging psychotic experiences.

6.2 Bringing results together

6.2.1 Converging cross-sectional and longitudinal findings

In Chapter 3 I found that there was a greater impairment in working memory and IQ in adults than children and adolescents, which could have represented a deterioration in previous abilities or a lag, where older individuals were not progressing at the same rate as previously, but strong conclusions could not be drawn due to the cross-sectional methodology. When examining these cognitive areas longitudinally over three timepoints in Chapter 4, I found that there were lags in working memory and IQ over time in individuals with 22q11.2DS 6-20 years old compared to controls, suggesting that this may be the underlying mechanism behind poorer performance at older ages, rather than deterioration. The previous longitudinal investigation across two timepoints in the ECHO study by Chawner et al. (2017) did not find lags in IQ or working memory, but rather deficits, suggesting that lags only become visible when there is a wider age range including older adolescents and young adults.

Furthermore, greater impairments in processing speed in children than adults were found cross-sectionally in Chapter 3, and when longitudinally examining differences between children with 22q11.2DS and controls at each wave, there was a difference in processing speed between groups at the first and second but not the third wave, suggesting that there is an improvement over time in 22q11.2DS. Both cross-sectional and longitudinal findings therefore indicate that processing speed is impaired to a greater extent in childhood than later in development. Additionally, sustained attention presented as a stable deficit longitudinally, which is in line with the cross-sectional findings that this was present at the same magnitude across developmental stages.

Given that the cross-sectional study only included the first wave of data collection from children and adolescents, and none of the adults from the cross-sectional study were part of the longitudinal assessment, this suggests that these patterns are robust and valid across different samples.

6.2.2 Attention as a transdiagnostic deficit

Deficits in attention have been hypothesised to be prevalent across different psychiatric disorders in 22q11.2DS (Baker and Vorstman, 2012), which is supported by the current

findings of Chapter 3 and 5 that attention problems were associated with ADHD, ASD, psychotic disorder and prodromal psychotic experiences. This supports the hypothesis that attention impairments are apparent at both at the clinical and high-risk stages of psychosis development (Niarchou et al., 2018).

Broadly, attention relates to our ability to focus on particular important or salient information, which is essential in a world where so much stimulation and information is constantly present (Racer and Dishion, 2012). Attention is composed of subcomponents; for example, attention can be demanded from e.g. hearing our name called, or deliberately applied to a task at hand e.g. writing a thesis (Racer and Dishion, 2012)! There are different theories pertaining to the specific subcomponents of attention, but an influential model has been that of Berger and Posner (2000) who proposed three main subcomponents of attention; alerting, orienting and executive attention. The alerting system contributes to initiating and maintaining an alert state; the orienting system relates to engaging and disengaging on information, and the executive system enables top-down focus on goal-directed activities (Berger and Posner, 2000). Racer and Dishion (2012) propose that these systems ideally work together harmoniously to maintain concentration, yet respond to new information when needed, but an imbalance between attentional systems can impact on other cognitive and emotional processes, which could then contribute to a range of psychopathology.

The attention task in this thesis tapped into sustained attention; this would fall into the category of an executive attention task. Sustained attention is defined as being able to readily maintain attention to a task where the target event occurs occasionally and unpredictably (Christakou et al., 2013). The specific task, the RVP, is conceptualised as a modified version of the widely-used Connors Continuous Performance Task (Coull et al., 1996) and in the CANTAB version participants must respond to a target sequence of digits over a few minutes of a continuous pseudo-random presentation of digits. The task predominantly requires sustained attention to complete, but there is also the working memory load of holding the target sequence in mind while performing the task (Coull et al., 1996). Functional brain imaging studies have found evidence for two underlying neural systems when individuals are engaged in the RVP task; a right fronto-parietal network which

is associated with sustained attention and left frontal activation associated with working memory (Coull et al., 1996, Lawrence et al., 2003).

Mansell et al. (2008) hypothesise that attentional imbalance can contribute to a range of psychiatric disorders, transdiagnostically, through a mechanism whereby individuals attend more greatly to experiences which align with concerns they have. This could explain why although psychiatric disorders present so differently, they may share cognitive commonalities such as poorer attention, as well as explaining the high rate of comorbidity across psychiatric disorders (Mansell et al., 2008). Beck and Haigh (2014) propose the Generic Cognitive Model (GCM), whereby genetic influences may affect physiological brain structures, which contribute to biases in attention and memory, leading to maladaptive cognitive schemas which can affect behaviour and present as psychological disorders. The tendency to interpret information in this way can be affected by environmental factors at any point.

The GCM can be applied to the current findings, whereby the genetic influence of 22q11.2DS may affect neural pathways, which could lead to biases in attention and memory. The following step, formation of maladaptive cognitive schemas which can affect behaviour, is less well characterised. One hypothesis could be that across psychopathology such as ASD, ADHD and psychotic disorders, poorer sustained attention could lead to incorrect interpretation of information which lead to maladaptive schemas and behaviours. Environmental influences would also contribute to this pathway. This is not to say cognitive processes can fully explain any disorder but rather that they may contribute to presentation and be a commonality across disorders (Mansell et al., 2008). This is supported by findings that attentional training is a successful transdiagnostic treatment for different psychopathology (Racer and Dishion, 2012).

Interestingly, other findings from our group have linked sustained attention to motor coordination ability (Cunningham et al., 2018) and restless sleep (Moulding et al., 2019), suggesting that impairment in this cognitive domain is prevalent across different markers of disrupted neurodevelopment. This suggests that attention may be a transdiagnostic marker of neurodevelopmental problems, cutting across different disorders.

6.2.3 Cognitive trajectories

Previous studies have reported a cognitive decline in individuals with 22q11.2DS and in those with psychotic symptoms (Vorstman et al., 2015, Gothelf et al., 2013, Duijff et al., 2012). This was generally due to age-standardised cognitive scores appearing to decrease over time in individuals with 22q11.2DS compared to controls, or in those with 22q11.2DS and psychotic symptoms compared to those without. This implied a decrease in ability over time and led some authors to suggest there was deterioration in at least a subset of individuals with 22q11.2DS. However, in this thesis I was able to examine raw scores longitudinally, with findings in Chapter 4 and 5 indicating that the underlying mechanism behind what appeared to be a “decline” in standardised scores was generally either a deficit or lag, rather than deterioration.

6.3 Implications

6.3.1 Dimensional measures of psychopathology

The finding that impairments in attention are linked to multiple mental health presentations in 22q11.2DS supports the concept of a common “attention-executive” symptom domain in 22q11.2DS (Baker and Vorstman, 2012). Furthermore, there was persistence of the link between attention problems and psychiatric disorders over different developmental stages (children, adolescents and adults), and there was evidence that early impairment in attention predicted later prodromal psychotic symptoms. Traditional diagnostic systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) may be unable to capture such cross-disorder commonalities. Therefore, developing our knowledge of symptom domains in 22q11.2DS could be the key to understanding the variable phenotype of 22q11.2DS.

Other proposed common symptom domains in 22q11.2DS are social–cognitive deficits, anxiety–affective dysregulation, and psychotic phenomena (Baker and Vorstman, 2012).

Psychotic phenomena in the current research were captured with the Structured Interview for Prodromal Symptoms (SIPS), where as well as categorising individuals as having prodromal psychotic symptoms or not according to whether they had experienced a moderate to severe symptom, it was possible to explore the severity of symptoms. This approach was more sensitive to differences between individuals with 22q11.2DS and controls than categorising according to the threshold of experiencing a moderate to severe symptom. Furthermore, psychotic symptoms were rated without regard to other diagnoses which could potentially explain them, resulting in a cross-diagnostic picture of psychotic phenomena in 22q11.2DS.

6.3.2 Control groups and reliable change

Another implication of this work is the importance of a control group and measuring reliable change when researching 22q11.2DS. Some of the findings, for instance that a subset of individuals with 22q11.2DS display a deterioration in cognition, would have suggested this is specific to 22q11.2DS without the presence of a control group in which the same pattern in a subset was observed. Similarly, when assessing cognitive deterioration, it is important to consider measurement error and construct indices of reliable changes against which to measure a drop in raw scores.

6.3.3 Schizophrenia risk and brain development

In the Introduction (section 1.7.3, see Figure 1.2), I discussed that there could be competing models which could fit the observed relationship between childhood and adolescence cognitive deficits and later schizophrenia risk; deficits, lags and deterioration, and that determining which of these models best explains the data found in this thesis could give insight into underlying mechanisms. I predicted in Chapter 5 that deficits and lags would most likely be observed over childhood and adolescence in individuals who later displayed prodromal psychotic symptoms, which was supported by trajectories in some cognitive domains.

The finding that there were deficits and lags in cognitive domains at timepoint one (mean age 10.2 years) in individuals who later experienced prodromal psychotic symptoms at age 15.5 years points to two processes contributing to schizophrenia risk. The first, an initial impairment which remains stable over time, would support the neurodevelopmental hypothesis of schizophrenia, whereby there is an early disruption to neurodevelopment which increases risk of schizophrenia and also of cognitive, social or motor deficits prior to onset of psychotic symptoms (Howes and Murray, 2014). I found this to be the case for full scale IQ, verbal IQ, performance IQ and sustained attention.

The second appears to be the widening gap in cognitive performance between those with and without prodromal symptoms over adolescence. I found this to be the case for verbal IQ subtest vocabulary and performance IQ subtests block design and matrix reasoning. This could implicate abnormal brain processes such as increased synaptic pruning (Boksa, 2012). This refers to excessive or inappropriate elimination of synapses during adolescence and early adulthood which has been associated with schizophrenia (Sekar et al., 2016). Environmental risk factors may also increase in this time period that could affect cognition (see section 6.5.3). As predicted, I did not find evidence for deterioration in individuals who later experienced prodromal symptoms, suggesting that there is not a neurodegenerative process linked to schizophrenia risk or an absolute loss of cognitive abilities.

It is important to note that the trajectory of many cognitive domains were the same between individuals with 22q11.2DS with or without prodromal psychotic symptoms (working memory, visual search, processing speed, planning and perseverative errors). This contrasts with previous research that has found differing working memory trajectories between those with or without psychosis or at high risk for psychosis in the general population (Dickson et al., 2018, Reichenberg et al., 2010) and has also been reported in 22q11.2DS (Antshel et al., 2010). Differing trajectories of perseverative errors have also been reported in individuals with 22q11.2DS and prodromal symptoms compared to those without (Antshel et al., 2017, Pontillo et al., 2019). Although initially I was surprised that I did not see these associations in my sample, as highlighted by previous longitudinal studies in 22q11.2DS associations between cognition and psychosis tend to vary across development and change over timepoints, and indeed working memory was linked to

psychotic symptoms in the two-timepoint ECHO sample, suggesting that these relationships are dynamic and possibly a response to changes in the brain over adolescence rather than a static constant. As the sample described in this thesis is relatively young and therefore at an early risk stage, it is entirely possible that other cognitive links will be visible at older ages when schizophrenia will be more common.

6.4 Strengths and Limitations

6.4.1 Sample size

Small sample sizes are a consistent issue in research on individuals with 22q11.2DS, as the syndrome is relatively rare, affecting 1:3000 to 1:6000 live births (McDonald-McGinn et al., 2015). Therefore, it is a concern that adequate power is reached for statistical testing. In Chapter 3, I sought to gain a large sample through collaboration with two European sites to maximise sample size and investigate development over a wider age range, including adults. There is a comparative dearth of studies of adults with 22q11.2DS. The ECHO study has well-established links with many other research groups investigating 22q11.2DS. Sharing resources was possible because collaboration led to the use of the same cognitive assessment battery at all three sites.

Need for larger samples in 22q11.2DS research has been recognised and has led to the International 22q11.2 Deletion Syndrome Brain Behaviour Consortium (IBBC) which has phenotypic and genotypic data on around 2000 individuals with 22q11.2DS (Gur et al., 2017). However, because this initiative brought together already collected phenotypic data (in addition to whole genome sequencing data), there were still site differences in assessment methodology; for example, rates of OCD and ADHD in individuals with 22q11.2DS have varied significantly across sites in previous multi-site studies of 22q11.2DS (Gothelf et al., 2013), possibly due to different clinical assessments being used. There have been efforts to use the same instruments throughout the IBBC where possible, such as the SIPS, and joint training sessions to standardise administration across sites to reduce concern over combining samples (Weisman et al., 2017). Additionally, case summaries of individuals

with 22q11.2DS with a diagnosis of psychosis that were included in IBBC were rated by several clinical experts to ensure the same criteria was applied across sites (Gur et al., 2017).

Alongside my PhD I have been involved with the European-wide project Maximising Impact of research in NeuroDevelopmental DisorderS (MINDDS) to standardise phenotyping of individuals with Copy Number Variants (CNV) such as 22q11.2DS across Europe to facilitate collaborations and data sharing. Efforts like this are essential in boosting sample sizes to deliver robust and valid research findings.

6.4.2 Ascertainment bias

It is possible that individuals with 22q11.2DS that participate in research may have a more severe phenotype than those who do not participant due to greater motivation by them or their families to understand the condition through taking part (Tang et al., 2014a). This is supported by a population study of individuals with 22q11.2DS in Denmark (i.e. every individual with 22q11.2DS in the country was in the study) that found that the rate of hospital admissions or outpatient treatment for schizophrenia and other disorders like ADHD was lower than previously reported in case-control 22q11.2DS research (for schizophrenia, around a 15x increased risk rather than 25x) suggesting that the true phenotype of 22q11.2DS may be less affected (Hoeffding et al., 2017). However, it has previously been reported that mental health problems are undertreated in 22q11.2DS, and therefore rates of help seeking are likely to underrepresent the prevalence of these issues (Tang et al., 2014a). Studies with varying ascertainment methods are essential for understanding the variable phenotype of 22q11.2DS.

6.4.3 Controlling for IQ

Throughout this thesis I have not controlled for IQ when examining any associations. It has been proposed that IQ is inappropriate as a covariate in studies of conditions like 22q11.2DS that are associated with neurodevelopmental disorders because there has never been a

period of “normal” development; therefore, the IQ score postdates the condition and is confounded with the condition (Dennis et al., 2009).

It has been argued that when the potential covariate is linked to the disorder, as lower IQ is linked to 22q11.2DS, it becomes meaningless to ‘adjust’ for it (Dennis et al., 2009). To control for IQ would be controlling out a large part of the 22q11.2DS phenotype and therefore would not add to our understanding of 22q11.2DS as a whole. It would make interpretation of what is going on more difficult as 22q11.2DS without lower IQ is not reflective of reality and is unrepresentative of the population of individuals with 22q11.2DS.

6.4.4 Specificity of findings

It could be argued that comparing against a high IQ sibling control group could lead to difficulty in interpreting findings from specific cognitive deficits such as working memory and sustained attention, which are likely to be correlated with IQ but possibly to different extents. Therefore, it could be that results are reflecting the amount to which each test is correlated with IQ which is different in the 22q11.2DS and control groups rather than pure differences in specific cognitive domains.

22q11.2DS investigators have discussed the difficulties of comparing against an appropriate control group; de Sonnevile et al. (2018) did not include a control group, and opined that “matching on age, intelligence, developmental age, or characteristics that make the 22q11DS group unique would likely introduce other problems”. Other studies have taken the step of including individuals with Developmental Delay (DD) as a control group (Gur et al., 2014), to determine whether cognitive deficits are specific to 22q11.2DS or nonspecific associations of DD. Gur et al. (2014) found that while speed of performance was similar in 22q11.2DS and DD, accuracy of performance was generally specifically impaired in 22q11.2DS, especially in social cognition, suggesting specific deficits in this area in 22q11.2DS which support neuroimaging findings suggesting brain differences in face processing areas in 22q11.2DS (Andersson et al., 2008), which have also been reported in schizophrenia (Pinkham et al., 2011). Therefore, including a DD control group can give

insight into cognitive processes which may overlap with those of psychiatric disorders over and above general learning difficulties.

6.5 Future directions

6.5.1 Early development

Future directions stretch out both forwards, and backwards, into the development of individuals with 22q11.2DS. I found cognitive deficits at 10 years old in those who later experience psychotic symptoms at age 15, which raises the question of when these deficits first emerge, which would provide insights into possible underlying mechanisms such as brain development. Therefore, more research on infants and children with 22q11.2DS is needed, which could follow them into adulthood to gain insight into very early developmental markers of schizophrenia risk.

6.5.2 Later development

In this thesis, the average age at the most recent timepoint was 15 years old, at which psychotic symptoms were fairly common but psychotic disorder was not. Looking forward, it is important to keep following up with established cohorts to determine which individuals with 22q11.2DS develop psychotic disorder, which is more likely to be diagnosed from around age 18 onwards (Tang and Gur, 2018). It has been reported that many individuals with 22q11.2DS may experience psychotic symptoms which do not convert to disorder (Schneider et al., 2016) or may experience psychotic disorder without a prodromal phase, demonstrating that more research is needed to understand the high risk phases in order to hone predictive power.

Furthermore, 22q11.2DS has been found to increase the risk of Parkinson's Disease (PD), specifically early onset with onset before 45 years (Mok et al., 2016). This demonstrates the importance of research in adults with 22q11.2DS and understanding early indicators of PD (Mok et al., 2016).

6.5.3 Environmental factors

The vulnerability-stress model of schizophrenia suggests that exposure to environmental stressors in those with biological vulnerabilities, such as a genetic predisposition, increases risk of schizophrenia (Mayo et al., 2019). However, environmental factors have not been much studied in 22q11.2DS, despite the high risk of schizophrenia in adulthood (Beaton and Simon, 2011). Most individuals with 22q11.2DS experience medical problems from birth, resulting in early and possibly also follow-up surgeries, as well as learning and social difficulties which may isolate them from peers and affect self-esteem (Mayo et al., 2019). Furthermore, individuals with 22q11.2DS may be at higher risk of bullying and victimisation (Mayo et al., 2019). Factors such as these have been related to schizophrenia development in the general population (Varese et al., 2012). Therefore, it is of great importance to investigate how adverse experiences such as these contribute to mental health outcomes in 22q11.2DS.

Bennett et al. (2019) found that childhood social isolation was linked to two or more psychotic experiences in early adulthood in the general population. There are multiple theoretic explanations for the link between lack of social interaction and psychosis, such as increased anxiety and depression which in turn increase psychotic symptoms, increased negative perception of self and others which could exacerbate paranoid thoughts, or the intriguing “anthropomorphism” where individuals are more likely to attribute human elements such as voices to nonhuman stimuli or the absence of stimuli (Michalska da Rocha et al., 2018). However, it is also possible that psychotic symptoms may come first and lead to social isolation.

As individuals with 22q11.2DS are reported to experience greater social difficulties than typically developing peers, such as social immaturity, withdrawal and shyness (Olszewski et al., 2017), it would make sense to investigate the link between social adversity and psychosis in 22q11.2DS. For example, measuring anxiety and depression, paranoid thoughts and anthropomorphism in individuals with 22q11.2DS and linking this to prevalence of

psychotic symptoms could distinguish between these models of the relationship between social adversity and psychosis.

Furthermore, examining the relationship between stressful life events and psychotic symptoms in 22q11.2DS would be interesting, as findings from a study of adolescents with Schizotypal Personality Disorder (SPD) found that they experienced a perceived greater amount of stressful life events on a daily basis than controls and that this was associated with prodromal psychotic symptoms (Tessner et al., 2009). This could suggest that perception of stress is an important mediating factor in the relationship between stressful life events and psychotic symptoms.

One study found that coping mechanisms mediated the relationship between stressful life events and psychotic symptoms in 22q11.2DS, suggesting that enhancing positive coping and reducing negative strategies could be a successful intervention in individuals with 22q11.2DS (Armando et al., 2018). More research is required to examine what form such an intervention could take and effectiveness in 22q11.2DS.

Taking inspiration from idiopathic schizophrenia studies, a randomised controlled trial showed effectiveness of a coping skills oriented treatment programme compared to a general supported therapy programme in reducing psychotic symptoms as well as depression and anxiety after two years follow-up (Schaub et al., 2016). The coping programme was based on the stress-vulnerability model and highlighted the links between biological and environmental factors through psychoeducation, as well as employing cognitive behavioural therapy principles to teach coping strategies and build confidence (Schaub et al., 2016). I believe this could be a strong basis for a study to examine the effectiveness of an adapted version which is tailored to the particular challenges of 22q11.2DS, such as learning difficulties, social communication difficulties and physical health concerns, in reducing psychotic symptoms.

6.5.4 Dimensional measures of psychopathology

Given that the complex and varied neuropsychiatric phenotype in 22q11.2DS is not well explained by current diagnostic systems (Baker and Vorstman, 2012), future research could approach psychopathology and cognitive features from a dimensional framework such as Research Domain Criteria (RDoC; Insel et al. (2010)), which may reveal core phenotypic characteristics in 22q11.2DS that may uncover new associations with biological or genetic components.

6.5.5 Care and outcomes for individuals with 22q11.2DS

The findings of this thesis could influence provision of care and outcomes for individuals with 22q11.2DS through three main messages that emerged. Firstly, the finding that despite an apparently “declining” IQ when looking at standardised measures, when viewing the raw scores it is clear that individuals with 22q11.2DS do continue to improve over time.

Therefore, when assessing change in cognitive ability of individual with 22q11.2DS, I believe that this thesis should guide professionals to monitor raw scores rather than standardised scores as a more indicative guide to change, and if using standardised scores to explain to the individuals and their families or caregivers that scores may appear to worsen but this does not mean the individual is losing previously gained ability. Furthermore, professionals should be aware that small fluctuations in cognitive test scores should be interpreted in the context of error and may not represent true change.

Secondly, the finding that presence of prodromal symptoms was very transient over ages 10-15 years old in this sample suggests that there may not be need for panic if these symptoms arise at this age, as it is common for these symptoms to ebb and flow. Indeed, I found that these symptoms are just about as common in typically developing youth. That is not to say that these symptoms should not be taken seriously; I feel that they should definitely be monitored and explored but it is important for the individual, families or caregivers and professionals to be aware that these symptoms may pass over development.

I also believe it is important to say that although there were links between cognitive trajectories and psychotic symptoms, this is not at the stage where cognitive functioning or change in functioning could be used to predict presence of psychotic symptoms. Rather I

think posing the question of the relationship between cognition and psychosis is useful for investigating possible underlying mechanisms of psychosis rather than prediction at present.

6.6 Conclusions

This thesis contributes to knowledge of the complex neurocognitive phenotype in 22q11.2DS and how this is related to psychopathology through cross-sectional and longitudinal methods, which converge on key findings. Impairments in particular cognitive domains at different developmental stages were highlighted from childhood to adulthood, demonstrating the importance of taking a developmental lens in assessing cognition over the lifespan. Impairment in attention was related to multiple domains of psychopathology, implicating this cognitive domain as a transdiagnostic symptom in 22q11.2DS. Furthermore, pre-existing and co-occurring cognitive changes linked to psychosis development were identified.

These findings corroborate previous work and build on it to yield new insights into 22q11.2DS. Collaboration and data sharing are essential to build large samples where associations can be tested robustly. Hopefully this thesis and future work will help in developing therapeutic targets for individuals with 22q11.2DS and those in the general population experiencing mental illness.

7. References

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