THE DEVELOPMENTAL COGNITIVE TRAJECTORY OF THE 22Q11.2 DELETION.

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ABSTRACT

Background: The 22q11.2 deletion (22qDS) is a microdeletion syndrome which commonly leads to an uneven profile of Learning difficulties (LD), with superior verbal compared to nonverbal intellectual and memory functions in children and adolescents. However, in adult samples these differences reduce. There are two accounts of the reduction in the verbal-nonverbal discrepancy with age. The dominant hypothesis is that normative measures of verbal intelligence decline and so approximate nonverbal intelligence. The other is that normative nonverbal intelligence increases while verbal intelligence remains stable. Few studies have investigated this longitudinally and none with a UK sample.

Aim: The aim was to examine longitudinally the pattern of developmental cognitive changes in verbal and nonverbal intellectual and memory functions.

Method: Twenty-four participants with 22qDS, who were previously cognitively assessed between 2004- 2008 were re-examined in 2011. Intellectual, memory and executive functions were assessed.

Results: Verbal and nonverbal intellectual functions were in the below average range and verbal was significantly superior to nonverbal intelligence at initial assessment. This discrepancy disappeared at follow-up as expected. Contrary to the dominant hypothesis, no cognitive scores declined with age. Nonverbal intellectual functioning improved to approximate the original level of verbal functioning, which remained stable. There were no verbal-nonverbal discrepancies in memory, but there were unexpected gender effects.

Conclusion: This is the first longitudinal study to show increasing nonverbal and stable verbal functioning with age in a UK 22qDS sample. Factors which could potentially account for this unexpected pattern are considered along with bias, confounding and other methodological issues. The potential clinical and educational implications of the findings are discussed. Further studies with large samples are required to examine in more detail the main findings.

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1.0 INTRODUCTION

1.1 OVERVIEW

The 22q11.2 deletion (22qDS) is a microdeletion syndrome which presents as a neurodevelopmental disorder with physical and learning difficulties (LD). A phenotypic cognitive profile of inferior nonverbal compared to verbal functions is widely reported in children with the syndrome but not in adults. This suggests differential atypical cognitive development, but there are very few exploratory studies. The key question on which this thesis focuses is what happens to the discrepancy between verbal and nonverbal cognitive functions as individuals with 22qDS grow up. Gender effects are also examined.

In this section I will describe the clinical profile of 22qDS and its main features. Cognitive functions are defined. The literature on the intellectual, memory and executive functions of children and adults with 22qDS is reviewed with a focus on development. Limitations of the evidence base and the rationale for the present study are discussed. First, I will consider the epistemological stance from which the research has been undertaken.

1.2 RESEARCH POSITION

This research has taken a critical realist position in relation to the constructs of ‘intelligence’, ‘memory’ and ‘psychiatric disorder’. Psychiatric disorder is herein referred to as ‘psychiatric diagnosis’ to recognise it as a social construction rather than merely a reflection of internal pathology. Previous research refers to IQ and non-/disabled IQ ranges. These terms are used below in a critical review of the literature. Cognitive terms are used critically; interactions between tests and the construct being measured are acknowledged. The ontological status of cognitive functions is not assumed. The critical realist stance acknowledges the objective reality of ‘abilities’, but understands that social interaction, language and context construct multiple versions of the environment through which dis/abilities are articulated.

1.3 22QDS

1.3.1 Definition, incidence and history

22qDS is a deletion on chromosome 22. Most affected individuals have the same large 3 megabases (3Mb) microdeletion in the region q11.2, while a few have a smaller 'nested' deletion (McDonald-McGinn & Zackai, 2008). 22qDS has only been detectable with virtually 100% accuracy since the introduction of the *fluorescence in situ hybridisation* (FISH) test in 1992. 22qDS is the most common genetic deletion syndrome (McDonald-McGinn, Kirschner & Goldmuntz, 1999), with an estimated incidence of 1 in 4000-7000 live births (Botto et al., 2003; Driscoll et al., 1993). The pattern of inheritance is autosomal dominant (Shprintzen, 2008). 22qDS mainly presents *de novo*, but familial inheritance is reported in around 6-10% of cases (McDonald-McGinn et al., 2001).

22qDS has been described for about 40 years under different labels according either to the primary medical condition, for example 'velo-cardio-facial syndrome' (VCFS) or 'conotruncal anomalies face syndrome', or eponomously, such as DiGeorge syndrome, Shprintzen syndrome, Cayler syndrome, Takio syndrome, Sedlackova syndrome and CATCH 22 (Antshel et al., 2005a). Since 22qDS became identifiable through FISH in 1992, there has been a 10-fold increase in published literature (Kates, 2008).

The clinical presentation of 22qDS is highly variable. The most commonly observed medical features of the syndrome include: cardiac abnormalities, sub-mucus cleft palate, hypocalcemia, facial dysmorphism, T-cell abnormalities, resulting in immune-deficiency, and mild LD (Cuneo, 2001; McDonald-McGinn et al., 1999; Shprintzen et al., 1978; Shprintzen et al., 2000). LD is defined as an IQ score (discussed later) below 70. There are more than 180 clinical features with no reported individual having all of them (Shprintzen, 2008). Psychiatric diagnoses are also common. Gothelf et al. (2004) found that 40 out of 43 children and adults with 22qDS had at least one psychiatric diagnosis.

Attention deficit hyperactivity disorder (ADHD) and oppositional-defiant disorder (ODD) are frequently diagnosed in preschool years, affective and anxiety disorders in adolescence, and by early adulthood up to 30% of affected persons receive a diagnosis of schizophrenia or schizophrenia-like psychosis (Feinstein, Eliez, Blasey & Reiss, 2002; Gothelf et al., 2004; 2007a; Green et al., 2009; Murphy, Jones & Owen, 1999).

1.3.2 The general cognitive phenotype

The concept of cognitive phenotype is discussed below (Section 1.4.4). Despite the high prevalence of LD reported in 22qDS, few research groups had investigated cognition until the last 20 years (Majerus, Linden, Braissand & Eliez, 2007), partly due to affected individuals surviving into adulthood following advances in cardiac surgery.

There is substantial variability in the cognitive phenotype of individuals with 22qDS. One consistent finding is that general intellectual functioning is in the 'low borderline' range (Antshel, Fremont & Kates, 2008). The child/adolescent 22qDS literature suggests that spelling, word decoding and verbal rote learning are relative strengths. Common weaknesses are in visuo-spatial reasoning/memory, maths attainment and executive functioning.

A nonverbal learning disability (NVLD) is widely reported in children and adolescents with 22qDS (Goldberg, Mootzkin, Marion, Scrambler & Shprintzen, 1993; Golding-Kushner, Weller, & Shprintzen, 1985; Moss, Batshaw & Solot, 1999; Scherer, D'Antonio, & Kalbfleisch, 1999; Scherer, D'Antonio, & Rodgers, 2001; Swillen, Devriendt & Legius, 1997), but not in adult samples. This suggests that the cognitive profile may change with age. Most of the evidence base comprises cross-sectional data with very few longitudinal studies exploring intra-individual changes in cognition. When reviewing the literature on the cognitive profile and development in 22qDS (below), it is important to consider the effects of other manifestations of 22qDS.

1.3.3 Psychosocial impact

Cleft palate can cause speech difficulties, affecting early verbal interactions and potentially social confidence at school (Fraser, 2007). Phenotypic facial differences, hearing, cardiac and speech difficulties could increase the likelihood of children with 22qDS experiencing marginalisation and exclusion (Fraser, 2007), potentially fostering low self-esteem, in turn impacting on individuals' school work, and subsequent cognitive development. Karmiloff-Smith (2008) notes that the frequent differential treatment by parents of an infant with 22qDS compared to a typically developing infant is likely to affect cognitive development. For example, Mervis and Bertrand (1997) argue that overcorrection of early linguistic categorisations in children with 22qDS compared to their siblings can paradoxically adversely affect later semantic abilities. Thus the meaning of 22qDS to parents impacts on the child's cognitive development.

Lepach and Petermann (2011) note how aspects of 22qDS, such as characteristic small stature, unclear speech (cleft palate), lack of sporting skills (due to cardiac problems), and academic difficulties can increase the risk of psychiatric diagnosis and social withdrawal as well as shape attitudes to school and general psychosocial development. The psychosocial stress of coping with the disabling features of 22qDS was considered throughout data collection and interpretation and is discussed in the critical review.

1.3.4 Mode of Inheritance

There are many features of 22qDS that are likely to contribute to the cognitive profile, for example the mode of inheritance. Parents with 22qDS usually display milder clinical impairments than their affected children or individuals with *de novo* 22qDS (Digilio et al., 2003; McDonald-McGinn et al., 2001; Ryan et al., 1997). In these studies most parents were diagnosed following the diagnosis in their child, implying that their functioning was, at worst, only mildly impaired.

Greater cognitive impairment is reported in familial compared to *de novo* cases with 22qDS (Gothelf et al., 2007b; Swillen et al., 1997). Swillen et al. (1997) attributed the familial/*de novo* difference to the lower educational and socioeconomic status of parents with 22qDS and also their partners, suggesting assortative mating. However, De Smedt, Devriendt, Fryns, Vogels, Gewillig & Swillen (2007) found that parental educational level influenced intellectual functioning in children with both familial and *de novo* deletions. Genomic imprinting or an effect from the sex of the parent from whom 22qDS is inherited may also be important (Glaser et al., 2002).

1.3.5 Nature of the Microdeletion

The possibility that atypical deletions may account for the heterogeneity of the cognitive phenotype has been investigated. It is unclear if the nature of the microdeletion affects cognition in 22qDS, with negative studies from Bassett, Marshall, Lionel, Chow and Scherer (2008), Gerdes, Solot, Wang, McDonald-McGinn and Zackai (2001) and Green et al. (2009). However, all are limited by small sample size, especially for atypical deletions.

1.3.6 Genotype

There is uncertainty regarding which of the 30 or so genes from the 22q region predispose children with 22qDS to cognitive deficits. The catechol-O-methyl transferase (COMT) gene, located in the 22q region, has been the focus of much research. The COMT gene contains a Val-108/158-Met polymorphism which code for two enzyme variants with high and low activity (Chen, Lipska & Halim, 2004). Individuals with 22qDS carry only one copy of the COMT gene. The COMT Met allele is hypothesised to increase the risk of cognitive deficits (Gothelf et al., 2005) and psychiatric diagnoses (Gothelf et al., 2005, 2007c; Lachman et al., 1996).

Gothelf et al. (2007d) found that children with 22qDS and the COMT Met allele had greater decline in normative measures of verbal intelligence (VIQ) and language in adolescence with worse psychotic symptoms than those with the COMT Val allele. However, Bearden et al. (2004) found that children with the Met allele had better executive function than those hemizygous for the Val allele. While it is important to keep COMT status in mind when reviewing the literature on cognition in 22qDS, not all studies have found differences between Met and Val allele carriers in cognition (Glaser, Debbane & Hinard, 2006; Kates, Antshel & Abdulsabur, 2006; van Amelsvoort et al., 2008) or the risk of schizophrenia diagnosis (Bassett, Caluseriu & Weksberg, 2007). Much of the research on genotypes does not consider psychosocial factors associated with psychiatric diagnoses or cognitive profiles.

1.3.7 Psychiatric Diagnosis

Psychiatric diagnoses of ASD and ADHD are common in children with 22qDS. Antshel et al. (2006) found that nearly half of their child/adolescent 22qDS sample met the DSM-IV criteria for ADHD. Antshel et al. (2010) diagnosed major depression and anxiety in one fifth and nearly half of participants respectively. These psychiatric diagnoses and their prescribed medications have associated neuropsychological deficits, which may complicate interpretation of the pure cognitive profile in 22qDS.

1.3.7.1 Psychosis

Shprintzen first reported psychotic symptoms resembling “chronic paranoid schizophrenia” in 12 of 90 participants with 22qDS (Shprintzen, Goldberg, Golding-Kushner & Marion, 1992). Since then, other studies have reported a high risk (25-30%) of schizophrenia diagnosis in those with 22qDS (Baker and Skuse, 2005; Feinstein et al., 2002; Gothelf et al., 2005; 2007a; Murphy et al., 1999), with a notable onset in childhood (Debbane, Schaer & Farhoumand, 2006). There is also an increased prevalence of 22qDS in people diagnosed

with schizophrenia compared to the general population (Gothelf, Schaer & Eliez, 2008; Karayiorgou et al., 1995; Usiskin et al., 1999).

The high prevalence of schizophrenia has influenced the focus of research on cognition in 22qDS. A lack of longitudinal studies means that 'risk factors' such as decreased VIQ (Gothelf et al., 2007d) are often viewed as static, whereas the findings from adult studies reviewed below (Henry, van Amelsvoort, Morris, Owen, Murphy & Murphy, 2002) indicate that cognition, and therefore 'risk factors', may change with age. More longitudinal data on cognitive development are needed.

1.3.8 Cardiac disease

Cardiac disease could affect cognition through episodes of hypoxia or cerebral emboli causing brain damage. Attallah et al. (2007) found that children with 22qDS who underwent neonatal cardiac surgery had a worse neurodevelopmental outcome than those who did not. However, Moss et al. (1999) and Swillen et al. (1997) found no differences in mean FSIQ between children with 22qDS with and without congenital heart disease or palatal abnormalities. Gerdes et al. (2001) found no association between cardiac status and developmental scores in preschool children. But there is a wider literature on the adverse effects of congenital heart disease on neurodevelopment in babies (Miller et al., 2007) and school entry age (Majnemer et al., 2006). The distinction between presence and absence of congenital heart disease may have been too crude to support the negative results of Swillen et al. (1997) and Gerdes et al. (2001). It should be considered as a potential complicating factor when investigating cognition in 22qDS.

1.3.9 Cleft palate and hearing impairment

Submucous cleft palate may cause articulation difficulties in 22qDS, which could contribute to pre-school deficits in expressive language (Solot et al., 2001).

Glue ear and middle ear infections are common in children with cleft palate. Prolonged middle ear infections between the ages of 6- and 12-months have been found to put children at risk of cognitive delay at 3-years, but the effect is not strong and no longer detectable at 5-years (Johnson et al., 2000) or 9-years (Chalmers Stewart, Silva & Mulvena, 1989). The potential indirect impact of both factors should be considered when reviewing the cognitive profile reported in 22qDS.

1.4 COGNITIVE FUNCTIONS

Before reviewing the literature on cognitive development in persons with 22qDS, cognitive functions are described. Cognition tends to be divided into several main areas. Here, the following three are considered: Intelligence, memory and executive functioning.

Cognitive function is usually described in terms of index and scaled scores, which refer to an individual's position along the normal distribution of scores for, usually, an age-matched sample. If a child of 5-years obtained a raw score of 8/10 on a spelling test, their score might place them in the top end of a normal distribution when compared to age-matched peers, but if a 20-year old achieved the same raw score on the same test, it could place them towards the lower end compared to an age-matched normative sample. Scaled and index scores therefore communicate more information about a person's performance.

1.4.1 Intelligence

1.4.1.1 Definition

The concept of intelligence has developed from Spearman's notion of 'general intelligence' as a single factor called 'g' (Spearman, 1904), to Thurstone's primary mental abilities (Thurstone, 1938), Sternberg's (1985) triarchic theory of intelligence and the Cattell-Horn-Carroll theory of intelligence (Carroll, 1993).

Over 90 definitions of intelligence existed in the early 1960s (Lezak, 1988). It is beyond the scope of this chapter to review the concept of intelligence, which is discussed elsewhere (Howe, 1990; Jensen, 1998; Sternberg, 1988). According to Sternberg (1985), intelligence is a person's "mental activity directed toward purposive adaptation to, selection and shaping of, real-world environments relevant to one's life".

Intelligence tests formerly yielded a unitary measure, 'g', but more recently are based on factor analysis and yield numerous measures, which purport to reflect different aspects, such as processing speed, 'working memory' (WM) and verbal and nonverbal intelligence.

1.4.1.2 Measurement

The concept of intelligence is operationalised through tests. The Wechsler series of intelligence tests is the most widely used. It comprises a set of subtests purporting to measure different cognitive functions. It yields a scaled score for performance on each subtest and overall index scores: Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Processing Speed Index (PSI) and Working Memory Index (WMI), which was previously called the Freedom from Distractibility Index (FDI). When reviewing the previous literature, the FDI and WMI are used interchangeably. These indices combine to produce one global measure of intellectual functioning: Full Scale Intelligence Quotient (FSIQ). The VCI score represents verbal intellectual functioning, and the PRI, nonverbal intellectual functioning. Different age appropriate versions of the Wechsler intelligence scales exist for children (6-16 years) and adults (17+ years). The subtests in each version are similar, but items differ in age appropriateness.

The Wechsler tests are updated with newer versions. Currently the Wechsler Intelligence Scale for Children –Fourth Edition (WISC-IV, Wechsler, 2004) and adult version, Wechsler Adult Intelligence Scales-Fourth Edition (WAIS-IV, Lichtenberger & Kaufman, 2009), are in use. Previously the third edition, WISC-III (Wechsler, 1991) and WAIS-III (Wechsler, 1997), were used. In addition to the index scores listed above, the WISC-III and WAIS-III also yield an overall estimate of verbal and nonverbal intellectual functioning, VIQ and PIQ respectively. The fourth edition no longer uses VIQ and PIQ, now considered outmoded, because they are confounded by other measures, such as WM and processing speed, respectively. The VCI and PRI are arguably purer measures of verbal and nonverbal functioning than VIQ and PIQ.

1.4.2 Memory

Memory is the ability to retain information and use it adaptively (Fuster, 1995). There are various classifications based on dual systems (Baddeley, 2002; Squire & Knowlton, 2000), broadly including storage (short-versus long-term), content (non-/declarative or implicit/explicit, semantic versus episodic, verbal versus visual), and retrieval (recall versus recognition). Memory can be broken down into three stages: encoding (information is registered), storage (information is consolidated) and retrieval (information is accessed).

1.4.2.1 Measurement

Batteries of memory tests are used to examine the components of memory. The Wechsler Memory Scale-third edition (WMS-III, Psych Corp, 1997) and Children's Memory Scale (CMS, Cohen, 1997) are the most widely used. They include subtests that yield individual scaled scores and overall index scores, which represent immediate and delayed recall and recognition memory for both verbal and visual material. The updated WMS-IV is available but, at the time of writing, the corresponding child version has not yet been published.

1.4.3 Executive Functioning

The term executive function refers to interrelated 'higher order' cognitive functions involved in planning, organisation, rule following, shifting focus between tasks, inhibition, initiation and WM (Stuss & Alexander, 2000). It is classically a frontal lobe function (Fuster, 2008; Goldman-Rakic, 1987).

1.4.3.1 Measurement

These concepts are operationalised through numerous tests, including concept formation, sorting, problem-solving, estimation, fluency, division and rapid switching of attention, and inhibition (Lezak et al., 2004). A review of all the tests is beyond the scope of this chapter but specific tests used in 22qDS research are discussed below.

1.4.4 Cognitive Phenotype

There are two contrasting definitions of cognitive phenotype. Flint and Yule (1994) propose that "a behavioural phenotype should consist of a distinctive behaviour that occurs in almost every case of a genetic or chromosomal disorder, and rarely (if at all) in other conditions". Secondly, "this behaviour has a direct and specific relationship to the genetic or chromosomal anomaly that gives rise to the physical manifestations of the syndrome". In contrast, Dykens (1995) proposes a less stringent definition, namely that a behavioural phenotype involves "the heightened probability or likelihood that people with a given syndrome will exhibit certain behavioural and developmental sequelae, relative to those without the syndrome".

The common ground between the definitions is that most behaviours characteristic of a syndrome manifest in individuals with that particular genetic disorder. But there are two key differences. The former definition (Flint & Yule, 1994) is deterministic, whereas the latter (Dykens, 1995) is probabilistic.

Secondly, the former definition demands uniqueness, whereas the latter allows for “shared” outcomes between disorders. The methodology of examining behavioural or cognitive phenotypes has been reviewed by Flint (1996), Hodapp and Dykens (2005), and Skuse (2000).

The concept of cognitive phenotype is important. It has clinical value for the parents of a child suffering from a genetic disorder whose disturbed cognition differs from that of its siblings. Framing cognitive deficits in the context of their diagnosis can provide parents with reassurance that cognitive weaknesses are neither their fault nor caused intentionally by the child. The concept of cognitive phenotypes can guide educational advice. Additionally, it aims to clarify the biological and genetic bases of cognition as well as environmental contributions.

The perspective taken here is that of Dykens (1995). Studies in 22qDS document a variable cognitive profile, partly related to variability in intellectual functioning (Jacobson et al., 2010). Research, reviewed below, has raised the possibility that the ‘cognitive phenotype’ in childhood may differ from that in adulthood.

1.5 LITERATURE REVIEW

1.5.1 Literature Search

A range of studies was read to address the evidence for the cognitive phenotype and its changing nature. Databases were searched for relevant literature: Psych info, Psych articles, Pubmed and Google Scholar. Articles from 1900 up until March 2012 were included. The search terms used were: ‘cognitive’, ‘cognition’, ‘intelligence’, ‘memory’, ‘neuro’, executive function, ‘psychiatric’ and ‘schizophrenia’ (included in the main text of any article rather than restricted to the title), ‘VCFS’, ‘22q’, ‘Shprintzen’, ‘Di George’ (in the title of an article). Papers were selected for inclusion in the literature review if they were relevant to the cognitive profile, cognitive development or experience of

22qDS. The names of delegates listed in attendance at the most recent biennial international 22qDS conference were also entered into the above databases to find any publications that could have been missed. Most articles were quantitative in method, but a few qualitative papers were also included.

1.5.2 Intelligence

Research into the intellectual functioning of school-aged children with 22qDS has typically used standardized IQ batteries, most commonly the WISC-III (Wechsler, 1991). Although the WISC-III and WAIS-III yield VCI and PRI, studies have tended to report the VIQ and PIQ. This means that much of the literature below examined the relationship between verbal and nonverbal intellectual functions using measures which are confounded by other factors.

1.5.2.1 Full Scale IQ

Table 1 reports all studies of IQ in this population and shows, where reported, discrepancies between VIQ and PIQ. The majority of child/adolescent samples' mean FSIQ scores falls in the 'borderline range', while 40-52% fall in the Mild LD range (De Smedt et al., 2007; Moss et al., 1999; Swillen et al., 1997). Moderate (FSIQ: 35-55) or severe LD (FSIQ: 20-35) are rarely described (Swillen et al., 1997; Zinkstok & van Amelsvoort, 2005).

Most studies find little effect of gender on FSIQ, though many are underpowered from small sample size. Antshel et al. (2005b; 2007) found a lower mean FSIQ in 50 male than in 40 female children with 22qDS (68.9 and 76.3, respectively). Two other studies support this finding (Niklasson & Gillberg, 2010; Óskarsdóttir et al., 2005), but there are also negative studies (De Smedt et al., 2007; Moss et al., 1999).

Table 1: IQ Results from the present and other studies investigating 22q11

Author and Year		**FSIQ** Mean	(SD)	**VIQ** Mean	(SD)	**PIQ** Mean	(SD)	**VIQ> PIQ** *Sig*	**Test**	**N**	**Age** *Mean*	*(SD) [range]*
Lepach & Petermann	(2011)	75.7	(13.9)	83.8	(11.70)	68.9	(16.9)	P<0.001	WISC-III	16	11y 8m	[7-16]
Baker et al.	(2011)	-		83		77		P<.05	WISC-III WAIS-R	14	17y 7m	(2.1)
Niklasson & Gillberg	(2010)	70.6	(15.5)	75.6	(15.9)	69.8	(15.6)	P<.01	WPPSI-R WISC-III WAIS-R	82	-	[1-16]
Jacobson et al.	(2010)	65.4	(9.7)	72.4	(12.77)	64.2	(8.7)	P<.001	WISC-III	31	11y 8m	(2.0)
De Smedt et al.	(2007)	73.5	(11.7)	78.7	(14.01)	72.6	(10.9)	P<.01	WISC-III	103	7y 9m	(3.1)
Lajiness et al.	(2006)	70.0	(11.2)	76.7	(11.4)	67.9	(10.3)	P<.001	WISC-III	14	12y 6m	(6.4)
Woodin et al.	(2001)	76	(12.7)	83.0	(14.12)	73	(12.4)	P<.001	WISC-III WPPSI-R WAIS-R	80	10y 3m	(3.2)
Moss et al.	(1999)	71.2	(12.8)	77.5	(14.9)	69.1	(12.0)	P<.01	WISC-III WAIS-R	33	10y 8m	(4.11)
Swillen et al.	(1997)	-		79.0		69		P<.001	WISC-R	11	12y 4m	[7-16]
Lewandow-ski et al.	(2007)	70.7	(12.4)	74.0	(12.3)	72.0	(12.9)	ns	WISC-III	26	9y 3m	(2.6)

Author and Year		**FSIQ** Mean	(SD)	**VIQ** Mean	(SD)	**PIQ** Mean	(SD)	**VIQ> PIQ** *Sig*	**Test**	**N**	**Age** *Mean*	*(SD) [range]*
Oskarsdot-tir et al. *(median):*	(2005)	*74.0*		*82.0*		*69.0*		ns	WPPSI WISC-III WAIS-R	26	7y 6m	[6-19]
van Amelsvoort et al.	(2004)	74.9	(10.7)	75.9	(7.51)	77.2	(16.9)	ns	WAIS-R	15	32y 5m	(10.71)
Henry et al.	(2002)	74	(11.5)	74.2	(7.59)	77.8	(17.7)	ns	WAIS-R	19	35y 1m	(11.42)
Antshel et al.	(2010)	-		74.8	(14.90)	70.5	(14.7)	-	WISC-III WAIS-III	70	15y 0m	(2.1)
Azuma et al.	(2009)	67	(8.0)	71.0	(15)	67	(7)	-	WISC-III	8	12y 0m	(2.0)
Green et al.	(2009)	72.6	11.9	76.3	13.9	73.6	(11.8)	-	WISC-III	50	-	[12-17]
Green et al.	(2009)	67.3	10.3	70.2	(10.5)	68.5	(11.8)	-	WAIS-III	27	-	[18-23]
Debbane´ et al.	(2008)	68.0	11.9	71.2	14.68	70.2	(12.1)	-	WISC-III	33	17y 2m	(7.43)
Majerus et al.	(2007)	65	[44–82]	72.0	[46–94]	64	[48–76]	-	WISC-III WAIS-III	14	15y 8m	[7–31]
Gothelf et al. *Original*	(2007d)	74.5	(15.1)	80.1	(14.3)	-		-	WISC-III WAIS-III	19	13y 1m	(4.0)
Gothelf et al. *Follow-up*	(2007d)	-		75.5	(15.4)	-		-			17y 9m	(3.8)

Author and Year		**FSIQ** Mean	(SD)	**VIQ** Mean	(SD)	**PIQ** Mean	(SD)	**VIQ> PIQ** *Sig*	**Test**	**N**	**Age** *Mean*	*(SD) [range]*
Antshel et al.	(2007)	78.3	(10.9)	-		-		-	WISC-III	67	10y 8m	(2.7)
Chow et al. *Schizophrenia subgroup*	(2006)	71.6	(8.0)					-	WAIS-R	29	30y 6m	(7.7)
Z-scores:				*-1.94*	*(0.54)*	*-1.54*	*(0.5)*					
Chow et al. *22qDS Controls*	(2006)	74.8	(6.1)								25y 0m	(9.0)
Z-scores:				*-1.54*	*(0.62)*	*-1.32*	*(0.6)*					
Gothelf et al.	(2005)	75.8	(13.8)	79.1	(13.9)	-		-	WISC-III WAIS-III	24	13y 3m	(3.7)
Antshel et al. Females	(2005)	76.3	(11.7)	79.2	(13.4)	77.2	(10.2)	-	WISC-III	40	10y 8m	(2.5)
Antshel et al. Males	(2005)	68.9	(12.8)	73.8	(14.4)	68.9	(11.0)	-	WISC-III	50	11y 1m	(2.7)
Lajiness et al.	(2005)	70.0	(11.2)	76.6	(11.4)	67.9	(10.3)	-	WISC-III	9	12y 6m	(6.4)
Bearden et al.	(2001)	75.6	(12.6)	-		-		-	WISC-III	29	10y 3m	(2.5)

Key:

VIQ>PIQ sig; VIQ>PIQ discrepancy significance for the sample

**SDs and ranges were not available for all studies.*

-: Not reported

WPPSC: Wechsler Primary and Preschool Scale for Children – Revised (Wechsler, 1989)

WAIS-R: Wechsler Adult Intelligence Scale – Revised (Wechsler 1981)

WISC-III: Wechsler Intelligence Scale for Children, 3rd edition (Wechsler 1991)

SBI-IV: Stanford-Binet Intelligence Scale, 4th Ed. (S-B; Thorndike et al*., 1987)*

T1=Time 1; T2=Time 2.

Con=controls

SZ=Schizophrenia diagnosis

1.5.3 Verbal and Nonverbal intellectual discrepancies in children with 22qDS

1.5.3.1 Statistical significance

Studies investigating the cognitive profile of children with 22qDS typically yield statistically significantly higher mean VIQ than PIQ for groups. While the reported VIQ>PIQ discrepancy suggests an NVLD, the opposite profile (PIQ>VIQ) is also reported in a small proportion. Campbell and Swillen (2005) reviewed four studies and found a mean VIQ>PIQ discrepancy of 8-10 IQ-points. However, Antshel et al. (2008) reviewed the same four studies with an additional three and found a mean VIQ>PIQ discrepancy of only 4-5 points; although still statistically significant in most studies, the effect sizes were smaller. The degree of VIQ>PIQ discrepancy presents mixed findings. Table 1 is grouped into three sections: studies that found a statistically significant VIQ>PIQ discrepancy, those that did not, and those that do not report it.

Moss et al. (1999) found a significant and greater discrepancy between mean VCI (79.2) and PRI (68.0) than between mean VIQ (77.5) and PIQ (69.1). As mathematics is a common weakness in children with 22qDS (Moss et al., 1999), performance on the arithmetic subtest, comprising VIQ, may have lowered the VIQ, reducing the verbal>nonverbal discrepancy; the VCI is a purer measure.

1.5.3.2 Clinical Significance of the VIQ>PIQ discrepancy

Most studies not only yield a statistically significant mean VIQ>PIQ discrepancy in child/adolescent 22qDS samples, but also a 'clinically significant' VIQ>PIQ discrepancy, which is defined in the WISC-III as a discrepancy of at least 11.3 points (Wechsler, 1997), although this figure varies for different ages. This level of discrepancy is termed 'clinically significant' because, according to the normative reference groups, it is unusual to have a discrepancy that large.

1.5.3.3 Base Rates

In the general population, the degree of discrepancy between VIQ and PIQ increases with FSIQ in children using the WISC-R (N=2200) (Kaufman, 1976;

Lezak et al., 2004) and in adults using the WAIS-R (Matarazzo & Herman, 1984; 1985; Matarazzo et al., 1988). The standardized US population norms for the WISC-III reveal that 40.5% of the 6-16 year old population have a VIQ-PIQ discrepancy of 11.3 points in either direction, and about half this figure in one direction (Wechsler, 1989; 1991). A VIQ>PIQ discrepancy of more than 12 points was found in only 10% of those with FSIQ<79 and 16% of those with FSIQ 80-89, (Kaufman, 1976). Similar results have been reported with the WAIS-R in healthy adults (Matarazzo & Herman, 1984) and psychiatric inpatients (Iverson et al., 2001). Although not formally examined, the positive correlation of degree of VIQ-PIQ discrepancy with FSIQ on the WISC-R probably applies to successive versions of the child and adult Wechsler intelligence scales.

The VIQ>PIQ trend has been widely replicated and reaches clinical significance in about 17.5%-38% of children with 22qDS (De Smedt et al., 2007; Goldberg et al., 1993; Golding-Kushner et al., 1985; Lajiness-O'Neill et al., 2005; 2006; Murphy et al., 2004;Niklasson, Rasmussen, Óskarsdóttir & Gillberg, 2001; Scherer et al., 1999; 2001; Swillen et al., 1997; Wang et al., 2000). Moss et al. (1999) and Jacobson et al. (2010) found that 13/33 and 15/31 children/adolescents with 22qDS respectively had a clinically significant VIQ>PIQ discrepancy, thus nearly four- and five-fold the expected rate in the general population with similar FSIQ.

1.5.3.4 Verbal and Nonverbal intellectual discrepancies in adults with 22qDS

Due to the high rates of diagnosis of schizophrenia in adults with 22qDS, the research focus in adults has centred on schizophrenia and its associated cognitive deficits (Chow, Watson, Young & Bassett, 2006; van Amelsvoort et al., 2004). In the only study to date reporting VIQ-PIQ discrepancies in adults with 22qDS, Henry et al. (2002) found only 3 of their 19 participants exhibited a clinically significant VIQ>PIQ discrepancy, while 6 had the reverse profile; with no overall group mean discrepancy. Relative to controls, the adults with 22qDS exhibited statistically significant impairments in visuo-perceptual functions, problem solving, planning and abstract reasoning.

The same research group investigated the cognitive profile of 28 adults with 22qDS, of whom 13 had a diagnosis of schizophrenia, including participants from the Henry et al. (2002) study (van Amelsvoort et al., 2004). Differences between the mean VIQ and PIQ were negligible, suggesting the VIQ>PIQ discrepancy reported in childhood may disappear by adulthood.

In the only study reporting on an entirely separate adult 22qDS sample, Chow et al. (2006) did not analyse the discrepancy between two verbal and nonverbal subtests. However, overall performance appeared worse for verbal than nonverbal functioning, unlike the general pattern found in childhood.

IQ scores are expected to remain relatively stable throughout life (Sigelman & Rider, 2006; Weinert & Hany, 2003). The lack of VIQ>PIQ discrepancy in these adult samples suggests atypical development from childhood to adulthood. Antshel et al. (2008) note that the lack of VIQ>PIQ discrepancy reported in adults by Henry et al. (2002) may reflect psychosis and/or a decline in normative verbal skills with age (Gothelf et al., 2005; Gothelf et al., 2007d). The results of the Henry et al, 2002, study are difficult to interpret because of confounding psychosis diagnosis, pharmacological treatment in eight participants and no separate subgroup analysis.

1.5.3.5 Theories about the nonverbal deficit and its causes

Shprintzen's group (Golding-Kushner et al., 1985) originally hypothesised that lower nonverbal performance was related to a combination of impairments in visuo-spatial functions, novel reasoning, and concept formation and planning. Various studies report deficits in object recognition and perception in children (Bish et al., 2007) and adults with 22qDS (Henry et al., 2002).

NVLD was conceptualised by Rourke (1987; 1989; 1995) as selective difficulties discriminating and recognising visual information and patterns, and deficits in problem solving, based on right hemisphere white matter abnormalities.

The performance of children with 22qDS suggests selective rather than global cognitive impairment. Swillen et al. (1999) and Moss et al. (1999) suggest that the combination of VIQ>PIQ discrepancy and higher scores in reading and spelling than in mathematics is consistent with NVLD (Rourke, 1995). This view has been challenged by the presence of specific language problems (Campbell & Swillen, 2005), which typically persist into adult life (Solot et al., 2001) and are unexpected in a pure NVLD profile. Nonetheless, deficits are generally greater in visuo-spatial perception, reasoning and processing (Simon et al., 2002).

As the VIQ>PIQ discrepancy is also observed in children with 22qDS without LD (FSIQ>70), Moss et al. (1999) suggest that it may characterise the syndrome per se rather than general LD. But the NVLD-like profile is not unique to 22qDS; it is also reported in Turner Syndrome and Williams syndrome (Martens, Wilson & Reutens, 2008; Swillen et al., 1993). Most children with 22qDS appear to have an NVLD profile with specific language deficits, but few studies have explored how the NVLD profile develops.

1.5.3.6 Changes in the cognitive profile with age

Cross-sectional studies suggest that the VIQ>PIQ discrepancy evident in childhood disappears by adulthood. The hypothesised underlying cognitive pattern could be increasing PIQ/PRI or decreasing VIQ/VCI. Preliminary conclusions may be drawn from cross-sectional designs, which report correlations of cognition with age, or from the few follow-up studies but these are not conclusive. They all suggest general decline or differential decline in VIQ compared to PIQ with age.

1.5.3.7 Cross-sectional Studies

Table 2 summarises the cross-sectional studies which have examined correlations of age with cognition, usually IQ. The value of the correlation coefficient is greater if there is more rather than less variability among the observations (Goodwin & Leach, 2006). The age range has usually been narrow (except in Green et al., 2009), risking underestimation of an age or developmental effect on IQ; or it has encompassed children either side of puberty or during adolescence, periods of major and non-linear change in the brain and cognition (Blakemore & Choudhury, 2006). Two studies had small sample sizes, so may be statistically underpowered to detect change.

Campbell, Stevens and Morris (2002) attributed a negative correlation of FSIQ with age to PIQ, with no such decline evident in healthy sibling controls. Green et al. (2009) found that FSIQ, VIQ and PIQ were all negatively correlated with age, including participants with and without a diagnosis of schizophrenia. The negative correlations between VIQ subtests and age were stronger than between PIQ subtests and age. Green et al. (2009) split their sample (n=172) into 4 age ranges. They yielded a mean VIQ>PIQ discrepancy of 4 points in the youngest age group (<12 years), which declined to 3 points in the next group (12-18 years), then 2 points in the next (18-24 years) and reached equivalence in the oldest age group (>24 years). This was due to a steeper decline in VIQ compared to PIQ. The authors do not report the statistical significance (if any) of the various discrepancies.

In their sample aged 6-15 years, Antshel et al. (2005b) yielded negative correlations of VIQ and PIQ with age in females (n=40) but not males (n=50). Niklasson and Gillberg (2010) yielded a VCI>PRI discrepancy in their entire sample ranging in age from 1 to 35. In both sexes they found a negative correlation of FSIQ with age, due to declining PSI. Correlations of VCI and PRI with age were not significant. The wide age range of their sample and the use of different batteries limit interpretation.

In another sample with a wide age range, Green et al. (2009) used different versions of the Wechsler intelligence scales to ensure that tests and normative samples were age-appropriate. Some of the subtests comprising VIQ and PIQ differ slightly between versions. The same methodological issue applies to the longitudinal studies reviewed below. Different test stimuli used with participants in various age brackets purport to measure the same cognitive function, but between-subgroup and sample differences could be an artefact of different test stimuli. Therefore when examining correlations between age and test performance, it is important to analyse the subtests that most similar among the different adult and child versions of the Wechsler tests. These subtests are: Vocabulary (VIQ/VCI subtest) and Block Design (PIQ/PRI subtest).

Green et al, 2009, yielded a negative correlation of Vocabulary with age but Block Design was considered stable. The decline of PIQ with age could have reflected other nonverbal functions. Block Design is arguably a purer measure of visuo-spatial reasoning than other WISC-III PIQ subtests, which require understanding of social rules and interactions or measure processing speed. Although some studies report declining PIQ with age, the lack of decline in Block Design performance is potentially more important than overall index scores when considering visuo-perceptual reasoning, particularly as the above finding for Block Design supports data from longitudinal studies that have not found deterioration in PRI with age (Antshel et al., 2010; Gothelf et al., 2007d).

With a cross-sectional design, Green et al. (2009) were unable to conclude whether intellectual functions comprising the VIQ scale actually worsen over time or fail to progress at a typical developmental rate. Conclusions are similarly limited in the other cross-sectional studies in table 2.

Table 2: Cross-sectional studies with an age-cognition correlation

Author	**Year**	**N**	**Gender** Fe:male	**Age range** (years)	**Finding**	**Tests**
Jacobson et al.	(2010)	31	14:17	7-14	No correlation of VCI, PRI, FDI or PSI with age.	WISC-III
Niklasson & Gillberg	(2010)	100	58:42	1-35	PSI & FSIQ decline with age (not VCI or PRI).	WIPSI-R, WISC-III & WAIS-R
Green et al.	(2009)	172	82:90	5-54	Declining VIQ, PIQ with age.	WISC-III,WAIS-III
Antshel et al.	(2005b)	90	40:50	6-15	Declining VCI & PRI in females not males.	WISC-III,WIAT-II, Vineland
Sobin et al.	(2005)	40	23:17	5-12	Quantitative skills decline with age.	Stanford-Binet, NEPSY
Campbell et al.	(2002)	26	-	6-16	PIQ and FSIQ decrease with age, but VIQ stable.	Not stated

1.5.3.8 Longitudinal studies

Two principal sets of investigators have published controlled follow-up studies (Table 3), with conflicting findings on whether or not verbal functions decline with age. The Gothelf et al. (2005; 2007d) studies report a fall in VIQ with age, which is affected by COMT genetic status and particularly evident in those diagnosed with psychosis. Decline in VIQ correlated (r= 0.59) with reduction of left cortical grey matter volume. Antshel et al. (2010) did not report the degree of VCI-PRI discrepancy. They yielded no reduction in VCI (z-score: .06) or PRI (z-score: .00) over time. The FSIQ in both samples declined with age, attributable to declining PSI and FDI in the Antshel et al. (2010) study, and to VIQ in the Gothelf et al. (2005; 2007d) studies. Antshel et al. (2010) also found that cognitive function declined more in females than males.

Participants were selected based on parental report of developmental delay in the Gothelf studies or to study risk factors for psychosis (Antshel et al., 2010). High rates of psychiatric diagnosis, especially psychosis, and use of psychotropic medication are likely to have lowered cognitive scores. Selection bias, psychiatric diagnosis and pharmacological intervention may contribute to inconsistencies in the results. Attrition, although modest, included those with lower FSIQ in the Gothelf et al. (2007d) study. Lack of an IQ-matched control group makes it difficult to determine the specificity of the cognitive developmental trajectory.

Table 3 Longitudinal studies of cognitive development

Author	**Year**	**T1/ T2**	**N**	**Mean age** (yrs)	(SD)	**Follow-up gap** (yrs, months)	**Finding**	**Tests**
Antshel et al.	(2010)	T1	80	11.9	(2.2)	3y	FSIQ, PSI, FDI, memory & maths declined with age. Executive functioning & reading improved.	WAIS/WISCIII, WIAT-II,CVLT, CPT, ToL, WCST, Visual Span, BASC.
		T2	70	15.0	(2.1)			
Schaer et al.	(2009)	T1	59	11.4	(3.5)	3y	Stable FSIQ - T1: 70.7; T2: 71.6.	Wechsler (version not reported).
		T2	32	14.5	(3.6)			
Gothelf et al.	(2007d)	T1	29	12.3	(4.0)	4y 9m	VIQ declined with age.	WAIS-III, WISC-III.
		T2	19	17.9	(3.8)			
Gothelf et al.	(2007a)	T1	31	12.5	(3.9)	As above	Predictors of psychosis: declining VIQ, COMT status, anxiety or depression.	WISC-III, WAIS-III, Vineland ABS.
		T2	28	17.4	(3.7)			
Gothelf et al.	(2005)	T1	24	13.3	(3.7)	4y 8m	VIQ declined in COMT Met not COMT Val subgroup.	WAIS-III, WISC-III, CELF-3.
		T2	24	18.1	(3.4)			

Key:

T1: Time One (original assessment); T2: Time Two (Follow-up assessment).

1.5.3.9 The differential nature of the developmental decline in VCI/VIQ versus PRI/PIQ

The absence of a consistent VIQ>PIQ profile in the Henry et al. (2002) adult sample, if replicated in a large and longitudinal study, could suggest differential atypical development during adolescence.

Cambell and Swillen (2005) suggest visuo-perceptual functions and abstract reasoning may develop at a slower rate than verbal functions, resulting in lower normative scores for PIQ than VIQ during childhood. Findings from several cross-sectional studies (above) show declining PIQ with age, but not a decline in raw scores (Campbell et al., 2002; Golding-Kushner et al., 1985; Shprintzen, 2000; Sobin et al., 2005). This could indicate that visuo-perceptual functions do not deteriorate with age, but progress more slowly than in the general population, and result in lower normative scores during early development. Visuo-spatial functions may take longer to develop but may catch up with verbal functions by adulthood, reducing the VIQ>PIQ discrepancy. Schaer et al. (2009) hypothesise that improvement visuo-perceptual functions with age may reflect progress in the delayed maturation of cortical thickness.

Longitudinal studies, with their stronger design, suggest competing hypotheses for a fall in FSIQ: Gothelf et al. (2005; 2007d) suggest declining VIQ, whereas Antshel et al. (2010) implicate declining PSI and FDI.

1.5.4 The importance of studying developmental trajectories

Kates (2008) stated that the need for longitudinal studies in 22qDS "cannot be overemphasised". Antshel et al. (2008) suggest the knowledge base about the developmental perspective of cognitive functioning in 22qDS is limited by the cross-sectional design of most studies. Prasad et al. (2008) argue that only longitudinal data will help delineate the neurocognitive and behavioural factors associated with individuals with 22qDS being at higher risk for psychiatric deterioration. Developmental studies can explore modifying factors on the

cognitive and cerebral maturation of individuals with 22qDS, including not only genotype and gender (Antshel et al., 2008; 2010; Gothelf et al., 2007d; Kates et al., 2011; Simon et al., 2008), but also education and social factors.

1.5.5 Memory in 22qDS

Lepach and Petermann (2011) note that the NVLD-like profile is well-established in children/adolescents with 22qDS for intellectual functions and academic attainment and accepted as a cognitive phenotype of the condition, but that "memory and learning aspects have hardly been investigated." Research tends to focus on the fractionation of memory rather than suggestions that memory may be relatively preserved compared to IQ in 22qDS (Jacobson et al., 2010; Lajiness-O'Neill et al., 2006; Óskarsdóttir et al., 2005). The superiority of memory scores over FSIQ is typical at lower IQ levels in the adult general population (Hawkins & Tulsky, 2001). The most frequently reported finding is that the child/adolescent NVLD-like intellectual profile is also reflected in memory with a significant verbal>visual episodic memory discrepancy. Published studies are limited by small sample size and sometimes by lack of age- and IQ-matched control groups.

1.5.5.1 Verbal and visual memory

Nearly all studies have yielded inferior visual compared to verbal memory scores in child/adolescent 22qDS samples (Bearden et al., 2001; Lajiness-O'Neill et al., 2005; 2006; Oskarsdóttir et al., 2005; Wang et al., 2000; Woodin et al., 2001). In their group, Debbane et al. (2008) describe a visual immediate memory score 14 points (just under one standard deviation) lower than its verbal counterpart. However, an anomalous finding of no discrepancy between verbal and visual memory in a sample of 31 children/adolescents with 22qDS was reported by Jacobson et al. (2010). This was attributed to the particularly low FSIQ of their sample.

Verbal memory is usually in the low-average to below-average range (Majerus et al., 2007), but average scores are also yielded (Lajiness-O'Neill et al., 2006; Óskarsdóttir et al., 2005), illustrating the heterogeneity of the profile.

Less is known about the developmental trajectory of memory compared to intellectual functions as there are even fewer longitudinal or cross-sectional adult studies. Although Debbane et al. (2008) researched memory in a wide age range (10-36 years), the effect of age was not explored.

1.5.5.2 Verbal Rote Learning and complex verbal memory

Several studies suggest that verbal rote learning is remarkably preserved in children with 22qDS, while other aspects of verbal memory are impaired. Swillen et al. (1999) reported normal group performance in memory for rote learned verbal information in nine children using the '15 words of Rey' task (Lezak, 1995). Similar findings are reported by others (Bearden et al., 2001; Lajiness-O'Neill et al., 2005; Sobin et al., 2005; Wang et al., 2000; Woodin et al., 2001).

Woodin et al. (2001) reported verbal rote learning for Word Lists as a particular strength but Story Recall a relative weakness, hypothesising that as information becomes more complex, greater demands on comprehension and memory reveal deficits. However, recalling random words requires strategy planning, potentially implicating an executive component, actually making it the more complex task. In their very small sample (n=9), Lajiness-O'Neill et al. (2005) found no significant difference in performance on Story Recall between children with 22qDS, their unaffected siblings or age and IQ-matched control group. The results are mixed for this and other memory findings. The implication for the present study is that group performance on a word list memory task might be superior to performance on a story recall task. Both contribute to overall memory scores.

1.5.5.3 Memory for faces

Children with 22qDS are reported to have a deficit in the perception and memory of faces. Anderson, Anderson, Jacobs and Smith (2008) found impaired visual categorization for faces but not objects (houses), suggesting specific facial perceptual deficits. Lajiness-O'Neill et al. (2005) found inferior performance in a Facial Memory task in children with 22qDS compared to siblings and controls, but similar to that of children with autism. Campbell et al. (2011) found performance of children with 22qDS inferior to that of healthy controls and a developmentally matched group with Williams Syndrome (Campbell et al., 2009) for tasks of facial processing involving identity, emotional expression and gaze direction. Retention for faces was also inferior to that for dots using the CMS (Campbell et al., 2010). McCabe, Rich, Loughland, Schall and Campbell (2011) found atypical visual scan path patterns for both face and non-face images compared to controls. Those with 22qDS were less able to appropriately adapt their information processing strategy when the visual task changed from weather scenes to faces. The authors propose cognitive inflexibility rather than a face specific deficit, implicating an executive deficit.

In summary, the research consistently reports poor memory and processing of faces in child/adolescent 22qDS samples compared to controls, but the evidence for a face specific deficit is mixed. McCabe et al. (2011) suggest that cognitive inflexibility may underlie facial perceptual deficits. No gender effects have been observed in memory.

1.5.5.4 Memory Development

In a study of adults with 22qDS (n=29), Chow et al. (2006) reported immediate and delayed verbal recognition and visual recall in the average range, but verbal recall was more than one standard deviation below the general population mean. Discrepancies between visual and verbal memory domains were not

reported, so speculation cannot be made about whether their relationship changes with age.

Antshel et al. (2010) are the only authors to have investigated memory in 22qDS longitudinally. They found no group change over time for visual memory span, but performance in the final verbal learning trial (CVLT) declined with age. Declining verbal memory with age might be expected given the finding of declining VIQ with age by Gothelf et al. (2007d).

1.5.6 Executive function and Working Memory

Executive function has been reported as an area of relative weakness (compared to IQ) in 22qDS (Woodin et al., 2001). The four executive functions most frequently studied in 22qDS are initiation, cognitive flexibility, response inhibition and WM (verbal and nonverbal).

1.5.6.1 Initiation

Niklasson and Gilberg (2010) suggest that weak initiation affects performance on some nonverbal intellectual subtests, such as Block Design, because of time features (bonus points for faster solutions). The authors report that it is less of an issue when individuals are shown what to do and helped to "get started", e.g. with processing speed subtests in the WISC-IV/WAIS-IV. The issue is not speed per se, but 'initiating' activities. Parental reports of children with 22qDS suggest lower initiation (Kiley-Brabeck & Sobin, 2006).

1.5.6.2 Cognitive Flexibility and response inhibition

Cognitive flexibility and response inhibition are important factors affecting performance in cognitive assessments. Studies in children with 22qDS report weak cognitive flexibility on the Trail Making Test B (Woodin et al., 2001) and Wisconsin Card Sorting Test (Lajiness-O'Neill et al., 2006; Lewandowski et al.,

2007; Rockers et al., 2009). By contrast, van Amelsvoort et al. (2004) found no evidence of lower cognitive flexibility on the Weigl task (Goldstein & Scheerer, 1941) in adults with 22qDS, consistent with possible developmental change.

One measure of inhibition is pre-potent inhibition, a phenomenon in which a weaker initial stimulus inhibits a second, stronger stimulus. Common tests include the Delis-Kaplan Colour-Word Interference Task (Delis, Kaplan & Kramer, 2001) and the Stroop (Stroop, 1935). Deficits have been found on the Stroop in child/adolescent 22qDS samples by Sobin et al. (2005) and in adults without diagnosis of schizophrenia (Chow et al., 2006). But using different tests, Lajiness-O'Neill et al. (2006) found no difference between children with 22qDS and unaffected siblings on impulsive errors. A similar negative result was reported by Gothelf, Hoeft and Hinard (2007e).

1.5.6.3 Working Memory

WM refers to a hypothesized memory structure and process used for temporarily storing and manipulating information (Baddeley & Hitch, 1974). WM deficits, especially nonverbal, that are disproportionate to general intellectual functioning in 22qDS have been reported (Bearden, 2001; Lajiness-O'Neill et al., 2005; Lewandowski et al., 2007; Majerus et al., 2006; Moss et al., 1999; Sobin et al., 2005; Wang et al., 2000; Woodin et al.2001).

Different assessment methods are used to measure WM in the 22qDS literature, which could contribute to mixed findings. The WISC-III FDI comprises two subtests: Arithmetic and Digit Span, and is frequently used as a measure of WM. Moss et al. (1999) and Woodin et al. (2001) reported reduced FDI scores in children with 22qDS compared to the VCI. However, the FDI score could be confounded by weak performance on the Arithmetic subtest, as mathematics is a known difficulty in children/adolescents with 22qDS. Óskarsdóttir et al. (2005)

found evidence for reduced WM in 19/26 children using the Arithmetic subtest, but only 12/26 when using the Digit Span subtest. WM scores derived from the WISC-III FDI should be treated cautiously.

1.5.6.4 Developmental considerations

Green et al. (2009) found a negative correlation between age and the Digit Span subtest. Antshel et al. (2010) found that FDI performance significantly declined from original assessment (T1) to follow-up (T2). Gothelf et al. (2007d) do not report the FDI changes.

1.5.6.5 Summary

A range of different tests has been used in the literature to measure executive function. Different results could reflect different assessment methods as well as heterogeneity within 22qDS and between-sample differences. The most common findings appear to be weaknesses, independent of IQ, in cognitive flexibility, inhibition, initiation and WM. These may contribute to wider cognitive deficits (McCabe et al., 2011).

1.5.7 Methodological challenges in previous research

There is considerable heterogeneity in the cognitive phenotype of 22qDS. This probably partly reflects methodological problems and confounders, which may interact with genetic and developmental factors.

1.5.7.1 Diagnostic Method

The wide phenotypic spectrum and variable severity of 22qDS has limited the sensitivity of clinical diagnosis in the past, resulting in ascertainment bias in all studies.

Although not all studies reviewed above used FISH to accurately diagnose 22qDS, Shprintzen (2008) found no evidence of statistically significant differences in neuropsychological findings between those studies with and without FISH confirmation of 22qDS. The FISH test has a false negative rate of 5-7%. The recently developed multiplex ligation dependent probe amplification test (MLPA) is more sensitive (Stachon et al., 2007).

1.5.7.2 Sample size

The sample size across studies has ranged from under ten (Lajiness-O'Neill et al., 2005) to 172 (Green et al., 2009). The larger sample sizes have all been from cross-sectional studies. Sampling methods are not always described. Small sample size limits statistical power (increasing the risk of type II errors).

1.5.7.3 Ascertainment and selection bias

Shprintzen (2008) estimates that at least one third of 22qDS cases remain undetected, unless brought to medical attention, primarily by severe congenital heart disease. Cardiac lesions may be silent, and are absent in 30%. The absence of characteristic facial features in individuals from some ethnic groups could result in lower detection rates in those populations (McDonald-McGinn et al., 2005). Children with 22qDS may not attract educational attention if cognitively typical. Parents of children with familial 22qDS are often undiagnosed until their child presents medically (McDonald-McGinn et al., 2008). Most studies therefore demonstrate ascertainment bias and may not represent the full range of 22qDS. Hospital samples usually include more severe cases. There is strong selection bias in published studies, limiting the generalisability of the findings.

1.5.7.4 Control groups

The performance of children with 22qDS is often compared to typically developing controls or those with LD. The use of an IQ-matched control group

controls for the effects of low intelligence on specific tests of cognitive functioning. This allows assessment of specific deficits directly related to 22qDS but may complicate interpretation (Karmiloff-Smith, 2009). To examine the specificity of a cognitive phenotype, a control group should have the same range of cognitive ability. Finding suitable control groups in 22qDS research is difficult. Controls with idiopathic LD have aetiological heterogeneity, which could confound interpretation. The cognitive phenotypes of Turner Syndrome and Williams Syndrome are comparable to that of 22qDS and enable investigation of gene-specific as well as more general influences on 22qDS phenotype (Campbell et al., 2009; Murphy et al., 2006).

1.5.7.5 Tests used across studies

Although most studies use the Wechsler intelligence scales, a wide range of assessment tools, including experimental tasks, is reported. Test variation between studies could obscure the 22qDS cognitive phenotype. However, the validity of a result is increased if it is consistent across different tests. Reasonable consistency has, in fact, been found across most studies.

1.6 SUMMARY

Recent research on the cognitive profile of children and adolescents with 22qDS has yielded several consistent findings. Verbal is frequently superior to nonverbal intellectual and memory function.

Henry et al. (2002) report absence of an expected group verbal>nonverbal discrepancy in their small sample of non-psychotic and psychotic adults with 22qDS, with a clinically significant reverse discrepancy found in one third, indicating that cognitive strengths and weaknesses may change with development. Other adult studies (Chow et al., 2006; van Amelsvoort et al. 2004) focus on cognitive differences between psychotic and non-psychotic 22qDS subgroups. Although they do not report analyses of verbal-nonverbal

discrepancies, they are negligible.

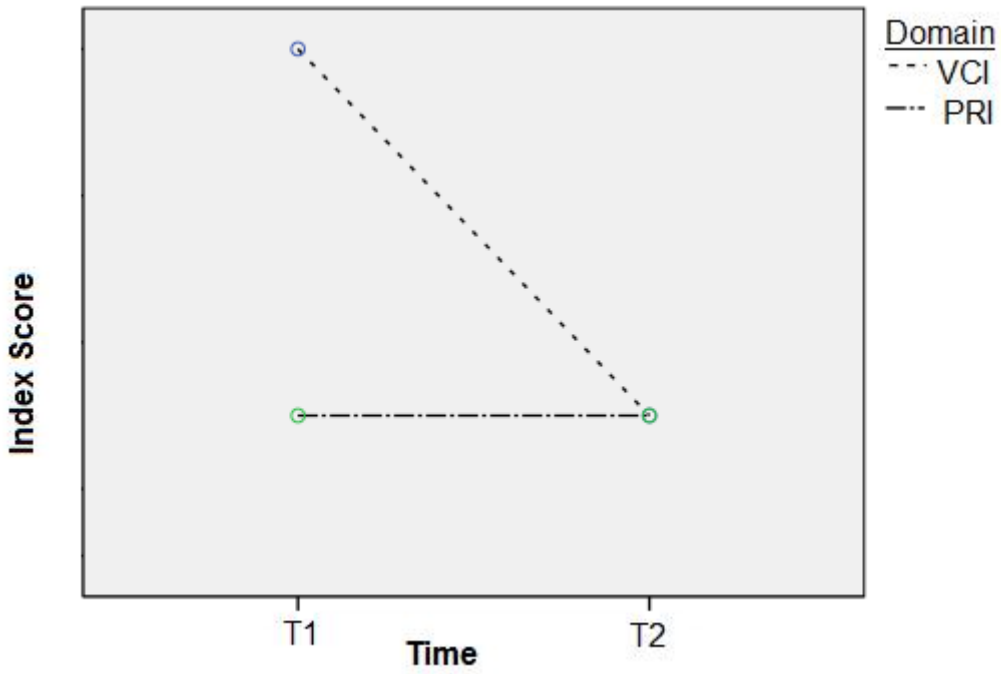
Cross-sectional studies report declining FSIQ with age. Longitudinal studies report conflicting findings. Gothelf et al. (2005; 2007d) found a reduction in mean FSIQ and of the degree of verbal>nonverbal discrepancy with age, secondary to declining VIQ, whereas Antshel et al. (2010) found no increase or decline in verbal or nonverbal intellectual functions with age. A substantial proportion of participants in both samples was receiving psychotropic medication.

1.7 HYPOTHESES

1.7.1 Intelligence

Verbal>nonverbal discrepancies are widely reported in children/adolescents with 22qDS but not in adults, for whom the evidence base is small. The first hypothesis was that the VCI>PRI discrepancy evident at time 1 (T1) in the present sample would reduce significantly at follow-up (time 2, T2). The second hypothesis was that the reduction would be attributable to declining VCI.

Figure 1: Hypotheses one and two



1.7.3 Memory

The evidence base for memory development with age is even smaller and suggests superior verbal compared to visual memory functioning in childhood/adolescence. In the only longitudinal study investigating memory, Antshel et al. (2010) found no discrepancy between verbal and visual memory but that verbal memory declined with age.

The third hypothesis for the present study would have been that memory would follow the same pattern as intelligence in that the discrepancy between verbal>visual memory would decrease due to declining verbal memory. However, as mentioned on page 30 (section 1.5.5.1), the present sample had an anomalous finding of no discrepancy between verbal and visual memory at T1 (Jacobson et al., 2010). Therefore it was hypothesised that the lack of discrepancy at T1 would remain at T2. The fourth hypothesis was that if VCI had declined or PRI had increased, memory would reflect a similar pattern. The

hypotheses for memory were tentative and analysis was fundamentally exploratory.

1.7.4 Executive Function

The literature reports deficits in WM and executive function in 22qDS. It was expected that performance on tasks of inhibition, set shifting and initiation would be lower than average compared to the general population. No hypothesis was made about executive function. Instead, data were collected to help contextualise the findings in the memory and intellectual domains of cognition.

1.7.5 Why is this important?

Establishment of the cognitive pattern underlying the hypothesised change in verbal>nonverbal discrepancy could inform the clinical and educational interventions that are offered at particular ages to those with 22qDS to optimise their cognitive development.

Gothelf et al. (2007d) propose that declining VIQ, amongst other factors, is a potential risk factor for later psychosis. The implications are that routine screening for "high risk predictive symptoms", e.g. declining VIQ, should be carried out and "subthreshold psychotic symptoms" should be treated with 'anti-psychotic' medication to improve the prognosis of the (predicted) later emerging psychotic disorder. This has also influenced the focus of other research groups, for example, the Antshel et al. (2010) study published three years later focuses on cognitive factors to identify 'prodromal psychotic symptoms' in a sample free from a psychotic diagnosis.

It is important for the future clinical and potential pharmacological management of individuals with 22qDS that the nature of such cognitive 'risk factors' is

explored further and understood within different frameworks. It is also important that research findings are presented in the context of social understandings of LD as well as within genetic frameworks. This will increase the availability of alternative perspectives on 22qDS for researchers and clinical professionals.

1.7.6 Present Study aims

This is the first longitudinal study investigating changes in the cognitive profile of individuals with 22qDS free from 'antipsychotic' or 'antidepressant' medication. It is also the first study in 22qDS to use the newer versions of the Wechsler intelligence tests, WISC-IV and WAIS-IV. To the author's knowledge, it is also the first longitudinal study of cognitive development in 22qDS with a UK sample. The study aimed to re-assess cognitively the original child/adolescent sample (n=31) previously assessed between 2004-2008, when aged 7-14 years (Jacobson et al., 2010).

2.0 METHODOLOGY

This section explains the rationale for particular methodological decisions and outlines some of the methodological challenges.

2.1.1 Different tests between T1 and T2

Use of the same test at two time points helps ensure the same cognitive functions are assessed and the same normative reference group is used to interpret scores. However, to monitor change in a clinically meaningful way that enables comparison across studies, standard not raw scores are typically used. Raw scores place individuals at particular points in the normal distribution of scores to relate their functioning to that of peers. To obtain standard scores, age stratified normative samples must be used to interpret the scores, and therefore age-appropriate tests must be administered. The child version of the Wechsler intelligence scales used at T1 would no longer be appropriate for participants aged 17-years or over at T2. Further, the most recent version of Wechsler test available at the time should be used, as it is more in keeping with changes in age-appropriate knowledge, the environment and culture (the Flynn effect). In the present study, participants were all assessed using the CMS and WISC-III at T1. At T2, the CMS, WMS-III, WISC-IV and WAIS-IV were used.

Tests used at T1 yielded some of the same index scores as tests used at T2, e.g. PRI, VCI, PSI and FSIQ. However, some subtests comprising these measures differed between T1 and T2 and within T2. For example, the WISC-III PRI (T1) comprises: Block Design, Picture Arrangement, Picture Completion and Object Assembly. The WISC-IV PRI comprises, Block Design, Matrix Reasoning and Picture Concepts. Only one subtest is common to both the PRI measure at T1 and T2: Block Design. To consider any statistically significant change between T1 and T2 as reflecting genuine atypical cognitive development and not just an artefact of the different subtests used, it should be demonstrated in the only common test between T1 and T2: Block Design.

Most cross-sectional and all longitudinal studies of cognition in 22qDS use different age-appropriate tests within their samples. Debbane et al. (2008) used the CMS for children and WMS-III for adults in their sample, combining the index scores for the group overall, despite slight subtest differences between the tests, e.g. the 'word pairs' subtest in CMS has more words than the 'word lists' subtest in the WMS-III. Standard scores aim to control for differences in complexity or cognitive load between subtests by interpreting performance with different normative tables for each subtest. Green et al. (2009), Gothelf et al. (2007a) and Antshel et al. (2010) all use both the child and adult versions of the Wechsler intelligence scales.

2.1.2 Standard scores versus raw scores in developmental trajectories

A child's raw score on the same test should increase with age. Therefore raw scores are not comparable across different age ranges or different tasks (Baron, 2004; Mervis & Klein-Tasman, 2004). Standard scores, however, are expected to remain relatively stable across an individual's lifespan from the age of 4-years onwards (Sigelman & Rider, 2006; Weinert & Hany, 2003). Substantial changes in standard scores over time can reveal whether participants have deviated from the normative developmental cognitive trajectory. However, once a deviation is revealed, only raw scores can help explore the underlying cognitive pattern. For example, if standard scores showed that VCI declined over time, raw scores could reveal whether verbal intellectual functions had actually deteriorated with age or development had stagnated and reached a plateau. However, comparison of raw scores between time points is only possible if the same test is administered at both points.

The different interpretations that can be made between raw and standard scores influenced the choice of tests used in the present study. Standard scores were preferred to raw scores so different age-appropriate tests were

used at T1 and T2, as in other studies (Antshel et al., 2010; Gothelf et al., 2005; 2007a). However, this relies on the assumption that the Wechsler tests all measure the same underlying construct of 'intelligence'.

2.1.3 Different within-sample cognitive batteries at T2

Participants aged 17-years and above were assessed with the WAIS-IV and WMS-III, and those younger with the WISC-IV and CMS. The Digit Span subtest differs between the WISC-IV and WAIS-IV. An additional task of arranging number strings into numerical order when repeating them back to the examiner is included in the adult version of the subtest. Therefore the WAIS-IV Digit Span score measures a slightly different function compared to the WISC-IV subtest.

Previous studies (Gothelf et al., 2007; Ramsden et al., 2011) used WAIS-III and WISC-III, which are closely correlated, suggesting that they both measure highly similar constructs (Kaufman & Lichtenberger, 2006). The WAIS-IV and WISC-IV tests are also strongly correlated, and a standard score on one broadly equates to the other, as all other subtests are identical in concept and rules. The Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999) could have been used instead because it has norms for all ages, but it does not include all the subtests required for measuring processing speed.

The CMS and WMS are used to assess memory. However, visual recall was measured differently between the CMS and WMS. A more recent version of the WMS-III (the WMS-IV) was not used because the corresponding child version is not yet available.

2.1.4 Prorating method

Intellectual and memory index scores in the present study were prorated, a method used in other 22qDS studies (van Amelsvoort et al., 2004; Rockers et al., 2009). To reduce testing time, enabling cognitive assessments to be completed in one rather than two appointments, only two of three subtests

comprising overall index scores were completed and an average was used to determine the index score. Prorating is a common procedure and tables to support the process are available in the WICS-IV and WAIS-IV manuals. Scores were cross-checked against these tables. Reid-Arndt, Allen and Schopp (2011) found strong correlation ($r > .91$, $p < .001$) between prorated FSIQ and FSIQ derived from all subtests on the WAIS-III in a sample (n=176), supporting the method as robust. Axelrod and Ryan (2000) reported strong reliability for prorated scores compared to standard VIQ and PIQ summary scores. Although prorating could be viewed as less thorough, it is unlikely to affect the accuracy of estimated cognitive functions.

2.1.5 Are the tests reliable enough to capture cognitive change?

The retest reliability of FSIQ in the WISC-IV was 0.93 and for the sub-indices it ranged from 0.86-0.93 (The Psychological Corporation, 2003). For the adult version (WAIS-IV), retest reliability for FSIQ and the sub-indices ranged from 0.87-0.96 (Lichtenberger & Kaufman, 2009).

Other methodological challenges include a focus on group averages (despite extensive cognitive heterogeneity in 22qDS), which obscures variability in rates at which verbal and nonverbal functions develop. There is also a need to consider regression to the mean, the phenomenon whereby extreme scores are more likely to change over time than scores that are less extreme. Thus the lowest IQ scores at T1 may reveal the greatest change at T2, which could reflect genuine cognitive change or regression effect.

3.0 METHOD

3.1 ETHICAL APPROVAL

The study was registered with the school of psychology at the University of East London (UEL, appendix one). Ethical approval was sought and obtained from: UEL ethics committee, Great Ormond Street Hospital (GOSH) psychology ethics committee, GOSH Clinical Research Adoptions Committee, NHS ethics and the GOSH Research and Development department (appendices two-four).

3.2 ETHICAL ISSUES

3.2.1 Informed consent

A letter and information sheet inviting individuals to participate in the study were posted to potential participants or their guardians depending on their age (appendices five-eight). An oral description of the study was given to individuals and their parents two weeks later over the telephone. For those aged under 16-years, parental consent was sought and for those over 16-years, capacity to consent was assessed by the author according to the Mental Capacity Act (2005). For child and guardian versions of the consent form, see appendices nine and ten.

3.2.2 Confidentiality and anonymity of the data

Participants were advised that their data were confidential. Raw data were stored in the psychology department of GOSH in a secure filing cabinet in a secure office in a secure building. Copies of the assessment results were put in participants' clinical records only if they consented to this.

Participants' data were anonymised and stored electronically on a database at GOSH in a password protected file. A copy of the database was also stored on

an encrypted, password protected memory stick to be used by the author at university and home.

3.2.3 Feedback

Feedback on participants' individual results was offered over the telephone and followed with a written summary once the study was completed. If participants wished to discuss their results further, they were put in contact with the author's clinical supervisor (Clinical Psychologist) who arranged to meet with them. A written summary of the overall results of the study and an oral description were also offered.

3.2.4 Implications of psychiatric screens

If participants' scores on screening measures were clinically significant, they were informed and offered the option of referral to their GP or the psychiatrist attached to the 22qDS team. Two participants were referred to the 22qDS MDT for general review.

3.2.5 Cost to participants

Travel expenses were reimbursed up to a maximum of £50. Reimbursement of participants' time was not available due to funding restrictions. Costs to participants in terms of time were made clear in the information sheet.

3.3 RESEARCH DESIGN

This was a longitudinal study. The original cohort had previously been cognitively assessed and this study required follow-up cognitive assessment. No control group was used because the original assessment involved a case note review and acquiring a retrospective control group was beyond the scope

of the present study. The limitations of this approach are reviewed in the discussion. A within-subjects design was used for most analyses and a between-subjects design was used for subgroup analyses.

3.4 ORIGINAL SAMPLE AT T1

All babies in the North Thames region in London with a suspected diagnosis of 22qDS are referred to the 22qDS Service at GOSH. Patients are assessed by the Consultant Paediatrician and multi-disciplinary team (MDT) comprising: an audiologist, genetic counsellor, plastic surgeon, clinical nurse specialist, speech and language therapist, clinical psychologist, orthodontist and psychiatrist. Thereafter patients are monitored by the MDT with regular reviews of their development at ages 2, 4, 10, 15 and 18 years, because these are the usual ages for decisions about education when discussions about behaviour or medical progress can be helpful.

3.4.1 Selection bias

Some patients are referred to clinical psychology within the MDT for an assessment of their cognitive strengths and weaknesses to provide educational recommendations and support. The referral criteria for a cognitive assessment require the patient to be aged between 6- and 16-years, to be struggling to meet educational goals and to lack adequate educational support. Between 2004 and 2008, the period during which cognitive assessments in the Jacobson et al. (2010) study were completed, a total of 75 patients within the 22qDS Service at GOSH were at an age eligible for cognitive assessment. Only 31 of the 75 patients (41%) within the Service were referred to Clinical Psychology for a cognitive assessment, indicating that the remaining 59% were either meeting educational goals or already had adequate support in place, e.g. through a statement of educational needs. The data at T1 were retrospectively collected as a case note review.

3.5 INCLUSION/EXCLUSION CRITERIA

For the follow-up assessment, any participants who completed the initial assessment between 2004 and 2008 were included. Exclusion criteria included any participants who had sustained neurological trauma since the initial assessment (n=0). Original inclusion and exclusion criteria at T1 were referral for cognitive assessment during 2004-2008 and head injury, respectively.

3.6 RECRUITMENT PROCEDURE

Following ethical approval from the above committees, potential participants received a letter, information sheet outlining the purpose and nature of the project and contact details. They were advised to expect a telephone call from the author, during which the goals of the research and participation requirements would be discussed in more detail. For those participants under the age of 16-years, the letter was sent to their guardian.

During the telephone conversation, participants were advised to take a week to consider their decision, and they were given the option not to contact the author should they wish to decline participation. Those who agreed to participate arranged a time to meet the author for an assessment. All participants were accompanied by a parent/guardian.

Attrition was attributable to two individuals declining participation, two having relocated too far away, one being medically unfit to participate, and two being uncontactable.

3.7 TESTING SITES

Participants aged 17-years and under were assessed at GOSH and the older cohort was assessed at the Institute of Psychiatry, because the insurance at GOSH would not permit participants aged 18+ years to be seen for research purposes on the GOSH premises.

Consent was obtained from all participants. Guardians of those aged under 16-years also signed a separate consent form (appendix six). Participants were offered breaks and water.

3.8 NEUROPSYCHOLOGICAL ASSESSMENT

Standardised tests of general cognitive functioning, memory, and executive functioning were administered to all participants. All cognitive assessments were conducted between July-October 2011. All assessments were conducted by the author under the supervision of a qualified Clinical Psychologist. The typical duration for the overall assessment was under two hours (including breaks to reduce fatigue). Cognitive tests were administered to all participants in the same fixed order to standardise their experience. All tests were scored and re-checked by the author before data entry, then cross-checked afterwards to minimise scoring error.

Participants were assessed in a similar way to those in other studies. Extraneous factors that could have influenced cognitive change between T1 and T2 were acknowledged and minimised as much as possible. Most participants were reassessed by the same examiner they had at T1 (the author). Although the author remained vigilant for any behaviour indicating influence of substances that might alter cognition, e.g. marijuana, participants were not screened for substance use.

The individual test batteries administered to the patient sample are briefly described below. The normative samples yield index scores with means of 100 (SD: 15) and scaled score means of 10 (SD: 3).

3.9 MEASURES OF COGNITIVE FUNCTION

Participants aged 17+ years were tested using the Wechsler Adult Intelligence Scales-IV (Wechsler, 2008). The younger cohort was examined with the Wechsler Intelligence Scale Children-IV (Wechsler, 2003). Both tests yield a Full Scale IQ (FSIQ), as well as four index scores: Verbal Comprehension (VCI), Perceptual Reasoning (PRI), Working Memory (WMI) and Processing Speed (PSI). The WMI was not obtained because only one subtest comprising this index was administered, Digit Span. Differences between the WAIS-IV and WISC-IV subtests in the WMI complicated comparison. Digit span was the most similar subtest between the two.

3.9.1 Subtests comprising VCI

3.9.1.1 Similarities

This requires participants to say how two words are alike, e.g. ‘bird’ and ‘dog’ are both ‘animals’. It is a measure of verbal abstract reasoning, semantic memory and conceptualisation.

3.9.1.2 Vocabulary

This subtest measures receptive and expressive vocabulary. Participants are required to define words, e.g. “what does the word ‘breakfast’ mean?”

3.9.2 Subtests comprising PRI

3.9.2.1 Block Design

This measures visuo-spatial perception and reasoning and visuo-constructional function. Participants arrange different coloured blocks to re-create two-dimensional designs varying in complexity.

3.9.2.2 Matrix Reasoning

This subtest measures abstract nonverbal reasoning. It requires the identification of patterns in a series of designs and the selection of the correct missing piece of the pattern from a range of choices.

3.9.3 Subtests comprising PSI

3.9.3.1 Symbol Search

This is a measure of processing and visual-motor speed. Rows of symbols are checked to see if they contain one of two target symbols.

3.9.3.2 Coding

This measures visual-motor speed and short-term visual memory. Symbols are matched with numbers or shapes according to a key. Additionally, coding requires fine motor skills, because participants are required to draw the symbols, whereas symbol search only requires a box to be ticked.

3.9.4 WM subtest Digit span

This is a measure of WM. Participants are required to listen to a series of numbers and repeat them back forwards and in the reverse order. Repeating the numbers forwards is arguably a measure of short term memory whereas

repeating the digits backwards is a measure of WM because the task requires manipulation of the information. The WAIS-IV includes an additional task of number-letter sequencing and the score from this task contributes to the overall 'Digit Span' score for the WAIS-IV.

The overlap in subtests between T1 and T2 can be seen in table 4.

Table 4: Subtests used in WISC-III (T1) and WISC-IV/WAIS-IV (T2)

WISC-III VIQ & PIQ	**Index**	**WISC-III (T1)**	**WISC-IV/WAIS-IV (T2)**
WISC-III VIQ	VCI	Vocabulary	Vocabulary
		Similarities	Similarities
		Information	-
		Comprehension	-
	FDI / WMI	Arithmetic	-
		(Digit Span)	Digit Span
WISC-III PIQ	PRI	Block Design	Block Design
		Picture Completion	Matrices
		Picture Arrangement	-
		Object Assembly	-
	PSI	Coding	Coding
		(Symbol Search)	Symbol Search

Key:

()- Not included in WISC-III VIQ or PIQ

3.9.4.1 Properties

The reliability coefficients for the standardisation sample in the WISC-IV are strong (Wechsler, 2008). The average internal consistency for subtests is good ranging from .78 for a cancellation subtest to .94 for vocabulary. The average internal consistency reliability coefficients for the WAIS–IV composites range from .90 for the PSI to .98 for the FSIQ (Wechsler, 2008).

3.9.7 Memory Measures

Participants aged 13-16 years completed the CMS and older participants completed the Wechsler Memory Scale – 3rd edition (WMS-III). The CMS and WMS-III comprise 8 Index scores: Immediate Verbal Memory, Delayed Verbal Memory, Delayed Recognition (verbal), Immediate Visual Memory, Delayed Visual Memory, General Memory, Learning, and Attention/concentration. The last index was not obtained because it involved repetition of the WAIS-IV/WISC-IV digit span subtest.

3.9.7.1 Memory Subtests

3.9.7.1.1 Verbal Paired Associates (WMS-III) / Word pairs (CMS)

These subtests measure verbal rote learning and immediate and delayed verbal recall. A list of unconnected word pairs is presented orally four times. After each presentation, participants are given one word and asked to recall the associated word. Finally they are asked to recall the list of word pairs without one of the pairing words being given as a prompt. They are asked to do this again 30 minutes later.

3.9.7.1.2 Logical Memory WMS-III)/Stories (CMS)

These subtests are designed to measure immediate and delayed verbal recall and verbal recognition memory for verbal information in a logical sequence and narrative context. Two age-appropriate short stories are read aloud by the examiner. Participants are required to recall everything they can about each story immediately after its presentation and also after a 30-minute delay. After their delayed recall attempt, participants are also required to answer closed questions about each story.

3.9.7.1.3 Faces (WMS-III & CMS)

This is intended to measure visual immediate and delayed facial recognition memory. A series of faces is presented with an oral cue given by the examiner of “remember this one”. Sixteen faces are presented in the CMS and 24 are shown in the WMS-III. Participants are then shown 48 faces and asked to identify whether each face was novel or one they had just been shown. Participants completed this recognition phase both immediately after the presentation of faces and after a 30-minute delay.

3.9.7.1.4 Dot Locations (CMS)

This purports to measure visual WM and visual rote learning. An image of eight blue dots in a particular arrangement on a grid is displayed for five seconds three separate times. After each display, participants then have to recreate the arrangement with blue chips on a blank grid. After the third attempt, participants are shown a different arrangement and asked to re-create it (as a distraction task). They are then asked to re-create the original pattern from memory. They are asked to do this again after a 30-minute delay.

3.9.7.1.5 Visual Reproduction (WMS-III)

This aims to measure visual memory although it also assesses visual-perceptual-motor functions. Unlike Dot Locations, it does not have a rote learning aspect. Participants are shown five images for 10 seconds each (although two images consist of two designs each). After each design, they are asked to draw the design from memory (immediate recall). After a 30-minute delay, they are required to do this again and then to distinguish previously shown from novel designs in a pool of 48.

3.9.7.1.6 Properties

Reliability coefficients for the index scores in the WMS-III range from 0.82-0.92 and are similar for the CMS (Cohen, 1997).

3.9.8 Rationale for using different tests

The rationale for using different Wechsler tests within the sample and T2 and between T1 and T2 is reviewed above (page 43, section 2.1). Although the most recently revised version of the Wechsler intelligence scales (WISC-IV and WAIS-IV) were used at follow-up, the most recently revised version of the WMS (WMS-IV) was not used.

3.9.9 Executive function

All participants were assessed using measures of phonemic and semantic fluency, and the colour-word interference test from the Delis-Kaplan Executive Function System (DKEFS; Delis, Kramer, Kaplan & Ober, 2001).

3.9.9.1 Phonemic fluency

For this task, participants are required to generate as many words as possible in one minute beginning with a specific letter (F, A, S). The participants are instructed not to repeat themselves and not to use numbers or proper nouns. Phonemic fluency is purported to reflect various aspects of frontal executive functions, namely initiation, strategy formation, rule following, organisation, self-monitoring and inhibition (Lezak, Loring & Hannay, 2004).

3.9.9.2 Semantic fluency

For this task, participants are again required to generate as many words as possible in one minute from a given category (animals were used in the current study). Semantic fluency depends on aspects of frontal executive function, similar to those required for phonemic fluency, with greater dependence on semantic activation (Lezak et al., 2004).

3.9.9.3 Colour-word interference

Participants are instructed to read aloud a list of colour names printed in incongruent ink colour as quickly as possible whilst being timed. They are then instructed to name the colour of the ink in which the word is printed as quickly as possible. The time taken and number of errors for each part of the test are compared against participants' performance when reading aloud colour names (printed in black ink) and squares of colours with no verbal association. This task addresses inhibition of the irrelevant task set and sustained response according to the target set.

3.9.10 Assessment of psychiatric pathology

3.9.10.1 Self-report measures

Adult and child versions of the Beck Depression and Anxiety Inventories (BDI & BAI; Beck et al, 1961; 1996; 2005) were used.

Low mood and anxiety are frequently reported in the 22qDS population. Due to regular MDT reviews, which include a Psychologist and Psychiatrist, it was presumed that any diagnoses of ASD, ADHD, ODD or psychosis would have been made and documented in the medical notes. However, anxiety and depression could have emerged subsequent to participants' MDT reviews. Mood and anxiety were assessed at T2 because they may impair performance on cognitive testing (Chepenik, Cornew & Farah, 2007). The Beck Depression and Anxiety Inventories (Beck et al, 1961; 1996; 2005) have been used before to measure low mood and anxiety in the 22qDS population. Their validity and reliability, while established in general, have not been investigated in the 22qDS population. Limitations of these tools are reviewed in the Discussion.

3.10 DATA MANAGEMENT

A database was created using SPSS version 18.0. Data from medical notes and psychological and cognitive assessments were inputted. Cognitive assessments were double scored to reduce the risk of errors. Data inputting was completed by the author and checked twice. Random spot checks were carried out, and the conversion of all raw scores into scaled and Index scores was cross-checked using age-appropriate tables in the test manuals.

3.11 PARTICIPANTS AT T2

All 31 participants (17 male, 14 female), currently aged 14-20 years, from the original Jacobson et al. (2010) study were approached initially by letter and

information sheet and then by telephone. Of the 31 participants, 24 consented to participate. The six participants from T1 who did not participate at T2 did not differ greatly from others in terms of age, FSIQ, VCI or PRI (table 5a). Diagnosis of 22qDS had already been confirmed using the FISH test at GOSH. Demographic information is displayed in table 5b. The mean age of the current sample at T1 (n=24) was 11.7 years (SD: 1.77) and at T2 16.4 years (SD: 1.79).

3.12 DEMOGRAPHIC INFORMATION

The following information was obtained at T1, re-checked at T2 and analysed: Date of birth, level of hearing/impairment, gender and history of cardiac surgery (table 5b), mode of inheritance (all parents have been FISH tested). Medical notes were checked for episodes of hypoxia and psychiatric diagnoses according to the DSM-IV (1994) criteria; the BDI and BAI were administered during data collection. The following diagnoses were not found in the sample: schizophrenia, schizoaffective disorder or ADHD. Two participants had a diagnosis of ASD and one participant had previously taken anti-depressant medication, but had discontinued this more than 6 months before assessment.

Table 5a: Differences between T1 participants and drop-outs at follow-up

Data at T1	**T1 Participants followed up at T2 (n=24)**	**T1 Participants not followed up (n=6)**
Mean Age (SD)	11.73 (1.77)	12.40 (2.87)
Mean FSIQ (SD)	60.71 (10.69)	65.86 (11.99)
Mean VCI (SD)	69.9 (13.01)	72.29 (12.26)
Mean PRI (SD)	62.43 (12.29)	66.29 (11.04)

Table 5b: Demographic information

Demographic variables	T2 Participants (n=24)
Female: Male	10:14
Cardiac surgery	5
Depression*	3
Anxiety*	6
ASD+	2

Key:

**Those who reached the cut-off criteria on the Beck Anxiety and Depression scales (adult and youth versions) (Beck* et al*, 1961; 1996; 2005).*

+ reported in medical notes, assessed elsewhere using Autism Diagnostic Observation Schedule (ADOS, Lord et al., 1989) and Autism diagnostic interview (ADI, LeCouteur, Rutter Lord & Rios, 1989).

4.0 RESULTS

4.1 DATA ANALYSIS

The data were quantitative and analysed using SPSS 18.0 for Windows. Normality was assessed to determine the non-/parametric properties of the data. General Linear Model (Repeated Measures) analyses and t-tests or their non-parametric equivalents were used. Where multiple comparisons were made there was risk of a type 1 error. The level of significance was set at $p<.05$ *a priori* for tests of the principal hypotheses, whereas for subsidiary analyses, greater weight was given to results at the $p<.001$ level.

4.2 EXPLORATORY DATA ANALYSIS

A normal distribution of the data (Normality) was assessed using skewness (cut-off >1), kurtosis (cut-off >3), Shapiro-Wilk, histograms and boxplots. Outliers were re-checked in the data but all found to be accurate data. Statistical analysis involving non-normally distributed variables (see tables 6 & 7) used parametric tests, but if a significant result was found, the analysis was repeated using the more conservative non-parametric tests.

Tables 6 and 7 show the variables that were not normally distributed at original assessment (T1) were: WISC-III Block Design subtest, CMS/WMS Words Pairs Delayed Recognition subtest and CMS Dot Locations Learning subtest. Variables not normally distributed at T2 were: WISC-IV/WAIS-IV Similarities and Digit Span Backwards subtests and CMS/WMS Visual Delayed Memory Index, Logical Memory Delayed Recall, Word Pairs Long Delay subtest and Word Pairs Delayed Recognition subtests.

Tables 6 and 7 also display the means and standard deviations of the sample's performance on the WISC-III at T1 and the WISC-IV/WAIS-IV at T2

respectively. The mean time interval between T1 and T2 was 4.66 years (SD: 1.09).

Data from the two participants with ASD did not yield any statistical outliers, but the numbers were too small for subgroup comparisons.

Table 6: Scores at T1

Test/Index	Mean	SD	Min-Max	Skew. SE= .472	Kurt. SE= .918	SW sig.
WISC/ WAIS Index scores						
Verbal Comprehension	74.46	11.93	50 -94	-.161	-1.094	.156
Perceptual Organisation	63.42	9.77	50 -85	.232	-.798	.129
Processing Speed	78.00	11.82	54-109	.557	.944	.487
Full Scale IQ	65.29	9.21	44 -79	-.510	-.360	.494
WISC/ WAIS Subtest Scaled Scores						
Block design	3.00	2.54	1-9	1.168	.154	*.000
Similarities	5.33	2.96	1-11	.128	-.587	.195
Digit Span	7.08	3.39	1-14	.588	.245	.091
Digit Span Backwards	-	-	-	-	-	-
Coding	5.88	2.79	1-13	.601	.451	.451
Vocabulary	5.54	2.62	1-10	.123	-.662	.273
Symbol search	6.04	2.87	1-13	.402	.679	.208
Matrices	-	-	-	-	-	-
WMS/ CMS Memory Index Scores						
Visual Immediate	84.54	15.86	50-109	-.533	.263	.189
Visual Delayed	82.88	14.28	60-109	.307	-.823	.267
Verbal Immediate	88.13	16.48	57-112	-.223	-.848	.335
Verbal Delayed	88.67	14.63	63-115	-.209	-.916	.404
Verbal Delayed Recognition	86.88	15.67	50-112	-.964	.677	.048

Test/Index	Mean	SD	Min-Max	Skew. SE= .472	Kurt. SE= .918	SW sig.
General Memory	79.92	12.20	57-101	-.273	-.624	.338
WMS/ CMS Subtest Scaled Scores						
Logical memory immediate	7.42	3.11	2-13	.220	-.884	.457
Logical memory Delayed	7.96	3.26	2-13	-.344	-.785	.230
Logical memory Recognition	7.04	3.20	1-14	.168	.238	.480
Faces Immediate	6.67	2.99	1-11	-.181	-1.016	.166
Faces Delayed	6.08	3.26	1-12	.414	-1.017	.069
Word Pairs Learning	8.54	3.40	3-14	.286	-.766	.091
Word Pairs total	8.50	3.45	2-14	-.166	-.704	.556
Word Pairs Long Delay	8.29	2.74	3-13	-.113	-.584	.474
Word Pairs Recognition	8.38	3.76	1-12	-.661	-1.091	*.002
Dot locations learning	8.58	3.06	1-14	.002	-.812	.174
Dot locations Immediate Recall	8.46	3.34	1-14	-.875	.796	*.041
Dot locations Delayed Recall	8.71	3.38	2-14	-.715	.385	.174

Key:

SD	-	*Standard Deviation*
Skew	-	*Skewness*
Kurt	-	*Kurtosis*
SW	-	*Shapiro-Wilk*
*	-	*Not normally distributed*

Table 7: Scores at T2

Test/Index	Mean	SD	Min-Max	Skew. SE=.472	Kurt. SE=.918	SW sig.
WISC/ WAIS Index scores						
Verbal Comprehension	76.46	9.76	59-99	.399	-.075	.801
Perceptual Organisation	73.13	10.78	57-98	.500	-.172	.504
Processing Speed	75.83	10.26	50-91	-.417	.210	.441
Full Scale IQ	72.33	10.39	48-87	-.633	-.422	.139
WISC/WAIS Subtest Scaled Scores						
Block design	5.25	2.33	1-11	.619	.517	.279
Similarities	6.38	1.97	4-13	1.868	4.755	*.001
Digit Span	8.67	3.61	4-17	.604	-.235	.158
Digit Span Backwards	8.87	3.76	3-19	1.019	.946	*.046
Coding	5.04	2.42	1-10	-.113	-.471	.344
Vocabulary	5.33	2.24	1-9	-.305	-.810	.294
Symbol search	6.21	2.13	1-10	-.149	.332	.165
Matrices	5.75	1.75	3-10	.418	-.137	.097
WMS/ CMS Memory Index Scores						
Visual Immediate	84.33	12.00	61-112	.176	.104	.742
Visual Delayed	91.86	12.75	75-132	1.322	2.929	*.023
Verbal Immediate	85.79	14.43	63-114	.002	-.968	.402
Verbal Delayed	90.58	13.47	63-109	-.615	-.173	.092

Test/Index	Mean	SD	Min-Max	Skew. SE=.472	Kurt. SE=.918	SW sig.
Verbal Delayed Recognition	87.63	16.52	60-118	.115	-1.030	.452
General Memory	87.21	14.07	57-104	-.719	-.353	*.034
WMS/ CMS Subtest Scaled Scores						
Logical memory immediate	8.21	2.00	4-12	.008	-.440	.446
Logical memory Delayed	8.42	2.10	5-12	.219	-1.328	*.030
Logical memory Recognition	6.25	2.94	1-11	-.122	-.971	.315
Faces Immediate	7.46	2.52	2-12	-.303	-.343	.577
Faces Delayed	9.29	1.90	6-15	.913	2.280	.055
Word Pairs Learning	7.29	3.37	1-12	-.342	-.537	.080
Word Pairs total	7.13	3.54	1-15	.278	-.337	.878
Word Pairs Long Delay	8.50	3.44	2-13	-.668	-.685	*.010
Word Pairs Recognition	8.92	3.98	1-12	-1.227	-.175	*.000
CMS Dot locations learning	8.13	3.14	4-15	.964	.798	.058
CMS Dot locations Immediate Recall	7.73	2.87	4-13	.582	-.338	.267

Test/Index	Mean	SD	Min-Max	Skew. SE=.472	Kurt. SE=.918	SW sig.
CMS Dot locations Delayed Recall	7.27	2.71	2-12	-.027	-.510	.397
WMS Visual Reproduction Immediate Recall (n=9)	9.22	4.68	2- 14	-.602	-1.595	.058
WMS Visual Reproduction Delayed Recall (n=9)	9.67	4.15	3-16	.196	-.644	.316
WMS Visual Reproduction Delayed Recognition (n=9)	6.44	4.22	2-14	.977	-.448	.099
DKEFS Scaled Scores n=24						
Verbal fluency FAS	5.67	2.66	1-12	.557	-.043	.266
Semantic fluency animals and boys names	6.63	2.10	3-10	.054	-.766	.137
Category switching total correct responses	7.50	2.55	2-11	-.393	-.470	.266
Category switching no. of switches	8.54	2.04	4-12	-.383	-.564	.269
Colour naming	6.63	3.21	1-11	-.418	-.916	.081
Colour reading	7.88	3.31	2-12	-.334	-1.186	.029
Incongruent colour naming	6.79	2.98	1-11	-.243	-1.003	.131
Incongruent colour and rule switching	6.38	3.45	1-11	-.444	-1.071	.017

Key:
SD - Standard Deviation
Skew - Skewness
Kurt - Kurtosis
SW- Shapiro-Wilk
** - Not normally distributed*

4.3 INTELLECTUAL FUNCTIONS

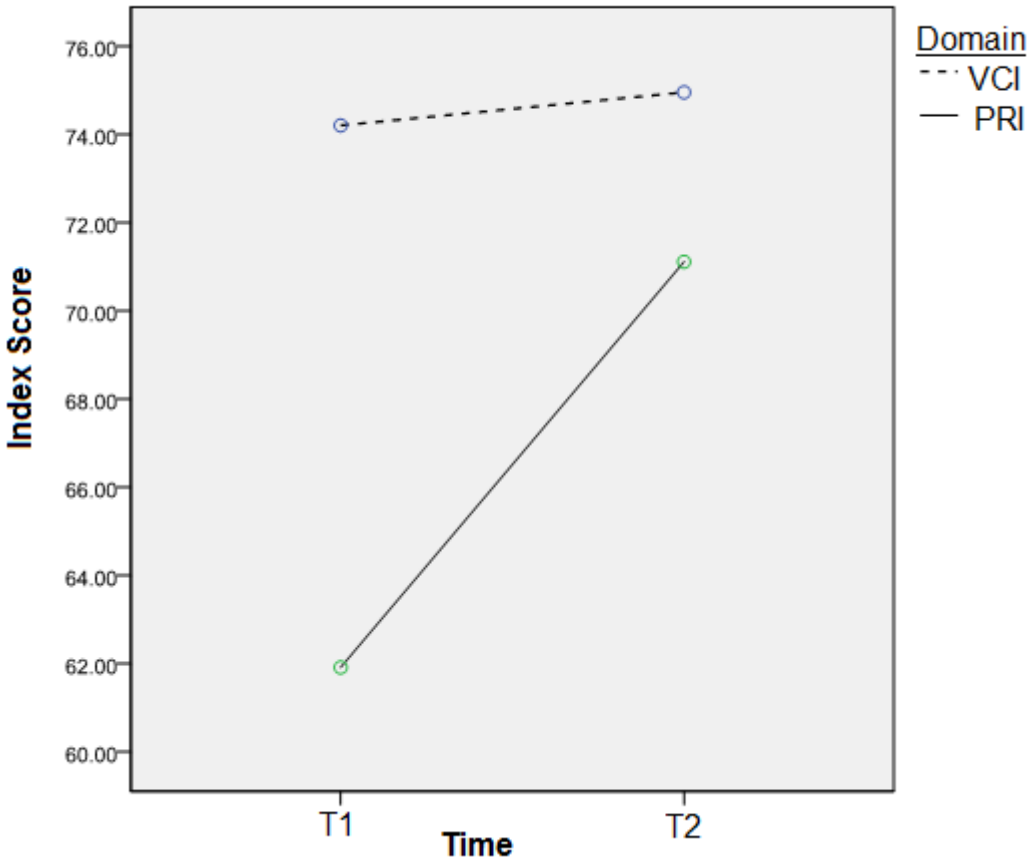
4.3.1 How the relationship between VCI and PRI at T2 compares with that at T1

A General Linear Model (Repeated Measures) test (GLM-RM) was performed to examine interaction effects between domain (VCI and PRI) and time with age group and gender as covariates. There were no main effects of gender [$F(1, 20)= 1.225$, $pe^2= .058$, $p= .282$] or age group when the sample was split into those aged above or below the median of 16 years [$F(1, 20)= 4.021$, $pe^2= .167$, $p= .059$].

There was a reliable one-way interaction between time points [$F(1, 20)=10.488$, $pe^2= .344$, $p=.004$] and a statistically significant one-way interaction between domains [$F(1, 20)=16.365$, $pe^2= .450$, $p=.001$]. The latter one-way interaction was not affected by gender [$F(1, 20)=.237$, $pe^2= .012$, $p=.632$] or age group [$F(1, 20)=2.757$, $pe^2= .121$, $p=.112$].

There was a significant two-way interaction between time and domain [$F(1, 20)=13.614$, $pe^2= .405$, $p=.001$] (see figure 2). There were no three-way interactions.

Figure 2: Interaction between VCI and PRI over time



Paired samples t-tests confirmed that the discrepancy between VCI>PRI was statistically significant at T1 [t(1, 23)= 5.275, p= .000] but not at T2 [t(1, 23)= 1.490, p= .150]. However, this was not due to the hypothesised decline of VCI between T1 and T2 [t(1, 23)= -1.041, p= .309]. It was attributable to PRI increasing between T1 and T2 [t(1, 23)= 5.610, p= .000]. The increase in PRI between T1 and T2 was large enough to cause a significant increase in FSIQ between T1 and T2 as well [t(1, 23)=-4.790, p= .000]. Mean FSIQ at T1 was more than two standard deviations below the general population mean and in the LD range (table 6), but at T2, it was above the cut-off for LD (table 7).

The number of individuals who had a clinically significant VCI>PRI discrepancy fell from 15 at T1 to 6 at T2.

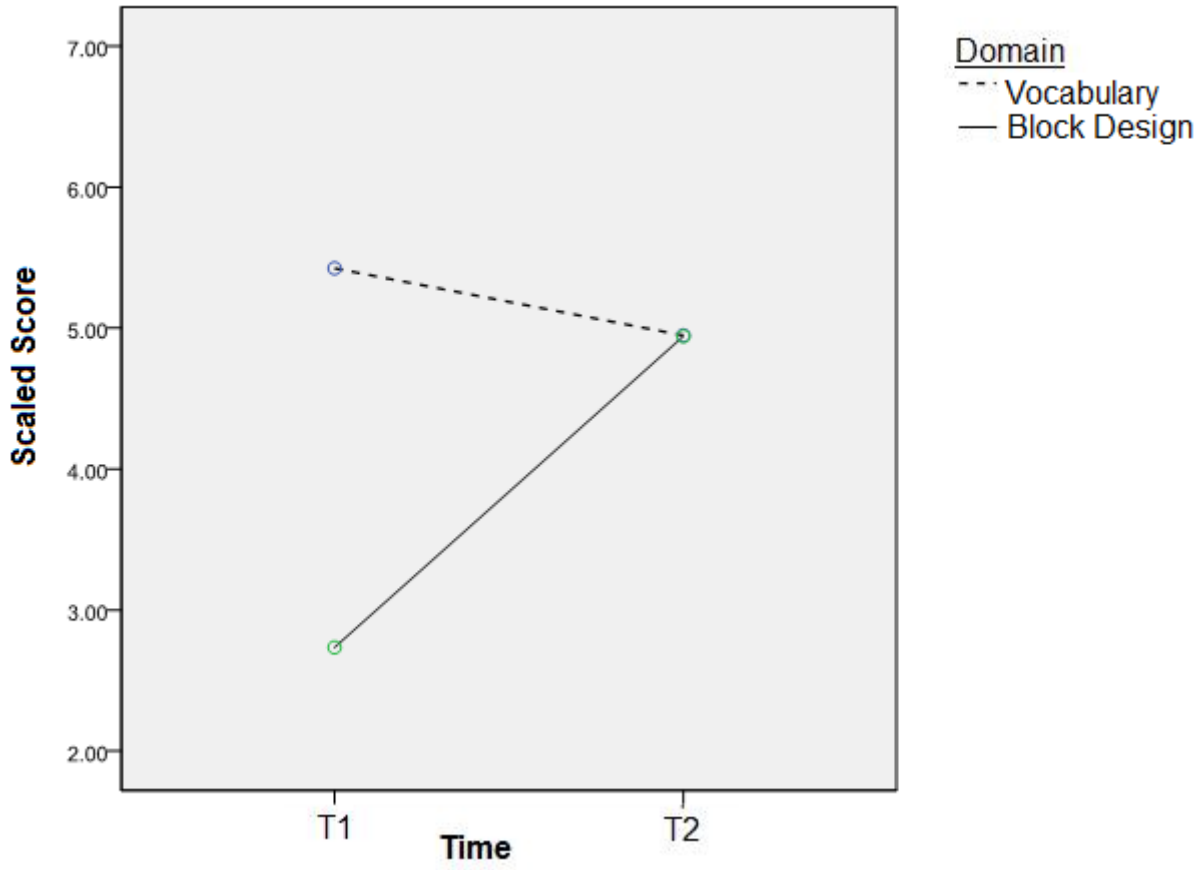
4.3.2 Is the temporal interaction between VCI and PRI confounded by using different subtests?

One of the two subtests in the PRI differs between T1 and T2. To ensure that the increase in PRI over time was a true cognitive change rather than an artefact of different subtests administered at T1 and T2, scores on Block Design, the only consistent subtest in PRI at T1 and T2, were analysed. Vocabulary and Similarities subtests comprised VCI at T1 and T2 but as Similarities was skewed at T2, only Vocabulary was selected for comparison with Block Design. A GLM-RM was used to investigate interactions between time and the subtests Block Design (PRI subtest) and Vocabulary (VCI subtest), whilst co-varying for the effects of gender and age group.

There were no main effects of age group [$F(1, 20)= 3.210$, $pe^2= .138$, $p= .088$] or gender [$F(1, 20)= 2.172$, $pe^2= .098$, $p= .156$]. There were one-way interactions for both time point overall [$F(1, 20)= 6.252$, $pe^2= .238$, $p= .021$] and subtest [$F(1, 20)= 4.105$, $pe^2= .170$, $p= .056$], but only the former reached statistical significance. There was a significant two-way interaction between time and subtest [$F(1, 20)=38.594$, $pe^2= .659$, $p=.000$] (figure 3). The interaction between time and subtest was not affected by gender [$F(1, 20)=.033$, $pe^2= .002$, $p=.857$] or age group [$F(1, 20)=3.578$, $pe^2= .152$, $p=.073$]. The findings support the observed interaction between PRI and VCI over time.

A Wilcoxon signed ranks test confirmed that the interaction between time and subtest was attributable to increasing mean performance on Block Design between T1 and T2 [$t(1, 23)= -6.044$, $p= .000$] rather than declining performance on the vocabulary subtest [$t(1, 23)= -.471$, $p= .642$] (Wicoxon Matched Pairs Test).

Figure 3: Interaction between time and subtest: Vocabulary and Block Design



4.3.3 Changes in other subtests between T1 and T2

To investigate the specificity of 'change' to Block Design, discrepancies between T1 and T2 for other subtests were analysed. A Related Samples Wilcoxon Signed Ranks Test yielded a significant improvement between T1 and T2 for Similarities, although this did not meet the significance criteria set out in the present study of $p < .001$. Paired samples t-tests were performed which yielded no discrepancies between T1 and T2 for any other subtests (table 8).

Table 8: Differences in mean WISC/WAIS subtest scaled scores between T1 and T2

Index subtest comprises	**Subtest**	**F (1, 23)**	**pe²**	**p**
PRI	Block Design	*Wilcoxon signed ranks*		.000
VCI	Vocabulary	.222	.010	.642
	Similarities	*Wilcoxon signed ranks*		.049
PSI	Coding	2.674	.104	.116
	Symbol Search	.086	.004	.773
N/A	Digit span	6.856	.230	.015

4.3.7 Within-domain subtest differences

There were no reliable differences between mean subtest scores at T2 within the same domain for VCI or PRI, indicating that each of these two cognitive domains has sufficient internal validity (table 9). A Related Samples Wilcoxon Signed Ranks Test was used to compare subtests within the VCI domain because the similarities subtest is not normally distributed. A Paired Samples t-test revealed a significant difference, however, between subtests within the PSI index (table 9), indicating that this index may have weak internal consistency. Any subsequent analyses investigating processing speed, e.g. changes between T1 and T2 should therefore be done at the level of subtest not index score. There was no significant difference between the mean subtest scores comprising PSI at T1 [t(1, 23)= -.233, p= .817] or either mean subtest score between T1 and T2 (table 8), indicating no significant change in the mean processing speed between T1 and T2.

Table 9: Differences between within-domain subtests at T2

Index subtest comprises	Subtest (T2)		t (1, 23)	p
PRI	Block Design		-1.081	.291
	Matrix Reasoning			
VCI	Vocabulary	*Wilcoxon signed ranks*		.06
	Similarities			
PSI	Coding		-2.488	.021
	Symbol Search			

4.4 MEMORY

The mean memory index scores at T1 and T2 were in the average to low-average range, except for the visual immediate memory index which fell in the below average range (tables 6 & 7).

4.4.1 Immediate memory

A GLM-RM was performed to examine interactions between domain (visual and verbal immediate memory), time, age group and gender. There was a main effect of age group with the older group performing better than the younger group overall across both memory domains and time point [$F(1, 20)=4.630$, $pe^2= .188$, $p=.044$]. There was no interaction between time and domain overall [$F(1, 20)= 1.918$, $pe^2= .088$, $p= .181$].

There was a two-way interaction between age group and gender [$F(1, 20)= 6.620$, $pe^2= .249$, $p=.018$]. The 4-way interaction of time x gender x age group x domain was not significant [$F(1, 20)= .879$, $pe^2= .042$, $p= .360$]. There were

three 3-way interactions, although only one was statistically significant at the level of $p < .05$:

- Time x domain x gender [$F(1, 20) = 4.662$, $pe^2 = .189$, $p = .043$]
- Time x domain x age group [$F(1, 20) = 4.211$, $pe^2 = .174$, $p = .053$]
- Time x age group x gender [$F(1, 20) = 3.233$, $pe^2 = .139$, $p = .087$]

It appears that age group has an effect in the interaction between gender and time, but the sample does not have sufficient power to investigate this. There may be a non-significant interaction between time and domain but it is modified by gender (figures 4 and 5). To be conservative, only the statistically significant 3-way interaction of time, domain and gender was investigated further with t-tests.

Figure 4: Interaction between time and immediate memory indexes (visual and verbal) for males

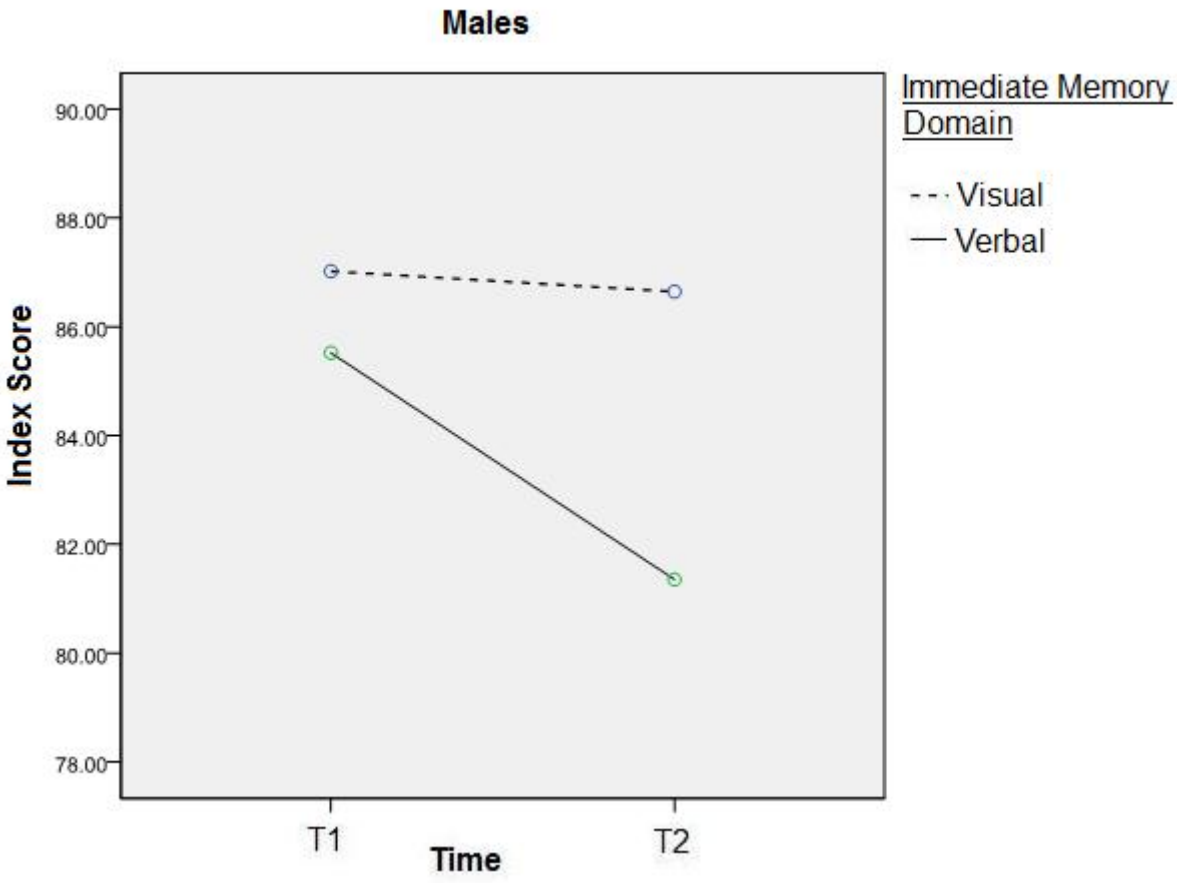
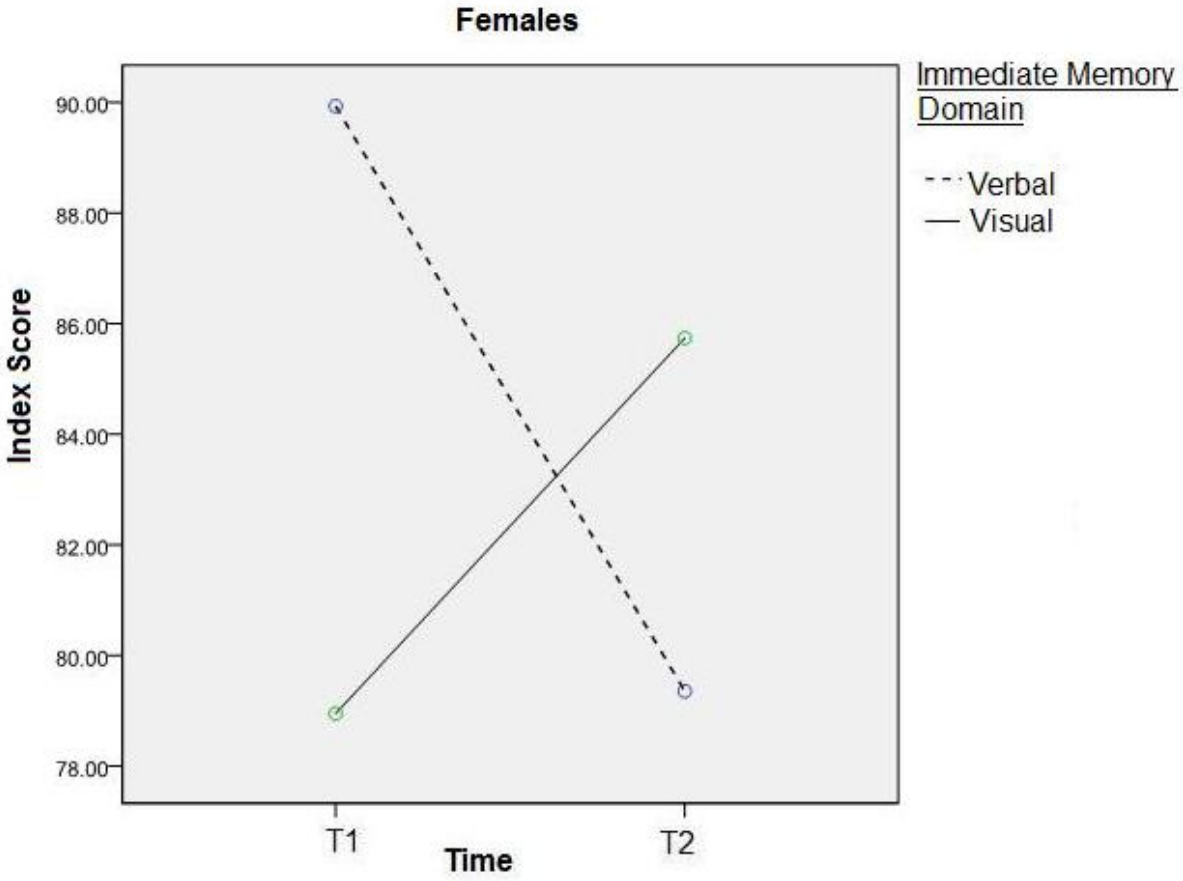


Figure 5: Interaction between time and immediate memory indexes (visual and verbal) for females



Paired samples t-tests revealed no significant differences between visual immediate memory at T1 and T2 [t(1, 13)= .883, p= .393] or verbal immediate memory between T1 and T2 [t(1, 13)= .092, p= .928] for males.

Paired samples t-tests revealed a significant increase in visual immediate memory between T1 and T2 [t(1, 9)= -2.694, p= .025], but no difference in verbal immediate memory between T1 and T2 [t(1, 9)= .841, p= .422] for females. The mean performance for visual immediate memory in females increased by 6 points from 83.2 (SD: 16.92) at T1 to 89.5 (SD: 13.90) at T2. Although it was not statistically significant, mean performance for immediate verbal memory in females fell by 5 points from 89.5 (SD: 16.63) at T1 to 84.3

(SD: 17.24) at T2. These changes in the opposite direction suggest a reverse discrepancy between immediate visual and verbal memory at T2 compared to T1 in females, although the discrepancy was not statistically significant.

When looking at the change in immediate visual memory for each individual female participant compared to each male participant, the change appeared more consistent and less variable but the numbers for each subgroup are small (see figures 6 and 7).

Figure 6: Each individual female participant's visual immediate memory performance at T1 and T2 (n=10)

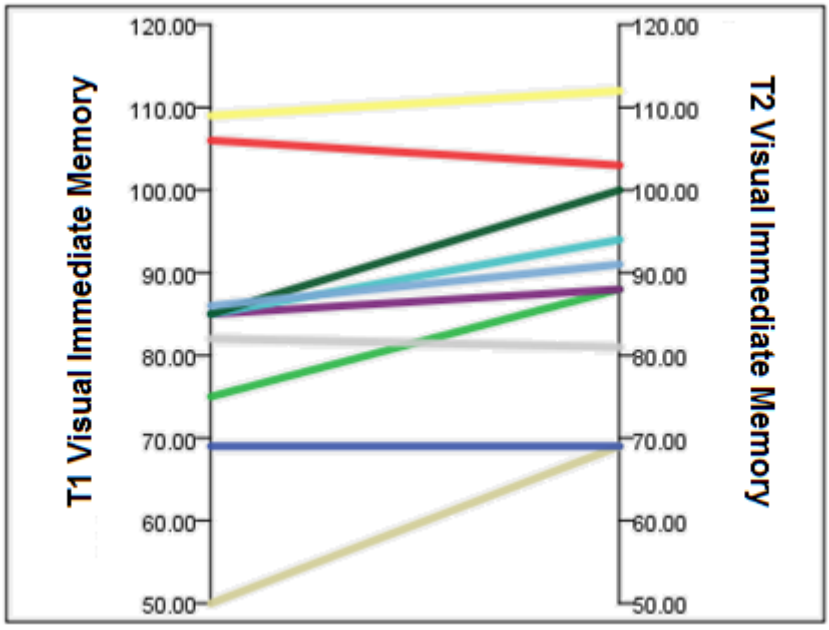
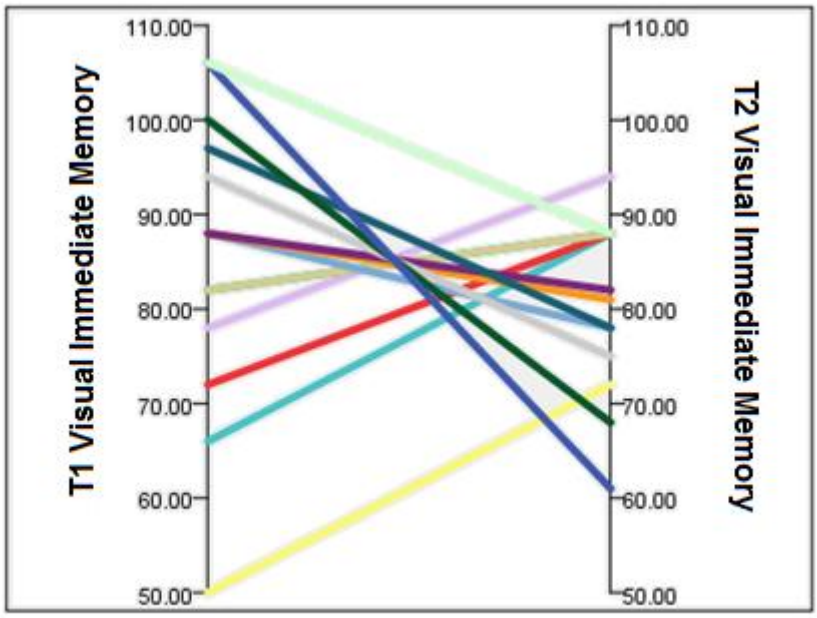


Figure 7: Each individual male participant's visual immediate memory performance at T1 and T2 (n=14)



4.4.2 Delayed Memory

Due to an outlier, delayed visual memory was not normally distributed. The data were subjected to GLM-RM analysis with time and memory domain as the criterion variables and gender and age group as covariates. Residuals for the model were saved, and examined for normality: a Shapiro-Wilk test confirmed that the model residuals were normally distributed, and so the GLM-RM procedure was appropriate.

Interactions between memory domain (visual and verbal delayed memory) and time, age group and gender were investigated. There was a main effect of age group again [$F(1, 20)= 9.047$, $pe^2= .311$, $p= .007$] with the older subgroup performing better overall.

There was a 2-way interaction between time and memory domain, but it did not reach statistical significance [$F(1, 20)= 3.906$, $pe^2= .163$, $p= .062$]. There were no 3-way interactions that approached statistical significance. However, there was a statistically significant 4-way interaction between time, domain, age group and gender [$F(1, 20)= 5.364$, $pe^2= .211$, $p= .031$]. Once the sample was split

into four subgroups, the numbers became too small to carry out further statistical analyses but main effects were observed in figures 8-11 (visual delayed memory) and 12-15 (verbal delayed memory) below. When the analysis was repeated, excluding the outlier, there were again no significant differences.

Figures 8-11 showing T1-T2 change for visual delayed memory

Figure 8: Males under 16

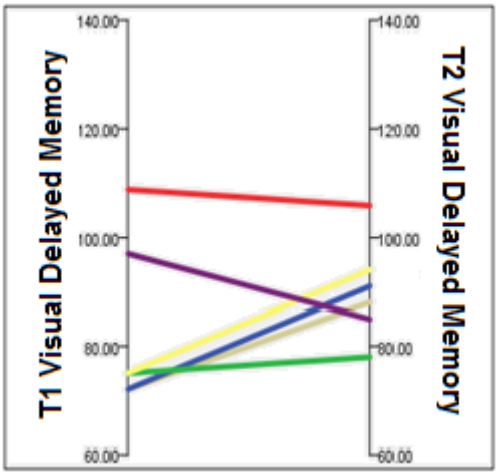


Figure 9: Males over 16

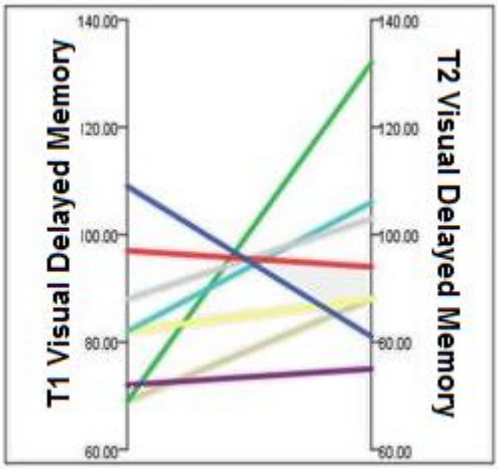


Figure 10: Females under 16

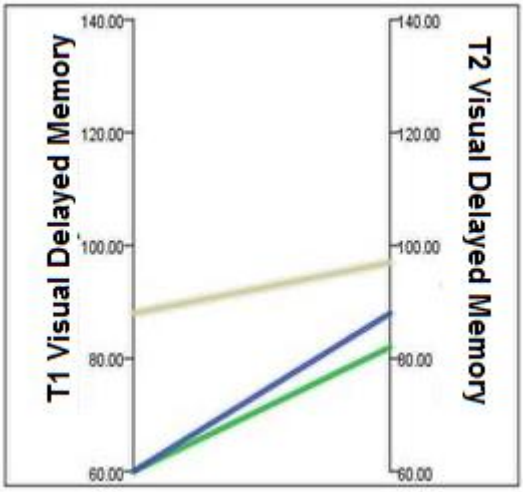
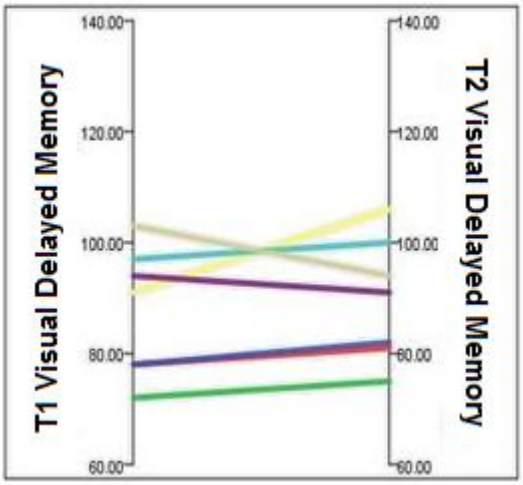


Figure 11: Females over 16



Figures 12-15 showing T1-T2 change for verbal delayed memory

Figure 12: Males under 16

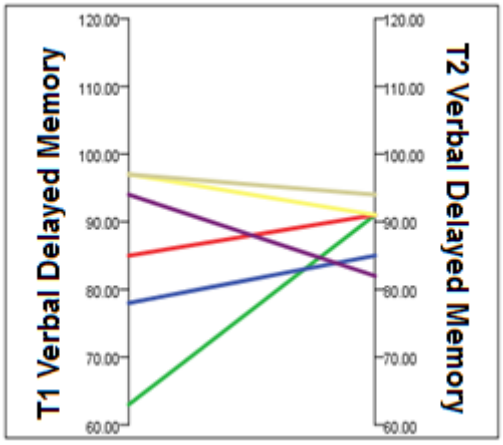


Figure 13: Males over 16

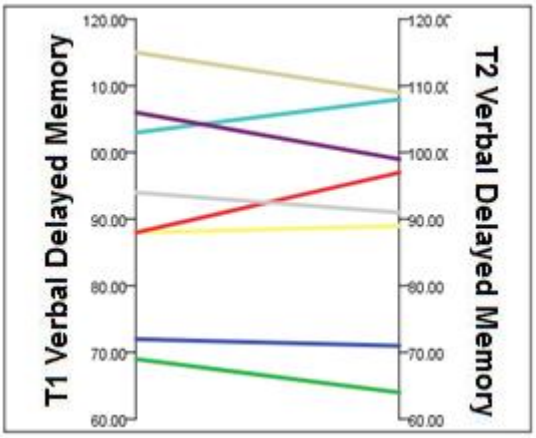


Figure 14: Females under 16

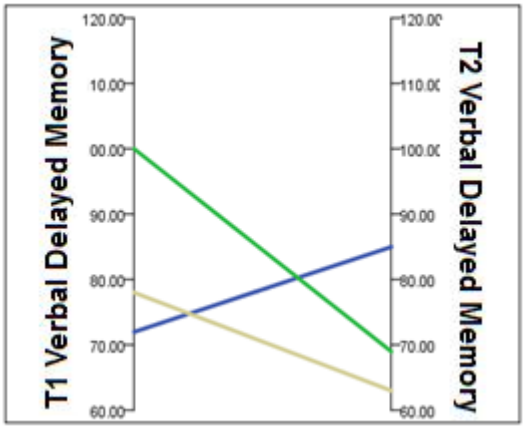
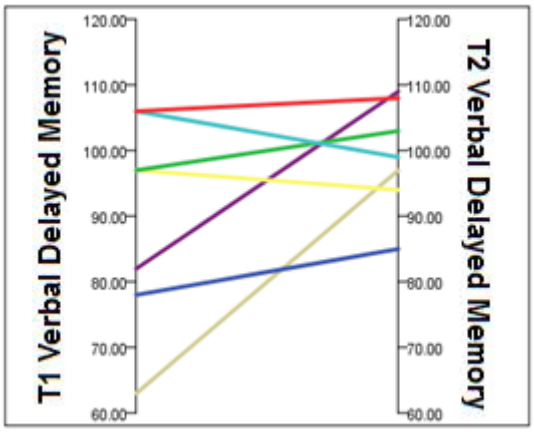


Figure 15: Females over 16



4.4.3 Rote Learning

Despite the literature reporting verbal rote learning as a relative strength within the cognitive profile, there was no difference between the mean visual and verbal rote learning subtests scores at T1. A GLM-RM procedure was used to see if this pattern was evident at T2. The visual rote learning subtest (Dot Locations) was only available through the CMS and therefore only administered to participants aged 16 and younger. Subsequently, participants older than 16 were excluded from this analysis, and age group was obviously not included as a between subjects factor.

There was no main effect for gender [$F(1, 13)= .102$, $pe^2= .008$, $p= .755$]. There was a reliable two-way interaction between gender and subtest [$F(1, 13)= 5.380$, $pe^2= .293$, $p= .037$]. Figures 16 and 17 show that performance on the verbal rote learning subtest deteriorates between T1 and T2 in males and females, while performance on the visual rote learning subtest deteriorates in males but increases in females. A paired samples t-test revealed a reduction in mean performance on the verbal rote learning subtest overall between T1 and T2 that bordered on statistical significance [$t(1, 13)= 2.134$, $p= .051$]. The criterion of $p< .001$ adopted for multiple significance tests means that this result was not considered significant.

Figure 16: Performance on verbal and visual rote learning subtests at T1 and T2 for males

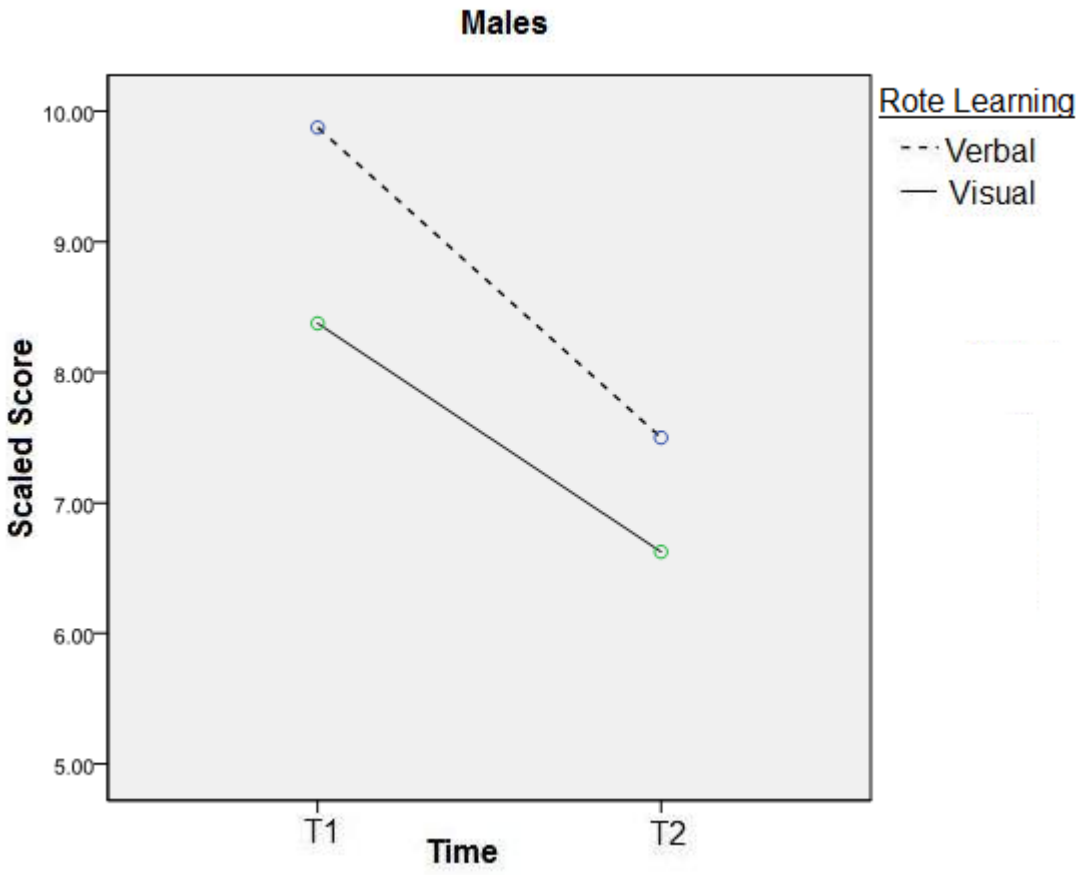
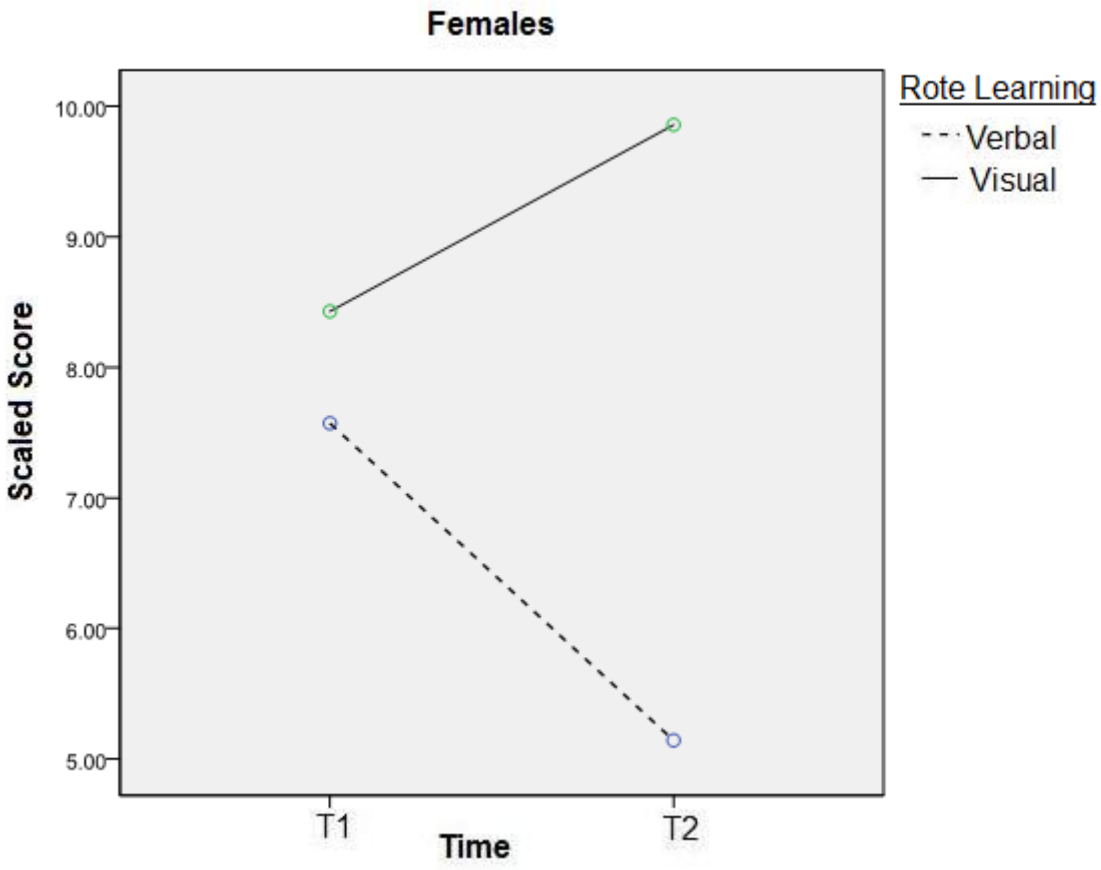


Figure 17: Performance on verbal and visual rote learning subtests at T1 and T2 for females



4.5 EXECUTIVE FUNCTION

All mean measures of executive function for the group were in the low average to below average range (table 7).

The Working Memory subtest (Digit Span Backwards) was not normally distributed because of an outlier obtaining a particularly high score. The mean score was in the average range (table 7).

5.0 DISCUSSION

This is the first longitudinal study investigating cognitive developmental trajectories in a UK sample of children/adolescents with 22qDS or a sample in which the participants were free from psychotropic medication, which can deleteriously affect cognition. It is also the first study in 22qDS, to the author's knowledge, to use the WISC-IV and WAIS-IV.

5.1 OVERVIEW

The finding for each hypothesis is presented and discussed in terms of previous research, theory, potential clinical and research implications, and methodological limitations. Then more general methodological issues, including bias, confounding factors and study design are reviewed. The broader clinical and research implications are discussed. A critical reflection of the research process is offered and recommendations for the future are made.

5.2 SUMMARY OF FINDINGS FOR INTELLECTUAL AND MEMORY DEVELOPMENT

The changing nature of the verbal>nonverbal intellectual discrepancy with age was of primary interest in this study. A secondary aim was to investigate whether the developmental change in verbal>nonverbal relationship generalised to memory. The lack of verbal>visual memory discrepancy at T1 created an atypical starting point (compared to the literature), so the hypothesised reduction in verbal>nonverbal discrepancy was not applicable to memory. However, what has been observed is a complex interaction between memory domain, aging, developmental stage and gender, which could not be explored further due to the sample size.

In summary, there is a theme of stability of verbal intellect and immediate memory during development. By contrast, nonverbal intelligence (estimated by the PRI), improves.

5.3 INTELLIGENCE

5.3.1 Hypothesis one

The hypothesis was that the VCI>PRI discrepancy present at T1 would reduce by T2. There was an interaction between intellectual domain (verbal and nonverbal) and time (T1 and T2), which was not affected by age group (above or below the group median) or gender. Regardless of age, the results indicate that development is associated with a reduction in verbal>nonverbal intellectual discrepancy.

The number of individuals who had a 'clinically significant' verbal>nonverbal discrepancy fell from 15/24 at T1 to 6/24 at T2. General population norms for groups with FSIQ under 80 (similar to the present sample) indicate that only 10% would be expected to have a VCI>PRI discrepancy large enough to be 'clinically significant' (Kaufman, 1976). At T1, the proportion of the sample with a clinically significant discrepancy was more than six times that expected in the general population with similar FSIQ. However, at T2, this figure had more than halved.

The cross-sectional literature suggests that the verbal>nonverbal discrepancy found in child and adolescent samples reduces with age (Baker et al., 2011; De Smedt et al., 2007; Lajiness-O'Neill et al., 2006; Moss et al. 1999; Niklasson & Gillberg, 2010; Swillen et al., 1997; Woodin et al., 2001), and may therefore not be found in adult samples (Henry et al., 2002; van Amelsvoort et al., 2004). The current results support these findings and those from longitudinal studies (Gothelf et al., 2005; 2007d), but in participants free from psychosis or the

influence of ‘antipsychotic’ or ‘antidepressant’ medication, which can affect cognition.

5.3.2 Hypothesis two

The hypothesis was that any reduction in VCI>PRI discrepancy would be attributable to VCI declining from T1 to T2. The reduction in verbal>nonverbal discrepancy was not due to declining VCI, which remained relatively stable. Unexpectedly, the mean PRI increased between T1 and T2 with moderate effect size (10 points, two thirds of an SD) with similar within-group variance at both time points. ‘Stability’ implies that the group’s cognitive functioning remains at the same point on the normal distribution. ‘Improvement’ implies that the group’s cognitive functioning develops more than expected, placing them at a higher point than before on the normal distribution.

This result could have been an artefact of PRI test stimuli differing between T1 and T2 so the subtests consistent at both time points were also examined: Block Design and Vocabulary. The pattern of stable verbal but improving nonverbal performance remained. Although other factors may have contributed to the change, this finding increases the validity of the interpretation that the data reflect change in cognitive function rather than the choice of test materials.

The reduction in verbal>nonverbal discrepancy with age was expected, but the pattern by which this occurred (increasing nonverbal rather than declining verbal functions) was unexpected. In a similarly aged sample with significant psychiatric comorbidity, Antshel et al. (2010) did not find any change in PRI or VCI with time. Gothelf et al. (2007d) found that PIQ remained relatively stable across time but VIQ declined significantly, causing the reduction in verbal>nonverbal discrepancy. Hypotheses for the differences between their and the present results are considered below in terms of: selection bias,

psychiatric diagnosis, differences between the countries, low FSIQ of the present sample and potential genotype differences.

It is crucial to note that the present study investigated cognition using PRI and VCI which are, arguably, purer measures of non-/verbal functions than PIQ and VIQ. The latter two include specific processing speed and WM tasks, respectively. The WISC-III VIQ, used by Gothelf and his colleagues, includes arithmetic, a known weakness in 22qDS (Moss et al., 1999). In the cross-sectional research by Green et al. (2009), PIQ and VIQ were negatively correlated with age, but of the subtests comprising PIQ, the subtest with the strongest negative correlation with age measured processing speed rather than perceptual reasoning. The Block Design subtest, arguably the purest measure of perceptual reasoning in the Green et al. (2009) study, was not correlated with age. Although Evers et al. (2009) reported cognitive deterioration, this was in a small series of single case studies.

Although no previous studies have found improvement in nonverbal functions, they have at least not found a decline, unlike verbal functions which have been shown either to deteriorate with age or remain stable. Campbell et al. (2002) are the only authors to hypothesise that nonverbal cognitive functions might improve with age due to a slower rate of development compared to verbal functions. They propose that this could result in nonverbal functions 'catching up' with verbal functions as affected persons grow up but, until now, there has been no empirical support for this hypothesis. The NVLD profile suggested in most children with 22qDS could therefore be age-dependent.

Although standard scores are generally considered to be stable with age in healthy people (Sigelman & Rider, 2006; Weinert & Hany, 2003), Ramsden et al. (2011) suggested that IQ may change during typical development. Out of 33 typically developing participants, VIQ changed (in either direction) by one SD for

7 and PIQ changed similarly for 6 between T1 (mean age: 14.1 years) and T2 (mean age: 17.7 years). However, the means for the groups at both time points only differed by one point for PIQ and FSIQ, and three points for VIQ. Despite individual fluctuation in IQ during adolescence, mean changes for entire cohorts are unexpected in the general population. Therefore the mean group increase in PRI of 10 points (moderate effect size) is highly likely to distinguish this sample from others in the general population.

5.3.3 Possible causes of the results

5.3.3.1 Neurocognitive 'Catch up'

Campbell et al. (2011) yielded a specific social cognition deficit in younger but not older participants with 22qDS (n=50), suggesting that deficit could be age-dependent. Although this result represented a different cognitive function from that of PRI, their interpretation is relevant. A developmental *delay* that catches up, rather than a static deficit is supported by Jablensky (2000), who found that maturation of the frontal cortex in children with 22qDS was delayed but caught up. Van Amelsvoort et al. (2001) reported that volumetric differences in frontal lobes in children with 22qDS normalise in adulthood, also suggesting that some aspects of neurocognitive development catch up. However, the relationship between frontal lobe volume and cognitive performance was called into question when Antshel et al. (2005b) found no correlation in their sample of 90 children/adolescents with 22qDS, sibling controls or community controls.

In support of the 'catch up' hypothesis are the neuroanatomical findings by Schaer et al. (2009). Compared to controls, participants with 22qDS had larger prefrontal thickness in childhood but greater cortical loss during adolescence, resulting in similarity with controls by adulthood. Their finding that brain maturation is delayed, rather than deficient, reaching convergence with controls by adulthood is consistent with the hypothesis that some cognitive functions develop at a slower rate, but catch up with other cognitive functions later.

5.3.3.2 Genotype variation

As discussed on page 5 (section 1.3.6), Gothelf et al. (2005) found greater VIQ decline in those with COMT Met compared to COMT Val status. The COMT status of participants in the present study is unknown. If the sample were homogenous for COMT Met, it could be associated with less severe VIQ decline, possibly contributing to the stable VCI here. However, it would not explain the rise in PRI. Moreover, the cognitive differences between COMT Val and Met have not been replicated (Glaser et al., 2006; Kates et al., 2006; van Amelsvoort et al., 2008).

5.3.3.3 Psychosocial interventions

It is possible that psychological and educational strategies contributed to the improving PRI (Blakemore & Frith, 2005). Following assessment at T1, all participants, parents and schools were given feedback and recommendations including strategies to maximise nonverbal functions, particularly for those who had a clinically significant VCI>PRI discrepancy. This hypothesis has implications for the type and timing of educational strategies. If educational strategies affect cognitive change, they may be useful in 'critical' time periods, and as intra-individual cognitive strengths change, different strategies may need to be introduced. The finding for hypothesis 2 also underlines the importance of follow-up assessment.

5.3.3.4 Methodological artefacts

Methodological factors are also relevant. These include the low FSIQ of the present sample, nature of the subtest and index, use of different tests at follow-up and the Flynn effect. Ascertainment and selection bias have undoubtedly affected the results of the study and are discussed in sections 1.5.6.3 and 5.4.2.1, respectively. The sample had a particularly low average FSIQ at T1 compared to other reported samples (Moss et al., 1999; Swillen et al., 1997), which means that the lower end of the distribution was investigated here. We

cannot be sure that the pattern of development for this group would be the same for higher functioning persons with 22qDS, as the low FSIQ could be related to differential cognitive development compared to the wider 22qDS population (discussed below). This could explain some discrepancies between the present and previous findings.

Gothelf et al. (2007d) and Green et al. (2009) both found stable PIQ and declining VIQ. As discussed above, PIQ comprises PSI and PRI, and VIQ comprises FDI and VCI. Therefore the pattern they found could reflect the status of PSI and FDI. Antshel et al. (2010) found significant decline in PSI. As this contributes to PIQ not VIQ, it would not explain declining VIQ with age.

Antshel et al. (2010), who used VCI and PRI instead of IQs, reported results similar to those of the present study for VCI but different for PRI, which they found was stable with age. Although the present findings are anomalous compared to the evidence base, Antshel et al. (2010) was the closest to supporting (at least one) of the present findings. The specificity of subtest and index may be important, as different tasks purport to capture the same underlying function (discussed below).

This is the only study so far to have used the WAIS-IV. Antshel et al. (2010) and Gothelf et al. (2007d) used the WISC-III and WAIS-III. The critical realist position encourages caution when assuming that different tests measure the same underlying cognitive construct. Use of inconsistent tests between samples at T1 and T2 and within the sample at T2 may account for a proportion of the findings. However, the WAIS-IV manual reports strong correlations between individuals' results (n=240) on the WAIS-III and WAIS-IV (Wechsler, 2008). Therefore it is unlikely that differences between present results (derived from the WAIS-IV) and previous research (derived from the WAIS-III) are entirely attributable to test differences.

Declining IQ scores with age can be understood in terms of the Flynn effect rather than a genuine decline in normative cognitive functions (Dickinson & Hiscock, 2010), but due to the small temporal gap between initial and follow-up assessments in previous studies, this is unlikely to explain the declining VIQ found by Gothelf et al. (2007d).

The implications of improving nonverbal intellectual functions are reviewed below. The findings for memory are now discussed.

5.4 MEMORY

5.4.1 Hypotheses three and four

Hypothesis three was that the lack of discrepancy between verbal and visual memory at T1 would remain at T2. Previous cross-sectional studies yielded discrepancies between visual and verbal memory in children and adolescents (Bearden et al, 2001; Lajiness-O'Neill et al, 2005; 2006; Óskarsdóttir et al, 2005; Wang et al, 2000; Woodin et al, 2001). The present sample is anomalous in that there was no verbal>visual memory discrepancy at T1, despite there being a significant VCI>PRI discrepancy. This could be a floor effect of particularly low FSIQ due to selection bias.

The fourth hypothesis was that if VCI had declined or PRI had increased, memory would reflect a similar pattern. The hypotheses for memory were tentative and analysis was fundamentally exploratory. Visual immediate memory performance increased between T1 and T2 in females but not males. The interaction between time and delayed memory domain (visual and verbal) was affected by both gender and age group. Unfortunately, the sample was underpowered to investigate this four-way interaction. Figures 8-11 provide a visual display of each subgroup in the interaction. Very crudely, it appeared that

there was greater variation within the male subgroups for change in visual delayed memory compared to females. Visual delayed memory performance in females over 16-years appeared relatively stable over time, but there was consistent improvement between T1 and T2 for females under 16. However, numbers in each subgroup were too small for meaningful or reliable interpretations.

In their longitudinal study, Antshel et al. (2010) found no changes between time points for performance on visual memory but a decline in the final verbal rote learning trial of the CVLT (discussed below). The present measures of memory were not comparable with those in the Antshel et al. (2010) study. Few cross-sectional studies comment on age and memory as age ranges and sample sizes tend to be narrow and small.

If there had been a decline in VCI, a decline in verbal memory might have also been expected. The increase in PRI for the sample is reflected somewhat in the increase in visual immediate memory for females in the group, but overall there appeared to be no consistency between the pattern for nonverbal intellectual functions and memory.

5.4.2 Possible reasons why the patterns for intellectual functioning and memory differ

5.4.2.1 Sample size

The small sample size in this study may limit the statistical power to reveal potential differences between verbal and visual memory (Type II error). Lepach and Petermann (2011) also had a small sample size (n=16) and found no discrepancy between performance on a verbal and visual memory task, despite a significant VIQ>PIQ discrepancy. Therefore we cannot be sure that there are

no potential memory differences. However, the sample size does not modify the finding of an improving PRI because of its moderate effect size.

5.4.2.2 Low FSIQ

As outlined on pages 30 and 95 (sections 1.5.5.1 & 5.3.3.4), this sample had a particularly low FSIQ compared to previously reported 22qDS samples. Although Bearden et al. (2001) showed the verbal>visual memory discrepancy was independent of FSIQ, their sample size was relatively small (n=29). If the discrepancy between verbal and visual memory increases with FSIQ, as does that between VIQ and PIQ (Hawkins & Tulsky, 2001), then the low mean FSIQ of this group could contribute to the negative finding, reflecting a floor effect.

5.4.2.3 Tests

Different memory tests often vary in novelty and complexity; some verbal memory tasks may not be comparable with nonverbal counterpart tasks across or within studies. For example, the verbal memory task used by Lepach and Petermann (2011) involved memory for common words, whereas the nonverbal task involved memory for novel, abstract designs. Differences in task complexity may contribute to the degree of non/verbal memory discrepancy reported in different 22qDS studies.

In the present study tasks were matched for recognition and recall; matching for complexity was attempted but inevitably tasks differed in novelty, e.g. words are familiar whereas some visual stimuli such as blue dots or abstract shapes are novel. However, visual and verbal memory subtests were from the same test battery, therefore standardised against the same normative sample.

Antshel et al. (2005b) note that patterns of cognitive impairment across different measures may also reflect the psychometric properties of tests rather than

differences in cognitive function. This could be relevant to the finding that 'age group' had an effect on the interaction in delayed memory. This result could be a potential artefact of the different measurement tools used for the younger (CMS) and older (WMS-III) subgroups of participants at T2. The CMS is used up until the age of 17. However, in the older subgroup (16+ years), nearly half the participants were still young enough to be examined on the CMS. Therefore the effect of age group is unlikely to be entirely attributable to the choice of test.

5.4.3 Were components in the Visual Memory Index differentially affected?

Bearden et al. (2001) distinguish between two types of visual memory: memory for objects ('what' – associated with the ventral visual pathway) and memory for spatial location ('where' – associated with the dorsal visual pathway). In participants with 22qDS, they found that spatial memory was significantly poorer than object memory, which was equivalent to verbal memory, implying that the visual memory deficit may be specific to spatial memory. However, Lajiness-O'Neill et al. (2005) found no deficits in spatial memory, and adults with 22qDS performed significantly worse than controls in object but not space perception (Henry et al., 2002) on the Visual Space and Object Perception Battery (VOSP, Warrington & James, 1991). The literature yields no consensus.

A specific deficit in visual memory could be masked by conflating visuo-spatial and visual-object memory scores. This could contribute to the lack of overall verbal>visual memory discrepancy because better object memory could inflate overall visual memory scores. The tests used in the present study did not allow for separate examination.

The CMS and WMS-III Faces subtest represents visual memory performance in combination with either the Dot Locations (CMS) or Visual Reproduction (WMS-III) subtest. A face specific deficit is debated in the 22qDS literature (Anderson et al., 2008; Campbell et al., 2009; 2010; 2011; Glaser et al., 2010; Lajiness-

O'Neill et al., 2005; McCabe et al., 2011; van Amelsvoort et al., 2006). The inclusion of two participants with a diagnosis of ASD could have influenced the group memory performance for faces, as deficits in facial recognition are reported in individuals with ASD (Dawson, Carver, Meltzoff, Panagiotides, McPartland, & Webb, 2002). However, scores for the Faces subtest were normally distributed with no outliers. The CMS and WMS-III are the memory tests most widely used in the 22qDS literature (Furniss et al., 2011), and therefore the most appropriate for comparison with the current evidence base.

5.4.4 Unexpected finding: A gender effect

As outlined briefly in the introduction, there is little research on the effect of gender on cognition in the 22qDS literature. There was a reasonably even split of males and females in this sample. Given the small sample size, it was surprising to find significant gender effects, with an improvement in visual immediate memory for females but not males, and an interaction between delayed memory and time moderated by gender and age group. These findings are treated cautiously due to limited statistical power and should be replicated in a larger sample.

Antshel et al. (2005b), who reported lower PIQ and FSIQ scores in males than females, explain the females' superiority in terms of research showing that females with developmental disorders tend to be less affected cognitively than males (Dykman & Ackerman, 1991; Richardson, Koller & Katz., 1987; Tallal, 1991; Volkmar, Szatmari, & Sparrow, 1993), and that they mature more rapidly physically (Eme, 1992). Antshel et al. (2005b) hypothesise that these factors might buffer females with 22qDS against negative influences on cognitive development. They also comment on the neuroprotective effect of progesterone in animal models (Asbury et al., 1998). These hypotheses could be considered in the context of the present finding that only females' visual

immediate memory performance increased. Although, interpretation of this result is tentative due to limited statistical power.

The nature of gender differences in brain development is unclear (Blakemore & Choudhury, 2006). Kates et al. (2006) found that gender, when combined with COMT status (val or met), interacted with regional frontal lobe volumes but not the total prefrontal cortex. The finding of gender effects in the brain could indirectly support the finding of gender effects in cognition, but the link is tenuous, with few studies and mixed results. Replication of the present findings in a larger sample with MRI and fMRI data could be a future step.

5.4.5 Implications for memory

There was an effect of age group, whereby older participants performed better overall on memory tests (immediate and delayed, verbal and nonverbal) at both time points. Age should not influence performance when measured in standard scores. Future research should explore memory at specific ages within the developmental trajectory, relating it to biological changes (puberty, neurological development) and stages/teaching strategies.

If the interaction between memory, age and gender is replicated in a large sample, the potential implications could include different educational interventions at different stages based on age and gender. For example, females may respond to visual teaching techniques in the classroom more than males and such techniques may be used at key stages of education. Findings could also motivate more MRI and fMRI research into brain-behaviour relationships between gendered aspects of verbal and nonverbal memory.

5.5 CURRENT COGNITIVE PROFILE WITH EXECUTIVE FUNCTIONING

The current intellectual functioning of the sample is below average with processing speed, verbal and nonverbal functions falling in the 'borderline' range. Most memory index scores were in the 'average' to 'low-average' range, within one SD of the general population. Current executive functioning is now described.

As expected, group mean performance for tasks representing initiation was below average. This supports parental perceptions of low initiation in children and adolescents with 22qDS (Kiley-Brabeck & Sobin, 2006). The mean performance for tasks of inhibition was also below average compared to general population norms. This supports some previous research (Chow et al., 2006; Sobin et al., 2005), although Lajiness-O'Neill et al. (2006) found no difference between those with 22qDS and sibling controls, suggesting that executive weakness is not specific to 22qDS. Performance for cognitive flexibility was more than one SD below the general population mean, which supports the results of McCabe et al. (2011). These results indicate that late adolescents/young adults with 22qDS may have difficulty generating ideas and initiating tasks, staying on task and switching fluidly between tasks and strategies in their daily functioning. However, executive weaknesses were consistent with the current level of deficit in intellectual functions and, therefore, not a relative weakness.

The WISC-IV/WAIS-IV Digit Span subtest measures verbal WM. The Digit Span subtest differed between the WISC-IV and WAIS-IV, as the latter included an additional task. Instead of using the overall subtest score, only the performance for Digit Span Backwards (DSB) was analysed. This is arguably a stronger measure of WM than Digit Span Forwards (DSF), because it requires manipulation as well as immediate recall.

The mean performance for DSB was in the average range. Lajiness-O'Neill et al. (2006) reported impaired performance on DSB but not on DSF in children with 22qDS compared to their unaffected siblings. However, Wang et al. (2000) found that, compared to controls, children with 22qDS had impaired verbal WM on the Digit Span task. Average performance on DSB suggests WM was unlikely to adversely affect the above results. WM was consistent with the level of memory functions but a relative strength compared to other executive functions.

The visual WM task was not administered to participants because it differs dramatically between the CMS and WMS-III. Future studies should include both measures of visual and verbal WM.

Change in WM with age was not a hypothesis. Instead, data were gathered at T2 to contextualise other findings. However, analyses investigating differences between T1 and T2 for all WISC/WAIS subtests yielded no change with age for the Digit Span subtest. Green et al. (2009) and Antshel et al. (2010) found decline with age in the WISC-III/WAIS-III FDI (comprising Digit Span). The lack of decline in the present sample does not support these findings.

5.5.1 Summary

Performance on tasks of executive function was consistent with intellectual functioning, but memory performance was a relative strength within the profile, as was working memory. These findings could inform Clinical Psychologists' hypotheses about the cognitive profile they expect to find in adolescents and young adults referred for neuropsychological assessment. The relative strength of memory and working memory could inform the type of clinical strategy offered following neuropsychological assessment.

5.6 GENERAL METHODOLOGICAL ISSUES

General methodological problems are now discussed. Selection bias and small sample size are reviewed above.

5.6.1 Psychiatric screening and diagnosis

In the present study one participant was in the severe range and two in the mild/moderate range for depression. These rates differ from those in other studies. Gothelf et al. (2007d) found over one third of their sample met DSM-IV criteria for psychotic disorder at T2 and more than half were receiving mood stabilizing or 'antipsychotic' medication. Forty-five of 70 participants described by Antshel et al. (2010) (mean age: 15 years, SD: 1.9) reached DSM-IV diagnostic criteria for major depressive disorder. The present sample differs from those in similar studies on methods of screening and rates found for psychiatric diagnosis.

This study used the self-report Beck Depression and Anxiety Inventories (Beck et al., 1961; 1996; 2005), whereas a semi-structured interview (The Schedule for Affective Disorders and Schizophrenia for School-aged Children: Present and Lifetime version; K-SADS-PL), administered by a Clinical Child Psychologist or Psychiatrist, was used in the Antshel et al. (2010) study, in which parents/primary caregivers were also interviewed. While the screening tool used here could have under-estimated depression, psychotic diagnosis was unlikely to have been missed. The cultural difference between the Antshel et al. (2010) sample and the present cohort could reflect differences in rates of depression and its expression.

Assuming the screens in this and the above two studies genuinely reflect psychiatric 'disorder', differences in prevalence between the present sample and those in the above two studies could contribute to the different results found here. The absence of psychosis and psychotropic medication in the present

sample removes two potential confounders of the interpretation that the data reflect developmental changes in cognitive function (improving PRI) related to 22qDS.

5.6.2 Use of different tests of intelligence at T1 and T2

A criticism of the study is the use of different measures between time points. Use of the same test at both time points helps to ensure that the same cognitive functions are being measured and the same normative reference group used. Baron (2004) and Mervis and Klein-Tasman (2004) note that test scores are only truly comparable when standardised on the same population. Flynn (2009) found that the average number of IQ points an individual would drop between being tested on the WISC-III and WISC-IV is 0.3 per annum. As mentioned on page 97 (section 5.3.3.4), for the present study this is negligible, given the T1-T2 time gaps for each individual and, in any event, IQ did not drop in this study.

Flynn and Weiss (2007) observe that "comparing one basket of subtests to another" distorts results. Although most studies use versions of the Wechsler tests, other cognitive tests differ between studies. The verbal learning subtests in the Wide Range Assessment of Memory Learning (WRAML, Sheslow & Adams, 1990) and the CVLT (Delis, Kramer, Kaplan & Ober 1994) are similar to the CMS word pairs and WMS-III word lists subtests used in the present study. However, the normative samples for the various tests differ, so although completing similar tasks, the raw scores of participants in the different studies are interpreted against different populations. If a normative sample is large enough, such variability should not result in meaningful statistical differences.

5.6.3 Construct validity

The present study relied on intelligence being viewed as several constructs. This framework of intellectual functioning is widely used in clinical and research

settings (Lezak, 2004). However, Antshel et al. (2005a) caution that relying on so few data points may limit the accuracy of estimated cognitive functioning in children with 22qDS.

5.6.3.1 Index Construct validity

The internal validity of PSI in this sample was weak, because group performance differed between the composite subtests at both time points. The symbol search subtest might be a more accurate representation of processing speed than the coding subtest, which relies more on fine motor skills, a known weakness in 22qDS (Niklasson & Gillberg, 2010). Similar concerns have been raised about subtest construct validity (Larrabee & Curtiss, 1995; William et al., 1998).

5.6.4 Appropriate Normative Samples

Although normative samples help interpret the level at which participants perform compared to the general population, Kates et al. (2006) debate the appropriateness of using them when investigating intra-individual cognitive discrepancies. The authors suggest using normative samples based on individuals with intellectual disabilities might yield clearer patterns in the cognitive profile, although they acknowledge that general population samples have been used meaningfully with a wide range of disabilities. The recommendation should be considered for future research.

5.6.5 Limitations of standard scores

As reviewed on page 44 (section 2.2), the advantage of standard compared to raw scores is comparison with an age-matched peer group, such that substantial change in a standard score over time reflects a deviation from the normal developmental trajectory. Raw scores, while not comparable across tasks or different age groups, could assist in the interpretation of changing

standard scores. Raw scores could show whether the decline in VCI reported elsewhere is due to verbal development having slowed, stagnated or deteriorated. Although no decline was found in the present sample, raw scores would have clarified the trajectory but would only be available if the same tests were used at T1 and T2.

5.6.6 Statistical considerations

Where multiple comparisons are made there is a risk of false positive results. The Bonferroni correction was not used, which means that results at the $p<.05$ level may not be significant. This level of significance was set a priori for tests of the principal hypotheses, whereas, greater weight was given to results at the $p<.01$ or $p<.001$ level for subsidiary analyses.

5.6.7 Puberty and non-linear developmental effects

Blakemore and Choudhury (2006) assert that typical cognitive developmental trajectories contain both linear and non-linear elements. They cite evidence of non-linear development in facial encoding, executive function and prospective memory, irrespective of gender. Typically the evidence they cite supports a pubertal dip (Anderson, Anderson, Jacobs & Smith, 2001; Diamond,Carey & Back, 1983; Dumontheil, Houlton, Christoff, & Blakemore, 2010; Mackinlay, Charman, & Karmiloff-Smith, 2003; McGivern, Andersen, Byrd, Mutter & Reilly, 2002). Non-linear effects may have obscured potential developmental changes.

5.6.8 The current sample's representativeness of the wider 22qDS population

The participants, as in most other 22qDS studies, are referrals to a tertiary centre. The age and gender ratio of the sample are similar to those reported elsewhere. The small sample size, selection bias (reviewed above) and lack of control group limit the generalisability of the findings. As such, the results are

treated cautiously. A larger sample size could have enabled exploration of the four-way interaction for memory.

Fung, McEvilly, Fong, Silversides, Chow and Bassett (2010) highlight the importance of considering the selection and ascertainment bias in 22qDS samples. Furniss, Biswas, Gumber & Singh (2011) emphasise the importance of recruiting samples from outside the clinic (milder cases) to improve the generalisability of findings and limit the between-study variability attributable to biased sampling. Other studies also suffer from selection and ascertainment bias. The sample from the Gothelf et al. (2007d) study was recruited from psychiatric referrals, and participants in the Antshel et al. (2010) study were recruited with a focus on psychiatric disorders. Green et al. (2009) found differences in FSIQ and PIQ between their two samples from Geneva and Tel Aviv; the higher functioning group was recruited from clinical genetics departments and the lower functioning group from parent associations.

Attrition is a problem for all longitudinal studies, and in 22qDS it is likely affected by high rates of psychiatric diagnosis and medication. While the attrition rate in this study was 22.7%, there was little difference in age or cognitive index scores between participants and initial drop-outs, hence no further reduction in representativeness. The 22qDS literature (Gothelf et al., 2007d; Green et al., 2009) reports declining VIQ as a risk factor for a later schizophrenia diagnosis. The absence of a diagnosis of psychosis could also account for the lack of VCI decline found in this sample.

5.6.8.1 Age range

The mean ages of samples at the T1 and T2 for the studies by Antshel et al (2010) [11.8years – 15.0 years] and Gothelf et al (2007d) [12.3 years – 17.2 years] are similar to those in the present study [11.8 years – 15.9 years]. The

age range of participants at T2 encompassed pubertal and post-pubertal phases. Evidence for a pubertal dip in cognition is discussed on page 108 (section 5.6.7). Participants were also at different stages of social and educational demands and of neuronal pruning. The independent variable in the above hypotheses has consistently been 'ageing'. The next stage of research could be to investigate critical periods of developmental cognitive change in 22qDS. The wide age range and small sample size prevent exploration of 'age' in this study. The gender effect could also be related to the pubertal phase of many participants.

5.6.8.2 Demographic data

Data regarding social class, parental educational attainment and ethnicity were not analysed, although they are known to affect cognition (De Smedt et al, 2007; McDonald-McGinn et al, 2005). The omission of this data means that the present sample cannot be compared on these grounds to other reported samples.

5.6.8.3 Potential Confounding factors related to 22qDS

The sample size did not have the statistical power to investigate within sample differences according to cardiac or ASD subgroup status. ASD has been shown to contribute to low PIQ in those with 22qDS (De Smedt et al., 2007), and neonatal cardiac surgery is associated with worse neurodevelopmental outcome in those with 22qDS (Attallah et al., 2007). This should be considered in future studies. The size of any adverse effect of cleft palate on cognition and educational attainment is not known in 22qDS. The potential effect of cleft palate was not evaluated because of insufficient data and statistical power. The proportions of hearing difficulties and cleft palate in the present sample could therefore not be compared to those of other reported samples.

5.6.8.4 Cultural and health care differences

This is the first UK sample in which cognitive development has been investigated longitudinally. Although the mean ages at both time points are similar to those in the Gothelf et al. (2007d) and Antshel et al. (2010) studies, the individuals are from different countries with different health and education systems. Differences between countries in the timing of surgery for cleft palate, and the availability of speech therapy are likely to affect the early development of verbal communication, which could also influence attitude towards school and potentially cognitive development. Variation in the amount, type, timing, quality and availability of medical, allied health and social interventions between the health care and education systems in different countries must be considered when comparing findings from the present sample with those from North American (Antshel et al., 2010) and Israeli (Gothelf et al., 2007d) samples.

5.7 CRITICAL REFLECTION OF THE RESEARCH

This research has added to the evidence base that addresses cognitive function in individuals with 22qDS. The latter has homogenised individuals as a diagnostic group, which detracts attention from within-group differences, individuality and encourages perception of the 'disabling' features of 22qDS. The individuals in this sample are grouped by a shared genetic microdeletion, which implies that the results discussed above are largely viewed in terms of genetic determinism. Although psychosocial and social constructionist approaches to LD and lived experience with medical difficulties have been considered, ultimately the organic pathology was considered the main independent variable.

This research has not challenged the deficit-led view of individuals with 22qDS. However, the results might facilitate dialogues in clinical teams, promoting the importance of psychology and neuropsychology, which may give a voice to ideas that help challenge the concept of 'IQ' and reframe 'LD'.

5.8 STRENGTHS OF THE STUDY

Key strengths of the study include its longitudinal design. Second, the sample was free both from diagnosis of schizophrenia, which is suggested to have associated cognitive deficits, and from the effects of psychotropic medication. Third, a more comprehensive examination of cognition was completed (intellectual, memory and executive functions) compared to other studies, which often just report intellectual functioning. Fourth, the author assessed all participants at T2 and the majority at T1, reducing inter-rater bias. Fifth, the sample is representative of referrals for educational concern. Finally, the sample is homogeneous for FSIQ under 80 and thus less heterogeneous than other studies for FSIQ.

Thomas et al. (2009) argue that an optimal design for studying developmental disorders is to combine initial cross-sectional designs with longitudinal follow-up. The latter is the best design to establish the developmental trajectory and to distinguish between different types of delay that are conflated in a cross-sectional design (Annaz et al., 2008). This supports the research design of the present study.

5.9 HOW TO FRAME FINDINGS IN 22QDS

Karmiloff-Smith (2011) suggests such findings should be viewed in terms of two-way brain-behaviour relationships. Although the present findings have been linked to neuroimaging studies in 22qDS, they have also been discussed in terms of psychosocial influences and systemic factors. This research aimed to increase the availability for researchers and clinical professionals of an alternative framework for understanding cognitive trajectories in 22qDS. This is important considering the recommendation by Gothelf et al. (2007d) for a pharmacological response to “subthreshold psychotic symptoms” in 22qDS, especially when combined with the suggested “risk factor” of declining VIQ. The

clinical implication of the genetic deterministic framework is that 'risk factors' could potentially be medicated. Investigating the developmental nature of such 'risk factors' and framing them in alternative ways is important.

Interest in 22qDS often appears to be from the position of genetic determinism, particularly in studies investigating the connection between 22qDS and diagnoses of schizophrenia. To understand the results in terms of 22qDS, several aspects of this condition and personhood are now considered.

5.9.1 Impact of research

The research colours the lens through which clinical professionals view the patient and parental expectations. For example, the evidence showing higher rates of psychiatric diagnoses in 22qDS populations compared to the general population has influenced the rationale and funding for psychologists and psychiatrists being part of the MDT in the service. This has led to individuals with 22qDS having more contact with these disciplines during childhood than other members of the general population, which could increase the likelihood of behaviours and experiences being pathologised and diagnoses being made.

The information given by professionals, for example about LD, may influence the parenting and teaching of that child compared to siblings. The meaning of the 22qDS label in an individual's systems may be associated more with the above results than the genetic deletion.

5.8.2 Psychosocial impact

Unlike the focus of most 22qDS research on genetic causes of psychiatric diagnoses, Lepach and Petermann (2011) refer to a biopsychosocial framework (page 6, section 1.3.6). They note that aspects of 22qDS, such as small

stature, unclear speech (cleft palate), lack of sporting skills (due to cardiac problems) and academic difficulties can increase risk of psychiatric diagnosis, stigma and social withdrawal as well as attitude to school and general psychosocial development.

Self-concept and the meaning of 22qDS within individuals' systems are likely to impact on social and cognitive development (Karmiloff-smith, 2008) cognitive functions do not 'exist' in a vacuum. Early social interaction and environment play a role in modularisation and specialisation of brain function which has not yet occurred in the typically developing neonate cortex. If parental interaction can affect gene expression and ultimately cognitive function (Karmiloff-Smith, 1998; Kuhl, 2004), it is important to consider the results in the context of these factors.

5.10 IMPLICATIONS AND FUTURE

5.10.1 Clinical implications

5.10.1.1 Routine assessment

The results support previous studies finding heterogeneity in the cognitive profile in individuals with 22qDS. Niklasson and Gillberg (2010) argue that assessment should be offered routinely to every child. It is crucial to note that despite improvement in PRI, both VCI and PRI remain below average and indicate intellectual difficulties compared to the general population.

5.10.1.2 Reassessment

The findings have positive implications. Contrary to reports of cognitive deterioration with age, improvement in PRI relative to peers is achievable with age in 22qDS in the absence of psychotic comorbidity. This supports the hypothesis that nonverbal cognitive functions are delayed but 'catch up'.

UK decisions about vocation, independence and lifestyle may be based on the cognitive strengths and weaknesses reported in assessments completed by neuropsychological services at the start of secondary school. The present finding indicates that cognitive strengths and weaknesses are dynamic. A parental decision to discourage a 17-year old with 22qDS from learning to drive based on reported visuo-spatial deficits at age 12, may be erroneous. Important decisions should be based on reassessment in early adulthood. The potential change in cognitive profile by this age could have important implications for recommendations made to examination boards for GCSE/AS-levels and the educational strategies advised. Reassessment at significant junctures should be offered to service-users.

5.10.1.3 Educational Strategies

While cognitive development is susceptible to environmental factors, 22qDS could potentially predispose affected persons to specific 'sensitive' periods that are optimal for improving nonverbal cognitive functions. That could have important implications for the nature and staging of educational strategies (Blakemore & Frith, 2005). Further research into the cognitive development at specific age bands is indicated. The findings tentatively suggest that different strategies could be used for females compared to males at particular stages of development. More research with larger sample is required to explore the effects of gender in development in persons with 22qDS.

5.10.1.4 Current information about 22qDS

Printed information routinely given by service-providers to schools, educational psychologists, colleges, employers, Local Education Authority and disability charities explaining some of the “hidden nonverbal difficulties” associated with 22qDS may need to be changed to reflect the shrinking verbal>nonverbal discrepancy with age. The communication is nonetheless useful because the intellectual functioning of participants was low and the inferiority of nonverbal compared to verbal functions remained at T2 for some participants. However, the general focus on nonverbal deficits may become less relevant with age.

5.10.1.5 Implications for Clinical Psychologists

The implications for Clinical psychologists are that they should offer routine and follow-up cognitive assessment for children with 22qDS as the recommendations made at the original assessment may no longer be relevant as the child ages. The NVLD-like profile seen in children with 22qDS may be age-dependent, which could inform the approach Clinical Psychologists take to cognitive assessment for different age groups.

Nonverbal intellectual functioning is amenable to improvement. Future research could indicate that the recommendations made by Clinical Psychologists and the way families implement them could have effects on cognitive development. Therefore the potential effectiveness of the intervention of feeding back cognitive assessment results and suggesting strategies should not be under-estimated.

The improvement in nonverbal intellectual functioning of this sample challenges the widely held view that cognition deteriorates with age in those with 22qDS. An important role of Clinical Psychologists in 22qDS MDTs could be to disseminate this information, fostering hope in families about ways of potentially

optimising cognitive development. Karmiloff-Smith (2011) noted that parental understanding of what is possible in their child with 22qDS influences their interaction with the child, which in turn can affect gene expression and cognitive development.

5.10.2 Research Implications

5.10.2.1 Evaluating the role of psychosocial intervention

Further research is needed to establish whether psychological and educational strategies given to participants at T1 affect the improvement in PRI at T2, using strategies which are manualised, monitored and evaluated.

5.10.2.2 Control groups

Karmilloff-Smith (2011) proposes that it is better to compare cognitive deficits to a similar group rather than typically developing healthy populations because it reveals more subtle differences. Therefore future studies should aim to include other genetic syndromes with reported verbal>nonverbal cognitive profiles, such as Williams syndrome and Turner syndrome as well as typically developing and sibling controls. This would allow examination of the specificity of the cognitive profile and its trajectory in 22q2DS.

5.10.2.3 Multi-centre research

Furniss et al. (2011) call for better sampling with less ascertainment and selection bias, outside clinic recruiting to improve generalisability and reduce between-study variability. They recommend multi-centre studies with the use of consistent test batteries across 22qDS studies to help distinguish between the different results that could advance the knowledge base versus those which are attributable to differences in psychometric testing batteries.

5.10.2.4 Tests

Use of assessment batteries that are suitable for all ages would enable comparison of intra-individual raw and standard scores longitudinally. This would not only provide richer data but also reduce the confounding effects of using different tasks and normative samples for different ages/time points. Karmiloff-Smith et al. (2004) and Annaz et al. (2008) emphasise the need for experimental as well as standardised tasks.

5.10.2.5 Longitudinal data from birth

Karmiloff-Smith (2008) argues that the idea there might be a specific gene pre-determining the structure of spatial cognition comes from applying research from adult neuropsychology to children. This involves applying research on the developed brain to the developing brain, which she argues is unhelpful. Karmiloff-Smith (2008) proposes that little in development is predetermined. She advises neuroconstructivist researchers to trace both areas of cognitive proficiency and deficit back to early infancy, during which there is high regional interconnectivity. Her approach suggests that multiple wave longitudinal data are required from babyhood to adulthood to truly understand the impact of 22qDS on cognitive development.

5.11 CONCLUSIONS

The profile of performance in 22qDS undergoes interesting development between childhood and early adulthood. We are yet to understand the nature of the cognitive processes underlying this development. Unlike some other studies, the present findings indicate that verbal functions do not inevitably decline with age in those with 22qDS. Nonverbal functions may improve with age in persons with 22qDS. This could reflect several factors, including psychosocial interventions or potentially delayed maturation of specific neuroanatomical regions causing a ‘catch up’ effect. Both hypotheses require more research. There may be gender differences and specific age ranges at

which improvement in nonverbal functions is optimal. More studies are required and should aim to include the methodological recommendations above. Recruiting larger samples is a challenge due to the rarity of 22qDS.

Differences between the results reported here and in previous studies could be related to multiple factors. Perhaps the most important are: the small sample size, the absence of a psychotic diagnosis and psychotropic medication, and the particularly low cognitive functioning of the sample at T1, limiting the generalisability of findings to the wider 22qDS population. This is the only follow-up study so far on cognitive development in a UK 22qDS sample. Consequently psychosocial and cultural influences are likely to differ from other reported samples. Therefore the novel results could be specific to 22qDS in the UK as well as to low initial cognitive functioning.

6.0 REFERENCES

Anderson, V., Anderson, P., Northam, E., Jacobs, R, & Catroppa, C. (2001). Development of executive functions through late childhood and adolescence in an Australian sample. *Developmental Neuropsychology*, *20*, 385–406.

Anderson, V., Anderson, P. J., Jacobs, R., & Smith, M. S. (2008). Development and assessment of executive function: From preschool to adolescence. In V. Anderson, R. Jacobs & P. Anderson (Eds). *Executive Function and the Frontal Lobes. A lifespan Perspective*. (pp. 123-154). New York, NY: Psychology Press, Taylor & Francis.

Andersson, F., Glaser, B., Spiridon, M., Debbané, M., Vuilleumier, P., & Eliez, S. (2008). Impaired activation of face processing networks revealed by functional magnetic resonance imaging in 22q11.2 deletion syndrome. *Biological Psychiatry, 63*(1):49–57.

Annaz, D., Karmiloff-Smith, A. & Thomas, M. C. (2008). The Importance of tracing developmental trajectories for clinical child neuropsychology. In J. Reed & J. Warner-Rogers (Eds.) *Child Neuropsychology: Concepts, Theory and Practice*. Oxford: Blackwell Publications.

Antshel, K. M., Shprintzen, R., Fremont, W., Higgins, A. M., Faraone, S. V., & Kates, W. R. (2010). Cognitive and psychiatric predictors to psychosis in velocardiofacial syndrome: A 3-year follow-up study. *Journal of American Academic Child and Adolescent Psychiatry, 49*, 333–344.

Antshel, K. M., Fremont, W., Roizen, N. J., Shprintzen, R., & Higgins, A. M. (2006). ADHD, major depressive disorder, and simple phobias are prevalent psychiatric conditions in youth with velo-cardio-facial syndrome. *Journal of American Academic Child and Adolescent Psychiatry, 45*, 596-603.

Antshel, K. M., Fremont, W., & Kates, W. R. (2008). The neurocognitive phenotype in velo-cardio-facial syndrome: a developmental perspective. Developmental disabilities research reviews 14: 43 – 51.

Antshel, K. M., Kates, W. R., Roizen, N., Fremont, W., & Shprintzen, R. J. (2005a). 22q11.2 Deletion Syndrome: Genetics, Neuroanatomy and Cognitive/Behavioral Features. *Child Neuropsychology, 11*, 5 - 19.

Antshel, K. M., AbdulSabur, N., Roizen, N., Fremont, W., & Kates, W. R. (2005b). Sex Differences in Cognitive Functioning in Velocardiofacial Syndrome (VCFS). *Developmental Neuropsychology, 28*(3), 849-869.

Antshel, K. M., Stallone, K., AbdulSabur, N., Shprintzen, R., Roizen, N.,Higgins, A. M., & Kates, W. R. (2007). Temperament in velocardiofacial syndrome. *Journal of Intellectual Disability Research, 51*(3), 218-227.

Asbury, E. T., Fritts, M. E., Horton, J. E., & Isaac, W. L. (1998). Progesterone facilitates the acquisition of avoidance learning and protects against subcortical neuronal death following prefrontal cortex ablation in the rat. *Behavioral and Brain Research, 97*, 99–106.

Attallah, J., Joffe, A. R., Robertson, C. M. T., Leonard, M., Blaykley, P. M., Nettel-Aguire, A., ...Rebeyka, I. M. (2007). Surgery for congenital heart disease. Two-year general and neurodevelopmental outcome after neonatal complex cardiac surgery in patients with deletion 22q11.2: A comparative study. *The Journal of Thoracic and Cardiovascular Surgery, 134,* 772–779.

Axelrod, B. N., & Ryan, J. J. (2000). Prorating Wechsler Adult Intelligence Scale-III summary scores. *Journal of Clinical Psychology, 56*(6), 807-11.

Baddeley, A. D. (2002). Is Working Memory Still Working? *European Psychologist, 7*(2), 85-97.

Baddeley, A.D., & Hitch, G. (1974). Working memory. In G. H. Bower (Ed.), *The psychology of learning and motivation: Advances in research and theory* (pp. 47–89). New York, NY: Academic Press.

Baker, K. D., & Skuse, D. H. (2005). Adolescents and young adults with 22q11 deletion syndrome: psychopathology in an at-risk group. *British Journal of Psychiatry, 18*(6), 115-120.

Baker, K. D., Chaddock, C. A., Baldeweg, T., & Skuse, D. H. (2011). Neuroanatomy in adolescents and young adults with 22q11 Deletion Syndrome: Comparison to an IQ-matched group. *Neuroimage, 55,* 491–499.

Baron, S. (2004). *Neuropsychological evaluation of the child*. Oxford: Oxford University Press.

Bassett, A. S., Caluseriu, O., & Weksberg, R. (2007). Catechol-o-methyl transferase and expression of schizophrenia in 73 adults with 22q11 deletion syndrome. *Biological Psychiatry, 15*, 1135-1140.

Bassett, A. S., Marshall, C. R., Lionel, A. C., Chow, E. W., & Scherer, S. W. (2008). Copy number variations and risk for schizophrenia in 22q11.2 deletion syndrome. *Human Molecular Genetics, 17,* 4045–4053.

Bearden, C. E., Jawad, A. F., Lynch, D. R., Sokol, S., Kanes, S. J., McDonald-McGinn, D. M., ...Simon, T. J. (2004). Effects of a functional COMT polymorphism on prefrontal cognitive function in patients with 22q11.2 deletion syndrome. *American Journal of Psychiatry, 161*, 1700-1702.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 53-63.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Beck depression inventory: second edition (BDI-II).* San Antonio, TX: The Psychological Corporation

Beck, J. S., Beck, A. T., & Jolly, J. B. (2005). *Beck Youth Inventories (2nd ed).* London, UK: The Psychological Corporation.

Bish, J. P., Chiodo, R., Mattei, V., & Simon, T. J. (2007). Domain specific attentional impairments in children with chromosome 22q11.2 deletion syndrome. *Brain and Cognition, 64*, 265-273.

Blakemore, S. J., & Choudhury, S. (2006). Development of the adolescent brain: implications for executive function and social cognition. *Journal of Child Psychology and Psychiatry, 47*(3-4), 296-312.

Blakemore, S. J., & Frith, U. (2005). The learning brain: Lessons for education: a précis. *Developmental Science, 8(*6), 459–471.

Botto, L. D., May, K., Fernhoff, P. M., Correa, A., Coleman, K., Rasmussen, S. A, ...Campbell, R. M. (2003). A population-based study of the 22q11.2

deletion: phenotype, incidence, and contribution to major birth defects in the population. *Pediatrics 112*,101–107.

Campbell, L. E., Stevens, A., & Morris, R. (2002). Cognitive Phenotype of children with velo-cardio-facial syndrome (VCFS). Proceedings of 8th Annual Meeting of the velo-cardio-facial syndrome Eductional Foundation held in Northampton, UK, 26-28 July 2002.

Campbell, L. E., & Swillen, A. (2005). The Cognitive Spectrum in velo-cardio-facial syndrome. In K. C. Murphy & P. J. Scambler (Eds). *Velo-cardio-facial-syndrome: A model for understanding Microdeletion Disorders* (pp. 147-164). London, UK: Cambridge University Press.

Campbell, L. E., Stevens, A., Daly, E., Toal, F., Azuma, R., & Karmiloff-Smith, A. (2009). A comparative study of cognition and brain anatomy between two neurodevelopmental disorders: 22q11.2 deletion syndrome and Williams syndrome. *Neuropsychologia, 47*(4),1034–44.

Campbell, L. E., McCabe, K., Leadbeater, K., Schall, U., Loughland, C., & Rich, D. (2010). Visual scanning of faces in 22q11.2 deletion syndrome: Attention to the mouth or the eyes? *Psychiatry Research, 177*(1), 211–215.

Campbell, L. E., Stevens, A. F., McCabe, K., Cruickshank, L., Morris, R. G., Murphy, D. G. M., & Murphy, K. C. (2011). Is theory of mind related to social dysfunction and emotional problems in 22q11.2 deletion syndrome (velo-cardio-facial syndrome)? *Journal of Neurodevelopmental Disorders, 3,* 152–161.

Carroll, J. B. (1993). *Human cognitive abilities: A survey of factor-analytic studies*. Cambridge, UK: Cambridge University Press.

Chalmers, D., Stewart, L, Silva, P., & Mulvena, A. (1989). *Otitis media with effusion in children -The Dunedin Study*. London, UK: Mac Keith Press.

Chepenik, L. G., Cornew, L. A., & Farah, M. J. (2007). The Influence of Sad Mood on Cognition. *Emotion, 7*(4), 804-811.

Chen, J., Lipska, B., & Halim, N. (2004). Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brains. *American Journal of Human Genetics, 75*, 807-821.

Chow, E. W., Watson, M., Young, D. A., & Basset, A. S. (2006). Neurocognitive profile in 22q11 deletion syndrome and schizophrenia. *Schizophrenia Research, 87*, 270–278.

Cohen, M. (1997). *Children's Memory Scale*. San Antonio, TX: Psychological Corporation.

Cuneo, B. F. (2001). 22q11.2 deletion syndrome: DiGeorge, velocardiofacial, and conotruncal anomaly face syndromes. *Current Opinion in Pediatrics, 13,* 465-472.

Dawson, G., Carver, L., Meltzoff, A. N., Panagiotides, H., McPartland, J., & Webb, S. J. (2002). Neural Correlates of Face and Object Recognition in Young Children with Autism Spectrum Disorder, Developmental Delay, and Typical Development. *Child Development, 73*(3), 700-17.

De Smedt, B., Devriendt, K., Fryns, J. P., Vogels, A., Gewillig, M., & Swillen, A. (2007). Intellectual abilities in a large sample of children with Velo–Cardio–

Facial Syndrome: an update. *Journal of Intellectual Disability Research, 51*, 666-670.

Debbane, M., Schaer, M., & Farhoumand, R. (2006). Hippocampal volume reduction in 22q11.2 deletion syndrome. *Neuropsychologia, 44*, 2360-2365.

Debbane, M., Glaser, B., & Eliez, S. (2008). Encoding and Retrieval Processes in Velo-Cardio-Facial Syndrome (VCFS). *Neuropsychology, 22*(2), 226-234.

Delis, D., Kramer, J. H., Kaplan, E., & Ober, B. A. (1994). *California Verbal Learning Test–Children's Version*. San Antonio, TX: Psychological Corporation.

Delis, D. C., Kaplan, E., & Kramer, J. (2001). *Delis-Kaplan Executive Function System*. San Antonio, TX: The Psychological Corp.

Department for Constitutional Affairs (2005). Mental Capacity Act 2005: Code of practice. London: The Stationery Office. Retrieved on 10 November 2010 from http://www.justice.gov.uk/guidance/mca-code-of-practice.htm.

Diamond, R., Carey, S., & Back, K. (1983). Genetic influences on the development of spatial skills during early adolescence. *Cognition, 13*, 167–185.

Dickinson, M. D., & Hiscock, M. (2010). Age-related IQ decline is reduced markedly after adjustment for the Flynn effect. *Journal of Clinical and Experimental Neuropsychology, 32*(8), 865-70.

Digilio, M. C., Angioni, A., De Santis, M., Lombardo, A., Giannotti, A. & Dallapiccola, B. (2003). Spectrum of clinical variability in familial deletion 22q11.2: from full manifestation to extremely mild clinical anomalies. *Clinical Genetics, 63*, 308-313.

Driscoll, D. A., Salvin, J., Sellinger, B., Budarf, M. L., McDonald-McGinn, D. M., Zackai, E. H., & Emanuel, B. S. (1993). Prevalence of 22q11 microdeletions in DiGeorge and velocardiofacial syndromes: implications for genetic counselling and prenatal diagnosis. *Journal of Medical Genetics, 30*, 813-817.

Dumontheil, I., Houlton, R., Christoff, K., & Blakemore, S. (2010). Development of relational reasoning during adolescence. *Developmental Science,13*(6), 15-24.

Dykens, E. M. (1995). Measuring behavioural phenotypes: provocations from the "New Genetics". *American Journal of Mental Retardation, 99*, 522-532.

Dykman, R. A., & Ackerman, P. T. (1991). Attention deficit disorder and specific reading disability: Separate but often overlapping disorders. *Journal of Learning Disabilities, 24*, 96–103.

Eme, R. F. (1992). Selective female affliction in the developmental disorders of childhood: A literature review. *Journal of Clinical Child Psychology, 21*, 354–364.

Evers, L. J., De Die-Smulders, C. E., Smeets, E. E., Clerkx, M. G., & Curfs, L. M. (2009). The velo-cardio-facial syndrome: the spectrum of psychiatric

problems and cognitive deterioration at adult age. *Genetic Counseling, 20*(4), 307-315.

Feinstein, C., Eliez, S., Blasey, C., & Reiss, A. L. (2002). Psychiatric disorders and behavioral problems in children with velo-cardio-facial syndrome: usefulness as phenotypic indicators of schizophrenia risk. *Biological Psychiatry, 51*, 312-318.

Flint, J. & Yule, W. (1994). Behavioural Phenotypes. In M. Rutter, E. Taylor & L. Hersov (Eds). *Child and Adolescent Psychiatry, Modern Approaches, 3rd ed* (pp. 666-687). Oxford, UK: Blackwell Scientific Publications.

Flint, J. (1996). Annotation: Behavioural Phenotypes: A Window Onto the Biology of Behaviour. *Journal of Child Psychology, 37*(4), 355-367.

Flynn, J. R. (2009). The WAIS-III and WAIS-IV: Daubert motions favor the certainly false over the approximately true. *Applied Neuropsychology, 16*, 98–104.

Flynn, J. R., & Weiss, L. G. (2007). American IQ gains from 1932 to 2002: The significance of the WISC subtests. *Journal of International Testing, 7*, 209-224.

Fraser, J. A. (2007). A study of the experiences of parents with 22q11, of children with 22q11. *Unpublished thesis Doctorate of Clinical Psychology at University of East London.*

Fung, W. L., McEvilly, R., Fong, J., Silversides, C., Chow, E., & Bassett, A. (2010). Elevated prevalence of generalized anxiety disorder in adults with 22q11.2 deletion syndrome. *American Journal of Psychiatry, 167*, 998.

Furniss, F., Biswas, A. B., Gumber, R., & Singh, N. (2011). Cognitive phenotype of velocardiofacial syndrome: a review. *Research in Developmental Disabilities, 32*, 2206–2213.

Fuster, J. M. (2008). The Prefrontal Cortex (4th ed). London, UK: Academic Press.

Gerdes, M., Solot, C., Wang, P. P., McDonald-McGinn, D. M., & Zackai, E. H. (2001). Taking advantage of early diagnosis: preschool children with the 22q11.2 deletion. *Genetic Medicine, 3*, 40–44.

Glaser, B., Mumme, D. L., Blasey, C., Morris, M. A., Dahoun, S. P., & Antonarakis, S. E. (2002). Language skills in children with velocardiofacial syndrome (deletion 22q112). *Journal of Paediatrics, 140*, 753-758.

Glaser, B., Debbane, M., & Hinard, C. (2006). No evidence for an effect of COMT Val158Met genotype on executive function in patients with 22q11 deletion syndrome. *American Journal of Psychiatry, 163*, 537-539.

Glaser, B., Debbane, M., Ottet, M. C., Vuilleumier, P., Zesiger, P., Antonarakis, S. E., & Eliez, S. (2010). Eye gaze during face processing in children and adolescents with 22q11.2 deletion syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(7), 665–674.

Goldberg, R., Mootzkin, B., Marion, R., Scrambler, P. J., & Shprintzen, R. J. (1993). Velocardiofacial Syndrome: A Review of 120 patients. *American Journal of Medical Genetics, 45*, 313-319.

Golding-Kushner, K. J., Weller, G., & Shprintzen, R. J. (1985). Velo-Cardio-Facial Syndrome: Language and Psychological Profiles. *Journal of Craniofacial Genetics and Developmental Biology, 5*, 259-266.

Goldman-Rakic, P. (1987). Higher functions of the brain. In F. Plum & V. Mountcastle (Eds.), *The Handbook of Physiology* (pp. 373–417). Bethesda, MD: American Physiological Society.

Goldstein, K., & Scheerer, M. (1941). Abstract and Concrete Behavior: An Experimental Study with Special Tests. In J. F. Dashiell (Ed.), *Psychological Monographs* (pp. 151).New York, NY: American Psychological Association.

Goodwin, L. D., & Leach, N. L. (2006). Understanding Correlation: Factors that affect the Size of r. *The Journal of Experimental Education, 74*(3), 249-266.

Gothelf, D., Presburger, G., Zohar, A. H., Burg, M., Nahmani, A., Frydman, M., ...Apter, A. (2004). Obsessive compulsive disorder in patients with velocardiofacial (22q11 deletion) syndrome. *American Journal of Medical Genetics, 126*, 99-105.

Gothelf, D., Eliez, S., Thompson, T., Hinard, C., Penniman, L., Feinstein, C., ...Reiss, A. L. (2005). COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome. *Nature Neuroscience, 8*(11), 1500-1502.

Gothelf, D., Feinstein, C., Thompson, T., Gu, E., Penniman, L., van Stone, E., ...Reiss, A. L. (2007a). Risk Factors for the Emergence of Psychotic Disorders in Adolescents with 22q11.2 Deletion Syndrome. *American Journal of Psychiatry, 164*, 663–669.

Gothelf, D., Aviram-Goldring, A., Burg, M., Steinberg, T., Mahajnah, M., Frisch, A., ...Weizman, A. (2007b). Cognition, psychosocial adjustment and coping in familial cases of velocardiofacial syndrome. *Journal of Neural Transmission, 114*, 1495-1501.

Gothelf, D., Michaelovsky, E., Frisch, A., Zohar, A. H., Presburger, G., Burg, M., ...Weizman, A. (2007c). Association of the low-activity COMT 158Met allele with ADHD and OCD in subjects with velocardiofacial syndrome. *International Journal of Neuropsychopharmacology, 10*, 301-308.

Gothelf, D., Penniman, L., Gu, E., Eliez, S., & Reiss, A. L. (2007d). Developmental trajectories of brain structure in adolescents with 22q11.2 deletion syndrome: a longitudinal study. *Schizophrenia Research, 96*, 72-81.

Gothelf, D., Hoeft, F., & Hinard, C. (2007e). Abnormal cortical activation during response inhibition in 22q11.2 deletion syndrome. *Journal of Human Brain Mapping, 28*, 533-542.

Gothelf, D., Schaer, M., & Eliez, S. (2008). Genes, brain development and psychiatric phenotypes in velo-cardio-facial syndrome. *Developmental Disabilities Research Reviews, 14*, 59-68.

Gothelf, D., Hoeft, F., Ueno, T., Sugiura, L., Lee, A. D., Thompson, R., & Reiss, A. L. (2011). Developmental changes in multivariate neuroanatomical patterns that predict risk for psychosis in 22q11.2 deletion syndrome. *Journal of Psychiatric Research, 45*(3), 322-331.

Green, T., Gothelf, D., Glaser, B., Debbane, M., Frisch, A., Kotler, M., ...Eliez, S. (2009). Psychiatric disorders and intellectual functioning throughout development in velocardiofacial (22q11.2 deletion) syndrome. *The Journal of the American Academy of Child and Adolescent Psychiatry, 48,* 1060-1068.

Hawkins, K. A., & Tulsky, D. S. (2001). The influence of IQ stratification on WAIS-III/WMS-III FSIQ-general memory Index discrepancy base-rates in the standardization sample. *Journal of the International Neuropsychological Society, 7*(7), 875-880.

Henry, J. C., van Amelsvoort, T., Morris, R. G., Owen, M. J., Murphy, D. G. M., & Murphy, K. C. (2002). An investigation of the neuropsychological profile in adults with velo-cardio-facial syndrome (VCFS). *Neuropsychologia, 40*, 471-478.

Hodapp, R. M. & Dykens, E. M. (2005). Measuring Behavior in Genetic Disorders of Mental Retardation. *Mental Retardation and Developmental Disabilities Research Reviews, 11*, 340–346.

Howe, M. J. A. (1990). *The origins of Exceptional abilities*. Oxford, UK: Blackwell Publications.

Iverson, G. L., Woodward, S., & Green, P. (2001). Base Rates of WAIS-R VIQ–PIQ Differences in 1593 Psychiatric Inpatients.' *Journal of Clinical Psychology*, *57*(12), 1579-1587.

Jablensky, A. (2000). Epidemiology of schizophrenia: the global burden of disease and disability. *European Archive of Psychiatry and Clinical Neuroscience, 250*(6), 274–85.

Jacobson, C., Shearer, J., Habel, A., Kane, F., Tsakanikos, E., & Kravariti, E. (2010). Core neuropsychological characteristics of children and adolescents with 22q11.2 deletion. *Journal of Intellectual Disability Research, 54*, 701–713.

Jensen, A. R. (1990). *The g factor: the science of mental ability*. Westport, CT: Praeger.

Johnson, D. L., Swank, P. R., Owen, M. J., Baldwin, C. D., Howie, V. M., & McCormick, D. P. (2000). Effects of Early Middle Ear Effusion on Child Intelligence at Three, Five, and Seven Years of Age. *Journal of Pediatric Psychology, 25*, 5-13.

Karayiorgou, M., Morris, M. A., Morrow, B., Shprintzen, R. J., Goldberg, R., Borrow, J., ...Lasseter, V. K. (1995). Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. *Proceedings of the National Academy of Sciences of the USA, 92*, 7612-7616.

Karmiloff-Smith, A. (1998) Development itself is the key to understanding developmental disorders. *Trends in Cognitive Sciences, 2*, 389-98.

Karmiloff-Smith, A., Thomas, M., Annaz, D., Humphreys, K., Ewing, S., Brace, N., ...Campbell, R. (2004). Exploring the Williams Syndrome Face Processing Debate: The importance of building developmental trajectories. *Journal of Child Psychology and Psychiatry, 45*, 1258-1274.

Karmiloff-Smith, A. (2008). Trajectories of Development and Learning Difficulties. Foresight Mental Capital and Wellbeing Project: The Government Office for Science, UK. Retrieved from http://www.foresight.gov.uk.

Karmiloff-Smith, A. (2011). Biological Embedding of Early Social Adversity. In From Fruit Flies to Kindergartners: Proceedings from presentation at National Academy of Sciences Sackler Colloquium held in Irvine, California, 9-10 December 2011. Retrieved on 14 January 2012 from http://www.youtube.com/watch?v=jArTVzqZ7kc.

Kates, W. R., Antshel, K. M., & Abdulsabur, N. (2006). A gender-moderated effect of a functional COMT polymorphism on prefrontal brain morphology and function in velo-cardio- facial syndrome (22q11.2 deletion syndrome). *American Journal of Medical Genetics, 141*, 274-280.

Kates, W. R., Antshel, K., Faraone, S. V., Fremont, W. P., Higgins, A. M., Shprintzen, R. J., ...McCarthy, C. (2011). Neuroanatomic Predictors to Prodromal Psychosis in Velocardiofacial Syndrome (22q11.2 Deletion Syndrome): A Longitudinal Study. *Biological Psychiatry, 69*, 945-952.

Kates, W. (2008). Introduction: advances in research on velo-cardio-facial syndrome/22q11.2 deletion syndrome. *Developmental Disabilities Research Reviews, 14*, 1–2.

Kaufman, A. S. (1976). Verbal-Performance IQ discrepancies on the WISC-R. *Journal of Consulting and Clinical Psychology, 44*(5), 739-744.

Kaufman, A., & Lichtenberger, E. O. (2006). Assessing Adolescent and Adult Intelligence. Chichester, UK: Wiley Publications.

Kiley-Brabeck, K., & Sobin, C. (2006). Social skills and executive function deficits in children with the 22q11 deletion syndrome. *Applied Neuropsychology, 13*, 258–268.

Kuhl, P. K. (2004). Early language acquisition: Cracking the speech code. *Nature Neuroscience, 5*, 831-843.

Lachman, H. M., Papolos, D. F., Saito, T., Yu, Y. M., Szumlanski, C. L., & Weinshilboum, R. M. (1996). Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics, 6*, 243–250.

Lajiness-O'Neill, R. R., Beaulieu, I., Titus, J. B., Asamoah, A., Bigler, E. D., Bawle, E. V., & Pollack, R. (2005). Memory and Learning in Children with 22q11.2 Deletion Syndrome: Evidence for Ventral and Dorsal Stream Disruption? *Child Neuropsychology, 11*, 55-71.

Lajiness-O'Neill, R., Beaulieu, I., Asamoahc, A., Titus, J. B., Bawle, E., Ahmade, S., ...Pollack, R. (2006). The neuropsychological phenotype of velocardiofacial syndrome (VCFS): Relationship to psychopathology. *Archives of Clinical Neuropsychology, 21*, 175-184.

Larrabee, G. J., & Curtiss, G. (1995). Construct validity of various verbal and visual memory tests. *Journal of Clinical and Experimental Neuropsychology, 17*(4), 536-547.

Lepach, A. C., & Petermann, F. (2011). Nonverbal and verbal learning: A comparative study of children and adolescents with 22q11 deletion syndrome, non-syndromal Nonverbal Learning Disorder and memory disorder. *Neurocase, 17(*6), 480-490.

Lewandowski, K. E., Shashi, V., & Berry, P. M. (2007). Schizophrenic-like neurocognitive deficits in children and adolescents with 22q11 deletion syndrome. *American Journal of Medical Genetics, 144*, 27-36.

Lezak, M. (1988). IQ: RIP. *Journal of Clinical and Experimental Neuropsychology,10*, 351-361.

Lezak, M., Loring, D. W., & Hannay, H. J. (2004). *Neuropsychological Assessment*. New York, NY: Oxford University Press.

Lezak, M.D. (1995). Neuropsychological assessment (3rd ed.). New York: Oxford University Press.

Lichtenberger, E. O. & Kaufman, A. (2009). *Essentials of WAIS-IV Assessment.* San Antonio, TX: The Psychological Corporation.

Kaufman, A. S., & Kaufman, N. L. (2003). *WISC-IV Technical Manual*. San Antonio, TX: The Psychological Corporation.

Mackinlay, R., Charman, T., & Karmiloff-Smith, A. (2003). Remembering to remember: A developmental study of prospective memory in a multitasking paradigm. Tampa, Florida: Poster presented at the Society for Research in Child Development, Biennial Meeting, 24–27 April.

Majerus, S., Van Der Linden, M., Braissand, V., & Eliez, S. (2007). Verbal Short-Term Memory in Individuals with Chromosome 22q11.2 Deletion: specific Deficit in Serial Order Retention Capacities? *American Journal on Mental Retardation, 112*, 79-93.

Majnemer, A., Limperopoulos, C., Shevell, M., Rosenblatt, B., Rohlicek, C., & Tchervenkov, C. (2006). Long-term neuromotor outcome at school entry of infants with congenital heart defects requiring open-heart surgery. *Journal of Paediatrics, 148*, 72-77.

Martens, M. A., Wilson, S. J., & Reutens, D. C. (2008). Research Review: Williams syndrome: a critical review of the cognitive, behavioral, and neuroanatomical phenotype. *Journal of Child Psychology and Psychiatry 49(*6), 576–608.

Matarazzo, J. D., & Herman, D. O. (1984). Base rate data for the WAIS-R: Test-retest stability and VIQ-PIQ differences. *Journal of Clinical Neuropsychology, 6*(35), 1-366.

Matarazzo, J. D., & Herman, D. O. (1985). Clinical uses of the WAIS-R: Base rates of differences between VIQ and PIQ in the WAIS-R standardization sample. In B. B. Wolman (Ed.), *Handbook of intelligence: theories, measurements, and applications* (pp. 899-932). New York, NY: John Wiley.

Matarazzo, J. D., Daniel, M. H., Prifitera, A., & Herman, D. O. (1988). Inter-subtest Scatter in the WAIS-R Standardization Sample. *Journal of Clinical Psychology, 44*(6), 940-950.

McCabe, K., Rich, D., Loughland, M., C., Schall, U., & Campbell, L. (2011). Visual scanpath abnormalities in 22q11.2 deletion syndrome: Is this a face specific deficit? *Psychiatry Research 189*, 292–298.

McDonald-McGinn, D. M., Kirschner, R., & Goldmuntz, E. (1999). The Philadelphia story: the 22q11.2 deletion: report on 250 patients. *Genetic Counselling, 101*, 11-24.

McDonald-McGinn, D. M., Tonnesen, M. K., Laufer-Cahana, A., Finucane, B., Driscoll, D. A., Emanuel, B. S., & Zackai, E. H. (2001). Phenotype of the 22q11.2 deletion in individuals identified through an affected relative: cast a wide FISHing net! *Genetic Medicine, 3*, 23-29.

McDonald-McGinn, D. M., Minugh-Purvis, N., Kirschner, R., Jawad, A., Tonnesen, M. K., Catanzaro, J. R., ...Zackai, E. H. (2005). The 22q11.2 deletion in African-American patients: an underdiagnosed population. *American Journal of Medical Genetics, 1343,* 242–246.

McDonald-McGinn, D. M. & Zackai, E. H. (2008). Genetic counselling for the 22q11.2 deletion. *Developmental disabilities research reviews, 14,* 69 – 74.

McGivern, R. F., Andersen, J., Byrd, D., Mutter, K. L., & Reilly, J. (2002). Cognitive efficiency on a match to sample task decreases at the onset of puberty in children. *Brain and Cognition, 50*, 73–89.

Mervis, C., & Bertrand, J. (1997). Developmental relations between cognition and language: Evidence from Williams Syndrome. In L. B. Adamson & M. A. Romski (Eds.), *Research on communication and language disorders: Contributions to theories of language development* (pp. 75-106). New York, NY: Brookes.

Mervis, C. B., & Klein-Tasman, B. (2004). Methodological issues in group-matching designs: Alpha levels for cognitive variable comparisons and measurement characteristics of control and target variables. *Journal of Autism and Developmental Disorders*, *34*(1), 7–17.

Miller, S. P., Patrick, C. M., McQuillen, S., Hamrick, S., Xu, D., Glidden, D. V., ...Vigneron, D. B. (2007). Abnormal Brain Development in Newborns with Congenital Heart Disease. *The New England Journal of Medicine, 357*, 1928-38.

Moss, E. M., Batshaw, M. L., & Solot, C. B. (1999). Psychoeducational profile of the 22q11.2 microdeletion: a complex pattern. *Journal of Paediatrics, 134*, 193-198.

Murphy, K. C., Jones, L. A., & Owen, M. J. (1999). High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Archives of General Psychiatry, 56*, 940-945.

Murphy, K. C. (2004). The behavioural phenotype in velo–cardio–facial syndrome. *Journal of Intellectual Disability Research, 48*, 524-530.

Murphy, M. M., Mazzocco, M. M., Gerner, G., & Henry, A. E. (2006). Mathematics learning disability in girls with Turner syndrome or fragile X syndrome. *Brain and Cognition, 61*, 195-210.

Niklasson, L., & Gillberg, C. (2010). The neuropsychology of 22q11 deletion syndrome: A neuropsychiatric study of 100 individuals. *Research in Developmental Disabilities, 31*, 185–194.

Niklasson, L., Rasmussen, P., Óskarsdóttir, S. and Gillberg, C. (2001). 'Neuropsychiatric disorders in the 22q11 deletion syndrome.' Genetics in Medicine, 3, 79-84.

Óskarsdóttir, S., Belfrage, M., Sandstedt, E., Viggedal, G., & Uvebrant, P. (2005). Disabilities and cognition in children and adolescents with 22q11 deletion syndrome. *Developmental Medicine and Child Neurology, 47*, 177-184.

Prasad, S. E., Howley, S., & Murphy, K. C. (2008). Candidate genes and the behavioral phenotype in 22q11.2 deletion syndrome. *Developmental Disabilities Research Reviews, 14*, 26-34.

Psychological Corporation. (1997). *WAIS-III WMS-III Technical Manual*. San Antonio, TX: The Psychological Corporation.

Ramsden, S., Richardson, F. M., Josse, G., Thomas, M. S., Ellis, C., Shakeshaft, C., ...Price, C. J. (2011). Verbal and nonverbal intelligence changes in the teenage brain. *Nature, 479*, 113–116.

Rauch, A., Zink, S., Zweier, C., Thiel, C.T., Koch, A., Rauch, R., ...Hofbeck, M. (2005). Systematic assessment of atypical deletions reveals genotype-

phenotype correlation in 22q11.2. *Journal of Medical Genetics, 42*, 871–876.

Reid-Arndt, S. A., Allen, B. J., & Schopp, L. (2011). Validation of WAIS-III four-subtest short forms in patients with traumatic brain injury. *Applied Neuropsychology, 18*(4), 291-297.

Richardson, S. A., Koller, H., & Katz, M. (1987). Sex differences in the classification of children as mildly mentally retarded. *Upsala Journal of Medical Science, 44*, 83–88.

Rockers, K., Ousley, O., Sutton, T., Schoenberg, E., Coleman, K., Walker, E., & Cubells, J.F. (2009). Performance on the Modified Card Sorting Test and its relation to psychopathology in adolescents and young adults with 22q11.2 deletion syndrome. *Journal of Intellectual Disability Research 53*, 665–676.

Rourke, B. P. (1987). Syndrome of nonverbal learning disabilities: The final common pathway of white-matter disease/dysfunction? *Journal of Clinical Neuropsychology, 1*, 209-234.

Rourke, B. P. (1989). *Nonverbal Learning disabilities: the syndrome and the model*. New York, NY: Guilford Press.

Rourke, B. P. (1995). *Syndrome of nonverbal learning disabilities: Neurodevleopmental manifestations*. New York, NY: Guilford Press.

Ryan, A. K., Goodship, J. A., Wilson, D. I., Philip, N., Levy, A., Seidel, H., ...Scambler, P. J. (1997). Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. *Journal of Medical Genetics, 34*, 798-804.

Schaer, M., Debbane, M., Bach Cuadra, M., Ottet, M. C., Glaser, B., ...Thiran, J. P. (2009). Deviant trajectories of cortical maturation in 22q11.2 deletion syndrome (22q11DS): a cross-sectional and longitudinal study. *Schizophrenia Research, 115*, 182–190.

Sheslow, D., & Adams, W. (1990). *Wide range assessment of memory and learning*. Wilmington, DE: Wide Range Incorporated.

Shprintzen, R. J. (2008). Velo-cardio-facial syndrome: 30 years of study. *Developmental Disabilities Research Reviews 14*, 3–10.

Shprintzen, R. J., Goldber, R. B., Lewin, M. L., Sidoti, E. J., Berkman, M. D., Argamaso, R. V., & Young, D. (1978). A new syndrome involving cleft palate, cardiac anomalies, typical facies, and learning disabilities: Velo-cardio-facial Syndrome. *Cleft Palate Journal, 5,* 56-62.

Shprintzen, R. J., Goldberg, R., Golding-Kushner, K. J., & Marion, R. (1992). Late-onset psychosis in the velocardio-facial syndrome. *American Journal of Medical Genetics, 42*, 141-142.

Shprintzen, R. J. (2000). Velo-cardio-facial syndrome: a distinctive behavioural phenotype. *Mental Retardation Developmental Disability Research Review*, *6,* 142-147.

Sigelman, C., & Rider, E. (2006). *Life-span human development*. Belmont, CA: Thomson Wadsworth.

Simon, T. J., Bearden, C. E., Moss, E. M., McDonald-McGinn, D., Zackai, E., & Wang, P. P. (2002). Cognitive development in VCFS. *Progress in Pediatric Cardiology, 15*, 109-117.

Simon, T. J., Bish, J. P., Bearden, C. E., Ding, L., Ferrante, S., Nguyen, V., & ...Emanuel, B. S. (2005). A multiple levels analysis of cognitive dysfunction and psychopathology associated with chromosome 22q11.2 deletion syndrome in children. *Developmental Psychopathology, 17*, 753–784.

Simon, T. J., Takarae, Y., DeBoera, T., McDonald-McGinn, D. M., Zackai, E. H., & Ross, J. L. (2008). Overlapping numerical cognition impairments in children with chromosome 22q11.2 deletion or Turner syndromes. *Neuropsychologia 46*, 82–94.

Skuse, D. (2000). Behavioural phenotypes, what do they teach us? *Archives of Disease of Childhood, 82*, 222-225.

Sobin, C., Kiley-Brabeck, K., Daniels, S., Khuri, J., Taylor, L., Blundell, M., ...Karayiorgou, M. (2005). Neuropsychological characteristics of children with 22q11 Deletion Syndrome: A descriptive analysis. *Child Neuropsychology, 11*, 39-53.

Solot, C. B., Kirschner, R. E., McDonald-McGinn, D., Moss, E., Woodin, M., David, A., ...Wang, P. P. (2001). Communication issues in 22q11.2 deletion syndrome: Children at risk. *Genetics in Medicine, 3*, 67-71.

Spearman, C. (1904). General Intelligence, objectively determined and measured. *The American Journal of Psychology, 15*(2), 201–292.

Squire, L. R. & Knowlton, B. J. (2000). The medial temporal lobe, the hippocampus, and the memory systems of the brain. In M. Gazzaniga (Ed.), *The New Cognitive Neurosciences (*2nd ed., pp.765-779*).* Cambridge: MIT Press.

Srivastava, S., Buonocore, M. H., & Simon, T. J. (2012). Atypical Developmental Trajectory of Functionally Significant Cortical Areas in Children with Chromosome 22q11.2 Deletion Syndrome. *Human Brain Mapping 33,* 213–223.

Stachon, A. C., Baskin, B., Smith, A. C., Shugar, A., Cytrynbaum, C., Fishman, L., ...Weksberg, R. (2007). Molecular diagnosis of 22q11.2 deletion and duplication by multiplex ligation dependent probe amplification. *American Journal of Medical Genetics, 143*, 2924-2930.

Sternberg, R. J. (1985). *Beyond IQ: A Triarchic Theory of Intelligence.* Cambridge: Cambridge University Press.

Sternberg, R. J. (1988). Explaining away intelligence: A reply to Howe. *British Journal of Psychology, 79*, 527-533.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology, 18*(6), 643–662.

Stuss, D. T., & Alexander, M. P. (2000). Executive functions and the frontal lobes: a conceptual view. *Psychological Research, 63,* 289-98.

Swillen, A., Fryns, J. P., Kleczkowska, A., Massa, G., Vanderschueren-Lodeweyckx, M., Van den Berghe, H. (1993). Intelligence, behaviour and psychosocial development in Turner syndrome: A cross-sectional study of 50 pre-adolescent and adolescent girls (4-20 years). *Genetic Counseling, 4*(1), 7-18.

Swillen, A., Devriendt, K. & Legius, E. (1997). Intelligence and psychosocial adjustment in velo-cardio-facial syndrome: a study of 37 children and adolescents with VCFS. *Journal of Medical Genetics, 34*, 453-458.

Swillen, A., Vandeputte, L., Cracco, J., Maes, B., Ghesquiere, P., Devriendt, K. & Fryns, J. (1999). Neuropsychological, learning and psychosocial profile of primary school aged children with the velo-cardio-facial syndrome (22q11 deletion): Evidence for a nonverbal learning disability? *Neuropsychology, Development and Cognition, Section C, Child Neuropsychology, 5*, 230-241.

Tallal, P. (1991). Hormonal influences in developmental learning disabilities. *Psychoneuroendocrinology, 16*, 203–211.

Thomas, M. S. C., Annaz, D., Ansari, D., Scerif, G., Jarrold, C., Karmiloff-Smith, A. (2009). Using Developmental Trajectories to Understand Developmental Disorders. *Journal of Speech, Language and Hearing Research, 52,* 336-358.

Thurstone, L. L. (1938). *Primary Mental Abilities*. Chicago, USA: University of Chicago Press.

Usiskin, S. I., Nicolson, R., Krasnewich, D. M., Yan, W., Lenane, M., Wudarsky, M., ...Rapoport, J. L. (1999). Velocardiofacial syndrome in childhood-onset schizophrenia. *Journal of American Academic Child and Adolescent Psychiatry, 38*, 1536 –1543.

Van Amelsvoort, T., Daly, E., Robertson, D., Suckling, J., Ng, V., Critchley, H., ...Murphy, D. G. M. (2001). Structural brain abnormalities associated with deletion at chromosome 22q11: quantitative neuroimaging study of adults with velocardio-facial syndrome. *British Journal of Psychiatry, 178*, 412–419.

Van Amelsvoort, T., Henry, J., Morris, R., Owen, M., Linszen, D., Murphy, K., ...Murphy, D. (2004). Cognitive deficits associated with schizophrenia in velo-cardio-facial syndrome. *Schizophrenia Research, 70*, 223–232.

Van Amelsvoort, T., Schmitz, N., Daly, E., Deeley, Q., Critchley, H., Henry, J., ...Muprhy, D. G. (2006). Processing facial emotions in adults with velo-cardio-facial syndrome: functional magnetic resonance imaging. *British Journal of Psychiatry 189*, 560–561.

Van Amelsvoort, T., Zinkstok, J., Figee, M., Daly, E., Morris, R., Owen, M. J., ...Murphy, D., G. (2008). Effects of a functional COMT polymorphism on brain anatomy and cognitive function in adults with velo-cardio-facial syndrome. *Psychological Medicine, 38*, 89–100.

Volkmar, F. R., Szatmari, P., & Sparrow, S. S. (1993). Sex differences in pervasive developmental disorders. *Journal of Autism & Developmental Disorders, 23*, 579–591.

Warrington, E. K., & James, M. (1991). *The Visual Object and Space Perception Battery*. London, UK: Thames Valley Test Co.

Wang, P. P., Woodin, M. F., Kreps-Falk, R., & Moss, E. M. (2000). Research on behavioural phenotypes: Velocardiofacial syndrome (deletion 22q11.2). *Developmental Medicine and Child Neurology, 42*, 422-427.

Wechsler, D. (1939). *Wechsler–Bellevue Intelligence Scale.* New York, NY: Psychological Corporation.

Wechsler, D. (1981). *WAIS-R Manual: Wechsler Adult Intelligence Scale: Revised*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1987). *Wechsler Preschool and Primary Scale of Intelligence: Revised.* San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1991). *Wechsler Intelligence Scale for Children: Third Edition*. San Antonio, (TX): The Psychological Corporation.

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale: Third Edition*. San Antonio, (TX): The Psychological Corporation.

Wechsler, D. (1999). Wechsler Abbreviated Scale of Intelligence (WASI). San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2004). *Wechsler Intelligence Scale for Children: Fourth Edition*. San Antonio, (TX): The Psychological Corporation.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale: Fourth Edition: Technical and interpretive manual*. San Antonio, (TX): The Psychological Corporation.

Weinert, F., & Hany, E. (2003). The stability of individual differences in intellectual development: Empirical evidence, theoretical problems, and new research questions. In R. J. Sternberg, J. Lautrey, & T. I. Lubar (Eds.), *Models of intelligence: International perspectives* (pp. 169–181). Washington, DC: American Psychological Association.

Williams, M. A., Rich, M. A., Reed, L. K., Jackson, W. T., LaMarche, J. A., & Boll, T. J. (1998). Visual reproduction subtest of the Wechsler Memory Scale-Revised: Analysis of construct validity. *Journal of Clinical Psychology, 54*(7), 963-71.

Woodin, M., Wang, P. P., Aleman, D., McDonald-McGinn, D., Zackai, E., & Moss, E. (2001). Neuropsychological profile of children and adolescents with the 22q11.2 microdeletion. *Genetics in Medicine, 3*, 34-39.

Zinkstok, J., & van Amelsvoort, T. (2005). Neuropsychological profile and neuroimaging in patients with 22q11.2 Deletion Syndrome: A Review. *Child Neuropsychology, 11*, 21-37.

Appendix One: Registration of Thesis with the UEL School of Psychology

SCHOOL OF PSYCHOLOGY
Dean: Professor Mark N. O. Davies, PhD, CPsychol, CBiol.

UEL
University of East London
www.uel.ac.uk

Professional Doctorate in Clinical Psychology

[redacted]

10 February 2011

Dear Clare

Re: Registration of research thesis

Thank you for your amended registration document and for your letter detailing your response to the points that the Clinical Psychology sub-group of the School Research Degrees Subcommittee raised in relation to your original proposal. I am satisfied that you have successfully addressed the issues identified in my letter to you of January 27th, and I am writing to inform you that your proposal has been accepted for registration. You should now submit one full hard copy of your registration document to me.

You are now permitted to proceed to apply for approval from the UEL Ethics Committee and other relevant ethics committees. You should submit two copies of the completed UEL Ethics form to me. I will have the Dean of School sign one copy and forward this to the Ethics Committee. I will notify you when I have been informed of their decision.

Best wishes for every success with your research.

Yours sincerely

Kenneth Gannon
Research Director

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Appendix Two: UEL Ethical Approval

SCHOOL OF PSYCHOLOGY
Dean: Professor Mark N. O. Davies, PhD, CPsychol, CBiol.

UEL
University of East London
www.uel.ac.uk

Professional Doctorate in Clinical Psychology

[redacted]

10 February 2011

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Best wishes for every success with your research.

Yours sincerely

Kenneth Gannon
Research Director

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Appendix Three: National Research Ethics Committee Approval letter

NHS

National Research Ethics Service

NRES Committee South East Coast - Brighton and Sussex REC

NHS Brighton & Hove
Level 4, Lanchester House
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BN1 4FU

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08 June 2011

[redacted]

Dear Miss Jacobson

Study title: **Developmental cognitive trajectory of the 22q11.2 Deletion**

REC reference: **11/LO/0509**

Thank you for your letter of 22 May 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair in consultation with Dr Duncan Angus

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of

Appendix Four: Approval with Research and Development at Great Ormond Street Hospital

SCHOOL OF PSYCHOLOGY
Dean: Professor Mark N. O. Davies, PhD, CPsychol, CBiol.

UEL
University of East London
www.uel.ac.uk

Professional Doctorate in Clinical Psychology

[redacted]

10 February 2011

Dear Clare

Re: Registration of research thesis

Thank you for your amended registration document and for your letter detailing your response to the points that the Clinical Psychology sub-group of the School Research Degrees Subcommittee raised in relation to your original proposal. I am satisfied that you have successfully addressed the issues identified in my letter to you of January 27th, and I am writing to inform you that your proposal has been accepted for registration. You should now submit one full hard copy of your registration document to me.

You are now permitted to proceed to apply for approval from the UEL Ethics Committee and other relevant ethics committees. You should submit two copies of the completed UEL Ethics form to me. I will have the Dean of School sign one copy and forward this to the Ethics Committee. I will notify you when I have been informed of their decision.

Best wishes for every success with your research.

Yours sincerely

Kenneth Gannon
Research Director

Stratford Campus, Water Lane, Stratford, London E15 4LZ
tel: +44 (0)20 8223 4966 fax: +44 (0)20 8223 4937
e-mail: mno.davies@uel.ac.uk web: www.uel.ac.uk/psychology

Appendix Five: Covering letter to participants

DATE

Dear Mr/Ms,

We would like to invite you to participate in some research being conducted with the 22q team at Great Ormond Street Hospital. An information sheet is enclosed to explain why you have been selected, what the research involves and what it is for.

If you have any questions or queries, please feel free to contact us on tel. XXXX. If you do not wish to participate, you can either tell Clare Jacobson when she telephones you or you can telephone the above number and ask to speak with me (XXX) or leave me a message and we will not contact you again about this.

Thank you very much for your time.

Yours Sincerely,

XXXX

(Clinical Psychologist)

XXXX

(Clinical Lead Paediatrician)

Appendix Six: Cover letter to participants' parents

DATE

Dear Mr/Mrs/Ms,

We would like to invite your son/daughter to participate in some research being conducted with the 22q team at Great Ormond Street Hospital. An information sheet is enclosed to explain why s/he has been selected, what the research involves and what it is for.

If you have any questions or queries, please feel free to contact us on tel. XXXX. If you do not wish to participate, you can either tell Clare Jacobson when she telephones you or you can telephone the above number and ask to speak with me (XXXX) or leave me a message and we will not contact you again about this.

Thank you very much for your time.

Yours Sincerely,

XXXX

(Clinical Psychologist)

XXXX

(Clinical Lead Paediatrician)

Appendix Seven: Information Sheet for Participants

Developmental cognitive trajectory of the 22q11.2 Deletion

Information Sheet

Project

With your help, we would like to find out a bit more about how memory and thinking skills develop in people who have a diagnosis of 22q. We don't yet know enough about this because there aren't enough studies. This study is being done as part of a doctoral qualification in Clinical Psychology.

Why we are asking you:

Some time ago you had an assessment of your learning, at Great Ormond Street Hospital. You did a number of tasks where you had to remember and understand stories and pictures.

This is a chance to have a further one-off assessment and get a copy of your results if you would like to find out how you are getting on. The results could be used to help plan college/employment and you would have the chance to speak to a Clinical Psychologist about how to use the results if you wish.

By participating in this research, we hope to increase our understanding of how 22q affects learning, memory and thinking over time. The results will also be useful to younger patients coming through the service.

We are writing you this letter so that you have all the information you need to decide whether or not you want to take part.

What do you need to do?

We would ask you to meet with Clare Jacobson (who might have done your previous cognitive assessment with you). Clare is the researcher in this project and she will ask you to do some tasks, drawing and puzzles with her, very similar to your previous cognitive assessment. The tasks involve things like

listening to a short story and trying to remember it and looking at shapes and picking the odd one out. You will also be asked some questions about your mood, e.g. whether you are feeling happy or sad, nervous or relaxed.

It will take two hours *maximum* but hopefully less.

If you are able to meet with Clare at Great Ormond Street hospital (if you are aged 17 or younger) or the Institute of Psychiatry (if you are aged 18 or over), we can pay you back for any money you spend on your travel. It is also possible for Clare to come to your home.

What happens to your results?

Your results will be kept confidential and they will be anonymized so that nobody, apart from Clare, will know whose results are whose. Your anonymized results will be put into a password-protected database stored on the GOSH Psychology Research computer drive. Your name will not appear on the database. Only Clare Jacobson and her supervisors will see the database.

If you indicate any difficulties with your mood or wellbeing during the assessment, Clare will ask you if you would like to be referred to your GP or one of the psychologists or psychiatrists attached to the 22q team for some help. Clare would need to tell your GP if she was worried that you might harm yourself or others but she would talk to you about doing this first.

Once the study is done (summer 2012), feedback on the results of the study and your individual results (if you would like these) will be offered in both a paper summary and a discussion over the telephone with Clare. If you would rather not know your results, that is fine too. If you would like to know your results, we can also send a copy to your GP if you would like. It is likely that your memory and thinking is roughly the same as it was the first time you had a cognitive assessment, but there is a chance that you may have got better or worse at some things. If you would like to speak in more detail about your results, you can meet with one of the psychologists attached to the 22q team.

What next?

Clare will telephone you in about a week to ask if you would like to take part in the study. However, if you have any questions in the meanwhile, please do not hesitate to contact Clare on tel. XXXX or email: XXXX.

What if I don't want to?

You do not have to take part in this study, and you are free to stop at any time during the assessment. If you agree to participate and then you change your mind, that is fine too. If you do not want to take part, you can either tell Clare when she telephones you or you can call tel. XXXX and leave a message for XXXX.

What if I am not happy about something?

If you have any concerns regarding the conduct of the research in which you are being asked to participate, please contact the Secretary of the University Research Ethics Committee, Ms Debbie Dada, Admissions and Ethics Officer, Graduate School, University of East London, Docklands Campus, London E16 2RD (Tel 020 8223 2976, Email: d.dada@uel.ac.uk)

Thank you very much for your time.

Yours Sincerely,

XXXX

(Clinical Psychologist)

XXXX

(Clinical Lead Paediatrician)

Appendix Eight: Information Sheet for Participants' Parents

Developmental cognitive trajectory of the 232q11.2 Deletion

Information Sheet

Project

With the help of you and your child, we would like to find out a bit more about how memory and thinking skills develop in people who have a diagnosis of 22q. We don't yet know enough about this because there aren't enough studies. This study is being done as part of a doctoral qualification in Clinical Psychology.

Why we are asking your child:

Some time ago your child had an assessment of their learning at Great Ormond Street Hospital. They completed a number of tasks that examined their memory and their ability to understand verbal and nonverbal information. There is a lack of studies investigating these areas of development over the long-term, which is what this project aims to do.

This is opportunity chance for your child to have a further one-off assessment and be given a copy of their results if they would like to find out how they are getting on. The results could be used to help plan college/employment and your child would have the chance to speak to a Clinical Psychologist about how to use the results if they wish.

By participating in this research, we hope to increase our understanding of how 22q affects learning, memory and thinking over time. The results will also be useful to younger patients coming through the service.

We are writing you this letter so that you and your child have all the information you need to decide whether or not they want to take part.

What does your child need to do?

We would ask your child to meet with Clare Jacobson (who might have carried out their previous cognitive assessment with them). Clare is the researcher in

this project and she will ask your child to do some tasks, drawing and puzzles with her, very similar to their previous cognitive assessment. The tasks involve things like listening to a short story and trying to remember it and looking at shapes and picking the odd one out. They will also be asked some questions about their mood, e.g. whether they are feeling happy or sad, nervous or relaxed.

It will take two hours *maximum* but hopefully less.

If your child is able to travel to Great Ormond Street hospital to meet with Clare, we can reimburse your and their travel expenses. But it is also possible for Clare to come to your home.

What happens to your results?

Your child's results will be kept confidential and they will be anonymized so that nobody, apart from Clare, will know whose results are whose. Their anonymized results will be put into a password-protected database stored on the GOSH Psychology Research computer drive. Their name will not appear on the database. Only Clare Jacobson and her supervisors will see the database.

If your child indicates any difficulties with their mood or wellbeing during the assessment, Clare will ask if they would like to be referred to their GP or one of the psychologists attached to the 22q team for some help. Clare would need to tell you and your child's GP if she was worried that they might harm themself or others, but she would talk to your child about doing this first.

Once the study is finished (summer 2012), feedback on the results of the study and your child's individual results (if they would like these) will be offered to them in both a paper summary and a discussion over the telephone with Clare. If your child would rather not know their results, that is fine too. If they would like to know their results, we can also send a copy to their GP if they would like. It is likely that your child's memory and thinking is roughly the same as it was the first time they had a cognitive assessment, but there is a chance that they may have got better or worse at some things. If your child would like to speak in

more detail about their results, you and they can meet with one of the psychologists attached to the 22q team.

What next?

Clare will telephone your child in about a week to ask if they would like to take part in the study. However, if you or your child have any questions in the meanwhile, please do not hesitate to contact Clare on tel. XXXX or email: XXXX.

What if I don't want to?

Your child is not obliged to take part in this study, and they are free to stop at any time during the assessment. Should they choose to withdraw from the project, they may do so without disadvantage to themselves and without any obligation to give a reason. If you do not want your child to take part or they do not want to take part, you can either tell Clare when she telephones you or you can call tel. XXXX and leave a message for XXXX.

What if I am not happy about something?

If you have any concerns regarding the conduct of the research in which your child is being asked to participate, please contact the Secretary of the University Research Ethics Committee, Ms Debbie Dada, Admissions and Ethics Officer, Graduate School, University of East London, Docklands Campus, London E16 2RD (Tel XXXX, Email: d.dada@uel.ac.uk)

Thank you very much for your time.

Yours Sincerely,

XXXX

(Clinical Psychologist)

XXXX

(Clinical Lead Paediatrician)

Appendix Nine: Consent form for Participants

Centre Number:

Study Number:

Participant Identification Number**:**

CONSENT FORM

Title of Project: Developmental cognitive trajectory of the 22q11.2 Deletion

Name of researcher: Clare Jacobson

Please initial box

1. I confirm that I have read and understand the information sheet dated..... (version.....) for the above study. I have been able to think about the information, ask all the questions I want and my questions have been answered in a way I understand. ☐

2. I understand that I don't have to take part and I can stop taking part at any time without giving a reason and my medical care and legal rights will not be affected. ☐

3. I understand that relevant sections of my medical notes and data collected during this study may be looked at by Clare Jacobson (researcher) and
XXXX (research supervisor), and by individuals from regulatory authorities, the NHS Trust and the research sponsor if it is important to the study. ☐
I give permission for these individuals to have access to my records.

4. I understand that if I tell Clare Jacobson that I might harm myself or somebody else, she will have to tell somebody like my GP and the psychiatrist/psychologist in the 22q team. ☐

5. I understand that if I tell Clare that I am having some problems with ☐

feeling very sad or nervous or hearing voices, she will arrange for me to meet with my GP or the psychiatrist/psychologist in the 22q team.

6. I wish to find out the results of my assessment. ☐

7. I agree that Clare can give a copy of my assessment results to my GP. ☐

8. I agree to take part in this study. ☐

If you don't want to take part, then don't sign your name!

_____	_____	_____
Name of Participant	Date	Signature

_____	_____	_____
Name of Person taking consent	Date	Signature

When completed: 1 copy for participant; 1 copy for researcher site file; 1 (original) to be kept in medical notes.

Appendix Ten: Consent form for Participants' Parents

Centre Number:

Study Number:

Participant Identification Number**:**

CONSENT FORM

Title of Project: Developmental cognitive trajectory of the 22q11.2 Deletion

Name of researcher: Clare Jacobson

Please initial box

1. I confirm that I have read and understand the information sheet dated..... (version.....) for the above study. My child and I have been able to think about the information, ask all the questions we want and our questions have been answered in a way we understand. ☐

2. My child and I understand that my child does not have to take part and they can stop taking part at any time without giving a reason and their medical care and legal rights will not be affected. ☐

3. I understand that relevant sections of my child's medical notes and data collected during this study may be looked at by Clare Jacobson (researcher) and XXXX (research supervisor), and by individuals from regulatory authorities, the NHS Trust and the research sponsor if it is important to the study. I give permission for these individuals to have access to my child's records. ☐

4. I understand that if my child tells Clare Jacobson that they might harm themselves or somebody else, Clare will have to tell somebody like my child's GP and the psychiatrist/psychologist in the 22q team. ☐

5. I understand that if my child tells Clare Jacobson that they are having ☐

some problems with their mood or hearing voices, Clare will arrange for them to meet with their GP or the psychiatrist/psychologist in the 22q team.

6. I would like to find out the results of my child's assessment. ☐

7. I agree that Clare Jacobson can give a copy of my child's assessment results to their GP. ☐

8. I agree that my child can take part in this study. ☐

If you don't want your child to take part, then don't sign your name!

_____	_____	_____
Name of Participant	Date	Signature

_____	_____	_____
Name of Person taking consent	Date	Signature

When completed: 1 copy for participant's guardian; 1 for researcher site file; 1 (original) to be kept in medical notes.