22q11 Deletion Syndrome
Neuropsychological and Neuropsychiatric Correlates

A Clinical Study of 100 Cases

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ABSTRACT

Objectives: Examine the prevalence and type of Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity-Disorder (AD/HD), Learning Disability (LD), behavioural profile, intellectual ability/profile, and executive function in 22q11 Deletion Syndrome (22q11DS) and to study the impact of AD/HD and ASD on these functions.

Methods: One hundred individuals (58 female, 42 male; 1-35 years of age) with 22q11DS, confirmed by FISH analysis, were included. They were the first 100 referred 22q11DS cases, of whom 92 came from a multidisciplinary team as part of routine 22q11DS assessments, and 8 were referred directly to a Child Neuropsychiatry Clinic for learning and/or behaviour problems. Neuropsychological evaluation made use of a test battery designed to provide information concerning developmental/intellectual level and profile, visuomotor development, executive functions (planning ability and attention), and mentalisation skills. Neuropsychiatric assessments included structured and semistructured interviews with parent(s), an evaluation of the individual including psychiatric assessment, physical examination, and age-appropriate neurological examination. Parents completed the Autism Spectrum Screening Questionnaire, the Conners Brief Parent Rating Scale, the Child Behavior Checklist, and the Five To Fifteen (FTF) questionnaire. Comprehensive diagnoses of ASD and AD/HD were made by a psychiatrist according to the DSM-IV taking the results of the various examinations (interview, medical examinations, observation, and the FTF questionnaire) into account.

Results: The prevalence of ASD and/or AD/HD with or without LD was 44%, of whom 21% had AD/HD "only", 14% ASD "only", and 9% a combination of these two diagnoses. In addition, 23% had LD "only", meaning that there were 33% without any of these diagnoses. Autistic disorder was found to be quite rare (5%). Other psychiatric diagnoses were found mainly among the adults. Altogether 51% met criteria for LD, and the mean IQ was 71 with a normal distribution around this mean. Higher IQ for females compared to males and a negative trend for IQ with increasing age were found. An overrepresentation of girls was found only in the group without ASD/AD/HD/LD. In the school age group and in the adult group significantly higher verbal IQ than performance IQ was found. In contrast, in the youngest group the lowest result was found in the "Hearing and Speech" subscale (Griffiths´ Mental scale) reflecting a delay in expressive language in the early years. The strength within the verbal area was mainly due to good Vocabulary. Deficits in performance ability were found. The intellectual and the visuomotor impairments were related to 22q11DS per se while the presence of ASD/AD/HD had a negative impact on planning ability in children. The ability to sustain attention was found to be critically impaired in school age children with 22q11DS. According to results of the questionnaires a variety of behaviour problems were reported. A characteristic combination of initiating difficulties and a "lack of mental energy" was observed in the majority.

Discussion and conclusions: The vast majority of all with 22q11DS had behaviour and/or learning problems and more than 40% met criteria for either ASD, AD/HD or both (even though typical autistic disorder was rather uncommon). Half the group had LD. The majority of the group with IQ in the normal to low normal range had learning difficulties. Many individuals with 22q11DS had social interaction difficulties that, in the presence of relatively good word skills, appeared to be related to initiation problems and language use deficits. Given the high rate and variety of problems found, a neuropsychiatric assessment, including neuropsychological testing, should be performed in all cases of 22q11DS. Such assessment will provide essential information about strengths and difficulties, crucial for providing optimal support for individuals with 22q11DS.

Key words: 22q11 Deletion Syndrome, Autism Spectrum Disorder, Attention-Deficit/Hyperactivity Disorder, Learning Disability, neuropsychology

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ISBN 978-91-628-7325-7 Printed in Sweden 2007

To
Karin, Arvid and Erik

CONTENTS

LIST OF PAPERS

This thesis is based on the following publications, which will be referred to in the text by the Roman numerals I-IV.

I. Niklasson, L., Rasmussen, P., Óskarsdóttir, S., Gillberg, C. (2002). ”Chromosome 22q11 deletion syndrome (CATCH 22): neuropsychiatric and neuropsychological aspects”. *Developmental Medicine and Child Neurology*, 44:44-50.

II. Niklasson L., Rasmussen P., Óskarsdóttir S., Gillberg C. (2007). “Autism, AD/HD, learning disability, and behaviour problems in 100 individuals with 22q11 deletion syndrome” *(submitted).*

III. Niklasson, L., Rasmussen P., Óskarsdóttir, S., Gillberg, C. (2005). ”Attention deficits in children with 22q11 Deletion Syndrome”. *Developmental Medicine and Child Neurology*, 47:803-807.

IV. Niklasson L. & Gillberg C. (2007). “The neuropsychology of 22q11 deletion syndrome. A clinical study of 100 individuals” *(submitted).*

ABBREVIATIONS

22q11DS	22q11 Deletion Syndrome
AD/HD	Attention-Deficit/Hyperactivity Disorder
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
ALC	Autistic-Like Condition
ASD	Autism Spectrum Disorder
ASSQ	Autism Spectrum Screening Questionnaire
BPRS	Conners Brief Parent Rating Scale
CBCL	Child Behavior Checklist
CHD	Congenital Heart Defect
CI	Confidence Interval of the mean
CNC	Child Neuropsychiatric Clinic
DCD	Developmental Coordination Disorder
DQ	Developmental Quotient
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition
FISH	Flourescence In-Situ Hybridization
FSIQ	Full Scale IQ
FTF	Five To Fifteen questionnaire
ICD-10	International Classification of Diseases. Tenth Edition
IQ	Intelligence Quotient
LD	Learning Disability
MR	Mental Retardation
OCD	Obsessive Compulsive Disorder
ODD	Oppositional Defiant Disorder
PDDNOS	Pervasive Developmental Disorder Not Otherwise Specified
PIQ	Performance IQ
SD	Standard Deviation
VIQ	Verbal IQ
VMI	Visual-Motor Integration Test
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WISC-III	Wechsler Intelligence Scale for Children-Third Revision
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence-Revised

INTRODUCTION

The 22q11 Deletion Syndrome (22q11DS) is a genetic condition with wide variability in clinical expression. It is caused by a deletion of band 11.2 on the q arm (the long arm) of chromosome 22. The 22q11DS, is one of the most common genetic syndromes, with an estimated rate of approximately 1 in 4000 live births (Devriendt et al., 1998; Botto et al., 2003; Óskarsdóttir et al., 2004).

Historical background

In 1992, the chromosomal deletion was reported in association with three distinct syndromes, namely DiGeorges Syndrome (DGS), Velo-Cardio-Facial Syndrome (VCFS) and Conotruncal Anomaly Face Syndrome (CAFS) (Driscoll et al., 1992; Scambler et al., 1992; Burn et al., 1993). DGS was originally characterized by Congenital Heart Defects (CHD), hypoparathyroidism and immune deficiency (DiGeorge et al., 1965); VCFS was associated with cleft palate, CHD, anomalous face, and learning difficulties (Shprintzen et al., 1978) and CAFS was characterized by conotruncal CHD and a distinct facial appearance (Kinouchi et al., 1976). These three clinical syndromes have overlapping symptom presentations and share a common chromosomal deletion. Thus 22q11DS reflects various outcomes of the same underlying genetic defect.

The genetics of 22q11DS

The genetic diagnosis of 22q11DS can be established on the basis of a blood test using fluorescence in situ hybridization (FISH) analysis (Driscoll et al., 1992; Scambler et al., 1992). This method picks up approximately 95% of individuals who have the deletion meaning that there are some individuals where the deletion is not identified or where an atypical deletion occurs (Gothelf and Lombroso, 2001). In a majority of cases the deletion occur spontaneously or *de novo*. However, in about 10-15% there has been familial transmission of the deletion (Ryan et al., 1997; Swillen et al., 1997; Digilio et al., 2003). The mode of inheritance is autosomal dominant, meaning that with one affected parent there is a 50% risk of transmitting the deletion. The long arm of chromosome 22 is rich in genes and many of the genes mapping to the deletion have been studied in some detail. Despite these efforts, no single gene has yet been shown to play any specific core role in 22q11DS, even if there have been many candidate genes (Scambler et al., 2000).

The "physical phenotype" of 22q11DS

The phenotypic spectrum of 22q11DS is very complex and includes a large variety of clinical features. Depending on the severity of syndrome expression an individual with 22q11DS can have only a few or a very large number of anomalies. The most frequent anomalies in individuals with 22q11DS include CHD (54-81%), velopharyngeal insufficiency (57-81%), cleft palate (12-49%), and immunodeficiency (75%) (Botto et al., 2003; McDonald-McGinn et al., 1999; Ryan et al., 1997; Óskarsdóttir et al., 2004). Even though immunodeficiency is very common, only one percent or less, have a profound immunodeficiency due to total absence of the thymus. Hypocalcaemia has been reported to be most common in the neonatal period (Óskarsdóttir et al., 2005; Botto et al., 2003; Ryan et al., 1997; McDonald-

McGinn et al., 1999). Given the diverse regions of the body affected, it is reasonable to assume that the diverse features seen in 22q11DS are contributed by at least several, if not many, genes (Antshel et al., 2005). 22q11 deletion syndrome is, after Down syndrome, the most frequent genetic condition associated with cardiovascular anomalies (Goodship et al., 1998). Velopharyngeal impairment is one of the very common features of the syndrome and is found in patients with or without cleft palate. It leads to speech abnormalities, most often hypernasal speech which is one of the most typical symptoms in individuals with the syndrome. Many individuals with 22q11DS have a characteristic pattern of mildly dysmorphic facial appearance and is characterised by a prominent nose, a broad nasal bridge, bulbous nasal tip, malar flatness and hooded eyelids (McDonald-McGinn et al., 1999; Matsouko et al., 1998).

The "behavioural phenotype" of 22q11DS

A behavioural phenotype has been defined by Flint (1994) as "a behavioural pattern, including cognitive processes and social interaction style, consistently associated with, and specific to, a syndrome with a chromosomal or genetic aetiology". Finegan suggests that knowledge gained in research in behavioural phenotypes can play a critical role in syndrome delineation, illuminating intrasyndrome variability, understanding intersyndrome similarities and differences, understanding brain-behaviour relationships and the genetic bases of behaviour, and informing clinical management and prevention (Finegan et al., 1998). The behavioural phenotype in 22q11DS is very complex, wide and variable in the same way as the physical features of the syndrome. Individuals with this syndrome are reported to have a characteristic behavioural phenotype regarding intelligence, language, behaviour, and psychiatric disorders (Wang et al., 2000; Goldberg et al., 1993; Swillen et al., 1997, 1999a; Gerdes et al., 1999, 2001; Moss et al.,1999; Feinstein et al., 2002; Prinzie et al., 2002; Murpy et al., 1999; Basset et al., 1998). Behaviour styles ranging from shyness and social withdrawal on the one hand to and impulsivity and disinhibition on the other, have been reported (Golding-Kushner et al., 1985; Swillen et al., 1997). The behavioural profile most often reported by parents tends to be social relationship problems (especially problems in relation with peers), withdrawn behaviours and attention problems (Eliez et al., 2000; Swillen et al., 1997). When a group of children with 22q11DS was compared with a non 22q11DS group of children with learning disability and speech-language impairment, the only differences noted were a higher incidence of withdrawal in the 22q11DS group, and aggressive behaviour in the comparison group (Swillen et al., 2001).

Neuropsychiatric disorders

"Neuropsychiatric disorders" are diagnosed and defined on the basis of specific combinations of various difficulties most commonly in accordance with the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 1994) or the ICD-10 (International Classification of Diseases, 1997). Some of the prevalent and most researched neuropsychiatric disorders are Autism Spectrum Disorder (ASD) and Attention Deficit/Hyperactivity Disorder (AD/HD).

ASD

Autism is characterized by impairment in three developmental areas: a) reciprocal social interaction, b) communication and c) behaviour and interest. According to DSM-IV (Table 1) the features of autistic disorder must be present before the age of three.

Table 1. Diagnostic criteria for DSM-IV autistic disorder, DSM-IV PDD-NOS, and Gillberg´s atypical autism

DSM-IV Autistic disorder (similar to ICD-10)	A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3): **(1) qualitative impairment in social interaction** (a) marked impairment in the use of multiple nonverbal behaviours such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction (b) failure to develop peer relationships appropriate to developmental level (c) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest) (d) lack of social and emotional reciprocity **(2) qualitative impairments in communication** (a) delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime) (b) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others (c) stereotyped and repetitive use of language or idiosyncratic language (d) lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level **(3) restricted repetitive and stereotyped patterns of behaviour, interests, and activities** (a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus (b) apparently inflexible adherence to specific, non-functional routines and rituals (c) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements) (d) persistent preoccupation with parts of objects B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play. C. The disturbance is not better accounted for by Rett´s Disorder or Childhood Disintegrative Disorder.
DSM-IV criteria for PDD-NOS	This category should be used when there is a severe and pervasive impairment in the development of reciprocal social interaction or verbal and nonverbal communication skills, or when stereotyped behaviour, interests, and activities are present, but the criteria are not met for a specific Pervasive Developmental Disorder, Schizophrenia, Schizotypal Personality Disorder or Avoidant Personality Disorder.
Gillberg´s proposed criteria for atypical autism	Autistic disorder's social interaction criterion met plus a total of at least 4 symptoms but not full criteria for Autistic disorder or Gillberg's Asperger syndrome met

The prevalence of all autism spectrum disorders (including autistic disorder, Asperger syndrome and Autistic-Like Condition (ALC)/Pervasive Developmental Disorder Not Otherwise Specified (PDDNOS) in the general school age population is around 1% (Wing and Potter, 2002; Baird et al., 2006). Within the ASD group autistic disorder accounts for 0.2-0.4% and Asperger syndrome and Autistic-Like Condition/PDDNOS (plus extremely rare cases of childhood disintegrative disorder) for the remainder.

The diagnostic criteria for Asperger syndrome according to the DSM-IV and ICD-10 have been much debated. Several studies have shown that these criteria do not fit patients presenting with the typical clinical picture that Asperger described (Miller and Ozonoff, 1997; Leekam et al., 2000). In the context of the present thesis Asperger syndrome is instead diagnosed according to criteria formulated by Gillberg and Gillberg (1989) and elaborated in Gillberg (1991) (Table 2). These criteria are based on the clinical case reports published by Hans Asperger in 1944.

Table 2. Diagnostic criteria for Gillberg's Asperger syndrome

Gillberg´s Asperger syndrome criteria	All six criteria must be met for confirmation of diagnosis: 1. Severe impairment in reciprocal social interaction (at least two of the following) -inability to interact with peers -lack of desire to interact with peers -lack of appreciation of social cues -socially and emotionally inappropriate behaviour 2. All-absorbing narrow interest (at least one of the following) -exclusion of other activities -repetitive adherence more rote than meaning 3. Imposition of routines and interests (at least one of the following) -on self, in aspects of life -on others 4. Speech and language problems (at least three of the following) -delayed development -superficially perfect expressive language -formal, pedantic language -odd prosody, peculiar voice characteristics -impairment of comprehension including misinterpretations of literal/implied meanings 5. Non-verbal communication problems (at least one of the following) -limited use of gestures -clumsy/gauche body language -limited facial expression -inappropriate expression -peculiar, stiff gaze 6. Motor clumsiness -poor performance on neuro-developmental examination

AD/HD

The prevalence rate for AD/HD is much higher than for ASD, and is usually reported at about 5% of the general population of Swedish school children (Kadesjö and Gillberg, 1999; Gillberg and Rasmussen 1982). Individuals with AD/HD have deficits in attention, impulse control, and hyperactivity. There are three subtypes of AD/HD: mainly inattentive, mainly hyperactive and the combined subtype (Table 3).

Table 3. Diagnostic criteria for DSM-IV AD/HD

Inattention (six or more)	Hyperactivity /Impulsivity (six or more)
often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities	often fidgets with hands or feet or squirms in seat
often has difficulty sustaining attention in tasks or play activities	often leaves seat in classroom or in other situations in which remaining seated is expected
often does not seem to listen when spoken to directly	often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace	often has difficulty playing or engaging in leisure activities quietly
often has difficulty organizing tasks and activities	is often "on the go" or often acts as if "driven by a motor"
often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)	often talks excessively
often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)	often blurts out answers before questions have been completed *
is often easily distracted by extraneous stimuli	often has difficulty awaiting turn *
is often forgetful in daily activities	often interrupts or intrudes on others (e.g., butts into conversations or games) *

A. Either six (or more) of the following symptoms of inattention and/or six (or more) symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.
B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.
C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).
D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).
* symptoms of "impulsivity

Learning Disability
Learning Disability (LD)/Mental Retardation (MR) is defined as FSIQ< 70 in individuals showing functional impairment and deficits in social adaptation (DSM-IV). Depending on tests used and the level of impairment required for diagnosis, prevalence rates in the general population range from about 1 to 2.5% (Gillberg, 1995). Mild LD is defined as FSIQ 50-69, moderate LD as FSIQ 35-49 and severe LD FSIQ< 35. Children with ASD and/or AD/HD have higher rates of LD than unselected groups from the general population.

ASD in 22q11DS
Social skills deficits, including withdrawn behaviours and shyness, difficulties initiating and maintaining social interactions, and limited facial expressions, are commonly encountered in individuals with Autism Spectrum Disorders (ASD). Several studies reported that these traits were found in individuals with 22q11DS (Eliez et al., 2000; Gerdes et al., 1999; Swillen et al., 1997). During the last years ASD has been reported in studies in 22q11DS. Our own group was first to report on the prevalence of ASD in 22q11DS. We found that 10 of 32 individuals (31%) met criteria for ASD, but only one individual met criteria for autistic disorder (Niklasson et al., 2001). In a further study of 60 patients, ages 9 through 18 years, high rates of ASD (50%) and psychotic symptoms (27%) (Vorstman et al., 2006) were found. The conclusion drawn was that autistic and psychotic disorders should be considered to be main elements in the behavioural phenotype of children with 22q11DS. In one study by Fine et al. (2005) the presence of ASD was assessed, in a group of 98 children, by caregiver screening measures of ASD behaviours, followed by ADI-R (Autism Diagnostic Interview-Revised) assessment in those with scores indicating significant levels of such behaviours. According to ADI-R assessment, 14 children qualified for a diagnosis of ASD, and for 11 of these (11% of the whole group) a diagnosis of autistic disorder was considered appropriate (Fine et al. 2005). In another recent study the phenotype in two groups with 22q11DS, with or without ASD, were studied. In the whole group (n=41; age range 6.5 years -15.8 years) 17 individuals (41%) met criteria, based upon ADI-R, for ASD (of whom 8 children (20% of the whole group) met criteria for autistic disorder). In this subgroup with ASD 94% had a co-occurring psychiatric disorder compared with 60% in the group with 22q11DS "only". (Antshel et al., 2006). Conversely, in one study, 103 individuals with a strict diagnosis of autism were tested for 22q11 deletion. No deletions were found, indicating that for an individual with classic autism, in the absence of other indications, it is unlikely that he/she will have 22q11DS (Ogilvie et al., 2000).

AD/HD in 22q11DS
Attention deficits are common in individuals with 22q11DS with AD/HD rates of about 40% in several studies (Antshel et al., 2006; Gothelf et al., 2003; Feinstein et al., 2002; Papolos et al., 1996). One study of 51 patients found 41% met criteria for AD/HD (Gothelf et al., 2004). There was a significantly greater prevalence of AD/HD in the first-degree relatives of the patients with AD/HD than in those without. The two groups (with or without AD/HD) had similar IQ scores (total, verbal and performance) and had similar average degree of severity of facial dysmor-

phism and cardiac and cleft palate anomalies. The conclusion drawn in the study was that AD/HD in 22q11DS has a genetic background and that the related developmental factors and physical illnesses play a lesser role.

Other psychiatric diagnoses in 22q11DS

Psychiatric disorders have been reported as co-occurring to ASD but have also been associated with non-AD/HD/non-ASD in 22q11DS. Anxiety disorder and mood disorder have been reported to be common. Baker et al., (2005) found that the rates of mood disorders and anxiety disorders were significantly higher in the 22q11DS group (36-40%), than in IQ matched controls (0-8%). In another study (of children aged 6-16 years), 33% met the DSM-IV criteria for Obsessive Compulsive Disorder (OCD). The most common OCD symptoms were related to aggression, somatic worries, repetitive questioning and cleaning. Moreover, 7 individuals (16%) had psychotic disorder (Gothelf et al., 2004b).

Bipolar spectrum disorders and schizophrenia have also been reported to be common in adults with the syndrome. In a group of 25 adults, 16 (64%) met DSM-IV criteria for bipolar spectrum disorders with full syndromal onset in late childhood or early adolescence (Papolos et al., 1996). High rates of psychotic disorders, particularly schizophrenia have been reported (Gothelf et al., 1997; Basset et al., 1998; Usiskin et al., 1999; Murphy et al., 1999). In the study by Murphy 30% (15 out of 50) of adults with 22q11DS were found to have a psychotic disorder, of whom 80% met DSM-IV criteria for schizophrenia. In addition, 6 (12%) of these adults had depression without psychotic features (Murphy et al., 1999). A very interesting question is if it is possible to identify early risk factors for the development of psychotic disorders. In a recent study 31 children with 22q11DS and 29 comparison subjects with idiopathic developmental disability matched for age and IQ, underwent a baseline evaluation and after 5 years they underwent a follow-up evaluation (Gothelf et al., 2007). The two groups had similar baseline neuropsychiatric profiles but at follow-up, 31% of the subjects with 22q11DS had developed psychotic disorders as compared with 4% of comparison subjects. In the 22q11DS group, baseline sub threshold psychotic symptoms interacted with baseline symptoms of anxiety and depression to predict 61% of the variance in severity of psychosis at follow-up evaluation. Lower baseline verbal IQ was also associated with more severe psychotic symptoms at follow-up evaluation. In another study, psychotic symptoms were found in 17% (reporting recurrent hallucinations) and were associated with decreased Verbal IQ in a preadolescent group (n=30) (Debbané et al., 2006). Compared with children without psychotic symptoms they were perceived by their parent as more anxious-depressed and withdrawn, with reduced adaptive socialization skills. AD/HD may constitute a risk factor for the later development of bipolar disorder in 22q11DS. Children with 22q11DS and AD/HD were compared with a group with learning disability and AD/HD, showing no differences in rate of manic symptoms between these two groups. However the manic symptoms found in the 22q11DS were related to four CBCL subscales (anxiety, somatization, thought and conduct problems) compared with only one (conduct problem) in the control group (Aneja et al., 2007).

The neuropsychology of 22q11DS

Assessing intellectual and developmental levels

The methods most frequently used for the assessment of overall intellectual level today are the Wechsler scales. They are translated and used all over the world which makes it possible to compare results found in different countries. Wechsler defined intelligence as "the capacity of the individual to act purposefully, to think rationally and to deal effectively with his or her environment" (Wechsler, 1992). There are currently three versions of the Wechsler scales that are in widespread use in Sweden: the WPPSI-R (Wechsler Preschool and Primary Scale of Intelligence-Revised, Wechsler, 1989), the WISC-III (Wechsler Intelligence Test for Children, Wechsler, 1992), and the WAIS-R (Wechsler Adult Intelligence Scale- Revised, Wechsler, 1981). The scales provide measures of global ability (Full scale IQ - FSIQ) with Verbal (VIQ) and performance IQ (PIQ) subscores. On the WISC and the WAIS separate statistical factors can be derived as suggested by Kaufman: Verbal Comprehension (comprising the subtests Information, Vocabulary, Comprehension and Similarities), Perceptual Organisation (Picture Completion, Picture Arrangement, Block Design and Object Assembly) and Freedom from Distractibility (Arithmetic and Digit Span). In addition, on the WISC-III there is a factor called Processing Speed (Coding and Symbol Search) (Kaufman, 1994). The Kaufman factors are not included in the WPPSI-R. For the youngest pre-school age group developmental scales have to be used for assessment of overall functioning/developmental level. In Sweden, the Griffiths Developmental scale (Griffiths, 1970) is the most widely used method for assessing children of a chronological and mental age of 0 - 7 years of age.

Intellectual and developmental level and profile in 22q11DS

One of the most well established features of 22q11DS is a general intellectual impairment. Mean IQ has been reported to be in the low borderline range (Swillen et al., 1997; Gerdes et al., 1999; Moss et al., 1999; Niklasson et al., 2001) with a bell-shaped distribution of cases around a mean of about 70. The prevalence of mental retardation (MR)/learning disability (LD) has been reported to be 40-50%. Mild LD (FSIQ 50-69) is common while severe LD (FSIQ <35) appears to be rare (Swillen et al., 1997; Moss et al., 1999; Gerdes et al., 2001; Niklasson et al., 2001). Several studies have shown a higher VIQ compared with PIQ (Swillen et al., 1997; Gerdes et al., 1999; Moss et al., 1999; Woodin et al., 2001; Niklasson et al., 2001). Such a profile can be suggestive of so called non-verbal learning disability (Rourke, 1988). Moss, in a study of 33 individuals with the syndrome, found that a better way of describing the profile in terms of a typical distributions on the Kaufman factor scores (Moss et al., 1999). Verbal Comprehension was much better than Perceptual Organization. The contrast between these two factors was larger than the verbal/performance IQ split. Much has been made of the verbal "strength" in 22q11DS once the children reach school age. Possibly major problems with visual-perceptual abilities have not been highlighted in the same way so far, even though there have been studies focusing on deficits with visual-perceptual abilities (Lajiness-O'Neill et al., 2006; Sobin et al., 2005; Simon et al., 2005; Bearden et al., 2001). Low scores for the factor Perceptual Organisation indicate deficits in integrating visual stimuli and nonverbal reasoning as well as visuospatial skills. Defi-

cient visuospatial skills, poor visual attention and problems with processing of new and complex material were documented in a small study of 9 preschool children (Swillen et al., 1999b). Children with 22q11DS in another study performed poorly, compared with controls, on test of visual attentional orienting, visual enumeration and relative numerical magnitude judgement. These performance deficits could not be explained by a global deficit in psychomotor speed (Simon et al., 2005). Children with 22q11DS and children with autism showed similar deficits in facial memory (Lajines-O'Neill et al., 2005).

Intellectual level in relation to gender and age in 22q11DS
Sex differences in cognitive function were investigated in children with 22q11DS compared with siblings and non 22q11DS controls (Antshel et al., 2005). The results indicated that boys with 22q11DS may be more cognitively affected than girls. A negative association between age and cognitive functioning was found in girls but not in boys. Neuroimaging investigation showed the same sex differences of frontal lobe as generally seen in general population (boys>girls) in all groups.

Developmental aspects in 22q11DS
In the preschool years developmental delays on major developmental milestones, including speech and language, cognition and motor skills have been found (Gerdes et al., 1999). Delayed speech and language development are well documented (Golding-Kushner et al., 1985; Sherer et al., 1999; Glaser et al., 2002; Persson et al 2003; Gerdes et al., 2001). Late onset of verbal speech was found in all children when the neurodevelopmental outcome was studied in a group with 40 preschool children (ages 13 to 63 months) (Gerdes et al., 1999). Expressive language was more impaired than receptive language even after controlling for general intellectual level. The global delays were found to be directly associated with the 22q11DS and could not be explained by physical anomalies or therapeutic interventions such as cardiac surgery. Between the age of 3 – 4 years an improvement in expressive language is typically observed (Solot et al., 2001). In school-aged children difficulties have been reported in a number of linguistic domains, including syntax, vocabulary, concepts, word finding, abstract reasoning and story re-telling (Solot et al., 2000; Persson et al., 2003, 2006).

Visuomotor integration skills
In one study the perceptual and visuo-motor ability of 26 3-17-year old children with 22q11DS was assessed. This screening test included the completion of form boards, block construction, geometric designs, bilateral integration and tactile discrimination. All children, regardless of age, failed the perceptual and visuo-motor screening test. (Golding-Kushner et al., 1985). In another smaller study (of just nine children) the mean group z-score on the VMI (Visual-Motor-Integration test) was within the wider normal range although 6 of the 9 children fell under 1 SD below what would be expected according to their age (Swillen et al., 1999b).

Executive functions
"Executive functions consists of those capacities that enable a person to engage successfully in independent, purposive, self-serving behaviour" (Lezak, 2004).

Areas included in executive function are planning, generation of strategies for action and monitoring of behaviour of response to environmental feedback. Executive dysfunction can result in difficulty with planning, organisation and using strategies with an inability to use feedback resulting in a rigid thought process.

Planning ability
Impairments regarding planning (Tower of London) were found in a group with adults with 22q11DS compared with IQ-, age- and gender- matched controls. The 22q11DS group was less accurate in their problem solving ability, and required significantly more moves to solve the problems than did the controls. The number of moves required to complete the tasks increased as the degree of difficulty increased (Henry et al., 2002). Comparison between two groups of adults with 22q11DS, one with schizophrenia and one without, showed no differences meaning that the difficulties found were associated with 22q11DS and not related to schizophrenia (van Amelsvoort et al., 2004).

Attention ability
There are many neuropsychological approaches to the analysis of various aspects of attention. Mirsky (Mirsky et al., 1991) places "attention" within the broader category of "information processing". According to the model by Mirsky, attentive processing involves four components: 1) sustain attention which refers to the duration of an individuals response to a task stimulus; 2) focus-execute attention, which means selecting or paying attention to a critical stimulus; 3) shift attention is the ability to change focus in an adaptive manner; and 4) encode attention, which approximates "working memory" (Mirsky et al., 1991). Deficits in sustaining attention have been found in children and young adults with 22q11DS (Levandowsky et al., 2007). The Trailmaking test was used in another study of children with 22q11DS. The result showed average results for brief, focused attention (Trail A), while the ability to shift attention and cognitive flexibility (Trail B) was below average (Woodin et al., 2001).

Social and empathy skills
Apart from the reported cooccurrence of ASD, children with 22q11DS have been reported to have problems with communication, social interaction initiation and decreased repertoire of facial expression (Fine et al., 2005; Woodin et al., 2001; Eliez et al., 2000). Extremes of behaviour have been reported: shyness and withdrawal as well as impulsivity and disinhibition (Swillen et al., 1997; Golding-Kushner et al., 1985). Problematic peer relationships have been reported from school age to adolescence (Swillen et al., 1999a).

22q11DS in Sweden

Since 1997, there has been a multidisciplinary team with a remit to diagnose and evaluate the phenotype of 22q11DS at the Queen Silvia Children's Hospital, part of Sahlgrenska University Hospital in Göteborg, Sweden. The aim has been to assess the spectrum and frequency of various symptoms associated with the syndrome. Many aspects of the syndrome have been covered, including neuropsychiatric, neurologic, neurodevelopmental, cardiologic, immunologic, speech and language

aspects, ear and hearing, eye and vision, face morphology, and oral health. The purpose of this assessment is to create a broad knowledge basis of each individual´s specific strengths and difficulties so as to provide an optimal opportunity for adequate medical, psychiatric, psychologic and educational interventions of various kinds.

AIMS OF THE PRESENT THESIS

The aims of this thesis were to:

- examine the prevalence and type of ASD, AD/HD and LD in 22q11DS;
- describe the behavioural profile in 22q11DS;
- investigate the general intellectual/developmental ability and profile and visuomotor integration skills in 22q11DS;
- investigate executive functions, with a particular focus on attention and planning ability in 22q11DS; and
- study the impact of AD/HD and ASD, gender and age on intellectual ability and profile, visuomotor integration skill and executive functions in the syndrome.

METHODS

An overview of the four studies of the present thesis is given in Table 4. The different substudies ("Preliminary", "Neuropsychiatry", "Attention", and "Neuropsychology") will be referred to using Roman numerals as outlined in the Contents section under "Papers".

Subjects

Table 4. Cases examined in each of the four substudies (I-IV)

Substudy	**I "Preliminary"**	**II "Neuro-psychiatry"**	**III "Attention"**	**VI "Neuro-psychology"**
Title of substudy	"Chromosome 22q11DS (CATCH 22): Neuro-psychiatric/ Neuro-psycholgical Aspects"	"Autism, AD/HD, Learning Disability and Behaviour Problems in 100 Individuals with 22q11DS"	"Attention Deficits in Children with 22q11DS"	"The Neuro-psychology of 22q11DS. A Clinical Study of 100 Individuals"
n examined	20	100	30	100
Females:males	12:8	58:42	16:14	58:42
Age range years	5-33	1-35	7-13	1-35

One hundred individuals were included in each of two of the substudies (II and IV). The target group of substudy I consisted of the first 20 of these 100 individuals seen at our clinic. In substudy III, all 30 children in the age range 7-13, taken from the first 80 individuals seen, were included (Figure 1).

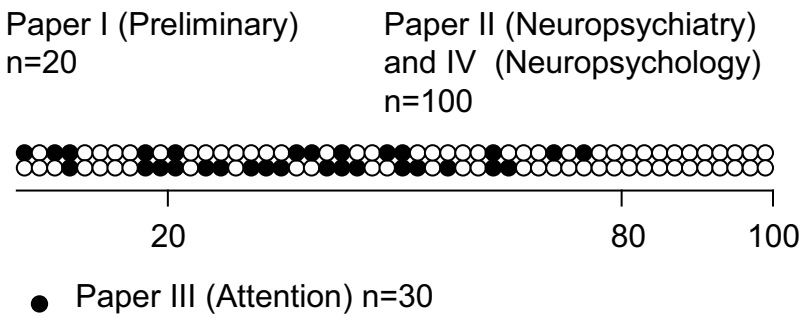

Figure 1. Participants in paper I-IV

Substudy I
In this substudy the group examined comprised the first 20 consecutively referred cases of 22q11DS referred to the CNC (Child Neuropsychiatry Clinic) (Figure 1). All 20 took part in a multidisciplinary assessment study at the Queen Silvia Children's Hospital in Göteborg, Sweden. The age range in this group was 5-33 years of age, 12 females and 8 males.

Substudy II and IV
The individuals included in these substudies comprised all the first 100 consecutive cases of 22q11DS referred to the CNC. This group included all cases in Substudy I and all cases in Substudy III (Figure 1). All except two of these 100 individuals with 22q11DS took part in a multidisciplinary assessment. Ninety-two had been referred to the CNC from the "22q11DS-team" for routine detailed neuropsychiatric/neuropsychological assessment which constituted one (large) portion of all the evaluations performed by the 22q11DS-team in each individual with a FISH-confirmed diagnosis of the disorder. Eight individuals had been referred directly to the CNC from other specialists because of learning and/or behaviour problems. Various aspects of the syndrome were covered, including neurospychiatric, neurologic, neurodevelopmental, cardiologic, immunologic, speech and language, ear and hearing, eye and vision, face morphology, and oral health (Óskarsdóttir et al., 2004, 2005a, 2005b; Persson et al., 2003, 2006; Klingberg et al., 2002, 2007).

Forty-eight of the 100 individuals had been referred from the Western Götaland Region in western Sweden, and the remainder from other parts of Sweden. At the time of the study, 35 parents (mother and father) of the children/young adults with 22q11DS had been tested for the deletion. In five of these one of the parents (all mothers) tested positive. In the untested group there were 3 individuals who had a parent with a clinical suspicion of 22q11DS.

Age and gender
The majority of the participants (62) were in the school age period (6-16 years of age), while 22 were aged 5 years or under, and 16 were 17 years or older (Table 5).

Table 5. Age range and gender of 100 individuals with 22q11DS

Age range years	All n=100	Female n=58	Male n=42
≤5	22	14 (64%)	8 (36%)
6-11	40	22 (55%)	18 (45%)
12-16	22	12 (55%)	10 (45%)
≥17	16	10 (62%)	6 (38%)

Background information regarding the substudy groups II and IV
The most common referral sources to the multidisciplinary team were speech pathology/cleft palate team (26), paediatric cardiology (24), and child neurology (20). The remainder had been referred from general paediatrics, child neuropsychiatry

services, adult psychiatry, endocrinology, audiology or immunology departments. The majority (14/22) in the group with the youngest children, 5 or below, were referred from paediatric cardiology, while the children of school age, 6-16 years, were mostly referred from neurology/general paediatrics (24/62) or speech pathology (22/62). In the group, aged 17 or more, 4/16 were referred from within the CNC and 3/16 from adult psychiatry. Four adult women were referred because they had a child with diagnosed 22q11DS, participating in this study, and had been confirmed by FISH-analysis to have the syndrome themselves.

A congenital cardiovascular anomaly had been confirmed in 55 individuals (29 females, 26 males) and 43 of these had undergone cardiac surgery. Cleft palate had been confirmed in 26 individuals. Two of these had cleft lip and two cleft lip and palate. Velopharyngeal insufficiency - due to cleft palate, deep pharynx, or pharyngeal hypotonia - was found in 71 individuals. Three individuals had Cerebral Palsy and five children had hearing impairment requiring hearing aid.

Substudy III
Thirty children (marked with • in Figure 1), in the age-range 7-13 years, were included (16 females, 14 males) in substudy III. These were all children in that age-range when 80 participants had been included in the study.

Methods

A detailed neuropsychiatric/neuropsychological evaluation was performed in order to elucidate the behavioural and cognitive characteristics of 22q11DS. All examinations were performed at the CNC. Throughout the study a psychiatrist and a psychologist worked closely together in order to make this evaluation as comprehensive as possible. The psychologist saw the child (or adult) separately for the neuropsychological evaluation or together with the parents (in cases of young children) where the support of the parents was necessary. The psychiatrist interviewed the parents separately and examined the child alone or together with the parents. In cases of adults, information from the adults themselves was combined with information from their parents. Finally, the psychologist and the psychiatrist saw the parents and their child together (or - in the case of adult patients - the adults themselves for a presentation of all results from the different examinations. In the diagnostic process all information from different examinations was considered important in the clinical evaluation of the individual, although neither the neuropsychological test results, nor the results on several collateral informant questionnaires (see below) were included in the diagnostic process of ASD and AD/HD.

Methods used in all substudies (I-IV)
In 94 of the 100 cases the neuropsychiatric evaluation was carried out by one of two senior, experienced CNC clinicians (Christopher Gillberg and Peder Rasmussen) and, in the remaining 6, by one of three psychiatrists from the same clinic.

Neuropsychiatric assessment
The neuropsychiatric evaluation included extensive structured and semistructured interviews with the parent(s). In the adult group both the probands themselves and

their parents were interviewed. The interview systematically covered aspects of heredity; medical factors pertaining to pregnancy, parturition, and the neonatal period; child's early psychomotor and speech-language development and adaptation; physical health problems; behaviour; sustained attention and impulse control; fine and gross motor control; social interaction skills; eating and sleeping habits. Any specific problems suggesting AD/HD, ASD, Tourette syndrome, Obsessive-Compulsive Disorder (OCD), Oppositional-Defiant disorder (ODD), conduct disorder, or any other DSM-IV psychiatric disorder were specifically asked for covering the appropriate DSM-IV criteria using a DSM-IV checklist. The evaluation of the child or adult affected included psychiatric assessment, a general thorough physical examination, and a clinical neurological age appropriate examination.

Questionnaires used

Parents completed the Autism Spectrum Screening Questionnaire (ASSQ: Ehlers and Gillberg, 1993; Ehlers, Gillberg and Wing, 1999; Posserud et al., 2006), the Conners Brief Parent Rating Scale (BPRS) (Conners, 1990), the Child Behavior Checklist (CBCL) (Achenbach, 1991), and the Five To Fifteen (FTF) questionnaire (Kadesjö et al., 2004). Of these, only the FTF was used in the diagnostic process.

ASSQ

The ASSQ 27-item scale (used from 5 years of age) yields a range of possible scores of 0-54, higher scores (of about 17 and above on the parent ASSQ) indicating a high probability of an ASD (Ehlers et al., 1999).

Conners BPRS

The Conners 10-item scale (used from 5 years of age) yields a range of possible scores of 0-30. Scores of 10 - 15 or more are sometimes taken as an indication that a diagnosis of AD/HD should be considered (Conners,1998).

CBCL

The CBCL 118-item scale (used for the age group 4-16 years), comprises statements related to behavioural/emotional problems divided into 8 domains (withdrawn, somatic complaints, anxious, social problems, thought problems, attention problems, delinquent behaviour, aggressive behaviour). Three of these domains (withdrawn, somatic complaints and anxious) are included in the Internalizing behaviour scale and two (delinquent behaviour and aggressive behaviour) are included in Externalizing behaviour scale. The Swedish general population mean total scores for children examined about 10 years ago was 14.3 (SD 12.6) for the norm group 6-16 years of age (Larsson and Frisk, 1999).

FTF

The FTF questionnaire, for the age group 5-15 years, comprises 181 statements related to behavioural or developmental problems, yields a range of possible mean scores of 0-2 on each item from eight domains (motor, executive functions, perception, memory, language, learning, social, and emotional problems) (Kadesjö et al., 2004). The norms are related to gender and to three different age bands (6-8 years; 9-12 years and 13-15 years).

Neuropsychological assessment
The neuropsychological assessment was carried out by the same neuropsychologist (LN) in 99 of the 100 cases. A neuropsychological test battery was designed to provide information concerning intellectual level and profile, visuo-motor development, executive functions and mentalisation skills. Different tests were chosen according to the age of the participants.
A semistructured behavioural observation of all participants was performed during the neuropsychological examinations. This observation covered aspects of attention, activity level and impulse control, social interaction, cooperation, emotion, speech and language.

Developmental ability and profile
The Griffiths´ Mental Developmental Scales I and II, was administered to the youngest children. Scale I consists of five subscales: Motor, Personal-Social, Hearing and Speech, Eye and Hand and Performance (Griffiths, 1970). In scale II another scale, Practical Reasoning, is included as well. Swedish norms were used (Alin-Åkerman, B and Nordberg, L. 1980). The results are given in developmental age and are transformed into Developmental Quotient (DQ).

Intellectual ability and profile
The wide age range of the probands made it necessary to use different tests. Psychometric assessment of general intellectual ability was performed in all participants. The Wechsler Primary and Preschool Scale of Intelligence - WPPSI-R (Wechsler, 1989), the Wechsler Intelligence Scale for Children - WISC-III (Wechsler, 1992), the Wechsler Adult Intelligence Scale-Revised - WAIS-R (Wechsler, 1981; Bartfai, 1992), the Vineland Adaptive Behaviour Scales (Sparrow et al., 1984) were used (as considered appropriate depending on the individual´s age and intellectual functioning. The three Wechsler Scales provides measures of global intellectual ability – (Full-scale IQ (FSIQ), Verbal IQ (VIQ) and Performance IQ (PIQ) subscores, as well as individual scores on each subtest. On the WISC-III and WAIS-R four and three, respectively, statistical factors can be derived as suggested by Kaufman: Verbal Comprehension (comprising the subtests Information, Vocabulary, Comprehension and Similarities), Perceptual Organisation (Picture Completion, Picture Arrangement, Block Design and Object Assembly), Freedom from Distractibility (Arithmetic and Digit Span), and Processing Speed on WISC-III (Coding and Symbol Search) (Kaufman, 1994). On the WAIS-R the subtest Symbol Search is not included which means that the factor Processing Speed can not be derived. The Kaufman factors are not included in the WPPSI-R.

In two cases FSIQ could not be established due to severe medical problems in combination with lack of language. In these two individuals (with clinical moderate and severe mental retardation, respectively), parts of the Vineland Adaptive Behaviour scales were used. These two individuals were excluded from statistical analysis concerning FSIQ.

Visuomotor integration skill
To evaluate the visuomotor integration ability the Developmental Test of Visual-

Motor Integration was used (VMI; Beery, 1997). This test consists of geometric forms, in a developmental sequence, to be copied with paper and pencil.

Methods used in some substudies

Executive function

Attention: focus-encode attention (III)

Four of the WISC-III subtests are considered to measure the focus and encode component of attention (Mirsky et., al. 1991). These are: Arithmetic and Digit Span (included in the Kaufman factor Freedom from Distractibility) and Coding and Symbol Search (included in the Processing Speed factor).

Attention function: sustain (III)

Attention, with special focus on the ability to sustain attention, was measured by using the Becker Go-No-Go and Conflict test (Becker et al., 1987). This test belongs to the group continuous performance tests. In the Go-No-Go condition the child is requested to respond once every time two stimuli are presented. In the Conflict condition the child is required to respond conflictingly, twice when one stimulus is presented and once when two stimuli are presented. There are two conditions (visual and auditory) and in both conditions reaction times, omissions and commissions are recorded. Each child's value is compared pair-wise with the corresponding age matched normative group.

Attention function: speed and shift (IV)

The speed and ability to shift attention was measured by Trail Making Test A and B (Spreen & Strauss, 1991) where the individuals were asked to connect numbers and letters with a pencil as quickly as possible. Trail A is regarded as a more straightforward spatial arrangement task while Trail B also involves dividing and/or shifting attention (Lezak, 2004).

Planning ability (I and IV)

Planning ability was measured with the Tower of London Test (Shallice, 1982). In this test the child is requested to "look ahead" to determine how to rearrange three pierced coloured beads from an initial position on two upright sticks to a new set of predetermined positions on two or more sticks. The results are given as number of trials correct and a "raw score", viz. the time taken to correctly complete the pattern (converted into a 9-graded scale) reduced by the number of attempts the child needs to achieve the correct configuration. For the adults a mental variant, where the coloured beads are reproduced in a picture, was used. The results were given in a number of moves for the two parts, 2-3 and 4-5 moves, and mean reaction times for respectively parts.

Theory of mind (I and II)

In a subgroup (n=20) of the 100 individuals included in the study, different tests of "theory of mind" as appropriate for age and development were used: the Smarties and Sally-Anne tasks (Frith, 1989), Strange Stories (Happé, 1994), Non-mental and Mental Cartoons (Happé et al., 1999). In the age range 0-6 years, four of five included children performed the Baron-Cohen Picture arrangement test and one the

Smarties and Sally-Anne task. In the age range 7-16 years, eight of eleven children performed the Strange Stories and three, due to low mental age, the Baron Cohen Picture Arrangement test. Four individuals were in the age of 17 or above, three of these performed Non-mental and Mental Cartoons and one was given the Strange Stories test.

We also used the Autism Diagnostic Observation Schedule - ADOS (Lord et al., 1994) in a subgroup but the results from those assessments will be reported separately.

Neuropsychiatric diagnostic process

ASD and AD/HD diagnoses

Comprehensive neuropsychiatric diagnoses (ASD and AD/HD) were made by the psychiatrist according to the DSM-IV (American Psychiatric Association, 1994) taking the results of the various examinations (interview, medical examinations, observations), and those of one of the parent questionnaires (see below) into account. ASD comprised autistic disorder, Asperger syndrome and Autistic-Like Condition (ALC), LD/MR, DCD. AD/HD and autistic disorder were diagnosed strictly in accordance with the DSM-IV. ALC was diagnosed in cases meeting the social criterion (i.e. at least 2 social symptoms) for autistic disorder, and the criteria for at least one more of the other two "triad" areas (communication or repetitive/stereotyped behaviour) and had a total symptom score for autistic disorder of 4 or more and did not meet criteria for autistic disorder or Asperger syndrome. These criteria are in accordance with the broad criteria of the ICD 10/DSM-IV. However given that these manuals do not supply an exact symptom algorithm, we felt the need to provide a stricter definition so that the present study might be replicated by future students of 22q11DS. In our study, AD/HD and ASD were not regarded as mutually exclusive diagnoses.

LD/MR diagnosis

Diagnosis of LD/MR was defined as the combination of FSIQ/DQ <70 *and* functional impairment and deficits in social adaptation. Within this group of LD/MR cases, mild LD was defined as IQ 50-69, moderate LD IQ 35-49, and severe LD IQ<35.

Ethics

The study was approved by the Research Ethics Committee at the Faculty of Medicine, Göteborg University, Sweden. Informed consent was obtained from parents and from patients depending on age and ability to assent/consent.

Statistical methods

The statistical methods used in the different substudies are detailed below under the Roman numeral of each substudy. The analyses were performed with SAS (Statistical Analyses System) or with SPSS.

(I) Statistical analyses were performed using non-parametric tests (Wilcoxon´s rank sum test, Spearman´s rank correlation test), and 95% confidence intervals, or t-test if data were found to be normally distributed.

(II) Independent groups were compared using Student´s t-test and Chi-square test. Wilcoxon non-parametric test was used for comparison of raw scores. For testing interaction between variables, ANOVA were used.

(III) For variables where age norms are available raw scores have been transformed into z-scores. Wilcoxon non-parametric test was used for comparison of raw scores.

(IV) For variables where age norms are available raw scores were transformed into z-scores. For comparing intra-individual results, paired t-test and 95% confidence interval were used. Adjustment for multiple comparison (Tukey´s Studentized Range (HSD) Test) was made.

RESULTS

Neuropsychiatric and neuropsychologic aspects in the preliminary study (I)

As can be seen under the results reported for substudies II and IV, it is clear that the first, and preliminary, results that we published in the early years of the 21st century from the first 20 children of the cohort were quite similar to those that we reported after having completed our assessments of the whole cohort of 100 cases.

ASD/AD/HD and other psychiatric diagnoses

In the first cohort 13 of the 20 individuals (65%) met criteria for ASD, AD/HD or a combination of these diagnoses. Eleven individuals (55%) had AD/HD (6 AD/HD inattentive subtype and 5 combined subtype). One child had autistic disorder (5%) and six (30%) had ALC. Five individuals (25%) had a combination of ASD and AD/HD. All three adults in this substudy had a psychiatric disorder with anxiety as their main complaint. Two of them met criteria for anxiety disorder and all three had a history of one or more episodes of depression. Three children showed a very marked tendency to have inappropriate anxiety reactions.

Behaviour according to questionnaires

The total problem mean score of CBCL was 42.8 (SD 22.7) which was significantly higher than for the normative group (mean 14.3 (SD 12.6)) ($p<.01$). The highest problem scores were found in the clusters Attention problems, Aggressive behaviour and Social problems.

The ASSQ was completed in 17 cases. In this group 6 individuals had scores of 19 or more (4 individuals with ASD, one with AD/HD "only", and one with no neuropsychiatric diagnosis). No correlation between FSIQ and the ASSQ score was found.

Intellectual ability

IQ≤69 was found in 10 of the 20 individuals (50%). The majority (8/10) were in the IQ range of 50-69 and only 2 were in the range of 35-49. Normal (IQ <85) or low normal intellectual level (IQ 70-85) was seen in five individuals each. VIQ was significantly higher than PIQ but there were no significant discrepancies across the Kaufman factors (Figure 2).

Correlations between FSIQ and neuropsychiatric diagnoses, age and gender

The five individuals with AD/HD "only" had an FSIQ of 86, one individual with autistic disorder and one with Autistic-like condition had a FSIQ of 54 and 73, respectively. Mean FSIQ for those five with a combination of ASD and AD/HD was 60. The seven individuals with no neuropsychiatric diagnosis had a mean FSIQ of 71. Mean FSIQ for the females was 79 and for the males 61. No correlation between age and FSIQ was found.

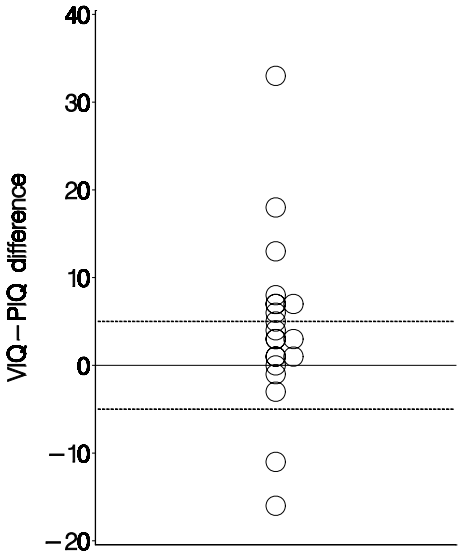

Figure 2. Distribution with regard to difference between Verbal IQ (VIQ) and Performance IQ (PIQ) in 18 individuals with 22q11DS (Preliminary study)

Visuomotor integration skill

The VMI-test yielded a mean quotient of 64 in the group tested with WISC-III with a range from 42 to 91. When comparing VMI-scores with PIQ on the WISC-III there were three children who had a marked discrepancy (lower VMI-result), implying a specific visuomotor impairment.

Schooling

Five of the eight children of school age had an IQ < 70 were in special classes for children with intellectual disabilities. Another five with normal or low-normal intelligence had marked learning and/or behavioural difficulties in school. These children needed at least part-time support by an assistant or to attend a small group with extra resources.

"Theory of Mind" test

In the majority, 15 individuals, the results of these tests implied some deficits within this area. There were three children in the age group 7-16 years, one in the age group 0-6 and one adult who succeeded in solving these tests. However, the wide age and developmental level range mean that this findings must be analysed with caution.

Autism, AD/HD and LD in the larger 100 cohort: "neuropsychiatry" (II)

Overall prevalence of ASD and AD/HD and overlap of ASD/AD/HD

Sixty-seven individuals had either ASD, AD/HD, LD or a combination of these diagnoses while the remainder (33 individuals) did not meet criteria for any of these diagnoses. There were 23 individuals with LD without ASD/AD/HD meaning that 44 individuals met criteria for ASD, AD/HD or a combination of the two with or without LD. Thirty individuals met criteria for AD/HD, 23 for ASD and 9 individuals had a combination of those two diagnoses. In the group with AD/HD 16 individuals had AD/HD the inattentive subtype while 14 individuals had the combined type. Five children had autistic disorder, 17 autistic-like condition and one Asperger syndrome of the group with ASD. In the ASD group two individuals with Autistic disorder and 7 with autistic-like condition also had AD/HD. In the group of 9 individuals with ASD+AD/HD 8 had AD/HD combined type and only one AD/HD the inattentive subtype (figure 3). The rate of ASD/AD/HD was not affected by the existence of cardiovascular anomaly, velopharyngeal insufficiency or hearing impairment.

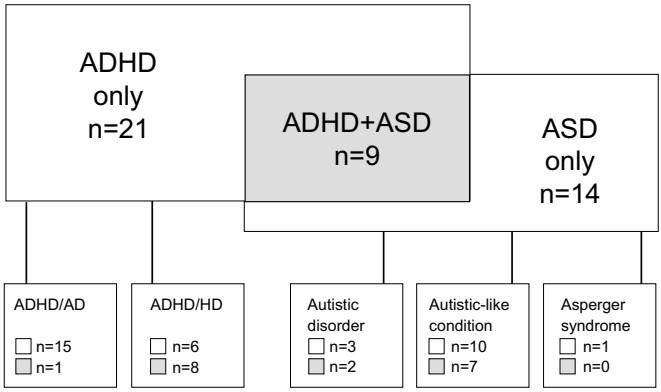

Figure 3. ASD, AD/HD and the overlap of these diagnoses

All shaded areas indicate AD/HD in combination with ASD.
AD/HD/AD=AD/HD inattentive subtype
AD/HD/HD=AD/HD combined subtype

Fifty-one individuals had LD. The majority had mild LD, 8 moderate LD, and 1 severe LD (IQ<35). Mean IQ, for the 82 individuals assessed with the Wechsler scales, was 71 (SD 15).

ASD diagnosis related to referral source
The rate of ASD was 20% (18/92) in the group referred routinely as part of the multidisciplinary assessment while the ASD rate was 63% (5/8) in the small subgroup referred directly to CNC due to behaviour and/or learning problems.

ASD, AD/HD, and LD related to age
The rate of ASD/AD/HD was similar in the subgroups of adults (>16 years) and children (16 years or younger). The diagnosis of AD/HD was most common in the age group 6-11 years of age (Table 6).

Table 6. ASD, AD/HD, and LD related to age

Diagnosis	All n=100	Age range ≤5 years n=22	Age range 6-11 years n=40	Age range 12-16 years n=22	Age range ≥17 years n=16
AD/HD "only"	21	2	12	3	4
ASD "only"	14	3	4	4	3
AD/HD+ASD	9	2	5	1	1
Autistic disorder	5	1	3	1	0
Autistic-Like Condition	17	4	6	4	3
Asperger syndrome	1	0	0	0	1
Mild MR	42	10	12	12	8
Moderate MR	8	0	2	5	1
Severe MR	1	0	0	1	0

ASD/AD/HD and LD in relation to gender
There were 32 females (55% of the female group) and 35 males (83% of the male group) in the group of 67 individuals who had either ASD, AD/HD, LD or a combination of these diagnoses. In the whole cohort ASD "only" was found in 9 females (16%) and in 5 males (12%), AD/HD "only" was found in 10 females (17%) and 11 males (26%), and the combination of ASD and AD/HD in 2 females (3%) and 7 males (17%).

The female/male ratios within the ASD group was: autistic disorder 3/2; ALC 7/10 and Asperger syndrome 1/0. Within the group with AD/HD the female/male ratio was: AD/HD mainly inattention subtype 9/7 and AD/HD combined subtype 3/11. LD was found in 24 (41%) females and in 27 (64%) males. In the group with ASD there were 1 female and 3 males without LD and in the AD/HD group there were 7 females and 6 males (1 of whom had a combination with ASD) without LD.

Other psychiatric/neurodevelopmental diagnoses related to age
Most of the diagnoses were found among the adults. Three adults had anxiety disorder, one adult psychosis (another three had a history of psychotic symptoms. One adult met criteria for depression but another 4 had a history of medication treated

depression. One child had a diagnosis of ODD and another child had a history of medication treated depression. Eighteen patients had DCD (9 females, 9 males; mean age 9.8 years, range 6.2-18.0), 10 of whom had a combination of DCD and AD/HD, and 8 of whom had DCD "only".

DSM-IV triad domains (Autistic disorder) in 23 individuals with ASD
The social symptoms of ASD were the ones most often endorsed (mean 2.3, SD=1) with lower rates (mean 1.7, SD=1) for communication domain and for the items in the repetitive/stereotyped behaviour domain (mean 1.3, SD=1).

DSM-IV symptom cluster domains (AD/HD) in 30 individuals with AD/HD
Inattentive symptoms (mean 6.5; SD 1.4**)** were much more commonly endorsed than hyperactive symptoms (mean 2.7; SD 1.9) and impulsive symptoms (mean 1.2; SD 1.1).

Overall clinical impression
One of the most striking features in a majority of individuals - regardless of psychiatric diagnosis - was a characteristic combination of initiation difficulties, general lack of energy and reduced facial expression (observation and interview data).

Questionnarie results
Parents reported high rates of behaviour problems on all questionnaires used. The results showed a wide variety of problems.

ASSQ
The mean ASSQ total score was 11.4 (SD 9.2). Forty-one individuals had values of 10 or below, 8 scored in the range 11-16 range, and 26 had scores ≥17 (indicating a suspected ASD). Sixteen of the 23 individuals (70%) with and 59/77 (77%) without ASD had an ASSQ completed for them. In this ASD-ASSQ group 13/16 (81%) individuals had scores of 17 or above vs 13/59 (22%) in the non ASD group ($p<0.001$). In the subgroup with autistic disorder all 3 individuals (one with a score of 18, and 2 with scores of 23), and in the subgroup with ALC 10 of 13 with a completed ASSQ had scores of 17 or above. Thus, within this sample, ASSQ sensitivity for ASD was 0.81, specificity 0.78, and the positive predictive value (PPV) 0.50 using a parent ASSQ score cut-off of 17. (It should be noted that the results of the ASSQ were not included in the ASD diagnostic process.)

Conners BPRS
The mean Conners BPRS total score was 9.0 (SD 7.2, n=81**).** Forty-four individuals had scores of 9 or below, 18 had scores in the range of 10-14, and 19 had scores ≥15. Twenty-eight of the 30 individuals with AD/HD had completed the Conners BPRS. In this group a score of 15 or above was found in 13 individuals while 15 had scores below this level. With a cut-off scores of 10, 21 individuals had scores

of 10 or above and 7 below this level. Thus, within this sample, sensitivity was 0.75, specificity 0.70 and positive predictive value 0.57 using a parent Conners BPRS cut-off score of 10. (The results of the Conners BPRS were not included in the AD/HD diagnostic process).

CBCL

Sixty of the 76 individuals for whom the CBCL was completed, were in the age range of the Swedish normative sample (6-16 years). The total mean score (m=39.1, SD 24.7) in this group was significantly higher than in the normative group (Figure 4).

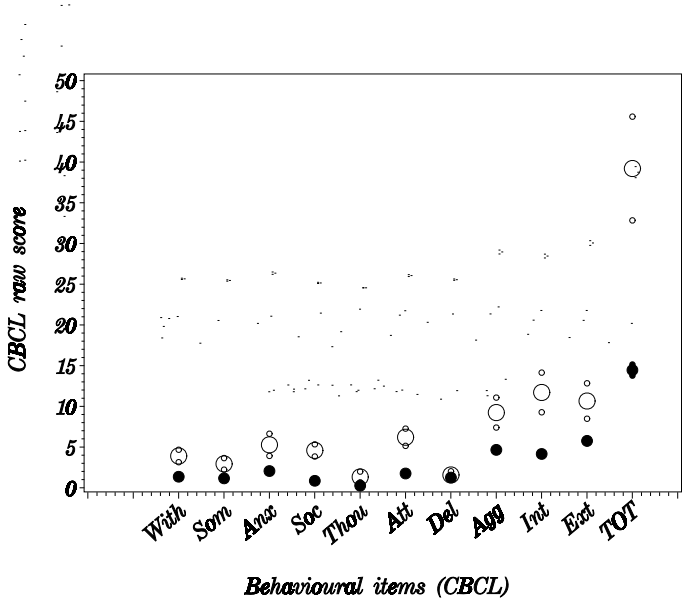

Figure 4. Behavioural profile according to CBCL (n=60)

Raw score means (large open circles) and 95% confidence intervals (small open circles) for study group and corresponding measures for normative group (filled circles) are given for the following items: withdrawn, somatic complaints, anxious, social problems, thought problems, attention problems, delinquent behaviour, aggressive behaviour, internal behaviour, external behaviour and total behaviour.

The highest problem scores were found in the clusters of Attention problems, Aggressive behaviour and Social problems. Scores for Aggressive behaviour in those with AD/HD+ASD were significantly higher than for either condition alone ($p<.05$).

FTF

FTF scores, for children 6-15 years of age (n=56) are shown in Figure 5. Scores were significantly higher than for the normative group on all scales although with the highest scores in the domains of Motor, Language, Learning and Perception.

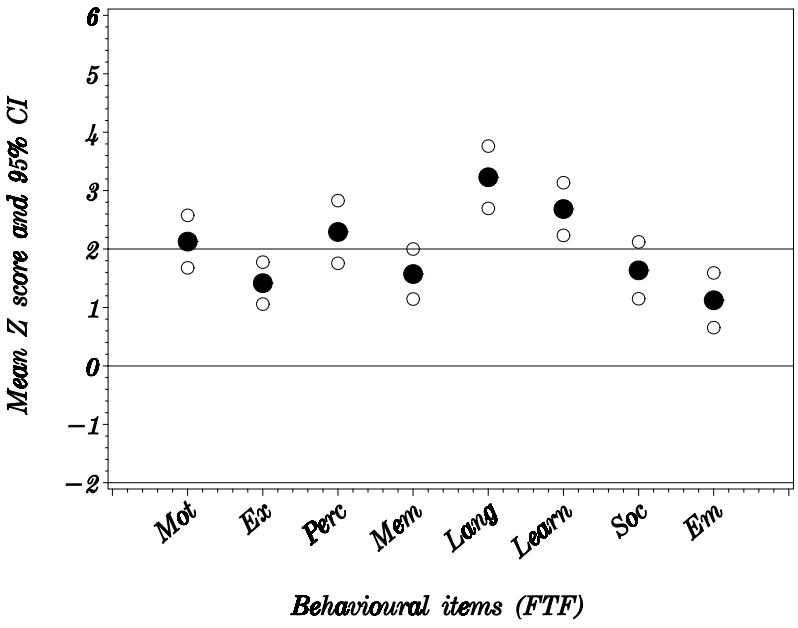

Figure 5. Behavioural profile according to FTF (n=56)

Z-score means (large filled circles) and 95% confidence intervals (small open circles) for study group by domains of FTF (correcting for gender and age). Comparison done with normative group (mean=0; SD=1). The domains are: Motor skills, Executive function, Perception, Memory, Language, Learning, Social skills and Emotional/behavioural problems.

Questionnaire results in relation to ASD/AD/HD and gender

There were significant differences between those, with and without ASD/AD/HD, on the total scores and on all 8 subscales of the CBCL ($p<.001$), the total score on ASSQ ($p<.001$) and the total score on the Conners BPRS ($p<.01$), individuals with ASD/AD/HD scoring more "abnormal". In the FTF, such differences were found in five of the eight domains while no differences were found for perception, learning and emotional problems. There were no gender differences across total scores on the ASSQ, Conners BPRS, or CBCL

Attention deficits in children with 22q11DS (III)

ASD, AD/HD and/or LD

In this group of 30, altogether 13 children had AD/HD, 9 children had AD/HD "only" and four had AD/HD in combination with ASD. The majority, 10 children, had AD/HD the inattentive subtype and three had the combined subtype. Eight individuals had ASD, one child autistic disorder and 7 autistic-like condition (of whom 4 had ASD in combination with AD/HD). Three individuals had LD "only" and 10 individuals did not have AD/HD, ASD or LD. In this group of 13 children with an FSIQ of 70 or below, most of them (11) had mild LD and only two moderate LD.

Intellectual ability and its relation to diagnostic subgroups in the Attention deficits study

The mean FSIQ in this group was 72.1 (SD 11.8). The lowest FSIQ was found for the group of children with ASD+AD/HD (mean FSIQ 59.3; SD 10.8) and the highest FSIQ for the ND group (mean FSIQ 80.3; SD 7.8) (Table 7).

Table 7. Intellectual ability in the whole group and related to diagnostic subgroups for the 30 individuals included in the Attention Deficit study

WISC-III: FSIQ, VIQ, PIQ, and Kaufman factors in 30 children included in the Attention Deficit study with 22q11 deletion syndrome (mean, SD and 95% confidence intervals).

Factor	AD/HD	AD/HD +ASD	ASD	MR	ND*	All
	n=9	n=4	n=4	n=3	n=10	n=30
FSIQ	73.9 (11.7)	59.3 (10.8)	68.5 (3.9)	61.7 (11.0)	80.3 (7.8)	72.1 (11.8)
	66.2-81.6	48.7-69.8	64.2-72.3	49.2-74.1	75.1-85.1	67.9-76.3
VIQ	79.8 (8.9)	66.0 (9.2)	76.5 (8.2)	67.7 (21.5)	87.6 (7.6)	78.9 (12.3)
	73.9-85.6	57.0-75.0	68.5-84.5	43.2-92.0	82.6-92.3	74.5-83.3
PIQ	72.0 (13.3)	59.3 (13.3)	65.8 (2.2)	60.7 (9.0)	76.4 (8.8)	69.8 (12.4)
	62.2-81.8	46.2-72.3	63.6-67.9	50.5-70.8	70.9-81.9	65.4-74.2
Kaufman factors						
Verbal Comprehension	83.1 (8.3)	67.0 (10.6)	78.0 (8.6)	69.7 (20.0)	89.8 (8.7)	81.7 (12.6)
	77.7-88.5	56.6-77.4	69.5-86.5	47.0-92.3	84.4-95.2	76.6-85.7
Perceptual Organisation	73.7 (14.6)	60.8 (13.0)	69.3 (3.9)	59.0 (11.4)	77.3 (10.1)	71.1 (12.8)
	64.1-83.2	48.0-73.5	65.5-73.0	46.1-71.9	84.4-95.2	66.5-75.7
Freedom from Distractibility	76.0 (11.8)	69.5 (14.6)	76.3 (6.7)	74.3 (12.5)	84.8 (9.3)	77.9 (11.5)
	68.3-83.7	55.2-83.8	69.7-82.8	60.2-88.5	79.6-90.6	73.8-82.8
Processing Speed	77.8 (13.8)	67.0 (14.4)	72.5 (10.6)	79.3 (13.9)	86.3 (12.3)	78.6 (13.8)
	68.7-86.8	52.9-81.1	62.1-82.9	63.6-95.0	78.7-93.9	73.7-83.6

* = no neuropsychiatric diagnosis

Attention functions

Focus-encode attention

For the whole group the result on the factor Freedom From Distractibility was 77.9 (SD 11.8) and Processing Speed 78.6 (SD 13.8).

Sustain attention

The results on Becker Go-No Go and Conflict tests showed that reaction time on the two visual and the two auditory tests were significantly longer in the whole group and particularly in the group with AD/HD compared with the normative

group (Table 8). There was a tendency towards discrepancy between the VGT (Visual Go-NO GO Test) and AGT (Auditory GO-NO GO Test) in the group with AD/HD "only" showing longer reaction times on the auditory subtest (p=.097) as for the whole group (p=.058). No such tendency was found when the two conflict tests VCT and ACT (Visual Conflict test and Auditory Conflict Test) were compared.

Table 8. Becker test results in 30 children with 22q11 deletion syndrome

Factor	AD/HD "only" n=9 (7)*	AD/HD +ASD n=3	ASD "only" n=4 (3)*	MR n=3	ND n=10	All n=29 (26)*
VGT	0.95 (1.13)[1] 0.61	0.35 (0.83)[ns]	0.22 (1.25)[ns]	0.067 (1.42)[ns]	0.66 (1.39)[ns]	0.60 (1.20)[2] 0.40
Omiss	-		-	-	-	-
Comm	0.04 (1.0)[ns]	2.04 (2.93)	0.06 (0.98)	-0.68 (0.11)	-043 (1.52)	0.31 (1.48)
AGT	1.92 (1.68)[2] 1.74	1.56 (1.16)[ns]	1.01 (1.67)[ns]	-0.16 (1.09)[ns]	1.03 (1.60)[1] 0.80	1.24 (1.58)[2] 0.96
Omis	1.00 (6.00)	-0.16 (-)	-0.16 (-)	-	-0.16 (0)	1.07 (2.76)
Comm	2.08 (3.80)	2.10 (1.87)	-0.65 (0.14)	0.26 (0.68)	1.05 (1.92)	1.11 (2.58)
VCT	1.10 (0.49)[2] 1.13	0.19 (0.82)[ns]	1.27 (1.39)[ns]	0.12 (1.31)[ns]	0.43 (1.20)[ns]	0.64 (1.0)[2] 0.98
Omiss	1.03 (2.31)	1.36 (2.38)	5.93 (6.62)	0.19 (0.96)	0.0 (1.19)	1.14 (3.03)
Comm	2.29 (2.24)	1.90 (2.74)	-0.20 (1.48)	-0.54 (1.40)	0.12 (0.90)	0.80 (1.92)
ACT	1.20 (0.79)[2] 1.17	0.71 (0.85)[ns]	2.78 (3.03)[ns]	0.12 (0.68)[ns]	0.44 (1.55)[ns]	0.88 (1.58)[2] 0.77
Omiss	- (-)	-0.12 (-)	8.51 (3.48)	0.26 (-)	3.28 (5.09)	3.67(4.91)
Comm	1.33 (4.39)	6.18 (1.90)	5.46 (6.01)	-0.33 (0.71)	2.65 (7.09)	2.69 (5.47)

Omiss=omission
Comm=commission
Values are given as mean (SD) of age related Z-score and with median value below if significant (Wilcoxon signed rank sum test)
( )[1] indicate p<0.05 and ( )[2] indicate p<0.01 ( )[ns] indicate not significant
n = (VGT/AGT) = 29
(n)* = (VCT/ACT) = 26
ND= no neuropsychiatric diagnosis

Behaviour according to questionnaires

CBCL

In the group with children, 7-13 years of age, 95% of the children with AD/HD, ASD, LD or a combination of these diagnoses scored above the 90th centile for the Swedish normgroup compared with 30 in the group without any of these diagno-

ses (p<.01). Total mean scores were highest in the group with AD/HD "only" (56.8) and AD/HD+ASD (61.6) and the lowest mean score in the ND group (26.4). The scores on the Attention problems factor were highest in the groups with AD/HD (9.5) and AD/HD+ASD (7.0).

Conners BPRS
Ten of the 13 children with AD/HD had scores of at least 10 compared with 3 of the 17 children without AD/HD (p<.01). None in the ND group had scores of at least 10.

The neuropsychology of 22q11DS (IV)

In the whole group of 100 individuals, 44 had ASD, AD/HD or a combination of these diagnoses (with or without LD) (see paper II). In this group of 44 individuals, 28 (mean age 11.0 years) had ASD/AD/HD + LD, while 16 (mean age 13.9 years) had ASD/AD/HD - LD. Thirty-three individuals (mean age 8.6 years) had No ASD/AD/HD - LD while the remainder, 23 individuals (mean age 14.0 years), had No ASD/AD/HD + LD.

General intellectual/developmental ability
Fifty-one of the 100 individuals met criteria for a diagnosis of LD. Forty-two of these had mild LD (IQ 50-69), 8 moderate LD (IQ 35-49), and 1 severe LD (IQ<35).

Griffiths' Mental Developmental Scale
For the youngest children assessed with the Griffiths' Mental Developmental the mean DQ was 70.1 (SD 16.5) (girls 74.3, SD 18.0**,** and boys 64.7, SD 13.8). In this small group there were no significant gender difference, only a trend for higher DQ among the girls compared to the boys (p=0.2). The developmental profile showed a significantly lower result on the subscale Hearing and Speech than on any of the three subscales Eye and Hand, Performance and Personal-Social (Table 9)

Table 9. Griffiths' Mental Development scale results

Variable	n	mean	95% CI
Developmental Quotient	14	**70.1**	60.6-79.7
Females	8	**74.3**	59.2-89.3
Males	6	**64.7**	50.2-79.1
Motor	13	**73.8**	61.8-85.9
Personal-Social	14	**74.8**	63.8-85.8
Hearing and Speech	14	**57.4**	47.5-67.3
Eye and Hand	14	**73.6**	61.4-85.9
Performance	14	**77.2**	63.9-90.5
Practical Reasoning	6	**66.8**	56.5-77.2

The Wechsler scales

The 82 children/adults assessed on one of the Wechsler scales (WPPSI, WISC-III or WAIS-R) had a mean FSIQ of 70.6 (SD 15.5), a VIQ of 75.6 (SD 15.9) and a PIQ of 69.8 (SD 15.6) (Figure 6). The VIQ-PIQ mean difference was 5.57 (95% CI 2.86-8.28) ($p<0.01$).

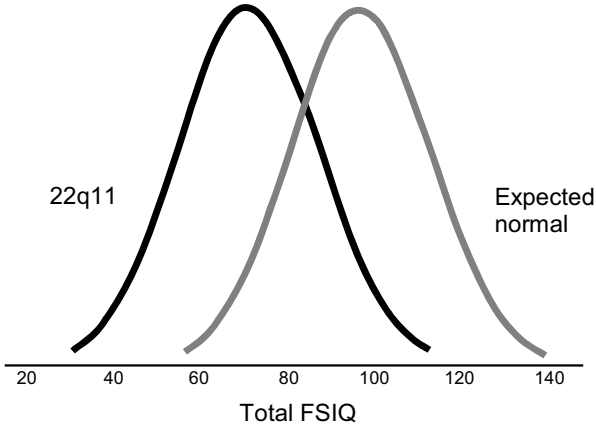

Figure 6. FSIQ distribution. in 82 individuals with 22q11DS compared with expected normal

Intelligence and gender

Females had higher FSIQ (75.3 SD 19.9) than males (64.6 SD 12.8) ($p<.002$). Females also had better results on each of the four Kaufman factors (Table 10). Similar gender differences were found for all subtests within the factors Verbal Comprehension and Processing Speed, for one subtest within Perceptual Organisation (Object Assembly) and one subtest (Digit Span) within Freedom from Distractibility.

Intellectual level/profile and diagnostic group effects for the whole group

For the whole group the Perceptual Organisation factor yielded uniformly poor results (Table 10). The results of this factor were significantly lower than the results of the other three factors. The results on the Verbal comprehension factor were better than those on the Perceptual Organisation factor and the Freedom from Distractibility factor (Table10). No significant differences across factors were found across the groups No ASD/AD/HD + LD and No ASD/AD/HD – LD (Table 11). No subtest discrepancies were found within the Perceptual Organisation factor. However, such discrepancies were found within the other factors. For the whole group (including in all the subgroups), the highest and lowest results were found for Vocabulary and Information, respectively (both these subtests are included in the Verbal Comprehension factor). Differences between these two subtests were significant for all subgroups ($p<.01$). In the group No ASD/AD/HD - LD Vocabulary was also superior to Similarities ($p<.01$). In the whole group, but not in the subgroups, Digit Span was superior to Arithmetic. Symbol Search was superior to Coding in the whole group (and in the subgroup ASD/AD/HD + LD).

Table 10. Wechsler scales results and gender effects for the whole group of tested individuals (n=84)

Variable	All mean*	(n)	Females mean*	(n)	Males mean*	(n)	Females: Males p-value
FSIQ	**70.6** (67.2-74.0)	(82)	**75.3** (70.6-80.0)	(46)	**64.6** (60.3-68.9)	(36)	p=0.002
VIQ	**75.6** (72.1-79.2)	(82)	**80.3** (75.6-85.0)	(46)	**69.7** (64.9-74.5)	(36)	p=0.002
PIQ	**69.8** (66.4-73.2)	(84)	**73.4** (66.6-78.1)	(48)	**65.0** (60.5-69.5)	(36)	p=0.014
Verbal Comprehension	**78.7** (75.1-82.3)	(68)	**83.3** (78.0-88.1)	(38)	**72.8** (67.8-77.9)	(30)	p=0.003
Vocabulary	**6.8** (6.1-7.5)		**7.7** (6.6-8.8)		**5.8** (4.6-7.0)		p=0.017
Similarities	**6.0** (5.3-6.7)		**6.7** (5.8-7.5)		**5.0** (4.0-6.2)		p=0.022
Comprehension	**5.9** (5.1-6.7)		**7.0** (5.7-8.2)		**5.0** (3.9-6.1)		p=0.020
Information	**5.1** (4.5-5.8)		**5.8** (4.7-6.9)		**4.3** (3.4-5.3)		p=0.047
Perceptual Organization	**72.0** (68.2-75.9)	(68)	**75.9** (70.5-81.3)	(38)	**67.2** (62.0-72.3)	(30)	p=0.022
Picture Completion	**5.9** (5.1-6.7)		**5.8** (4.7-6.9)		**4.5** (3.2-5.7)		p=0.123
Object Assembly	**5.6** (4.9-6.4)		**5.8** (4.6-7.0)		**3.8** (2.9-4.8)		p=0.014
Block Design	**5.1** (4.3-5.9)		**5.8** (4.6-7.1)		**4.2** (2.8-5.6)		p=0.084
Picture Arrangement	**5.0** (4.3-5.7)		**5.0** (4.0-6.1)		**4.9** (3.8-6.0)		p=0.835
Freedom from Distractibility	**75.8** (72.8-78.9)	(68)	**79.6** (76.0-83.2)	(38)	**70.9** (66.3-75.5)	(30)	p=0.003
Digit Span	**6.1** (5.5-6.7)		**6.8** (6.0-7.7)		**5.2** (4.3-6.2)		p=0.010
Arithmetic	**5.5** (4.9-6.1)		**5.9** (5.0-6.7)		**4.7** (3.7-5.7)		p=0.074
Processing Speed	**75.6** (71.5-79.8)	(54)	**81.5** (76.3-86.8)	(29)	**68.8** (62.9-74.6)	(25)	p=0.002
Symbol Search	**6.0** (5.1-6.9)		**7.2** (6.0-8.3)		**4.6** (3.4-5.9)		p=0.004
Coding	**4.7** (3.9-5.6)		**5.7** (4.6-6.8)		**3.6** (2.5-4.8)		p=0.001

84 cases tested with WPPSI-R. WISC-III and WAIS-R. For Kaufman factors only 68 cases (not included on WPPSI-R) and Processing Speed only 54 cases (only included on WISC-III).
*mean followed by 95% CI

Table 11. Wechsler scale results by ASD/ADHD and LD in 84 cases with 22q11DS tested

Variable	ASD/ADHD -LD mean* n=16	(n)	No ASD/ADHD -LD mean* n=33	(n)	ASD/ADHD + LD mean* n=28	(n)	No ASD/ADHD +LD mean* n=23	(n)
FSIQ	**79.4** (75.6-86.2)	(15)	**84.0** (79.9-88.0)	(27)	**60.1** (56.2-63.9)	(20)	**56.5** (52.8-60.2)	(20)
VIQ	**83.7** (76.9-90.6)	(15)	**88.9** (83.9-92.3)	(27)	**66.1** (60.5-71.6)	(20)	**62.4** (57.2-67.5)	(20)
PIQ	**77.9** (69.9-86.9)	(15)	**81.9** (77.1-86.7)	(27)	**60.8** (57.2-64.6)	(22)	**57.2** (53.4-60.9)	(20)
Verbal Comprehension	**87.1** (80.5-93.6)	(15)	**89.6** (85.1-93.9)	(20)	**69.9** (63.2-76.7)	(20)	**67.0** (61.7-72.3)	(18)
Vocabulary	**8.5** (7.3-9.8)[1]		**9.3** (8.1-10.4)[1, 2]		**5.2** (3.8-6.7)[1]		**4.1** (2.7-5.5)[1]	
Similarities	**7.9** (6.7-9.1)		**7.7** (6.9-8.5)		**4.6** (3.1-6.1)		**3.6** (2.5-4.7)	
Comprehension	**8.3** (6.2-10.3)		**8.3** (7.1-9.4)		**4.1** (3.0-5.3)		**3.5** (2.1-4.9)	
Information	**6.9** (5.6-8.2)		**7.3** (6.2-8.4)		**3.8** (2.9-5.2)		**2.5** (1.4-3.5)	
Perceptual Organization	**80.0** (71.4-88.6)	(15)	**83.5** (77.2-89.9)	(20)	**61.7** (57.5-65.9)	(15)	**61.3** (56.3-66.4)	(18)
Picture Completion	**6.1** (4.3-8.0)		**8.1** (7.1-9.4)		**3.5** (1.8-5.2)		**2.7** (1.7-3.7)	
Object Assembly	**6.7** (5.0-8.5)		**6.9** (5.4-8.4)		**2.9** (1.6-4.1)		**3.0** (1.9-4.1)	
Block Design	**6.9** (4.5-9.3)		**7.5** (5.9-8.9)		**3.3** (1.8-4.9)		**2.5** (1.4-3.6)	
Picture Arrangement	**6.3** (4.3-8.4)		**6.7** (5.8-7.7)		**3.4** (2.3-4.5)		**3.3** (2.1-4.5)	
Freedom from Distractibility	**80.6** (77.1-84.1)	(15)	**86.3** (82.1-90.5)	(20)	**69.1** (62.7-75.4)	(15)	**65.7** (61.7-69.7)	(18)
Digit Span	**6.9** (6.0-7.8)		**7.9** (6.9-8.8)		**5.6** (4.0-7.2)		**4.1** (3.1-5.0)	
Arithmetic	**6.1** (5.1-7.0)		**7.7** (6.7-8.6)		**3.9** (2.6-5.2)		**3.6** (2.5-4.6)	
Processing Speed	**84.1** (73.4-90.8)	(10)	**86.3** (80.3-92.4)	(18)	**63.9** (58.8-69.1)	(13)	**65.9** (57.5-74.4)	(13)
Symbol Search	**7.6** (6.4-8.9)		**8.3** (7.0-9.6)		**4.2** (2.8-5.5)[3]		**3.5** (1.6-5.5)	
Coding	**6.6** (4.8-8.5)		**6.9** (5.5-8.3)		**2.3** (1.4-3.2)		**3.1** (2.2-3.9)	

84 cases tested with WPPSI-R. WISC-III and WAIS-R. For Kaufman factors only 68 cases (not included on WPPSI-R) and Processing Speed only 54 cases (only included on WISC-III).

*mean followed by 95% CI

1 = p<.01 Vocabulary versus Information

2 = p<.01 Vocabulary versus Similarities

3 = p<.01 Symbol Search versus Coding

FSIQ and age

Lower FSIQ was found for those with higher age (WAIS-R-tested) compared to those of lower age (WPPSI-tested) (p<.002). This result was found for both males and females. We performed correlation analyses between age and FSIQ within the Wechsler test groups and found that it was only in the WISC-III-tested group that the negative correlation (lower FSIQ for those of higher age), was significant. There was a tendency of such a correlation in the WPPSI-R group but not in the adult group tested with the WAIS-R (table 12).

Table 12. FSIQ by type of Wechsler test and in correlation to age

Test	N	Mean	SD	95% CI	Correlation age-FSIQ	p-value
WPPSI-R	14	75.4	15	66.9-83.8	-0.442	0.113
WISC-III	54	70.4	15	66.2-74.6	-0.633	<0.001
WAIS-R	14	66.7	16	57.3-76.9	-0.051	0.864

Visuomotor integration skill

The VMI (n=56) mean quotient was 64.3 (95% CI: 59.7-68.9) which was rather low given a mean PIQ of 68.8 (95% CI: 64.9-72.8) and an FSIQ of 69.5 (95% CI: 65.5-73.5). Females (n=26) scored better than males (n=30) (p=.004). The best result was found in the group with No ASD/AD/HD - LD (n=19), where the mean quotient was 78.2 (95% CI: 70.4-86.0) and the lowest result, 51.1 (95% CI 46.6-55.6), in the group No ASD/AD/HD + LD (n=14). The group ASD/AD/HD - LD (n=10) had a mean quotient of 68.9 (95% CI: 59.2-78.6), which was a superior result to 54.7 (95% CI 47.5-61.9) found in the group ASD/AD/HD + LD (n=13) (p=.015).

Executive function – children

Planning ability

Tower of London test

Thirty of the 45 children performed the Tower of London test, were in the age-range of the normative group (6 years to 13 years). The total standard score for the whole group of 30 was 91.7 (95% CI 85.5-97.9) and the stanine value for correct solutions was 4.1 (95% CI 3.3-4.8). No gender differences were found. In the group No ASD/AD/HD - LD (n=14) the mean quotient was 102.7 (95% CI 96.5-108.9) and the mean correct solutions 5.4 (95% CI 4.5-6.4) were both significantly higher than for the group ASD/AD/HD - LD (n=8), who had a mean quotient of 85.8 (95% CI 74.3-97.3) (p=.01) and mean correct solution: 3.3 (95% CI 2.1-3.7) (p=.005). Between the two groups, ASD/AD/HD + LD and ASD/AD/HD – LD, no differences were found. The number of cases in the group No ASD/AD/HD +LD (n=3) was too low for separate meaningful analyses.

Attention function

Trail Making A and B

For the whole group of 27 children who were in the age range for the normative

group (7-15 years) the mean z-score was -2.3 (95% CI -1.6 - -3.1) on Trail A and -2.8 (95% CI -1.8 – -3.9) on Trail B. Both of these were significantly lower than for the normative group. No differences were found between the results on Trail A and Trail B and there were no differences regarding gender. No differences between the two groups, No ASD/ADH - LD and the group ASD/AD/HD – LD, were found.

Executive function – adults
The number of adults was too low for meaningful comparison across diagnostic subgroups.

Attention function
The adult version of the Trailmaking test was performed by 7 individuals. The mean z-score for Trail A was -2.5 (95% CI: -1.4 - -3.5) and for Trail B -5.7 (95% CI -1.4- -9.5). For both Trail A and Trail B significantly lower mean z-score was found and a tendency (p=.06) for lower mean z-score on Trail B compared to Trail A.

Planning ability
Ten individuals performed the adult version of the Tower of London test. The total score, mean correct solutions, was 9.2 (95% CI: 8.1–10.3) for the whole test (12 items) and corresponding scores for the six test items included in level 1 was 5.5 (95% CI: 5.0–6.0) and 3.7 (95% CI: 2.7–4.7) for the six test items in level 2. The total number of correct solutions was lower than for normative group (p=.05).

Comparison of results from the first 20 individuals reported (I) and those of the following 80 individuals reported as part of the larger cohort of 100 (II, IV)

The rate of ASD, AD/HD or a combination of these diagnoses, was 13/20 (65%) in the first cohort compared with 31/80 (39%) in the later group (p<.001). Eleven out of 20 individuals (55%) had AD/HD (6 AD/HD inattentive subtype and 5 combined subtype) in the preliminary study while the rate in the group of 80 was 24% (10 AD/HD inattentive subtype and 9 combined subtype) (p<.001). In the first cohort 7/20 (35%) met criteria for ASD (1 Autistic disorder, 6 Autistic-like condition) compared to 16/80 in the larger group (4 Autistic disorder, 11 Autistic-like condition, 1 Asperger syndrome) (n.s.). A combination of ASD and AD/HD was found in 5/20 in the small group and in 4/80 in the larger group (p<.01). Thus, in summary, there were relatively more cases of AD/HD in the preliminary study. One contributing factor to this result could be that 4 of the 8 individuals referred directly to CNC belonged to preliminary study group.

The rate of LD was 50% and 49%, respectively. Mean FSIQ for females was 77.6 (SD 14.1) and for males 63.4 (SD 20.5) while corresponding FSIQ in the large cohort were 74.5 (SD 16.5) and 64.9 (SD 10.8), respectively. Lower FSIQ for those with higher age was found in the group of 80 while no such correlation was found in the group of 20.

In the first cohort the mean scores of CBCL was 42.8 (SD 22.7) with the highest problem scores in the clusters Attention problems, Aggressive behaviour and So-

cial problems, comparing with 38.5 (SD 25.8) in the 80 group, with highest problem scores in the same three clusters (n.s.).

DISCUSSION

Summary of main findings

The major results of this thesis are summarized here. 1) There was a high rate of ASD and AD/HD in 22q11DS. In the 22q11DS group of 100 individuals almost half the group (44%) fulfilled criteria for ASD, AD/HD (with or without LD) or a combination of these diagnoses. About one fourth of the group had ASD. The majority of these had "non-autistic disorder" ASD, and only 5% had autistic disorder. About one third had AD/HD of whom half had the inattentive subtype and half the combined subtype. An overlap of ASD and AD/HD was found in 9%. 2) There was a wide variety of behaviour problems (regardless of diagnostic category), and rates of such problems were high. 3) Half of all individuals in the study had LD of whom the majority had mild LD, a few moderate LD, and only one individual had severe LD. Half the group of those with LD had LD in combination with ASD/AD/HD. Altogether, there were 33 individuals without ASD, AD/HD or LD. However, these children and adults were not "problem-free" in more than a very few cases altogether. 4) IQ-levels showed normal distribution around FSIQ 70. Females had higher FSIQ than males, and there was a negative correlation between age and FSIQ among school-age children. 5) The poorest Wechsler scale result was found for the Perceptual Organization factor (showing deficits in the integration of visual stimuli, non-verbal reasoning, visuospatial and visuomotor skills), and the best result was demonstrated for the Verbal Comprehension factor (mainly related to good vocabulary). 6) A fairly specific type of attention deficit was found in school age children with 22q11DS, including deficits in sustained attention and speed of attention against a background of no major problems in focus-encode attention. Attention deficits were also found in the adult group. We did not find any specific planning deficits in the group of children, but such problems appeared to be common in the small group of adults. 7) The presence of ASD/AD/HD did not influence LD or visuomotor skills but had a negative impact on planning ability in children. ASD/AD/HD had a negative impact on the total scores of the CBCL, Conners BPRS and ASSQ. 8) All but one of the cases with non-ADHD/non-ASD diagnoses were found in the group of adults. 9) There were interesting gender differences as regards ASD and ADHD in 22q11DS as compared with findings in the general population.

Generalisability of findings

The conclusions that can be drawn are contingent upon the size and the representativeness of the sample. Study II (Neuropsychiatry) and IV (Neuropsychology) included 100 individuals, and this must be considered quite a large sample. The majority of the group, 92 of the 100, were consecutively referred individuals from the multidisciplinary team as part of routine 22q11DS assessment while a subgroup of 8 were referred directly to the Child Neuropsychiatric Clinic (CNC) due to learning and/or behaviour problems. The 100 cohort (or at least the 92 multidisciplinary team referrals) is probably as close to a general population sample of cases with 22q11DS as you are likely to be able to find. In study III (Attention deficits study) all 30 children in the age range 7-13 years, at time of the study, were

included which would argue in favour of these results being representative for this age group. In study I (Preliminary study) the first 20 individuals of the whole cohort were included. The relatively small sample might have had an impact on the representativeness of the findings from this study. Another important aspect relating to the representativeness of the findings is the way these individuals had been recruited to the study. The high rate of ADHD in this substudy compared to the (significantly lower) rate of ADHD in the larger sample may have been an effect of referral bias or chance significance. Four of the eight individuals who were referred directly to the CNC belonged to this first group of 20 individuals. Another explanation for bias in the Preliminary study could be that when starting to focus on a specific syndrome, the first cases seen include those with the most obvious symptoms. Today, there are many different inroads (cardiac problems, nasal voice, speech-language delay, behaviour problems etc.) to the molecular diagnosis of 22q11DS, and we still do not know if there are individuals with fewer medical and behaviour problems who remain undetected. Blood tests analysed with FISH technique of all newborn infants would be the only way to get information about the whole spectrum of the clinical presentation of 22q11DS. The reasons that this has not been done are mainly of an ethical nature.

Prevalence and type of ASD and AD/HD

We found that almost one in four with 22q11DS had ASD which should be compared with the rate of about one in a hundred in the general population (Wing, 1996; Baird et al., 2006). This is a very high rate of ASD, albeit lower than that reported by other recent authors (Vorstman et al., 2006)**.** However, only a small fraction of those with 22q11DS in our study had "autistic disorder". This is in contrast with previous research, which has shown classic autism to be quite frequent in 22q11DS**.** In a recent study, 41% of children with 22q11DS (n=41) met criteria for ASD, according to ADI-R, and 20% of the whole group had autistic disorder (Antshel et al., 2007). A few other studies have also focused on the prevalence of ASD. Vorstman found that 50% fulfilled criteria for ASD (Vorstman et al., 2006). The majority had PDDNOS/Autistic-Like condition and 10% of the whole group had autistic disorder. A similar rate of autistic disorder (11%) out of 14% who had ASD have been reported (Fine et al., 2005). However, the total rate of ASD in that study was lower than the rate that we found and much lower in comparison with what Vorstman and Antshel found. Nevertheless, the rate of autistic disorder found by Antshel was much higher than the one we found and higher than the rates found by the other groups publishing in the field. Factors contributing to the discrepant findings could be referral bias or the different methods applied in these studies. In all three studies the diagnosis of ASD was made according to the results of ADI-R (including telephone ADI-R interviews).

I believe our finding may be more valid than most, given that we have relied on an extensive clinical database and the clinical judgement of two leading clinical autism experts. We have felt, throughout this study, that while a small number of individuals with 22q11DS present with classic variants of autism and Asperger syndrome, the majority who fulfil some criteria for pervasive developmental disorders have atypical presentations. The majority of the individuals in this sample with

"non-autistic-disorder ASD" had several symptoms of autism, including unusual gaze contact, poor facial mimicry, reduced amount of communication with others, and some unusual behaviours, but they did not have the "gestalt" of autism. In fact, the rate of classic autism in our study was extremely low, given the high prevalence of LD, which would have indicated a high rate of autism quite regardless of any associated behavioural phenotype syndrome. Even Down syndrome - with its almost mythical "non-association" with ASD - has been reported to be "comorbid" with autism at a higher rate than what we have reported here in 22q11DS (Howlin et al., 1995, Rasmussen et al., 2001).

An overlap of ASD and AD/HD was found in 9%. An interesting finding was that the majority of those with ASD in combination with AD/HD, had AD/HD combined subtype and only one had the inattentive subtype.

The frequency and the specificity of ASD in 22q11DS has been a subject for discussion in a few studies, with arguments presented that the autistic traits identified in 22q11DS may reflect underlying communication disability (Mills et al., 2006; Swillen et al., 2001). Swillen found that a group of children matched for cognitive ability and speech and language impairment showed similar problems with respect to problematic social interaction (as well poor attention and anxiety) as the 22q11DS group (both groups FSIQ <70) (Swillen et al., 2001). The only differences found were that the 22q11DS group was more withdrawn and the control group more aggressive. Eliez has argued that the social deficits in 22q11DS differ from those found in classic autism. According to his opinion individuals with 22q11DS often start out overly familiar with others and then become withdrawn during adolescents a pattern more associated with the onset of schizophrenia than autism (Eliez, 2007).

I believe that the behavioural profile with low mental energy, initiation difficulties and deficits in sustained attention may have an impact on the social interaction ability. Limited facial expression and communication and speech problems, often hypernasal speech, can also be seen as negative factors in social interaction. The non-verbal deficits found might also have a negative impact on the social interaction ability and lead to problems in understanding other people's non-verbal communication.

Abberant cerebellar vermal size has been found in 22q11DS (Eliez et al., 2001; Devriendt et al., 1996) and is also found in the fragile X (Kates et al., 2002) and Joubert syndrome (Holroyd, et al., 2006). In all these three syndromes ASD is prevalent. Normal cerebellar hemispheres was found in subjects with Williams syndrome. Individuals with this syndrome are perceived as unusually friendly and socially outgoing, even though a small subgroup in this genetic syndrome also has ASD (Gillberg and Rasmussen, 1994). The autistic-like deficits in facial recognition found in children with 22q11DS implicate the ventral temporal system (Lajiness-O'Neill et al., 2005). In this context, it is intresting to note that grey matter reduction in the cerebellum, and white matter reductions in the frontal lobe, cerebellum and internal capsula were found in a recent study using advanced MRI

technique (Campbell et al., 2006).

We found a prevalence of AD/HD of 30%, of whom half had the inattentive subtype and half the combined subtype. Since the end of the nineties several reports of AD/HD in 22q11DS - with rates of about 40% - have been published (Antshel et al., 2006; Gothelf et al., 2003; Feinstein et al., 2002; Papolos et al., 1996). The AD/HD rate found in our group was about the same that has been reported in these other studies. Although there was the subgroup with AD/HD combined type (including hyperactivity/impulsivity as well as attention deficits) of about 15% of the total cohort, the majority of all individuals with 22q11DS have a low activity level. This, in combination with the fact that initiation difficulties were clinically striking, suggests that the attention deficits might be related to general arousal problems which, in turn, might be the effect of brainstem or cerebellar dysfunction or both.

Fifty per cent of the group had LD. The majority had mild LD, fewer than 10% had moderate LD, and only one individual had severe LD. Even in the group without LD, the majority had learning problems. The majority of the non-LD-group had an intellectual ability in the low normal range, which, in combination with different behavioural problems, can be the main reasons why the great majority have learning problems.

In the whole group 23% had LD without the combination of ASD or AD/HD meaning that two thirds (67%) had ASD, AD/HD or LD diagnoses or a combination of these. On the basis of the results presented in this thesis, it would be reasonable to expect about one third of all patients with 22q11DS to have relatively better intellectual function (i.e. in the FSIQ 70-100 range) and fewer problems within the area of ASD and AD/HD.

Behavioural profile

Behaviour according to questionnaires and clinical observation (II)

The main clinical impression from observation of the 100 cohort with 22q11DS – supported by data from behaviour questionnaires – was striking initiation difficulties and a general lack of energy. We were also struck by the limited facial expression and speech problems, which we have suggested might have a negative impact on the social interaction ability. Other authors have remarked on other clinically observed behaviours including withdrawal, shyness, person-dependence and anxiety (e.g. Swillen et al., 1997).

High rates of behaviour problems were found on all the questionnaires used indicating a wide variety of parent reported behaviour difficulties. Those with ASD/AD/HD had higher total scores on all subscales of the CBCL and on five of the eight domains of the FTF than those without these diagnoses. These results were to be expected given that many of the problem areas included in these questionnaires are those that are common in these diagnoses. On the CBCL aggressive behaviour, attention difficulties and social problems were the areas in which abnormality was most often reported. Perhaps the most surprising finding here was the high scores for aggressive behaviour given that the impression at clinical consultation often is

one of hypoactivity, lack of energy, and, if anything, docility. A high rate of aggressive behaviour has been reported in one previous study (Jansen et al., 2007), whereas in an early study in the field, aggressive behaviour was rated much lower than attention and social problems (Swillen et al., 1997). According to the results of the FTF, other parent reported problems were in the areas of language, learning, perception and motor skills.

Interestingly, unlike the situation in the general population of children, we did not find any gender differences on total scores of the CBCL, ASSQ or the Conners BPRS in our relatively large sample of young people with 22q11DS.

Neuropsychological functioning

General intellectual/developmental ability and profile and visuomotor integration skills (IV)

We found that about 50% had a FSIQ below 70 which is a result in accordance with earlier studies (Swillen et al.,1997; Moss et al., 1999; Gerdes et al., 1999). The same FSIQ result was found in the first group of 20 individuals and quite similar (FSIQ 72) in the group of 30 children (7-13 years of age). There was a normal distribution around a mean FSIQ of 70 showing that the mean FSIQ was 30 scores below the expected 100 in the normal population. The mean DQ for the youngest children assessed with the Griffiths' scale was also 70.

In the preschool years delayed speech and language development are well documented (Persson et al., 2003; Glaser et al., 2002; Gerdes et al., 2001; Sherer et al., 1999). We found for the youngest children of our group, assessed with Griffiths' Mental Developmental Scale, the significantly lowest result on the subscale Hearing and Speech. So for the youngest children of our cohort there was a developmental delay in expressive language. A contrary result to this was found in the school-age group and the adults assessed with one of the Wechsler scales. When the results were analysed according to the Kaufman statistically derived factors the highest result was found on the factor Verbal Comprehension. The result on this factor was significantly higher than the result of the factor Perceptual Organisation. However when analysing the subtest results within the Verbal Comprehension factor we found significant discrepancies between the subtest results. This finding makes the result of this factor less solid and the result must therefore be interpreted with caution (Kaufman 1994). The relatively high result of the factor was mainly related to high scores on the Vocabulary subtest. In contrast to this the lowest scores were found on Information. So it seems that their ability to define words is relatively good while the ability to answer questions about events, places and people is weak. In contrast to our results, Moss found the highest score on the subtests Information and Comprehension within the Verbal Comprehension factor (Moss et al., 1999). Difficulties in a number of linguistic domains including syntax, vocabulary, concepts, word finding, abstract reasoning and story re-telling have been reported in school-age children (Person et al., 2003, 2006; Solot et al., 2000). Altogether, these different aspects of the verbal ability contribute to understanding the deficits within this area. This can be the reason why this "verbal strength", mainly related to a generally good vocabulary, rarely is recognized by parents or teachers.

A major finding was that the poorest result was found on the factor Perceptual Organisation. No subtests discrepancies within this factor was found which gives strength to the result and supports the notion that the major neuropsychological deficit in 22q11DS lies within this functional area. This means that there are deficits in the integration of visual stimuli, non-verbal reasoning, visual-spatial and visual-motor skills. Initiation difficulties might have had a negative impact on the subtests within this factor where time (given bonus for fast solution) are included. There are other studies that have found deficits regarding visual-perceptual abilities (Sobin et al., 2005; Simon et al., 2005; Bearden et al., 2001; Swillen et al., 1999b). In the study by Bearden the impairment in visual-spatial information processing had an impact of the academic achievement in mathematics. In this study, as well as in earlier studies, the reading and spelling ability exceed the mathematic ability (Wang et al., 2000; Moss et al., 1999; Swillen et al., 1997). In the area of mathematics specific difficulties, in number comparison, execution of calculation strategy and word problem solving, involving the semantic manipulation of quantities, have been found (De Smedt et al., 2007). We have not in our study systematically evaluated the academic achievements but from our clinical experience we have found that deficits in mathematics are often reported. Interestingly, most children seem to have no specific problems in the learning to read process.

Executive functions (I, III, IV)

Attention ability and planning ability

We studied the specificity of the attentional functioning in a group of 30 school aged children (III). Deficits in sustaining attention were found while there were no specific problems regarding the ability to focus/encode attention. This means that they can focus on important stimuli while suppressing awareness of distracting stimuli but have problems in maintaining an attentional activity over time. These problems were common but most pronounced in the group of 9 children with AD/HD. Deficits with speed of attention and/or shift attention (IV) were also found so it seems that there are different kind of deficits in attention in children with 22q11DS. Attention deficits were also found in the small group of adults with a tendency of more specific problems with shifting attention.

For the whole group of children no specific problems in the planning ability were found. However, from our clinical experience we have noticed that parents often report that the children have planning difficulties. The reason could be that these difficulties seen by the parents are related to their initiation difficulties more than planning problems. Planning deficits were found in the small group of adults which is in accordance with an earlier finding by Henry (Henry et al., 2002).

The impact of ASD, AD/HD and age on neuropsychological functions

The presence of ASD/AD/HD did not predict LD status. It appeared that the cognitive impairment is related to the syndrome and not to the coexistence of ASD/AD/HD. The highest FSIQ was, as could be expected, found in the group with no ASD/AD/HD -LD. One contributing factor to this result could be that the mean age was lower in the group without diagnoses compared to the other groups. The lowest FSIQ was found in the group with LD but without ASD/AD/HD. Within all

diagnostic subgroups significant differences between the two subtests Vocabulary and Information was found. So it seems that this finding is related to the syndrome and not to the coexistence of ASD/AD/HD. Interestingly, no significant differences across the factors within the two groups No ASD/AD/HD -LD comparing with No ASD/AD/HD+LD. It seems that the nonexistence of ASD/AD/HD gives a more even factor profile.

We found that the coexistence of LD and not of ASD/AD/HD had an impact on the visuo-motor ability. This result is in accordance with the reported correlation between PIQ and VMI (Beery, 1997). Gender differences, females performing better than males, were found and in accordance with the gender differences found in the intellectual ability.

However, we did find that the coexistence of ASD/AD/HD had a negative impact on the planning ability in children. One explanation could be that, according to Lezak, the whole conceptual activity of planning require a capacity for sustained attention (Lezak 2004). Deficits in sustained attention was one of our main findings in children with 22q11DS specifically in the group with AD/HD.

Gender aspects

Females in our study had significantly higher FSIQ (including the 4 Kaufman factors) than males. They scored higher than males on all subtests within the factors Verbal Comprehension and Processing Speed. Gender differences have not been unequivocally documented in most earlier reports. However, one study focusing on gender differences in 22q11DS (Antshel et al., 2005) found females had higher FSIQ than males. One possible explanation for these findings could be that girls have a higher threshold than boys for the level of liability needed to manifest cognitive dysfunction. This should be in accordance with the finding that girls have a better outcome following premature birth (Elsmén et al., 2004). However, a recent study (De Smedt et al., 2007) focusing on gender differences found similar FSIQ levels in girls and boys with 22q11DS (total n=103).

There were significantly more females than males in the group with No ASD/AD/HD -LD while in all other groups there were an even gender distribution. There appears to be a group with females that are better functioning than the majority of the males. Another interesting result from our study was that there was a negative correlation between age and FSIQ for both females and males in the school-age children but not in the small groups of adults and pre-school children. Thus, in the school-age group there might be a decrease in intellectual ability. Another research group (Antshel et al., 2005) found the same negative association in girls but not in boys. It could be that girls were unable to make developmental progress in the same way as the boys. However, to evaluate the intellectual development a follow up study is needed.

Taken together, there were very interesting gender findings in the present study. First, of course, the females were slightly overrepresented among individuals with 22q11DS (for completely unexplained reasons) and were particularly overrepre-

sented in the youngest group of patients. Girls presenting to services at a younger age (if this had been the reason for the overrepresentation at low ages) would - logically – indicate more severe problems, or more focus on girls in services catering to the needs of children with LD or other major adjustment problems. However, both research (e.g. Kopp 2005) and clinical experience would tend to contradict this explanation, and, if anything, girls are underrepresented or even ignored by services at younger ages. Second, the females had significantly higher FSIQs than the males. This appears to be a "real" finding and not one that can be explained away by bias in the selection for entry into the study. Third, and in view of this better intellectual level of functioning in females, it is even more surprising that within the groups of individuals diagnosed with AD/HD and/or ASD, the level of overrepresentation of males that is to be expected in these diagnostic categories was not observed. It does appear that if a person is "hit" by 22q11DS, in respect of AD/HD and ASD, it does not matter whether it is a she or a he; both genders have a very high risk of AD/HD/ASD. This is very much unlike the situation in the general population where such diagnoses are extremely overrepresented among males.

The gender differences found are of interest, and there is a need of further studies to elucidate different aspects of gender differences in 22q11DS.

Specificity of behavioural findings to 22q11DS

This study showed that there was often a characteristic mix of cognitive problems, attention deficits and social interaction difficulties. However, one very interesting question is how specific the findings are for 22q11DS. Some comparison regarding certain aspects of 22q11DS with other syndromes have been made. The personality profile, rated by parents using the California Child Q-set, of children with 22q11DS has been compared with the personality profile with three other syndromes: Williams syndrome, Prader-Willi and Fragile X syndromes (Prinzie et al., 2002). The personality profile of 22q11DS was markedly different from the other groups. The groups were equally extrovert and agreeable but the 22q11DS group was more irritable and dependent and less emotionally stable than the other diagnostic groups. The CBCL result for a group with Prader-Willi syndrome, showed high rates of social problems, attention problems, aggressive behaviour and thought problems (Gross-Tsur et al., 2001). This result was quite similar to our findings in 22q11DS. However, in order to know more about the specificity of the findings in 22q11DS, similar neuropsychiatric evaluations to those that we have done, including a neuropsychological assessment, need to be performed in groups with other syndromes.

Strengths and limitations

There are several strengths in this study. 22q11DS is a rare syndrome with a rate of about 1/4000 births meaning that about 25 children are born with the syndrome in Sweden every year. In spite of this fairly low prevalence rate, we have managed to perform neuropsychological and neuropsychiatric evaluations in a large group of 100 consecutively referred patients. It is a strength that we have such a large group and also that the same psychologist (LN) made the neuropsychological assess-

ments in 99 of the 100 cases. One of two very experienced clinicians made 94 of the 100 neuropsychiatric evaluations. All individuals were examined in a thorough and uniform manner using a broad variety of examination methods. We used well validated instruments for the study of neuropsychology and behaviour. All of them have been validated and normed both internationally and in the context of young Scandinavian general population samples. For the clinical diagnoses of ASD and AD/HD I relied on the in-depth clinical examinations of expert clinicians who had more than thirty years of experience in the field rather than on instruments such as the ADI or the ADOS (both of which have been validated against the clinical assessments of expert clinicians and, therefore, cannot really be better – or more "valid" than the assessment of such clinicians).

One limitation is that no comparison group was used. However, there are major problems defining what would constitute a reasonable "control group".

This study mainly addresses the clinical characteristics and neuropsychology of children with 22q11DS. The adult group is very small. This is a clear limitation, and, therefore, any conclusions drawn regarding adults on the basis of the present study must be done with caution.

Research implications

My study has documented a high rate of ASD in 22q11DS. However, the rate of classic autism was relatively very low, in actual fact lower than in the vast majority of disorders associated with LD. This finding begs the question of whether "ASD" in 22q11DS is very "atypical". Could it be that the relative dearth of facial expressions, the nasal voice and ensuing communication difficulties lead to clinical "overdiagnosis" of ASD? New studies should examine this possibility in more detail.

In a similar fashion, AD/HD was very common. Could some cases of "AD/HD" in 22q11DS be atypical? Could it be that the lack of energy and initiation difficulties typical of 22q11DS "masquerade" as AD/HD? Is the deficit in sustained attention different from "garden variety" AD/HD? Children with 22q11DS and AD/HD should be compared on the Becker tests - in a blinded fashion - with non-22q11DS children with AD/HD matched on IQ in order to shed light on this issue.

22q11DS has been the focus of considerable research efforts in children as well as adults. Several studies have reported a high rate of psychosis - including schizophrenia - in adults with the syndrome. However, we still know very little about what type of dysfunctions - if any - found in children might be precursor symptoms related to severe psychiatric disorder in adulthood. One important question is whether or not there will turn out to be a relationship between ASD, AD/HD or LD diagnosed in childhood and the rate and type of psychiatric illness appearing in adult age. Higher rates of co-occurring psychiatric disorders have been found when comparing those with 22q11DS and ASD and those with 22q11DS "only" (Antshel et al., 2006). Prospective longitudinal studies are needed now to elucidate the issue of childhood "signals" of later psychiatric disorder in 22q11DS.

I also found that within the group of school-aged children lower FSIQ was present in the older children. However, given the cross-sectional nature of my study it would not be appropriate at this stage to conclude that IQ declines with age during the school age period. Here also, prospective longitudinal studies are needed to get a better understanding of intellectual development in 22q11DS.

The main focus in Sweden has so far been on children with 22q11DS. There is a need for research regarding older adolescents and adults with the syndrome so that a fuller understanding of the life span spectrum of assets and deficits associated with 22q11DS can be achieved. It is likely that a considerable number of adults with the disorder remain unrecognized and undiagnosed. Research on the cognitive and behavioural phenotype of adults with 22q11DS will have important clinical implications for awareness of the phenotype and for the ongoing care and for the planning of right type of interventions.

One important study that needs to be done is the follow-up of the individuals included in the present thesis.

Clinical implications

I found a large variability regarding behavioural, psychiatric, and cognitive profiles behaviour in 22q11DS. I also found a high rate of ASD, AD/HD or a combination of these diagnoses, even though the rate of classic autism was relatively very low. Given that ASD/AD/HD are main elements of the behavioural profile in 22q11DS, such diagnoses, as well as other psychiatric diagnoses, should be considered in all individuals with 22q11DS. Another important finding was that half of all individuals with 22q11DS had LD and quite a few functioned in the low normal range of intellectual functioning resulting in learning problems and need for educational interventions. Low intellectual level in combination with different kinds of behavioural problems indicates the need for individualised support in school, work, and social life. A neuropsychological assessment providing a description of the individual's assets and deficits will provide invaluable information in planning different kinds of interventions.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to:

• Christopher Gillberg, my supervisor, for inspiring me to do research, for excellent and enthusiastic scientific guidance, encouragement, generosity, patience and never failing support all the way through the process. His extensive knowledge in neuropsychiatry has always been a source of inspiration to me in research as well as in clinical work. I am grateful to him for sharing this, as well as clinical experience, with me during the examinations of those participants we have examined together,

• Peder Rasmussen, co-author, for never-failing friendly support and encouragement, interesting and constructive discussions, and for sharing his experience of scientific as well as clinical work with me. I am grateful for his contribution in the examinations of the group of participants we have seen together,

• Sólveig Óskarsdóttir, the leader of the Multidisciplinary team and co-author, for inviting us at the CNC to be members of that team, for interesting multidisciplinary collaboration, and for her efforts to keep the team together,

• Carina Gillberg, Agneta Nydén, Maria Råstam, Elisabet Wentz, senior researchers, for taking an interest in my research, sharing their experience of scientific work with me, constructive criticism and friendship. Special thanks to Agneta Nydén for valuable advice and interesting discussions about neuropsychological issues,

• Paul Uvebrant for constructive criticism,

• Eva Billstedt, Mats Cederlund, Susanna Danielsson, Bibbi Hagberg, Maria Johansson, Carmela Miniscalco, Gudrun Nygren, and Svenny Kopp, fellow researchers, who all contributed to make the work worthwhile. Special thanks go to Eva Billstedt for supporting me during all my "ups-and-downs" during the work with this thesis,

• All the members of the 22q11DS multidisciplinary team for enjoyable teamwork and for sharing knowledge and experience in different areas with me. Special thanks to Christina Persson for interesting collaboration and Anna Söderholm for organising the time schedule,

• My colleagues at the CNC for your friendship and encouragement, especially, Björn Kadesjö for letting me go "in and out" of the clinical work during my research periods, Gun Andersson and Kerstin Hjalmarsson for excellent help in organising the patient schedule, Thomas Ahlsén for doing the ADOS examinations with me, and Berith Börjesson for practical help,

• Ola Ståhlberg for arranging the data into SPSS-files and for immediate support in problematic situations,

• Björn Areskoug for statistical advice and support,

• Kerstin Lamberg for kind support and practical help at the Department of Child and Adolescent Psychiatry,

• Ann-Sofie Petersson for help with lay-out of figures, tables and text,

• Aimon, my husband, for help with statistics and figures but primarily for giving me the best kind of support and encouragement when I most needed it,

• Elsa, my mother, for love and support,

• Last but not least - I would like to thank all children, adolescents, adults and their families for participating so well in this study. It's my sincere hope that this thesis will contribute to a better understanding of their special needs and thereby be beneficial for obtaining the right kind of support.

The Wilhelm and Martina Lundgren Research Foundation, the Queen Silvia's Jubilee Foundation, Linnea and Josef Carlsson Foundation, Per and Mandis Mohlin Foundation and the Swedish Science Council provided the financial support for this research.

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