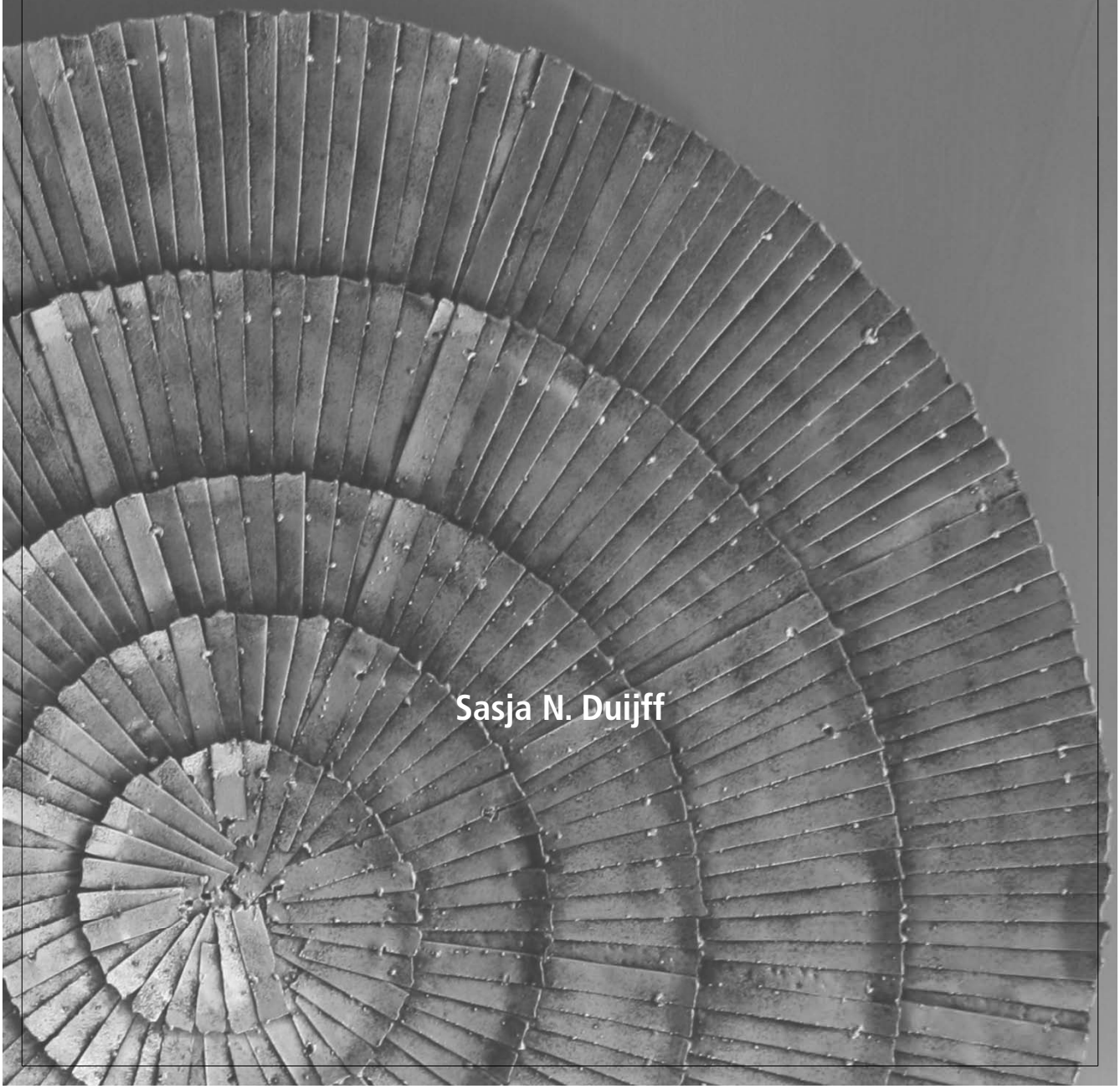
The cognitive development of children with the 22q11.2 deletion syndrome



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The cognitive development of children with the 22q11.2 deletion syndrome

De ontwikkeling van intelligentie in kinderen met het 22q11.2-deletiesyndroom

(met een samenvatting in het Nederlands)

Proefschrift

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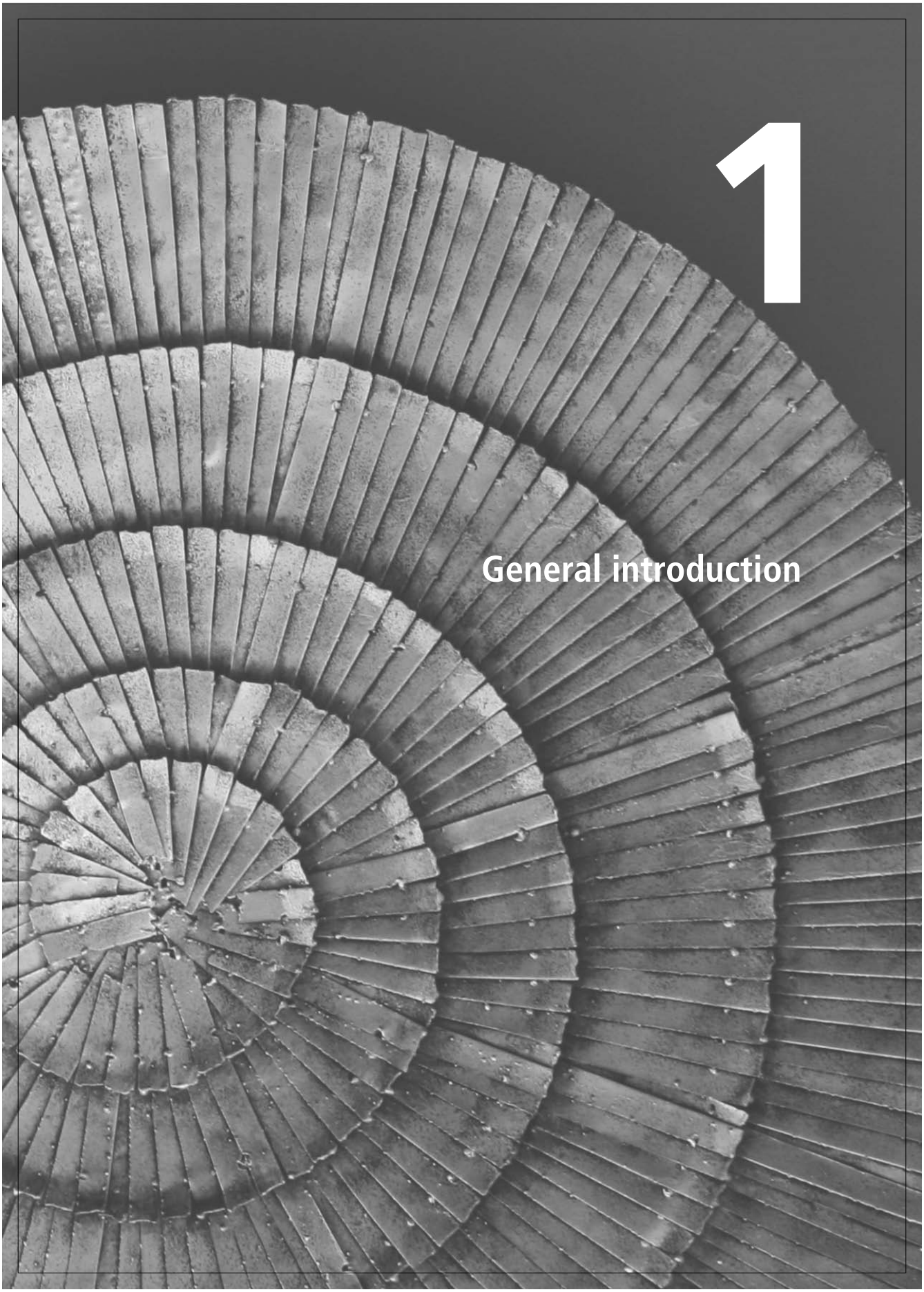

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General introduction

INTELLIGENCE – THE INFLUENCE OF ENVIRONMENT AND GENES

'Intelligence is the ability to acquire knowledge, to think and reason effectively and to deal adaptively with the environment'.[1] Intelligence or general cognitive ability plays an important role in the development of a child and his or her successful adaptation in the world. It is also one of the determinants of how a child will function as an adolescent and as an adult. A way of quantifying and assessing the level of intelligence is by use of developmental tests in younger children and intelligence tests in older children (and adults). Intelligence tests are a useful way of gaining insight into a child's level of functioning; it is important to know when a child is gifted, but also when a child has a learning disability. Based on the test results, for example, school choices and adjustments in home and/ or school environment can be made. Psychometric level of intelligence (IQ) – as measured by tests – is considered to be a highly stable trait in time in both children and adults.[2-5]

It is known that both genes (nature) and environment (nurture) influence IQ and cognitive development. Examples of early environmental factors are maternal infections and alcohol or drug abuse by the mother, which can all be of influence on a developing foetus. After birth, environmental factors such as family (which is also in part nature) and education can influence the development of intelligence, both positively and negatively. Studies have shown that general intelligence correlates with the social economic status of the parents and school attendance can raise IQ while lack of attending can have a negative influence.[1] Some environmental factors can be influenced, others less so. The influence of genes on intelligence is a factor beyond our control. Longitudinal twin studies have shown that, in time, the influence of genes on intelligence increase while the influence of environmental factors decreases.[6,7]

It is becoming increasingly evident that in some cases learning disabilities have an underlying genetic cause and are part of a congenital syndrome. After recognizing the genetic cause of syndromes, research has started to focus on determining syndrome-specific characteristics.[8] Aside from more or less specific physical characteristics, syndromes can also have distinctive behavioural patterns (also known as behavioural phenotypes) and distinctive profiles of intellectual functioning (known as cognitive phenotypes). Whereas intelligence is considered to be a highly stable construct in time in normally developing children, the cognitive development of children with a genetic syndrome is less predictable. In some syndromes a slowing in the rate of acquisition of skills with age and a decline in IQ is reported. Children may 'grow into deficit', meaning that they progress cognitively, but not fast enough to keep in track with the age appropriate cognitive demands.[9-11]

22q11.2 deletion syndrome

One of the syndromes that can result in a learning disability is the 22q11.2 deletion syndrome (22q11DS), also known as Velocardiofacial syndrome (VCFS), DiGeorge- or Shprintzen syndrome. It is caused by a deletion of the long arm of chromosome 22, band 11, subband 22. The syndrome has an estimated prevalence of 1 in 4000 births,[12] resulting in 40–50 newborns per year in The Netherlands and it equally affects males and females. It is an autosomal dominant inheriting syndrome, meaning that if one parent has the syndrome, every child has a 50% chance of inheriting it. However, in approximately 90% of cases the deletion is a 'de novo' mutation only present in the child, while the parents have normal chromosomes and are unaffected.[13-15] The main physical manifestations of the syndrome include velopharyngeal insufficiency (VPI) (a condition resulting in the improper closing of the soft palate muscle, thereby allowing air to escape through the nose instead of the mouth during speech), cleft palate, cardiac defects and characteristic facial features such as a broad nose tip, almond shaped eyes, and long fingers. In addition to these most frequently found characteristics, there are numerous other, less frequently occurring symptoms of 22q11DS which can be related to almost every organ or system of the body.[16]

At the Wilhelmina Children's Hospital, University Medical Centre of Utrecht, the clinical importance of 22q11DS was first recognized in the early eighties by Frits A. Beemer, clinical geneticist, and Josien A. Heineman-de Boer,[17] clinical psychologist. They were involved in the clinical care and research of these patients and in 1999 they wrote the first national guidelines for the management of 22q11DS patients.[18] Together they also initiated the systematic collection of data within this group, part of which are described in the current thesis.

It is thought that 22q11DS is still an underdiagnosed syndrome, mainly due to the fact that clinical symptoms can be very subtle (few facial features, slight hypernasality). Several parents of children with 22q11DS have only been diagnosed with 22q11DS after their child was diagnosed. However, clinical awareness of the syndrome is growing and has recently also resulted in International Guidelines.[19]

Besides the various physical aspects of the syndrome, 22q11DS also has cognitive and behavioural/ psychiatric consequences. At the start of this study in 2000, it was already becoming clear from research that the cognitive characteristics (or phenotype) of 22q11DS were characterized by a delay in speech/ language- and cognitive development, as also often seen in other genetic disorders.[9,10] A mean intelligence quotient (IQ) ± 1 standard deviation of 70–80 (± 15) was reported, with older children performing less well than younger children.[20,21]

On a behavioural/ psychiatric level, children with 22q11DS are at an increased risk for various psychiatric problems, including Autism Spectrum Disorders (ASD), Attention Deficit/

Hyperactivity Disorder (ADHD), various anxiety disorders and psychotic disorders.[22-31] During adolescence and early adulthood, up to 30% of patients develop schizophrenia compared to about 1% in the general population. In 2000, Shprintzen suggested that: '*…understanding the relationship between the learning- and psychiatric disorders associated with VCFS is critical to solving the relationship between the genotype and the phenotype of the syndrome.*'[32]

Objective of the study

At the start of this thesis in 2000, literature on the *systematic* examination of the cognitive development of children with 22q11DS was still scarce and reports were largely based on cross-sectional data with small patient groups and wide age ranges. Therefore the objective of this study was to go 'back- to-basics' by focusing on the systematic gathering and analysis of the cognitive and behavioural development of children with 22q11DS by assessing them at set ages. The focus of this thesis is the cognitive aspect of 22q11DS, behavioural aspects are incorporated where necessary.

Research question

The main research question for this thesis was: how do children with 22q11DS develop cognitively from early childhood (3 years) into adolescence (15 years)? In particular we focused on stability of IQ as children age, the relationship between IQ and behaviour and the influence of potential confounders such as gender, heart conditions, origin of deletion and level of parental education on IQ.

Methodology

The study was designed as a prospective, longitudinal study as the interest was on the individual cognitive and behavioural development of children with 22q11DS. This information can only be collected by reassessing the same children. For this study, parents/ caregivers were able to enlist their children in the study at any age between 0 and 15 but children were only assessed at set ages: 1.5, 3.5, 5.5, 7.5, 9.5 and 15.5 years. Data was collected between 2000 and 2011. The study included 281 children with a genetically confirmed diagnosis of 22q11DS. Of these, 122 (43.4%) were male and 159 (56.6%) were female. Due to the study design, numbers of participants vary across the different parts of the study, to be described in the respective chapters.

To gain insight into the development of children we tried to reassess children with the same test, thereby allowing for the best possible comparisons. However, in children, different ages

Table 1.1 Assessment battery of study

Age at assessment (in years)	Developmental test/ Intelligence test	Visuo-motor integration	Behavioural Checklist
1.5	BSID-II-NL		CBCL 1–5 & TRF 1–5
3.5	BSID-II-NL		CBCL 1–5 & TRF 1–5
5.5	WPPSI-R/ SON-R 2.5–7	VMI – Beery	CBCL 1–5 & TRF 1–5
7.5	WISC-III-NL/ WISC-RN	VMI – Beery	CBCL 6–18 & TRF 6–18
9.5	WISC-III-NL/ WISC-RN	VMI – Beery	CBCL 6–18 & TRF 6–18
15.5	WISC-III-NL/ WISC-RN	VMI – Beery	CBCL 6–18 & TRF 6–18 & YSR 11–18

require different competencies, resulting in the use of different tests. Table 1.1 presents the assessment battery used in this thesis.

Outline of the thesis

Chapter 2. In this chapter we described the study of the developmental level of children with 22q11DS at the mean (*SD*) age of 42 months (1.2). As professionals are becoming more familiar with the syndrome, more children are being diagnosed at an early age. The need for understanding the specific challenges young children with 22q11DS are facing, is growing.

Chapter 3. The purpose of the study described in this chapter, was to explore the relationship between intelligence and visual motor integration skills in 5-year-old children with 22q11DS. At this age children are in the early stage of formal education (copying, drawing, writing) and insight into the relations between cognitive and visual motor integration skills is clinically very relevant for accurate interpretation of test results. Also, due to the narrow age range of this study, we were able to provide an insight into the neurocognitive phenotype of 5-year-olds with 22q11DS.

Chapter 4. In this chapter we described the relationship between intelligence level and behavioural problems in children with 22q11DS (age range 5–15 years). There is much debate as to whether the behavioural problems reported are caused by factors such as medical discomfort, facial abnormalities or a lower intelligence, or whether they are independently related to the genetic abnormality ('behavioural phenotype'). In the general population, intellectual disabilities are generally a predictor of behavioural problems. A group of 69 children with 22q11DS was compared with 69 children with craniofacial anomalies (CFA) using the child behaviour checklist (CBCL). The matches between individual children were based on their total IQ scores.

Chapter 5. In the study described in this chapter, we followed the cognitive development of 65 children from the mean age of 5.5 (.2) years to the age of 9.5 (.1). The developmental course of intelligence in young children with 22q11DS is highly relevant given the increased risk of schizophrenia in 22q11DS patients and the observed premorbid decline in cognitive abilities associated with schizophrenia in the general population. If, as literature suggests, cognitive abilities decline with age in 22q11DS children, this implies that one or several genes within the 22q11.2 region are possibly related to cognitive deterioration during childhood. We investigated whether any observed decrease in IQ was due to growing into deficit (when insufficient cognitive development leads to an increasing discrepancy with age-required norms), or rather a result of an *absolute* decline in cognitive capabilities. To this end, both subtest scaled scores (i.e. age specific normative scores) and subtest raw scores (i.e. absolute test scores, prior to age-normative adjustment) were analysed.

Chapter 6. The purpose of the study in this chapter was to investigate the cognitive and behavioural development as children with 22q11DS transit from childhood into adolescence. Fifty-three children with 22q11DS were assessed at age 9.5 years (T1) and 15.3 years (T2). In addition, in about a third of this group (n = 16) intelligence data obtained at age 7.5 years (T0) (from chapter 5) were also available. Once again, both subtest scaled scores and subtest raw scores were analysed.

Chapter 7. In the **Summary and general discussion** the findings of the various chapters of this thesis are integrated and discussed. Also recommendations for future psychological care of children with 22q11DS as they develop are discussed.

Abbreviations used

22q11DS	22q11.2 deletion syndrome
CBCL	Child Behaviour Checklist
TRF	Teacher Report Form
IQ	Intelligence Quotient
FSIQ	Full Scale IQ
PIQ	Performance IQ
VIQ	Verbal IQ
WPPSI	Wechsler Pre-school and Primary Scale of Intelligence-Revised
WISC	Wechsler Intelligence Scales for Children
BSID	Bayley Scales of Infant Development
VMI Beery	(Beery test of) Visual-Motor Integration

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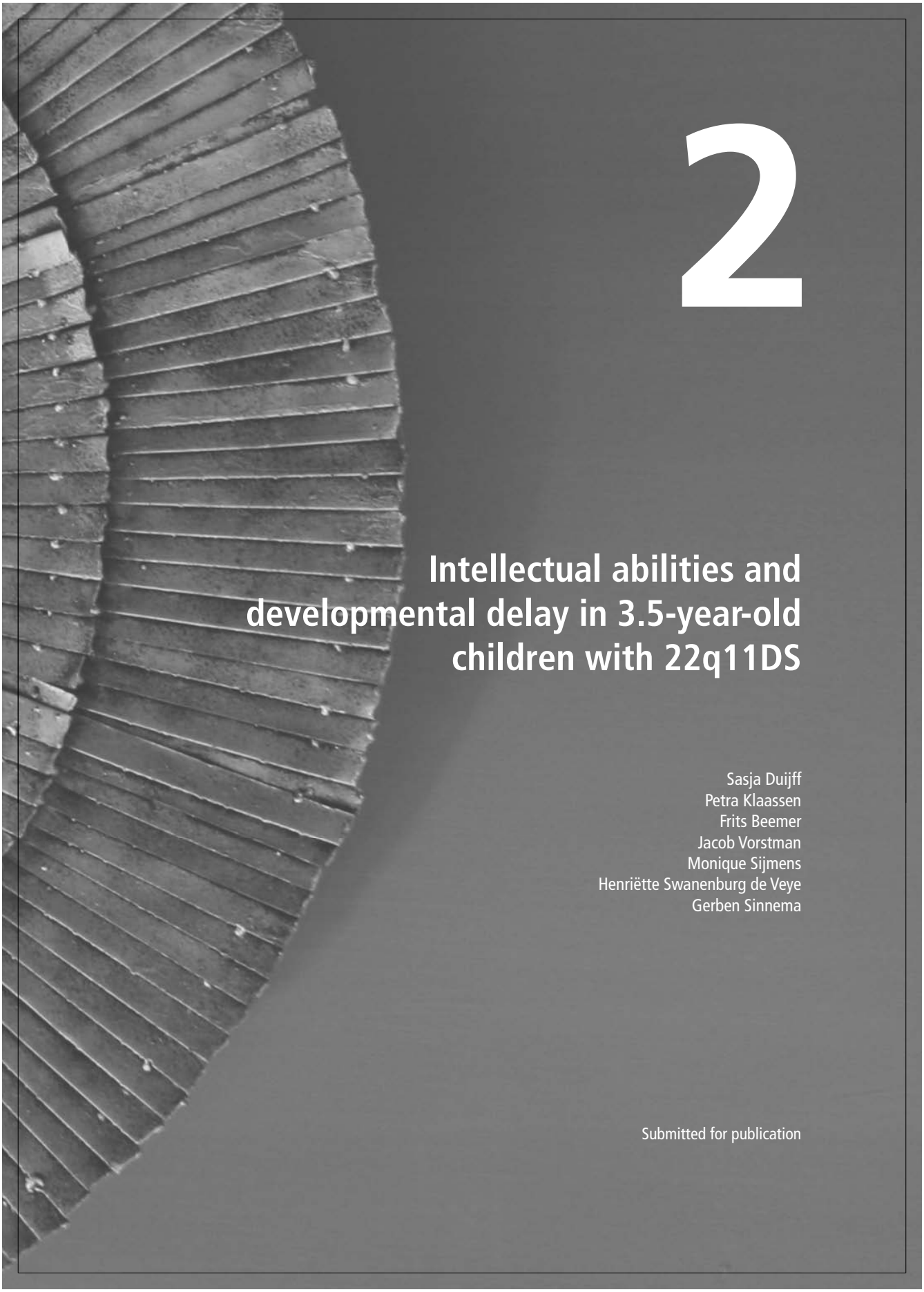

2

Intellectual abilities and developmental delay in 3.5-year-old children with 22q11DS

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ABSTRACT

Background: Developmental reports on young children (< 4 years) with 22q11.2 deletion syndrome (22q11DS) are limited and are characterized by wide age ranges or retrospective data. The purpose of this study was to investigate the intellectual abilities of 3.5-year-old children with 22q11DS and to identify related variables.

Method: The intellectual abilities of 34 children, mean (*SD*) age 42 months (1.2 months; age range 38.6–44.6 months) were examined with the Dutch Bayley Scales of Infant Development (BSID-II-NL).

Results: At time of assessment 24 children had language and speech delays, 5 were not speaking. A mean (*SD*) mental developmental index (MDI) of 61.8 (12.0) was found, with 15/25 children scoring below 55, indicating at least moderate delays. Mean mental delays ranged from 1.7 months – 30 months; a mean (*SD*) mental delay of 9.2 (6.4) months was found ($N = 34$). Girls performed significantly better than boys. A mean (*SD*) psychomotor delay of 9.0 (4.3) months was found ($N = 18$), with no gender differences. No significant predictors of delay (gender, familial deletion, cardiac anomalies) were found.

Conclusion: The results of this study show that a 3.5-year-old with 22q11DS and a mental delay between 6.9–11.4 months is developing in a way comparable to 95% of other children with 22q11DS. As such, this might be reassuring for parents although early intervention is advised. If the delay exceeds this range, extra attention is needed to exclude other possible causes contributing to the delay.

INTRODUCTION

22q11.2 deletion syndrome (22q11DS), also known as Velocardiofacial syndrome (VCFS) or DiGeorge syndrome, has an estimated incidence of 1 in 4000 live births.[1] In most cases the deletion occurs spontaneously (de novo); a recent study on a sample of 103 children reported a prevalence of 11% of a familial deletion.[2] Inherited in an autosomal dominant pattern the main physical manifestations of the syndrome include velopharyngeal insufficiency (VPI) with or without cleft palate, congenital cardiac defects and characteristic facial features. In addition, almost every organ or system can be affected.

Studies of the cognitive profile of older, school aged children report mild to moderate learning difficulties with IQ scores in the borderline to low-normal intelligence range (70–85).[2,3] Within this group, children with a familial deletion are reported to show greater developmental delays than children with a de novo deletion. Studies on gender differences remain inconclusive. In a recent study however, gender differences were found with girls performing significantly better than boys.[4]

Children with 22q11DS can also show various developmental problems at a young age. Feeding disorders and delayed mental and motor development are reported. Mild to significant delays in speech and language are found in most children.[5,6] Only a few studies have investigated the intellectual abilities of young children (< 4 yrs) with 22q11DS. Gerdes et al. reported on the cognitive development of a group of toddlers (n = 55) aged 13-42 months; the mean age and *SD* of this group was not mentioned. 5 Speech and language delays were reported in all 55 children and intellectual abilities assessed with the Bayley Scales of Infant Development (BSID-II) showed a mean mental developmental index (MDI) of 67 (*SD* = 15). Of this group, 20% performed in the average range (within 1 *SD* of the mean), the remaining participants showed a mild (between 1–2 *SD* below the mean) to significant delay (more than 2 *SD* below the mean). Swillen et al. reported on the cognitive spectrum of 13 children aged 1–47 months, using the Bayley Developmental Scales (BOS 2–30) or the McCarthy Developmental Scales.[7] The participants IQ scores ranged from normal to moderate mental retardation. In 5/13 cases an IQ score was not mentioned. Another study on early motor development in 11 children with 22q11DS and conotruncal heart defect (age range 24–58 months) reported a mean MDI of 78, as measured with the BSID-II.[8] In a study on language development from 6–30 months in 4 children with 22q11DS, Scherer et al. used the BSID-II.[9] They found that the children actually showed a decline in MDI when measured at 6, 18 and 30 months, suggesting a progressive delay in development.

As professionals are becoming more familiar with the syndrome, more children are being diagnosed at an early age. The need for understanding the specific challenges facing young

children with 22q11DS is growing. Information on the intellectual abilities of young children with 22q11DS is still scarce and the information that is available is based on wide age ranges and/ or based on retrospective data.

This study focuses on intellectual abilities in children with 22q11DS aged 3.5 years. The study aims to describe the intellectual abilities of children at this age based on developmental assessments and parental reports. The main questions to be answered are:

1. When assessed with BSID-II-NL, how does the development of 3.5 year olds with 22q11DS compare to published norms?
2. Are gender, the presence of a familial deletion, parental level of education or a cardiac anomaly predictive of intellectual abilities of children with 22q11DS at 3.5 years of age?

METHODS

Participants

Participants were recruited through referrals from genetic counselors, cleft clinics and/ or pediatric cardiologists from hospitals throughout The Netherlands; others learned of the study through postings on the website of the Dutch parent support group VCFS/ 22q11. Participants had a 22q11.2-deletion as confirmed by FISH analysis (fluorescence in situ hybridization); this was the only criterion for inclusion in the study. The assessment protocol was approved by the Dutch Central Committee on Research involving Human Subjects (C.C.M.O.) and is part of an ongoing national study on intelligence and behavior in children with 22q11DS. Written informed consent was obtained from all parents or guardians. The demographics of the 34 3.5 year old children involved in this study are presented in Table 2.1. The data were collected over a period of 5.5 years.

Parental education

Parents were asked to report on the highest level of education attained and were categorized according to the International Standard Classification of Education (ISCED) as designed by UNESCO.[10] In the general Dutch population 27% of men and 24% of women have completed higher 'tertiary' education.[11]

Table 2.1 Characteristics of children with 22q11DS (*N* = 34)

Characteristic	
Gender (male/ female)	17/17
Age range in months	38.6–44.6
Mean age in months (*SD*)	42.0 (1.2)
Birth	
At term (38–42 weeks)	28 (82%)
> 2 weeks early	5 (15%)
Missing	1
Average birth weight in kg (*SD*)	3.1 (.5)
Age at diagnosis	
< 1 years	22 (65%)
1–2 years	4 (11%)
2–3 years	6 (18%)
3–4 years	2 (6%)
Familial deletion (%)	3 (8.8%)
Physical impairments	
Cardiac anomalies	22 (65%)
Velopharyngeal Insufficiency (VPI)	6 (18%)
Submucous cleft palate	3 (9%)

Measures

The children were assessed with the Bayley Scales of Infant Development, second Dutch edition (BSID-II-NL).[12] The BSID-II-NL is a standardized and norm-referenced instrument for evaluating the general development of children between the (developmental) ages of 1–42 months. It yields a Mental Developmental Index (MDI) and a Psychomotor Developmental Index (PDI) with a mean of 100 (*SD* = 15) or a developmental equivalent. Above the age of 42 months and 15 days only a developmental equivalent can be reported.

The BSID-II-NL is the Dutch translation of the American BSID-II. The reliability of the mental and psychomotor scales of the BSID-II-NL has been found to be sufficient to high in every category by the authors.[13] Construct validity could only be determined for the group of children older than 30 months.

The BSID-II-NL items are clustered in age groups. When administering the test the child starts in its own age group unless the assessor has reason to believe that a younger age group should be chosen because of known disabilities. If a child is unable to obtain a certain amount

of correct answers (< 8 items for mental scale; < 5 items for psychomotor scale), the assessor 'steps down' an age group and administers the items belonging to that age group until enough items have been scored correctly.

Procedure

The BSID-II-NL was administered individually in the morning in the Department of Pediatric Psychology at our hospital. The test duration ranged from 60–75 minutes. All 34 children were administered the items assessing mental development; 18 children were also able to complete the psychomotor developmental scale. In the other cases the administration of the mental scale took too long and/ or was too tiring, making it impossible to also assess the psychomotor development in the same session. Parents and children participated from all over the country, which often made it difficult to make a second appointment.

Analyses

All statistical analyses were conducted with SPSS version 12.0.1. MDI, PDI and the amount of mental and psychomotor delay were summarized using descriptive statistics. The relationship between developmental (mental) delay in months and gender was assessed by use of the Mann-Whitney test. The relationship between psychomotor delay in months and gender was also assessed by use of the Mann-Whitney test. A univariate analysis of variance was used to test the effect of gender and age at assessment on mental delay. A chi-square test was used to check if the number of familial deletions found in the group was representative of that found in literature. Multiple regression analyses were used to investigate possible underlying variables contributing to the amount of delay.

RESULTS

The participants were 34 children with a mean (*SD*) age of 42.0 months (1.2; age range 38.6–44.6 months). At the time of assessment 24 children were reported by their parents to have some form of speech or language delay, 5 children were not speaking.

MDI and mental delay

MDI could be reported for the 26 children who were younger than 42.5 months (mean age 41.5; *SD* = 0.9) at time of assessment. The results of this group are shown in Table 2.2. Of this group, 15 children (58%) had an MDI < 55, indicating at least moderate delays. The amount of mental delay expressed in months could be reported for the whole group (*N* = 34). The results are presented in Table 2.3, mean delays ranged from 1.7–30.2 months. On average boys showed a significantly greater delay than girls (*U* = 82.00, *p* = 0.031, two-tailed). Despite the narrow age range it was decided to look into a possible effect of age at assessment on the amount of mental delay in boys and girls; no such relationship was found.

PDI and psychomotor delay

On the psychomotor scale PDI scores were available for 15/32 children, as they were younger than 42.5 months at time of assessment (see Table 2.2). The psychomotor delay in months of the group (*n* = 18), when compared to published norms, is shown in Table 2.3 and ranged from 2.9–26.2 months. The difference in gender in psychomotor delay was not found to be significant, *U* = 19.00, *p* = 0.08, two-tailed.

Predictive variables

In 3/32 children a familial deletion was reported, all were boys with a deletion of maternal origin. Of 2 children this information is missing, one child is an adopted child, the parents of the other child have not been screened for the deletion. The number of children with a familial deletion in the group (9%) was comparable to results found in literature ($\chi^2_1 = 0.014$, $p = 0.91$). Children with

Table 2.2 Mean MDI and PDI in 3.5-year-old children with 22q11DS as a group and by gender

	Group				Girls				Boys				
	n	Mean	*SD*	95% CI	*n*	Mean	*SD*	95% CI	*n*	Mean	*SD*	95% CI	*p*
MDI	26[1]	61.8	12.0	57.0–66.7	11	66.7	15.0	56.6–76.8	15	58.2	8.0	53.8–62.6	0.043*
PDI	15[2]	77.9	13.0	70.7–85.1	8	84.9	13.1	73.9–95.8	7	70	7.7	62.9–77.1	0.012

*$p < 0.05$ (difference between girls and boys)
MDI = mental developmental index; PDI = psychomotor developmental index
[1] 15 children have MDI < 55 (4 girls, 11 boys)
[2] 1 child has PDI < 55

Table 2.3 Mean mental and psychomotor delay (in months) in 3.5-year-old children with 22q11DS as a group and by gender

	Group				Girls				Boys				
	n	Mean	*SD*	95% CI	*n*	Mean	*SD*	95% CI	*n*	Mean	*SD*	95% CI	*p*
Mental delay	34	9.2	6.4	6.9–11.4	17	7.5	6.1	4.4–10.6	17	10.8	6.5	7.5–14.2	0.031*
Psychomotor delay	18	9.0	4.3	6.9–11.1	11	7.8	5.1	4.4–11.2	7	10.8	1.6	9.3–12.3	0.077

* $p < 0.05$ (difference between girls and boys)

a familial deletion showed a mean (*SD*) delay of 13.6 (4.6) months (95% CI, 2.3–24.9) compared to a mean (*SD*) delay of 8.6 (6.6) months (95% CI, 6.1–11.2) in children with a de novo deletion. This difference was not found to be significant ($U = 14.50$, $p = 0.06$, two-tailed).

Cardiac anomalies were found in 22 of 34 children and included tetralogy of Fallot, ventricular septal defect and interrupted aortic arch. Children with a cardiac anomaly showed a mean (*SD*) mental delay of 9.7 (5.8) months (95% CI, 7.1–12.3) compared to a mean (*SD*) mental delay of 8.2 (7.5) months (95% CI, 3.4-13.0) in children without a cardiac anomaly. This difference was not found to be significant ($U = 94.5$, $p = 0.18$, two-tailed).

To assess the predictive value of the variables on the amount of mental delay we performed multiple regression analyses. The presence of a familial deletion (versus de novo) was not found to be significant in predicting mental developmental delay. The presence of a cardiac anomaly was not found to be predictive of mental delay. Within the group 41% of the fathers and 33% of mothers completed higher 'tertiary' education. Parental level of education was not found to be a predictor of mental delay (data not shown).

BSID-II-NL item analysis

From a more exploratory perspective we were interested in which items on the mental scale children with 22q11DS did well on and which posed more difficulties. To be assessed within their own age group (38–42 months) children had to obtain a minimum of 8 correct items as designated by the test manual. Only 17 out of 34 children (50%) met these minimum requirements: the analysis of the items will therefore yield more information on what the children as a group cannot do than on what they can do. Two children had a significant impairment, consistent with mental delays of 31 months and 28 months respectively; in item analysis there was no overlap in items with the other 32 children. Table 2.4 provides an insight into those items that posed a problem the group.

Table 2.4 Items in oldest age group of the BSID-II-NL (38–42 mo) that were too difficult (*n* = 32). Included is the normative age.

Item	*N* correct (%)	Item description	Difficulty in months
157	10 (31)	Counts (1-to-1 correspondence)	33;3
152	8 (25)	Repeats 3 number sequences	36;3
159	8 (25)	Counts (stable number order)	38;2
160	7 (22)	Remembers sequence	> 40
163	6 (19)	Discriminates sizes	36;0
164	6 (19)	Counts (cardinality)	> 40
148	6 (19)	Uses past tense	42;2
153	6 (19)	Understands 4 prepositions	36;3
158	6 (19)	Understands another's perspective I	> 40
169	5 (16)	Finds most direct route on map	> 40
171	5 (16)	Picks up 2 friends on map	39;2
174	5 (16)	Classifies objects	> 40
167	4 (13)	Relates temporal sequence of events	> 40
170	3 (9)	Finds alternate route on map	39;3
168	2 (6)	Completes pattern	> 40
175	2 (6)	Counts (order invariance)	> 40
172	1 (3)	Understands another's perspective II	> 40
176	1 (3)	Builds steps	> 40
178	1 (3)	Solves bridge building problem	> 40
173	1 (3)	Builds T	> 40
177	0 (0)	Comprehends congruent and incongruent tasks	> 40

DISCUSSION

In the first years of life there are large individual differences amongst children, including the age of attainment of various developmental milestones. These individual differences can fall within the normative range, or point to maturational lags or to developmental disabilities; the distinction, however, is not necessarily easy to make.[14] As early child development is complex and progresses rapidly, studies should focus on homogeneous age groups. There are only a few studies that have reported on the developmental status of young children with 22q11DS; wide age ranges or the use of retrospective data characterizes those that have. The purpose of this study was to investigate the intellectual abilities of 3.5-year-old children with 22q11DS and to identify related variables within this group of children. All participating children were assessed at 42 months (± 3 months). Results were checked for effects of age at time of assessment; no effects were found due to the narrow age range.

The first question to be answered was: when assessed with BSID-II-NL, how does the development of 3.5 year olds with 22q11DS compare to published norms? It was found that

15/25 children had an unspecified MDI < 55, indicating at least moderate delays. These results are not comparable to other studies of older, school-aged children with 22q11DS, suggesting that this severe delay at a young age might in fact be caused by variables that are less influential at an older age. Considering the fact that 83% of the children in our study had some form of language or speech delay at time of assessment, it seems safe to say that this has probably influenced their performance on verbal items, which in turn influences their results. The BSID-II is useful as a general measure for development but it would be advisable to combine it with a test that measures verbal abilities when assessing children older than 30 months; below the age of 30 months it is possible to measure non-verbal abilities in children with this test.

The second question focused on possible underlying variables associated with the intellectual abilities of children with 22q11DS at 3.5 years of age. Girls performed significantly better than boys on the mental scale. This is in concurrence with the recent results of Antshel et al. who reported on a group of 90 children with 22q11DS, albeit in an older age group (age range 6–15 yrs).[4] It is our clinical impression that the boys involved in the study had more difficulty concentrating, were more distracted and less compliant. Further research would have to confirm this impression. Interestingly enough, no gender differences were found in delay on the psychomotor scale. This could however also be the result of the size of the group (18/32).

The presence of a familial deletion in a child was not found to be predictive of a larger mental delay than in children with a de novo deletion; this is unlike results of earlier studies.[2,15] These results must however be interpreted with caution, considering the small sample size (3/32).

In contrast to De Smedt et al., the level of education of either one of the parents was not found to be predictive of the amount of mental delay.[2] A possible explanation could be that our sample size was smaller. In accordance with other findings the presence of a cardiac anomaly was not found to be predictive for a cognitive delay in our group of children with 22q11DS.[2,15,16]

The BSID-II is a test that can be used for children aged 1–42 months. Above the age of 42 months 15 days the test can still be used for children with developmental delays, but in those cases only a developmental equivalent can be reported. In our study the children were at the upper age limit for this test. Standard psychological practice discourages the use of instruments whose lower or upper age limits are close to the age of the child. In normally developing children this could result in a ceiling effect with an underestimation of the child's true ability. However, in our study all children showed a developmental delay, thereby remaining far from this ceiling. An inventory of the administered items of the mental scale of the BSID-II-NL resulted in a series of items which proved to be too difficult for children with 22q11DS, when ideally it would also have resulted in an impression of the childrens' strengths. This is the result of the

assessment protocol of the test, in which meeting minimum requirements within an age group suggests mastered capabilities of an earlier age group. It is the authors' clinical impression however that children with 22q11DS often have not yet mastered all of these earlier skills. A consequence of this protocol is that these children are at risk of being overestimated in their abilities. Results of the current study suggest that the BSID-II-NL assessment protocol should be adjusted for children with 22q11DS. It seems best in the case of these children that more items are assessed, without the restriction of age groups, allowing for a more accurate insight into the developmental milestones of children with 22q11DS and the consequences for later intellectual and social functioning.

CONCLUSION

The current study stresses the importance of working with homogenous age groups when reporting on a complicated syndrome such as 22q11DS. As far as authors can tell, there are no reports on the amount of developmental delay expressed in months in children with 22q11DS. In young children this is important information, especially for practitioners when communicating with parents. This study shows that all children with 22q11DS show mental and psychomotor delays when compared to published norms.

The development of children with 22q11DS should be closely monitored, preferably at set ages, in order to offer parents and professionals the best possible insight. Our study also suggests that the BSID-II offers a suitable framework for assessment but requires an adjusted protocol. Developmental norms for children with 22q11DS are warranted.

It will be interesting to see if the current results are predictive of future mental and psychomotor functioning; as research into 22q11DS continues this will hopefully become apparent.

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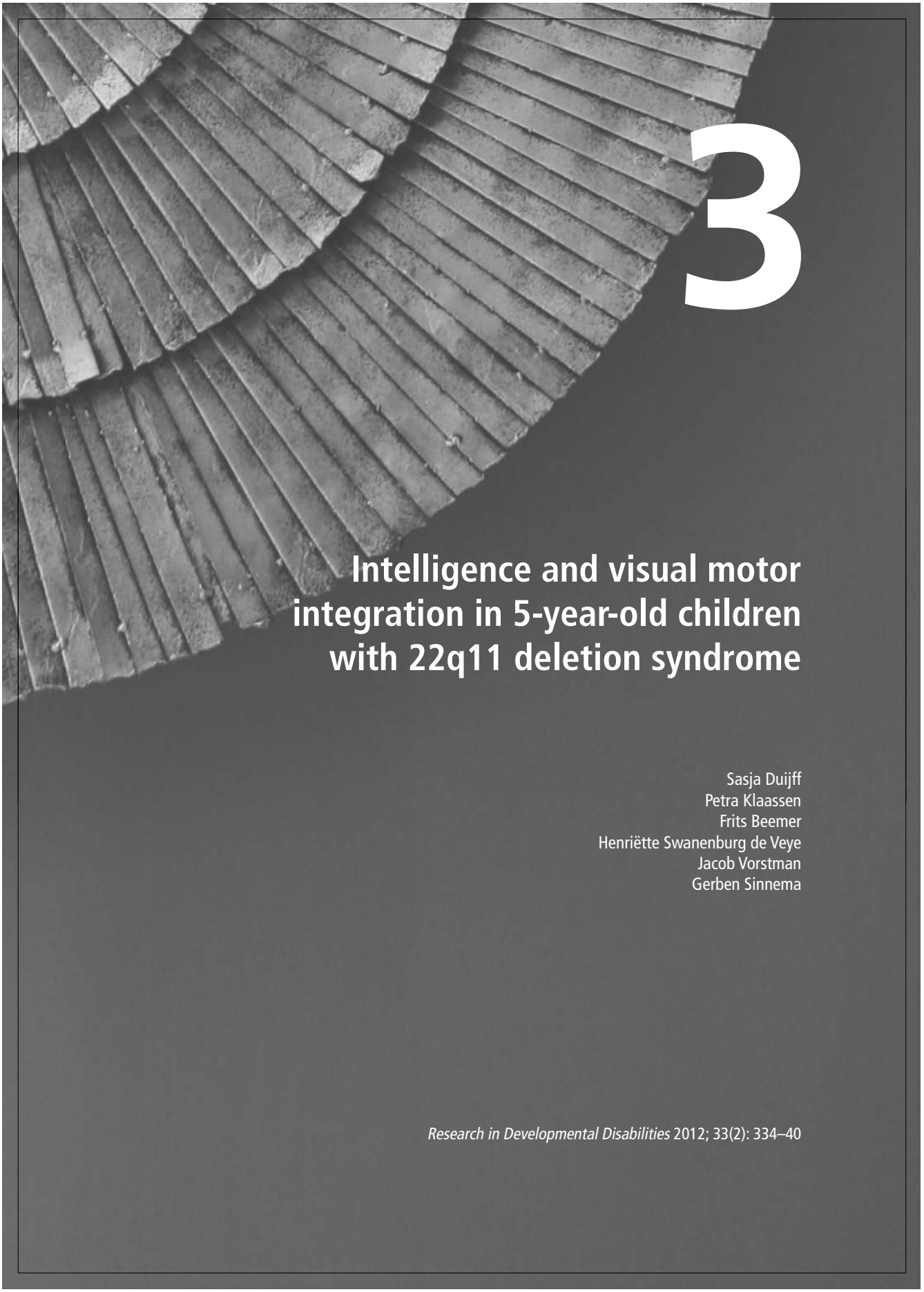

3

Intelligence and visual motor integration in 5-year-old children with 22q11 deletion syndrome

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ABSTRACT

The purpose of this study was to explore the relationship between intelligence and visual motor integration skills in 5-year-old children with 22q11 deletion syndrome (22q11DS) (N = 65, 43 females, 22 males; mean age 5.6 years (SD = 0.2), range 5.23–5.99 years). Sufficient VMI skills seem a prerequisite for IQ testing. Since problems related to these skills are reported in children with 22q11DS, weak VMI skills may contribute to the lower than average IQ scores commonly reported. To investigate if the correlation of VMI and IQ score was mainly influenced by problems with visual perception skills (VP), motor coordination skills (MC) or difficulties with the integration of both skills (VMI), a subgroup (n = 28) was also administered the *Beery VMI* supplemental developmental tests. Due to the narrow age range of this study, we were also able to provide an insight into the neurocognitive phenotype of 5-year-olds with 22q11DS and the influence of gender, heart disease and origin of deletion on this phenotype. Results show a mean full scale IQ (FSIQ) = 73.0 (SD = 10.4) and mean VMI = 86.2 (SD = 8.4). A significant correlation between FSIQ and VMI was found (r = .45, p = .000), with most variation (26%) explained in the performance IQ score ((PIQ), r = .51, p = .000). VP correlated significantly with FSIQ (r = .44, p = .01) and PIQ (r = .49, p = .004). MC was not significantly correlated with IQ (FSIQ, r = .21, p = .15; PIQ, r = .28, p = .07), suggesting that problems with motor coordination do not influence results on IQ-tests in a significant way at this age. Girls scored significantly higher on FSIQ and PIQ than boys; cardiac anomalies were not predictive of FSIQ or VMI scores. The results of this study suggest a characteristic neurocognitive phenotype for 5-year-olds with 22q11DS. Deficiencies in visual perception and/or processing are negatively correlated with IQ scores, whereas deficiencies in motor skills do not have a relevant negative impact at this age. These findings provide further insight into 22q11DS specific neurocognitive deficiencies.

INTRODUCTION

The 22q11 deletion syndrome (22q11DS) is a genetic syndrome with a supposed incidence of 1 in 4000 live births.[1,2] It is also known as Velocardiofacial syndrome (VCFS), DiGeorge syndrome or Shprintzen syndrome. In 90% of cases the deletion occurs de novo, in 10% the deletion is passed on as an autosomal dominant trait. 22q11DS is characterized by a wide range of features. Common physical manifestations include velopharyngeal insufficiency with or without cleft palate, cardiac anomalies and a characteristic facial appearance.[3]

Psychiatric diagnoses are frequently reported and include autism spectrum disorders and attention deficit/ hyperactivity disorder; children are also at an increased risk of developing psychotic symptoms and schizophrenia in adolescence.[4-8] Also behavioral problems in childhood are often reported.[9,10] Neuropsychological characteristics of children with 22q11DS include an overall delay in cognitive development and IQ scores in the range of 70–85.[11,12] Significant differences between verbal and performance IQ (in favor of verbal IQ) are repeatedly reported.[5,11,13] Research into the factors contributing to variability in IQ in 22q11DS focus on gender differences, familial versus de novo deletions and medical conditions such as cardiac anomalies. Reports on gender differences are inconclusive and cardiac anomalies are not found to be related with IQ.[11,14] Inheritance of the deletion has been found to have a (negative) influence on IQ.[11] Common to all reports, however, is that the included patients are characterized by broad age ranges.

Motor deficits are another important characteristic of 22q11DS. Difficulties in gross motor skills, hypotonia and difficulties with coordination and balance are reported in young children.[9,15-17] In school children (age 5–17 years) with 22q11DS not only gross but also fine motor deficits are present, such as poor eye-hand coordination and graphomotor deficits.[18-20] Visual-motor integration is an important contributor to those academic skills that require a response on paper (eg, maths, spelling and essays) and requires accurate perception of visual-spatial objects and monitoring one's own movements. Visual-motor integration in 22q11DS as specifically measured by *VMI Beery* has been studied by four authors.[12,18,20,21] Mean *Beery VMI* scores results were reported ranging from more than 2 *SD* below the mean to .5 *SD* below the mean. Two authors also assessed VMI motor coordination, resulting in scores 1.5 *SD* below the mean. One author also investigated Visual Perception skills (mean: -1 *SD*). All authors stressed the possible influence of poor motor skills on the test results and Sobin et al. stress the importance of recognizing these motor deficits in children with 22q11DS for accurate interpretation of a child's performance, both on tests as well as in the classroom.[17] In general, the *Beery VMI* correlates moderately with intelligence tests and shares approximately 25% of variance.[22]

The purpose of this study is to explore the relationship between intelligence and visual motor integration skills in 5-year-old children with 22q11DS. As these children are in the early stage of formal education (copying, drawing, writing), insight into the relations between cognitive and visual motor integration skills is clinically very relevant for accurate interpretation of test results. To avoid too much developmental variability, a narrow age range has been chosen.

The second aim of this study is to analyze the respective roles of visual perception, fine motor coordination skills and /or the (in)ability to integrate both in cognitive performance. Clearly, problems in VMI skills can confound the results on an IQ test if these skills are required but are not yet suitably mastered.

Also, due to the narrow age range of this study, we are able to provide an insight into the neurocognitive phenotype of 5-year-olds with 22q11DS. All current reports on, for example, the influence of cardiac problems, origin of deletion, possible NLD profiles and gender differences on IQ are based on wide age ranges while it is very possible that, as suggested by Sobin et al.: 'in this population the patterns of neurocognitive strengths and weaknesses shift with age; future studies will be needed to accurately characterize the neurocognitive phenotype … at various points of development'.[23]

MATERIAL AND METHODS

Participants

Participants were recruited through referrals from genetic counselors, cleft clinics and/ or pediatric cardiologists from hospitals throughout The Netherlands through postings on the website of the Dutch parent support group VCFS/ 22q11DS. All participants have a 22q11 deletion as confirmed by FISH analysis (fluorescence in situ hybridization). The procedure was approved by the Dutch Central Committee on Research involving Human Subjects (C.C.M.O.) and is part of an ongoing national study on intelligence and behavior in children with 22q11DS. Written informed consent was obtained from all parents or legal guardians.

In the current study age was an inclusion criterion: all children between the age of 5.0 and 5.99 years were included, resulting in 77 children. Five children could not be assessed due to moderate or severe mental retardation (n = 5, all females). Seven children (3 female, 4 male) were unable to speak or speak comprehensibly, these children were assessed with a different, non-verbal intelligence test (SON-R 2.5–7).[24] However, to avoid heterogeneity of assessment tools, these results were not used in the current study. The demographics of our final study

group are presented in Table 3.1. Difference in sex distribution is significant, $p = .006$ (binomial test). Cardiac anomalies were found in 35 children (54%) and included Tetralogy of Fallot, Ventricular septal defect and Interrupted aortic arch. The number of children with a familial deletion (4/63 (6%), 2 missing) was comparable to results found in literature χ^2 (df 1, $N = 63$) = .93, $p = .33$.

Measures

Intelligence

Intelligence level was assessed by the Dutch version of the Wechsler Preschool and Primary Scale of Intelligence-Revised (*WPPSI-R*).[25] The *WPPSI-R* is a battery of tests aimed at intelligence assessment of children aged 4–7 years. The test consists of 2 scales, a verbal scale and a performance scale. The verbal scale measures verbal abilities such as language expression, comprehension, listening, and the ability to apply these skills to solving problems. The questions are given verbally; the child must give a spoken response. The performance scale assesses nonverbal problem solving, perceptual organization, speed, and visual-motor proficiency. The instructions are given verbally but do not require a spoken response. The test yields a score with a mean of 100 and a standard deviation of 15. For the *WPPSI-R* internal consistency ranges from .9 for PIQ to .94 for VIQ and FSIQ.[25]

Table 3.1 Demographics of 5-year-old children with 22q11DS (*N* = 65)

Variable	Incidence (%) (range)
N	65
Age (*SD*)	5.6 years (.2) (5.23-5.99)
Female	43 (66)
Age at diagnosis	
< 1 year	27 (41)
1-2 years	3 (5)
2-3 years	9 (14)
3-4 years	16 (24)
4-5 years	7 (11)
5 years	3 (5)
Origin of deletion	
De novo	59 (91)
Familiar	4 (6)
Missing	2 (3)
Cardiac anomaly (including Tetralogy of Fallot, VSD, ASD and Interrupted aortic arch)	35 (54)

Visual motor integration

Visual-motor integration was assessed with the *Beery-Buktenica Developmental Test of Visual-Motor Integration Short Form* (*VMI*) for children ages 2 through 7.[22] The test consists of 21 items. It is a pencil and paper task in which children are required to copy different geometric forms, organized in a developmental sequence. The test has no time limit but takes 10 minutes on average. It results in a standardized score with a mean of 100 (*SD* = 15).

Visual perception and motor coordination

The *VMI Supplemental Tests for Visual Perception* (*VP*) consists of 30 items. The child is required to visually identify the geometric form that is identical to the stimulus from a group of forms that are not exactly the same. Motor requirements are minimal; the child has to point out the right answer. The task is timed (3 minutes).

The *VMI Supplemental Tests for Motor Coordination* (*MC*) also consists of 30 items and requires the child to trace the geometric forms with a pencil, staying between the double-lined paths. Visual Perceptual demands have been reduced to a minimum. The task duration is 5 minutes. Both *VP* and *MC* result in a standard score with a mean of 100 (*SD* = 15).

The *Beery VMI* is well validated and has sound reliability: .92 (*Beery VMI*), .91 (*VP*) and .90 (*MC*).[22,24]

Assessment

The current study is part of an ongoing prospective study on children with 22q11DS. At the age of 5, all children in our study were assessed (if possible) by use of the *WPPSI-R* and the *VMI Beery*. To investigate if the effect of *VMI* on IQ scores was caused by problems with visual perception skills (*VP*), motor coordination skills (*MC*) or difficulties with the integration of both skills (*VMI*) the children assessed after November 2005 were all additionally administered the *VMI supplemental tests for Visual Perception and Motor Coordination*. This addition was allowed for by an expansion of the longitudinal test protocol.

All assessments were administered individually by a trained mental health professional who held at least a bachelor level degree in her respective field. All measures were administered at the Childrens' Hospital in a special assessment room and were administered in the morning in a set order: *WPPSI-R*, *VMI*, and where applicable *VP* and *MC*.

Calculation

All statistical analyses were conducted with SPSS version 15.0. IQ and VMI scores and all demographics were summarized using descriptive statistics. Differences in scores were checked for significance by use of independent samples *t*-test. Chi-square test was used to check if the proportion of familial deletions and cardiac problems found in the group was similar to that found in literature. Pearson's correlations (one-tailed) were used to investigate the correlations between *WPPSI-R*, *VMI*, *VP* and *MC* test results. Linear multiple regression was performed to test the effect of the variables (gender, cardiac anomalies, origin of deletion) on IQ and *VMI* while controlling for the effect of the other variables. All correlations were Bonferroni corrected.

RESULTS

IQ and VMI

Mean IQ and *Beery VMI* results of the group ($N = 65$) as a whole and by gender are presented in Table 3.2. Also, the subtest scores are presented by group and gender. Females scored significantly higher on FSIQ and PIQ. Within the performance subtests, girls performed significantly better on the subtest Object Assembly, Block Design and Animal Pegs. There was no gender difference in VIQ scores. A subgroup of 28 children (17 females, 11 males) was additionally assessed with the *Beery VMI* supplemental developmental tests. The results of this subgroup are also presented in Table 3.2. Girls performed significantly better on Motor Coordination.

Pearson correlation results between FSIQ, PIQ and VIQ scores and *Beery VMI* scores are presented in Table 3.3, FSIQ and PIQ correlated significantly with *Beery VMI*. The results of the correlations of the *Beery VMI* with the six *WPPSI-R* Performance subtests are also presented in Table 3.3. Five out of six performance subtests correlated significantly with *VMI*, even after Bonferroni correction. The results of the subgroup ($n = 28$) that was additionally assessed for *VP* and *MC* are also presented in Table 3.3. *VP* correlated more with FSIQ and PIQ than *MC*. Significant correlations for *VP* with 3 out of 6 performance subtests (Geometric Design, Block Design and Picture Completion) were found after Bonferroni correction, whereas *MC* correlated significantly with only 1 subtest (Mazes).

Table 3.2 IQ profile and mean VMI test results in 5-year-old children with 22q11DS (*N* = 65), as a group and by gender

	All			Females			Males			Females:males
	M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*p*-value
FSIQ	73.0	10.4	65	75.0	11.4	43	69.1	6.8	22	**.01**
VIQ	78.8	11.4	65	79.8	12.2	43	76.8	9.5	22	.31
PIQ	71.8	12.0	65	74.6	12.8	43	66.3	7.8	22	**.002**
VMI	86.2	8.4	65	87.1	8.7	43	84.4	7.8	22	.21
Visual perception	81.3	17.9	28	82.1	19.7	17	80.2	15.5	11	.79
Motor coordination	77.8	14.8	28	82.6	13.7	17	70.1	13.8	11	**.03**
Verbal subtests			65			43			22	
Information	7.5	2.6		7.7	2.9		7.1	2.0		.30
Vocabulary	6.3	2.5		6.1	2.8		6.9	1.6		.15
Similarities	7.9	2.5		8.3	2.3		7.1	2.7		.07
Comprehension	5.0	2.7		5.0	2.8		4.9	2.4		.82
Arithmetic	6.2	2.0		6.3	2.0		5.8	1.9		.31
Sentences	5.9	3.2		5.6	3.0		6.4	3.5		.42
Performance subtests			65			43			22	
Object assembly	7.0	2.9		8.0	2.9		5.2	2.1		**.000**
Geometric design	5.2	2.4		5.5	2.5		4.5	2.1		.13
Block design	5.2	2.7		5.7	2.9		4.3	2.2		**.048**
Mazes	5.3	2.8		5.7	2.8		4.6	2.6		.16
Picture completion	6.1	2.5		5.9	2.4		6.4	2.8		.51
Animal pegs	5.8	2.8		6.4	2.8		4.6	2.2		**.014**

Table 3.3 *WPPSI-R* performance subtest Pearson correlations with *Beery VMI* and *VMI* supplemental developmental tests

				Performance subtests					
	FSIQ	VIQ	PIQ	ObA	GD	BD	Mazes	PC	AnP
VMI (*N* = 65)	.45**	.29	.51**	.37*	.65**	.53**	.55**	.35*	.28
VMI visual perception (*n* = 28)	.44	-	.49	.25	.52*	.54*	.36	.51*	-.07
VMI motor coordination (*n* = 28)	.21	-	.28	.26	.42	.04	.50*	-.11	.11

* $p < .004$; ** $p < .001$ (both after Bonferroni correction).
FSIQ = full scale IQ; VIQ = verbal IQ; PIQ = performance IQ; VP = visual perception; MC = motor coordination; ObA = Object Assembly; GD = Geometric Design; BD = Block Design; PC = Picture Completion; AnP = Animal Pegs.

Neurocognitive phenotype and possible confounders

Figure 3.1 shows the distribution of subtest scaled scores on the *WPPSI-R*, thereby providing an insight into the cognitive subtest profile of 5-year-old children with 22q11 DS. The subtest scores by gender are presented in Table 3.2. Children with a cardiac anomaly showed a mean (*SD*) FSIQ of 73.6 (11.9, 95% CI, 69.5 – 77.7) compared to a mean (*SD*) FSIQ of 72.3 (8.4, 95% CI, 69.2 – 75.4) in children without a cardiac anomaly. This difference was not significant $t(63) = -.50$, $p = .62$. Children with a familial deletion showed a mean (*SD*) FSIQ of 63.3 (2.8, 95% CI, 58.9 – 67.6) compared to a mean (*SD*) FSIQ of 74.1 (10.3, 95% CI, 71.4 – 76.7) in children with a de novo deletion. The difference was significant $t(10.9) = 5.6$, $p = .000$. The results were confirmed by linear multiple regression, which indicated that gender was a predictor of FSIQ scores in favour of girls ($p = .003$, 95% CI, -10.53 – -2.33). The presence of a cardiac anomaly was not predictive for FSIQ ($p = .26$, 95% CI, -2.07 – 7.49) and a nonsignificant trend for origin of deletion: ($p = .08$, 95% CI, -18.54 – 1.13) was found. Gender, the presence of a cardiac anomaly and/or origin of deletion were not found to be predictive for VMI scores.

In 26/65 cases (40%; 14 females, 12 males). VIQ exceeded PIQ significantly, by more than 11 points, in 6/65 cases (9%; 5 female, 1 male) PIQ exceeded VIQ by more than 11 points. In 51% there was no significant difference found between VIQ and PIQ.

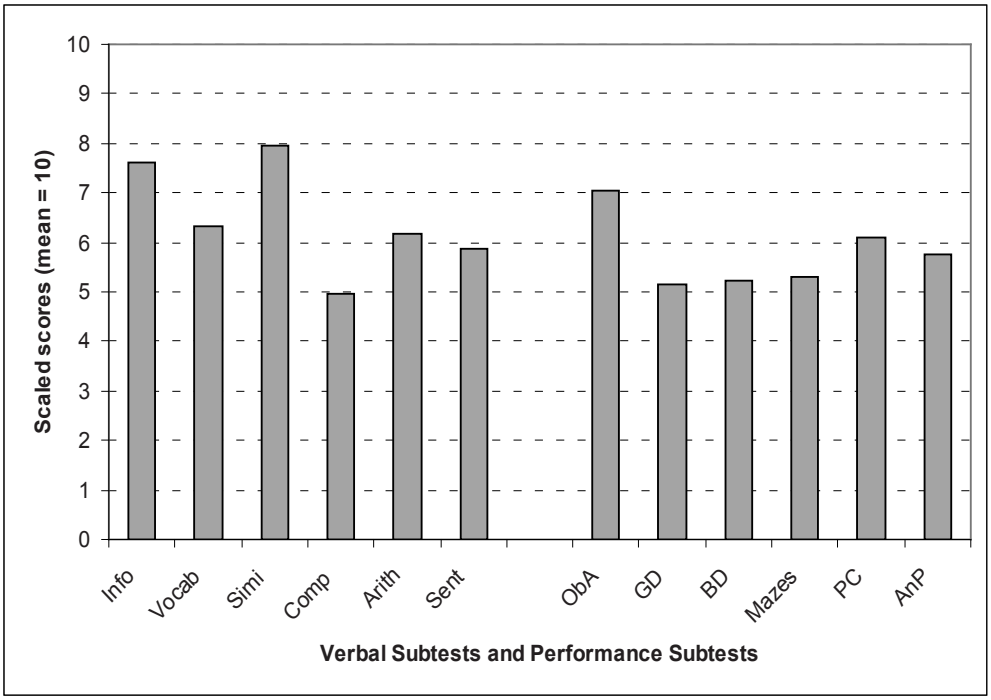

Figure 3.1 *WPPSI-R* profile of 5-year-old children with 22q11DS (*N* = 65).

DISCUSSION

The aim of this study was to examine the influence of visual-motor integration skills on IQ scores in 5-year-old children with 22q11DS. Unlike most studies to date, this study focuses on a very narrow age range to avoid too much developmental variability. In line with our hypothesis, the results indicate that poor visual-motor integration skills are directly negatively associated with FSIQ. Visual-motor integration as measured by the *Beery VMI* and FSIQ as measured by the *WPPSI-R* show a moderate correlation at .1% level for FSIQ, accounting for 21% of variance. This percentage is slightly lower than the findings of Beery & Beery and Sortor & Kulp, who respectively reported 25% and 36% of common variance.[22,26] In our study, this correlation seems largely due to the correlation of the *Beery VMI* with PIQ, which explains 26% of variation, and to a much lesser extent due to the correlation with VIQ, which accounts for only 8% of variation. Our results show significant correlations for 5 out of 6 performance subtests with the *VMI*, suggesting that the *WPPSI-R* and the *VMI* are partly assessing the same underlying neurocognitive skills.

Visual-motor integration as measured by the *Beery VMI* shows a left shift from the mean when compared to published norms, but children with 22q11DS score just within the normal range. We found no differences in scores due to gender; these findings are consistent with those in the general population.[22] Cardiac anomalies and origin of deletion also did not contribute to differences in *VMI* scores. To investigate if the correlation of *VMI* with IQ scores was caused by problems with visual perception skills (*VP*), motor coordination skills (*MC*) or difficulties with the integration of both skills (*VMI*), a subgroup of 28 children was also administered the *Beery VMI supplemental developmental tests*. Surprisingly, results indicated that *MC* was not significantly correlated with IQ (FSIQ, VIQ and PIQ). On the other hand, *VP* was moderately correlated with FSIQ (r = .44) and PIQ (r = .49), accounting for 19% and 24% of variance respectively. Besides the subtest 'Geometric Design', which is a subtest very comparable to *Beery VMI*, the performance subtests 'Block Design' and 'Picture Completion' correlated significantly with both VMI and VP skills, suggesting that children with 22q11DS may actually have difficulty with the analysis and processing of visual information. This suggestion was also made by Bearden et al., who reported impairments in visual-spatial information processing in a group of older children (age range 5–17), although based on a slightly different set of tests.[27]

Our results suggest that in 5-year-old children with 22q11DS, visual-motor integration and visual perception are actually of more influence on the results of some performance subtests than the degree of motor coordination. This differs from other reports on this subject. In previous articles that have focused on motor skills in children with 22q11DS, it was suggested that specifically weak graphomotor control and fine motor coordination contributed to a poorer performance in classroom settings or on tests requiring these skills.[17,23] Lajiness-O'Neill et al. suggested that children with 22q11DS (N = 14, age range 7–17) might have problems at the level of integration of motor and perceptual skills while the visuospatial skills might be somewhat better developed than often reported.[21] Niklasson et al. reported more difficulties in VMI than our study did and attributed the poorer scores to poor fine motor skills whereas Van Aken et al. found comparable results for VMI and VP to our study, but much higher correlations for MC.[12,20] Possibly, the results reported are characteristic for 5-year-olds with 22q11DS.

Due to the narrow age range studied, it was also possible to provide a more accurate neurocognitive phenotype of 5-year-olds with 22q11DS than is available to this date. A mean FSIQ and distribution that are very similar to results reported in literature on larger age ranges, was found. Gender differences were found in FSIQ and PIQ, with girls performing significantly better than boys. This is consistent with some reports yet inconsistent with others.[11,12,14,28] There were significantly more girls than boys in the current study although 22q11DS is not considered gender specific, this overrepresentation is characteristic for the entire

Dutch 22q11DS population as known at our hospital. There is no suitable explanation for this difference as of yet. However, the suggestion by Antshel et al. that the difference in FSIQ (in favor of females) may be the result of age at assessment cannot be confirmed by these sturdy, cross-sectional results.[29] Consistent with literature there were no differences in FSIQ when children with cardiac anomalies were compared to those without.[30] Also, children with a de novo deletion tended to perform significantly better than children with an inherited deletion, as has been described previously.[11] However, it must be noted that the group of children with a familial deletion was very small. In 40% of cases VIQ exceeded PIQ significantly by more than 11 points. Bearden et al. found comparable results for VIQ exceeding PIQ (34%), but no cases of PIQ exceeding VIQ significantly, compared to 9% in our study.[27]

The lack of control group could be considered a limitation of this study. On the other hand, and as mentioned by various authors reporting on patients with 22q11DS, a fitting control group is difficult to define for this group of patients.[12,27]

Our findings suggest that there is a characteristic neurocognitive phenotype for 5-year-old children with 22q11DS that is characterized by weak visual-motor integration skills that negatively affect IQ scores and should be taken into account when interpreting test results. In addition, our results indicate that the analysis of visual information processing appears to be particularly relevant in this context at this specific age, rather than the influence of poor motor coordination. In future research and clinical practice, when assessing a child's capabilities visual motor integration (including visual perception and motor coordination skills) should be part of the standard assessment protocol, to better understand a child's strengths and weaknesses.

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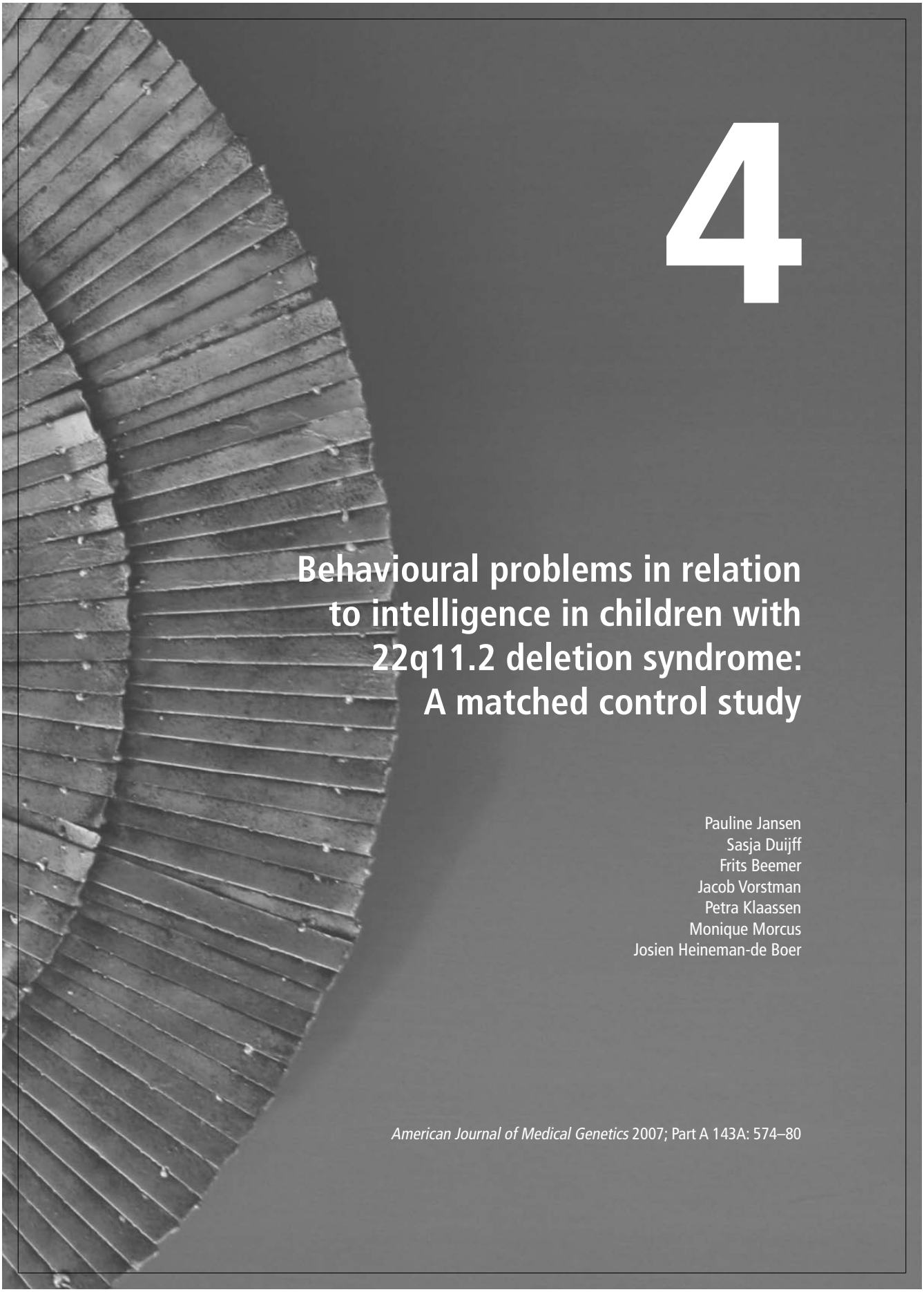

4

Behavioural problems in relation to intelligence in children with 22q11.2 deletion syndrome: A matched control study

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ABSTRACT

The 22q11.2 deletion syndrome (22q11DS) is a genetic disorder associated with palatal abnormalities, cardiac defects, a characteristic facial appearance, learning difficulties, and delays in speech and language development. Various behavioural disorders and psychiatric illnesses have also been reported. There is much debate as to whether the behavioural problems are caused by factors such as medical discomfort, facial abnormalities or a lower intelligence, or whether they are independently related to the genetic abnormality ("behavioural phenotype"). We examined the relationship between intelligence level and behavioural problems. A group of 69 children with 22q11DS was compared with 69 children with craniofacial anomalies (CFA) using the child behaviour checklist (CBCL). The matches between individual children were based on their total IQ scores. Use of the CBCL norm scores covered the corrections for age and sex. The group of 22q11DS children showed significantly more behavioural problems than the CFA group: this was especially apparent on the CBCL subscales "withdrawn", "anxious/depressed", "delinquent behaviour", "aggressive behaviour", "somatic complaints", and "social problems". We found no correlation between IQ score and behavioural problems in the 22q11DS group, which was remarkable because, comparable with the general population, intellectual disabilities were a predictor of behavioural problems in the CFA group. 22q11DS children with relatively higher IQs showed more problems of an internalizing than an externalizing nature, whereas the 22q11DS children with lower IQs showed various behavioural problems. The absence of a statistically significant correlation between intelligence and behavioural problems in the group of 22q11DS children is tentative evidence for a 22q11DS behavioural phenotype.

INTRODUCTION

The 22q11.2 deletion syndrome (22q11DS) is a genetic disorder associated with many characteristics and its clinical expression is wide and variable.[1] The most frequent features are anatomical and/or functional palatal abnormalities, cardiac defects, characteristic facial appearance, learning difficulties, and delays in speech and language development. A variety of behavioural disorders and psychiatric illnesses have also been reported. A study of the influence of physical anomalies on IQ suggested that global delays in development and variations in intelligence were directly associated with 22q11DS and could not be explained by cardiac defects or palatal defects.[2,3] Outcomes of behavioural observations included both inhibition and attention disorders. In a previous study, children with 22q11DS were compared with children with craniofacial anomalies (CFA).[4] The CFA children seemed to be an adequate control group because both 22q11DS and CFA originate early in embryogenesis and are characterized by facial anomalies and medical discomfort. The 22q11DS children showed significantly more behavioural problems than the CFA children. The authors concluded that the behavioural problems could not be explained by such factors as facial anomalies or medical discomfort. They did, however, indicate that their data did not allow for adequate matching of intelligence level. They mentioned that it has been frequently reported that lower intellectual capacities are a good predictor of behavioural problems in the general population, and that it is therefore important to take the influence of intelligence into account when studying behaviour in children with 22q11DS.[5,6]

Only a few studies have focused on the relationship between cognitive capacities and behaviour in children with 22q11DS. A study of 60 children showed that 22q11DS children with an IQ score below 70 had more social-, attention-, and thought problems than those with an average IQ.[7] In a relatively small study of 28 children with 22q11DS and 29 cognitively matched control children, Feinstein et al. found no difference between the two groups in frequency of psychiatric diagnoses and behavioural problems as measured by the child behaviour checklist (CBCL).[8] The purpose of this study was to take into account the influence of intelligence level on behavioural problems and thus complete the study performed by Heineman-de Boer et al.[4] The questions we asked were:

1. Do children with 22q11DS have more behavioural problems than children with CFA?
2. What is the relationship between intelligence level and behavioural problems in children with 22q11DS and in children with CFA?
3. Is the relationship between intelligence level and behavioural problems in children with 22q11DS different to that in children with CFA?

MATERIALS AND METHODS

Patients

The children involved in this study came from a nationwide group of over 170 Dutch children with 22q11DS, as confirmed by FISH. They were reported by medical genetic departments and by child cardiology and cleft palate teams. Members of the Dutch parents' association also referred their children for participation in these psychological assessments. The control group consisted of children with CFA such as craniosynostosis, Apert syndrome, Crouzon syndrome, and Treacher Collins syndrome. They were selectively recruited from two major CFA teams. The children from both groups were individually matched based on their total IQ scores. It was possible to find a match for 69 children of the 22q11DS group. When there was a choice, the match was made at random. In both groups the age varied from 5 to 15 years. There were 23 boys and 46 girls in the 22q11DS group, and 32 boys and 37 girls in the control group.

Psychometric tests

Data on intelligence level was acquired by means of formal IQ tests (Table 4.1). In both groups the Dutch version of the CBCL was completed by the mothers to obtain standardized information about behavioural and emotional problems. This checklist consists of 118 items describing as many behaviours in different circumstances, adding up to a total problems score. The CBCL defines eight syndrome scales of specific problem behaviour: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behaviour, and aggressive behaviour. The results yield the syndrome scores

Table 4.1 Number of children with 22q11DS and with craniofacial anomalies (CFA) studied with various intelligence tests (*N* = 69 for both groups)

	Number of children	
Intelligence tests	22q11DS	CFA
Wechsler preschool and primary scale of intelligence (WPPSI-R)	23	1
Wechsler intelligence scale for children – revised/Netherlands (WISC-RN)	30	12
Wechsler intelligence scale for children – third edition (WISC-III)	6	-
Snijders-Oomen non-verbal intelligence scales 2½–7 (SON-R 2½–7)	10	7
Snijders-Oomen non-verbal intelligence scales 5½–17 (SON-R 5½–17)	-	41
Other tests	-	8

aggregated into groups: an internalizing score (withdrawn, anxious/depressed, and somatic complaints) and an externalizing score (delinquent behaviour and aggressive behaviour). The remaining three subscales (social problems, thought problems, and attention problems) are in the middle. The results of the CBCL are expressed as T-scores, based on Dutch norms for a particular age and gender. The mean of the T-scores is 50 with a standard deviation of 10. Children with a total problems score over 63 or with a T-score of 66 or higher on one of the syndrome scales are classified as scoring in the "clinical range". These scores discriminate between normal and disturbed behaviour.[9,10]

Statistics

Statistical analysis of the results was performed with descriptive statistics, Levene's test for equality of variances, Student's *t*-test, Chi-Square test, Pearson's *r* correlation coefficient and a principal component analysis (PCA).

RESULTS

No differences were found in age and gender between the 22q11DS group and the control group, as measured by a *t*-test ($t = 1.760$; $p = 0.081$) and a Chi-Square test ($\chi^2 = 2.449$; $p = 0.118$). The match based on IQ score was adequate since the *t*-test showed no difference in IQ scores between the two groups ($t = 0.750$; $p = 0.454$).

The CBCL scores in the 22q11DS group and the CFA control group

The frequencies of CBCL scores in the clinical range for both groups are presented in Table 4.2. Children (53.6%) with 22q11DS had a total problems score in the clinical range (≥63) compared to 26.1% in the CFA group. Half of the 22q11DS children reached a clinical score on the internalizing scale (50.7%), and a quarter on the externalizing scale (26.1%). This was 13.0% for each scale in the CFA group. Only 16 of the 22q11DS children (23.2%) had no clinical score on any of the subscales. The CFA group showed fewer problems on the subscales than the 22q11DS group.

The mean CBCL scores of the 22q11DS and controls are shown in Table 4.3. The highest average scores for the subscales in the 22q11DS group were found for social problems and attention problems, followed by withdrawn and somatic complaints. The highest average scores for the controls were also found for the social problems and attention problems subscales. Comparing the scores for both groups showed statistically highly significant differences: 22q11DS children

had both higher total problems scores as well as higher internalizing and externalizing scores (Table 4.3). For the subscales, the 22q11DS children scored significantly higher ($p < 0.01$) on withdrawn, anxious/depressed, social problems and to a lesser degree ($p < 0.05$) on somatic complaints, delinquent behaviour, and aggressive behaviour.

Table 4.2 Clinical scores for the 22q11DS and craniofacial anomalies (CFA) children (*N* = 69 for both groups)

	Frequency and %	
Clinical scores	22q11DS	CFA
Total problems	37 (53.6%)	18 (26.1%)
Internalizing	35 (50.7%)	9 (13.0%)
Externalizing	18 (26.1%)	9 (13.0%)
0 subscales	16 (23.2%)	29 (42.0%)
1 subscale	14 (20.3%)	17 (24.6%)
2 subscales	14 (20.3%)	11 (15.9%)
3 subscales	10 (14.5%)	3 (4.3%)
>3 subscales	15 (21.7%)	9 (13.0%)

Table 4.3 Differences in and Child Behaviour Checklist (CBCL) scores between children with 22q11DS and with craniofacial anomalies (CFA) (*N* = 69 for both groups)

CBCL factors and subscales	22q11DS mean (*SD*)	CFA mean (*SD*)	*t*-test
Total problems	62.57 (9.84)	54.99 (10.45)	4.387*
Internalizing	59.78 (12.58)	52.52 (10.95)	3.617*
Externalizing	55.99 (9.49)	49.70 (9.83)	3.824*
Withdrawn	62.00 (9.02)	55.30 (9.69)	4.202*
Somatic complaints	61.28 (9.50)	57.61 (7.71)	2.490**
Anxious/depressed	58.71 (9.79)	54.00 (7.62)	3.153*
Social problems	66.49 (8.73)	61.25 (9.28)	3.421*
Thought problems	59.68 (10.84)	57.28 (7.89)	1.490
Attention problems	63.20 (8.56)	62.10 (10.07)	0.693
Delinquent behaviour	55.07 (6.10)	52.93 (4.76)	2.303**
Aggressive behaviour	57.61 (8.47)	54.43 (6.59)	2.458**

* $p < 0.01$; ** $p < 0.05$. *SD* = standard deviation.

The relationship between intelligence level and behavioural problems

In both groups the relation between total IQ scores and behaviour was examined using the Pearson *r* correlation coefficient (Table 4.4). In the 22q11DS group no significant correlation was found between intelligence level and total problems score ($r = 0.047$; $p = 0.699$), whereas in the CFA group there was a statistically significant correlation ($r = -0.314$; $p = 0.009$). In both groups no significant relation was found between intelligence and internalizing and externalizing scores. In the 22q11DS group no syndrome scale correlated significantly with intelligence. Two subscales were significantly correlated to intelligence scores in the CFA group, namely social problems and attention problems.

Differences in the relationship between intelligence level and behavioural problems in children with 22q11DS and with CFA

A PCA was performed to measure clustering between intelligence and the syndrome scales in order to explore the relations in more detail. For both groups this resulted in two components with an Eigenvalue greater than 1. In the 22q11DS group these two components accounted for 61.9% of the variance. The first component mainly consisted of the attention problems, social

Table 4.4 Differences in and Child Behaviour Checklist (CBCL) scores between children with 22q11DS and with craniofacial anomalies (CFA) (*N* = 69 for both groups)

	Pearson *r* correlation coefficient	
CBCL factors and subscales	22q11DS	CFA
Total problems	0.047	-0.314*
Internalizing	0.199	-0.066
Externalizing	0.035	-0.121
Withdrawn	0.181	0.040
Somatic complaints	0.213	-0.189
Anxious/depressed	0.168	0.061
Social problems	-0.108	-0.293**
Thought problems	-0.156	-0.234
Attention problems	-0.218	-0.372*
Delinquent behaviour	-0.032	0.056
Aggressive behaviour	-0.007	-0.074

* $p < 0.01$; ** $p < 0.05$.

problems, aggressive behaviour, and thought problems (Table 4.5). The second component was formed by the variable "intelligence", which loaded positively with the subscales anxious/depressed, somatic complaints, and withdrawn. This implied that for children with 22q11DS, a higher intelligence coincided with withdrawn, anxious and depressed behaviour, and physical complaints. In the CFA group, the two selected components accounted for 57.3% of the variance. The aggressive behaviour, anxious/depressed, delinquent behaviour, withdrawn, and somatic

Table 4.5 Rotated component matrix of the 22q11DS group (*N* = 69)

	Components	
Variables	1	2
Attention problems	0.875	0.020
Social problems	0.818	0.083
Aggressive behaviour	0.786	0.202
Thought problems	0.739	0.215
Delinquent behaviour	0.554	0.132
Intelligence	-0.325	0.797
Anxious/depressed	0.553	0.620
Somatic complaints	0.356	0.607
Withdrawn	0.526	0.598

Table 4.6 Rotated component matrix of the craniofacial anomalies (CFA) group (*N* = 69)

	Components	
Variables	1	2
Aggressive behaviour	0.765	0.223
Anxious/depressed	0.754	0.115
Delinquent behaviour	0.672	-0.002
Withdrawn	0.655	0.113
Somatic complaints	0.499	0.214
Intelligence	0.241	-0.803
Attention problems	0.374	0.800
Thought problems	0.418	0.659
Social problems	0.575	0.579

complaints subscales made up the first component, while the second component consisted of "intelligence", which loaded negatively with the attention problems, thought problems, and social problems subscales (Table 4.6). The results of the second component indicated that, for CFA children, lower intelligence scores were related to difficulties in thinking and attention and to social problems.

DISCUSSION

Children with 22q11DS displayed many behavioural problems (53.6% showed a significant total problems score), while only 26.1% of the CFA group scored in the clinical range of the total problems score. The scores of both groups were higher than those of the CBCL norm group in which only 18% had a total problems score in the clinical range (≥63).[9,10] Within the 22q11DS group the highest scores were found on the social problems, attention problems, withdrawn and somatic complaints scales. The children showed more internalizing than externalizing behavioural problems. These findings were consistent with comparable studies.[4,7,8,11] Gerdes et al. reported on the behaviour of preschool children from parental interviews and investigators' observations, and found that during assessment more active and impulsive than inhibited behaviour was observed.[2,3]

In the present study 20% of the children scored in the clinical range both on the internalizing and the externalizing factor. This apparent discrepancy may be explained by frequently occurring changes in state of mind and behaviour. This has also been reported by other authors.[8,11,12,13] Several studies in the general population have demonstrated that there is a direct relationship between behavioural problems and intelligence level in children.[5,6] We found a comparable statistically significant correlation in the CFA group but, remarkably enough, not in the 22q11DS group. No significant relation between intelligence and internalizing and externalizing scores was found in either group. On the subscale level no significant relation was found in the 22q11DS group. In the CFA group significant negative correlations were found between intelligence level and the subscales social problems and attention problems.

In addition to the calculation of the correlation coefficients, a PCA was performed to gain more insight into the relation between intelligence and the syndrome scales. Results from the PCA indicated that children with 22q11DS and a relatively higher intelligence score showed more behavioural problems on the internalizing cluster: anxious/depressed, somatic complaints and withdrawn. Children with a lower IQ also showed many behavioural problems but of a more variable nature: there was no dominant pattern within this group. One could hypothesize that the more intelligent children are more aware of their own problems and are therefore more

inclined to display depressive symptoms and withdrawn behaviour. This hypothesis, however, does not hold for the more intelligent children with CFA, who follow the pattern seen in the general population. This may be indicative of a behavioural phenotype pertaining to the 22q11.2 deletion syndrome.

Strengths and limitations of the present study

In the remainder of the Discussion we will address the strengths and limitations of our study design and analysis.

Sample size

It has been widely stated that the heterogeneity of 22q11DS leads to a broad and variable expression of features. Therefore, the study of small groups involves a certain risk, since results cannot be easily generalized and results from different studies cannot be compared. Feinstein et al. studied groups consisting of 28 subjects with 22q11DS and 29 control subjects, and stated quite rightly: "Ascertainment bias and small sample size should be considered as possible design factors that could have obscured differences in psychopathology between the two groups. How representative was our VCFS sample?".[8] Swillen et al. studied 60 subjects, divided into subgroups.[7] When using the CBCL on two of the subgroups (16 primary school children and 9 adolescents) they stated that: "According to teachers, the anxious/depression syndrome significantly increases with age. During primary school, 10% of the VCFS children score within the clinical range. In puberty this increases to 30% of the adolescents". These percentages correspond to a number of 1.6 and 2.7 children respectively, so that the results may be due to observations of a few individuals. One strength of our present study is the use of two relatively large groups consisting of 69 subjects each, without division into subgroups.

Representation of the sample

A population-based study yielded 43 children with a 22q11.2 deletion among 255849 births: a prevalence of 1 in 5950 births.[14] Translated to the Dutch situation, with 200000–210000 newborn babies each year, about 35 new babies with a deletion could be expected each year. In the literature the estimated prevalence is 1 per 2000–4500 live births, implying that 44–105 children are born with 22q11DS in the Netherlands annually.[15] The 69 subjects in this study were born in a 10-year period, whereas, based on the above, between 350 and 1050 children

with 22q11DS might have been born in the same period. This is difficult to conclude the representative nature of our sample. However, the challenges of accomplishing a large study of this nature are well known.

Control group

As in Heineman-de Boer et al.'s previous study, we used a group of children with CFA as a control group, based on several similarities between CFA and 22q11DS.[4] Both groups have an anomaly originating in the early embryonic development stage, sometimes but not always leading to visible facial abnormalities. In the CFA group, participants have non-syndromic or syndromic craniosynostosis, (e.g., Crouzon syndrome). Like the 22q11DS group, their intellectual capacities or the severity of their physical condition are not related to their facial features. In both groups the influence of eventual brain malformations remains unpredictable. The children in both groups often need medical treatment, sometimes including heart or skull operations, considered hazardous by the parents. Finally, both types of conditions can lead to problems in everyday life or have practical consequences. Children with CFA seem to be an adequate control group for 22q11DS children in this study. The 22q11DS children were matched individually with controls based on their total IQ scores. This is a more precise method than a "group matched to the VCFS sample with comparable distributions in the range of IQ" or a control group with "FSIQ between 70 and 99 on formal testing".[8,16]

Psychometric tests – Intelligence

In the 22q11DS group, 53 out of 69 children had a verbal and performance intelligence assessment. The Dutch version of the Wechsler intelligence test was used for most of the 22q11DS children, with the type depending on the child's age. The WPPSI-R and WISC-RN results could be compared satisfactorily. The WISC-III NL was used for six participants although the Dutch norms have not yet been definitely established. Dutch non-verbal intelligence tests (SON-R 2½–7 and SON-R 5½–17) were used. They are frequently chosen in the Netherlands because they are pleasantly applicable assessments, taking less time than the WPPSI-R or the WISC-RN. Although the psychometric aspects of these tests are good, even better than those of the Wechsler tests, a problem could arise when the choice of test is dictated by a participant's speech and language difficulties. The SON tests were used more often in the CFA group than in the 22q11DS group (48 vs. 10). In both groups the choice for this non-verbal test was not dictated by expected speech or language difficulties. A statistically satisfactory correlation between the SON 2½–7 and the WPPSI-R/WISC-R has been reported in several studies: $r = 0.68$

and $r = 0.70$; between the SON 5½–17 and the WISC-R a correlation of 0.80 for the full scale IQ, 0.66 for the verbal IQ score and 0.80 for the performance IQ score has been reported.[17,18]

Psychometric tests – Behaviour

By definition, a behaviour checklist only measures those behaviour components that have been built into the list. Sometimes parents reported that their children had other problems not represented in the checklist. To do justice to a wider range of behaviour and personality problems, it could therefore be interesting to also use alternative methods, such as child psychiatric examination. This could provide more insight into the nature of fears, anxieties, and sleeping problems, which are frequently reported. A problem that can arise by using a behaviour checklist filled out by parents has to do with speech and language problems. When a child has limited language skills, some items of the CBCL can be difficult for parents to assess. Moreover, in the 22q11 group several children had seemingly high verbal qualities that were not reflected in their verbal intelligence: their verbal IQ was disappointingly low compared with the strong verbal impression they made. This aspect could also have clouded the behaviour assessments. Speech and language problems were not measured in either group. Furthermore, issues surrounding the mother's emotional relationship with her child remained unobserved in both groups. Aspects like anxiety, over-protectiveness, ambivalence, fears and denial could have influenced the scoring. In sum, the completion of the behaviour lists by the mothers had to be accepted at face value.

CONCLUSION

Our findings indicate that children with 22q11DS show more problems in specific behavioural domains than the CFA control group. We conclude that behavioural problems in 22q11DS children are directly associated with the syndrome and cannot be explained by other factors like intelligence level, medical discomfort or facial anomalies. Our findings provide tentative evidence for the existence of a specific behavioural phenotype associated with 22q11DS, but more specific research will be necessary to confirm this.

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5

Cognitive development in children with 22q11.2 deletion syndrome

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ABSTRACT

Background: People with 22q11.2-deletion syndrome (velo-cardio-facial syndrome) have a 30-fold risk of developing schizophrenia. In the general population the schizophrenia phenotype includes a cognitive deficit and a decline in academic performance preceding the first episode of psychosis in a subgroup of patients. Findings of cross-sectional studies suggest that cognitive abilities may decline over time in some children with 22q11.2 deletion syndrome. If confirmed longitudinally, this could indicate that one or more genes within 22q11.2 are involved in cognitive decline.

Aims: To assess longitudinally the change in IQ scores in children with 22q11.2 deletion syndrome.

Method: Sixty-nine children with the syndrome were cognitively assessed two or three times at set ages 5.5, 7.5 and 9.5 years.

Results: A mean significant decline of 9.7 Full Scale IQ points was found between 5.5 and 9.5 years. In addition to the overall relative decline that occurred when results were scored according to age-specific IQ norms, in 10 out of a group of 29 children an absolute decrease in cognitive raw scores was found between 7.5 and 9.5 years. The decline was not associated with a change in behavioural measures.

Conclusions: The finding of cognitive decline can be only partly explained as the result of 'growing into deficit'; about a third of 29 children showed an absolute loss of cognitive faculties. The results underline the importance of early psychiatric screening in this population and indicate that further study of the genes at the 22q11.2 locus may be relevant to understanding the genetic basis of early cognitive deterioration.

INTRODUCTION

Children with 22q11.2 deletion syndrome (22q11DS) are reported to have learning difficulties and are at a greater risk of psychiatric disorders including autism-spectrum disorders and attention-deficit hyperactivity disorder. During adolescence and early adulthood up to 30% of people with the syndrome develop schizophrenia, thus suggesting that 22q11DS can be considered the highest known genetic risk factor for schizophrenia other than having a monozygotic twin sibling with the illness.[1-5]

Several cross-sectional studies have found a negative correlation between age and IQ scores in 22q11DS,[6-10] suggesting that at least some of these individuals show a gradual decline in cognitive development as they grow into adulthood. Results of two longitudinal studies, respectively in adolescents and 22q11DS patients in late childhood/ adolescence, are consistent with this suggestion.[11,12] There may be several explanations for these observations. The normative scale might have become more stringent with the introduction of a revised version of the scale to compensate for the 'Flynn effect', an upward drift of approximately 3 points per decade in normative performance on IQ tests.[13] Alternatively, adolescents with weaknesses in the area of abstract reasoning might 'grow into deficit', meaning that a decrease in IQ scores with age is not indicative of an absolute decline in cognition, but rather parallels an inability to adapt to the gradual increase of the level of cognitive requirements with age. Although these factors may play a part in the presumed decline in cognitive abilities in young people with 22q11DS, the high prevalence of schizophrenia in this syndrome strongly suggests that there might be an alternative explanation. Research into cognitive development in schizophrenia in the general population indicates that cognitive decline occurs in late adolescence,[14] but some studies also suggest that academic or cognitive deficits can be found as early as in the first grade of school.[15-18] These findings are in keeping with the neurodevelopmental model of schizophrenia. Against this background, a cognitive decline in people with 22q11DS – in this study defined as a decrease in IQ scores shown by repeated measurements – may be viewed as the first manifestation of schizophrenia. Indeed, in a cross-sectional study of 43 children with 22q11DS, Debbané et al. reported that children with psychotic symptoms had significantly lower verbal IQ (VIQ) scores than those without such symptoms.[19] Gothelf et al. reported that a decline in VIQ in adolescence may be associated with an increased risk of psychotic symptoms during follow-up.[11,20] In an attempt to replicate these findings and predict psychotic symptoms in 22q11DS, Antshel et al. reported a positive association between deterioration of several cognitive functions, in particular executive and verbal abilities, and the development of prodromal symptoms in late childhood/ adolescence.[12] In the largest cross-sectional study to date (n = 172) a negative correlation between age and Full Scale IQ (FSIQ) was reported, with a stronger negative correlation between verbal IQ subscales and

age compared with performance IQ.[8] The authors noted that the cross-sectional design of their study was a limitation and suggested that in future, longitudinal studies 'the use of raw scores, in addition to age-normed scores, should be used to help assess cognitive change over time'.[8]

Given the increased risk of schizophrenia in people with 22q11DS and the observed premorbid deficit in cognitive abilities associated with schizophrenia in the general population, the study of cognitive development in young children with 22q11DS is highly relevant. If, as research suggests, cognitive abilities decline with age in these children, this implies that one or several genes within the 22q11.2 region are causally related to cognitive deterioration during childhood. Second, this study may clarify at what age this cognitive decline can be observed, and – perhaps more importantly – whether all children display this decline or alternatively only a subgroup. The latter question is particularly relevant and could be a focus of subsequent studies, as only a subgroup of children with 22q11DS go on to develop schizophrenia later in adolescence or adulthood. The objective of this prospective longitudinal study was to assess changes in IQ levels in children between the ages of 5.5 and 9.5 years. To investigate whether any observed decrease in IQ score was due to insufficient cognitive development leading to an increasing discrepancy with age-required norms (growing into deficit), or rather a result of an absolute decline in cognitive capabilities, both subtest scaled scores (i.e. age-specific normative scores) and subtest raw scores (absolute test scores, prior to age-normative adjustment) were analysed. It is important to note that although we included global measures of behaviour, the study was not designed to assess neuropsychiatric symptoms, in particular the onset of psychotic symptoms.

METHOD

This study was part of a nationwide prospective longitudinal psychological study of IQ levels and behaviour in children with 22q11DS. In this ongoing study, enlistment is allowed at any age between 1 and 15 years. Participants were recruited through referrals from genetic counsellors, cleft palate clinics and paediatric cardiologists from hospitals throughout The Netherlands or through postings on the website of the Dutch parent support group VCFS/ 22q11. The inclusion criterion was the presence of a 22q11.2 deletion confirmed by fluorescence in situ hybridization analysis (FISH) or multiplex ligation-dependent probe amplification (MLPA).[21] The assessment protocol was approved by the Dutch Central Committee on Research involving Human Subjects. Written informed consent was obtained from all parents or guardians.

A total of 77 children (27 boys, 50 girls) were originally included. Of this group 8 children (1 boy, 7 girls) were estimated to have intellectual disabilities below the range of the DSM-IV category 'moderate mental retardation'. Data pertaining to the latter children were excluded

from all statistical analyses because the longitudinal development of IQ levels as assessed by the test protocol could not be monitored (see Supplement S5.1 for additional information on this group). Of the remaining group of 69 children (26 boys, 43 girls), 41 were assessed twice and 28 were assessed three times at the age of 5.5, 7.5 and/or 9.5 exactly (Table 5.1). Drop-out at various measurement points are also described in Table 5.1.

Education

Parents were asked to report their highest level of education attained and were categorised according to the International Standard Classification of Education (ISCED) designed by the United Nations Educational, Scientific and Cultural Organization (UNESCO).[22] In the general Dutch population 27% of men and 24% of women have completed higher (tertiary) education.[23] When controlling for the effects of FSIQ with level of parental education, it was found that within the group, 31-34% of fathers and 31-40% of mothers had completed higher 'tertiary' education.

Assessment

At 5.5 years of age the Dutch version of the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) was used.[24] However, 15 (of 53) children could not be assessed with this test due to speech problems. In these cases the Snijders-Oomen non-verbal test (SON-R 2½–7) was used. Correlations between FSIQ scores derived using the SON-R 2.5–7 and WPPSI-R are high (r = 0.75).[25]

Table 5.1 Distribution of assessments at 5.5, 7.5 and 9.5 years (N = 69)

Mean age (*SD*)	5.5 (.2) yrs	7.5 (.2) yrs	9.5 (.1) yrs
Number of children assessed at:			
5.5 and 7.5 years	20	20	*
7.5 and 9.5 years	**	16	16
5.5 and 9.5 years	5	***	5
5.5, 7.5 and 9.5 years	28	28	28
Total per age group	**53**	**64**	**49**
Total number of children assessed at least twice: 69			
Total number of children assessed at 7.5 & 9.5 years with WISC-III: 29			

* 2 declined further participation, 1 moved abroad, 17 did not reach age of 9.5 yet
** 15 not participating in study at this age, 1 with somatic health problems at this age
*** 2 with somatic health problems, 3 not able to be tested with standard test protocol

At 7.5 years and 9.5 years of age the children's Full Scale IQ was assessed using the Dutch versions of the Wechsler Intelligence Scale for Children – Revised (WISC-RN) and/ or the Wechsler Intelligence Scale for Children Third Edition (WISC-III-NL).[26,27] The Wechsler tests consist of 2 scales, one assessing verbal IQ (VIQ) and a scale assessing performance IQ (PIQ). The test thus yields three scores: FSIQ, VIQ and PIQ, each with a mean of 100 and a standard deviation of 15. The study started before the WISC-III-NL was published in The Netherlands; therefore early participants (n = 15) have been assessed with the WISC-RN at 7.5 years and with the WISC-III-NL at 9.5 years. All other participants (n = 29) were assessed with the WISC-III-NL at both ages. Research on the correlation between WISC-RN and WISC-III-NL suggests that the two tests yield similar results for FSIQ (r = .88).[27] Since changes in cognitive test performance can be associated with changes in behaviour or influenced by the use of psychotropic medication, parents were asked to fill in the Child Behaviour Checklist (CBCL 6–18) while the child was being assessed.[28] Also, use of psychotropic medication was recorded at all assessment points.

Statistical analysis

In total 69 participants were successfully assessed two or three times. Descriptive analyses were used. In order to take missing values into account, the research design chosen was a multilevel analysis by use of mixed models. Mixed models are used for the analysis of data measured over time to study population-level change and individual differences in change characteristics and allow for missing data. The sensitivity of parameter estimates to missing data assumptions can be studied, for example, by fitting multiple models that make different assumptions about the missing data process.

Potentially confounding variables (gender and used test) were controlled for. First, multilevel analyses of the development of FSIQ, VIQ and PIQ scores between 5.5 and 9.5 years were performed (N = 69). Second, given that only the WISC-RN and the WISC-III-NL allow for analysis of the progression of the subtest scores (the WPSSI-R results in different subtest scores), measurement at 5.5 years was discarded and a paired samples t-test was used to analyse the subtest scaled scores at 7.5 and 9.5 years for children assessed with either WISC-RN or WISC-III-NL (n = 44). Third, to differentiate between growing into deficit and the possibility of an absolute decline in cognitive abilities, the results of a subgroup of children that were tested with the WISC-III-NL at both ages 7.5 years and 9.5 years (n = 29) were examined using the raw subtest scores. An independent-samples t-test was used. Finally, a number of statistical tests were compared to exclude the possibility of relevant test-related confounding effects on the results. To compare the results of the various tests used at the different ages (SON-R 2.5–7 and WPPSI-R at 5.5 years;

WISC-RN and WISC-III-NL at 7.5 years), the possibility of test related effects on the changes in IQ scores over time was examined. This was especially important because the primary interest of this study is the longitudinal development of cognition. To this end IQ changes were compared between children who were tested with the WISC-III-NL at both ages (n = 29) and those tested with WISC-RN at 7.5 and WISC-III-NL at 9.5y (n = 15), using an independent samples t-test.

Significance level was set at 5%. All statistical calculations were carried out using SPSS version 15.0.

RESULTS

Cognitive development 5.5 – 9.5 years

Table 5.2 presents the cross-sectional data and gender-specific development in IQ levels for the sample (n = 69). Gender differences in favour of girls were found for FSIQ at 5.5 years and 7.5 years of age, for VIQ at 5.5 years and for PIQ at 7.5 years. Multilevel analyses of the cognitive

Table 5.2 Descriptive information and cross-sectional group means of 22q11 sample and results of the comparisons of gender for FSIQ, VIQ and PIQ at three age levels (N = 69)

Age	5.5 yrs	7.5 yrs	9.5 yrs
Mean age at assessment (*SD*)	5.5 (.2)	7.5 (.2)	9.5 (.1)
n	53	67	49
Gender, female (%)	35 (66)	43 (67)	29 (59)
Familial deletion (%)	4 (8)	3 (5)	3 (6)
FSIQ (*SD*)	78.8 (14.4)	72.6 (12.0)	69.1 (12.2)
Female/ male FSIQ (*SD*)	82.1 (13.8)/ 72.6 (13.6)*	75.4 (11.6)/ 67.3 (11.3)**	71.6 (11.9)/ 65.4 (11.8)
VIQ (*SD*)	80.1 (14.2)	76.4 (12.3)	71.4 (12.8)
Female/ male VIQ (*SD*)	82.8 (14.8)/ 72.2 (8.7)*	77.9 (11.9)/ 73.3 (12.6)	73.7 (12.7)/ 68.0 (12.4)
PIQ (*SD*)	77.0 (14.3)	75.0 (12.1)	72.3 (12.2)
Female/ male PIQ (*SD*)	78.9 (15.1)/ 70.4 (8.6)	77.2 (12.1)/ 70.3 (10.8)*	74.8 (11.8)/ 68.7 (12.2)

FSIQ = Full Scale IQ; VIQ = Verbal IQ; PIQ = Performance IQ; *SD* = standard deviation
95% CI = 95% Confidence Interval
* $p < .05$
** $p < .01$

tests indicated that FSIQ scores declined significantly ($p < 0.0001$) by -2.93 IQ points per year ($SE = 0.32$, 95% CI, -3.56 – -2.30).Verbal IQ also declined significantly ($p < 0.0001$) by -2.25 points per year ($SE = 0.38$, 95% CI, -3.01 – -1.50), as did PIQ ($p = 0.015$) by -1.07 points per year ($SE = 0.44$, 95% CI, -1.96 – -0.18). There was a more severe cognitive decline in girls than in boys for FSIQ ($p = 0.02$, $SE = 2.85$, 95% CI, 1.1 – 12.49) and PIQ ($p = 0.019$, $SE = 2.78$, 95% CI, 1.16 – 12.26). This difference was not found for VIQ ($p = 0.07$; $SE = 2.96$; 95% CI, -0.47 – 11.4). Figure 5.1 shows the development of FSIQ, VIQ and PIQ from age 5.5 years to 9.5 years based on the results of the multilevel analyses.

The proportion of children with a familial deletion in the group (6%) was comparable to other published results (11%), ($\chi^2_1 = 1.65$, $p = 0.20$)[29] and showed no significant difference in FSIQ, VIQ or PIQ at any age when compared with children with a de novo deletion. Cardiac anomalies were found in 31 of 69 children (45%) and included tetralogy of Fallot, ventricular septal defect and interrupted aortic arch. No significant difference in FSIQ, VIQ or PIQ score at any age was found.

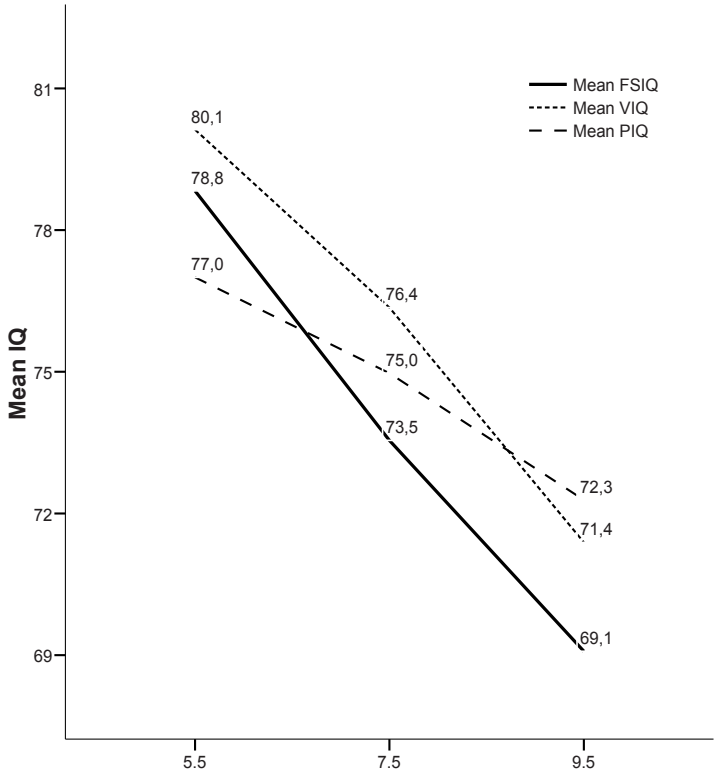

Figure 5.1 Mean development of IQ in children with 22q11DS from 5.5 years to 9.5 years (based on results of mutilevelanalysis, $N = 69$).

Cognitive development 7.5 - 9.5 years

Figure 5.2 presents the progression of age-normative (scaled) subtest scores per subtest from 7.5 years to 9.5 years ($n = 44$). Within the VIQ scale significant declines were found for the subtests Arithmetic ($p = 0.008$, 95% CI, -1.77 – -.28), Vocabulary ($p < 0.0001$, 95% CI, -2.29 – -.97) and Comprehension ($p < 0.0001$, 95% CI, -2.07 – -.77). Within the PIQ scale significant declines were found for the subtest Block Design ($p = 0.035$, 95% CI, -1.48 – -.06). See Supplemental Table 5.3.

Change in raw test scores 7.5 - 9.5 years

Among the group assessed with the and WISC-III-NL at both 7.5 years and 9.5 years of age ($n = 29$) were children who obtained a lower absolute (raw) score at 9.5 years for the same series of questions or tasks that had been presented at age 7.5 (Figure 5.3). A lower raw score implies a decrease in performance where normally an increase would be expected due to ageing and maturation of the child. In a substantial subgroup of 10 children (34%), this absolute decline

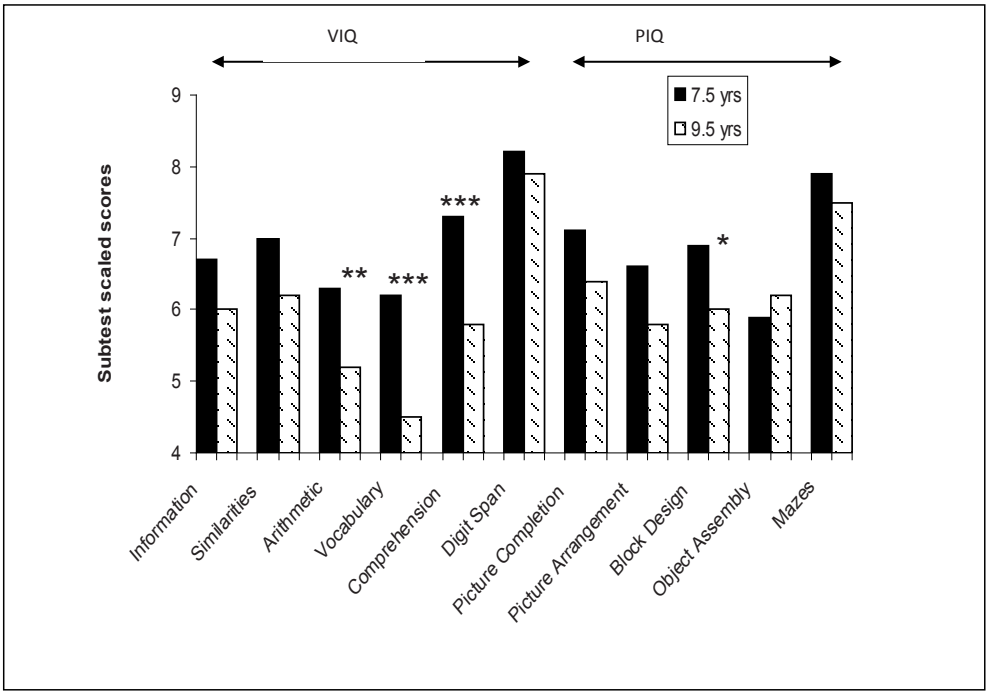

Figure 5.2 Change in subtest scaled scores from 7.5 to 9.5 years ($n = 44$) as assessed with the WISC-R and WISC-III-NL. * $p < .05$; ** $p < .01$; *** $p < .001$.

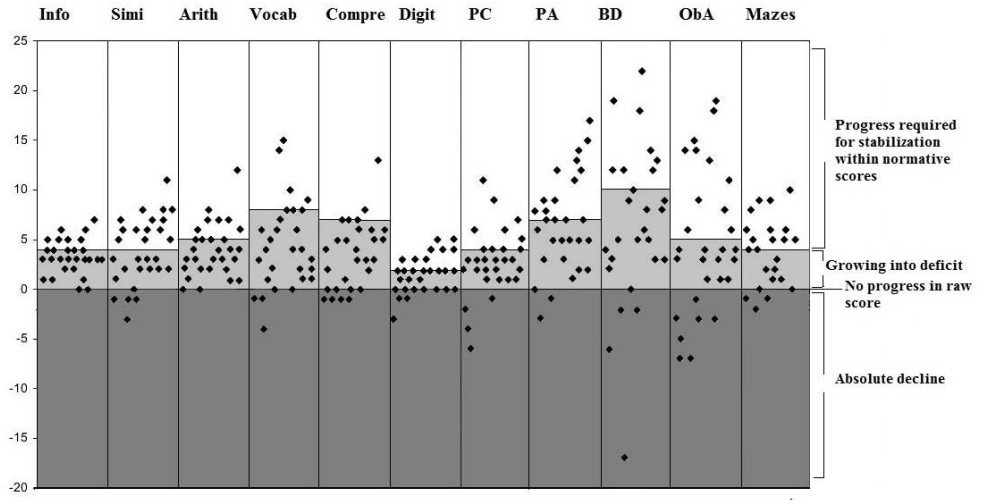

Figure 5.3 Progression in raw (i.e. not adjusted to age-specific norms) WISC-III subtest scores between 7.5 and 9.5 years (n = 29), expressed as the delta raw score (raw score 9.5y – raw score 7.5y). In the area between the lines "No progress" and "Growing into deficit" subtest raw scores indicate an absolute progress, which is however not enough to keep up with the normatively required progress. Note that scores in this area, although improving, contribute to a *decrease* in scaled subtest scores, and ultimately in total IQ score at age 9. Thus, this area can be considered consistent with the concept of "growing into deficit". Raw scores above this area contribute to a stable or improved subtest score at age 9. Scores in the gray area indicate an absolute decline; implying that the subject performed less well on the exact same subtest, regardless of age norms.

in abilities was observed for two or more subtests (Supplemental Table S5.2). Furthermore, Figure 5.3 shows clearly the area in which children were growing into deficit: their raw scores were better than they were at age 7.5, but did not meet the age-related increase required and seen in their peers without the syndrome. Some children showed enough progress in two or more subtests to obtain the same age-specific normative score at age 9.5 years as they did at 7.5 for at least some subtests (Supplemental Table S5.2). Further analysis demonstrated that an absolute decline in two or more subtests was significantly associated with a decreased probability of stabilisation in the normative score in the remaining subtests (Fisher's exact test, $p = 0.04$).

Comparing the subgroup of children ($n = 10$) with a cognitive decline in two or more subtests with the remainder of the participants ($n = 19$) showed that there was no worsening in the decline group as measured by changes in CBCL scores ($p = 0.85, .36, .15$ respectively for total, internalizing and externalizing problem scores). The CBCL results are presented in more detail in Supplemental Tables S5.3 and S5.4.

Possible inter test effects

At age 5.5 years the SON-R 2.5–7 (n = 15) and the WPPSI-R (n = 41) FSIQ scores were not significantly different (p = 0.45). At 7.5 years a trend towards a significant difference between FSIQ scores measured by WISC-RN and WISC-III-NL was found (p = 0.073). This was to be expected and is in concordance with results described in the WISC-III-NL manual.[27] Indeed, a larger (and significant) difference in VIQ (10.1 points, p = 0.006) was found, with the WISC-RN yielding the higher scores. Performance IQ scores were not significantly different between WISC-RN and WISC-III-NL (p = 0.47) at 7.5 years. However, regarding the longitudinal development of cognitive performance, and therefore of particular relevance to the current study, no significant differences were found for the mean change from 7.5 years and 9.5 years in FSIQ, VIQ and PIQ scores as measured by WISC-RN and WISC-III-NL respectively (Supplemental Table S5.5). These results suggest that the identified changes in IQ scores were not significantly affected by the cognitive tests used. Nevertheless, to exclude any bias due to the use of different test versions, only WISC-III-NL results were used to analyse the longitudinal course of the raw scores. Parental level of education was not found to be a predictor of cognitive delay (data not shown).

DISCUSSION

On average, cognitive abilities as expressed by Full Scale IQ scores declined significantly by a mean of 9.7 IQ points between the three assessments at ages 5.5 years, 7.5 years and 9.5 years in this population. Consistent with previous reports, this decline was twice as great for verbal IQ as it was for performance IQ. Within the VIQ scale, significant declines were found for the subtests Vocabulary, Comprehension and Arithmetic, suggesting that the overall cognitive decline is mainly driven by a progressive delay in verbal comprehension and expression. Within the scale measuring PIQ a significant decline was found for the subtest Block Design. Furthermore, an absolute decline in cognitive performance at age 9.5 years as manifested by lower subtest raw scores for at least two subtests (when compared with the same subtests as used at age 7.5 years) was found in 10 of the 29 children who were tested twice with the WISC-III-NL. These results indicate that the cognitive decline cannot be fully explained by an inability of the children to keep up with the required age-related increase of raw scores in the cognitive test, a phenomenon also known as growing into deficit. Rather, they indicate the possibility of cognitive deterioration.

The foremost relevance of the results of the current study is that they strongly suggest the possibility that one or more genes at the 22q11.2 locus are contributing to an early cognitive decline as measured by repeated standardised IQ testing. In this regard, there may be several

plausible candidate genes, including Catechol-O-Methyl Transferase (COMT), Proline Dehydrogenase (PRODH) Phosphatidyl-inositol-4-kinase-catalytic-a PIK4CA and T-Box 1 (TBX1).[11,30-32] Comprehensive reviews of 22q11.2 genes with potential to influence cognitive development are provided elsewhere.[33,34] Hence, future genetic studies focusing on the 22q11.2 region may elucidate one of the genetic factors involved in this phenotype.

Implications of cognitive decline

Early cognitive deficits and academic decline, occurring before the onset of the first psychosis, are frequently reported in schizophrenia and therefore considered an important potential aspect of the schizophrenia phenotype.[14,35] It could be speculated that the observed decline in this study is likely to be the first symptom of schizophrenic disorder in 22q11DS. Interestingly, the absolute decline does not occur in all subjects, but rather in a subgroup, parallel to the observation that only a subgroup of people with 22q11DS will develop schizophrenia. However, in order to answer this question a continued follow-up into adulthood is required as the participants in our study are currently too young to be ascertained for the emergence of schizophrenia. Our clinical test protocol ensures that all children have psychiatric assessments from the age of 11 years (end primary school) and earlier if thought necessary by parents or professionals.

The finding of a cognitive decline, which is mainly driven by a decrease in verbal IQ, is consistent with the findings of previous (mostly cross-sectional) studies in people with 22q11DS. Also, the verbal and performance subscales that appear to be most affected are almost entirely consistent with results of previous studies.[8,20,36] The cross-sectional IQ data of this study shows gender differences in favour of girls; in other words, boys are more cognitively affected than girls, and this is already evident at the age of 5.5 years. This is consistent with some findings[37,38] yet inconsistent with others that found no gender differences.[39] Our results, however, also show that girls undergo a more severe cognitive decline than boys between the assessments at ages 5.5, 7.5 and 9.5 years. This is consistent with another recent longitudinal study in older children.[12] It could be argued this finding is actually the result of a floor effect of the test: boys simply cannot decline more severely because the test does not allow for it.

A number of children showed adequate progress in their performance on various subtests: that is, their subtest performance improved beyond the minimum raw score required to maintain the same age-specific normative score. In light of these findings, one could reason that the observed absolute decline in subtest performance is the result of stochastic events rather than being indicative of an underlying process in a subgroup of children. In that case one would expect a random distribution of subtest raw scores showing progress and those showing an

absolute decline in the children. However, further analysis demonstrated that an absolute decline in two or more subtests was significantly associated with a decreased probability of progress in the remaining subtests, thus refuting stochastic variability in performance as an explanation of the findings. In other words, the results strongly suggest the existence of a subgroup of children with 22q11DS who show a marked decline in cognitive abilities, including an absolute decline in performance on two or more subtests.

Limitations of the study

The use of different cognitive tests at various ages can be considered a limitation of this study. Two different approaches were used to overcome this problem. First, additional statistical analyses were performed to rule out any test-specific effects of IQ scores with regard to both the cross sectional and the longitudinal (IQ change) data. Except for a significant difference in cross-sectional VIQ scores between the WISC-RN and the WISC-III-NL, a well-known distinguishing characteristic of these scales, no difference was found in relation to the different tests. More importantly, the change in IQ was not significantly affected by the use of the different tests. In addition, the second approach to rule out test-related effects consisted of the analysis of a subgroup of patients that were tested twice with exactly the same test (WISC-III-NL). Findings of this analysis confirmed the cognitive decline, and in addition indicated the absolute loss of abilities in a subgroup of patients. The small size of this subgroup ($n = 10$) did not provide sufficient power to examine the possibility of a distinguishing cognitive profile.

Another limitation of our study is that neuropsychiatric assessment of these young age children was not part of the test protocol. Therefore, we cannot evaluate whether the observed changes in IQ are correlated to psychiatric diagnoses such as attention-deficit hyperactivity disorder and autism-spectrum disorder. However, previous studies by different groups strongly suggest that such a correlation does not exist, or at least, is likely to be of modest strength at most.[4,38,40]

Clinical relevance

Apart from the relevance to the understanding of the genetic underpinnings of cognitive deterioration, the observed decline also has clinical consequences for individuals with 22q11DS. The results stress the importance of early screening and continuous monitoring of the cognitive development of children with this syndrome. Over the years some of these children may be increasingly challenged beyond their cognitive capabilities, but are expected to function at the same academic level they were able to meet previously. A chronic situation of too much stress is a known risk factor for a range of internalizing and externalizing psychiatric disorders.

In conclusion, the results of this longitudinal study into the cognitive development of young children with 22q11.2 deletion syndrome show a progressive decrease in FSIQ starting as early as 5.5 years of age, mainly driven by a declining VIQ. The decline appears as an average group effect, but not all children are (equally) affected. In part the results show that this decline occurs as a result of stagnation of cognitive development relative to increasing cognitive requirements. However, there appears to be a subgroup of children in whom this decline is characterised by an absolute loss of cognitive faculties.

Future research

From a research perspective the 22q11.2 deletion syndrome can be viewed as a unique experiment of nature providing a powerful model in which the same genetic variant is associated with a highly increased risk of developing brain-related phenotypes. Elucidating these various 22q11DS related phenotypes, as well as identifying the underlying genetic mechanism that can account for them may provide important novel insights in neuroscience. The findings reported here suggest the possibility that one or several genes at the 22q11.2 locus contribute to an early cognitive decline.

Acknowledgments

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SUPPLEMENT

S5.1 Excluded patients

For all the following children intelligence level was estimated to be below the range of moderate mental retardation. Intelligence scores were not able to be derived, in some cases an age equivalent was available. Data pertaining to these children was excluded from all statistical analyses.

Case 7 (f)

At age 5.7y patient was unable to be tested, intelligence level was estimated to be below the range of moderate mental retardation. Patient is also physically handicapped. At age 7.5y parents declined assessment although they are still participating in the study.

Case 71 (f)

At 7.8y and 9.5y scores from the SON-R 2.5–7 indicated IQ levels below the range of moderate mental retardation (age equivalent of 2.7y and 3.7y respectively were found).

Case 107 (f)

At age 7.2y and 9.6y patient was unable to be assessed by use of WISC-III-NL. No alternative tests were used in this instance.

Case 112 (f)

At age 5.6y patient was unable to be tested. At age 7.6y IQ levels indicated levels below the range of moderate mental retardation (age equivalent of 3.9y by use of SON-R 2.5–7). At 9.6y patient was unable to be assessed by use of WISC-III-NL.

Case 126 (f)

At 7.11y and 9.5y scores from the SON-R 2.5–7 indicated IQ levels below the range of moderate mental retardation (age equivalents of 3.8y and 4.2y respectively were found).

Case 131 (f)

At 7.5y and 9.6y scores from the SON-R 2.5–7 indicated IQ levels below the range of moderate mental retardation (age equivalent of 2.5y and 2.11y respectively were found). Their daughter is still not speaking.

Case 145 (m)

At 7.6y scores from the SON-R 2.5–7 indicated IQ levels below the range of moderate mental retardation (age equivalent 2.7y). At 9.5y parents declined assessment although they are still participating in the study.

Case 153 (f)

At 5.7y and 7.6y scores from the SON-R 2.5–7 indicated IQ levels below the range of moderate mental retardation (age equivalent of 2.6y and 3.3y respectively were found). At 9.5y parents declined assessment for their daughter, they are still participating in the study. Their daughter is still not speaking.

Table S5.2 Change in subtest raw scores from 7.5 to 9.5 years per individual, sorted by amount of subtests showing a negative development. corresponding change in FSIQ, VIQ and PIQ are presented as absolute scores (*n* = 29)

		Change in VIQ subtest raw scores							Change in PIQ subtest raw scores						Subtests with absolute decline in raw scores	Subtests with enough progress
Gender	Δ FSIQ	Δ VIQ	Information	Similarities	Arithmetic	Vocabulary	Comprehension	Digit Span	Δ PIQ	Picture Compl.	Picture Arr.	Block Design	Object Assembly	Mazes		
f	-15	-13	3	3	0	-1	-1	-3	-16	2	0	4	-3	-1	5	0
f	-18	-15	1	-1	2	-1	4	0	-19	-2	8	-6	3	6	4	2
m	-15	-11	4	1	1	-1	2	-1	-18	-4	6	2	4	.	3	0
m	-13	-13	1	5	3	3	-1	1	-14	-6	8	3	-5	4	3	2
f	-12	-6	4	7	3	6	0	3	-16	3	-3	19	-7	8	2	4
f	-14	-14	3	6	4	-4	0	2	-12	6	3	12	-7	5	2	4
f	-8	-13	4	2	5	4	-1	2	-2	3	7	5	6	-2	2	1
f	-1	-7	5	-3	6	1	5	1	6	2	9	-2	14	.	2	4
m	-7	-10	5	-1	0	5	7	0	-4	3	-1	12	14	4	2	3
m	2	-4	5	-1	5	2	5	.	8	11	9	-17	15	.	2	4
f	-9	-11	6	0	2	0	1	2	-7	2	7	28	-1	0	1	2
m	-7	-6	4	6	2	6	-1	2	-6	1	12	9	9	.	1	3
f	-5	-5	2	3	8	14	0	1	-4	3	5	0	-3	9	1	3
f	-12	-5	5	2	5	7	7	0	-18	-1	5	10	3	9	1	2

f	0	10	4	8	7	15	7	3	-10	9	3	-2	4	2	1	5				
f	-7	-4	2	5	3	8	4	3	-9	2	7	5	1	-1	1	2				
f	-1	0	3	6	4	8	6	-1	-2	3	5	18	13	6	1	4				
f	-2	-2	3	3	7	10	0	4	-4	3	5	22	-3	1	1	4				
f	-7	-9	0	2	3	0	3	2	-3	1	1	6	18	2	0	1				
m	11	3	5	3	5	4	8	2	16	6	11	8	19	.	0	5				
m	-3	0	1	2	2	6	3	5	-1	4	13	5	3	3	0	2				
m	2	4	6	7	7	4	2	.	0	1	14	14	1	5	0	5				
f	-9	-12	0	6	1	2	6	2	-4	4	12	12	4	.	0	3				
f	0	-1	3	7	4	8	3	2	2	1	7	3	8	1	0	2				
f	-2	-2	3	8	3	1	5	0	-4	4	5	13	1	5	0	3				
f	13	15	7	11	12	9	13	4	11	7	15	28	11	6	0	11				
m	-6	-11	3	2	4	1	5	4	1	2	17	8	6	5	0	4				
m	-9	-9	3	5	6	2	5	5	-9	4	2	3	3	10	0	3				
m	-3	-7	3	8	1	3	6	0	-4	5	2	9	4	0	0	1				

Table S5.3 Reported (change in) behaviour as assessed by CBCL at 7.5 and 9.5 years by subgroup (*n* = 29) by child and in percentages

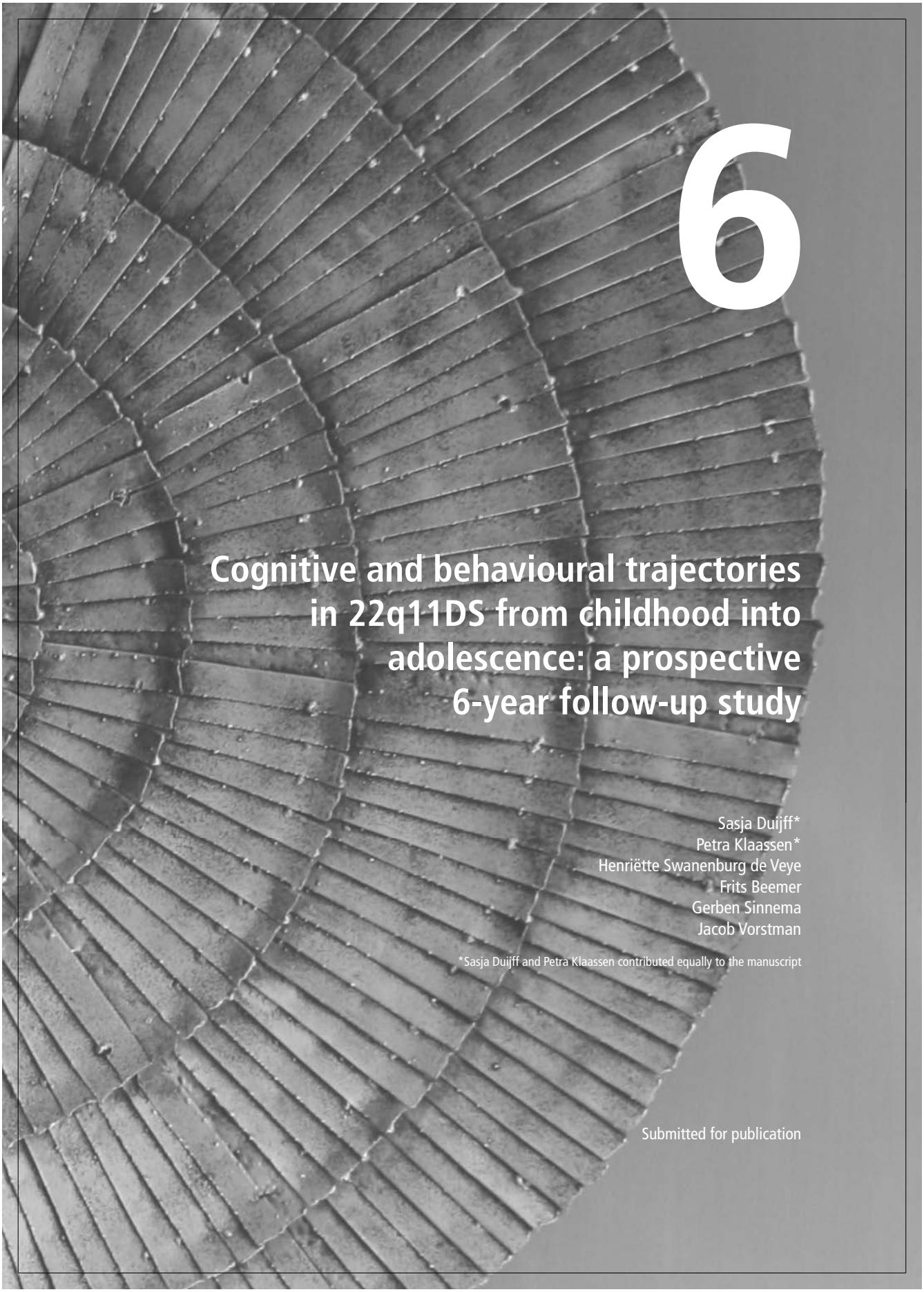
			Total problems at 9.5y		
			Normal range	Borderline range	Clinical range
Total problems at 7.5y	Decline group[1]	Normal range	3 (33%)	0 (0%)	0 (0%)
		Borderline range	0 (0%)	0 (0%)	1 (11%)
		Clinical range	0 (0%)	2 (22%)	3 (33%)
	Remaining group[2]	Normal range	9 (47%)	1 (5%)	0 (0%)
		Borderline range	1 (5%)	1 (5%)	0 (0%)
		Clinical range	0 (0%)	0 (0%)	7 (37%)
			Internalizing problems at 9.5y		
Internalizing problems at 7.5y	Decline group[1]	Normal range	2 (22%)	0 (0%)	2 (22%)
		Borderline range	0 (0%)	2 (22%)	0 (0%)
		Clinical range	0 (0%)	0 (0%)	3 (33%)
	Remaining group[2]	Normal range	8 (42%)	1 (5%)	1 (5%)
		Borderline range	2 (11%)	2 (11%)	1 (5%)
		Clinical range	0 (0%)	0 (0%)	4 (21%)
			Externalizing problems at 9.5y		
Externalizing problems at 7.5y	Decline group[1]	Normal range	4 (44%)	1 (11%)	0 (0%)
		Borderline range	1 (11%)	0 (0%)	0 (0%)
		Clinical range	0 (0%)	1 (11%)	2 (22%)
	Remaining group[2]	Normal range	11 (58%)	1 (5%)	1 (5%)
		Borderline range	0 (0%)	0 (0%)	2 (11%)
		Clinical range	1 (5%)	0 (0%)	3 (16%)

[1] Absolute decline in raw scores of 2 or more subtests (*n* = 10)
[2] No decline in raw scores or in less than 2 subtests (*n* = 19)

Table S5.4 Change in mean CBCL scores per subgroup and corresponding Confidence Intervals (*n* = 29). No significant differences were found between the two groups.

	7.5y		9.5y		
	Decline group[1] (*SD*)	Remaining group[2] (*SD*)	Decline group (*SD*)	Remaining group (*SD*)	95% CI
Total problems	60.9 (11.9)	58.6 (11.1)	63.0 (10.0)	57.8 (12.0)	-7.2 – 5.9
Internalizing problems	60.3 (14.3)	56.0 (11.1)	62.6 (11.6)	58.7 (11.1)	-8.8 – 3.3
Externalizing problems	57.4 (10.2)	55.4 (10.1)	58.3 (9.2)	53.7 (12.4)	-9.7 – 1.6

[1] Absolute decline in raw scores of 2 or more subtests (*n* = 10)
[2] No decline in raw scores or in less than 2 subtests (*n* = 19)



6

Cognitive and behavioural trajectories in 22q11DS from childhood into adolescence: a prospective 6-year follow-up study

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ABSTRACT

Background: Patients with 22q11DS are at risk of psychiatric problems and cognitive impairment. Recent studies suggest a possible intellectual decline in 22q11DS children. To date it is unknown if cognitive development is related to the behavioural problems in 22q11DS.

Aims: To examine cognitive and behavioural development in 22q11DS from childhood into adolescence.

Method: 53 children with 22q11DS underwent cognitive and behavioural assessments at 9.5y (T1) and 15.3y (T2). In about one third, IQ data obtained at 7.5y (T0) were also available. Development of behavioural problem scores and the possibility of correlations to IQ were examined.

Results: Internalizing behaviours intensified while externalizing behaviours decreased. Simultaneously, in about a third a significant decline in IQ was found, which, surprisingly, was unrelated to the behavioural changes.

Conclusions: Children with 22q11DS follow a unique developmental trajectory. Cognitive deterioration is severe in some but does not appear to predict behavioural problems in early adolescence.

INTRODUCTION

The 22q11 deletion syndrome (22q11DS) is a genetic disorder affecting approximately 1 in 4000 live births.[1] The cognitive phenotype of 22q11DS in children and adolescents is characterized by a borderline range of functioning (Full Scale IQ 70-75).[2,3] However, cognitive level may be unstable in the 22q11DS population; cross-sectional studies suggest a negative correlation between age and FSIQ[3,4] and recent longitudinal studies also describe a decrease in FSIQ, mainly driven by a decline in verbal IQ (VIQ).[5,6] Duijff et al.[7] report declines in FSIQ, VIQ and PIQ starting as early as age 5 which can only be partly explained as the result of 'growing into deficit'; a subgroup of children showed an absolute loss of cognitive faculties as measured by a substantial decline in raw scores over a 2 year period.

Although psychiatric problems occur in individuals with cognitive abilities across the entire IQ range, several studies have demonstrated that within the general population a lower intelligence is associated with a higher frequency of psychiatric /behavioural problems.[8-10]

Children and adolescents with 22q11DS also display various behavioural problems. According to standardized psychiatric classifications, Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), psychotic disorder and various anxiety disorders are commonly reported.[4,11-19] In about one third of adults with 22q11DS a psychotic disorder has been reported; but even in childhood hallucinations and delusions appear to be frequent and are reported in up to a quarter of children.[4,13,18,19] It is questionable whether children with 22q11DS are really at an increased risk for all these different DSM-IV disorders. Possibly, the same behavioural manifestations are labelled differently as a result of age at assessment, methods of examination and differences in interpretation of observed symptoms. As an alternative to the categorical method of classification, the observed behavioural symptoms can also be described using a more dimensional approach.[20] This implies that the nature and intensity of psychiatric symptoms are observed and recorded, regardless of whether they meet criteria for a dichotomous classification for a specific diagnosis. From this perspective, there appear to be clear recurring problem areas in 22q11DS children. These domains of symptoms include social problems, attention problems, psychotic symptoms, and anxiety problems.[3,4,6,21-26] A way of assessing these behavioural problems dimensionally is by use of the Child Behavior Checklist (CBCL),[27] a questionnaire filled out by parents. In various cross-sectional studies on children with 22q11DS in which the CBCL is used, parents report higher total impairment scores in older children[15,22,25,28,29] than those studies describing younger children.[26,30,31] This suggests a negative relationship between age and problem behaviour in children with 22q11DS.

In summary, thus far studies indicate that, in comparison to the general population, children with 22q11DS: 1) have a lower FSIQ on average, 2) may show a decline of cognitive abilities with age, and 3) display more behavioural/ psychiatric problems. To date it is unknown to what extent changes in cognitive abilities over time could be used as a predictor for the onset of behavioural/ psychiatric problems in 22q11DS, in particular of psychotic disorder in late adolescence or early adulthood. This knowledge could increase our understanding of this complex genetic syndrome as well as improve the quality of clinical care for these patients.

Based on the above literature discussion we formulated 3 hypotheses:

1. With respect to cognitive development, we expect a subgroup of children with 22q11DS to show a decline in cognitive level over time.
2. In line with cross-sectional results we hypothesize that with age, more behavioural problems will emerge in children with 22q11DS.
3. We hypothesize that a decline in cognitive level increases the probability of the onset, or worsening, of behavioural problems in children with 22q11DS.

METHOD

Subjects

This study is part of a nationwide prospective longitudinal psychological study on intelligence and behaviour in children with 22q11DS. In this ongoing study, enlistment is allowed at any age between 1 and 15 years.

Participants were recruited through referrals from genetic counsellors, cleft palate clinics and/ or paediatric cardiologists from hospitals throughout The Netherlands or through postings on the website of the Dutch parent support group VCFS/ 22q11 (http://www.vcfs.nl). This website is freely accessible to the public. Inclusion criterion was the presence of a 22q11.2 deletion confirmed by FISH analysis (fluorescence in situ hybridization) or MLPA (multiplex ligation-dependent probe amplification).[32] The assessment protocol was approved by the Dutch Medical Ethical Review Commission (M.E.T.C.). Written informed consent was obtained from all parents or guardians.

The current study focuses on the transition from childhood (T1) into adolescence (T2). Mean (*SD*) age at T1 was 9.5 (0.4) years and 15.3 (0.6) years at T2. Between T1 and T2 there was a mean (*SD*) time of 5.8 (0.6) years. Originally a total of 62 children were assessed at T1. Of this group 3 children could not be tested with formal IQ tests, however they were estimated to have

an intelligence level below the range of moderate mental retardation (see Supplement S6.1). Data pertaining to these children were excluded from all statistical analyses, resulting in 59 children at T1 (37 girls, 22 boys). From this cohort 89% (53 children, 36 girls, 17 boys) were re-assessed at T2 (drop out of 6 children at T2 is described in Supplement S6.2). Although 22q11DS is not gender specific, in this study significantly more girls than boys participated at T2: χ^2 (1) = 6.8, p = .009, mainly caused by male dropout at T2.

Sixteen of the children reported in this study have also been described in an earlier article on the development of children between the age of 5 and 9.7 Including this data in the current study in a posthoc analysis allowed for the analysis of the development of cognitive abilities of children with 22q11DS from the age of 7.5 (T0).

Education

Parents were asked to report on the highest level of education attained and were categorized according to the International Standard Classification of Education (ISCED) as designed by UNESCO.[33] In the general Dutch population 30% of men and 26% of women have completed higher 'tertiary' education while 43% of both men and women completed secondary education.[34]

It was found that within the 22q11DS group, 29% of fathers and 31% of mothers had completed higher 'tertiary' education and 39% of fathers and 43% of mothers had completed 'secondary' education, implying that the parent's level of education is representative for the Dutch population.

Assessments

All assessments were administered individually by a trained mental health professional holding at least a bachelor level degree. Most measures were administered during the morning at the University Medical Centre Utrecht in a special assessment room. Eight children were assessed at school at either T1 or T2. Behavioural questionnaires were filled in at home by parents.

Cognitive assessment

At T1 all participants were assessed using the Wechsler Intelligence Scale for Children – Revised (WISC-RN)[35] and/ or the Wechsler Intelligence Scale for Children Third Edition (WISC-III-NL).[36] The Wechsler tests consist of 2 scales, a scale assessing verbal IQ (VIQ) and a scale assessing performance IQ (PIQ). The test yields three scores: FSIQ, VIQ and PIQ, each with a mean norm score of 100 and a standard deviation of 15. The study started before the WISC-III-NL was published in The Netherlands; therefore early participants (n = 22) have

been assessed with the WISC-RN at T1 and with the WISC-III-NL at T2 (WR-W3 group). All other participants (n = 31) were assessed with the WISC-III-NL at both ages (W3-W3 group). The high correlation between WISC-RN and WISC-III-NL derived scores (r = .88)[36] suggests that FSIQ results from both tests are comparable.

Any observed decrease in IQ in this population could be due to insufficient cognitive development leading to an increasing discrepancy with age-required norms (a concept referred to as 'growing into deficit'), or alternatively, to an absolute decline in cognitive capabilities. To investigate both scenarios, the subtest scaled scores (i.e. age specific normative scores) as well as the subtest raw scores (i.e. absolute test scores, prior to age-normative adjustment) were analysed.

Behavioural assessment

The Dutch version of the Child Behavior Checklist 6–18 (CBCL)[27] was completed by the children's parents. It is a questionnaire with 120 items describing the behaviour in children from a parent's point of view. It investigates internalizing problems (anxious/depressed, withdrawn/depressed and somatic complaints), externalizing problems (rule breaking behaviour and aggressive behaviour) and social problems, thought problems and attention problems.

The CBCL results are expressed as T-scores, based on age and gender norms. The mean T-score is 50 (SD = 10). A T-score of either 70 or higher on one of the subscales, or 64 or higher on the internalizing, externalizing or total problems scales is classified as 'clinical', indicating psychopathology.

To evaluate if an individual child displayed more behavioural problems over time, changes in raw scores were compared with the standard error of measurement (SEs). The manual for the ASEBA School-age Forms & Profiles[27] provides these SEs for each scale, based on age and gender. Also, use of psychotropic medication was recorded at both time points.

Statistics

First, paired t-test analyses were performed to analyse the change in cognitive level as measured by the development of FSIQ, VIQ and PIQ between T1 and T2 (N = 53).

Secondly, to differentiate between growing into deficit and the possibility of an absolute decline in cognitive abilities the results of a subgroup of children that were tested with exactly the same test (WISC-III-NL) at T1 and T2 were examined (n = 31) using the raw subtest scores.

The possibility of test related effects on the changes in IQ scores over time was examined. This was especially important, as the primary interest of this study is the longitudinal development

of cognition. To this end IQ changes were compared between children who were tested with the WISC-III-NL at both ages (W3-W3, n = 31) and those tested with WISC-RN at T1 and WISC-III-NL at T2 (WR–W3, n = 22), using an independent-samples t-test. Also, in a posthoc analysis the FSIQ results of 16 children assessed at T0 were examined.

Change in behaviour as measured by the CBCL behavioural scales were analysed between T1 and T2 by use of paired t-test. To evaluate if the individual child displayed an increase in behavioural problems with age, the changes in raw scores were analysed with Cross Tab analyses, using Fisher's Exact Tests because of the small expected count.

Finally, to test the possibility of an association between cognitive development and behavioural changes logistic regression analysis was used. Total score, internalizing score and externalizing score at T2 were controlled for the effect of gender, parental education, delta change in IQ (FSIQ, VIQ and PIQ) and FSIQ, VIQ and PIQ scores at T1.

Significance level was tested two-sided with $\alpha = 0.05$. All statistical calculations were carried out using SPSS version 19.0 statistical analysis software.

RESULTS

Longitudinal changes in cognition

Between T1 and T2 mean FSIQ declined significantly with 5.9 points ($p < .0001$, SE = .95, 95% CI, 3.98 – 7.79). Change in FSIQ ranged from -24 to +10 FSIQ points. See Figure 6.1 for the distribution of delta FSIQ; this figure illustrates a substantial left shift in the distribution of FSIQ change between time points.

VIQ and PIQ both declined significantly. VIQ declined ($p < .0001$) with 4.75 VIQ points (SE = 1.06; 95% CI, 2.91 – 7.17), VIQ change ranged from -23 to +8. PIQ declined significantly ($p < .0001$) with 5.17 IQ points (SE = 1.37; 95% CI, 2.55 – 8.04), ranging from -32 to +26 PIQ points. Verbal Comprehension and Perceptual Organization declined significantly. Processing Speed did not decline over time. Results are presented in Table 6.1.

No gender differences were found in the longitudinal changes after correcting for multiple testing for FSIQ, VIQ or PIQ.

At T1 no significant differences were found between the mean scores on the WISC-RN when compared with the WISC-III. Both the WR-W3 group (n = 22) and the W3-W3 group (n = 31) showed a significant decline in the mean development of FSIQ, VIQ and PIQ from T1 to

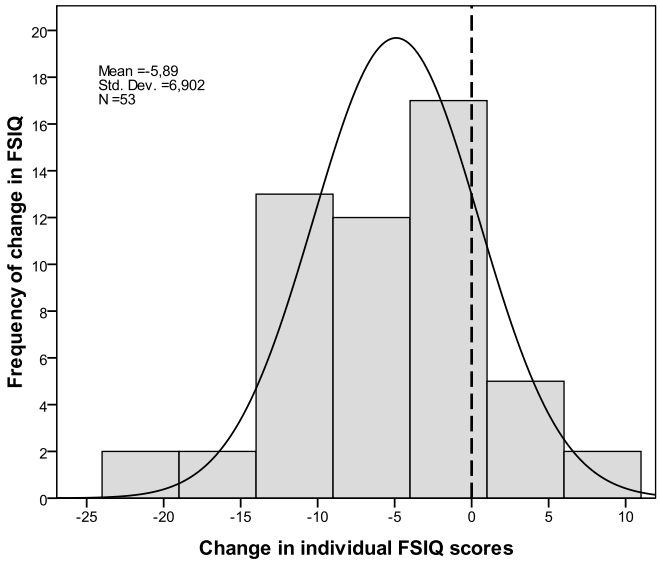

Figure 6.1 Distribution of delta FSIQ from T1 to T2 (*N* = 53).

Table 6.1 Mean longitudinal change in cognition in 22q11DS from 9.5 years (T1) to 15.3 years (T2) including gender differences (*n* = 53)

	T1 (*SD*)	T2 (*SD*)	T2-T1 (*SD*)	*p*
FSIQ (*SD*)	69.8 (12.1)	63.9 (11.5)	-5.9 (6.9)	<0.0001
Min – max	48 – 99	45 – 92	-24 – 10	
Female/male FSIQ (*SD*)	72.5 (11.6)/ 64.1 (11.3)*	66.4 (11.5)/ 58.6 (9.8)*		
VIQ (*SD*)	72.0 (13.1)	67.1 (11.8)	-4.8 (7.5)	< 0.0001
Min – max	48 – 103	55 – 101	-23 – 8	
Female/ male VIQ (*SD*)	74.3 (13.4)/ 67.5 (11.5)	69.9 (12.4)/ 62.2 (8.5)*		
PIQ (*SD*)	73.0 (12.6)	67.6 (10.6)	-5.2 (9.7)	< 0.0001
Min – max	48 – 96	55 – 96	-32 – 26	
Female/ male PIQ (*SD*)	76.0 (12.0)/ 66.8 (11.8)*	69.3 (9.5)/ 64.1 (12.3)		
Verbal Comprehension (*SD*)	71.5 (12.6)	68.5 (13.0)	-3.0 (6.3)	0.013
Min – max	54 – 103	54 – 106	-15 – 8	
Perceptual Organisation (*SD*)	73.2 (11.5)	70.0 (11.1)	-3.2 (7.1)	0.017
Min – max	49 – 98	48 – 91	-17 – 14	
Processing Speed (*SD*)	79.7 (14.3)	75.7 (15.2)	-4.1 (13.5)	0.096
Min – max	55 – 102	55 – 105	-28 – 33	

* gender difference $p < 0.05$

T2. FSIQ and VIQ declined more severely when children were assessed with the WISC-R at T1 (see Supplemental Table S6.3).

The subtest raw scores of the children assessed with the WISC-III NL at both T1 and T2 ($n = 31$) were analysed. The delta raw scores of this W3-W3 group are presented in Supplemental Table S6.4. Twelve children (38%) showed either a stagnation (delta raw score = 0) and/or decline in raw scores on one or more subtests between T1 and T2 (mean time span 5.8 years).

The change in both FSIQ and subtest raw scores of 16 children who had also been assessed at 7.5 years (T0) with the WISC-III-NL were included in the analysis. Between T0 and T2, changes in mean FSIQ ranged from -24 to +6. The results are plotted in Supplemental Figure S6.5; the raw score development is shown in Supplemental Table S6.7 Some children show a decline between T0 and T1 whereas others decline between T1 and T2.

Longitudinal changes in behaviour

Paired *t*-test analyses of the behavioural scales indicated that, between T1 and T2, mean scores showed a significant increase in Withdrawn/ Depressed Behaviour ($p = .001$), even after Bonferroni correction for multiple testing (see Table 6.2). Figure 6.2 clearly shows a change

Table 6.2 Mean longitudinal change in CBCL scores of 22q11DS children from 9.5y (T1) to 15.3 y (T2) ($n = 41$) and significance of difference

CBCL factors and subscales	T1 mean (*SD*)	T2 mean (*SD*)	*p*
Anxious/ depressed	59.00 (8.75)	60.73 (10.22)	0.23
Withdrawn/ depressed	58.63 (7.33)	63.78 (9.40)	0.00
Somatic complaints	61.93 (7.50)	61.34 (9.40)	0.72
Social problems	68.51 (8.47)	65.88 (6.78)	0.04
Thought problems	60.51 (8.06)	60.22 (7.72)	0.80
Attention problems	57.27 (5.32)	58.68 (6.08)	0.05
Rulebreaking behaviour	52.93 (4.10)	53.59 (5.83)	0.52
Aggressive behaviour	60.22 (8.18)	56.85 (6.34)	0.01
Internalizing	59.76 (9.36)	62.83 (9.39)	0.06
Externalizing	55.80 (8.80)	53.07 (9.02)	0.06
Total Problem	60.54 (9.57)	60.37 (7.94)	0.90

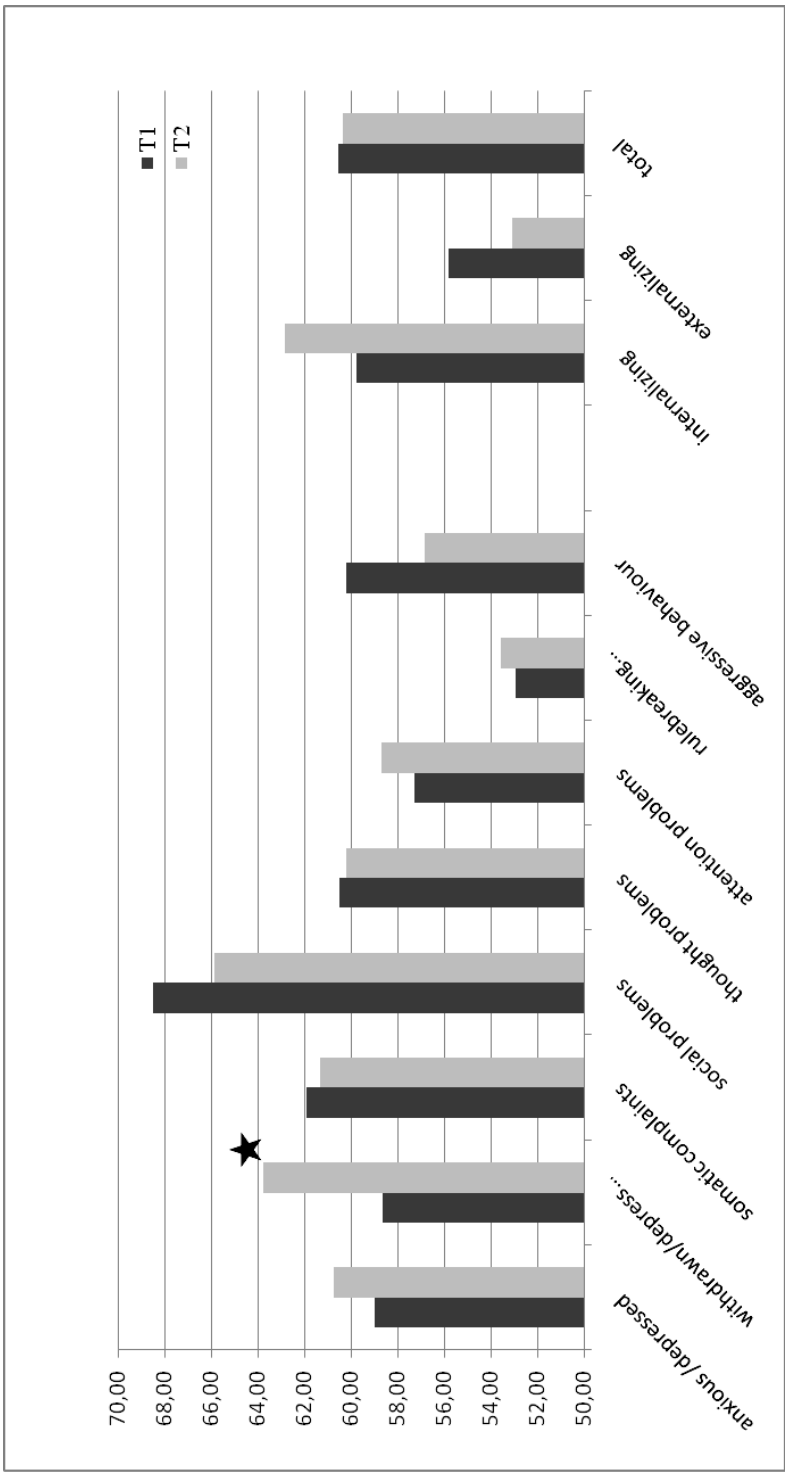

Figure 6.2 Mean CBCL scores at 7.5y (T1) and 15.3y (T2) in children with 22q11DS.

in behavioural profile with age, characterized by a shift in the proportion of internalizing/ externalizing behaviour. At T1 the difference between the internalizing and externalizing scale is 3.95 (p = .001, SE = 1.12; 95% CI, 1.70 – 6.20), at T2 the difference is 9.76 (p < .0001, SE = 1.49; 95% CI, 6.74 – 12.77). Mean Total Problem behaviour stayed constant.

An analysis of the individual child's delta raw scores showed a 50% increase in internalizing behaviour and a 37% increase in total problem behaviour. A 70% increase in withdrawn/ depressed behaviour and an increase of nearly 50% in attention problems at T2 was noted. The results are presented in Table 6.3.

No significant gender differences were found in behaviour at T1, T2 or in longitudinal changes after correcting for multiple testing.

Cognition and behaviour

No relation was found between a change in mean FSIQ and worsening behaviour as reported by parents in the CBCL on any of the scales. No significant correlation was found between change in FSIQ and change in behavioural problems. Figure 6.3 illustrates this more clearly.

Covariates were controlled for in logistic regression analysis, none of these analyses showed significant results (data not shown).

Table 6.3 Increase in behavioural problems as measured by the change in raw scores (n = 41)

	Increase in raw scores (%) T2-T1	p
Anxious/ depressed	31.7	.146
Withdrawn/ depressed	70.7	.063
Somatic complaints	36.6	.128
Social problems	17.1	.020
Thought problems	24.4	.302
Attention problems	48.8	.001
Rulebreaking behaviour	22.0	1.000
Aggressive behaviour	14.6	.039
Internalizing	51.2	.118
Externalizing	19.5	.030
Total Problem	36.6	.122

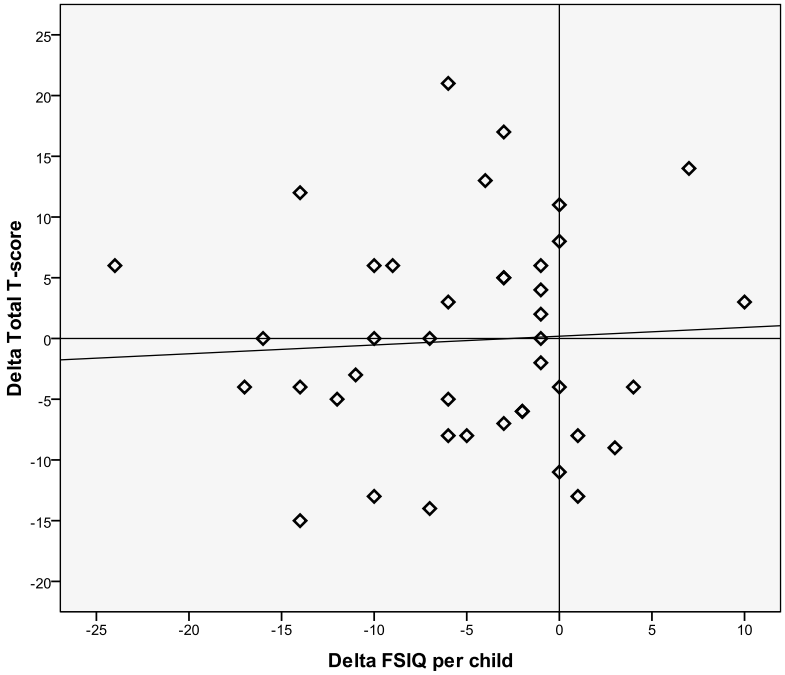

Figure 6.3 Change in FSIQ and change in Total Problem Score per child (a negative score is a decline).

CONCLUSION

This study focuses on the changes in IQ and behaviour during the transition from childhood into adolescence in children with 22q11DS. It was hypothesized that a subgroup of children with 22q11DS would show a decline in FSIQ over time; that with age, more behavioural problems would emerge in children with 22q11DS and that a decline in FSIQ would be associated with an increase in behavioural problems.

Changes in FSIQ were found, mainly characterized by a decline. In 32% of the group (N = 53) IQ declined with ≥ 10 FSIQ points between 9.5 and 15.3 years. The average FSIQ of the remaining 68% of children stayed relatively stable. However, after incorporating the data of those children who were also assessed at 7.5 years the picture changed. Of the children who had seemed stable between 9.5 and 15.5 years, 31% turned out to already have declined between the age of 7.5 and 9.5. Therefore, when combining the data of these 3 time points it can be concluded that, based on this study, in approximately 42% of 22q11DS children a significant and clinically relevant decline in FSIQ occurs somewhere between the age of 7.5 and 15.

Also, when analyzing the data of the group assessed with the same test at T1 and T2 (n = 31) either a stagnation or a regression in raw subtest scores was found on one or more subtests in approximately a third of children.

Behaviour as measured by the CBCL (parental report) showed a significant shift in the behavioural profile of children with 22q11DS although mean total problem scores remained constant. Scores on the internalizing problem scale increased and were characterized by more withdrawn/ depressed behaviour while externalizing problem behaviour decreased. However, there was no relationship between the changes in cognitive level and behaviour problems, thus refuting our third hypothesis.

The question raised by these results is: how stable is stable in 22q11DS? The negative correlation between age and IQ is especially interesting, considering the fact that in the general population intelligence is considered a relatively stable trait. A recent longitudinal study of 9-year-old twin pairs and their siblings assessed with the WISC-III-NL at two time points showed a high stability of FSIQ and VIQ over a 3 year span, and a slightly lower stability of PIQ.[37] This study excluded children with any known major medical or psychiatric history or who were attending special education.

Longitudinal reports on the cognitive and behavioural development in other genetic disorders associated with intellectual disabilities are scarce. In one study longitudinal decreases in IQ are reported in children with Fragile X syndrome, Williams-Beuren Syndrome and neurofibromatosis type 1 over a 2-year period.[38] IQ differences of ≥ 10 IQ points in some children are reported, unfortunately raw scores are not provided. Also adaptive behaviour declined significantly in children with Fragile-X syndrome, but not in the other two syndromes described. In another syndrome (Prader Willi) no declines were found.[39] Thus, available data suggests that 1) cognitive decline during childhood may not be present in all genetic disorders associated with mental retardation, and 2) it is uncertain to what extent an absolute decrease in IQ, such as reported here, is common in genetic disorders other than 22q11DS. The results of the current study replicate, in a different age group, our previous findings in younger children.[7] The results also suggest the possibility that children whose IQ appears relatively stable up to their early teens may still go on to decline in adolescence or adulthood.[4]

The outcome of this study may be particularly relevant in the context of the well established increased risk of schizophrenia in patients with this genetic disorder.[4,6,15,23] For instance, one could argue that a growing discrepancy between cognitive abilities and the expectations of school and home environment lead to increase in stress. Subsequently, enduring chronic stress may induce in those vulnerable the emergence of psychosis.[41] Possibly, behavioural changes may

precede the onset of psychosis and could therefore be a first indicator of schizophrenia. However, against our expectations, in children with 22q11DS cognitive decline was not associated with an increase in behavioural problems. The age at assessment T2 precluded the possibility of taking psychosis as a primary outcome measure in this study as many of the children without psychotic symptoms can still be expected to develop psychosis in the coming years.

It could be hypothesized that as a result of participation in this study, there has been constant monitoring of the child's cognitive level, allowing for adjustments in school and home and managing expectations. Perhaps, in some cases the early detection of decline has lowered the potential risk of a mismatch between a child's cognitive abilities and the expectations of the environment, thereby reducing the possible development of stress. Also, during the course of the study, a psychologist was always available for consultation and advice, including information with regard to rearing and educating a child with a cognitive impairment.

Along with the results it is also important to note the limitations of our study. For one, the lack of psychiatric assessments could be considered a limitation. As a result we cannot evaluate whether any observed changes in IQ are correlated to psychiatric diagnoses such as ADHD and ASD. However, several previous studies by different groups strongly suggest that such a correlation does not exist, or at least, is likely to be of modest strength at most.[3,18,25,42]

Females are overrepresented in this study, but no gender differences are found in the longitudinal change of FSIQ and behaviour. In our previous study a more severe decline was found for girls than boys, concurrent with Antshel et al.[43] We suggested then that the difference found may have been the result of a floor effect of the WISC-III-NL: boys could not decline more severely because the test does not allow for it. For the current results the same may be true for both genders: FSIQ is lower at this age for both boys and girls, with a greater chance of a floor effect.

This study indicates that children and adolescents with 22q11DS follow a unique developmental trajectory unlike any other genetic disorder causing intellectual disabilities, as far as we know. The cognitive deterioration is rapid and severe in some children and urges for a closer investigation of the relationship with possible development of psychosis.

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SUPPLEMENT

S6.1 Excluded patients

For all the following children intelligence level was estimated to be below the range of moderate mental retardation. Intelligence scores were not able to be derived, in some cases an age equivalent was available. Data pertaining to these children was excluded from all statistical analyses.

Case 71 (f)

At 7.8y and 9.5y scores from the SON-R 2.5–7 indicated IQ levels below the range of moderate mental retardation (age equivalent of 2.7y and 3.7y respectively were found). At age 15.7 when assessed with the WISC-III an age equivalent below 6 years was found.

Case 122 (m)

At age 5.6y patient was unable to be tested. At age 7.6y IQ levels indicated levels below the range of moderate mental retardation (age equivalent of 3.9y by use of SON-R 2.5–7). At 9.6y patient was unable to be assessed by use of WISC-III-NL. At age 15.7 an age equivalent of about 5 years was found when assessed with the SON-R 5.5–17.

Case 126 (f)

At 7.11y and 9.5y scores from the SON-R 2.5–7 indicated IQ levels below the range of moderate mental retardation (age equivalents of 3.8y and 4.2y respectively were found). At age 15.5 when assessed with the WISC-III an age equivalent below 6 years was found.

S6.2 Drop out at T2

Case 81 (m)

At age 9.7 scores from the WISC-III indicated a FSIQ of 91 (VIQ = 95, PIQ = 87). Patient died at the age of 10 due to his heart condition.

Case 135 (m)

At age 9.7 scores derived from the WISC-III indicated a FSIQ of 59 (VIQ < 55, PIQ = 71). At age 15 this boy was hospitalized with a severe scoliosis and was awaiting his operation. His mother also has 22q11DS.

Case 136 (f)

At age 9.6 scores derived from the WISC-III indicated a FSIQ of 72 (VIQ = 76, PIQ = 72). Parents declined participation at T2.

Case 139 (m)

At age 9.6 scores derived from the WISC-III indicated a FSIQ of 62 (VIQ = 58, PIQ = 72). At age 15 this boy had a tumour in his ear for which he was awaiting operation, parents declined participation while he is recuperating.

Case 171 (m)

At age 9.4 scores derived from the WISC-III indicated a FSIQ of 50 (VIQ < 55, PIQ < 55). Patient had a severe epileptic attack days before assessment. Parents declined further participation while he is recuperating.

Table S6.3 Comparison of the change in FSIQ scores from T1 to T2 by test for children assessed at both age levels (*n* = 53)

		Test used at age of assessment					
	n	T1	T2	Mean T1-T2 (*SD*)	T1-T2 *p*	95% CI of difference	Test difference *p*
ΔFSIQ	31	WISC-III-NL	WISC-III-NL	-3.45 (5.9)	.003	-9.40 – 2.33	.002
	22	WISC-RN	WISC-III-NL	-9.32 (6.7)	.000		
ΔVIQ		WISC-III-NL	WISC-III-NL	-2.94 (5.3)	.005	-9.27 – -.29	.038
		WISC-RN	WISC-III-NL	-7.71 (9.1)	.001		
ΔPIQ		WISC-III-NL	WISC-III-NL	-3.06 (8.3)	.049	-10.59 – .14	.056
		WISC-RN	WISC-III-NL	-8.29 (10.9)	.002		

Table S6.4 Change in subtest raw scores from 9.5 years (T1) to 15.3 years (T2) per child, sorted by ΔFSIQ. The corresponding change in VIQ and PIQ are also presented as absolute scores (*n* = 31).

		Δ FSIQ	Δ VIQ	Verbal scale						Δ PIQ	Performance scale						
Subject	Gender	T1-T2	T1-T2	Info	Simi	Arith	Vocab	Comp	DS	T1-T2	PC	Sub	PA	BD	OA	SS	
22	f	-13	-6	2	8	2	18	6	0	-20	2	6	8	12	-4	5	
167	m	-13	-7	2	3	2	8	-1	1	-12	0	7	1	22	5	14	
146	f	-12	-12	5	5	2	8	5	2	-11	4	15	6	7	5	12	
180	m	-11	-12	5	12	0	18	5	1	-8	5	5	11	16	6	-2	
24	m	-10	-9	3	6	6	1	0	6	-10	0	17	20	15	3	13	VIQ < 55 at T2
25	f	-10	-14	8	6	1	10	5	1	-6	1	5	8	12	16	-1	
74	f	-10	-10	3	7	1	17	6	-1	-8	3	16	8	11	5	12	
232	f	-10	-9	-	-	-	-	-	-	-9	-	-	-	-	-	-	
73	f	-7	-1	13	14	2	22	8	2	-11	1	31	17	4	7	9	
116	f	-6	-3	-	-	-	-	-	-	-9	-	-	-	-	-	-	
148	f	-6	-6	8	3	3	13	8	2	0	9	13	6	22	11	0	
174	f	-6	2	4	0	5	4	10	1	-4	2	10	-2	21	8	-7	
109	f	-4	-11	11	8	2	12	12	1	-11	1	4	21	14	3	16	
15	f	-3	4	4	8	4	11	11	0	-8	8	14	3	4	3	3	
144	f	-3	-1	2	5	8	3	7	3	-1	3	4	4	25	11	8	VIQ and PIQ < 55 at T2
147	f	-3	0	13	3	6	23	8	1	-7	-2	25	16	12	11	15	
157	f	-3	0	5	6	7	17	7	5	-7	1	18	1	8	-4	4	VIQ < 55 at T1 and T2

Table S6.4 continues on next page

Table S6.4 ***Continued***

		Δ FSIQ	Δ VIQ	Verbal scale						Δ PIQ	Performance scale					
Subject	Gender	T1-T2	T1-T2	Info	Simi	Arith	Vocab	Comp	DS	T1-T2	PC	Sub	PA	BD	OA	SS
165	m	-2	-4	14	1	1	14	13	4	-1	9	11	10	12	12	5
205	f	-2	-1	9	5	6	16	6	2	2	3	16	16	19	14	1
68	f	-1	0	5	0	4	0	8	1	0	6	14	5	13	9	7
92	m	-1	0	1	-1	9	9	9	0	0	13	20	5	6	9	6
18	f	0	4	5	2	2	14	15	4	3	4	35	11	16	9	11
21	f	0	1	7	9	5	17	15	3	0	4	25	30	11	6	22
23	m	0	-2	11	2	9	11	14	1	0	3	10	6	29	3	-
28	f	0	0	12	10	5	11	7	2	-5	5	15	14	16	3	0
16	f	1	-1	6	7	1	28	14	3	2	7	32	13	12	8	12
176	f	3	3	6	9	4	13	8	1	4	6	23	4	18	13	12
105	m	4	3	12	7	3	21	14	3	1	2	23	14	17	6	-5
254	m	4	6	-	-	-	-	-	-	5	-	-	-	-	-	-
209	f	7	5	9	7	5	26	9	7	10	10	21	10	20	11	7
115	m	10	-4	2	1	1	3	5	2	26	6	43	21	-7	14	10

Info = Informtion; Simi = Similarities; Arith = Arithmetic; Vocab = Vocabulary; Comp = Comprehension; DS = Digit Span; PC = Picture Completion; Sub = Substitution; PA = Picture Arrangement; BD = Block Design; OA = Object Assembly; SS = Symbol Search.

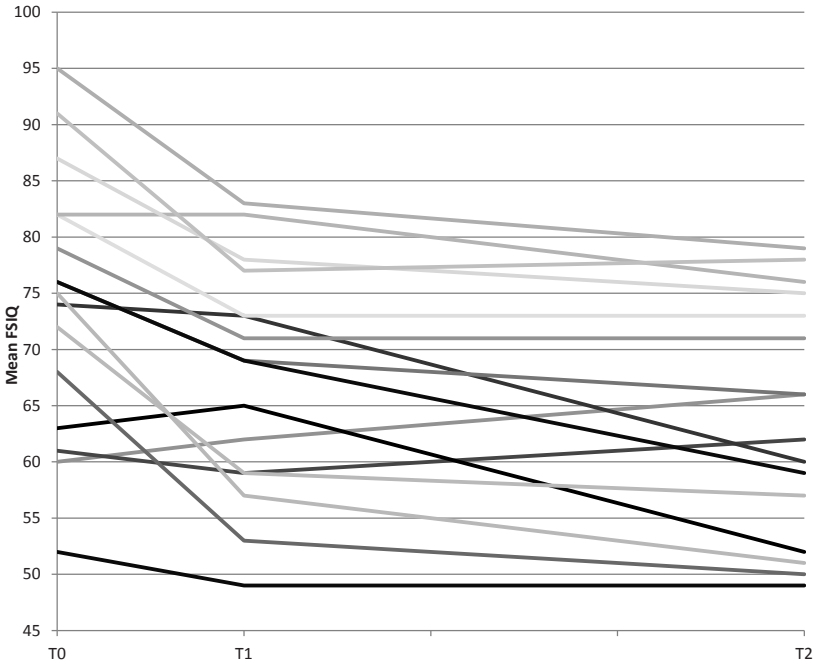


Figure S6.5 Development of FSIQ from T0 (7.5y) thru T1 (9.5y) to T2 (15.3 y) in 22q11DS (*n* = 16) as measured by WISC-III-NL at all time points.

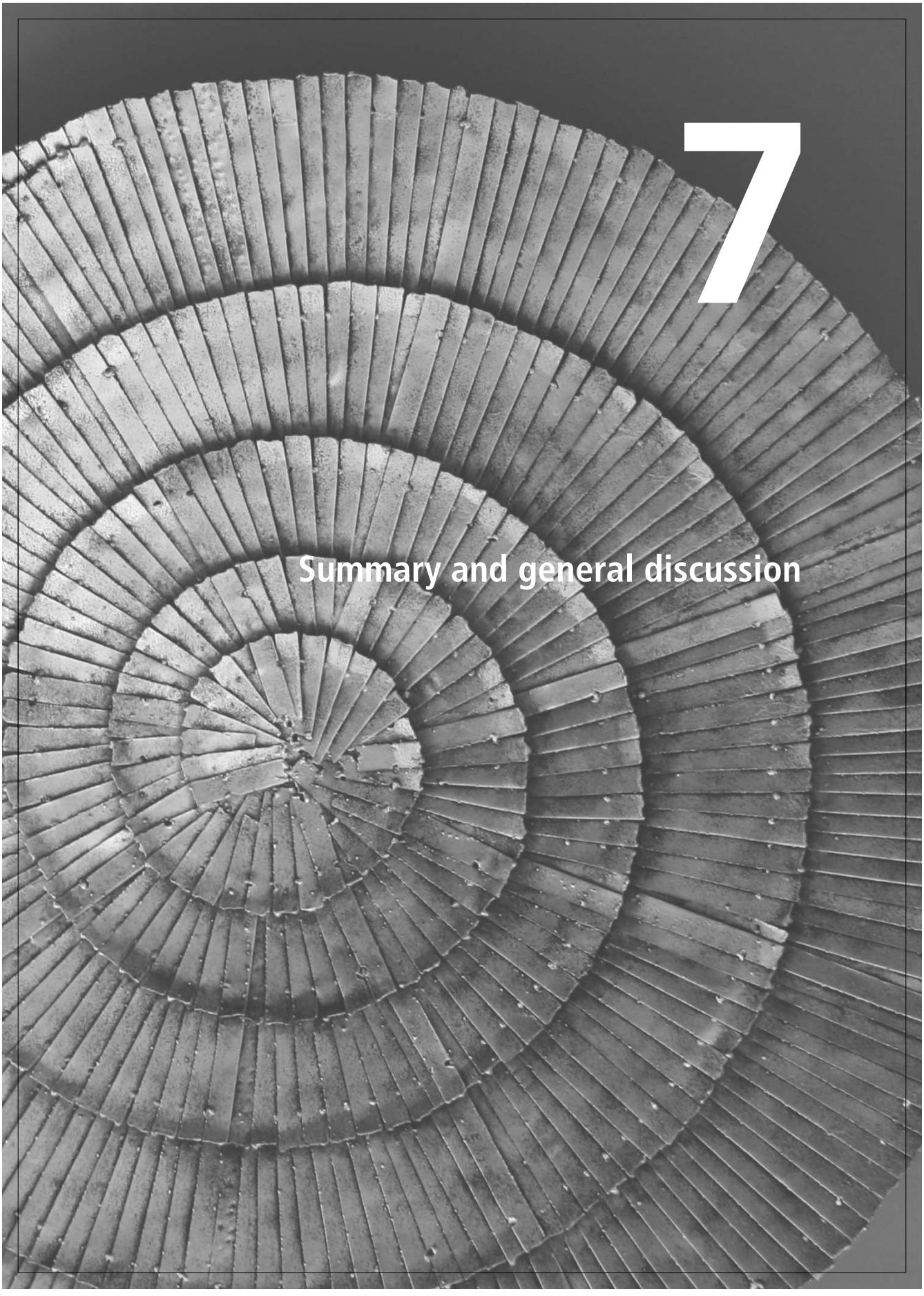
Table S6.6 Development of FSIQ (complementary data to Supplemental Figure S6.5)

	FSIQ		
Gender	T0	T1	T2
m	52	49	49
m	60	62	66
f	61	59	62
m	63	65	52
f	68	53	50
m	72	59	57
f	74	73	60
f	75	57	51
f	76	69	66
m	76	69	59
f	79	71	71
f	82	73	73
f	82	82	76
f	87	78	75
f	91	77	78
f	95	83	79

Table S6.7 Change in subtest raw scores from 7.5 years (T0) through 9.5 years (T1) to 15.3 years (T2) per child, sorted by ΔFSIQ. The corresponding change in VIQ and PIQ are also presented as absplute scores (*n* = 16).

Subject	ΔFSIQ			ΔVIQ			ΔPIQ			VIQ raw score development per subtest											
										T0T1	T1T2	TOT1	T1T2	TOT1	T1T2	TOT1	T1T2	TOT1	T1T2	TOT1	T1T2
	T0-T1	T1-T2	T0-T2	T0-T1	T1-T2	T0-T2	T0-T1	T1-T2	T0-T2	Information		Similarities		Arithmetic		Vocabulary		Comprehension		Digit Span	
174	-18	-6	-24	-15	-6	-21	-19	-4	-23	1	4	-1	0	2	5	-1	4	4	10	0	1
144	-15	-3	-18	-13	-1	-14	-16	-1	-17	3	2	3	5	0	8	-1	3	-1	7	-3	3
24	-7	-10	-17	-10	-9	-19	-4	-10	-14	5	3	-1	6	0	6	5	1	7	0	0	6
109	-12	-4	-16	-5	2	-3	-18	-11	-29	5	11	2	8	5	2	7	12	7	12	0	1
165	-13	-2	-15	-13	-1	-14	-14	-1	-15	1	14	5	1	3	1	3	14	-1	13	1	4
22	-1	-13	-14	-7	-6	-13	6	-20	-14	5	2	-3	8	6	2	1	18	5	6	1	0
16	-14	1	-13	-14	-1	-15	-12	2	-10	3	6	6	7	4	1	-4	28	0	14	2	3
147	-9	-3	-12	-12	0	-12	-4	-7	-11	0	13	6	3	1	6	2	23	6	8	2	1
167	2	-13	-11	-4	-7	-11	8	-12	-4	5	2	-1	3	5	2	2	8	5	-1	-	1
15	-7	-3	-10	-9	0	-9	-3	-8	-11	0	4	2	8	3	4	0	11	3	11	2	0
21	-9	0	-9	-11	1	-10	-7	0	-7	6	7	0	9	2	5	0	17	1	15	2	3
18	-8	0	-8	-13	-2	-15	-2	3	1	4	5	2	2	5	2	4	14	-1	15	2	4
148	0	-6	-6	-1	-11	-12	2	0	2	3	8	7	3	4	3	8	13	3	8	2	2
23	-3	0	-3	0	0	0	-1	0	-1	1	11	2	2	2	9	6	11	3	14	5	1
176	-2	3	1	-2	3	1	-4	4	0	3	6	3	9	7	4	10	13	0	8	4	1
105	2	4	6	4	6	10	0	1	1	6	12	7	7	7	3	4	21	2	14	-	3

Subject	ΔFSIQ			ΔVIQ			ΔPIQ			VIQ raw score development per subtest							
										TOT1	T1T2	TOT1	T1T2	TOT1	T1T2	TOT1	T1T2
	T0-T1	T1-T2	T0-T2	T0-T1	T1-T2	T0-T2	T0-T1	T1-T2	T0-T2	Picture Compl.		Picture Arr.		Block Design		Object Assembly	
174	-18	-6	-24	-15	-6	-21	-19	-4	-23	-2	2	8	-2	-6	21	3	8
144	-15	-3	-18	-13	-1	-14	-16	-1	-17	2	3	0	4	4	25	-3	11
24	-7	-10	-17	-10	-9	-19	-4	-10	-14	3	0	-1	20	12	15	14	3
109	-12	-4	-16	-5	2	-3	-18	-11	-29	-1	1	5	21	10	14	3	3
165	-13	-2	-15	-13	-1	-14	-14	-1	-15	-6	9	8	10	3	12	-5	12
22	-1	-13	-14	-7	-6	-13	6	-20	-14	2	2	9	8	-2	12	14	-4
16	-14	1	-13	-14	-1	-15	-12	2	-10	6	7	3	13	12	12	-7	8
147	-9	-3	-12	-12	0	-12	-4	-7	-11	4	-2	12	16	12	12	4	11
167	2	-13	-11	-4	-7	-11	8	-12	-4	11	0	9	1	-17	22	15	5
15	-7	-3	-10	-9	0	-9	-3	-8	-11	1	8	1	3	6	4	18	3
21	-9	0	-9	-11	1	-10	-7	0	-7	2	4	7	30	28	11	-1	6
18	-8	0	-8	-13	-2	-15	-2	3	1	3	4	7	11	5	16	6	9
148	0	-6	-6	-1	-11	-12	2	0	2	1	9	7	6	3	22	8	11
23	-3	0	-3	0	0	0	-1	0	-1	4	3	13	6	5	29	3	3
176	-2	3	1	-2	3	1	-4	4	0	3	6	5	4	22	18	-3	13
105	2	4	6	4	6	10	0	1	1	1	2	14	14	14	17	1	6



7

Summary and general discussion

The main objective of the research described in this thesis was to study the cognitive development of children with 22q11DS in the period between early childhood (3 years) and adolescence (15 years). In particular the focus was on stability of IQ in time, the relationship between intelligence level and behaviour and the influence of potential confounders such as gender, heart conditions, origin of deletion and level of parental education on IQ.

The research was embedded in the clinical, medical setting of the Wilhelmina Children's Hospital, University Medical Centre of Utrecht. Set up as a prospective, longitudinal and nationwide study the objective was to go 'back to basics' by systematically describing the cognitive and behavioural development of children with 22q11DS by assessing them at set ages (at 1.5, 3.5, 5.5, 7.5, 9.5 and 15.5 years of age). As a result, children were monitored at regular intervals, allowing for adjustments in school and home environment and managing school- and parental expectations. Parental motivation was high and drop-out low. Parents were more than willing to travel from all over the country to have their children assessed every 2 years.

The increasing awareness of the syndrome in paediatric care and the close collaboration with the Dutch parent support group VCFS/22q11DS[*] resulted in a growing number of participants of this psychological study. As a result, there was also a growing number of medical questions from parents which we were unable to answer. Therefore in 2007, the 22q11-multidisciplinary specialist team of the UMC Utrecht was formed. Main specialists involved are a clinical geneticist, a dentist, an ENT (ear-nose-throat) specialist, a paediatrician, a plastic surgeon, a child psychiatrist, a psychologist and a speech-therapist. Specialists in cardiology and orthopaedics can be consulted when indicated. The out-patient clinic is on a monthly basis; efforts are made to concentrate all consultations in one day.[†]

MAIN FINDINGS

1. Instability of FSIQ in 22q11DS

The findings presented in this thesis indicate that there are some features of cognitive development that may be specific to children with 22q11DS, suggesting the possibility of a 22q11DS cognitive phenotype. In 22q11DS, for example, at the age of 42 months (**Chapter 2**) children with 22q11DS already have a mean (*SD*) mental delay of 9.2 (6.4) months when compared to peers. Another novel finding is that at 5 years of age (**Chapter 3**) children

[*] www.vcfs.nl and www.vgnetwerken.nl/netwerken/vcfs-22q11%20deletie

[†] www.umcutrecht.nl/subsite/vcfs

with 22q11DS have difficulty with the analysis and processing of visual information while deficiencies in motor skills do not show a relevant negative impact at this age. Most importantly, the findings of this thesis indicate that in 22q11DS cognitive level is an unstable trait that declines with age. In some children this is the result of not being able to keep up with their peers. This phenomenon of 'growing into deficit' is often reported in children with learning disabilities as a result of a syndrome.[1-3] However, in about a third of the children a cognitive deterioration beyond 'growing into deficit' was detected. In this group either a complete stagnation or a decline in raw test scores was found (**Chapter 5** and **Chapter 6**). This implies that in more than a third of children with 22q11DS there is a measurable loss of cognitive abilities between the age of 5 and 15. The mean longitudinal development of FSIQ, VIQ and PIQ in children with 22q11DS, based on the results presented in the various chapters of this thesis are presented in Figure 7.1.

The cognitive assessment of children with a mental disability and/or behavioural problems is a challenge. There are many factors that can influence the results of a developmental- or intelligence test besides actual intelligence level, such as motivation, span of attention and the ability to concentrate. This is especially true for children with developmental disabilities, which complicates assessment and interpretation of cognitive test results.[4] Although this may have played a role in some of the 22q11DS assessments, a stagnation or decline in raw scores, where an increase would be expected due to aging and maturation of the child, is hard to explain from these factors.

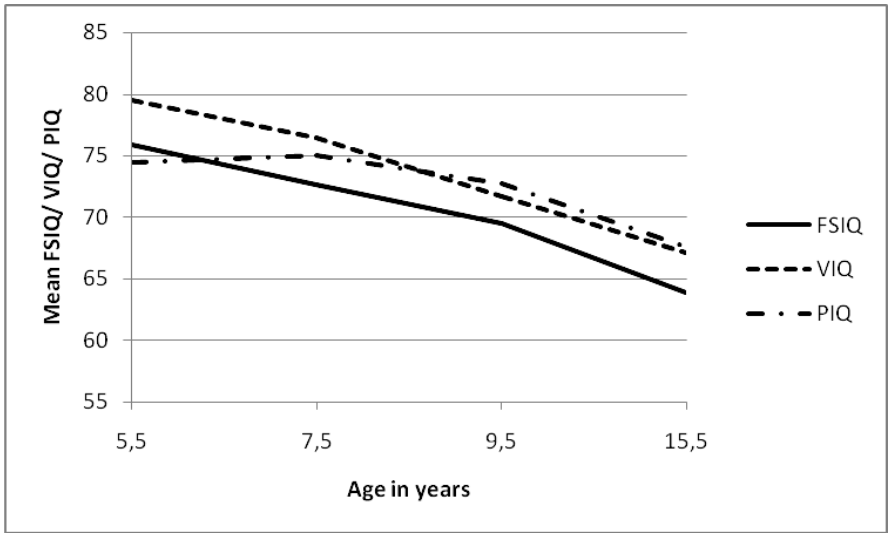


Figure 7.1 Mean longitudinal development of FSIQ, VIQ and PIQ in children with 22q11DS.

2. Lack of relationship between IQ and behavioural problems

In all studies that incorporated behavioural data (**Chapters 4**, **5** and **6**) we came to the same conclusion: there was no relationship between IQ and the behavioural problems described by parents. This was surprising because in the general population decreased intellectual capacities are a good predictor of behavioural problems.[5,6] In **Chapter 6** we report that the behavioural profile in 22q11DS changed in time with more prominent internalizing behaviours as children grew into adolescence. The emergence or worsening of behavioural problems, in particular the increase of withdrawn behaviours such as observed in **Chapter 6**, has been shown to be a relevant clinical phenomenon often preceding the onset of psychosis. However at 15 years, a reliable distinction between those with and those without schizophrenia could not yet be made.

3. The marginal influence of confounders on FSIQ in 22q11DS

Possible confounders were studied, in this case gender, heart conditions, origin of deletion and level of parental education on FSIQ. As discussed in the introduction, intelligence level is influenced by both environment and genes. An environmental (and in part genetic) factor that was investigated was the level of parental education as this can influence level of intelligence. The level of education in the parents of our group of patients was representative of the Dutch population. However, no effect on FSIQ was found in the various chapters, contrary to earlier reports.[7] It would seem that the influence of the genetic syndrome dominates this factor. No relationship was found between level of intelligence and the presence of a heart condition, consistent with other reports,[7,8] Also no relationship was found between FSIQ and the origin of the chromosomal deletion (parental or spontaneous), except in the study described in **Chapter 3**, where a trend was found.

Gender was found to be a main confounder and predictor of intelligence level. At all studied ages (3, 5, 7, 9 and 15 years) girls performed significantly better than boys on FSIQ scores. **Chapter 5** also showed that between the age of 5 years and 9 years, girls underwent a more severe cognitive decline than boys.

CLINICAL IMPRESSION OF CHILDREN WITH 22Q11DS, AND PITFALLS FOR CARE

Based on the cognitive assessments as described in **Chapters 5** and **6** and our clinical experience we consider the following cognitive strengths and weaknesses to be characteristic for children with 22q11DS, especially the older children (7 years and up):

- Relatively good short term memory.
- Relatively high processing speed.
- Verbally fluent (after the initial delays in speech production), thereby often making a stronger impression.
- Poor comprehension and expression skills.
- Poor perceptual organization.

It is a pitfall in care to take these children at face value. The relatively good short term memory often found, allows the child to be able to literally repeat what the teacher has just instructed. This masks the fact that the child probably does not know how to go about the task at hand. As a result of the relatively high processing speed the child will not necessarily be last in the class. Also, the strong verbal impression they make is most likely not representative of their overall cognitive level. If taken at face value, then teachers and parents will miss the fact that comprehension and social competence is actually very low. At the same time it is important to note that although characteristic phenotypes were found, we also found many individual differences. As also suggested by van Balkom:[9] '*…genetic syndromes usually exist along a continuum of varying physical and neurodevelopmental severity*'.

CLINICAL IMPLICATIONS

The results of this thesis stress the clinical importance of regular cognitive and behavioural evaluation of the development of children with 22q11DS. Over the years at least some children with 22q11DS will be increasingly challenged beyond their cognitive capabilities, while they are expected to function at the same academic level they were able to meet previously. A chronic situation of too much stress is a known risk factor for a range of internalizing and externalizing psychiatric disorders.[10] Perhaps in some cases the early detection (as a result of participating in this longitudinal study) of cognitive decline has lowered the potential risk of a mismatch between a child's cognitive abilities and the expectations of the environment. This may have reduced the development of chronic stress.

Another clinical implication resulting from this thesis is the need to inform parents and professionals through a specialized expertise centre of 22q11DS. Parents need to learn about, and become familiar with, the syndrome that their child is born with. Children with the syndrome are not always easily recognisable: characteristics can be mild, children with 22q11DS seek social contact (although often in an ill adjusted manner) and make a strong verbal impression. Knowing that children with 22q11DS have a distinctive cognitive phenotype and realizing that certain behaviour is characteristic of 22q11DS will aid parents and professionals in anticipating

on these abnormalities and adjusting home or school environments accordingly. During the course of the study, a psychologist was available in person at and between assessments for consultation and advice, including information with regard to rearing and educating a child with a cognitive impairment. It is possible that these health care interventions have also aided in managing the behavioural problems reported in other studies.

Also, this longitudinal study shows the importance of working with homogeneous age groups when reporting on a complicated syndrome such as 22q11DS. In working with the 6 different age groups, it has become clear that developmental and IQ norms for children with 22q11DS are warranted. Normally, when studying the development of a child, results are compared to peer norm scores. However, specific 22q11DS norms are of the essence. If these were available, the results of for example Chapter 2 could also be read as: 'if a 3.5-year-old with 22q11DS has a mental delay between 6.0–12.4 months he/ she is actually developing in a way comparable to 95% of other children with 22q11DS'. This gives both parents and specialists an additional insight into how a child with 22q11DS is doing, besides the obvious fact that he/she is developmentally delayed compared to unaffected children.

SCIENTIFIC IMPLICATIONS AND FUTURE RESEARCH

The questions raised by these results are: how is it possible that IQ declines in some children with 22q11DS? And does a stable IQ during childhood guarantee 'cognitive stability' in adolescence and adulthood?[11]

In the general population a decline in IQ can be a premorbid marker of psychosis.[12-15] Knowing that between 25-30% of 22q11DS patients will develop schizophrenia, the need to identify factors that can predict or influence the onset of this illness is clinically very relevant. Therefore, it is important to know whether the subgroup of children who showed a cognitive decline (see Chapters 5 and 6) are those most at risk of developing psychosis. And are there any other psychological/ cognitive variables influencing this vulnerability? If so, can such factors be subject to intervention in order to reduce the child's risk for psychopathology? For instance, studies in the general population have shown that stress can induce psychiatric illness, including psychosis. Perhaps stress in children with 22q11DS, who are already genetically at risk, could be a factor that precipitates the emergence of psychosis.[10] Assuming this to be true, then what could be a cause of (chronic) stress in 22q11DS children? Could it be that the cognitive development of some 22q11DS children is such that they are at risk of enduring chronic stress? From both a clinical and scientific point of view, these questions are highly relevant and require further investigation.

CONCLUSION

Children with 22q11DS have a distinctive cognitive development. A novel finding of our study is that the cognitive transition from childhood to adolescence in 22q11DS is characterized by an absolute cognitive decline in a substantial amount of these children. Where in the general population, intelligence level is a predictor of behavioural problems, this is not the case in 22q11DS. Whether a decline in intelligence predicts psychosis in 22q11DS remains to be investigated.

Multidisciplinary evaluation of children with 22q11DS after diagnosis is highly recommended. The International guidelines advise both medical and psychological/ behavioural evaluation.[16] We fully agree with this recommendation. However, based on our own findings, we strongly recommend to re-study the children at set ages to ensure that they are still being challenged both socially and cognitively at their current – and not their former – level. Also, this would help in acquiring norms for children with 22q11DS. Keeping all those involved with the care of children with 22q11DS appropriately informed will aid in reducing frustrations, avoid chronic stress and maximize the potential of this characteristic group.

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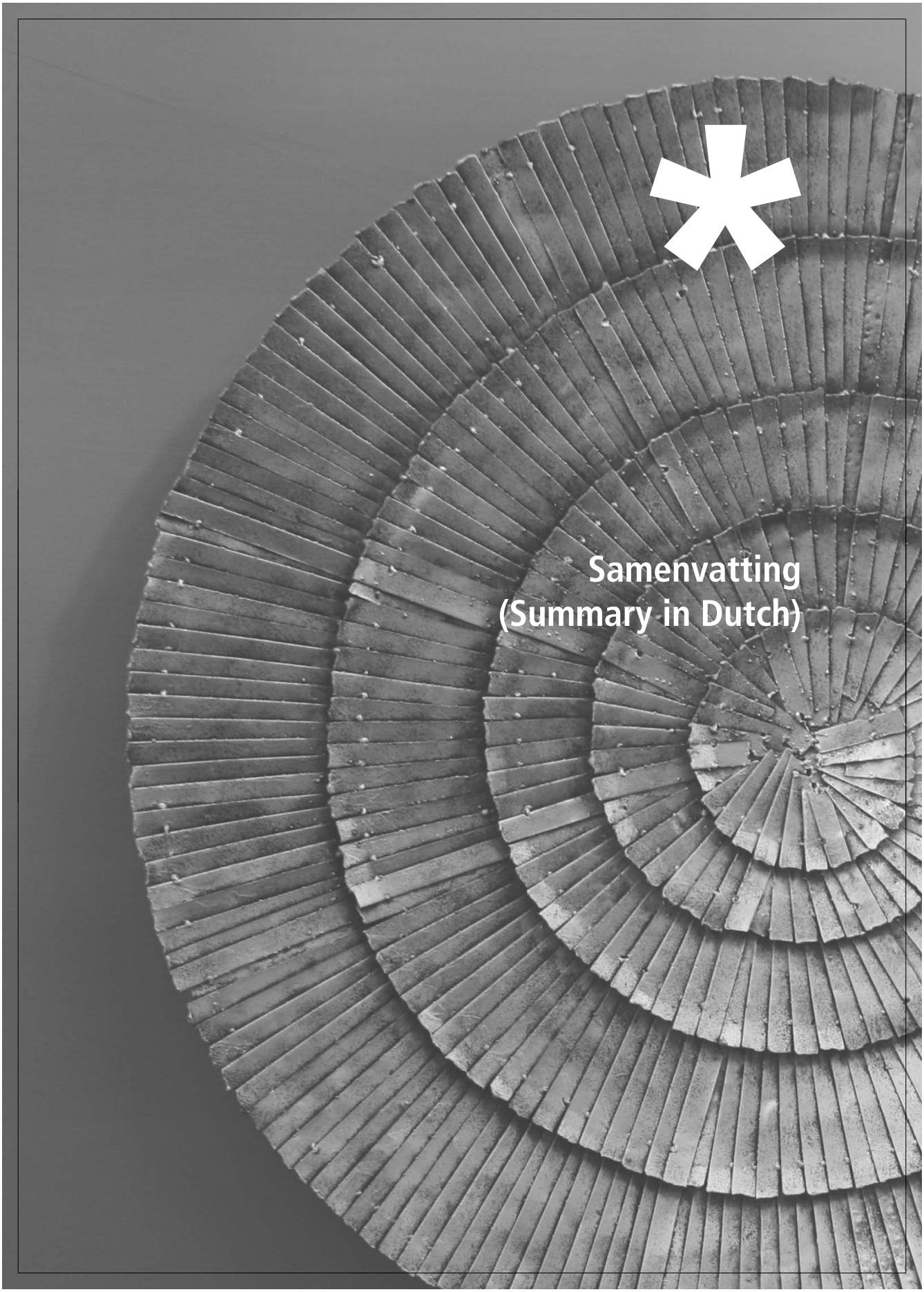


Samenvatting (Summary in Dutch)

22Q11.2-DELETIESYNDROOM

Het 22q11.2-deletiesyndroom (22q11DS) is een genetische afwijking die ook wel bekend staat als Velo-cardio-faciaal syndroom (VCFS), DiGeorge syndroom of Shprintzen syndroom. Deze aandoening is aangeboren en erft autosomaal dominant over. Indien een van de ouders zelf het 22q11DS heeft, is de kans voor elk van de kinderen om ook de aandoening te krijgen 50%. In meer dan 90% van de gevallen echter heeft alleen het kind de aandoening en zijn beide ouders gezond; de aandoening is spontaan (de novo) bij het kind ontstaan.[1-3] De geschatte incidentie van 22q11DS is 1 op 4000 geboortes, wat inhoudt dat er in Nederland elk jaar 40 à 50 kinderen met 22q11DS geboren zouden worden.[4] Zowel jongens als meisjes kunnen het syndroom hebben. De lichamelijke kenmerken kunnen zeer variabel zijn. Vaak zijn er karakteristieke gelaatskenmerken zoals een brede neusbrug en -punt, klein en laag ingeplante oren, amandelvormige ogen en lange dunne vingers. Daarnaast zijn er vaak aangeboren hartafwijkingen, immuunstoornissen, een gebrekkige functie van spieren in het mond-keelgebied en een gehemeltespleet. Afwijkingen aan praktisch elk systeem of orgaan zijn beschreven bij het 22q11DS.[5] Het vermoeden bestaat dat 22q11DS nog steeds wordt ondergediagnosticeerd omdat de kenmerken soms erg subtiel zijn, zoals beperkte karakteristieke gelaatskenmerken en lichte hypernasaliteit. Dit vermoeden wordt versterkt door het feit dat er regelmatig ouders gediagnosticeerd worden met 22q11DS als gevolg van de diagnose van hun kind.

Naast de fysieke kenmerken hebben kinderen met 22q11DS vaker problemen op het gebied van cognitie en gedrag en kunnen er psychiatrische problemen zijn. Bij de start van onze studie in 2000 was al bekend dat er sprake was van een kenmerkende ontwikkeling met een vertraagde spraak-taalontwikkeling en cognitieve ontwikkelingsachterstanden. In de literatuur werd gerapporteerd dat het gemiddelde IQ van deze kinderen rond de 70–80 (± 15 IQ punten) lag en dat oudere kinderen lagere IQ's behaalden dan jongere kinderen. Deze uitkomsten waren het resultaat van cross-sectioneel onderzoek, met kleine onderzoeksgroepen en een groot leeftijdsbereik. Op gedrags- en psychiatrisch vlak hebben kinderen met 22q11DS een verhoogd risico op het ontwikkelen van psychiatrische problematiek.[6-15] Diagnoses waaronder Autismespectrumstoornis (ASS), Aandachtstekort met hyperactiviteit (ADHD) en verschillende angststoornissen worden met regelmaat gesteld. Daarnaast hebben onderzoeken aangetoond dat ongeveer 30% van de adolescenten en jongvolwassenen met 22q11DS schizofrenie ontwikkelt. In de algemene bevolking is dit ongeveer 1%.

ONDERZOEKSOPZET EN KLINISCHE SETTING

Het onderzoek dat in 2000 van start ging werd uitgevoerd op de afdeling Medische Psychologie en Maatschappelijk Werk van het Wilhelmina Kinderziekenhuis, UMC Utrecht. Het doel was om de cognitieve en gedragsmatige ontwikkeling van kinderen met 22q11DS systematisch in kaart te brengen door dezelfde kinderen op vaste leeftijden te onderzoeken door middel van longitudinaal onderzoek. De testleeftijden waren 1,5 jaar, 3,5 jaar, 7,5 jaar, 9,5 jaar en 15,5 jaar (± 3 maanden). De toewijding van ouders en kinderen om deel te nemen en met regelmaat terug te komen was indrukwekkend hoog en er zijn maar weinig gezinnen met deelname gestopt. Het longitudinale karakter van het onderzoek bood de mogelijkheid om, waar nodig, bij te sturen op verwachtingen van ouders en school.

Door de toenemende herkenning van het syndroom door professionals en de nauwe samenwerking met het oudernetwerk[*] zijn 281 kinderen met 22q11DS minimaal 1 keer getest tussen 2000 en 2011. In 2007 is de maandelijkse landelijke 22q11-poli van start gegaan.[†] Deze multidisciplinaire poli heeft tot doel (dreigende) lichamelijke en ontwikkelingsstoornissen bij kinderen met 22q11DS tijdig op te sporen en de ouders een passend medisch en psychologisch behandelplan te geven.

DOEL VAN HET ONDERZOEK

Het doel van de studies beschreven in dit proefschrift was om inzicht te krijgen in de cognitieve ontwikkeling van kinderen met 22q11DS tussen de leeftijd van 3 en 15 jaar. Hierbij lag de nadruk op 1) het in kaart brengen van de stabiliteit van het IQ met toenemen van de leeftijd bij deze groep, en 2) het toetsen van het eventuele verband tussen IQ en gedragsproblemen. Er werd gecontroleerd op de invloed van geslacht, soort deletie (de novo versus familiair), de aanwezigheid van een hartafwijking en het opleidingsniveau van ouders.

Hoofdstuk 2

Het onderzoek beschreven in dit hoofdstuk richt zich op de vroege ontwikkeling van kinderen met 22q11DS. Door de steeds grotere bekendheid van het syndroom bij professionals worden kinderen steeds jonger gediagnosticeerd. Daarmee groeide ook de behoefte van specialisten en ouders om meer inzicht te krijgen in de mogelijk syndroomspecifieke sterke en minder sterke

[*] www.vcfs.nl en www.vgnetwerken.nl
[†] www.umcutrecht.nl/subsite/vcfs

kenmerken. In dit hoofdstuk wordt het ontwikkelingsniveau van 34 kinderen met 22q11DS op de leeftijd van 42 maanden (± 1,2 maanden) beschreven. Uit het onderzoek blijkt dat op deze leeftijd kinderen met 22q11DS een gemiddelde (*SD*) achterstand van 9,2 maanden (± 6,4 maanden) hebben op leeftijdsgenootjes.

Hoofdstuk 3

Dit onderzoek richtte zich op kinderen van 5 jaar met 22q11DS. Het doel was om het verband te onderzoeken tussen IQ en visuo-motorische integratie (VMI). Op de leeftijd van 5 jaar zitten kinderen op school en wordt steeds meer een beroep gedaan op de fijn-motorische vaardigheden van kinderen zoals kopiëren, tekenen en letters schrijven. Een slechte beheersing van deze motorische vaardigheden is al eerder beschreven bij kinderen met 22q11DS. Mogelijk werken problemen in de visuo-motorische integratie door in het benedengemiddelde IQ dat ook wordt beschreven bij deze groep kinderen. Inzicht in mogelijke verbanden tussen cognitief niveau en deze vaardigheden zou kunnen helpen bij het zorgvuldig interpreteren van testresultaten. Onze hypothese was dat een slechte VMI (zoals gemeten door de *VMI-Beery*) van invloed is op het benedengemiddelde IQ dat vaak wordt beschreven bij kinderen met 22q11DS. Hiertoe werden de testresultaten van 65 kinderen met 22q11DS van 5 jaar (leeftijdsbereik 5.23–5.99 jaar) onderzocht. Er werd een significante correlatie gevonden tussen FSIQ en de resultaten op de *VMI*. Deze correlatie was alleen significant voor de visuele perceptie en de visuo-motorische integratie. De kwaliteit van de fijn-motorische vaardigheden was niet van noemenswaardige invloed op de IQ-scores van de kinderen op deze leeftijd. Deze resultaten suggereren dat op de leeftijd van 5 jaar kinderen met 22q11DS meer moeite hebben met de analyse en verwerking van visuele informatie. De resultaten zijn anders dan die welke beschreven zijn in andere publicaties. Dit is echter de eerste studie die zoveel kinderen van dezelfde leeftijd beschrijft. Mogelijk zijn de gevonden resultaten kenmerkend voor het cognitieve fenotype van 5-jarigen met 22q11DS.

Hoofdstuk 4

Bij kinderen met 22q11DS worden vaak gedragsproblemen gerapporteerd. De vraag in dit onderzoek was of deze gedragsproblemen veroorzaakt worden door factoren zoals medische problemen, afwijkende gelaatskenmerken of een laag IQ, of dat ze het rechtstreekse gevolg zijn van – en kenmerkend zijn voor – deze genetische afwijking (het gedragsfenotype). Het verband tussen IQ en gedragsproblemen van kinderen met 22q11DS in de leeftijd van 5–15 jaar werd onderzocht. Hiertoe werd met behulp van een gedragsvragenlijst (CBCL) het gedrag van een groep van 69 kinderen met 22q11DS vergeleken met het gedrag van 69 kinderen met

een craniofaciale afwijking (CFA). Kinderen met CFA hebben ook vaak medische problemen en afwijkende gelaatskenmerken. De kinderen uit de twee groepen werden gekoppeld op basis van IQ. De kinderen met 22q11DS lieten significant meer gedragsproblemen zien dan de kinderen met een CFA op de CBCL. Met name op de subschalen angstig/ depressief, delinquent gedrag, agressief gedrag, somatische klachten en sociaal probleemgedrag waren de scores anders. Er werd geen correlatie gevonden tussen het IQ en de gedragsproblemen. Dit resultaat was onverwacht omdat zowel in de algemene bevolking als in de CFA-groep een lager intelligentieniveau wel voorspellend is voor gedragsproblemen. Kinderen met 22q11DS en relatief hogere IQ's lieten meer internaliserend gedrag zien, bij kinderen met een lager IQ was het scala aan gedragsproblemen zeer uiteenlopend. De afwezigheid van een significante correlatie tussen IQ en gedragsproblemen bij kinderen met 22q11DS lijkt een aanwijzing voor een specifiek 22q11DS gedragsfenotype.

Hoofdstuk 5

Bekend is dat IQ een relatief stabiel kenmerk is. Uit verschillende onderzoeken wordt gesuggereerd dat het IQ bij mensen met 22q11DS lager wordt met het toenemen van leeftijd. Bovendien is het zo dat mensen met 22q11DS een ernstig verhoogd risico hebben op het ontwikkelen van schizofrenie. In de algemene bevolking is een afname in IQ en een verslechtering in schoolprestaties een aanwijzing voor een zich ontwikkelende psychose. De hypothese was dat als het IQ afneemt bij kinderen met 22q11DS, zoals gesuggereerd in de literatuur, dat dat een aanwijzing zou kunnen zijn dat genetische oorzaken een relatief grote rol spelen in de cognitieve achteruitgang. In dit hoofdstuk wordt de cognitieve ontwikkeling van 65 kinderen met 22q11DS beschreven. Het IQ is op minimaal 2 testmomenten gemeten op de testleeftijden 5 en/ of 7 en/ of 9 jaar. De resultaten van het onderzoek laten zien dat het FSIQ tussen de leeftijd van 5 en 9 jaar met gemiddeld 9,7 IQ-punten afneemt. Conform andere literatuur op dit vlak is deze achteruitgang twee keer zo groot voor het verbaal IQ als voor het performaal IQ. De resultaten laten zien dat de achteruitgang ten dele past in het beeld van het niet kunnen voldoen aan het hogere abstractievermogen dat gevraagd wordt naarmate kinderen ouder worden. De kinderen blijven zich wel ontwikkelen, maar de achterstand ten opzichte van leeftijdsgenootjes wordt groter; dit wordt in het Engels ook wel 'growing into deficit' genoemd. Een aantal kinderen laat zelfs een absolute achteruitgang in cognitieve vaardigheden zien. Op de leeftijd van 9,5 jaar werd door een subgroep op 2 of meer subtests minder goede antwoorden gegeven dan op dezelfde vragen op de leeftijd van 7,5 jaar. Er werd een achteruitgang in ruwe scores geconstateerd. Opmerkelijk is dat er wederom (zie **hoofdstuk 4**) niet alleen geen verband werd gevonden tussen IQ en gedragsproblemen, maar ook dat er geen verband werd gevonden

tussen de afname in IQ en gedragsproblemen. Mogelijk is de gesignaleerde *afname* in IQ in deze studie een eerste symptoom van de ontwikkeling van schizofrenie. Op deze jonge leeftijd is dat echter nog niet aan te tonen of uit te sluiten. De resultaten benadrukken wel het belang om vanaf diagnose regelmatig te testen en psychiatrische diagnostiek te doen bij kinderen met 22q11DS.

Hoofdstuk 6

In dit hoofdstuk wordt de cognitieve en gedragsmatige ontwikkeling van kind naar adolescent in 53 kinderen met 22q11DS beschreven. Deze groep werd op de gemiddelde leeftijd van 9,5 jaar (T1) en 15,3 jaar (T2) onderzocht. Tevens waren van een subgroep van 16 kinderen ook gegevens beschikbaar van toen ze aan het onderzoek deelnamen op de leeftijd van 7,5 jaar (T0) (zie **hoofdstuk 5**). Opnieuw werd een significante afname van FSIQ gevonden: 32% van de kinderen ging 10 of meer FSIQ-punten achteruit. Binnen de groep die op T1 en T2 met dezelfde test was gemeten, werd bij 30% een stagnatie of een achteruitgang in ruwe scores gezien. Toen de T0-gegevens ($n = 16$) werden geanalyseerd, bleek dat eenderde van deze groep al tussen T0 en T1 een forse achteruitgang in FSIQ had laten zien, terwijl er tussen T1 en T2 een relatief stabiel IQ werd gemeten. Het toevoegen van de T0-data laat zien dat op basis van deze studie ongeveer 42% van de kinderen met 22q11DS een significant en klinisch relevante achteruitgang in FSIQ heeft ergens tussen de 7 en 15 jaar. Deze achteruitgang kan niet alleen verklaard worden uit een 'growing into deficit'.

Voor wat betreft het gedrag rapporteerden ouders middels ingevulde gedragsvragenlijsten (CBCL) een verandering in het gedragsprofiel. Hoewel de totale probleemscore tussen T1 en T2 nagenoeg gelijk bleef, namen de internaliserende problemen toe en werd er meer teruggetrokken/ depressief gedrag gerapporteerd door ouders; de externaliserende problemen namen af. Ook nu weer werd er geen verband gevonden tussen een afname in FSIQ en gedragsproblemen. Mogelijk is, zoals ook gesuggereerd in **hoofdstuk 5**, de gesignaleerde afname in IQ in deze studie een eerste symptoom van de ontwikkeling van schizofrenie. Op de leeftijd van 15 jaar is dat echter nog niet aan te tonen of uit te sluiten. Anderzijds zou de verandering in gedrag, en met name de toename in teruggetrokken gedrag zoals gesignaleerd in deze studie, een klinisch relevant fenomeen kunnen zijn dat aan psychose voorafgaat.

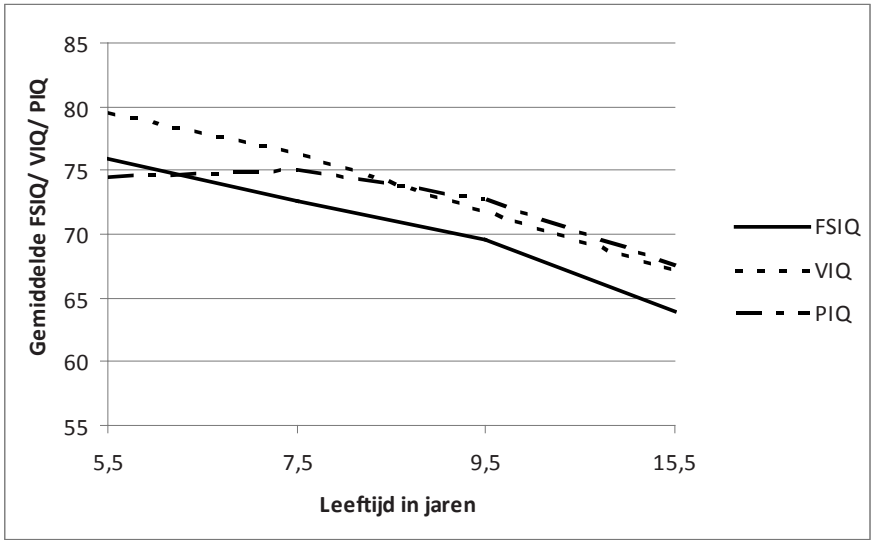
CONCLUSIES EN AANBEVELINGEN

Uit de resultaten van de studies beschreven in dit proefschrift volgt een aantal conclusies en aanbevelingen.

Kinderen met 22q11DS hebben een kenmerkende cognitieve ontwikkeling. Al op jonge leeftijd is er sprake van een ontwikkelingsachterstand. De belangrijkste conclusie uit de beschreven resultaten is dat het IQ bij kinderen met 22q11DS een instabiel kenmerk is dat afneemt met toename van de leeftijd. In Figuur S.1 is zichtbaar gemaakt hoe het IQ, VIQ en PIQ zich ontwikkelen in de loop van de tijd, gebaseerd op de onderzoeksresultaten van dit proefschrift.

Ten dele wordt deze afname verklaard vanuit het 'growing into deficit', waarbij kinderen zich nog wel ontwikkelen, maar minder snel dan hun leeftijdsgenootjes. Dit fenomeen wordt ook gezien bij kinderen met andere syndromen.[16,17] In ongeveer een derde van de onderzochte 22q11DS groep werd zelfs een stagnatie of achteruitgang in ruwe testscores gezien. Met andere woorden: sommige onderzochte kinderen wisten 2 of 6 jaar later evenveel of minder goede antwoorden op dezelfde vragen te geven dan eerst. Een dergelijke afname in IQ kan een voorbode zijn van een zich ontwikkelende psychose.

In de algemene bevolking is er een verband tussen de hoogte van het IQ en gedragsproblemen; bij kinderen met 22q11DS is dat niet het geval (zie **hoofdstuk 4**, **5** en **6**).[18,19] Uit de studie beschreven in **hoofdstuk 6** bleek wel dat het gedragsprofiel meer naar binnen gericht (internaliserend) werd met toenemende leeftijd. Een toename in teruggetrokken gedrag is iets dat vaker wordt gezien voordat zich een psychose ontwikkelt. Op de leeftijd van 15 jaar was deze groep kinderen echter nog te jong om daar onderscheid in te maken.



Figuur S.1 De longitudinale ontwikkeling van IQ, VIQ en PIQ bij kinderen met 22q11DS.

Deze studie benadrukt het belang van het bestuderen van kinderen op vaste leeftijden om een complex syndroom als 22q11DS goed te kunnen vatten. In alle beschreven studies zijn de onderzochte kinderen vergeleken met normgroepen. Het zou wenselijk zijn om 22q11DS-normen te ontwikkelen. Als deze beschikbaar waren zou de conclusie van bijvoorbeeld **hoofdstuk 2** ook als volgt kunnen luiden: '…als een kind van 42 maanden met 22q11DS een achterstand heeft tussen de 6,9 en 11,4 maanden, dan ontwikkelt hij zich op een vergelijkbare wijze als 95% van andere kinderen met 22q11DS'. Aangezien ouders een grote behoefte hebben om hun kind te vergelijken met leeftijdsgenoten, kan het geruststellend zijn te weten hoe andere kinderen met 22q11DS zich ontwikkelen. Dit neemt niet weg dat ook bij deze kinderen goed gekeken moet worden waar mogelijke ontwikkelingsproblematiek ligt en waar extra stimulering/ ondersteuning in de ontwikkeling geboden kan worden.

De multidisciplinaire 22q11-poli in ons ziekenhuis speelt een belangrijke rol in de zorg voor kinderen met 22q11DS. De vroege onderkenning van medische problemen en achterstanden in ontwikkeling en/ of IQ kan ouders helpen meer inzicht te krijgen in de mogelijkheden en beperkingen van hun kind. Psycho-educatie voor ouders en professionals draagt bij aan het vergroten van de kennis rondom 22q11DS en het tijdig bijstellen van verwachtingen thuis en op school. De belangrijkste aanbeveling die voortvloeit uit de resultaten van dit onderzoek is het belang van het op gezette leeftijden in kaart brengen van de cognitieve en gedragsmatige ontwikkeling van kinderen met 22q11DS. Door goed zicht te houden op de intellectuele, gedragsmatige en sociaal-emotionele ontwikkeling van deze kinderen kan een situatie van chronisch overvragen en stress hopelijk worden voorkomen.

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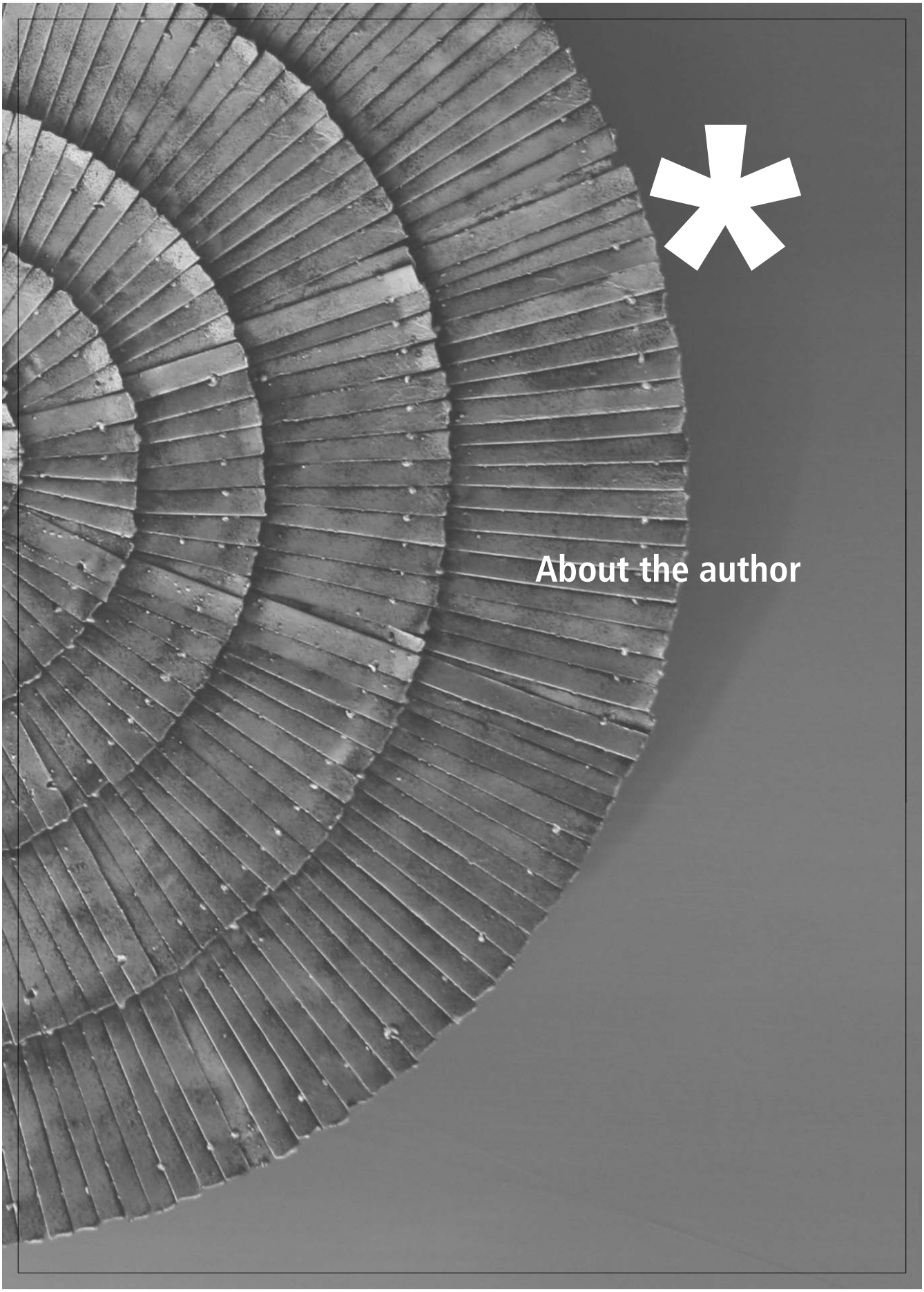

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CURRICULUM VITAE

1984 – 1987	Framlingham College, Framlingham, Great Britain
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2009 – current	Child Psychologist, Wilhelmina Children's Hospital, University Medical Centre Utrecht

Sasja Duijff werd geboren op 24 september 1972 in Fukuoka, Japan. Zij begon haar middelbare school op Framlingham College in het Verenigd Koninkrijk en rondde het af met een VWO-diploma op het Rijnlands Lyceum te Sassenheim, Nederland. Na haar eindexamen reisde zij een jaar rond met het internationale zang- en dansgezelschap "Up with People" om vervolgens in 1991 te starten aan de studie Psychologie aan de Universiteit van Leiden.

Na haar studie (1997) werkte zij eerst als intercedent bij Randstad Transportdiensten, waar zij verantwoordelijk was voor de werving van klanten in de transportsector en het uitzenden van vrachtwagenchauffeurs. In 1999 stapte zij over naar TNT Post waar zij in het kader van haar management traineeship 4 jaar verschillende managementfuncties in het Sorteercentrum Rotterdam bekleedde. Ze werkte daar ondermeer als productieleider, bedrijfsleider en coördinator teamgericht werken. In de leidinggevende functies was zij verantwoordelijk voor het efficiënt verwerken van de post en de medewerkers.

Maar het bloed kroop waar het niet gaan kon. In 2003 startte zij aan het promotie-onderzoek bij kinderen met 22q11.2-deletiesyndroom in het Wilhelmina Kinderziekenhuis (WKZ) aan het Universitair Medisch Centrum Utrecht. Dit deed zij onder begeleiding van dr. J.A. Heineman-de Boer, prof.dr. G. Sinnema en prof.dr. F.A. Beemer. Ze was nauw betrokken bij de oprichting van de '22q11-poli', die in 2007 van start ging in het WKZ. Van 2007 tot 2010 was zij secretaris bij de Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen (NVSCA). Sinds

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Video recordings by youngsters of the VCFS network.
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