Neurocognitive mechanisms and vulnerability to autism and ADHD symptoms in the 22q11.2 deletion syndrome

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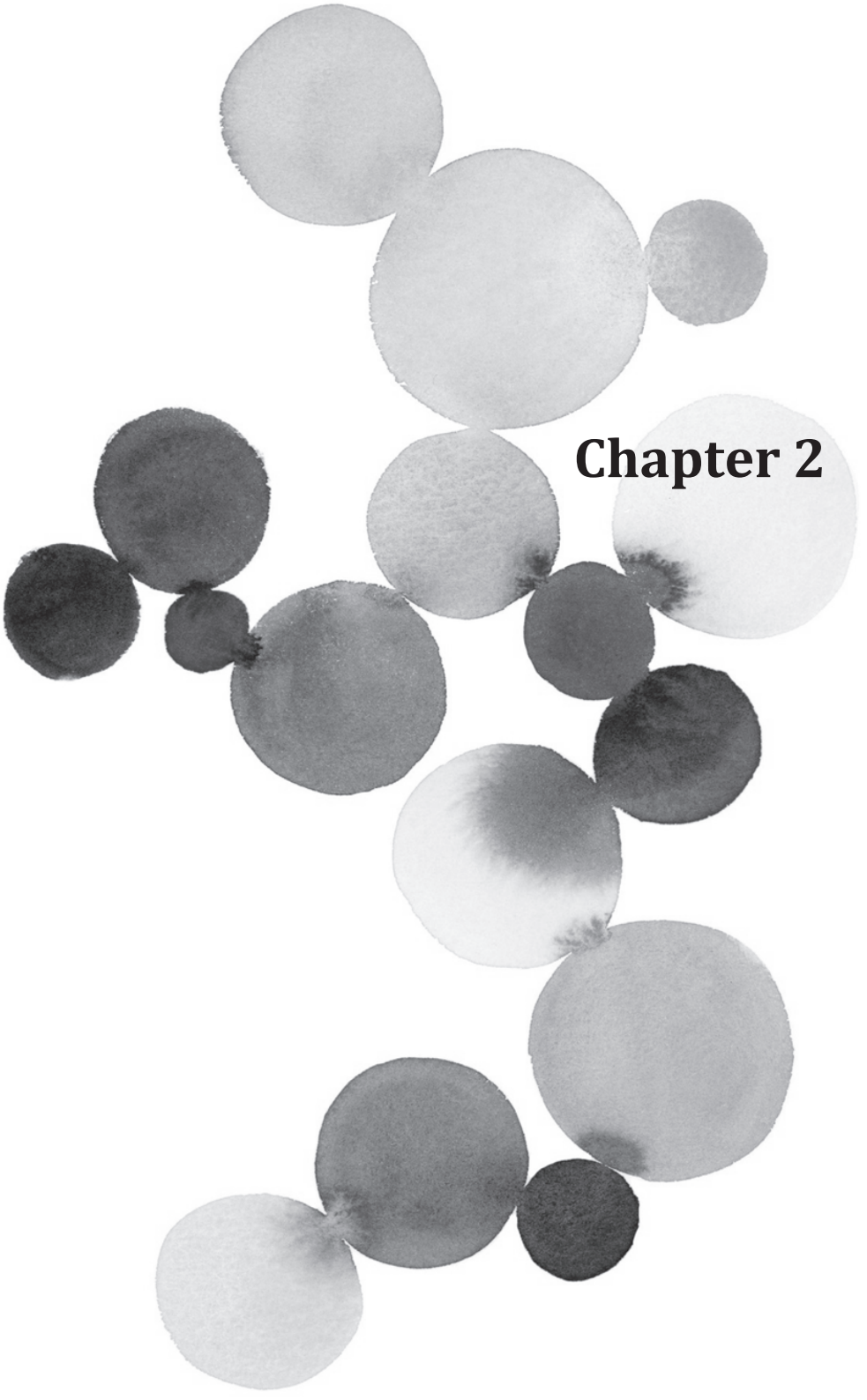

Chapter 2

Intellectual functioning in relation to autism and ADHD symptomatology in children and adolescents with 22q11.2 Deletion Syndrome

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Abstract

The 22q11.2 deletion syndrome (22q11DS; velo-cardio-facial syndrome) is associated with an increased risk of various disorders, including autism spectrum disorder (ASD) and attention-deficit-hyperactivity disorder (ADHD). With this study we aimed to investigate the relation between intellectual functioning and severity of ASD and ADHD symptomatology in 22q11DS.

A sample of 102 individuals (62 females) with 22q11DS aged 9 to 18.5 years was assessed using age appropriate Wechsler scales of intelligence as well as psychological and psychiatric assessment to evaluate the presence of ASD and ADHD symptomatology.

Intelligence profiles were characterized by lower scores on the factor Perceptual Organization and higher scores on the factor Processing Speed, with on subtest level higher scores on Digit Span and lower scores on Arithmetic and Vocabulary as compared to the mean factor or subtest score respectively. No differences in intelligence profiles were found between subgroups with and without ASD and/or ADHD. Low scores on Coding were associated with higher severity of ASD symptomatology, while lower scores on Block Design were associated with more severe ADHD symptomatology.

On several subdomains of intelligence poorer performance was associated with higher severity of ASD and ADHD symptomatology. The impact of developmental disorders in 22q11DS can be traced in specific domains of intellectual functioning as well as in severity of symptomatology.

Introduction

The 22q11.2 deletion syndrome (22q11DS), also known as velo-cardio-facial syndrome (VCFS), is a congenital syndrome with an estimated incidence of 1 in 4000 live births (Devriendt *et al*. 1998; Oskarsdottir *et al*. 2004; Shprintzen 2008). The 22q11DS can be considered as a genetic disorder associated with altered development of the brain (Antshel *et al*. 2008). The clinical phenotype during childhood includes lower intelligence and higher vulnerability to symptomatology of specific disorders, such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) (Antshel *et al*. 2005b; Gothelf *et al* 2008; Meechan *et al*. 2011; Philip & Bassett 2011; Vorstman *et al*. 2006). There is robust evidence for an important role of hereditary factors in the etiology of ASD and ADHD in the general population (Faraone *et al*. 2005; Ronald & Hoekstra 2011; Freitag 2007; Rommelse et al. 2010). As particular cognitive profiles have been found in idiopathic ASD and ADHD, one might question whether specific cognitive characteristics are associated with higher vulnerability to develop ASD and ADHD symptomatology in 22q11DS as well. Therefore, analysis of the relation between these symptoms and intellectual functioning on global and subdomain levels might help to further understand the dynamics of developmental vulnerability in 22q11DS.

In both ASD and ADHD, profiles of the Wechsler Scales according to the factors of Kaufman (1981) are characterized by low scores on the factors Freedom from Distractibility (reflecting attention and short term memory) and Processing Speed (reflecting visual information processing and visual memory) as compared to scores on Verbal Comprehension (reflecting verbal knowledge and use of verbal skills) and Perceptual Organization (reflecting non-verbal reasoning and visual spatial organization). Looking at the level of subtest performance groups of children with ASD and ADHD both are found to show fewer difficulties on a visual-motor subtest (Symbol Search) that requires constant shifting between symbols as compared to a subtest (Coding) in which the symbols are fixed, or, alternatively, they show poorer perceptual motor integration in more complex tasks (Calhoun & Mayes 2005; Oliveras-Rentas et al. 2012; Sattler 2001). Characteristically, children with ASD show more difficulties with reasoning when a social component is incorporated (Comprehension) as compared to reasoning apart from the social context (Block Design: Calhoun & Mayes 2005; Oliveras-Rentas *et al*. 2012; Sattler 2001). Further, communication abilities in children with ASD appear to be associated with speed in visual motor integration (Coding) and perceptual discrimination (Symbol Search). Also more difficulties with social interaction are associated with lower verbal learning ability (Vocabulary) and poorer verbal social judgment (Comprehension). These findings indicate that specific impairments in subdomains of intelligence and ASD symptomatology are associated, probably reflecting the impact of cognitive weaknesses increasing the risk for higher levels of ASD symptoms (Oliveras-Rentas *et al.* 2012).

Despite these findings in idiopathic ASD and ADHD populations, in 22q11DS research only limited attention has been given to the relation between ASD or ADHD symptoms and domains of intellectual functioning. This might be due to the fact that in the 22q11DS population intelligence is found to be highly variable as reflected in

mean full scale intelligence scores (FSIQ) ranging from moderate intellectual disability to borderline or even average scores (De Smedt *et al*. 2007; Moss *et al*. 1999; Niklasson & Gillberg 2010; Swillen *et al*. 1997; Duijff *et al*. 2012). The verbal domain (VIQ) of intellectual functioning is often found to be better developed as compared to the performance domain (PIQ) (De Smedt *et al*. 2007; Jacobson *et al*. 2010; Moss *et al*. 1999; Swillen *et al.* 1997). However, other studies found reversed differences or reported profiles without significant differences between scales (Campbell *et al*. 2009; Lewandowski *et al*. 2007). The variability in intelligence level and inconsistency in VIQ-PIQ discrepancies in 22q11DS may complicate the search for a relation between intellectual functioning and vulnerability to symptoms of developmental disorders. Using the Kaufman factors, Moss *et al.* (1999) found a significant discrepancy with higher scores on Verbal Comprehension as compared to Perceptual Organization in participants with 22q11DS that was larger than the more global VIQ-PIQ discrepancy. In addition to these findings on factor levels of intelligence, research also indicated significant variability within the subtest profile of the Wechsler Intelligence Scales (Moss *et al.* 1999; Duijff *et al.* 2012). Most studies investigating intelligence in 22q11DS in relation to ASD and ADHD symptomatology did not find a relation between FSIQ level and ASD symptoms (Vorstman *et al*. 2006), or between FSIQ, VIQ or PIQ and ADHD symptoms, respectively (Gothelf *et al*. 2007; Green *et al*. 2009; Hooper *et al*. 2013). By contrast, the group of Niklasson and Gillberg found higher levels of intelligence to be associated with lower levels of ADHD and ASD symptomatology (Niklasson *et al*. 2005). However, after extending their cohort (n=100) they could not replicate this finding, although they reported differences in subtest profiles within the factors Verbal Comprehension, Freedom from Distractibility and Processing Speed between groups with and without ADHD or ASD (Niklasson & Gillberg 2010).

Hence, studies so far did not find consistent profiles in 22q11DS and rarely focused on factor and subtest levels of intelligence in relation to developmental disorders, although other studies suggest that such consistent profiles of intelligence exist in clinical groups with idiopathic ASD and ADHD (Calhoun & Mayes 2005; Oliveras-Rentas *et al*. 2012). Therefore, we set out to investigate the relation between profiles of intelligence and severity of ASD and ADHD symptomatology. To understand the mechanisms that result in vulnerability to ASD and ADHD, it has been argued that the use of categorical diagnostic systems to identify these disorders is inadequate in 22q11DS because individuals with the syndrome often appear to meet the criteria for multiple diagnoses simultaneously (Baker & Vorstman 2012). Therefore, a focus on symptom severity instead of diagnoses seems justified.

Based on the results of Niklasson and Gillberg (2010), we hypothesized that we would find relations between specific subtests of intelligence and severity of ADHD or ASD symptomatology in 22q11DS. In their study, however, ASD and ADHD were analyzed categorically and results were grouped. Because of the evidence for different intelligence profiles in idiopathic ADHD and ASD groups, we hope to expand knowledge about these relations by focusing on severity of ASD and ADHD symptomatology separately. Supported by findings in children diagnosed with these disorders in the general population, we hypothesized shifting abilities and poorer perceptual motor skills to be related to more severe ASD and ADHD symptomatology

(Calhoun & Mayes 2005; Oliveras-Rentas *et al.* 2012). Further, difficulties with social reasoning (as measured with the subtest Comprehension) are expected to be related to more severe ASD symptoms only. Given the evidence in 22q11DS of more deficits in cognitive functioning in males versus females (Antshel *et al*. 2005a; Niklasson & Gillberg 2010) and the higher prevalence and severity of ASD and ADHD symptoms in males (Novik *et al*. 2006; Werling & Geschwind 2013; American Psychiatric Association 2013), we also expected more severe impairments in males as reflected by lower scores on domains of intellectual functioning and more severe ASD and ADHD symptomatology.

Method

Recruitment

This study was part of a nationwide study and included 102 children and adolescents, (inclusion criterion age 9-20 yr.), with 22q11 Deletion Syndrome, as confirmed with a fluorescence in situ hybridization. Participants were recruited through the Department of Child and Adolescent Psychiatry of the University Medical Center Utrecht as well as from the 22q11DS parents' network in the Netherlands by posting a request on the network's newsletter and website. When an application for participation was received, parents and participants were informed and received a complete description of the study in writing before they decided on participation. Written informed consent was obtained from participants and parents or caretakers. The assessment protocol is part of a larger ongoing longitudinal behavioral and genetic study on 22q11DS that has been approved by the Dutch Central Committee on Research Involving Human Subjects . Assessments took place at the outpatient center of the University Medical Center and were carried out under supervision of an experienced child psychiatrist and child neuropsychologist.

Sample

In the present study, 62 female and 40 males with 22q11DS participated (mean age 13.2, SD=2.6, range 9-18.5). Females had significant higher FSIQ compared to males. In a previous study the FSIQ data of 60 of these participants were reported in relation to psychiatric symptoms (Vorstman *et al*. 2006). In the current study the dataset was extended to n=102, while the analyses were expanded including a thorough investigation of intelligence on factor and subtest level and by focusing on severity of ASD and ADHD symptomatology separately.

Measures

Psychiatric classifications were made according to DSM-IV criteria, resulting from a multidisciplinary consensus meeting headed by an experienced child psychiatrist, on the basis of clinical structured and semi-structured interviews (with both the child and the caregivers), observations of the child and questionnaires, and intelligence assessments.

The assessment protocol included *the Autism Diagnostic Interview-Revised* (ADI-R*;* Rutter *et al*. 2003), scored by certified interviewers, used to quantify autistic symptoms. The ADI-R provided scores for the three domains in which children with ASD experience difficulties (reciprocal social interaction, communication impairment, repetitive and stereotyped behaviors). The classifications of autism and pervasive developmental disorder not otherwise specified are referred to as ASD. In addition the *Schedule for Affective Disorders and Schizophrenia for School-Age-Children-Present and Lifetime* Version (K-SADS-PL; Kaufman *et al*. 1997) was used to quantify mood disorders and psychotic symptoms.
Furthermore, information from the caregivers and the teachers was obtained using the Child Behavior Checklist, the Teacher Rating Form (CBCL 6-18, TRF 6-18; Achenbach 1991, Achenbach & Rescorla 2001) and Conners' Rating Scales-Revised (CRS-R; Conners 1997). Table 1 provides an overview of the formal psychiatric classifications of the sample, reflecting the multidisciplinary clinical consensus based on all available patient information.

Severity of ASD and ADHD symptomatology

In some cases, the formal diagnoses deviate from the classifications that would be obtained if only the outcomes of the questionnaires were used. The DSM-IV guidelines do not allow to diagnose both ADHD and ASD in one individual (American Psychiatric Association 2000), as a result, a formal diagnosis of ADHD was only made in four individuals (Table 1). In those cases in which the ASD symptomatology was more dominantly present explaining also the ADHD symptoms, no (additional) ADHD diagnoses was made based on such present symptoms. Two individuals were diagnosed with ADHD comorbid to an ASD diagnosis because this ASD diagnosis could not explain the severely present comorbid ADHD symptomatology (Table 1). Because of the high prevalence of both ASD and ADHD in 22q11DS the possible co-occurrence of symptoms of both disorders was also investigated. To this end, we allocated the diagnosis ADHD to any subject who passed six or more items in any of the three ADHD domains (inattention, hyperactivity, impulsivity) as rated with a semi-structured interview based on the criteria of DSM-IV. This interview consisted of comparable items as the CRS-R (Conners 1997) and the Dutch version of the ADHD DSM-IV rating scale (Kooij *et al*. 2004). Likewise, the diagnosis ASD was assigned in accordance to the ADI-R score. Table 2 provides the distribution of ASD, ADHD and ASD comorbid ADHD, other comorbidity not included. The sum scores of the items of the three ADHD domains as rated with the structured interview were used as a measure of severity of ADHD symptoms. The algorithmic scores of the three domains of the ADI-R were used as a measure of autism symptoms.

Intellectual functioning

Intellectual functioning was assessed, using the Wechsler Intelligence Scales for Children WISC-III (Wechsler 2002, Wechsler 2005b). In three cases the former version WISC-R was used (Wechsler 1974), in eight cases the adult scale (WAIS-III; Wechsler 2005a) for adolescents older than 16 years was used. According to the Kaufman factor structure and validity research of the Dutch Wechsler Intelligence scales (Wechsler 2002), factors were defined as follows: *Processing Speed (PS)*,

including the subtests Symbol search and Coding (WAIS-III: Digit symbol coding and Symbol Search), *Verbal Comprehension (VC)*, composed by the four subtests Information, Similarities, Vocabulary, and Comprehension (WAIS-III: Information, Similarities, Vocabulary), reflecting a verbal component of intelligence excluding the more mathematical tests and tests that ask for working memory and processing speed, and *Perceptual Organization (PO)*, composed by the four subtests Picture Completion, Picture Arrangement, Block Design, and Object Assembly (WAIS-III: Block Design, Matrix Reasoning, Picture Completion). Research comparing performances on the WAIS-III and WISC-III for a group of 16-year-olds found high correlations between performances of those group on both tests on the factors (Groth-Marnat, 2003; VC =.87, PO =.74, PS =.79).

Statistical analyses

Differences in intelligence profiles of children with 22q11DS with and without ASD and/or ADHD were tested using General Linear Model (GLM) – mixed models with *Factor* (PS, PO, VC) and *Subtest* (Information, Similarities, Arithmetic, Vocabulary, Comprehension, Digit Span, Picture Completion, Coding, Picture Arrangement, Block Design, Object Assembly, Symbol Search) as within subject (WS) factors, respectively, and *Group* (no ASD or ADHD, ASD and ADHD, and ASD only) as between subjects factor. The subtests Matrix Reasoning and Letter-Number Sequencing of the WAIS-III were not included because data of only eight participants were available. To bring out relative strengths and weaknesses in intelligence factor and subtest profiles, deviation contrasts, comparing scores with the overall mean subtest or factor score of each group, were used. Because the ADHD-only group consisted of eight participants, this group was excluded from analyses. Prior to analysis, normality of the data was examined and confirmed using Shapiro-Wilk tests (α=.01).
To examine the relation between intelligence and severity of ADHD and ASD symptomatology, multiple regression analyses were performed. Pearson correlations were calculated first, to determine whether age and gender were related with severity of autistic or ADHD symptoms. Only gender appeared to be correlated with symptom severity. Next, partial correlations were computed of intelligence factor and subtest scores with severity of autistic and ADHD symptoms, controlling for gender (small effect size: r = 0.1-0.23; medium: r = 0.24-0.36; large: $r \geq 0.37$; Cohen 1992).
Subsequently, factors or subtests of intelligence that were significantly correlated ($p \leq .05$, 1-tailed) with ASD or ADHD severity were planned to be included in the first step of the regression analyses. Additionally, the variable gender, when significantly correlated with the outcome variable, was entered in the second step of the regression analyses.
Moderation and mediation analyses were performed using methods of Baron & Kenny (1986) and Aiken & West (1991).

Table 1. ***Psychiatric classifications according to DSM-IV criteria with primary diagnoses and comorbid diagnoses.***

Diagnostic classification (primary)		**Comorbid diagnoses****				
	N	ASD	ADHD	Dep.dis	ODD*	Psych.dis
Autism spectrum disorder (ASD)	49		2	8	1	7
Attention Deficit Hyperactivity Disorder	4	1			1	1
Anxiety Disorder	3					
Conversion Disorder	1					
Depressive disorder (Dep.dis)	2					
Psychotic disorder (Psych.dis)	2					
Without psychiatric classification	41					
Total	102	1	2	8	2	8

* Oppositional defiant disorder
** Represent comorbid diagnoses within the total N of 102

Table 2. ***Distribution of groups with and without ASD, ADHD, and ASD comorbid ADHD*.***

Classification	*N*
No ASD or ADHD	44
Comorbid ASD and ADHD	16
ADHD only	8
ASD only	34
Total	102

*based on ADI-R score and the ADHD score of the DSM-IV structured questionnaire

Results

Comparisons on factor level

A significant WS effect of Factor was found [$F(2,164)=8.349$, $p<.001$, $\eta_p^2=.092$], but no main effect of Group ($p=.662$). The deviation contrast showed that performance on the factor PO was significantly poorer [$F(1,82)=13.681$, $p<.001$, $\eta_p^2=.143$] than the mean performance of the three factor scores ($M=72.19$), while performance on PS was significantly better [$F(1,82)=13.794$, $p<.001$, $\eta_p^2=.144$] (Table 3). The interaction between Factor and Group was not significant ($p=.327$), indicating that the factor profile did not differentiate between the groups.

Comparisons on subtest level

A significant WS effect of Subtest was found [$F(11,858)=9.748$, $p<.0001$, $\eta_p^2=.111$], but no main effect of Group ($p=.620$). The deviation contrast revealed better performances on Digit Span [$F(1,78)=47.690$, $p<.0001$, $\eta_p^2=.379$] as compared to the mean subtest score ($M=5.2$) and poorer performances on Arithmetic [$F(1,78)=51.281$, $p<.0001$, $\eta_p^2=.397$] and Vocabulary [$F(1,78)=21.411$, $p<.0001$, $\eta_p^2=.215$] (Table 3). The interaction between Subtest and Group was not significant ($p=.153$), indicating that the subtest profile did not differentiate between the groups.

Table 3. ***Intelligence profiles of subjects with and without ASD/ADHD[1].***

	No ASD or ADHD			**ASD and ADHD**			**ASD only**			**Total**		
	N	*M*	*SD*	*N*	*M*	*SD*	*N*	*M*	*SD*	*N*	M	*SD*
TIQ	39	67.8	13.6	16	64.7	12.5	34	65.6	11.8	89	66.4	12.6
VIQ	38	71.9	14.9	16	69.5	13.2	34	67.9	13.0	88	69.9	13.8
PIQ	38	69.6	12.9	16	65.1	12.8	34	67.5	12.7	88	67.9	12.8
VCF	38	73.1	15.1	16	72.6	15.1	34	69.2	14.0	85	71.5	14.7
POF	39	70.1	12.6	16	66.8	14.6	34	70.4	12.8	85	69.8*	12.9
PSF	37	77.7	13.9	15	74.9	15.2	33	72.8	14.3	85	75.3*	14.3
Information	39	5.2	3.5	16	5.1	2.9	34	4.8	2.8	81	4.9	3.1
Similarities	39	5.6	3.2	16	5.6	3.6	34	5.5	3.1	81	5.5	3.1
Arithmetic	39	4.6	2.8	16	2.8	2.1	34	4.2	2.2	81	4.1*	2.5
Vocabulary	39	4.6	2.9	16	4.4	2.7	34	3.5	2.6	81	4.2*	2.8
Comprehension	39	4.8	2.9	16	5.7	3.5	34	4.5	3.5	81	4.9	3.2
Digit Span	39	7.4	3.4	16	6.6	2.9	34	6.4	2.9	81	6.9*	3.1
Picture Completion	39	5.3	2.6	16	4.5	2.9	34	5.2	3.2	81	4.9	2.7
Coding	39	6.1	2.7	16	5.1	3.0	34	4.9	2.9	81	5.6	2.8
Picture Arrangement	39	5.0	2.7	16	4.8	3.2	34	5.0	3.0	81	5.1	3.0
Block Design	39	5.1	2.6	16	4.1	2.5	34	5.3	2.7	81	4.9	2.7
Object Assembly	39	5.5	2.9	16	4.7	3.4	34	5.7	3.1	81	5.5	3.1
Symbol Search	37	5.7	3.4	15	5.7	3.3	33	4.8	3.2	81	5.4	3.3

*≤.001 when compared to factor mean and subtest mean, respectively
[1]based on ADI-R score and the ADHD score of the DSM-IV structured questionnaire

Severity of autism symptomatology in relation to intelligence

Both the ADI-total score and the ADI-reciprocal social interaction score were negatively correlated with the factor VC, reflecting more severe autism symptomatology to be related to lower scores on VC. No other correlations were found between any of the Kaufman factors and autism symptomatology (Table 4). ADI-total correlated negatively with the intelligence subtests Vocabulary and Coding, with lower scores being related to more severe ADI-total scores. Autism severity was also related to gender, with males having more severe autism symptomatology (Table 5). Regression analysis, entering Vocabulary and Coding as predictors and ADI-total as dependent variable, resulted in a model with R^2 =.075. Adding gender to the equation enlarged R^2 to .093. The negative coefficient of gender indicates that severity scores were higher for males (Table 6). Similarly, ADI-reciprocal social interaction was negatively associated with Vocabulary and Coding and multiple regression resulted in a model with R^2 =.086. Following the inclusion of gender increased R^2 to .106 (Table 6). Coding was negatively correlated with two ADI domains of impairment: reciprocal social interaction and stereotyped and repetitive behavior, with more severe impairments on the ADI domains related to weaker performances on Coding. Severity of repetitive behavior was negatively related to Information and Coding as well as to gender (Table 5), with more severe repetitive behavior related to poorer scores on Information and Coding. Again, males showed more severe symptoms of repetitive behavior. Including the subtest scores in the regression analyses predicting severity of repetitive behavior resulted in a model with R^2 =.062. Adding gender to the model increased R^2 to .081 (Table 6).

Severity of ADHD symptomatology in relation to intelligence

On factor level, no correlations were found between severity of ADHD symptomatology and intelligence (Table 4). On subtest level, Block Design was negatively correlated with total severity of ADHD symptoms (ADHD-total), and with the ADHD domains hyperactivity and impulsivity, with weaker performances on Block Design in children with more severe ADHD symptoms (Table 5). Severity of inattention problems was related to gender but not with any of the intelligence subtests (Table 5). Males had relatively more inattention problems than females. More severe hyperactivity symptoms were related to weaker performances on Arithmetic and Block Design. Regression analysis resulted in a model with R^2= .100 (Table 6). Moderation and mediation analyses were performed demonstrating that gender had no moderating or mediating role between subtests and severity of ASD or ADHD symptomatology.

Table 4. ***Correlation matrix with Pearson correlations of sex and age with ASD and ADHD severity and partial correlations of Full Scale-, Verbal-, Performance- and factor intelligence scores, controlling for sex with ASD and ADHD severity.***

	FSIQ	**VIQ**	**PIQ**	**VC**	**PO**	**PS**	**Sex**
Mean (SD)	66.0(12.3)	69.4(13.5)	67.7(12.5)	71.0(14.3)	69.3(12.7)	75.4(14.3)	-
ADI total	-.128	-.183*	-.098	-.185*	-.016	-.108	-.215*
Social interact	-.120	-.176*	-.093	-.177*	-.006	-.150	-.231*
Communication	-.093	-.124	-.094	-.120	-.033	-.037	-.153
Repetitive behaviour	-.089	-.139	-.008	-.142	.048	-.087	-.204*
ADHD total	-.066	-.003	-.091	.036	-.105	-.025	-.169
Inattention	-.014	-.033	-.053	.069	-.053	-.005	-.223*
Hyperactivity	-.102	-.026	-.098	-.007	-.139	-.036	-.127
Impulsivity	-.110	-.046	-.116	-.027	-.121	-.047	-.061

*Correlation is significant at the 0.05 level (1-tailed).

Table 5. ***Partial correlation matrix of Wechsler subtests, controlling for sex with ASD and ADHD domains***

	Information	Similarities	Arithmetic	Vocabulary	Comprehension	Digit Span	Picture Completion	Coding	Picture Arrangement	Block Design	Object Assembly	Symbol Search
Mean (SD)	5.0 (3.0)	5.4 (3.1)	4.1 (2.5)	4.0 (2.7)	4.9 (3.2)	6.8 (3.0)	5.1 (2.9)	5.5 (2.9)	4.9 (2.8)	4.9 (2.6)	5.4 (3.0)	5.4 (3.3)
ADI total	-.110	-.090	-.134	-.196*	-.090	-.063	-.103	-.172*	.077	-.018	-.030	-.014
Social interaction	-.078	-.081	-.126	-.204*	-.073	-.074	-.074	-.189*	.073	-.001	-.029	-.007
Communication	-.055	-.054	-.092	-.111	-.052	-.012	-.146	-.112	.054	-.014	-.046	-.051
Repetitive behaviour	-.177*	-.058	-.138	-.132	-.097	-.052	.085	-.173*	.104	-.079	-.013	-.028
ADHD total	.058	-.036	-.146	-.010	.115	-.086	-.048	-.035	-.041	-.228**	-.093	-.040
Inattention	.102	-.024	-.071	.051	.154	-.078	-.031	-.002	-.001	-.133	-.048	-.011
Hyperactivity	-.000	-.108	-.190*	-.011	.039	-.065	-.042	-.044	-.037	-.301**	-.155	-.074
Impulsivity	-.033	.014	-.181	-.081	.019	-.067	-.064	-.085	-.123	-.218*	-.065	-.043

* Correlation is significant at the 0.05 level (1-tailed) ** Correlation is significant at the 0.01 level (1-tailed).

Table 6. ***Regression analyses to predict ASD severity (Total severity, Social Interaction, Repetitive Behaviour) and ADHD severity (Hyperactivity) in subjects with 22q11DS.***

Total severity						
		F(df)	R^2	β	*p*	
	Step 1	3.532(2,87)	.075		.034	
	(constant)				.000	
	Vocabulary			-.157	.178	
	Coding			-.165	.158	
	Step 2	2.954(3,86)	.093		.037	
	(constant)				.000	
	Vocabulary			-.151	.193	
	Coding			-.115	.343	
	Sex			-.145	.191	
Social Interaction						
		F(df)	R^2	β	*p*	
	Step 1	4.071(2,87)	.086		.020	
	(constant)				.000	
	Vocabulary			-.157	.174	
	Coding			-.185	.110	
	Step 2	3.410(3,86)	.106		.021	
	(constant)				.000	
	Vocabulary			-.151	.189	
	Coding			-.133	.271	
	Sex			-.154	.162	
Repetitive Behaviour						
		F(df)	R^2	β	*p*	
	Step 1	2.869(2,87)	.062		.062	
	(constant)				.000	
	Information			-.098	.405	
	Coding			-.187	.115	
	Step 2	2.518(3,86)	.081		.063	
	(constant)				.000	
	Information			-.111	.346	
	Coding			-.128	.308	
	Sex			-.148	.187	
Hyperactivity						
		F(df)	R^2	β	*p*	
	Step 1	4.822(2,87)	.100		.010	
	(constant)				.000	
	Arithmetic			-.039	.755	
	Block Design			-.292	.021	

Discussion

This study evaluated domains of intellectual functioning of 102 individuals with 22q11DS, investigating differences between subgroups with and without symptoms of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Further, the relation between intelligence on factor and subtest levels of intelligence with severity of ASD and ADHD symptomatology was explored. Outcomes revealed no significant differences in intelligence profiles between participants with and without ASD or a dual diagnosis ASD and ADHD. For the total group a higher mean score on Processing Speed and a lower score on Perceptual organization was found, relative to the mean factor score. On subtest level, a significantly higher score was found on Digit Span together with lower scores on Arithmetic and Vocabulary, relative to the mean subtest score. Notable, these profiles did not differ between participants with and without ASD and/or ADHD, which enabled us to examine the relation between intelligence profiles and severity of ASD and ADHD symptoms in the total sample. Lower scores on Vocabulary and Coding were related to more severe ASD symptoms, while lower scores on Block Design and Arithmetic were related to more severe ADHD symptomatology.
In participants with 22q11DS intelligence did not discriminate between individuals with and without ASD and/or ADHD. However, the intelligence profile differed from the intelligence profiles reported in idiopathic ASD and ADHD groups. In those groups, lower scores were reported for Coding relative to Symbol Search in ADHD as well as ASD (Calhoun & Mayes 2005; Oliveras-Rentas *et al*. 2012) while this association was not found in our group with 22q11DS with or without developmental disorders. Also the typical finding of low Comprehension scores relative to Block Design scores in idiopathic ASD populations (Calhoun & Mayes 2005; Oliveras-Rentas *et al*. 2012) was not found in the 22q11DS sample. Possibly, these differences can be explained by the fact that in our study a genetically defined subgroup was selected from an otherwise idiopathic and heterogeneous population of individuals with ASD or ADHD. Another explanation for this difference could be that most studies in idiopathic ASD or ADHD populations investigated relative high functioning individuals, while the current 22q11DS sample (mean FSIQ of 68) was functioning on a below average cognitive level.
In contrast to the study of Niklasson and Gillberg (2010), no differences between participants with or without ASD or ASD and ADHD were found. They also investigated intelligence on subtest level in individuals with 22q11DS with or without ASD and ADHD, but compared subtest scores within factors against each other instead of comparing all subtests with the mean subtest score (our study). Therefore, both studies are not fully comparable. Our finding of relatively higher scores on Digit Span and lower scores on Arithmetic in children with 22q11DS, consistent with findings of Niklasson and Gillberg, suggests relatively stronger quality of functions that are used for Digit Span such as quality of short term attention and memory in individuals with 22q11DS. On the other hand functions involved in Arithmetic such as concentration during a longer period and long term memory seem to be weaker (Sattler 2001). The lower scores on Vocabulary suggest that participants with 22q11DS are less able to understand or express the meaning

of individual words relative to their overall intellectual capacities (Sattler 2001). However, this finding was not supported by the study of Niklasson and Gillberg who found superior scores on Vocabulary in their ASD and No ASD/ADHD groups. This might be explained by the different age ranges (7-35 years - Niklasson & Gillberg vs. 9-18 years in our study). Decreases in Vocabulary and Arithmetic were reported in a longitudinal study between age 7.5 and 9.5 years by Duijff *et al*. (2012), who argued that the overall cognitive decline may be explained by a progressive delay in verbal comprehension and expression. The current study shows a comparable weakness in Vocabulary and Arithmetic. Underlying mechanisms of these poor performances could be poor verbal comprehension or difficulties in verbalization. However, the performance on subtests of intelligence requires multiple cognitive functions and could also be influenced by factors like anxiety or poor concentration (Sattler 2001). It is therefore necessary to investigate the underlying mechanisms of cognitive functions involved in the subtests such as executive function skills.

A second aim of this study was to expand existing knowledge by investigating the relation between performances on subtest levels of intelligence and severity of ASD and ADHD symptomatology. Regression analysis indicated a negative association between quality of reciprocal social interaction in individuals with 22q11DS and performances on Vocabulary and Coding, what might suggest that poorer perceptual-motor integration of visual information processing and more difficulties with verbal comprehension or expression are possible underlying mechanisms of more severe problems with reciprocal social interaction. It is difficult to determine which cognitive abilities are exactly involved because performance on subtests depends on multiple functions (e.g. Coding performances may also result from poor pencil control, poor motivation or impulsivity). However, the consistent finding of relations between specific subtests and severity measures which resulted in regression models explaining up to 10% of the variance are an important contribution in exploring the relation between cognitive problems and the vulnerability to developmental disorders in 22q11DS. Poorer performances on the subtests Information and Coding were associated with increased severity of repetitive and stereotyped behavior. This implies that the presence and severity of these behaviors is associated with the quality of general factual knowledge and quality of long-term memory in children with 22q11DS as well as with their short-term visual memory, accuracy and attention capacities. Performances on the subtest Block Design were negatively related to total ADHD severity as well as to severity of hyperactivity and impulsivity. Weaker visuospatial information processing in individuals with 22q11DS therefore seems to be related to ADHD symptomatology. Hyperactivity was also influenced by processes that subserve performance on Arithmetic. These processes are poor numerical reasoning, concentration, attention, short and long term memory.

Gender was related to total autism severity, difficulties in reciprocal social interaction and repetitive and stereotyped behavior as well as to inattention. Higher severity scores were found on these domains for males. They also had lower scores on the intelligence measures. No moderation or mediation of gender was found. The relations between cognitive functioning and severity scores of males and females are both in the same direction. Our data suggest this relation is less strong for females,

although this effect was not significant. These differences between males and females contrasts with the results of studies that did not find a relation between gender and intelligence in 22q11DS (De Smedt *et al*. 2007; Moss *et al.* 1999; Niklasson *et al*. 2005), but are in line with findings of others (Antshel *et al*. 2005a; Duijff *et al*. 2012; Niklasson & Gillberg 2010). No explanation for these gender differences is suggested yet and it therefore remains important to look at gender when assessing individuals with 22q11DS, especially because the syndrome is not gender-specific, meaning that females and males are equally represented in the 22q11DS population.

Strengths and limitations

The investigation of ASD and ADHD symptoms in 22q11DS and the relation to intellectual functioning is a valuable contribution to the understanding of developmental disorders in 22q11DS. Given the high rate of co-morbid occurrence of ASD and ADHD symptoms in this syndrome, we investigated the co-occurrence of both disorders and their relation to cognitive abilities in children with 22q11DS. This study supports the approach of the DSM-5 which provides the opportunity to specify other associated disorders, separately classifying autism or ADHD. It also proves the usefulness of defining severity of diagnostic symptoms of both disorders, as is required by the DSM-5 (American Psychiatric Association 2013). A limitation of this study could be the absence of a control group. However, it is difficult to determine whether such a control group should be matched on age, intelligence, developmental age or on other characteristics that makes this group unique by its syndrome specific features. Providing insights in functioning on different aspects within the syndrome seems more relevant than comparing these children to control populations.

Conclusion and implications

From this study it can be concluded that investigating intelligence in relation to severity of developmental disorders in 22q11DS can contribute to our understanding of this complex disorder. Consistent with previous studies intellectual functioning does not discriminate between 22q11DS participants with and without ASD and ADHD (Vorstman *et al*. 2006; Gothelf *et al.* 2007; Green *et al.* 2009; Hooper *et al.* 2013). However, the current study demonstrates that on subtest level, intelligence is related to severity of the symptomatology of these disorders in 22q11DS. Poorer performance on different aspects of cognitive functioning is related to higher severity of the different symptom domains of these developmental disorders. From these findings it is recommended to focus on multiple and more detailed levels of cognitive functioning in evaluating the developmental impact of 22q11DS. Intelligence is a global measure of cognitive functioning and our findings on subtest level are promising in that specific aspects of cognitive functioning seems to be related to the severity of autism and ADHD symptomatology. It is likely that both ASD and ADHD symptoms are present in individuals with 22q11DS at varying levels of severity, and sometimes without an explicit diagnosis (Baker & Vorstman 2012). Hence, focusing on the severity of this symptomatology seems relevant and

can provide new and valuable insights into the relation between cognitive functioning and this psychopathology. Expanding the investigation of these relations to underlying mechanisms of cognitive abilities such as executive functioning is recommended. In the current study intelligence performances on subtest level explained only up to 10% of the variance in ASD and ADHD symptomatology. This suggests that other factors or mechanisms may also be contributing to the severity of the symptomatology. The presented evidence for the relations between cognitive function profiles and severity of symptomatology may have clinical implications in that it may help to adjust treatment strategies and demands to the needs of the individual. Knowledge of the cognitive strengths and weaknesses of an individual may provide a starting point for the development of interventions that may possibly be customized to suit individual needs and enables to formulate realistic expectations of the effect interventions might have. In addition, this knowledge may help monitoring cognitive development of individuals during different stages of life and finally lead to a better adjustment of demands to the capacities of the individual.

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