



Universiteit
Leiden
The Netherlands

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

Hidding, E.

Citation

Hidding, E. (2015, June 10). *Neurocognitive mechanisms and vulnerability to autism and ADHD symptoms in the 22q11.2 deletion syndrome*. Retrieved from <https://hdl.handle.net/1887/33187>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/33187>

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/33187> holds various files of this Leiden University dissertation

Author: Hidding, Elske

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

Issue Date: 2015-06-10



Chapter 3

Executive functioning and its relation to autism and ADHD symptomatology in 22q11.2 Deletion Syndrome

Hidding, E., de Sonnevile, L. M. J., van Engeland, H., Vorstman, J. A. S., Sijmens-Morcus, M. E. J., & Swaab, H. Executive functioning and its relation to autism and ADHD symptomatology in 22q11.2 Deletion Syndrome. *Under review.*

Abstract

Children with 22q11.2 deletion syndrome (22q11DS; velo-cardio-facial-syndrome) are at risk for the developmental disorders attention-deficit-hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). In the present study the relation between executive functioning (EF) and severity of ADHD and ASD symptoms was examined, since EF is known to be important in relation to emotional and behavioral problems.

58 children (38 females) with a mean age of 13.5 (SD 2.6) years participated. Standardized assessment was used to evaluate the presence of ASD and ADHD symptomatology. Major aspects of EF, including cognitive flexibility, inhibition, sustained attention, distractibility, working memory, reaction speed, perseveration, and planning were evaluated.

The profile of EF in 22q11DS was characterized by weaker performance, compared to the norm, on all subdomains of EF, except for perseveration. Poor cognitive flexibility and inhibition, and high distractibility were found to be related to more severe ASD symptoms, while poor quality of sustained attention, and high distractibility were related to more severe ADHD symptoms.

Children with 22q11DS experience impairments in EF and the degree of impairment on specific EF subdomains is related to severity of ASD or ADHD symptomatology. These results may help in defining the mediating role of neurocognitive dysfunctions in the development of social and behavioral problems in 22q11DS.

Background

Children with the congenital genetic disorder 22q11.2 deletion syndrome (22q11DS) are at risk for developmental disorders such as attention-deficit-hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) (Antshel *et al.* 2006; Antshel *et al.* 2007; Niklasson *et al.* 2009). Already in childhood and adolescence there is a substantially higher prevalence, compared to typical controls, of different behavioral and emotional problems, such as problems in attention regulation, impulsivity, communication and social interaction, that are part of ADHD and ASD (Antshel *et al.* 2007; Fine *et al.* 2005; Vorstman *et al.* 2006). Because it is widely known that genetic factors are involved in those developmental disorders, investigating a genetic syndrome that is associated with symptoms of these disorders is an unique opportunity to improve our knowledge about the neural basis of these disorders (Rutter 1997; Scourfield 1999). Especially, investigating neuropsychological dysfunctions as possible underlying mechanisms of the behavioral and emotional problems of those disorders in 22q11DS may provide insight in the etiology of ASD and ADHD. Deficits in these executive functions that regulate behavior and thought (Blakemore and Choudhury 2006; Anderson 2001), are found to underlie behavior and adaptation problems observed in ADHD (Barkley 1997; Sonuga-Barke 2003) and ASD (Ozonoff *et al.* 1991; Hill 2004; Gargaro *et al.* 2011). EF could therefore be important in determining vulnerability to ASD and ADHD symptomatology in individuals with 22q11DS. Insight in this relation may provide opportunities to develop interventions that improve cognitive functioning in children with 22q11DS and may lead to a better developmental outcome. Recently, one preliminary study reported gains in cognition after a cognitive remediation program in adolescents with 22q11DS (Harrell *et al.* 2013).

Across studies in 22q11DS, a broad range of EF has been investigated with different aspects studied in different samples. Dysfunctions have been found in processing speed, cognitive flexibility, mental set-shifting, sustained and selective attention, working memory, inhibition, planning and problem solving (Ousley *et al.* 2007; Woodin *et al.* 2001; Rockers *et al.* 2009; Campbell *et al.* 2010; Lewandowski *et al.* 2007; Shashi *et al.* 2010; Antshel *et al.* 2008; Niklasson *et al.* 2005; Furniss *et al.* 2011; Stoddard *et al.* 2011; Lajiness-O'Neill *et al.* 2006; Sobin *et al.* 2005; Gur *et al.* 2014). The heterogeneity in methods precludes to determine a clear EF profile and may have contributed to the lack of consistent patterns in findings so far. For example, in some studies response inhibition has been reported to be impaired in 22q11DS (Sobin *et al.* 2005; Antshel *et al.* 2008; Campbell *et al.* 2010), whereas in other studies such impairment was not found (Lajiness-O'Neill *et al.* 2006; Gothelf *et al.* 2007).

Importantly, a relation between executive dysfunctions and developmental disorders in 22q11DS has not convincingly been demonstrated yet. Therefore, a study investigating multiple aspects of EF in individuals with 22q11DS is necessary to unravel the relation between executive dysfunctions and behavioral outcomes in 22q11DS. Especially because only a few studies have focused on EF in relation to ASD and ADHD symptomatology. Results thus far suggest that EF deficits are different for individuals with and without psychopathology. For example, in a study that did not differentiate between individuals with and without psychopathology planning ability was found to be impaired in 22q11DS (Henry *et al.* 2002). Indeed, in a subsequent study, planning ability was found to be impaired *only* in those children who also had ASD/ADHD symptoms, while children without these symptoms had average planning abilities (Niklasson and Gillberg 2010). This suggests a relation between EF and ASD and ADHD symptomatology in 22q11DS and underlines the importance of examining this issue further including a wide range of EF.

Differences in EF within the 22q11DS population may also depend on age since EF develops with age as a result of the ongoing development of the brain during childhood and adolescence (Anderson 2001; Best and Miller 2010). It can be argued that differences in EF could also explain differences in developmental trajectories within this population. Investigating executive aspects of attention in relation to age, Stoddard *et al.* (2011) found more pronounced impairments in younger children with 22q11DS (age range 7-14 years). In a longitudinal study it was shown that some but not all cognitive performances of individuals with 22q11DS declined with age: learning and memory skills did, but perseveration and planning improved (Antshel *et al.* 2010).

In conclusion, studying the relation between EF and behavior in subjects with 22q11DS may help to clarify the relation between a genetic factor (22q11DS) and the development of social and behavioral problems through the mediating role of neurocognitive dysfunctions. Importantly, knowledge about the specificity of impairments in EF and its relation to vulnerability to ASD and ADHD symptoms provides an opportunity to develop cognitive interventions for these children. The aim of our study was to extend previous findings by the evaluation of a wide range of EF, focusing on the relation between EF and severity of ADHD and ASD symptoms. In line with previous results we anticipated that EF is impaired in individuals with 22q11DS. Based on the lack of consistent patterns in findings so far, we expected that some but not all of the EF included in the assessment are impaired. We hypothesized that poorer EF is associated with increased severity of ASD and ADHD symptoms. More specifically, based on research thus far, we expected impairments in working memory and inhibition to be related to more severe ADHD symptoms and impairments in planning, inhibition and flexibility to be related to more severe ASD symptoms. We

also explored the relation between dysfunctions in EF and age because of inconsistencies in findings thus far. Since other studies have not found sex differences in relation to EF in 22q11DS, we did not expect to find an effect of sex (Woodin *et al.* 2001; Niklasson and Gillberg 2010).

Methods

Sample

In this study 58 children (38 females, Age: $M=13.48$; $SD=2.6$; $min = 9$; $max = 18.5$, FSIQ: $M=65.2$; $SD=13.3$) with 22q11DS, as confirmed with a fluorescence in situ hybridizations, participated. The study was part of a nationwide study. Recruitment took place at the Department of Psychiatry, Brain Center Rudolph Magnus of the University Medical Centre Utrecht (UMCU) as well as through a request that was posted on the website and in the newsletter of the 22q11DS parents' network in the Netherlands. Parents and participants were informed by phone about the aims of the study and received a complete description of the study in writing before they decided on participation. Informed consent was obtained from participants and parents or caretakers. The assessment protocol was approved by the Dutch Central Committee on Research Involving Human Subjects. Assessments took place at the outpatient center of the UMCU and were carried out by an experienced child neuropsychologist and child psychiatrist. At the time of assessments 3 children were treated with atypical antipsychotics and 1 with stimulant medication. Other medication used by participants were anti epileptics ($n=1$), Beta blocker ($n= 1$) and thyroid medication ($n= 2$).

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 clinically structured and semi-structured interviews (with both the child and the caregivers), observation of the child questionnaires and intelligence assessment.

The assessment protocol included *the Autism Diagnostic Interview-Revised (ADI-R)* (Rutter *et al.* 2003), scored by certified interviewers. The ADI-R provides algorithmic scores for the three domains in which children with ASD experience difficulties (reciprocal social interaction, communication impairment, repetitive and stereotyped behaviors), which were used to quantify autistic symptoms (Rutter *et al.* 2003).

Classifications of autism and pervasive developmental disorder not otherwise specified are both 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 psychotic symptoms.

Furthermore, information from the caregivers and the teachers was obtained using the Child Behavior Checklist, the Teacher Rating Form (Achenbach 1991; Achenbach & Rescorla 2001) and Conners' Rating Scales-Revised (CRS-R; Conners 1997).

Intellectual functioning was assessed, using a current version of the Wechsler Intelligence Scale (Wechsler 2002; Wechsler 2005b; Wechsler 1974) for children and the Wechsler Adult Intelligence Scale-III (Wechsler 2005a) for adolescents older than 16 years.

An overview of the formal psychiatric classifications of the sample is provided in Table 1, 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 diagnosing ADHD and ASD in the same individual (American Psychiatric Association 2000). As a result, in most cases with prominent ASD symptomatology and ADHD symptoms, only a formal diagnosis of the former was made. In two individuals ADHD symptoms were prominent justifying a formal (comorbid) diagnosis of ADHD (Table 1).

Because of the high prevalence of both ASD and ADHD symptoms in 22q11DS the possible co-occurrence of symptoms of both neurodevelopmental disorders was also investigated. To this end, we used the three ADHD domains (inattention, hyperactivity, impulsivity) as rated with a semi-structured interview based on the criteria of DSM-IV as a measure of severity of ADHD symptoms. The interview consisted of items comparable to those of the CRS-R (Conners 1997) and the Dutch version of the ADHD DSM-IV rating scale (Kooij *et al.* 2008). Likewise, the '4.0 to 5.0/ever' algorithmic scores of three domains of the ADI-R were used as a measure of autism symptoms (Rutter *et al.* 2003; McDuffie *et al.* 2010). Table 2 provides the means and distribution of the ASD and ADHD severity scores.

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

Diagnostic classification (primary)	N	Comorbid diagnoses**				
		ASD	ADHD	Dep.dis	ODD*	Psych.dis
Autism spectrum disorder (ASD)	31		2	4	1	5
Attention Deficit Hyperactivity Disorder	1					
Anxiety Disorder	1					
Conversion Disorder	1					
Depressive disorder (Dep.dis)	2					
Psychotic disorder (Psych.dis)	2					
Without psychiatric classification	20					
Total	58	0	2	4	1	5

* Oppositional defiant disorder ** Represent comorbid diagnoses within the total N of 58

Table 2 Autism and ADHD severity scores.

	N	M	SD	Range
ADHD-total	57	11.47	8.34	0-30
Inattention	57	7.75	6.06	0-23
Hyperactivity	57	1.84	2.32	0-8
Impulsivity	57	1.88	2.13	0-9
ADI-total	58	24.17	13.35	0-49
Reciprocal social interaction	58	10.76	6.92	0-26
Communication impairment	58	7.47	5.05	0-19
Repetitive and stereotyped behaviors	58	2.12	2.06	0-8

Executive Functioning

The Amsterdam Neuropsychological Tasks (ANT) program (De Sonneville 1999; De Sonneville 2005) was used to evaluate major components of executive functioning (EF), i.e., alertness, sustained attention, working memory, distraction, inhibition, and cognitive flexibility. The ANT has been proven to be a well-validated and sensitive instrument to evaluate attentional processes and EF in psychiatric disorders such as ADHD (Slaats-Willemse *et al.* 2007) and ASD (Van Rijn *et al.* 2013). Test-retest reliability, construct-, criterion-, and discriminant validity of the computerized ANT are satisfactory and have extensively been described and illustrated elsewhere (Gunther *et al.* 2005; Huijbregts *et al.* 2002; Rowbotham *et al.* 2009; De Sonneville 2014). To obtain a measure of perseveration and planning skills, the Wisconsin Card

Sorting Test (WCST) (Heaton *et al.* 1993) and the Rey-Osterrieth Complex Figure (RCFT) (Rey 1964) were used.

Alertness was evaluated using the Baseline Speed task (BS) (Van Rijn *et al.* 2013; Gunther *et al.* 2011), which is a simple reaction time task. A fixation cross presented on a screen changes unexpectedly into a square, the imperative signal. The child is instructed to press a mouse key as fast as possible when the square appears. Reaction speed is operationalized as the mean reaction time (RT) to signals. Fluctuation in reaction speed is operationalized as the within subject standard deviation (SD) of RT across the 32 trials.

Sustained attention was assessed using the SA-dots task (SAD) (Van Rijn *et al.* 2013). This task measures the ability to maintain performance at a certain level during a longer period of time. During this task 600 random patterns of 3, 4 or 5 dots are successively presented in 50 series of 12 trials. Children are required to respond to the 4-dots pattern (target) by pressing the mouse button with their preferred hand ('yes'-response) and to the 3- or 5-dots patterns (nontargets) by pressing the mouse with their non-preferred hand ('no'-response). The ratio targets/nontargets is 1/2 which invokes a response bias to press the 'no-key'. Failure to inhibit this 'prepotent response' is expected to result in the production of relatively more misses than false alarms (De Sonneville *et al.* 1994). Task duration is approximately 15-20 minutes. Main outcome measures are mean series completion time (tempo), within-subject SD of tempo across 50 series (fluctuation in tempo) as measures of sustained attention, impulsivity (misses) and poor stimulus evaluation (false alarms).

Inhibition of prepotent responses and Cognitive flexibility were measured with the Shifting Attentional Set Visual task (SSV) (Huijbregts *et al.* 2010). During trials a colored square moves across a horizontal bar in the center of a screen, randomly to the right or left. The task consists of three parts. In part 1 (fixed compatible condition) the child is asked to follow the movement of a green block by pressing the left button upon a left move and the right button upon a right move. In part 2 of the task (fixed incompatible condition), using a red block, the child is asked to do the opposite, i.e. 'mirror' the movement of the block, by pressing the left button upon a right move and vice versa, requiring the inhibition of prepotent responses. Inhibition is operationalized as the contrast in performance (speed/accuracy) between part 1 and part 2. In part 3 (random condition), the block changes color randomly asking the child to follow or 'mirror' the movement, depending on the color of the block. In this part the child needs to shift response sets, i.e. to readily switch between execution of a prepotent response and inhibition of a prepotent response (in favor of the requested response), which switch requires cognitive flexibility. Cognitive

flexibility is operationalized as the contrast in performance between part 1 and part 3.

Working Memory and Distraction were measured using the Memory Search Letters task (MSL) (De Sonneville *et al.* 2002). This letter detection task consists of three parts increasing the memory load from one item in part 1 (k), to two items in part 2 (k+r), and three items (k+r+s) in part 3. The display set of four letters that contains the complete target set requires a 'yes'-response, incomplete target sets requires a 'no'-response. Target letters in nontarget trials act as distractors. Memory search rate is operationalized as the contrast in speed/accuracy of responses to target signals in part 1 (low load) and part 3 (high load). Distraction is operationalized as the contrast in speed/accuracy of responses to nontarget signals in part 3 between signals with 0 distractors (low distraction) and two distractors (high distraction).

Planning was operationalized as the accuracy copy score of the Rey Complex Figure test (RCFT) (Rey 1964). Children are instructed to copy an abstract figure as accurately as possible. Accuracy of the drawing was scored according to the Taylor scoring criteria (Straus *et al.* 2006).

Perseveration was measured using the Wisconsin Card Sorting Task (WCST) (Heaton *et al.* 1993). Perseveration was measured by contrasting the number of perseverative errors and non-perseverative errors. Perseverative errors are made when the child continues sorting the cards based on a previously successful principle or initial erroneous guess in the first serie (Lezak *et al.* 2012, Barneveld *et al.* 2013). Thus, in this task perseveration is operationalized as the inability to discontinue the use of a certain strategy in favor of another one despite feedback prompting to do so, with both strategies not being associated with prepotency (as is the case in task SSV).

Statistical analyses

Main outcome parameters of the ANT-tasks, the RCFT and the WCST were transformed to z-scores (De Sonneville 2005; De Sonneville 2014; Strauss *et al.* 2006). For the ANT the z-scores that were entered in the analyses are the results of computations, based on nonlinear regression functions that describe the relation between test age and task performance. These functions are fully implemented in the ANT program, based on norm samples varying in size between 3,100 to 6,700 subjects, depending on the task, and are therefore considered to be reliable estimates of performance level.

Results on each ANT-task were examined for extreme values. As extreme values are a clinical reality in this population, z-scores ≥ 6 were set to 6 to keep these subjects in

the analyses (Table 3). Not all subjects completed the entire assessment battery, therefore degrees of freedom will vary between analyses. Subjects with substantial missing data were excluded from analyses ($n=5$), resulting in a final sample of $n=58$. In addition, missing values in the final sample are the consequence of an inability of the subject to complete difficult task parts, or skipping parts because of running out of time.

Comparison to the norm

To decide whether mean performance of the subjects with 22q11DS differed from the norm, i.e. differed from zero for z-scores, the intercept test of the (M)ANOVAs was used. Alpha was set to 0.01. Multivariate group effects were analyzed using Pillai's trace. Effect sizes were calculated using partial eta squared with $\eta_p^2 \sim 0.03$ representing a weak effect, $\eta_p^2 \sim 0.06$ representing a moderate effect and $\eta_p^2 \geq 0.14$ significantly a large effect (Cohen 1992). ANOVA's were used for all *post hoc* analyses of group effects. Prior to analysis, assumptions for the analyses were examined and confirmed to be satisfactory.

Alertness: mean RT and fluctuation of RT during Baseline Speed were entered as dependent variables in a MANOVA.

Sustained Attention: Tempo and fluctuation in tempo were entered as dependent variables in MANOVA of speed. Number of misses and number of false alarms were entered as dependent variables in MANOVA of accuracy.

The results of the remaining ANT tasks were analyzed using Repeated Measures ANOVAs. Separate runs were made with RT and accuracy (errors) as dependent variables. The within-subject (WS) factors were, respectively:

Cognitive flexibility: contrast between performance in Part 1 (compatible responses) and Part 3 (compatible responses)

Inhibition: contrast between performance in Part 1 (compatible responses) and Part 2 (incompatible responses).

Memory load: contrast between performance on target signals in Part 1, 2 and 3

Distraction: contrast of performance on nontarget signals in Part 3 with 0, 1 and 2 distractors.

A significant WS effect reflects that task conditions result in different levels of performance. As z-scores are used, this implies that differences in performance between patients and the norm depend on task condition/level (interaction).

Planning: Planning score was entered as dependent variable in an ANOVA.

Perseveration: The percentage perseverative errors and non-perseverative were entered as levels of the WS factor *Perseveration* in a repeated measures ANOVA.

Severity of ASD and ADHD symptomatology

Pearson correlations were calculated in order to assess the relation between severity of ASD and ADHD symptoms and EF (small effect size: $r=0.1-0.23$; medium: $r=0.24-0.36$; large: $r \geq .37$, Cohen 1992). In case of significant correlations, regression analysis was performed to test the relation between EF and severity of ASD or ADHD symptoms, respectively. Prior to these analyses we examined whether age, full scale IQ and sex were correlated with *both* EF and symptom severity.

Table 3 Distribution of scores on EF across the standard deviations (SD) in %.

		≤1SD	≥2SD	≥6SD
Reaction Speed	RT	52.6	28.1	5.2
	Fluc	56.1	31.6	7.0
Sustained Attention	Tempo	35.1	47.4	7.0
	Fluc	29.8	43.9	5.3
	Miss	64.9	17.5	1.8
	FA	78.9	10.5	1.8
Attentional Flexibility	RTC1	69.2	9.6	0.0
	RTC3	75.6	8.9	2.2
	AccC1	69.2	15.4	1.9
	AccC3	22.9	66.7	27.1
Inhibition	RTC1	69.2	9.6	0.0
	RTI2	75.5	16.3	2.0
	AccC1	69.2	15.4	1.9
	AccI2	28.8	53.8	25.0
Working Memory	RT1	71.4	10.7	1.8
	RT3	71.9	10.5	1.8
	Acc1	66.7	12.3	1.8
	Acc3	78.9	8.8	5.3
Distraction	RT0	73.2	14.3	1.8
	RT2	75.0	16.1	1.8
	Acc0	87.7	5.3	3.5
	Acc2	68.4	15.8	5.3
Planning		28.1	38.6	10.3
Perseveration	Perr	87.0	12.1	0
	NPerr	83.3	3.4	0

Note: Scores for Speed (RT), Tempo, Fluctuation in speed or tempo (Fluc), Misses (Miss), False alarms (FA), Accuracy (Acc.), Perseverative errors (Perr) and NonPerseverative errors (NPerr). C1, C3 compatible condition part 1 and part 3 (SSV); I2 incompatible condition part 2 (SSV); 1,3 part 1 (low load condition) and 3 (high load condition)(MSL); 0,2 part 3 with 0 distractors (low distraction condition) or 2 distractors (high distraction condition)(MSL)

Results

Standardized means of total group performances on all executive functioning tasks are presented in Figure 1. Negative deviations from zero indicate more efficient EF, while positive deviations reflect worse performances. An overview of the distribution of scores across the standardized scores is presented in Table 3.

Alertness

Subjects with 22q11DS were slower [$F(1,56)=28.421, p<.0001, \eta_p^2=.337$] and showed more fluctuation in reaction speed [$F(1,56)=27.388, p<.0001, \eta_p^2=.328$] as compared to the norm (Fig.1).

Sustained Attention

Subjects with 22q11DS demonstrated a slower tempo [$F(1,56)=61.761, p<.0001, \eta_p^2=.524$] and more fluctuation in tempo [$F(1,56)=68.278, p<.0001, \eta_p^2=.549$] as compared to the norm (Fig. 1). They also made more misses than the norm [$F(1,56)=6.989, p=.011, \eta_p^2=.111$], but not more false alarms ($p=.170$) (Fig. 1), suggesting a difficulty to keep the response bias (increasing during time-on-task) under control.

Cognitive Flexibility

Regarding speed, the WS factor Flexibility was significant [$F(1,44)=7.082, p=.011, \eta_p^2=.139$], indicating that the 22q11DS sample did (slightly) better than the norm when flexibility was required (Fig.1). The average speed of the 22q11DS sample did not differ from the norm ($p=.699$). Regarding accuracy, the mean performance was less accurate compared to the norm [$F(1,47)=84.984, p<.0001, \eta_p^2=.644$]. The effect of Flexibility was significant [$F(1,47)=58.723, p<.0001, \eta_p^2=.555$], reflecting a steep increase in error rate compared to the norm when flexibility was required (Fig.1).

Inhibition

Regarding speed, the effect of Inhibition was not significant ($p=.974$) and mean performance of the 22q11DS sample was not significantly slower compared to the norm ($p=.041$). The 22q11DS sample made more errors compared to the norm

[F(1,51)=68.536, $p<.0001$, $\eta_p^2=.573$]. An effect of Inhibition was found, with a decrease in accuracy compared to the norm when inhibition demands were high [F(1,51)=38.733, $p<.0001$, $\eta_p^2=.432$].

Working Memory

On speed, subjects with 22q11DS performed slower as compared to the norm [F(1,55)=7.788, $p=.007$, $\eta_p^2=.124$] (Fig. 1). No effect of Memory load was found ($p=.217$), indicating that memory load did not discriminate between patients and the norm. Regarding accuracy, the effect of Memory load was significant [F(1,56)=7.080, $p=.010$, $\eta_p^2=.112$], reflecting a larger decrease in accuracy compared to the norm with memory load (Fig. 1). Mean accuracy of the 22q11DS was not significantly lower as compared to the norm ($p=.028$)

Distraction

The 22q11DS sample was on average slower as compared to the norm [F(1,54)=10.028, $p=.003$, $\eta_p^2=.157$]. No effect was found for Distraction ($p=.397$), indicating that the presence of distractors did not differentiate the 22q11DS sample from the norm on speed (Fig.1).

Mean accuracy across distraction conditions of the subjects with 22q11DS did not differ as compared to the norm ($p=.946$), but an effect of Distraction was found for the 22q11DS sample [F(1,56)=26.521, $p=.0002$, $\eta_p^2=.321$] reflecting that the unfavorable effect of distraction on accuracy was larger in the 22q11DS sample compared to the norm (Fig.1).

Planning

The 22q11DS sample performed poorer on planning as compared to the norm [F(1,56)=46.009, $p<.0001$, $\eta_p^2=.451$] (Fig.1).

Perseveration

Subjects with 22q11DS did not differ from the norm on perseveration ($p=.043$, Fig.1).

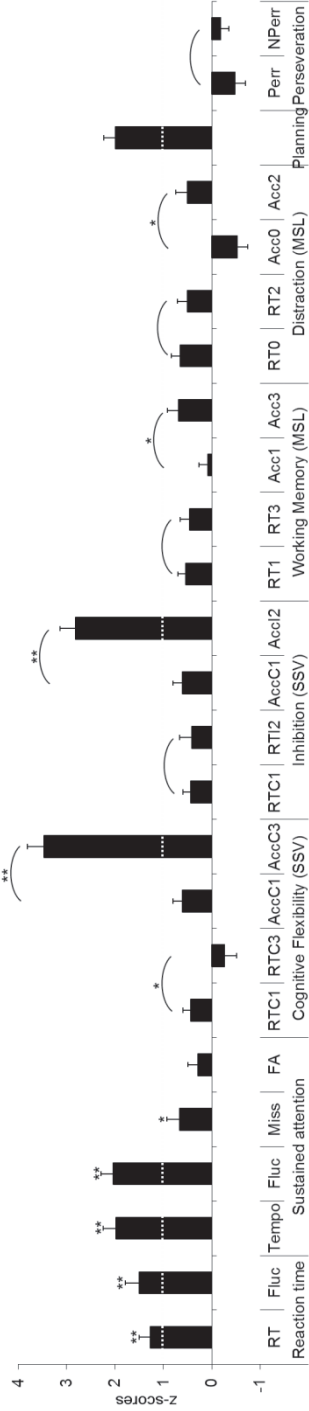


Figure 1 Mean z-scores of the total group showing level of performance on Executive Functioning
 With scores for Speed (RT), Tempo, Fluctuation in speed or tempo (Fluc), Misses(Miss), False alarms (FA), Accuracy (Acc.), Perseverative errors (Perr) and NonPerseverative errors (NPerr). * Significant different from norm population at $p < 0.01$, ** Significant at $p < 0.001$.
 Important contrasts between tasks conditions are indicated by the curved line elements. C1, C3 compatible condition part 1 and part 3 (SSV); I2 incompatible condition part 2 (SSV); 1,3 part 1 (low load condition) and 3 (high load condition)(MSL); 0,2 part 3 with 0 distractors (low distraction condition) or 2 distractors (high distraction condition)(MSL).

Age and full scale IQ in relation to executive functioning

A positive correlation was found between age and performances on fluctuation in reaction speed, tempo of sustained attention and planning ($p \leq .01$). This indicated that older children performed worse on these EF tasks. Reaction speed, sustained attention, working memory, and planning were correlated with full scale IQ, indicating that children with a lower full scale IQ performed worse on these EF tasks, which is not surprising since executive functions are needed to perform intelligence tests. Beside the reasons for not including IQ as a covariate as argued by Dennis et al. (2009), both age and full scale IQ were not correlated with severity of ASD or ADHD symptoms and were therefore not included in the regression models.

Severity of autism symptomatology in relation to executive functioning

A more severe ADI-total score was associated with decreases in speed when flexibility or inhibition was required (.05 level, Table 4), but regression analysis with these variables resulted in a non-significant model with $R^2 = .069$ ($p = .257$). Decreases in speed when flexibility or inhibition was required correlated in a similar way to Reciprocal social interaction (Table 4) with a non-significant regression model with $R^2 = .087$ ($p = .177$). A more severe Communication impairment was related to decreases in speed when inhibition was required and when distraction was present as well as to an increase in accuracy when flexibility was required (Table 4). Regression analysis with these variables resulted in a non-significant model with $R^2 = .158$ ($p = .107$). No relation between Repetitive and stereotyped behaviours with any of the EF measures was found.

Severity of ADHD symptomatology in relation to executive functioning

Higher scores on Hyperactivity and Impulsivity were significantly correlated to an increase in accuracy when memory load increased, a decrease in speed when distraction was present (Table 4). Inattention was not correlated to any of the EF measures (Table 4). More severe hyperactivity symptoms were also related to more misses (impulsive errors) during sustained attention (Table 4). Regression analysis, entering these three EF measures as predictors in a model with Hyperactivity as dependent, resulted in a significant model with $R^2 = .189$ (Table 5). A regression model with Impulsivity as dependent and the three EFs as predictors resulted in a significant model with $R^2 = .129$ (Table 5).

Table 4 Pearson correlations (1-tailed) of EF measures with ASD and ADHD symptom severity

	ASD total	Social interaction	Communication	Repetitive Behavior	ADHD total	Inattention	Hyperactivity	Impulsivity	Age	Full scale IQ
Reaction Speed	.104	.182	.015	.121	-.042	-.026	-.001	-.087	.119	-.354**
Fluctuation	.133	.190	.101	.129	.128	.090	.059	.179	.459**	-.295*
Tempo	-.096	-.035	-.090	-.160	-.115	-.087	-.141	-.050	.353**	-.543**
Sustained Attention	-.031	.016	-.025	-.093	-.204	-.145	-.209	-.159	.235*	-.548**
Misses	.212	.143	.193	.169	.182	.086	.243*	.202	-.006	-.177
Attentional Flexibility RT ¹	.255*	.295*	.210	.075	.030	.059	-.012	-.039	.086	.130
Attentional Flexibility PE ²	-.167	-.115	-.248*	-.016	-.012	-.068	.045	.097	.164	-.181
Inhibition RT ¹	.261*	.273*	.267*	-.015	.008	-.008	-.007	.066	.139	.074
Inhibition PE ²	-.183	-.174	-.213	-.045	-.004	-.065	.079	.083	.184	-.087
Working Memory RT ³	.146	.203	.116	-.084	-.080	-.094	-.051	.015	.145	-.236*
Working Memory NM ³	-.124	-.083	-.065	-.200	-.206	-.069	-.335**	-.254*	-.030	-.249*
Distraction RT ⁴	.170	.096	.290*	.144	.217	.086	.277*	.298**	-.116	-.063
Distraction PF ⁴	.162	.108	.125	.123	.106	.057	.069	.175	.096	-.067
Planning	.106	.128	.113	-.066	.100	.010	.158	.191	.601**	-.431**
Age	-.026	.038	-.031	-.212	-.117	-.109	-.202	.069	-	-.268*
Full Scale IQ	-.149	-.162	-.092	-.084	-.017	-.052	-.143	-.058	-	-

**Correlation is significant at the 0.01 level (1-tailed), *Correlation is significant at the 0.05 level (1-tailed) ¹Denotes decrease in speed when respectively flexibility or inhibition is required, ² Denotes decrease in accuracy when respectively flexibility or inhibition is required, ³ Denotes decrease in speed (RT) or accuracy (NM) when memory load increased, ⁴Denotes decrease in speed (RT) or accuracy (PF) when distraction is present.

Table 5 Regression ADHD severity

Hyperactivity				
	<i>F</i> (df)	<i>R</i> ²	β	<i>p</i>
	3.883(3,50)	.189		.014
(constant)				.000
Sustained Attention ¹			.202	.123
Working Memory ²			-.264	.047
Distraction ³			.205	.121
Impulsivity				
	<i>F</i> (df)	<i>R</i> ²	β	<i>p</i>
	3.769(2,51)	.129		.030
(constant)				.000
Working Memory ²			-.203	.133
Distraction ³			.262	.054

¹Denotes number of misses during sustained attention ²Denotes decrease in accuracy when memory load increased ³ Denotes decrease in speed (RT) when distraction is present

Discussion

This study investigated executive functioning (EF) in subjects with 22q11DS and examined whether EF is related to the severity of ASD and ADHD symptoms. The use of an extensive battery of EF tasks allowed to generate a detailed profiles of executive dysfunctions, reflected in processing speed, stability and/or accuracy. We found less accurate responses when task demands required cognitive flexibility, resistance against distraction, inhibition or working memory capacity. Poorer alertness was reflected in slower reaction times and larger fluctuations in reaction speed. There were also deficits in sustained attention, as reflected in a higher fluctuation in tempo and a higher miss rate, the latter result indicates a decreased ability to maintain inhibitory control during time-on-task. Furthermore, planning skills were below average. We found that severity of ASD symptoms was correlated to poorer cognitive flexibility, inhibition and distractibility, while ADHD symptoms were found to be related to poorer quality of sustained attention and higher distractibility.

The majority of EF deficits were reflected in accuracy and not in reaction time. This finding is in line with the findings of Gur *et al.* (2014) but partly contradicts the results of Campbell *et al.* (2010), who did not find a difference in accuracy of performances on a mental flexibility task between 22q11DS and siblings. However, they also found poorer inhibition, planning skills and working memory capacity in individuals with 22q11DS (Campbell *et al.* 2010). Both studies are complementary in that findings give reason to believe that specific EF deficits, mostly reflected in lower accuracy, are present in 22q11DS.

As argued before, deficits in executive functions are believed to underlie behavioral and emotional problems and these deficits are possible developmental signs of vulnerability to more severe ASD and ADHD symptoms. The current study showed that decreases in tempo when cognitive flexibility or inhibition was required were related to ASD symptom severity. Focusing on detailed levels of ASD symptoms, a similar relation was found with severity of problems in reciprocal social interaction. Decreases in speed when inhibition and resistance to distraction were required were related to severity of impairment in communication. An increase in accuracy when flexibility was required was also related to a more severe impairment in communication. Together these results suggest that children with more severe autism symptoms decrease their tempo during complex tasks which allows them to perform relatively more accurately.

With respect to ADHD symptoms, severity of hyperactivity was related to poorer inhibition during sustained attention, higher distractibility and an increase in accuracy when memory load increased. Severity of impulsivity was related to higher distractibility and an increase in accuracy when memory load increased. This indicates that children with more ADHD symptoms do have problems with inhibition of responses and are easily distracted. However, when a higher demand is imposed on their working memory capacities, forcing them to focus on the task and be less easily distracted, individuals with more hyperactive or impulsive behavior seem to perform relatively better.

Interestingly, the relations between EF and ASD or ADHD partly seem to differ from findings in clinical groups with ASD and ADHD without 22q11DS. In children with ADHD, impairments in working memory and inhibitory control have been reported (Barkley 1997; Sonuga-Barke 2003), while in the current study inhibitory control was not associated with severity of ADHD symptoms in children with 22q11DS. This finding suggest a preliminary support of the idea of different neurobiological pathways, also on a neuropsychological level, leading to ADHD symptomatology as proposed by Durston and colleagues (Durston *et al.* 2011; De Zeeuw *et al.* 2012). In children with idiopathic ASD deficits have been found in planning, inhibition and cognitive flexibility (Robinson *et al.* 2009; Ozonoff *et al.* 1991). In the current study deficits in inhibition, flexibility and distractibility were related to severity of ASD symptoms but so far poor distractibility has not been reported in children with ASD. Our findings therefore suggest that in children with 22q11DS partly comparable EF deficits seem to influence the severity of ASD symptoms as compared to children with idiopathic ASD. These differences in findings may be explained by the fact that the current study investigated children who shared the same genetic etiology (22q11DS) whereas studies on idiopathic ASD or ADHD examine - by definition - samples of children with unknown genetic etiologies (Bruining *et al.* 2010), although heterogeneity in methods, i.e. the use of different tasks measuring the same constructs may also explain part of the differences in findings.

Age was found to be related to quality of EF. Older children demonstrated poorer sustained attention and planning skills than younger children. This outcome contradicts findings of others who found more pronounced impairments of EF in younger children with 22q11DS (Stoddard *et al.* 2011; Antshel *et al.* 2010), but is in line with the decline with age in the more general measures of cognitive functioning

(e.g. intelligence assessment, learning and memory) reported by Antshel *et al.* (2010). It is important to notice that inconsistencies between studies may be partly explained by the use of different EF concepts across studies and the use of general measures of cognitive functioning instead of detailed EFs.

It is important to replicate findings in a larger sample to disentangle the relation between behavioral and social problems involved in ASD and ADHD and EF in 22q11DS. The outcome of the current study suggests a relation between specific EF deficits and severity of both ASD and ADHD symptoms with medium to large effect sizes, thereby providing a helpful starting point for future research and the development of cognitive interventions. Because of the role of age emerging from this study, future research should be designed longitudinally.

The use of an extensive evaluation of EF and the investigation of EF in relation to ASD and ADHD separately are considered strengths of this study. There are also limitations.

The sample size can be considered relatively large for a study of individuals with a specific genetic disorder, but for some analyses the sample size was relatively small because data were not available for all cases on all measures. This complicates the generalization of the findings to the 22q11DS population, especially because of the large variability within the population. Results therefore need to be interpreted with caution. One may also argue that the lack of a control group can be seen as another limitation. The z-scores that were entered in the analyses are the results of computations, based on nonlinear regression functions that describe the relation between test age and task performance. These functions are fully implemented in the ANT program, based on norm samples varying in size between 3,100 to 6,700 subjects, depending on the task (De Sonneville 2014), and therefore considered to be reliable estimates of performance level. In addition, we think it is very difficult to determine what can be seen as an appropriate control group and whether such a control group should be matched on age, intelligence, developmental age or on other characteristic that makes this group unique by its syndrome specific features. Lastly, it needs to be mentioned that the Rey Complex Figure is not only a measure of planning abilities. Besides planning, the copy score of the RCFT also depends on the quality of other cognitive processes including visuo-perceptual, visuo-constructional and graphomotor skills (Straus *et al.* 2006). Although our findings are in line with previous studies that investigated planning using other measures, our results need to be interpreted with caution.

Conclusions

With this study we provided a detailed profile of impairments in EF experienced by a sample of children with 22q11DS. Some evidence has been found that the degree of impairment on specific EFs is related to the severity of ASD and ADHD symptoms in children with the syndrome. These results may help in defining the mediating role of neurocognitive dysfunctions in the development of social and behavioral problems in 22q11DS. Although it is not yet clear how this relation can be interpreted in a developmental perspective, it provides even more reason to monitor the development of individuals with 22q11DS carefully. At the same time this knowledge may help to develop cognitive interventions or adjust interventions to the needs of these children.

References

- Achenbach, T. M. (1991). *Manual for the Child Behavior Checklist/4-18 and 1991 YSR and TRF profiles*, Burlington, VT: University of Vermont Department of Psychiatry.
- Achenbach, T.M. & Rescorla, L.A. (2001). *Manual for the ASEBA school-age forms & profiles*, Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.
- American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders : DSM-IV-TR*, 4th ed., Washington, DC: American Psychiatric Association.
- Anderson, V. (2001). Assessing executive functions in children: biological, psychological, and developmental considerations. *Pediatric rehabilitation* 4,119-36.
- Antshel, K.M., Aneja, A., Strunge, L., Peebles, J., Fremont, W.P., Stallone, K., Abdulsabur, N., Higgins, A.M., Shprintzen, R.J., Kates, W.R.(2007). Autistic spectrum disorders in velo-cardio facial syndrome (22q11.2 deletion). *Journal of Autism and Developmental Disorders*, 37, 1776-86.
- Antshel, K.M., Fremont, W., Roizen, N.J., Shprintzen, R., Higgins, A.M., Dhamoon, A., Kates, W.R. (2006). ADHD, major depressive disorder, and simple phobias are prevalent psychiatric conditions in youth with velocardiofacial syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry*, 45, 596-603.
- Antshel, K.M., Peebles, J., AbdulSabur, N., Higgins, A.M., Roizen, N., Shprintzen, R., et al.(2008). Associations between performance on the Rey-Osterrieth Complex Figure and regional brain volumes in children with and without velocardiofacial syndrome. *Developmental Neuropsychology*, 33, 601-22.
- Antshel, K.M., Shprintzen, R., Fremont, W., Higgins, A.M., Faraone S.V., Kates, W.R. (2010) Cognitive and Psychiatric Predictors to Psychosis in Velocardiofacial Syndrome: A 3-Year Follow-Up Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 49, 333-44.
- Barkley, R.A.(1997). Behavioral inhibition,sustained attention, and executive functions: constructing an unifying theory of ADHD. *Psychological Bulletin*, 121, 65-94.
- Barneveld, P.S., de Sonnevile, L., van Rijn, S., van Engeland, H., Swaab, H.(2013) Impaired Response Inhibition in Autism Spectrum Disorders, a Marker of Vulnerability to Schizophrenia Spectrum Disorders? *Journal of the International Neuropsychology Society*, 19, 646-55.
- Best, J.R., Miller, P.H.(2010). A developmental perspective on executive function. *Child Development*, 81,1641-60.
- Blakemore, S.J., Choudhury, S. (2006). Development of the adolescent brain: implications for executive function and social cognition. *Journal of Child Psychology and Psychiatry*, 47,296-312.
- Bruining, H., de Sonnevile, L., Swaab, H., de Jonge,M., Kas, M., van Engeland, H. and Vorstman, J. (2010). Dissecting the Clinical Heterogeneity of Autism Spectrum Disorders through Defined Genotypes, *PLoS One*, 5(5).
- Campbell, L.E., Azuma, R., Ambery, F., Stevens, A., Smith, A., Morris, R.G., Murphy, D.G.M., Murphy, K.C. (2010). Executive functions and memory abilities in children with 22q11.2 deletion syndrome. *Australian & New Zealand Journal of Psychiatry*, 44, 364-371.
- Cohen, J. (1992). A power primer, *Psychological Bulletin*, 112, 155-9.

Conners, C. K. (1997). *Conners' Rating Scales - Revised*, North Tonawanda, NY: MultiHealth System Publishing.

Dennis, M., Francis, D.J., Cirino, P.T., Schachar, R., Barnes, M.A., Fletcher, J.M. (2009). Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. *Journal of the International Neuropsychology Society*, 15, 331-43.

De Sonneville, L.M.J.(1999). Amsterdam neuropsychological tasks: A computer-aided assesment program. In *Cognitive ergonomics, clinical assessment and computer-assisted learning: Computers in psychology, Volume 6*. Edited by Den Brinker, B.P.L.M., Beek, P.J., Brand, A.N., Maarse, S.J., Mulder, L.J.M. Lisse, The Netherlands: Swets & Zweitlinger;187-203.

De Sonneville, L.M.J.(2005). Amsterdam Neuropsychologische Taken: Wetenschappelijke en klinische toepassingen [Amsterdam Neuropsychological Tasks: Scientific and clinical applications. *Tijdschrift voor Neuropsychologie*, 0, 27-41.

De Sonneville L.M.J. (2014) *Handboek Amsterdamse Neuropsychologische Taken [Handbook Amsterdam Neuropsychological Tasks]*. Amsterdam: Boom Testuitgevers.

De Sonneville, L. M. J., Boringa, J. B., Reuling, I. E., Lazeron, R. H., Ader, H. J. and Polman, C. H. (2002). Information processing characteristics in subtypes of multiple sclerosis, *Neuropsychologia*, 40(11), 1751-65.

De Sonneville, L. M. J., Njokiktjen, C. and Bos, H. (1994). Methylphenidate and information processing. Part 1: Differentiation between responders and nonresponders; Part 2: Efficacy in responders, *Journal of Clinical Experimental Neuropsychology*, 16(6), 877-97.

De Zeeuw, P., Weusten, J., van Dijk, S., van Belle, J. and Durston, S. (2012). Deficits in cognitive control, timing and reward sensitivity appear to be dissociable in ADHD, *PLoS One*, 7(12), e51416.

Durston, S., van Belle, J. and de Zeeuw, P. (2011). Differentiating frontostriatal and fronto-cerebellar circuits in attention-deficit/hyperactivity disorder, *Biological Psychiatry*, 69(12), 1178-84.

Fine, S.E., Weissman, A., Gerdes, M., Pinto-Martin, J., Zackai, E.H., McDonald-McGinn, D.M., Emanuel, B.S. (2005). Autism spectrum disorders and symptoms in children with molecularly confirmed 22q11.2 deletion syndrome. *Journal of Autism and Developmental Disorders*, 35, 461-70.

Furniss, F., Biswas, A. B., Gumber, R. and Singh, N. (2011). Cognitive phenotype of velocardiofacial syndrome: A review, *Research in Developmental Disabilities*, 32(6), 2206-13.

Gargaro, B.A., Rinehart, N.J., Bradshaw J.L., Tonge, B.J., Sheppard, D.M. (2011). Autism and ADHD: How far have we come in the comorbidity debate? *Neuroscience & Biobehavioral Reviews*, 35, 1081-88.

Gothelf, D., Hoefft, F., Hinard, C., Hallmayer, J.F., Stoecker, J.V., Antonarakis, S.E., et al.(2007). Abnormal cortical activation during response inhibition in 22q11.2 deletion syndrome. *Human Brain Mapping*, 28, 533-42.

Gunther, T., Herpertz-Dahlmann, B. and Konrad, K. (2005). [Reliability of attention and verbal memory tests with normal children and adolescents—clinical implications], *Z Kinder Jugendpsychiatr Psychother*, 33(3), 169-79.

Gunther, T., Konrad, K., De Brito, S. A., Herpertz-Dahlmann, B. and Vloet, T. D. (2011). Attentional functions in children and adolescents with ADHD, depressive

disorders, and the comorbid condition, *Journal of Child Psychology and Psychiatry*, 52(3), 324-31.

Gur, R. E., Yi, J. J., McDonald-McGinn, D. M., Tang, S. X., Calkins, M. E., Whinna, D., Souders, M. C., Savitt, A., Zackai, E. H., Moberg, P. J., Emanuel, B. S. and Gur, R. C. (2014). Neurocognitive development in 22q11.2 Deletion syndrome: comparison with youth having developmental delay and medical comorbidities, *Molecular Psychiatry*, 1-7.

Harrell, W., Eack, S., Hooper, S.R., Keshavan, M.S., Bonner, M.S., Schoch, K., et al. (2013). Feasibility and preliminary efficacy data from a computerized cognitive intervention in children with chromosome 22q11.2 deletion syndrome. *Research in Developmental Disabilities*, 34, 2606-13.

Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G. G. and Curtiss, G. (1993). *Wisconsin card sorting test manual: Revised and expanded*, Odessa, FL: Psychological Assessment Resources.

Henry, J.C., van Amelsvoort, T., Morris, R.G., Owen, M.J., Murphy, D.G., Murphy, K.C. (2002). An investigation of the neuropsychological profile in adults with velo-cardio-facial syndrome (VCFS). *Neuropsychologia*, 40, 471-8.

Hill, E.L.(2004). Evaluating the theory of executive dysfunction in autism. *Developmental Review*, 24, 189-233.

Huijbregts, S., de Sonnevile, L., Licht, R., Sergeant, J. and van Spronsen, F. A. (2002). Inhibition of prepotent responding and attentional flexibility in treated phenylketonuria', *Developmental Neuropsychology*, 22(2), 481-99.

Huijbregts, S., Swaab, H. and de Sonnevile, L. (2010). Cognitive and motor control in neurofibromatosis type I: influence of maturation and hyperactivity inattention,

Developmental Neuropsychology, 35(6), 737-51.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., et al. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL): initial reliability and validity data', *Journal of the American Academy of Child & Adolescent Psychiatry*, 36(7), 980-8.

Kooij, J. J. S., Boonstra, A. M., Swinkels, S. H. N., Bekker, E. M., de Noord, I., & Buitelaar, J. K. (2008). Reliability, Validity, and Utility of Instruments for Self Report and Informant Report Concerning Symptoms of ADHD in Adult Patients, *Journal of Attention Disorders*, 11(4), 445-58.

Lajiness-O'Neill, R., Beaulieu, I., Asamoah, A., Titus, J.B., Bawle, E., Ahmad, S., Kirk, J. W. and Pollack, R. (2006). The neuropsychological phenotype of velocardiofacial syndrome (VCFS): relationship to psychopathology, *Archives of Clinical Neuropsychology*, 21(2), 175-84.

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

Lezak, M. D., Howieson, D. B., Bigler, E. D. and Tranel, D. (2012) *Neuropsychological assessment*, New York: Oxford University Press.

McDuffie, A., Abbeduto, L., Lewis, P., Kim, J.S., Kover, S.T., Weber, A., Brown, W.T. (2010). Autism Spectrum Disorder in Children and Adolescents with Fragile X Syndrome: Within-Syndrome Differences and Age-Related Changes. *American Journal of Intellectual and Developmental Disabilities*, 115(4), 307-26.

- Niklasson, L. and Gillberg, C. (2010). The neuropsychology of 22q11 deletion syndrome. A neuropsychiatric study of 100 individuals, *Research in Developmental Disabilities*, 31(1), 185-94.
- Niklasson, L., Rasmussen, P., Oskarsdottir, S. & Gillberg, C. (2005). Attention deficits in children with 22q.11 deletion syndrome, *Developmental Medicine and Child Neurology*, 47(12), 803-7.
- Niklasson, L., Rasmussen, P., Oskarsdottir, S. & Gillberg, C. (2009). Autism, ADHD, mental retardation and behavior problems in 100 individuals with 22q11 deletion syndrome. *Research in Developmental Disabilities*, 30, 763-73.
- Ousley, O., Rockers, K., Dell, M.L., Coleman, K., Cubells, J.F. (2007). A review of neurocognitive and behavioral profiles associated with 22q11 deletion syndrome: implications for clinical evaluation and treatment. *Current Psychiatry Reports*, 9, 148-58.
- Ozonoff, S., Pennington, B.F., Rogers, S.J. (1991). Executive function deficits in high-functioning autistic individuals: relationship to theory of mind. *Journal of Child Psychology & Psychiatry*, 32, 1081-1105.
- Rey, A. (1964) *L'examen clinique en psychologie*, Paris: Presses Universitaires de France.
- Robinson, S., Goddard, L., Dritschel, B., Wisley, M. and Howlin, P. (2009). Executive functions in children with autism spectrum disorders, *Brain and Cognition*, 71(3), 362-8.
- Rockers, K., Ousley, O., Sutton, T., Schoenberg, E., Coleman, K., Walker, E. and Cubells, J. F. (2009). Performance on the Modified Card Sorting Test and its relation to psychopathology in adolescents and young adults with 22q11.2 deletion syndrome. *Journal of Intellectual Disability Research*, 53(7), 665-76.
- Rowbotham, I., Pit-ten Cate, I. M., Sonuga-Barke, E. J. S. and Huijbregts, S. C. J. (2009). Cognitive Control in Adolescents With Neurofibromatosis Type 1, *Neuropsychology*, 23(1), 50-60.
- Rutter, M. (1997). Implications of genetic research for child psychiatry. *Canadian Journal of Psychiatry*, 42(6), 569-76.
- Rutter, M., LeCouteur, A. & Lord, C. (2003). *Autism diagnostic Interview Revised (ADI-R) Manual (WPS Edition)*, Los Angeles: WPS.
- Sonuga-Barke, E. J. (2003). The dual pathway model of AD/HD: an elaboration of neuro-developmental characteristics, *Neurosci Biobehav Rev*, 27(7), 593-604.
- Scourfield, J., Martin, N., Lewis, G., & McGuffin, P. (1999). Heritability of social cognitive skills in children and adolescents. *British Journal of Psychiatry*, 175, 559-64.
- Shashi, V., Kwapil, T. R., Kaczorowski, J., Berry, M. N., Santos, C. S., Howard, T. D., Goradia, D., Prasad, K., Vaibhav, D., Rajarethinam, R., Spence, E. and Keshavan, M. S. (2010) 'Evidence of gray matter reduction and dysfunction in chromosome 22q11.2 deletion syndrome', *Psychiatry Research Neuroimaging*, 181(1), 1-8.
- Slaats-Willems, D. I. E., De Sonneville, L. M. J., Swaab-Barneveld, H. J. T. and Buitelaar, J. K. (2007). Family-genetic study of executive functioning in attention-deficit/hyperactivity disorder: Evidence for an endophenotype?, *Neuropsychology*, 21(6), 751-60.
- Sobin, C., Kiley-Brabeck, K. and Karayiorgou, M. (2005). Lower prepulse inhibition in children with the 22q11 deletion syndrome, *American Journal of Psychiatry*, 162(6), 1090-9.

Stoddard, J., Beckett, L. and Simon, T. J. (2011). Atypical development of the executive attention network in children with chromosome 22q11.2 deletion syndrome, *Journal of Neurodevelopmental Disorders*, 3(1), 76-85.

Straus, E., Sherman, E., Spreen, O. (2006) *A compendium of neuropsychological tests: Administration, norms and commentary (3rd edition)*. NY: Oxford University Press.

Van Rijn, S., De Sonnevile, L., Lahuis, B., Pieterse, J., Van Engeland, H. and Swaab, H. (2013). Executive function in MCDD and PDD-NOS: A study of inhibitory control, attention regulation and behavioral adaptivity, *Journal of Autism and Developmental Disorders*, 43(6), 1356-66.

Vorstman, J. A. S., Morcus, M. E. J., Duijff, S. N., Klaassen, P. W. J., Heineman-de Boer, J. A., Beemer, F. A., *et al.* (2006). The 22q11.2 deletion in children: High rate of autistic disorders and early onset of psychotic symptoms, *Journal of the American Academy of Child & Adolescents Psychiatry*, 45(9), 1104-13.

Wechsler, D. (1974). *Wechsler Intelligence Scal for Children-Revised, Dutch version, manual*, New York/Lisse: Psychological Corporation/Swets & Zeitlinger B.V.

Wechsler, D. (2002). *Wechsler Intelligence Scale for Children, third edition, manual Dutch version.*, Amsterdam: Harcourt Assessment/Pearson.

Wechsler, D. (2005a). *Wechsler adult intelligence scale (WAIS-III), third edition, Dutch version, manual*, Amsterdam: Harcourt Test Publishers.

Wechsler, D. (2005b). *Wechsler Intelligenc Scale for Children, third edition, Dutch version, manual revised*, London: Hartcour Assessment.

Woodin, M., Wang, P. P., Aleman, D., McDonald McGinn, D., Zackai, E. and Moss, E. (2001). Neuropsychological profile of children and adolescents with the 22q11.2 microdeletion, *Genet Med*, 3(1), 34-9.