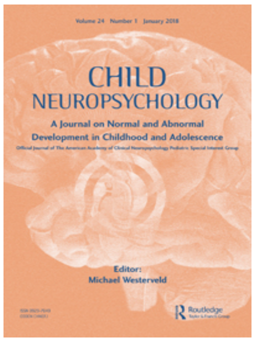

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Executive functioning and its relation to ASD and ADHD symptomatology in 22q11.2 deletion syndrome*

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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 this study, the relation between executive functioning (EF) and the severity of ADHD and ASD symptoms is examined, since EF is known to be important in relation to emotional and behavioral problems. The participants consist of 58 children (38 females) with a mean age of 13.5 years (*SD* 2.6). Standardized assessment was used to evaluate the severity of ASD and ADHD symptomatology. The major aspects of EF, i.e., cognitive flexibility, inhibition, sustained attention, distractibility, working memory and reaction speed, were evaluated. The profile of EF in 22q11DS was found to be characterized by weaker performance compared to the norms on all subdomains of EF. Poor cognitive flexibility and inhibition, as well as high distractibility, were found to be related to more severe ASD symptoms, while poor quality of sustained attention and high distractibility were found to be related to more severe ADHD symptoms. It is concluded that children with 22q11DS experience impairments in EF, and that the degree of impairment on specific EF subdomains is related to the severity of ASD and/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.

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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., 2007, 2006; Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2009). There is a higher prevalence of different behavioral and emotional problems in children and adolescents with 22q11DS compared to their typically-developing peers, including problems in attention regulation,

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*This article is dedicated to Herman van Engeland, an inspiring child psychiatrist and a great mentor and teacher.
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impulsivity, communication and social interaction that are related to ADHD and ASD (Antshel et al., 2007; Fine et al., 2005; Vorstman et al., 2006). Because genetic factors are involved in these developmental disorders, investigating a genetic syndrome that is associated with symptoms of these disorders is a unique opportunity to learn more about the neural basis of these disorders (Rutter, 1997; Scourfield, Martin, Lewis, & McGuffin, 1999).

Executive Functioning and Vulnerability to ASD/ADHD Symptomatology

In particular, investigating neuropsychological dysfunctions as possible underlying mechanisms of the behavioral and emotional problems in 22q11DS may provide insight into the etiology of ASD and ADHD. Deficits in executive functioning (EF) that regulate behavior and thought (Anderson, 2001; Blakemore & Choudhury, 2006) have been found to underlie behavior and adaptation problems observed in ADHD (Barkley, 1997; Sonuga-Barke, 2003) and ASD (Gargaro, Rinehart, Bradshaw, Tonge, & Sheppard, 2011; Hill, 2004; Ozonoff, Pennington, & Rogers, 1991). EF could therefore be important in determining vulnerability to ASD and ADHD symptomatology in individuals with 22q11DS, which may help to develop interventions that improve cognitive functioning in children with 22q11DS, as recently demonstrated in adolescents with 22q11DS (Harrell et al., 2013).

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 (Antshel et al., 2008; Campbell et al., 2010; Furniss, Biswas, Gumber, & Singh, 2011; Gur et al., 2014; Lajiness-O'Neill et al., 2006; Lewandowski, Shashi, Berry, & Kwapil, 2007; Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2005; Ousley, Rockers, Dell, Coleman, & Cubells, 2007; Rockers et al., 2009; Shashi et al., 2010; Sobin, Kiley-Brabeck, & Karayiorgou, 2005; Stoddard, Beckett, & Simon, 2011; Woodin et al., 2001). The heterogeneity in the methods used might preclude the determination of a clear EF profile and may have contributed to inconsistent patterns in the findings so far. For example, some studies report impaired response inhibition in 22q11DS (Antshel et al., 2008; Campbell et al., 2010; Sobin et al., 2005), which has not been found in other studies (Gothelf et al., 2007; Lajiness-O'Neill et al., 2006).

Heterogeneity of EF Dysfunctions and ASD/ADHD Symptoms

Importantly, since a relation between executive dysfunction and behavioral outcomes in 22q11DS has not yet been convincingly demonstrated, it is necessary to investigate multiple aspects of EF in 22q11DS in order to determine a profile of assets and deficits, acknowledging the heterogeneity of EF impairments. As yet, only a few studies have focused on EF in relation to ASD and ADHD symptomatology, suggesting that EF deficits are different for individuals with and without psychopathology. For example, in a study that does not differentiate between individuals with and without psychopathology, planning ability was found to be impaired in 22q11DS (Henry et al., 2002), while another study reported impaired planning ability *only* in those children who also have ASD/ADHD symptoms (Niklasson & Gillberg, 2010). This suggests a relation between

EF and ASD/ADHD symptomology in 22q11DS, and underlines the importance of examining this issue further, including a wide range of EF. The nature of ASD and ADHD symptoms is admittedly heterogeneous; therefore, in the present study, the three major symptom domains of ADHD (inattention, hyperactivity, impulsivity), and ASD (reciprocal social interaction, communication impairment, repetitive and stereotyped behaviors) are evaluated.

Age

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 (Anderson, 2001; Best & Miller, 2010). Investigating executive aspects of attention in relation to age, Stoddard et al. (2011) found more pronounced impairments in younger children with 22q11DS (aged 7 to 14 years). In a longitudinal study, it was shown that not all cognitive performances of individuals with 22q11DS decline with age; learning and memory skills declined, while perseveration and planning improved (Antshel et al., 2010).

Given the above, 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 may help to develop cognitive interventions. The first aim is thus to extend previous findings through the evaluation of a wide range of EF. The second aim is to explore the relation between EF and the severity of ADHD and ASD symptoms. In line with previous results, it was hypothesized that EF is impaired in individuals with 22q11DS. Based on the lack of consistent patterns in findings so far, it was expected that some but not all of the EF tested would exhibit impairments. Based on the research thus far, impairments in working memory and inhibition were expected to be related to more severe ADHD symptoms, and impairments in inhibition and flexibility were expected to be related to more severe ASD symptoms. The relation between dysfunctions in EF and age are also explored, because of inconsistencies in findings to date. Since sex differences in relation to EF in 22q11DS have not been found, an effect of sex was not expected (Niklasson & Gillberg, 2010; Woodin et al., 2001).

METHOD

Sample

A total of 58 children (38 females, age: M = 13.48 years, SD = 2.6, min = 9, max = 18.5; full-scale IQ [FSIQ]: M = 65.2, SD = 13.3) with 22q11DS, as confirmed with a fluorescence in situ hybridization, participated in this study, which is 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 before they made a decision on participation. Informed consent was obtained from participants and parents/caregivers. 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 the assessment, three children were being treated with atypical antipsychotics and one with stimulant medication. Other medication that was being used by participants consisted of anti-epileptics (n = 1), Beta blockers (n = 1) and thyroid medication (n = 2).

Measures

Psychiatric classifications were made according to *Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition* (*DSM-IV*; American Psychiatric Association, 2000) 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) and analysis of the findings of the child questionnaires and intelligence assessments.

The assessment protocol included the Autism Diagnostic Interview – Revised (ADI-R; Rutter, LeCouteur, & Lord, 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.

Information from caregivers and teachers was obtained using the Child Behavior Checklist (CBCL), the Teacher Rating Form (Achenbach, 1991; Achenbach & Rescorla, 2001) and the Conners' Rating Scales – Revised (Conners, 1997).

Intellectual functioning was assessed using a current version of the Wechsler Intelligence Scale for Children - Revised/Third Edition/Third Edition Revised (WISC; Wechsler, 1974, 2002, 2005b) for participants aged 16 years and under and the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 2005a) for participants aged 17 to 18 years.

An overview of the formal psychiatric classifications with comorbid diagnoses 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. In two individuals, ADHD symptoms were prominent, justifying a formal (comorbid) diagnosis of ADHD (Table 1).

Table 1. Psychiatric Classifications According to *DSM-IV* Criteria with Primary Diagnoses and Comorbid Diagnoses.

		Comorbid diagnoses*				
Diagnostic classification (primary)	*n*	ASD	ADHD	Depressive disorder	ODD	Psychotic disorder
Autism spectrum disorder (ASD)	31		2	4	1	5
Attention deficit hyperactivity disorder (ADHD)	1					
Anxiety disorder	1					
Conversion disorder	1					
Depressive disorder	2					
Psychotic disorder	2					
Without psychiatric classification	20					
Total	58	0	2	4	1	5

Note. *Represents comorbid diagnoses within the total of 58 participants. ODD = oppositional defiant disorder.

Table 2. ASD and ADHD Severity Scores for All Participants and Subgroups.

	All participants				With diagnosis (n = 37/38)			Without diagnosis (n = 20)		
	n	*M*	*SD*	Range	*M*	*SD*	Range	*M*	*SD*	Range
ADHD total	57	11.47	8.34	0–30	14.00	8.64	1–30	6.80	5.34	0–16
Inattention	57	7.75	6.06	0–23	9.08	6.49	0–23	5.30	4.32	0–16
Hyperactivity	57	1.84	2.32	0–8	2.35	2.44	0–8	0.90	1.77	0–7
Impulsivity	57	1.88	2.13	0–9	2.57	2.30	0–9	0.60	0.82	0–2
ADI total	58	24.17	13.35	0–49	29.79	11.11	9–49	13.50	10.55	0–39
Reciprocal social interaction	58	10.76	6.92	0–26	13.47	6.02	1–26	5.60	5.52	0–20
Communication impairment	58	7.47	5.05	0–19	9.45	4.75	1–19	3.70	3.11	0–11
Repetitive and stereotyped behaviors	58	2.12	2.06	0–8	2.71	1.90	0–7	1.00	1.92	0–8

Because of the high prevalence of ASD and ADHD symptoms in 22q11DS, the possible co-occurrence of symptoms of both neurodevelopmental disorders is investigated. The severity of ASD and ADHD symptoms varies along dimensional scales. Since the primary objective of this study is to evaluate how EF deficits are related to severity of ASD and ADHD symptomatology, the focus is not on categorical entities but on *all* subjects with 22q11DS, as well as those not reaching the clinical cut-off criteria. The three ADHD domains (inattention, hyperactivity, impulsivity) as rated with a semi-structured interview based on *DSM-IV* criteria were used as a measure of the severity of ADHD symptoms. The interview consisted of items comparable to those of the Conners' Rating Scales – Revised (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 (McDuffie et al., 2010; Rutter et al., 2003). Table 2 provides the means and distributions of the scores for ASD and ADHD symptom severity. Similar data for the two groups identified in Table 1—those with a psychiatric diagnosis (n = 38) and those without (n = 20)—are also included in Table 2. In particular, the range of scores shows that variation in symptom severity is not limited to the psychiatric diagnosis group.

Executive Functioning (EF)

The Amsterdam Neuropsychological Tasks (ANT; De Sonneville, 1999, 2005) program was used to evaluate major components of EF. The ANT has been proven to be a wellvalidated and sensitive instrument that is suitable for evaluating attentional processes and EF in psychiatric disorders such as ADHD (Slaats-Willemse, De Sonneville, Swaab-Barneveld, & Buitelaar, 2007) and ASD (Van Rijn et al., 2013).

Alertness was evaluated using the Baseline Speed (BS; Gunther, Herpertz-Dahlmann, & Konrad, 2005) task, which is a simple reaction-time (RT) task. A fixation cross presented on a screen changes unexpectedly into a square—the imperative signal. The participant has to press a mouse key as fast as possible after the change occurs. The reaction speed is operationalized as the mean RT for 32 signals. Fluctuations in reaction speed are operationalized as the within-subject *SD* of RTs to the signals.

Sustained attention was assessed with the SA-dots (SAD; Van Rijn et al., 2013) task, which measures the participant's ability to maintain performance at a certain level over 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. Participants are required to respond to the 4-dot pattern (target) by pressing the mouse button with their preferred hand (the *yes* response) and to the 3- and 5-dot patterns (non-targets) by pressing the mouse with their non-preferred hand (the *no* response). The target to non-target ratio is 1:2, which invokes a response bias for the *no* key. Failure to inhibit this bias is expected to result in the production of relatively more misses than false alarms. The task duration is approximately 15 to 20 minutes. The main outcome measures are the mean series completion time (tempo), the within-subject *SD* of the 50 series completion times as a measure of sustained attention, along with measures of impulsivity (misses) and poor stimulus evaluation (false alarms).

*Inhibition of prepotent responses*and *cognitive flexibility* were measured with the Shifting Attentional Set Visual (SSV; Huijbregts, Swaab, & de Sonneville, 2010) task. During the 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 (the fixed compatible condition) the participant is asked to follow the movement of a green square by pressing the left button upon seeing the square move to the left and the right button upon seeing the square move to the right. In part 2 (the fixed incompatible condition), the participant is asked to follow the movement of a red square, but this time to do the opposite of the actions performed in part 1 by pressing the left button when the square moves to the right and the right button when the square moves to the left, requiring the inhibition of prepotent responses. Inhibition is operationalized as the contrast in performance (speed and accuracy) between parts 1 and 2. In part 3 (the random condition), the square changes color randomly, requiring the participant to follow or "mirror" the movement, depending on the color of the square. Now the participant needs to shift response sets, i.e., readily switch between the execution of a prepotent response and the inhibition of a prepotent response. This requires cognitive flexibility, which is operationalized as the contrast in performance between parts 1 and 3. (compatible responses).

*Working memory*and *distraction* were measured using the Memory Search Letters (MSL; De Sonneville et al., 2002) task. 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 in part 3 (k + r + s). The display set of four letters that contains the complete target set requires a *yes* response, while incomplete target sets require a *no* response. Target letters in non-target trials act as distractors. The memory search rate is operationalized as the contrast in the speed and accuracy of responses to target signals in part 1 (low load) and part 3 (high load), while distraction is operationalized as the contrast in the speed and accuracy of responses to the non-target signals in part 3 between signals with no distractors (low distraction) and signals with two distractors (high distraction).

The test–retest reliability and validity of the computerized ANT are satisfactory and have extensively been described (De Sonneville, 2014; Gunther et al., 2005; Huijbregts, de Sonneville, Licht, Sergeant, & van Spronsen, 2002; Rowbotham, Pit-ten Cate, Sonuga-Barke, & Huijbregts, 2009). Mean test–retest reliabilities for the variables per task are .73 for the BS task, .80 for the SAD task, .75 for the SSV task, and .75 for the MSL task (De Sonneville, 2014).

Statistical Analyses

The main outcome parameters were transformed into z-scores (De Sonneville, 2005, 2014), which are the results of computations based on nonlinear regression functions that describe the relation between test age and task performance. These functions are intrinsically implemented in the ANT program based on norm samples varying in size between 3100 to 6700 subjects depending on the task (De Sonneville, 2014), and are therefore considered to be reliable estimates of performance level.

The results 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 participants in the analyses (Table 3). Not all participants completed the entire assessment battery (e.g., failing to

Table 3. Distribution of scores on EF across the *SD*s in %.

Measure		≤ 1 *SD*	≥ 2 *SD*s	≥ 6 *SD*s
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
	Misses	64.9	17.5	1.8
	FAs	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

Note. Acc = accuracy; FAs = false alarms; Fluc = fluctuation; RT = reaction time. With regard to the numbers used in the "Measure" column, C1 and C3 = the compatible conditions in part 1 and part 3 of the SSV task, I2 = the incompatible condition in part 2 of the SSV task, 1 and 3 = part 1 (low load condition) and part 3 (high load condition) of the MSL task, and 0 and 2 = part 3 with 0 distractors (low distraction condition) or 2 distractors (high distraction condition) of the MSL task.

complete a difficult task part or running out of time), therefore the degrees of freedom vary between analyses. Participants with missing data on more than one task were excluded from the analyses (n = 5), resulting in a final sample of 58.

Comparisons with Norms

To decide whether or not the mean performance of the participants differed from the norm, i.e., differed from zero for the z-scores, a multivariate analysis of variance (MANOVA) intercept test was used. The alpha was set to .01 and the multivariate group effects were analyzed using Pillai's trace. The effect sizes were calculated using partial eta squared with ${\eta_p}^2$ ~ .03 representing a weak effect, ${\eta_p}^2$ ~ 0.06 representing a moderate effect and ${\eta_p}^2 \geq .14$ representing a significantly large effect (Cohen, 1992). Analyses of variance (ANOVAs) were used for all *post hoc* analyses of group effects. The psychometric properties of the data were inspected prior to analysis. The criterion of z = 6 is admittedly arbitrary, but by setting this criterion, the skewness of the task variables entered into the MANOVAs and ANOVAS, and in the correlational analyses, all stayed within an acceptable range (0.95 for the BS task, 0.49 to 1.19 for the SAD task, −0.47 to 1.50 for the SSV task, and 1.41 to 1.80 for the MSL task). Assumptions for the analyses were examined and confirmed to be satisfactory.

For *alertness*, the mean RT and fluctuation of RT for the baseline speed were entered as dependent variables in a MANOVA. For *sustained attention*, the tempo and fluctuation in tempo were entered as dependent variables in a MANOVA for speed, while the number of misses and false alarms were entered as dependent variables in a MANOVA for 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, and the within-subject factors were as follows:

- the contrast between part 1 (compatible responses) and part 3 (compatible responses) for *cognitive flexibility*;
- the contrast between part 1 (compatible responses) and part 2 (incompatible responses) for *inhibition*;
- the contrast between the performance on target signals in all three parts for *memory load*;
- the contrast of performance on non-target signals in part 3 with 0, 1 and 2 distractors for *distraction*.

A significant within-subject 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 a task condition/level interaction.

Finally, for *severity of ASD and ADHD symptomatology*, Pearson correlations were calculated to explore the relation between the severity of ASD and ADHD symptoms and EF (small effect size: r = .10 to .23; medium effect size: r = .24 to .36; large effect size: $r \geq .37$)(Cohen, 1992). Prior to these analyses, an effort was made to find any correlations linking age, FSIQ and sex with *both* EF and symptom severity.

Results

Standardized means of total group performances on all EF tasks are presented in Figure 1. Negative values indicate better EF, while positive values reflect poorer EF compared to the norm. Deviation of EF performances from the norm in *SD*s is presented in Table 3.

Alertness

The participants were slower, $F(1, 56) = 28.421$, $p < .0001, \eta_p^2 = .337$, and showed more fluctuation in reaction speed, $F(1, 56) = 27.388$, $p < .0001, \eta_p^2 = .328$, compared to the norm (Figure 1).

Sustained Attention

The participants demonstrated a slower tempo, $F(1, 56) = 61.761$, $p < .0001, \eta_p^2 = .524$, and greater fluctuation in tempo, $F(1, 56) = 68.278$, $p < .0001, \eta_p^2 = .549$, compared to the norm (Figure 1). Their performances also exhibited more misses than the norm, $F(1, 56) = 6.989$, $p = .011, \eta_p^2 = .111$, but not more false alarms, $p = .170$, suggesting a difficulty to keep the response bias under control (Figure 1).

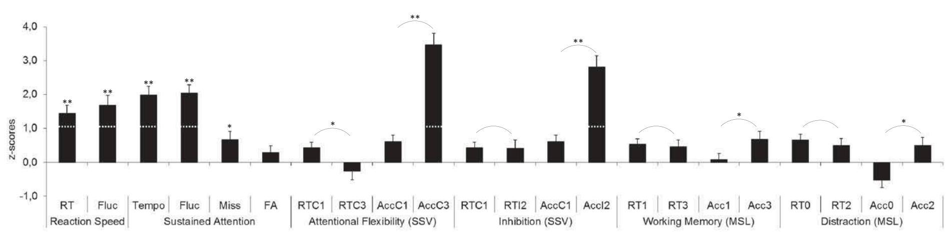

Figure 1. Mean *z*-scores of the participants showing level of performance on EF.

Note. *Significantly different from norm at $p < .01$; **Significantly different from norm at $p < .001$. Acc = accuracy; FAs = false alarms; Fluc = fluctuation; Miss = misses; RT = reaction time. With regard to the numbers used on the *x*-axis, C1 and C3 = the compatible conditions in part 1 and part 3 of the SSV task, I2 = the incompatible condition in part 2 of the SSV task, 1 and 3 = part 1 (low load condition) and part 3 (high load condition) of the MSL task, and 0 and 2 = part 3 with 0 distractors (low distraction condition) or 2 distractors (high distraction condition) of the MSL task. Important contrasts between task conditions are indicated by the curved line elements. For example, AccC1 vs. AccC3 reflects accuracy in part 1 of the SSV task when cognitive flexibility is not required (AccC1) vs. accuracy in part 3 of task SSV (AccC3) when cognitive flexibility is required. Another example is Acc0 vs. Acc2, which reflects accuracy in part 3 of the MSL task when 0 distractors are present (Acc0) vs. accuracy in part 3 of task MSL when 2 distractors are present (Acc2, ignoring distractors is required).

Cognitive Flexibility

Regarding speed, the within-subject factor of *cognitive flexibility* is significant, $F(1, 44) = 7.082$, $p = .011, \eta_p^2 = .139$, indicating that the participants did slightly better than the norm where flexibility was required (Figure 1). The average speed of the participants 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 *cognitive flexibility* is significant, $F(1, 47) = 58.723$, $p < .0001$, $\eta_p^2 = .555$, reflecting a larger increase in error rate compared to the norm where flexibility was required (Figure 1).

Inhibition

Regarding speed, the effect of *inhibition* was not significant, $p = .974$, and the mean performance of the participants was not significantly slower compared to the norm, $p = .041$.

The participants 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 greater decrease in accuracy compared to the norm when inhibition demands are high, $F(1, 51) = 38.733$, $p < .0001, \eta_p^2 = .432$.

Working Memory

Regarding speed, the participants performed slower compared to the norm, $F(1, 55) = 7.788$, $p = .007$, $\eta_p^2 = .124$ (Figure 1). No effect of memory load was found for speed, $p = .217$.

Regarding accuracy, the effect of the memory load is significant, $F(1, 56) = 7.080$, $p = .010$, $\eta_p^2 = .112$, reflecting a larger decrease in accuracy compared to the norm where memory load is a factor (Figure 1). The mean accuracy of the participants is not significantly lower compared to the norm, $p = .028$.

Distraction

The participants were slower on average compared to the norm, $F(1, 54) = 10.028$, $p = .003$, $\eta_p^2 = .157$. No effect was found for *distraction* in terms of speed, $p = .397$, indicating that the presence of distractors did not slow down the participants compared to the norm (Figure 1).

The mean accuracy across the distraction conditions does not differ compared to the norm, $p = .946$, but an effect of *distraction* was found, $F(1, 56) = 26.521$, $p = .0002, \eta_p^2 = .321$, reflecting that the unfavorable effect of distraction on accuracy is more pronounced in the participants compared to the norm (Figure 1).

Age and FSIQ in Relation to EF

A positive correlation was found between age and fluctuation in reaction speed and tempo of sustained attention ($p \leq .01$) which indicates that the older children performed worse on these EF tasks. Reaction speed, sustained attention, and working memory are correlated with FSIQ, indicating that children with a lower FSIQ performed worse on these EF tasks, which is not surprising since EF is needed to perform adequately on intelligence tests. Both age and FSIQ are not correlated with severity of ASD or ADHD symptoms, and therefore no partial correlations were calculated using FSIQ or age as a control variable.

Severity of ASD Symptomatology in Relation to EF

A more severe ADI total score is associated with decreases in speed when flexibility or inhibition are required (.05 level, Table 4). Decreases in speed when flexibility or inhibition are required are in a similar way associated with reciprocal social interaction (Table 4). A more severe communication impairment is related to decreases in speed when inhibition is required and when distraction is high, while an increase in accuracy is noticed when cognitive flexibility is required (Table 4). No relation between repetitive and stereotyped behaviors and any of the EF measures was found.

Severity of ADHD Symptomatology in Relation to EF

Higher scores on hyperactivity and impulsivity are associated with an increase in accuracy when memory load increases and a decrease in speed when distraction is present (Table 4). More severe hyperactivity symptoms are also related to more misses (impulsive errors) during sustained attention (Table 4). Inattention is not correlated with any of the EF measures (Table 4).

Discussion

This study investigate EF in children and adolescents with 22q11DS and examines whether EF is related to the severity of ASD and ADHD symptoms. The use of an extensive battery of EF tasks made it possible to generate a detailed profile of executive dysfunctions, reflected in processing speed, stability and/or accuracy. The results show a reduction in accuracy when task demands require cognitive flexibility, resistance against distraction, inhibition or working memory capacity. Poorer alertness is reflected in slower reaction times and larger fluctuations in reaction speed. There are also deficits in sustained attention, as reflected in a higher fluctuation in tempo and a higher miss rate, the latter result indicating a decreased ability to maintain inhibitory control during time-on-task. It was found that the severity of ASD symptoms is related to poorer cognitive flexibility, inhibition and distractibility, while the severity of ADHD symptoms is related to poorer quality of sustained attention and higher distractibility.

The majority of EF deficits are reflected in accuracy rather than 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 found no differences in accuracy on a mental flexibility task between 22q11DS participants and their siblings, but reported poorer inhibition, planning skills and working memory capacity in individuals with 22q11DS. Both studies are complementary in that the findings give reason to believe that specific EF deficits, mostly reflected in lower accuracy, are present in 22q11DS.

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	FSIQ
Reaction Speed	Speed	.104	.182	.015	.121	−.042	−.026	−.001	−.087	.119	−.354**
	Fluctuation	.133	.190	.101	.129	.128	.090	.059	.179	.459**	−.295*
Sustained Attention	Tempo	−.096	−.035	−.090	−.160	−.115	−.087	−.141	−.050	.353**	−.543**
	Fluctuation	−.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
Age		−.026	.038	−.031	−.212	−.117	−.109	−.202	.069	-	−.268*
FSIQ		−.149	−.162	−.092	−.084	−.017	−.052	−.143	−.058	-	-

Note. *Correlation significant at the .05 level (1-tailed); **Correlation significant at the .01 level (1-tailed); [1]Denotes a decrease in speed when flexibility or inhibition is required; [2]Denotes a decrease in accuracy when flexibility/inhibition is required; [3]Denotes a decrease in speed (RT) or accuracy (NM) when memory load increases; [4]Denotes a decrease in speed (RT) or accuracy (PF) when distraction is present. NM = number of misses; PE = percentage of errors; PF = percentage of false alarms; RT = reaction time.

As argued before, deficits in EF 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 shows that decreases in tempo when cognitive flexibility or inhibition are required are related to ASD symptom severity. Focusing on detailed levels of ASD symptoms, a similar relation is found with the severity of the problems in reciprocal social interaction. Decreases in speed when inhibition and resistance to distraction are required are related to severity of impairment in communication. An increase in accuracy when cognitive flexibility is required is also related to a more severe impairment in communication. Together, these results suggest that children with more severe ASD symptoms decrease their tempo during complex tasks in order to perform them relatively more accurately.

With respect to ADHD symptoms, severity of hyperactivity is related to poorer inhibition during sustained attention, higher distractibility and an increase in accuracy when memory load increases. Severity of impulsivity is related to higher distractibility and an increase in accuracy when memory load increased. This indicates that children with more ADHD symptoms have problems with inhibition of responses and are easily distracted, but also that when a higher demand is imposed on their working memory capacities—forcing them to focus on the task and thus making them less easily distracted—they can perform relatively better. Inattention is not correlated to any of the EF measures, which may well reflect differences in attention processes that are captured by the questionnaire (compound score of behavioral inattention indices) and the task paradigm (the ability to ignore distractors). Usually, substantial correlations of task performance data with questionnaire data that “operate” in the same domain are barely noticeable. For example, in a study by Wolters Gregorio et al. (2015) conducted on adults with acquired brain injury and neuropsychiatric symptoms, performance on EF tests did not correlate with the self-report measures of EF measured by the Life Satisfaction Questionnaire. Toplak, West, and Stanovich (2013) argue that objective assessments and self-ratings measure two different constructs, in that objective tests assess the processing *efficiency* of EF, while self-ratings assess the extent to which goals are achieved, hence *efficacy*.

Interestingly, the relations between EF and ASD and ADHD symptoms partly seem to differ from findings in clinical groups with ASD and ADHD but without 22q11DS. In children with ADHD, impairments in working memory and inhibitory control have been reported (Ozonoff et al., 1991; Sonuga-Barke, 2003), while in the present study inhibitory control was not found to be associated with severity of ADHD symptoms in children with 22q11DS. This finding suggests preliminary support for the idea of different neurobiological pathways, also on a neuropsychological level, leading to ADHD symptomatology (de Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012; Durston, Van Belle, & De Zeeuw, 2011). In addition, the nature of the ADHD symptoms in individuals with 22q11DS seems to be different from the idiopathic ADHD population in that most youth with 22q11DS (also in the present sample) primarily show inattentive symptoms (Niarchou, Martin, Thapar, Owen, & van den Bree, 2015).

In children with idiopathic ASD, deficits have been found in planning, inhibition and cognitive flexibility (Hill, 2004; Robinson, Goddard, Dritschel, Wisley, & Howlin, 2009). In the current study, deficits in inhibition, flexibility and distractibility were found to be related to the severity of ASD symptoms, but so far poor distractibility has not been reported in children with ASD. These findings therefore suggest that in children with 22q11DS, partly comparable EF deficits seem to influence the severity of ASD symptoms 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 and ADHD by definition examine 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 in that the older participants demonstrated poorer sustained attention compared to the younger participants. This outcome contradicts the results of other studies which showed more pronounced EF impairments in younger children with 22q11DS (Antshel et al., 2010; Stoddard et al., 2011), but it is in line with the decline with age in the more general measures of cognitive functioning 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 EF.

To further explore these findings, an important step will be to attempt to replicate them in a larger sample. The outcome of this exploratory study suggests a relation between specific EF deficits and severity of both ASD and ADHD symptoms with medium 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 and the fact that EF is developing with age, future research should be designed longitudinally. For example, distinguishing between children and adolescents seems relevant but would result in the current study in sample sizes that are too small for comparisons.

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. In terms of limitations, although sample size can be considered relatively large for a study of individuals with a specific genetic disorder, 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 this population. The results therefore need to be interpreted with caution. The lack of a control group can be seen as another limitation. It is difficult, however, to decide which criteria can be used to select an appropriate control group; matching on age, intelligence, developmental age, or characteristics that make the 22q11DS group unique would likely introduce other problems.

Compared to the *DSM – Fifth Edition* (*DSM-5*), the *DSM-IV* guidelines do not allow a diagnosis of 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 is made. Using *DSM-5* criteria however would probably increase the number of subjects with ADHD (Niklasson et al., 2009).

One may question whether the impairments seen are representative of 22q11DS as a whole or whether there are significant subgroups. Only be one subgroup analysis is feasible (Table 1), i.e. contrasting subjects with (n = 32) and without (n = 20) a psychiatric diagnosis. These groups do not differ in age (13.1 ± 2.7 years vs. 12.8 ± 2.56 years) or FSIQ (65.0 ± 12.0 vs. 68.5 ± 14.0). All MANOVAs and ANOVAs were carried out again, adding subgroup as a between-subjects factor. No significant differences were found between the groups on any task, and neither were there significant group × task level interaction effects, demonstrating that the presented EF deficit profile is representative for this sample, allowing the focus to be placed on variations in this profile as being associated with ASD and ADHD symptom severity by correlational analysis. Further, it is noted that 20 participants (35%) had no psychiatric diagnosis, which corroborates with findings of other studies, such as Green et al. (2009) (35%) and Niklasson et al. (2009) (33%).

As expected, mean intelligence is lower compared to the norm (FSIQ: M = 65.2, SD = 13.3). Inspection of the data show that the distribution is appropriately bell-shaped, suggesting a normal variation, refuting the existence of an intellectual subpopulation. Dennis et al. (2009) provide a number of valid arguments to not use IQ as a covariate in studying neurodevelopmental disorders. Nevertheless, all analyses of the task performance data were rerun with IQ as a covariate, resulting in outcomes that are similar to the results when not controlling for IQ. For example, the decrease in accuracy, compared to the norm, when flexibility or inhibition is required (see Figure 1) is still significant after the removal of all IQ-related variance. Furthermore, Table 4 shows that IQ is not correlated to changes in accuracy or speed of attentional flexibility and inhibition.

The outcomes are presented as they are, i.e. without Bonferroni corrections. In line with the arguments and advice of Perneger (1998), the tests of significance that have been performed are described. When significant differences with the norm are found in EF, these are associated with very small p-values ($p < .0001$). The main significant results would not be affected by the application of Bonferroni corrections. With regard to the correlational analysis, flat (Bonferroni) corrections for correlated measures are questionable.

This study provides a detailed profile of impairments in EF experienced by children with 22q11DS. Some evidence has been found that the degree of impairment on specific aspects of EF 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.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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