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Age-Related Improvements in Executive Functions and Focal Attention in 22q11.2 Deletion Syndrome Vary Across Domain and Task

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Abstract

Objective: Executive functions (EF) and focal attention have been identified as a weakness in the profile of 22q11.2 deletion syndrome (22q11DS). However, due to a high variety of tasks used across previous studies, it remains unclear whether impairments may be more pronounced for specific subdomains of EF and focal attention. Furthermore, age-related changes have only been examined in a few studies, so far only yielding a partial view of the overall developmental profile. **Method:** In a broad age range (8–35 years) composed of longitudinal data, 183 participants (103 diagnosed with 22q11DS) completed an extensive assessment of EF and attention. To get a more comprehensive overview of specific *versus* global impairments, several tasks were assessed within multiple domains. **Results:** Results suggest differential impairments and trajectories in specific EF subdomains. Specifically, our findings suggest that individuals with 22q11DS not only showed lower overall inhibition skills, but also that initiation skills developed at a slower pace compared to healthy controls. Results are less clear regarding cognitive flexibility, updating and focal attention, for which performance strongly depended on the tasks that was selected to assess the domain. **Conclusions:** Findings confirm and extend knowledge on differential developmental patterns of EF and attention domains in 22q11DS. They further stress the necessity to administer extensive, multifaceted evaluations to gain a more reliable overview of patients' cognitive profile.

Keywords: Executive functions, Attention, 22q11.2 deletion syndrome, Developmental trajectories, Age

INTRODUCTION

Chromosome 22q11.2 deletion syndrome (22q11DS) is a genetic condition affecting multiple systems, including the brain, and is associated with a specific neuropsychological profile involving deficits in multiple cognitive domains (McDonald-McGinn et al., 2015). Among these domains, executive functions (EF) are part of the key cognitive abilities affected by the deletion. Given that EF play a critical role in formulating goals, planning, and carrying out successful goal-directed behaviors, EF inherently contribute to academic and professional success, as well as autonomy in daily life (Anderson & Reidy, 2012; Diamond, 2013). More specifically, performance of individuals with 22q11DS on EF measures in childhood predict adaptive behavior and social adjustment in young adulthood (Albert, Abu-Ramadan, Kates, Fremont, & Antshel, 2018).

For over two decades, deficits in EF and attention have been studied in 22q11DS. A recent meta-analysis reported a moderate to large EF impairment in 22q11DS (Moberg et al., 2018). Similarly, deficits in EF are supported by neuroimaging studies showing structural and functional alterations of frontal regions (known to underlie EF) that correlate with

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task performance (Da Silva Alves et al., 2011; Harrell et al., 2017; Padula et al., 2017; Rogdaki et al., 2020; Scariati, Padula, Schaer, & Eliez, 2016; Shashi et al., 2010). Yet, previous studies have used a wide range of different methodologies and samples, yielding sometimes contradictory findings and an inconsistent overall profile. Furthermore, the current literature is inconclusive as to whether 22q11DS is associated with an overall EF impairment, or whether impairments may be more pronounced for specific subdomains of EF. This is mainly due to methodological shortcomings regarding task selection and developmental trajectories of EF.

More specifically, despite the recognized diversity of EF models (Karr et al., 2018; Miyake et al., 2000), early studies aiming to describe the neuropsychological profile of 22q11DS have considered EF as a unitary construct and thus have assessed the participants' overall executive functioning with only one or two global EF measures such as Wisconsin Card Sorting Test or Trail-Making Test (Lewandowski, Shashi, Berry, & Kwapil, 2007; Woodin et al., 2001). In contrast to examining overall executive functioning, later studies focused on one specific executive domain at a time, such as inhibition, working memory, or multitasking (Kates et al., 2007; Majerus, Van der Linden, Braissand, & Eliez, 2007; McCabe et al., 2014; Montojo et al., 2014; Schneider et al., 2016; Shapiro, Wong, & Simon, 2013). These studies contributed important information on specific EF impairments in 22q11DS. However, in order to achieve a more fine-grained understanding of EF and attentional deficits in the syndrome, multiple executive domains need to be assessed simulatenously in the same sample. In addressing this goal, a major challenge is task impurity, as tests designed to measure EF recruit both executive and nonexecutive abilities. The use of different measures across studies to assess the same construct could contribute to explain the observed differences, and this issue could be solved by the use of several tasks assessing the same executive domain in the same sample, which so far has never been done in this population.

Moreover, the role of age in the development of EF has not always been considered for 22q11DS, as most previous studies separately focused either on children/adolescent populations or on adults (Campbell et al., 2010; Chow, Watson, Young, & Bassett, 2006; Henry et al., 2002). Yet, studies conducted in the general population show that both EF and attention strongly rely on the frontal brain regions, which reach maturation only during early adulthood (Sousa, Amaro, Crego, Gonçalves, & Sampaio, 2018). In 22q11DS, pre-frontal regions undergo excessive cortical thinning during adolescence (Ramanathan et al., 2017; Schaer et al., 2009), suggesting abnormal maturation processes which could, on a behavioral level, be associated with atypical developmental trajectories of EF. Thus, to fully apprehend EF development in 22q11DS, the full age range from childhood to (early) adulthood should be examined. Unfortunately, as highlighted in Morrison et al. (2020), the literature on the cognitive trajectories from childhood to adulthood in 22q11DS is scarce and inconsistent.

Different study designs have been used for investigating developmental trajectories of EF and attention in 22q11DS. Using a cross-sectional design, a large multisite study examined the cognitive performance of 236 participants with 22q11DS aged between 6 and 60 years (Morrison et al., 2020). They showed that the magnitude of impairment not only differed by developmental stage (i.e., how old patients are) but also differed across distinct cognitive domains. More specifically, processing speed seemed to be more impaired in children, whereas working memory was more impaired in adults, and sustained attention was altered across age groups. Although this study provides important insights into developmental differences between age groups, age was modeled as a categorical variable based on the definitions of "childhood," "adolescence," and "adulthood" provided by the World Health Organization guidelines (https://www.who.int). However, EF and attention mature in a nonlinear dynamic way, with different domains showing different trajectories over time (Akshoomoff et al., 2014; Anderson, 2002; Romine & Reynolds, 2005; Waber et al., 2007). Therefore, to fully grasp the complex dynamic of EF trajectories, age should preferably be considered as a continuous variable. To our knowledge, only a few of studies on 22q11DS have examined continuous age-related trajectories of EF and attention while also assessing multiple executive domains. One study showed a lack of improvement of inhibition and cognitive flexibility performance with age (Shapiro, Tassone, Choudhary, & Simon, 2014). However, there was a significant effect of age on working memory (verbal and nonverbal) performance, with older participants exhibiting a higher working memory span. Another study found that executive control of attention is affected by age, with younger children having more pronounced impairments and more variable scores (Stoddard, Beckett, & Simon, 2011). However, both studies that were limited by a cross-sectional design preclude the assessment of individual variability. In addition, the ages range from 7 to 14 years, thereby yielding only a partial view of the full childhood-to-adulthood trajectory.

Using longitudinal data (several assessment per participants), one study examined neurocognitive changes over a 3.5-year interval in children and adolescents (Hooper et al., 2013). They reported significantly lower performance in the 22q11DS group compared to healthy controls for intellectual functioning, attention, cognitive flexibility, working memory, and processing speed at first and second evaluation. When controlled for chronological age, changes in raw scores over time between evaluations were significantly different only for one measure of sustained attention, with slower gain for 22q11DS participants. Furthermore, from a developmental perspective (for a visualization, see Figure 1), a study discussing the use of raw scores found that most measures of reasoning (verbal and nonverbal), EF (planning, set-shifting, and spatial working memory), and attention follow a developmental deficit model (i.e., static cognitive impairments that emerged early in development and remain stable) (Chawner et al., 2017). Only one measure of nonverbal reasoning (block design) showed a development lag pattern (i.e., syndromic

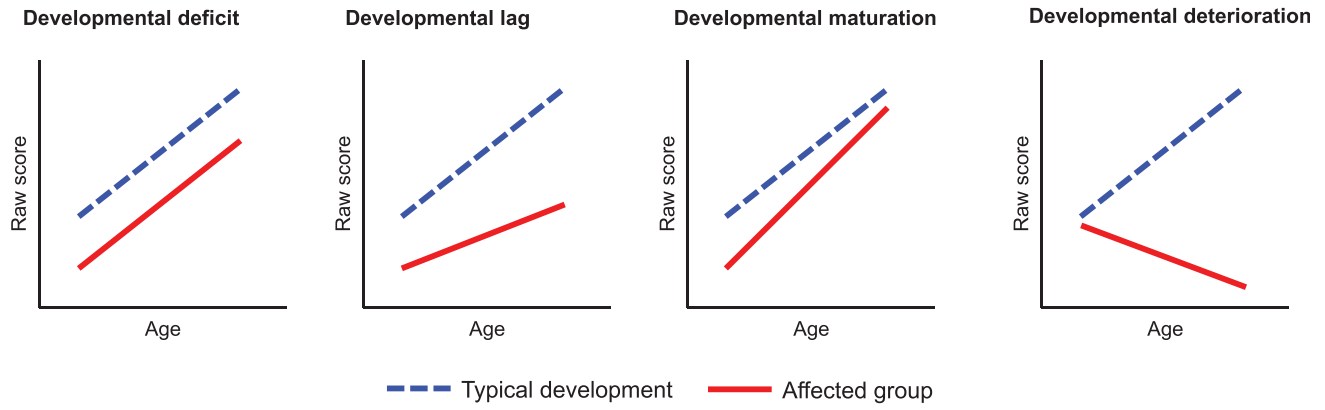

Fig. 1. Visualisation of four developmental patterns of raw scores with age (Adapted from Chawner et al., 2017).

individuals showed absolute growth in cognitive ability but were lagging behind compared to typical developing individuals) and one measure of processing speed yielded a developmental maturation pattern (i.e., individuals with 22q11DS showed initial cognitive impairment but caught up with the control group at later stages of development). No developmental deterioration (i.e., decline in absolute ability) was observed. Thus, encouraging new insights have emanated from longitudinal approaches to EF maturation. However, the age range of the study (mean age visit 1 = 9.9, standard deviation = 2.4; mean age visit 2 = 12.5, standard deviation = 2.3) again prevented a characterization of the full developmental trajectory of EF.

Finally, in the only prior study assessing a larger age range (individuals aged 6–26 years), findings revealed deviant trajectories of updating (small improvement with age in the 22q11DS with individuals reaching a developmental plateau much faster than controls) and verbal fluency (very modest improvement with age in the 22q11DS group compared to controls) with age (Maeder et al., 2016). In contrast, inhibition followed the same trajectory as controls, even though performances were overall significantly weaker in 22q11DS. However, only a modest number of EF domains were examined in this study, yielding again only a partial view of the overall developmental profile of EF and attention in 22q11DS.

Taken together, the available literature has provided evidence for distinct patterns of development in different cognitive domains or tasks but has thus far been limited by the age range examined and the number of cognitive domains examined in the same sample of participants. Identifying developmental patterns in specific domains (developmental deficit, lag, deterioration or maturation) is however crucial for the development of age-appropriate guidelines for evaluation, as well as for the selection of relevant intervention strategies (such as compensation or remediation).

The present study aimed to confirm and further extend previous findings on the developmental trajectories of EF and attention in 22q11DS through two major aspects. First, a wider range of cognitive domains was examined to determine whether 22q11DS patients perform worse than controls on all EF and attention domains or whether some domains are less affected, yielding no group difference. To address the issue of impurity, each domain was examined using at least two different tasks. For a domain to be considered as truly impaired, we expected that multiple tasks in the same domain would yield converging results. Otherwise, group differences could be related to specific aspects to the task (e.g., speed, visual, or motor skills).

Second, participants were examined using a wide age range (8-35 years), considering age as a continuous variable and using raw scores to fully observe developmental patterns. We hypothesized that overall, we would observe an effect of age on all variables showing improvement in raw performance with age. We expected results to show either a developmental deficit or a lag, demonstrated by linear or quadratic trajectories. More specifically, based on previous literature, we expected to find a developmental lag for verbal and nonverbal updating and initiation processes (Maeder et al., 2016; Morrison et al., 2020; Shapiro et al., 2014, 2013), a developmental deficit for inhibition and visual attention (Chawner et al., 2017; Hooper et al., 2013; Stoddard et al., 2011), and finally, either a developmental lag or a deficit in cognitive flexibility (Chawner et al., 2017; Hooper et al., 2013; Shapiro et al., 2014).

METHOD

Participants

One hundred and eighty-three participants (103 with 22q11DS and 80 controls) were recruited as part of a longitudinal cohort of 22q11DS patients (Geneva cohort, e.g., Maeder et al., 2016; Schaer et al., 2009). The control group was mainly composed of participants' siblings (80%) and community controls. The age ranged from 8 to 35 years. Participants of the two groups did not differ in terms of age or gender distribution (see Table 1). The presence of the deletion was confirmed using quantitative fluorescent polymerase chain reaction. All participants were recruited through advertisement in patient association reunions, newsletters, and word of mouth. Written informed consent, based

Table 1. Participant characteristics

			Diagnostic group		Comparison		
			22q11.2DS	Controls	ANOVA *F*	Pearson's chi-square χ^2	p-Value
Cross-sectional *N*			103	80			
Longitudinal (two evaluations) *N* (% of full sample)			32 (31.07%)	20 (25%)		.815	.367
Time interval between multiple evaluations in years (SD)			2.47 (1.28)	3.45 (.33)	11.058		**.002**
Evaluations with all tasks complete (% of full sample)			114 (84.44%)	82 (82.00%)			
Gender (*N* male (%))			53 (51.5%)	35 (43.8%)		1.071	.301
Age at first evaluation (mean (SD))			16.72 (5.84)	15.68 (5.63)	1.476		.226
Full-Scale IQ at first evaluation (mean(SD))			72.26 (13.74)	112.71 (13.62)	389.778		**<.001**
Psychiatric diagnosis (%)	Total		66 (64.08%)				
	Categories	Psychosis	10 (9.71%)				
		Attention-deficit disorder	28 (27.18%)				
		Simple phobia	29 (28.16%)				
		Social phobia	5 (4.85%)				
		Generalized anxiety disorder	20 (19.42%)				
		Separation anxiety disorder	3 (2.91%)				
		Major depressive episode	9 (8.74%)				
		Obsessive compulsive disorder	4 (3.88%)				
		Oppositional defiant disorder	3 (2.91%)				
Medication (%) total			46 (44.66%)				
	Categories	Methylphenidate	19 (18.45%)				
		Antidepressants	23 (22.33%)				
		Antipsychotics	20 (19.42%)				
		Antiepileptic	6 (5.83%)				
		Anxiolytics	4 (3.88%)				

Significant values at the .05 level are displayed in bold.
NB: Participants who had the same diagnosis or received the same medication at several evaluations were only counted once.

on protocols approved by the Swiss Ethical Committee of Geneva (CCER, Switzerland), was obtained for all participants and their parents (if the participant was younger than 18 years of age).

Longitudinal data were collected at 2 different time points for a subset of 52 participants (28.42%) with a mean time interval of 2.88 years. As shown in Table 1, a similar proportion of longitudinal data (two evaluations) was available for 22q11DS and control participants. Mean time interval between visits was significantly smaller in 22q11DS due to the presence of additional assessments with slightly shorter delays in a subset of 22q11DS participants ($N = 13$) obtained through a supplementary longitudinal project.

A trained psychiatrist (SE) interviewed all participants with 22q11DS and their caregivers using the computerized Diagnostic Interview for Children and Adolescents-Revised (DICA-R; Reich, 2000) or the Structured Clinical Interview for DSM-IV Axis I (SCID-I; First, Spitzer, & Williams, 1996). Psychotic disorders and psychotic symptoms were assessed with the supplement of the Schedule for Affective Disorders and Schizophrenia for School-age children Present and Lifetime (K-SADS-PL; Kaufman et al., 1997). At the time of testing, 66 (64.08%) of the participants with 22q11DS had at least 1 psychiatric diagnosis and 46 (44.66%) were taking medication that can affect cognitive performance (for details, see Table 1). Typically developing controls were screened for psychiatric illnesses and medication prior to inclusion in the study.

Due to the longitudinal design of the cohort, half of the individuals (49.18%) were included in a previous study (Maeder et al., 2016), although assessed at an older age and with a broader task set (only four similar tasks).

Materials

Assessment of EF and attention

All participants completed an extensive assessment with several tasks of EF and attention, including visual focal attention, inhibition, flexibility, updating, and initiation (see description in Table 2). For visual focal attention, the omission errors from Conners' Continuous Performance Test (CPT-II and CPT-III; Conners & MHS Staff, 2000, 2014), the first part of the Color Trails Test (D'Elia & Satz, 1989; Williams et al., 1995), and Symbol search from age-appropriate Wechsler Intelligence Scales (WISC-IV, WISC-V, WAIS-III, and WAIS-IV; Wechsler, 1997, 2004, 2011, 2016) were used. For inhibition, indicators included commission errors (CPT-II and CPT-III), the Stroop task (Albaret & Migliore, 1999), and the stop-signal reaction time form the Stop-Signal Task from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition Ltd., 2013). Flexibility was assessed with the Color Trails Test and the extra-dimensional errors from the Intra-/Extra-Dimensional Shift task (CANTAB). For updating, the digit span (backward span) and Letter–Number Sequencing Task (Letter–Number Span) from the age-appropriate Wechsler Intelligence Scale were used, as well as the between error score from the Spatial Working Memory task (CANTAB). Finally, initiation was assessed with a verbal and nonverbal fluency task (Sevino, 1998), considering number of items produced. Tasks were chosen to evaluate different aspects of attention and EF in different modalities (verbal and nonverbal) and with different types of tools (paper/pencil and computerized tasks). EF subdomains were regrouped based on the a priori construct stated by the author who developed the test. Correlations between indicators are available in Supplementary Table 1. Tests from the CANTAB were administered using the CANTABeclipse version 6, on a portable touch-screen tablet running on a Windows-based PC system. Detailed descriptions of the tasks can be found on the CANTAB website (https://www.cambridgecognition.com). As shown in Table 1, all the tasks were completed for 196 (83.40%) time points.

Intellectual functioning

Intellectual functioning was assessed using the Wechsler Intelligence Scale for children (aged 6–16 years) or adults (aged 17 years and above) (Wechsler, 1997, 2004, 2011, 2016). Due to the longitudinal design of this study, different versions of the test battery were used. Therefore, only the Full-Scale Intellectual Quotient (FSIQ) is reported. FSIQ at first time point was missing for two participants (both with 22q11DS) for whom only data on EF and attention were collected.

Statistical Analyses

As previously mentioned in the participant description, the dataset included both cross-sectional and longitudinal data. For descriptive statistics, groups were compared at baseline (first assessment) on age, gender, and FSIQ using SPSS 25 (IBM). Trajectories of performance with age were examined using mixed model regression analyses in MATLAB R2018b (Mathworks) (for studies using similar approaches, see Maeder et al., 2016; Mancini et al., 2019; Mutlu et al., 2013). This method is optimally suited for studies combining participants with variable number of time points and with different time intervals between assessments (Shaw et al., 2006; Thompson, Hallmayer, & O'Hara, 2011). Within-subject factor was modeled as a nested variable, whereas population parameters (age and diagnosis) were modeled as fixed effects (Dedrick et al., 2009). For each variable, a constant, linear, quadratic, or cubic model was fitted using the *nlmefit* function in MATLAB. The best model was selected based on the Bayesian information criterion (BIC) method. Statistical significance for differences in trajectories between groups was assessed using a likelihood ratio test. Developmental trajectories resulting from this type of analysis can reveal group differences (i.e., trajectories that follow a parallel path but not on the same intercept) and/or interactions with age (i.e., trajectories that do not follow the same path). To fully

Table 2. Details of the measures of executive functions and attention and information about missing data

Cognitive domain	Test name	Variable name	Description	Interpretation	Missing data
Visual attention	Conners' Continuous Performance Test (CPT 2nd and 3rd editions) (Conners & MHS Staff, 2000, 2014)	*CPT omission %*	Percentage of omission errors, with omissions defined as missed targets	Lower score is better	6 participants (4 with 22q11DS) 2 because of lack of time 4 scores were not calculated by the program due to validity issues with the evaluation
	Color Trails Test (D'Elia & Satz, 1989)	*Adjusted time part A*	Time to complete part A where participants are asked to draw a line between number following chronological order. Since two versions of the test were used with increasing level of difficulty (8–16 years old = 15 numbers to connect; from 17 years old = 25 numbers to connect), we adjusted the score by dividing the time to complete part A by the number of items to connect	Lower score is better	4 participants (2 with 22q11DS) due to errors in the administration of the test
	Symbol Search, Wechsler Intelligence Scales (Wechsler, 1997, 2004, 2011, 2016)	*Number of symbols*	Raw score of items correctly identified (either recognized or with a yes/no answer)	Higher score is better	No missing data
Inhibition	Stroop task (Albaret & Migliore, 1999),	*Stroop inhibition ratio*	Inhibition ratio calculated to measure the cost of inhibition by dividing the number of colors named in the interference condition (naming the color of the ink of the word during 45 s), by the number of colors named in the color denomination condition (naming rectangles of colors during 45 s) (see Maeder et al., 2016)	Value closer to 1 indicate better inhibition	7 participants (5 with 22q11DS) due to technical errors in the administration of the task
	Conners' Continuous Performance Test (CPT 2nd and 3rd editions)	*CPT commission %*	Percentage of commission errors was extracted. Commission errors are defined as incorrect responses to nontargets	Lower score is better	6 participants (4 with 22q11DS) 2 because of lack of time 4 scores were not calculated by the program due to validity issues with the evaluation
	Stop-Signal Task (SST, CANTAB) (Cambridge Cognition Ltd., 2013)	*Stop-Signal RT*	Estimate of the length of time between the go stimulus and the stop stimulus at which the participant is able to successfully inhibit his/her response on 50% of trials	Lower score is better	14 participants (6 with 22q11DS) due to the malfunction of a cable
Flexibility	Color Trails Test (D'Elia & Satz, 1989; Williams et al., 1995)	*Flexibility ratio*	Flexibility ratio was calculated to account for processing speed by dividing the time to complete part B (drawing a line between number following chronological order while alternating between colors) by time to complete part A (drawing a line between number following chronological order)	Value closer to 1 indicates better flexibility	4 participants (2 with 22q11DS) due to errors in the administration of the test
	Intra-/Extra-Dimensional Shift task (IED, CANTAB) (Cambridge Cognition Ltd., 2013)	*EDS errors*	Number of extra-dimensional shift errors	Lower score is better	1 control participant was excluded because of a lack of comprehension of the instruction (only completed 1/9 stages).

(*Continued*)

Table 2. (*Continued*)

Cognitive domain	Test name	Variable name	Description	Interpretation	Missing data
Updating	Digit Span, Wechsler Intelligence Scales (Wechsler, 1997, 2004, 2011, 2016)	*Backward span*	Longest sequence of numbers repeated in invers order	Higher score is better	No missing data
	Letter–Number Sequencing, Wechsler Intelligence Scales (Wechsler, 1997, 2004, 2011, 2016)	*Letter–Number Span*	Longest sequence of letters and numbers correctly ordered	Higher score is better	No missing data
	Spatial Working Memory (SWM, CANTAB) (Cambridge Cognition Ltd., 2013)	*Total between error* *Between error 4 boxes, between error 6 boxes, between error 8 boxes*	Number of times the participant revisits a box in which a token has previously been found. Three different memory loads (4, 6, 8 boxes)	Lower score is better	No missing data
Initiation	Verbal fluency task (animal category)	*Number of animals*	Number of different animal names produced under 1 min	Higher score is better	3 participants (2 with 22q11DS) due to a lack of time
	Nonverbal fluency task (5 points task, Sevino, 1998)	*Number of designs*	Number of different designs produced under 3 min	Higher score is better	12 participants (9 with 22q11DS) 9 due to a lack of time 4 difficulties following the instructions given by the examiner

grasp the pattern of development with age, raw scores were used in the analysis. As different versions of tests were pooled together at times, the test version was included as a covariate where appropriate (Conners' Continuous Performance Test, Color Trails Test, and Wechsler batteries).

RESULTS

Comparison of Developmental Trajectories Between 22q11DS and Healthy Controls

Developmental trajectories followed a linear or a quadratic model for most included variables, suggesting an effect of age in a majority of EF and attentional domains (see Table 3 for details). Only two measures of flexibility, one measure of inhibition, and additional updating measures showed constant trajectories, indicating no relationship with age.

Significant group differences were observed in all measures of visual focal attention, with lower performance in the 22q11DS group for *Conners' Continuous Performance Test omission error %* ($p = .002$), *Color Trails Test Adjusted time part A* ($p < .001$), and *number of symbols* ($p < .001$). Only the latter displayed a significant interaction with age ($p < .001$), with 22q11DS participants improving less with age and reaching a plateau earlier than the control group (for a visual representation of the different trajectories, see Figure 2).

Inhibition measures showed mixed results depending on the task. Both cognitive inhibition (measured by the *Stroop inhibition ratio*) and motor inhibition (measured by *Conners' Continuous Performance Test commission error %*) yielded significant group differences with better performance in the control group (respectively: $p = .013$ and $p = .040$) and similar developmental trajectories across groups. No group difference was, however, observed for *stop signal reaction time* ($p = .223$).

Out of the flexibility measures, only the *extra-dimensional shift errors* from the Intra-/Extra-Dimensional Shift task showed a significant difference, with higher rates of errors for the 22q11DS group ($p < .001$). The *Color Trails Test Flexibility ratio* showed comparable performance between groups ($p = .092$).

Updating measures were significantly poorer in the 22q11DS group in both verbal and nonverbal performance ($p < .001$). Only the *backward span* displayed a significant interaction with age ($p = .041$), with a smaller performance increase with age in the 22q11 group. Interaction with age was not significant for *Letter–Number Span* ($p = .481$) and *Spatial Working Memory Total between errors* only reached trend level ($p = .075$). *Post hoc* analyses on the Spatial Working Memory task dividing results according to the working memory load showed a significant interaction with age ($p = .025$) at the highest load (*between errors 8 boxes*). Specifically, error rate was diminishing drastically with age in the control group, but changes with age in the 22q11DS group were minimal. Significant group effects were found in all loads (*between errors 4 boxes* $p < .001$; *between errors 6 boxes* $p < .001$; *between errors 8 boxes* $p < .001$) characterized systematically by higher error rates in the 22q11DS group.

Finally, initiation showed significant group effects with better performance in the control group in both *number of animals* ($p < .001$) and *number of designs* ($p < .001$). In both variables, significant interactions with age showed that performance of the 22q11DS group prematurely reached a plateau compared to healthy controls (*number of animals*: $p < .001$ and *number of designs*: $p = .007$).

DISCUSSION

The goal of this study was to delineate EF and focal attention development in 22q11DS. To address this, we comprehensively characterized childhood-to-adulthood developmental trajectories, in several domains using multiple tasks per domain, a broader age range (8–35 years), and a partially longitudinal design. Overall, age-related improvement was observed in a majority of cognitive variables. Results moreover point to a variety of developmental trajectories across domains or tasks, with 22q11DS participants showing both developmental deficits and developmental lags compared to healthy controls.

No Evidence for Cognitive Decline

When considering raw score changes in 22q11DS, participants demonstrated an age-related performance increase (i.e., raw score increase) for almost all examined domains of EF and focal attention. This is in line with the literature on healthy controls demonstrating continuous development during childhood, extending to early adulthood (e.g., Romine & Reynolds, 2005). When comparing 22q11DS with controls, however, examination of raw scores yielded patterns of both developmental deficit (i.e., lower levels of performance but regular improvement) and developmental lag (i.e., improvement at a slower pace with age) in this sample during this age window. In contrast, neither developmental maturation (i.e., initial cognitive impairment but development catches up with the control group) nor deterioration (i.e., decline in absolute ability) were observed. Previous studies examining changes in neurocognitive measures in samples with smaller age ranges have often suggested patterns of developmental deficit in 22q11DS (Antshel, Fremont, Ramanathan, & Kates, 2017; Chawner et al., 2017; Hooper et al., 2013). Some exceptions are observed, with evidence for a developmental maturation of processing speed in Chawner et al. (2017), as well as evidence for a developmental lag of sustained attention in Hooper et al. (2013) and working memory (verbal and visual) in Antshel et al. (2017). Discrepancies with our findings could come either from the limited age window examined in these studies (as they did not considered adults but only focused on

Table 3. Results from the mixed model regression analyses. Group comparison (22q11DS *vs.* controls)

			Group effect				Interaction with age						
							Linear			Quadratic			
Domain	Variable	Model order	*p*-Value	Likelihood ratio (df)	Intercept 22q11DS beta (SD)	Intercept controls beta (SD)	*p*-Value	Likelihood ratio (df)	Slope 22q11DS beta (SD)	Slope controls beta (SD)	Likelihood ratio (df)	Slope 22q11DS beta (SD)	Slope controls beta (SD)
Visual attention	CPT omission errors %	Linear	**.002**	12.71 (2)	6.90 (1.52)	9.13 (1.30)	.958	.003 (1)	-.27 (.09)	-.27 (.07)			
	CTT adjusted time part A	Quadratic	**<.001**	44.27 (3)	4.18 (.70)	5.83 (.68)	.416		-0.25 (.08)	-.38 (.07)	1.75 (2)	0.005 (.002)	0.01 (.002)
	Number of symbols	Quadratic	**<.001**	82.74 (3)	-9.03 (5.43)	-5.65 (5.05)	**<.001**		3.77 (.75)	2.92 (.63)	20.52 (2)	-.06 (.02)	-.06 (.02)
Inhibition	CPT commission errors %	Linear	**.040**	6.43 (2)	73.85 (5.58)	70.99 (4.90)	.236	1.41 (1)	-1.47 (.34)	-.95 (.28)			
	Stroop inhibition ratio	Quadratic	**.013**	10.72 (3)	.002 (.12)	-.004 (.11)	.921		0.06 (.01)	0.05 (.01)	.16 (2)	-.001 (.000-4)	-.001 (.000-3)
	SST SSRT	Constant	.223	1.48 (1)	210.51 (10.33)	227.108.78)							
Flexibility	CTT flexibility ratio	Constant	.092	2.84 (1)	2.02 (.06)	2.16 (.05)							
	IED EDS errors	Constant	**<.001**	36.83 (1)	11.73 (1.11)	21.07 (.97)							
Updating	Backward span	Quadratic	**<.001**	38.18 (3)	-.50 (1.01)	.81 (.95)	**.041**		0.55 (.13)	0.32 (.11)	6.38 (2)	-.01 (.004)	-.01 (.003)
	Letter–Number Span	Quadratic	**<.001**	57.41 (3)	1.41 (.91)	1.27 (.86)	.481		0.42 (.12)	0.31 (9.10)	1.46 (2)	-.01 (.003)	-.01 (.003)
	SWM total between errors	Linear	**<.001**	89.40 (2)	45.41 (5.78)	59.29 (5.08)	.075	3.17 (1)	-1.47 (.34)	-.68 (.28)			
	SWM between errors 4 blocks	Constant	**<.001**	28.73 (1)	.65 (.27)	2.64 (.24)							
	SWM between errors 6 blocks	Constant	**<.001**	58.75 (1)	5.46 (.76)	13.79 (.06)							
	SWM between errors 8 blocks	Linear	**<.001**	86.90 (2)	31.22 (3.55)	36.94 (3.10)	**.025**	5.04 (1)	-.98 (.21)	-.36 (.17)			
Initiation	Number of animals	Linear	**<.001**	31.00 (2)	7.37 (1.60)	13.26 (1.46)	**<.001**	17.88 (1)	0.72 (.10)	0.12 (.09)			
	Number of designs	Quadratic	**<.001**	73.96 (3)	-12.39 (7.11)	-.68 (6.57)	**.007**		5 (.92)	2.75 (.79)	9.96 (2)	-.12 (.03)	-.07 (.02)

Significant values at the .05 level are displayed in bold.

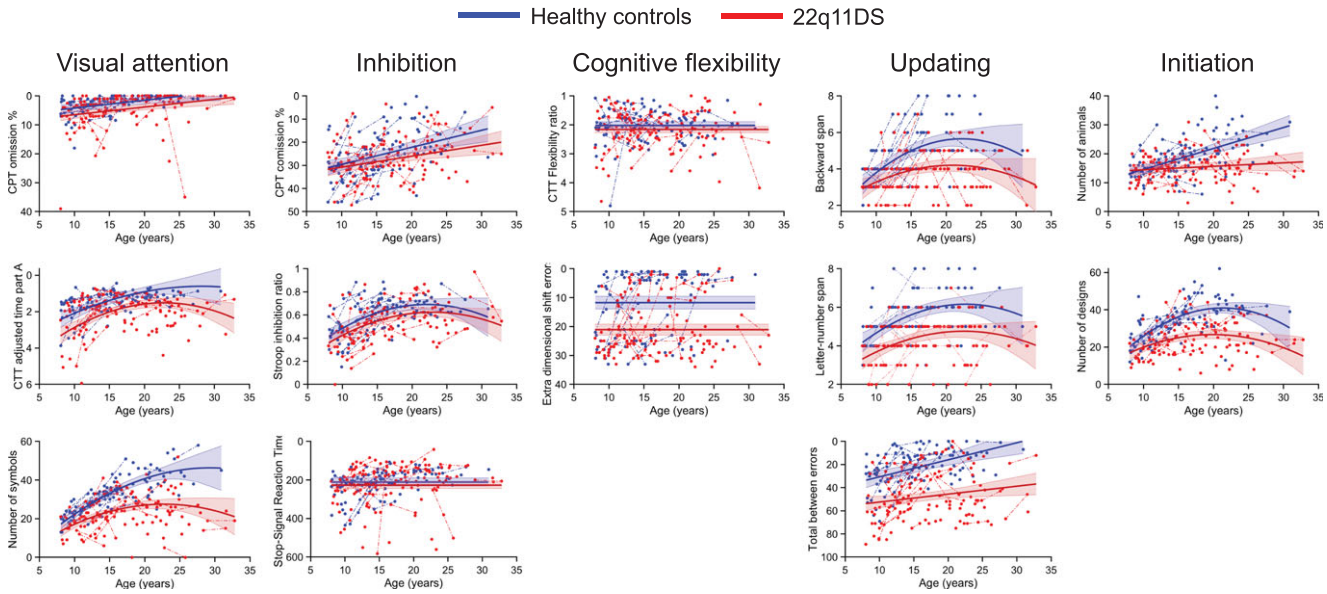

Fig. 2. Developmental trajectories of executive functions and attention domains. The solid lines show the developmental model best fitting the data. Data points from a single subject are connected by a dotted line. Scores from the 22q11DS group are displayed in red and healthy controls in blue. Note that in all sub-figure, scores depicted toward the top of the figure represent better performance whereas score depicted toward the bottom represent worse performance. To improve clarity of interpretation, scales of the y axis have therefore been reversed when lower scores indicated better performance (e.g., less errors), with low scores at the top of the figure and high scores at the bottom.

development across childhood) or from the study design (i.e., mix of cross-sectional and longitudinal measures) in our study. Nevertheless, in line with our results, no previous study reported deterioration for measures of EF and focal attention. Indeed, as previously demonstrated, prevalence of individual decline from one visit to another was observed but did not differ from the control group, reflecting developmental fluctuation rather than a 22q11DS-specific pattern of deterioration (Chawner et al., 2017). Regarding cognitive decline, previous studies using overall intellectual abilities as an indicator of cognitive functioning have shown that some individuals with 22q11DS do present a more severe deterioration over time (Duijff et al., 2013). Particularly, in a large sample from a collaborative study including over 800 22q11DS carriers, early cognitive decline of verbal intellectual abilities (verbal IQ) was suggested as a robust indicator for the emergence of a psychotic illness (Vorstman et al., 2015). However, results should be interpreted carefully as the analyses were based on standardized composite scores. Indeed, while a drop in standardized scores reads as a decline, it may result from two different processes: either from a loss of ability (deterioration) or a slower pace of improvement leading to a gap compared to controls (lag).

Diversity of Developmental Patterns Across Domains

Exploration of multiple cognitive domains in the same sample highlighted different patterns of developmental trajectories across domains. This in line with previous results reporting different developmental models depending on the domains examined (Antshel et al., 2017; Maeder et al., 2016; Shapiro et al., 2014). Different patterns across cognitive domains were also reported in Chawner et al. (2017); however, measures of EF and attention (spatial working memory, spatial planning, set-shifting, and visual attention) only yielded a single type of pattern (developmental deficit). This contrasts with results of the current study and evidence from previous literature, suggesting that EF and focal attention show that different developmental patterns across domains. Indeed, some domains show a steady increase in raw performance with age (developmental deficit), whereas others display a gap with the control group that widens with age (developmental lag). Differences in findings likely originate form methodological differences between studies (chosen tasks, age range, and cross-sectional of longitudinal design).

Only two domains (inhibition and initiation) yielded a consistent developmental pattern on all tasks, while the other three (flexibility, updating, and focal attention) yielded different developmental models, depending on the task. Furthermore, using different outcome measures (speed *vs.* accuracy), we showed that accuracy mostly distinguished 22q11DS from controls, whereas speed sometimes did not show any group differences (e.g., for *stop-signal reaction time*). These results highlight that even when measuring the same domain, changes in tasks, testing modality (verbal *vs.* nonverbal) or outcome measure can yield different developmental pattern. In this context, future studies may use latent variable approaches to extract communalities across variables sharing variance, which may provide a better way to identify similar patterns of development in 22q11DS. However, such undertaking would need larger samples with comparable age groups, which might be particularly challenging in the context of a rare genetic condition such as 22q11DS.

Clinical Implications

Results from this study have several implications for clinicians and caregivers. First, different patterns of development were observed across domains and sometimes across tasks from one domain or outcome measure. This result should be considered in relation to neuropsychological assessments. Not only does it suggest that different types of indicators can give very different results, but it also indicates that depending on the chosen task or indicator, performance could be only partially represented. With regard to intervention, specific patterns of development for a certain ability should help guiding professionals towards different strategies. Indeed, particular attention should be given to domains exhibiting developmental lag and action should be taken to prevent the gap from widening during adolescence, for example, by introducing early cognitive training targeting the affected domain. Similarly, in domains showing developmental deficits, compensatory strategies could be implemented depending on identified strength in the cognitive profile.

Second, across all domains of EF and focal attention, impairments and/or divergence of developmental trajectories were observed in childhood or early adolescence. This implies that cognitive and educational interventions should be implemented as early as possible during childhood to prevent or lessen future impairments (e.g., Cioni, Inguaggiato, & Sgandurra, 2016; Cutler-Landsman, 2020; Wass, 2015).

Limitations

Firstly, the developmental trajectories modeled in this paper originated from both cross-sectional and longitudinal data, with a relatively small proportion of participants with two assessments (28.42% of participants). We argue that adding this longitudinal data and combining between- and within-subject variability in one study provides a better estimation of developmental patterns compared to only using cross-sectional data such as in previous studies (e.g., Morrison et al., 2020; Shapiro et al., 2014). However, the present findings will need replication in future studies including predominantly longitudinal data.

Secondly, although the examined age range was much larger in our sample compared to most of the previous studies, it remained limited from school age to young adulthood due to the following reasons. On one hand, we had to limit the age range to ensure that the same task could be used across the entire sample. On the other hand, as the Swiss longitudinal cohort focuses on childhood and adolescence, participants older than 35 years of age are only rarely included. Literature on adults 22q11DS carriers older than 30 years of age is still very scarce; however, there is evidence for early onset of neurodegenerative disorders (such as Parkinson's disease), increasing the risk for cognitive decline in this population (Butcher et al., 2013; Fung et al., 2015). Future studies should therefore further extend the age range in order to investigate lifespan developmental trajectories, particularly at later adult stages.

Thirdly, only cognitive tasks were selected for this study. Additional questionnaires with observations from the parents could provide supplementary information to the developmental picture of EF and attention in 22q11DS, by increasing ecological validity. For example, analysis of the predicting value of questionnaires measuring EF suggested that parents reports are more sensitive than cognitive performance when it comes to identify children at risk of negative developmental outcome (Albert et al., 2018).

Fourthly, tasks were clustered together in different subdomains of EF based on their theoretical construct (i.e., previous research indicating/establishing that tasks measure the respective domain). However, as shown in the correlation matrix provided in supplementary material, correlations between tasks within a certain a priori domain (e.g., cognitive flexibility) were not always significant. This suggests that although some tasks are thought to measure the same theoretical construct, they may actually measure mechanisms that are not correlated. This is an important limitation to consider in regard to the findings of different developmental patterns within a single domain. A data-driven grouping of task into a similar construct, for example, using correlations or principal component analysis (as applied in Fiksinski et al., 2019), should be considered in future work.

Finally, patterns of maturation were solely examined based on accuracy or speed indicators extracted from behavioral tasks. However, previous studies using functional magnetic resonance imagery to study working memory have shown significant differences in brain activation during a task, while behavioral results were comparable between groups (Harrell et al., 2017; Montojo et al., 2014). Combined with evidence of atypical maturation of brain regions who support these abilities in 22q11DS (Ramanathan et al., 2017; Schaer et al., 2009), future work should focus on linking neuroimaging and behavioral results in order to get a more fine-grained understanding of the developmental mechanisms and their underlying neural pathways.

Conclusion

In sum, the current findings confirm and extend knowledge on the developmental patterns of EF and focal attention in 22q11DS. Results indicated age-related improvements on most of the domains examined, although some tasks did not. Contrasting with previous research, the inclusion of a larger age range in this study uncovered not only developmental deficits of individuals with 22q11DS (i.e., lower levels of performance), but also developmental lags for certain cognitive domains (i.e., delayed onset or slower pace of developmental improvement). Specifically, individuals with 22q11DS had worse inhibition as well as a delayed development of initiation skills compared to healthy controls. In contrast, developmental differences between the two groups seemed less clear regarding cognitive flexibility, updating, and visual focal attention, for which performance appeared to strongly depend on the tasks selected to assess a given

domain. Overall, findings of the current study demonstrated that EF and focal attention are not affected as a unitary construct, but instead different patterns of development are found across domains and tasks in 22q11DS requiring specific and adapted intervention strategies.

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/S135561772100059X

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CONFLICT OF INTEREST

The authors have nothing to disclose.

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