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The uneven landscape of cognitive domains in 22q11.2 deletion syndrome: A large consortium study

Ania M. Fiksinski[1,2], Rielle Wierenga[3], Donna McDonald-McGinn[4,5], Anne S. Bassett[6,7,8], Carrie E. Bearden[9], Bernice Morrow[10], Beverly Emanuel[4], Raquel E. Gur[11], Ann Swillen[12,13], Stephen R. Hooper[14], Eva W.C. Chow[15], Marianne B.M. van den Bree[16], Joris R. Vermeesch[12], Michael J. Owen[17], Stephan Eliez[18], Doron Gothelf[19,20], Celso Arango[21], Wendy R. Kates[22], Tony Simon[23], Kieran C. Murphy[24], Declan Murphy[25], Gabriela M. Repetto[26], Jaume Morey Canyelles[27], Stefano Vicari[28], Joseph Cubells[30,29], Nicole Philip[31,32], Linda Campbell[33], Covadonga M. Díaz-Caneja[34], Maude Schneider[35], Vandana Shashi[36], Marco Armando[37], Elemi J. Breetvelt[38,39], Henriette de Veye[40], International Brain and Behavior Consortium on 22q11.2DS[41], Therese van Amelsvoort[42] and Jacob Vorstman[43]

[1]Department of Pediatrics and Department of Psychology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, Netherlands; [2]Department of Psychiatry and Neuropsychology, Division of Mental Health, Maastricht University, Maastricht, Netherlands; [3]Department of Pediatrics, University Medical Center Utrecht, Utrecht, Netherlands; [4]Division of Human Genetics, 22q and You Center, Clinical Genetics Center, and Section of Genetic Counseling, The Children's Hospital of Philadelphia, Philadelphia, USA; [5]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, USA; [6]The Dalglish Family 22q Clinic, Toronto General Hospital, Toronto, Canada; [7]Clinical Genetics Research Program, Center for Addiction and Mental Health, Toronto, Canada; [8]Department of Psychiatry, University of Toronto, Toronto, Canada; [9]Departments of Psychiatry and Biobehavioral Sciences and Psychology, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, US; [10]Department of Genetics, Albert Einstein College of Medicine, Bronx, USA; [11]Department of Psychiatry and Lifespan Brain Institute, Penn Medicine-CHOP, University of Pennsylvania, Philadelphia, USA; [12]Center for Human Genetics, University Hospital Gasthuisberg, Leuven, Belgium; [13]Department of Human Genetics, KU Leuven, Leuven, Belgium; [14]Department of Health Sciences, School of Medicine, University of North Carolina-Chapel Hill, Chapel Hill, USA; [15]University of Toronto Department of Psychiatry, Canada; [16]Centre for Neuropsychiatric Genetics and Genomics, Neuroscience and Mental Health Innovation Institute, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Cardiff, UK; [17]Centre for Neuropsychiatric Genetics and Genomics, Neuroscience and Mental Health Innovation Institute, Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK; [18]Developmental Imaging and Psychopathology, Department of Psychiatry, University of Geneva, Geneva, Switzerland; [19]The Child Psychiatry Department, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel; [20]Gray Faculty of Medical & Health Sciencs and Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel; [21]Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, IiSGM, CIBERSAM, School of Medicine, Universidad Complutense, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [22]Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, USA; [23]MIND Institute and Department of Psychiatry and Behavioral Sciences, University of California Davis, Sacramento, USA; [24]Department of Psychiatry, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland; [25]Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, London, UK; [26]Centro de Genética y Genómica, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, Santiago, Chile; [27]Instituto Balear de Salud Mental de la infancia i la Adolescencia (IBSMIA), Hospital Universitario Son Espases, Palma de Mallorca, Spain; [28]Department of Life Sciences and Public Health, Catholic University; Child and Adolescent Psychiatry Unit, Bambino Gesu Pediatric Hospital, Rome, Italy; [29]Department of Human Genetics, Emory University School of Medicine, Atlanta, USA; [30]Emory Autism Center, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, USA; [31]Département de Génétique Médicale, APHM, CHU Timone Enfants, Hopital de la Timone, Marseille, France; [32]MMG, INSERM, Aix Marseille Université, Marseille, France; [33]School of Psychology, The University of Newcastle, Newcastle, Australia; [34]Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, iSGM, CIBERSAM, School of Medicine, Universidad Complutense, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [35]Clinical Psychology Unit for Intellectual and Developmental Disabilities, Faculty of Psychology and Educational Sciences, University of Geneva, Geneva, Switzerland; [36]Division of Medical Genetics, Department of Pediatrics, Duke University School of Medicine, Durham, USA; [37]Division of Child and Adolescent Psychiatry, Department of Psychiatry, and Faculty of Biology and Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [38]Department of Psychiatry, The Hospital for Sick Children, Toronto, Canada; [39]Department of Psychiatry and Psychology, Leiden University Medical Center, Leiden, the Netherlands; [40]Department of Psychology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, Netherlands; [41]IBBC, USA; [42]Maastricht University Hospital: Maastricht Universitair Medisch Centrum+, Netherlands and [43]Hospital for Sick Children Research Institute: SickKids Research Institute, Canada

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Corresponding author:
Ania M. Fiksinski;
Email: a.m.fiksinski@umcutrecht.nl

Supplement includes full list of contributing consortium members of International Brain and Behavior Consortium on 22q11.2DS.

T.v.A. and J.V. contributed equally to this work.

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Abstract

Background. 22q11.2 deletion syndrome (22q11DS) is strongly associated with aberrant neurodevelopment, including decreased cognitive functioning and schizophrenia spectrum disorders (SSDs). While the different core domains of IQ have distinct clinical ramifications, their collective profile has not been well-characterized in 22q11DS. Here, in the largest 22q11DS sample to date, we elucidate the overall IQ profile, including Verbal and Performance IQ (VIQ and PIQ), Processing Speed (PS), and Working Memory (WM), including associations with developmental stage and SSDs.

Methods. We included 1,328 individuals with 22q11DS from the International Brain and Behavior Consortium. We derived an overall IQ profile using VIQ, PIQ, PS, and WM scores at initial assessment, from age-appropriate Wechsler scales. Using both cross-sectional and longitudinal IQ data from a subset (n = 496; 37.35%) of individuals, we examined IQ profiles across three age groups and compared profiles between individuals with and without SSDs.

Results. IQ profiles in 22q11DS exhibited differences between IQ domains ($p < 0.001$), ranked from relatively strongest to weakest: PS > WM > VIQ > PIQ. This profile was similar across age groups, with scores highest in children, lower in adolescents, and lowest in adults. Individuals without SSDs had higher IQ scores than those with SSDs ($p < 0.001$), with no significant domain-specific effects.

Conclusions. The results indicate a tendency toward a characteristic IQ profile in 22q11DS, regardless of SSD status. A clinical implication of these divergent IQ domains, in particular the relative weakness in PIQ, is that functional expectations are likely to be overestimated. The domain-specific differences across age-groups highlight the need for repeated and comprehensive cognitive assessments in this high-risk population, and may suggest differing underlying mechanisms that require further investigation.

Introduction

An ever-increasing number of pathogenic genetic variants associated with atypical neurodevelopment is being identified (Lowther et al., 2017; Malhotra & Sebat, 2012; Sun et al., 2024). While each of these high-impact variants is individually rare, they collectively contribute substantially to neurodevelopmental morbidity (Sanders et al., 2019). The 22q11.2 deletion is the most common recurrent pathogenic microdeletion, with an estimated prevalence of 1 in 2,000–4,000 (Blagojevic et al., 2021); and has preceded the discovery of most other pathogenic variants by approximately two decades (McDonald-McGinn et al., 2015). The 22q11.2 deletion syndrome (22q11DS) thus serves as a useful clinical model for the study of other pathogenic variants associated with aberrant neurodevelopment, and for variation in neurodevelopmental expression more generally (Fiksinski et al., 2021c; Gur et al., 2017; Insel, 2010; Sommer et al., 2016). Among many organ systems that can be affected by 22q11DS (McDonald-McGinn et al., 2015), brain-related psychiatric and developmental phenotypes are prominent and include schizophrenia spectrum disorders (SSDs; prevalence ~20–25%) (Fiksinski et al., 2018b; Schneider et al., 2014). The spectrum of intellectual functioning in individuals with 22q11DS is broad, ranging from severe ID to (above) average intellectual functioning (De Smedt et al., 2007). Diverse trajectories of cognitive development have been described, with, on average, a modest decline in IQ in early adolescence (Duijff et al., 2012b; Fiksinski et al., 2021a; Swillen & McDonald-McGinn, 2015), and a continued decline into older adulthood in some individuals (Evers et al., 2014).

In individuals with 22q11DS, studies of cognition have largely focused on overall IQ (i.e. Full Scale IQ [FSIQ]), and/or Verbal and Performance IQ (VIQ and PIQ, respectively), complementary to studies of various operationalizations of narrower neurocognitive domains (e.g. attention, executive functioning, motor performance, and visuospatial function) (Fiksinski et al., 2018a, Goldenberg et al., 2012, Henry et al., 2002, Hooper et al., 2013, Maeder, J., et al., 2016, Morrison et al., 2020, van Amelsvoort et al., 2004). However, in addition to VIQ and PIQ, the core domains of global cognitive functioning also include Processing Speed (PS) and Working Memory (WM) (Wechsler, 2008). These components and their association with overall IQ have not yet been well studied in sufficiently large cohorts of individuals with 22q11DS, mostly due to limited availability of such data. This is a relevant knowledge gap: first, PS and WM are assessed independently from VIQ and PIQ in Wechsler IQ tests (i.e. with different tasks), while in almost all Wechsler versions they contribute equally to overall IQ (FSIQ). Second, PS and WM represent neuropsychological processes distinct from VIQ and PIQ and the real-life ramifications associated with scores on any of the four IQ domains are distinct (Wechsler, 2003, 2008). Third, these domains may be differentially associated with psychopathology (Leib et al., 2021; Morrison et al., 2020; Oberauer, Schulze, Wilhelm, & Süß, 2005; Schubert, Hagemann, & Frischkorn, 2017).

Beyond 22q11DS, atypical levels and trajectories of cognitive functioning are inherent to virtually all known pathogenic genetic variants associated with atypical neurodevelopmental trajectories, often with significant but variable consequences for the daily functioning of affected individuals. In addition, parameters of cognitive functioning have been associated with psychopathology in people with 22q11DS, consistent with findings in the general population (Mollon et al., 2018; Woodberry, Giuliano, & Seidman, 2008). Acting as a potential 'magnifying lens' (Fiksinski et al., 2021c; Sanders et al., 2019), such findings begin to provide insight into etiology and mechanisms of neurodevelopmental conditions. For example, previous studies using a partially overlapping cohort (IBBC 22q11DS) have demonstrated that in individuals with 22q11DS, a significant decline in IQ is not only phenotypically associated with subsequent risk of developing SSDs (Fiksinski et al., 2021a; Vorstman et al., 2015), but that it also shares, at least in part, the same genetic underpinnings (Davies et al., 2020. This finding suggests that cognitive decline is an early stage of the SSD disease trajectory, both in 22q11DS patients and in the idiopathic SSD population (Mollon et al., 2018). Furthermore, the association with SSD risk in 22q11DS was most pronounced for a decline in VIQ versus PIQ, underlining the relevance of examining the different IQ domains, VIQ, PIQ, PS, and WM, independently.

Here, building on previous studies of IQ, including those in the 22q11DS dataset (Davies et al., 2020; Fiksinski et al., 2021a; Vorstman et al., 2015), we examine the complete cognitive IQ profile in individuals with 22q11DS, including the four key components of global cognitive functioning (VIQ, PIQ, PS, and WM) as defined by

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the Wechsler Intelligence Scales. We focus on the profile of these domains using the earliest available IQ assessment, capturing relative cognitive performance across domains at the first observed measurement point. In addition, we explore the cognitive profile over three different developmental stages, comparing children, adolescents, and adults. Given known associations between level of cognitive functioning and cognitive decline and SSD risk (Mollon et al., 2018; Weinberger et al., 2016), we also compare these profiles between individuals with 22q11DS with SSDs and without SSDs.

Methods

Participants and instruments

Participants were part of the international Brain and Behavior Consortium on 22q11DS (IBBC), an international collaboration that included 1,789 individuals with a molecularly confirmed 22q11.2 deletion (Gur et al., 2017). We have previously reported on IQ data in this sample, not including PS and WM data (Davies et al., 2020; Fiksinski et al., 2021a; Vorstman et al., 2015). For the current study, at least one (Wechsler-based) assessment of IQ, including at least one of the four core IQ domains, was available in n = 1,328 individuals (n = 647 [48.72%] males). In line with previous work (Fiksinski et al., 2021a), we included participants aged between 6 and 39 years (mean = 14.17, SD = 7.12). Demographic details of the sample are described in Table 1. All individuals and, when appropriate, their legal guardians provided informed consent, and the local institutional research ethics boards approved the study of each site.

Global cognitive functioning (FSIQ) and the four core IQ domains were assessed using age-appropriate Wechsler scales (Wechsler, 1981, 1997, 1991, 2002, 2003, 2008, 2011) (Table 1). All IQ data underwent extensive quality control, as previously described (Davies et al., 2020; Fiksinski et al., 2021a). For analyses involving the association of IQ parameters and SSDs, participants were divided into three clinical subgroups, as previously described (Davies et al., 2020): SSDs (i.e. where the participant had received a formal psychiatric diagnosis of schizophrenia, schizoaffective disorder, delusional disorder, or psychotic disorder not otherwise specified); subthreshold psychosis (i.e. any participant who had never met criteria for any psychotic disorder diagnosis, but had endorsed clinically significant positive psychotic symptoms at any time point, based on structured diagnostic interview); and controls (i.e. participants without a lifetime diagnosis of any psychotic illness and who had never endorsed subthreshold psychotic symptoms). SSD group status was based on semi-structured in-person interviews at each site (Kaufman et al., 1997; Kay, Fiszbein, & Opler, 1987; McGlashan, Walsh, & Woods, 2010; Yung et al., 2005) and clinical diagnoses of SSDs were determined by experienced clinicians in accordance with the Diagnostic and Statistical Manual of Mental Disorders (2013; American Psychiatric Association, 2000).

Statistical analyses

All data quality control/preparation and statistical analyses were conducted in R 3.6.2 GUI 1.70 (R Core Team, 2019).

Overall IQ profile

Primary analyses focused on the overall IQ profile, using the first available Wechsler-assessed IQ data. Data from 1,328 participants

Table 1. Descriptive data of total sample of 1,328 individuals with 22q11DS

		Sample
Available IQ data		
	Individuals with at least one IQ assessment, *N*	1,328 (100%)
	Sex (% males)	647 (48.72%)
	Mean age in years (SD)	14.17 (7.12)
	Individuals with longitudinal IQ data[a], *N* (%)	496 (37.35%)
Available IQ domains		
	VIQ, *N* (%)	1,322 (99.55%)
	PIQ, *N* (%)	1,229 (92.54%)
	PS, *N* (%)	659 (49.62%)
	WM, *N* (%)	398 (19.97%)
Administered IQ test		
	WASI, *N* (%)	185 (13.93%)
	WAIS-III, *N* (%)	184 (13.86%)
	WAIS-R, *N* (%)	64 (4.82%)
	WAIS-IV, *N* (%)	59 (4.44%)
	WPPSI, *N* (%)	29 (2.18%)
	WISC-III, *N* (%)	505 (38.03%)
	WISC-IV, *N* (%)	212 (15.96%)
	WISC-R, *N* (%)	79 (5.95%)
	WPPSI-R, *N* (%)	11 (0.83%)
Psychotic illness categorization		
	Nonpsychotic[b], *N* (%)	852 (64.16%)
	Subthreshold psychosis, *N* (%)	212 (15.96%)
	SSD[c], *N* (%)	232 (17.47%)
	Unknown/other[d], *N* (%)	32 (2.41%)
Categorization in age groups		
	Total IQ assessments included[e]	1,824 (100%)
Children (6–9 y)	*N* (%)	446 (24.45%)
	Mean age in years (SD)	8.04 (1.07)
Adolescents (10–17 y)	*N* (%)	844 (46.27%)
	Mean age in years (SD)	12.88 (2.12)
Adults (18–39 y)	*N* (%)	534 (29.28%)
	Mean age in years (SD)	23.00 (5.11)

[a]This includes individuals who have one or more subsequent IQ assessment(s) in a *different* age category.
[b]Consistent with previous studies (Davies et al., 2020; Fiksinski et al., 2021a), individuals were included in the nonpsychotic group if they had never experienced psychotic symptoms nor psychotic illness, regardless their age, suggesting that a portion of individuals in the nonpsychotic group might still go on to develop psychosis as they mature. However, both previous results[14, 30] and current data demonstrate no effect differences as a function of including or excluding nonpsychotic individuals based on their age at last psychiatric assessment (e.g. whether or not they were over 25 years, the age after which novel SSD onset is highly unlikely).
[c]SSD, schizophrenia spectrum disorder, including schizophrenia, schizoaffective disorder, delusional disorder, or psychotic disorder not otherwise specified.
[d]As previously described (Davies et al., 2020; Fiksinski et al., 2021a[14, 30]), these individuals either had insufficient data available to determine psychosis status, or had affective psychotic disorder and were thus excluded from analyses involving psychosis group-status.
[e]For individuals with multiple IQ assessments, only one (first) IQ assessment per age group is included.

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were available, with differing numbers across the 4 domains (Table 1).

Our first objective was to investigate the absolute differences between the four core IQ domains. We conducted multiple paired *t*-tests, given that multiple domain scores are measured within individual participants (when available). We carried out six comparisons in total (VIQ-PIQ, VIQ-PS, VIQ-WM, PIQ-PS, PIQ-WM, and PS-WM) and used Bonferroni corrections to account for multiple testing. We explored whether the profile differed as a function of biological sex.

In addition, we used a median split to divide the sample into a higher and a lower FSIQ group. We explored whether results for the IQ profile were comparable in both (median-split FSIQ) groups.

To obtain a more detailed indication of how the four IQ domains and the complete profile relate to FSIQ, we calculated difference scores between FSIQ and each IQ domain (difference score [DS] = FSIQ – IQ domain). Then, we compared the DSs between the four IQ domains (resulting in six comparisons in total) using multiple paired *t*-tests, and applied Bonferroni corrections for multiple testing.

IQ profile across developmental stages

Consistent with other cognition studies in 22q11DS (Morrison et al., 2020), we divided participants into three age groups: children (6–9.9 years), adolescents (10–17.9 years), and adults (18 years and older), following World Health Organization (WHO) guidelines (WHO, 2017). A subset of participants (n = 496; 37.35%) had multiple IQ datapoints across varying time points and IQ domains. To maximize sample size, these longitudinal data points were included in the age-group analyses using the first available data point per age group. To account for the mixed data structure, linear mixed models were used to compare IQ-domain scores across the three age groups and examine the timing of developmental IQ differences. We also assessed IQ profiles (i.e. the relative positions of the four core IQ domains) across age groups by testing whether between-domain differences (paired Wilcoxon *t*-tests with Bonferroni correction) were comparable across groups. As an additional sensitivity analysis to examine whether results would be impacted differentially by the addition of longitudinal data points, we repeated analyses without the longitudinal data (ANOVA).

IQ profile and SSDs

We analyzed differences in overall IQ profile associated with the presence or absence of SSDs. For each IQ domain, we compared IQ scores between individuals with an SSD, individuals with subthreshold psychosis, and nonpsychotic individuals (NP; as previously described [Davies et al., 2020]), using ANOVA and appropriate subsequent comparisons. We also examined whether there were domain-specific differences between the three groups, that is, investigated whether the profile of IQ domains within the three groups was comparable, using paired *t*-tests with Bonferroni corrections. To control for potential age effects, we repeated analyses excluding NP individuals under 25 years of age (Davies et al., 2020; Gur et al., 2023; Vorstman et al., 2015).

Finally, we visually explored potential differences in the IQ profile across the three age groups between the three SSD groups, as sample sizes of subgroups based on the intersection of age *and* SSD status did not permit adequately powered statistical analyses.

Results

Overall IQ profile

Exploration of the absolute IQ-domain scores at initial assessment resulted in the IQ score distributions presented in Figure 1. The overall IQ profile was discrepant, indicating significant differences between most components (VIQ > PIQ, VIQ < PS, PIQ < PS, and PIQ < WM; all p < 0.001; Supplemental Table 1). Ranked from strongest to weakest, the order of IQ domains was PS (mean = 79.83, SD = 15.85), WM (mean = 79.08, SD = 15.05), VIQ (mean = 76.65, SD = 14.54), and PIQ (mean = 73.53, SD = 14.02).

Absolute pairwise IQ differences are displayed in Supplemental Figure 1, illustrating the distribution and directionality of group-level differences. Supplemental Figure 2 shows the distribution of 'maxdif', a measure of within-individual IQ discrepancy defined as the maximum difference between any two IQ domains within a single assessment per individual.

Compared to females, the average PS score in males was relatively lower, changing the order of the relative ranking to WM > PS > VIQ > PIQ (vs. PS > WM > VIQ > PIQ in females) (Supplemental Figure 3).

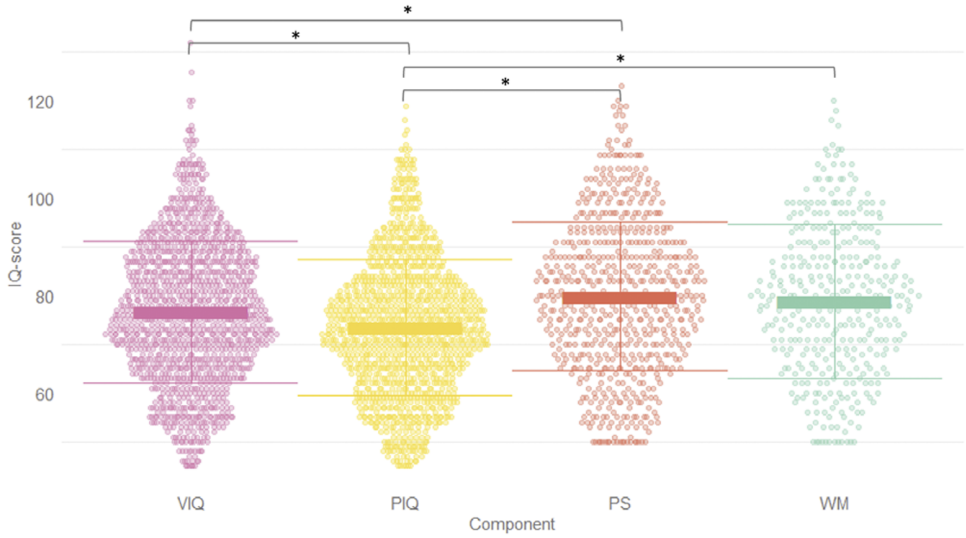

Figure 1. Overall complete IQ profile in individuals with 22q11DS. VIQ mean = 76.65, SD = 14.54; PIQ mean = 73.53, SD = 14.02; PS mean = 79.83, SD = 15.85; WM mean = 79.08, SD = 15.05. * indicates significant difference at p < 0.001 level, after Bonferroni correction. Details regarding between-domain comparisons are provided in Supplemental Table 1.

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Implementing a median FSIQ split of 73, IQ profile characteristics remained consistent comparing those with lower IQ (40–72) to those with higher IQ (73–114), showing similarly discrepant profiles, the same domain rankings, and comparable magnitude and distribution of scores (means and SDs).

Analyses of the difference score (DS) of each IQ domain compared with FSIQ provided highly similar results (Supplemental Figure 4), showing, on average, IQ domain values higher than FSIQ as demonstrated by negative DS. The largest mean difference with FSIQ was observed for PS (mean DS = −8.21, SD = 11.91), followed by WM (mean DS = −6.50, SD = 9.61), VIQ (mean DS = −3.79, SD = 6.45), and PIQ (mean DS = −0.81, SD = 6.59), with significant differences in the effect size of DS (VIQ > PIQ, VIQ < PS; PIQ < PS, and PIQ < WM; all $p < 0.001$).

IQ profile across developmental stages

The overall IQ profile was discrepant in all three age groups, but with differences in the order of ranking. In children, the strength ranking of IQ domains was PS > WM > VIQ > PIQ, with significant differences between VIQ and PIQ, VIQ and PS, PIQ and PS, and PIQ and WM ($p < 0.001$). In adolescents, the ranking was WM > PS > VIQ > PIQ, with significant differences between all IQ domains ($p < 0.001$). In adults, the ranking was VIQ > PS > WM > PIQ, with significant differences between VIQ and PIQ, and between PIQ and PS (Table 2).

The linear mixed model analysis revealed significant between-age-group differences for all four IQ domains (Table 2). Each of the four IQ domains had significantly lower mean scores in the adult group compared to the children group. Specifically, VIQ, PIQ, and PS scores were significantly lower for adolescents compared to children. PS and WM scores were significantly lower for the adult group compared to the adolescent group (Figure 2).

Table 2. Comparisons between mean IQ scores (SD) per IQ domain across three developmental age groups in individuals with 22q11DS (linear mixed model [LLM])

	Children (6–9 y)	Adolescents (10–17 y)	Adults (18–39 y)	*p* (LLM)
VIQ				
N	266	413	244	
Mean (SD)*	79.50 (13.40)	75.76 (14.95)	75.29 (13.62)	**4.20e–09**[a]
PIQ				
N	241	395	239	
Mean (SD)*	76.69 (12.49)	72.10 (13.87)	72.66 (13.49)	**7.64e–13**[b]
PS				
N	152	236	99	
Mean (SD)*	84.65 (15.26)	79.23 (14.68)	75.08 (14.57)	**1.38e–14**[c]
WM				
N	84	124	93	
Mean (SD)*	82.03 (14.09)	81.52 (15.51)	74.09 (13.46)	**4.84e–09**[d]

*Of first available IQ data point.
[a]$\chi^2(2) = 38.58$; (adjusted) pairwise comparisons: children versus adolescents **$p < 0.0001$**; adolescents versus adults $p = 0.39$; children versus adults **$p = 0.0004$.**
[b]$\chi^2(2) = 38.58$; (adjusted) pairwise comparisons: children versus adolescents **$p < 0.0001$**; adolescents versus adults $p = 0.12$; children versus adults **$p < 0.0001$.**
[c]$\chi^2(2) = 38.58$; (adjusted) pairwise comparisons: children versus adolescents **$p < 0.0001$**; adolescents versus adults **$p < 0.0001$**; children versus adults **$p < 0.0001$.**
[d]$\chi^2(2) = 38.58$; (adjusted) pairwise comparisons: children versus adolescents p = 0.89; adolescents versus adults **$p < 0.0001$**; children versus adults **$p < 0.0001$.**
Bold font indicates significance at the $p < 0.001$ level.
In a post-hoc ANOVA analysis, including only cross-sectional data points, results remained unchanged.

IQ profile and SSDs

From the individuals with complete IQ data at initial assessment available, 17.47% ($n = 232$) fell in the SSD group, 15.96% ($n = 212$) fell in the subthreshold psychosis group, and 64.16% ($n = 852$) fell in the no psychosis group (Table 1). There were $n = 32$ (2.41%) individuals who did not fall in any of these three SSD groups and were thus excluded from this portion of the analyses. ANOVAs revealed significant between-group differences for all four IQ domains. Specifically, IQ scores were higher on all domains in the nonpsychotic group compared to the SSD group ($p < 0.001$). In the subthreshold psychosis group, IQ scores across all domains were intermediate between those of the SSD and NP groups, with significant differences compared to the IQ scores in the SSD group ($p < 0.01$), and differences compared to the NP group not reaching statistical significance ($p > 0.05$) (Supplemental Table 2). Notably, the relative positions of the four IQ domains (i.e. PS > WM > VIQ > PIQ) and between-domain differences were almost identical across the three groups (Figure 3 and Supplemental Table 3). Results were unchanged in post-hoc analyses restricted to nonpsychotic individuals aged ≥25 years.

Exploration of the between-age *and* between-SSD groups IQ-profile differences suggests that the developmental group differences are largely similar between those with SSDs, those with subthreshold psychosis, and those with no psychotic illness, and are in line with the total sample developmental group IQ-profile differences. For VIQ, there appear to be only very minor developmental group differences in the nonpsychotic group, compared to decreasing VIQ scores in higher age groups in individuals with SSDs or subthreshold psychosis (Supplemental Figure 5).

Discussion

In the current study, comprising the largest sample available to date, we examined the complete IQ profile of individuals with 22q11DS, including VIQ, PIQ, PS, and WM scores. Alongside substantial individual-level variability, we observed a tendency toward a distinct IQ profile at group level, with, on average, PS emerging as the relatively strongest domain, followed by WM, VIQ, and PIQ as the relatively weakest domains. The differences between IQ domains are significant in children, adolescents, and adults with 22q11DS. IQ scores on all domains are lower in consecutive age groups, with subtle domain-specific differences in the timing of these IQ differences. Finally, while IQ scores on all domains are lower in individuals with SSDs compared to nonpsychotic individuals or those with subthreshold psychotic symptoms, the profile of IQ domains remains similar, regardless of psychosis status.

In the general population, intra-individual discrepancies between IQ domains are common but typically occur bidirectionally, resulting in small mean differences at the group level. Accordingly, group-level averages of between-domain discrepancy scores close to zero likely reflect the cancellation of opposing individual patterns rather than uniform cognitive profiles (Gorlyn et al., 2006; Gyurke, Prifitera, & Sharp, 1991; Iverson, 2001; Matarazzo & Herman, 1984; Wechsler, 1997). In this context, the mean discrepancies (between 0 and 8 IQ points) observed in our sample suggest a systematic directional shift in cognitive profile shape among

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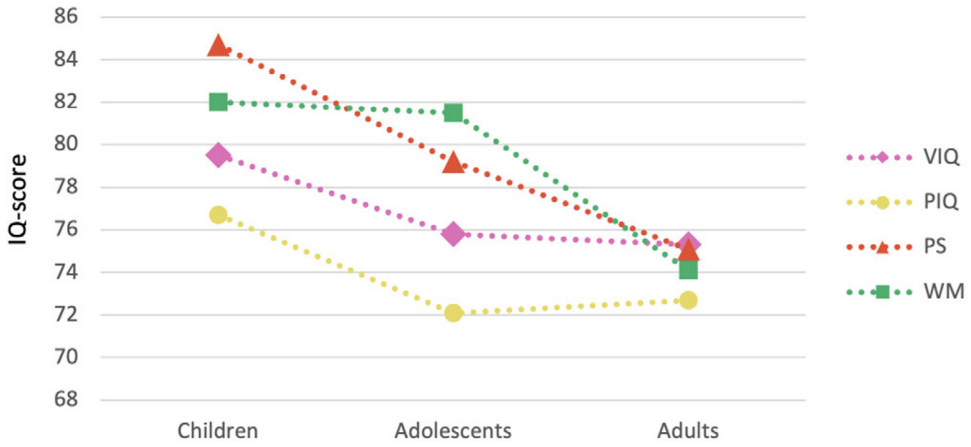

Figure 2. Visualization of mean IQ scores per IQ domain across developmental age groups in individuals with 22q11DS. *Note:* Details of mean scores per IQ domain across age groups can be found in Table 2. Data included in this figure include all available IQ points, that is, including the (first) available IQ score per domain for each participant (n = 1,328, 100%), and for those with multiple IQ assessments available (n = 496, 37.35%), also the first available IQ score per domain in each age group. Results remained unchanged when excluding these longitudinal data points in post-hoc analyses.

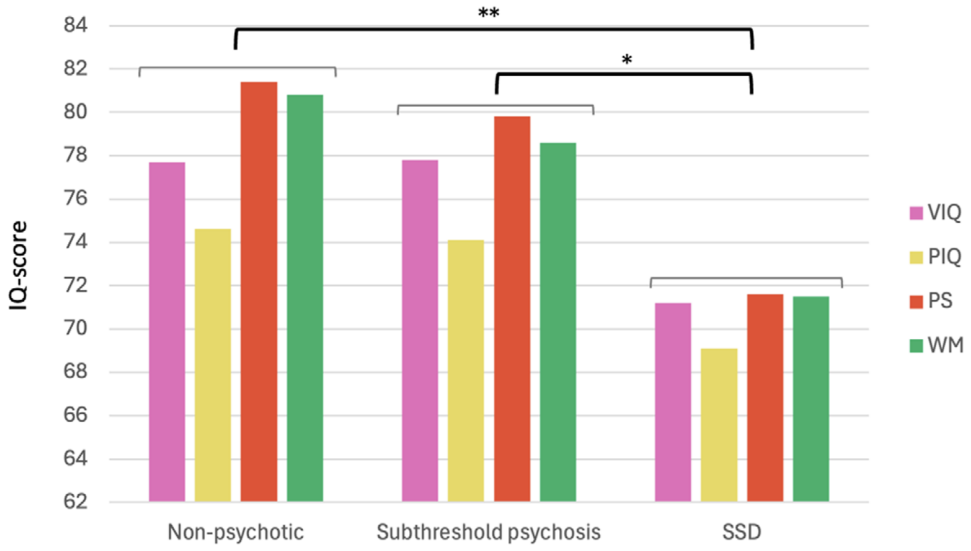

Figure 3. IQ profile including four core IQ domains in individuals with 22q11DS: comparison between individuals with no psychotic illness, with subthreshold psychosis, and with an SSD. SSD: schizophrenia spectrum disorder, including schizophrenia, schizoaffective disorder, delusional disorder, or psychotic disorder not otherwise specified. *Significant between-group difference at $p < 0.01$ level, after Bonferroni correction. **Significance at the $p < 0.001$ level, after Bonferroni correction. More details are provided in Supplemental Tables 2 and 3.

individuals with 22q11DS (Supplemental Figure 1). Although modest at the individual level, such a shift may have important population-level implications, as it increases the proportion of individuals showing discrepancies in the same direction and, consequently, those exceeding clinically relevant thresholds. Therefore, even relatively small average differences may reflect meaningful changes in the distribution of cognitive profiles at the group level.

Beyond the previously observed higher VIQ than PIQ scores (De Smedt et al., 2007; Fiksinski et al., 2021a; Niarchou et al., 2014), this study suggests that PS and WM are relative strengths in individuals with 22q11DS across age groups and IQ levels. Alongside impairments in executive functioning (Bish et al., 2005), social cognition (Campbell et al., 2015), visual motor integration (Duijff et al., 2012a), and memory (Campbell et al., 2010), visuospatial processing deficits have consistently been reported in individuals with 22q11DS (Everaert et al., 2021). However, visuospatial processing appears less impaired on tasks requiring less complex spatial processing (Attout, Noël, Vossius, & Rousselle, 2017), while simple visual memory is generally better preserved than verbal memory (Fiksinski et al., 2018a). These observations align with our findings of relatively higher scores on PS and WM and may reflect a shared reliance on simple and unidirectional processing (speed or memory; Wechsler, 2003), rather than the more complex integrative skills required for multiplex and manipulative processing tasks (Attout, Noël, Vossius, & Rousselle, 2017).

Overall, our results are consistent with a gradual decline over development in all IQ domains in individuals with 22q11DS, as

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previously reported for VIQ and PIQ (Duijff et al., 2012b; Fiksinski et al., 2021a; Vorstman et al., 2015). About a decade ago, it was suggested that despite a negative association between cognitive function and age in 22q11DS, not all cognitive domains may be equally affected (Antshel et al., 2010). Indeed, our findings suggest that while scores on all four core IQ domains decline with age, the timing of these changes is domain-specific: VIQ and PIQ scores are lower in adolescents versus children; a similar picture is observed for PS, but with a further decrease in adults; while WM is similar in children and adolescents, but substantially lower in adults. The latter raises the possibility that WM-related difficulties may not only reflect differential developmental pathways but may also become more prominent in adulthood, warranting longitudinal monitoring given their relevance for adaptive functioning and psychiatric vulnerability (Bassett et al., 2018; Gur et al., 2023).

Cognitive developmental trajectories in 22q11DS reported by Morrison et al. (2020) largely align with our findings, demonstrating higher VIQ and PIQ in children than adults (but not adolescents), as well as higher childhood PS and WM scores, with WM declining from adolescence to adulthood. However, unlike our findings, PS scores did not differ between childhood and adolescence or between adolescence and adulthood. These discrepancies may reflect methodological differences, including the smaller sample size (22q11DS, N = 236), use of different instruments, broader age range, and exclusively cross-sectional data (Morrison et al., 2020). Further studies integrating such complementary approaches are needed to further elucidate the cognitive circuits and genetic architecture (Van Rheenen et al., 2018) that may be differentially affected in individuals with 22q11DS and contribute to domain-specific developmental differences.

Findings that the IQ profile was similarly distributed across SSD status suggest an association with the primary impact of 22q11DS and/or genetic *liability* for schizophrenia, rather than secondary to SSD expression. This is consistent with work on executive performance, where no distinct impairment pattern has been linked to SSDs (Dickinson, Ragland, Gold, & Gur, 2008; Fiksinski et al., 2018a; Ruiz, Raugh, Bartolomeo, & Strauss, 2020; Snitz, Macdonald, & Carter, 2006). The greater overall IQ decrements in individuals with SSDs compared to those with no or subthreshold psychosis align with prior findings in 22q11DS (Butcher et al., 2012; Fiksinski et al., 2022; Weinberger et al., 2016) and in idiopathic schizophrenia and clinical high-risk populations (Dickinson, 2008; Mollon et al., 2018).

Moreover, VIQ differences between childhood and adolescence appeared more pronounced in the SSD group than in the other groups. This corroborates previous findings for a largely overlapping 22q11DS cohort, showing that VIQ decline is most strongly associated with later schizophrenia onset (Fiksinski et al., 2021a, Vorstman et al., 2015) and with genetic overlap between VIQ decline and schizophrenia risk (Davies et al., 2020, as well as increased schizophrenia risk in the general population (Agnew-Blais & Seidman, 2013; Velthorst et al., 2021).

Potential implications

At the individual level, statistically significant between-domain differences observed at the group level are not necessarily clinically meaningful and should rather be interpreted in light of base-rate discrepancy norms provided in test manuals. These norms guide the interpretation of IQ differences by indicating how commonly such discrepancies occur in the population and thereby supporting judgments about their potential relevance for day-to-day functioning, as well as their utility for informing assessment, diagnosis, or intervention (e.g. when exceeding established thresholds for meaningful index discrepancies and/or impacting functional outcomes) (Gorlyn et al., 2006; Gyurke, Prifitera, & Sharp, 1991; Iverson, 2001; Matarazzo & Herman, 1984; Wechsler, 1997). Although our findings may be consistent with a tendency toward increased intra-individual variability across IQ domains in individuals with 22q11DS, evidence for such differences relative to the general population remains limited. Importantly, intra-individual IQ-domain variability is common and not, in itself, indicative of atypical cognitive functioning or clinical comorbidity (Binder & Binder, 2011; Lichtenberger & Kaufman, 2013). Accordingly, both clinical and everyday practice must account for substantial interindividual variability, as has been described across neurodevelopmental phenotypes associated with high-impact genetic variants (Chawner et al., 2021; Farmer et al., 2025; Sanders et al., 2019).

A key challenge, therefore, is to obtain a sufficiently detailed understanding of an individual's cognitive profile in order to align environmental demands with abilities, thereby preventing mismatches while also identifying opportunities to support and strengthen individual capacities. Our findings highlight that cognitive assessments in individuals with 22q11DS ought to be *comprehensive*; that is, providing insight into the full profile rather than merely FSIQ, and *repeated throughout development*, given the changes in IQ (domains) with age observed in 22q11DS (Boot et al., 2023; Oskarsdottir et al., 2023).

One implication of our findings, consistent with clinical observations worldwide (Butcher et al., 2012; Fiksinski et al., 2018b; Swillen, Moss, & Duijff, 2018), is that the IQ-profile characteristics of 22q11DS carry the risk of overestimating individuals with 22q11DS and, consequently, imposing expectations that exceed abilities. Relatively higher PS, WM, and VIQ compared to more impaired PIQ may result in an appearance of adequate cognitive functioning, given preserved performance on simple, time-limited tasks and repetition of straightforward information. However, this may mask underlying difficulties in problem-solving and deeper comprehension. Such profile discrepancies often constitute 'hidden disabilities' that become apparent only in more complex tasks. The resulting mismatch between external expectations and internal capacities may contribute to feelings of being overwhelmed or isolated, and in some cases, emotional dysregulation or outbursts (Fiksinski et al., 2021c).

Ensuring an optimal match between environmental demands and an individual's profile of strengths and weaknesses is relevant not only for cognitive and academic development, but also for reducing or preventing undue stress – an important consideration in a multisystem condition such as 22q11DS. Minimizing chronic stress exposure may be particularly relevant in this population (Armando et al., 2018; Gothelf et al., 2013; Sommer et al., 2016; van Duin et al., 2019; Yui et al., 1999), although further research is needed to clarify dysregulation of neurobiological stress systems and its relationship to psychopathology (Cullen et al., 2024).

Likewise, as pathogenic genetic variants associated with neurodevelopmental conditions are increasingly identified, alongside growing insight into their differential effects on cognition (Davies et al., 2020; Huguet et al., 2018; Moreno-De-Luca et al., 2015), studies such as ours may help advance understanding of the mechanisms underlying cognitive phenotypes and potentially related, treatable psychopathology. Although neuropsychiatric pleiotropy and variable expressivity are the rule rather than the exception for high-impact variants such as the 22q11.2 microdeletion (Fiksinski et al., 2021c; Sanders et al., 2019), these conditions nevertheless offer unique opportunities for early identification and intervention

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(Fiksinski et al., 2021c; Insel, 2010; Lord & Veenstra-VanderWeele, 2016; Moreno-De-Luca, 2016).

Strengths and limitations

This study provides a comprehensive overview of IQ characteristics, with a developmental perspective, for individuals with 22q11DS. There have been studies assessing other domains of neurocognitive functioning, including various operationalizations of constructs related to PS and WM. However, novel to our study is the inclusion of all four core domains of IQ (i.e. VIQ, PIQ, PS, and WM) as assessed by the same family of IQ instruments (Wechsler), allowing investigation of the complete IQ profile in this population. The availability of the largest sample to date, with a wide age range, including longitudinal IQ data for about one-third of the sample, allowed for nuanced characterization of developmental differences between IQ domains.

Although the use of Wechsler-based assessments enhances overall comparability relative to mixing fundamentally different intelligence or cognitive capacities tests, it does not entirely eliminate variability in how specific cognitive domains are operationalized between different versions over time and tailored to age groups. This may be especially relevant for PS and WM, which were not consistently operationalized as distinct indices in earlier Wechsler versions and whose subtest composition has varied across editions.

IQ data were not uniformly available for all IQ domains in all individuals, resulting in smaller sample sizes for some between-component analyses and for subgroups based on SSD status and age group, thereby hindering sufficiently powered analyses. As the pattern of missing data was not entirely random (i.e. varying with respect to variables, including FSIQ, age, and SSD status), potential bias in interpretation of the observed group differences and developmental comparisons cannot be excluded. However, the data presented may help shape further hypotheses and future studies.

In line with previous work from the IBBC, we employed the upper age limit of 39 years for inclusion of IQ data, as available data points above this threshold were too limited and likely more subject to ascertainment bias (Fiksinski et al., 2021a). Characterization of IQ profile and IQ development in older adults with 22q11DS, as well as consideration of the potential impact of other factors, such as parental cognitive functioning (Fiksinski et al., 2022), mode of inheritance (de novo vs. familial [McGinn et al., 2022]), or (socio-) environmental factors (McKinney, Williford, Abbeduto, & Schmitt, 2024) remain important research objectives to be addressed in future studies. Other clinical comorbidities and medication status were not included in the present analyses due to incomplete and nonuniform availability across participants and study sites. Although previous work in 22q11DS has generally not found clear associations between IQ and most psychiatric comorbidities other than SSDs, suggesting that these factors are unlikely to fully account for the observed cognitive differences, the potential influence of comorbid conditions and medication use (e.g. Latrèche et al., 2025) on cognitive outcomes cannot be excluded and warrants further investigation in even more comprehensively characterized cohorts.

In addition, the incorporation of polygenic risk scores (PRS) may provide important insight into the genetic underpinnings of IQ profiles and psychosis risk in 22q11DS, and represents a promising direction for future research aiming to integrate common-variant genetic liability with the high-impact 22q11.2 deletion. Finally, the present study focused exclusively on individuals with 22q11DS. Comparative studies across other pathogenic genetic variants will be important to determine which findings are syndrome-specific versus shared, including through consortium-based efforts (Jacquemont et al., 2022).

Conclusion

Our analyses of comprehensive IQ data from over 1,300 individuals with 22q11DS revealed a tendency toward a discrepant and characteristic IQ profile, despite substantial interindividual variability, and regardless of psychosis status. In addition, examination of IQ domains across different age groups revealed domain-specific differences in timing of IQ differences. The within-individual discrepancy in IQ profiles may impart the risk for overestimating cognitive abilities, and thus functional expectations, in individuals with 22q11DS. Collectively, the results provide impetus for including repeated comprehensive cognitive assessments into the routine clinical care of individuals with 22q11DS, particularly at key transition points (preschool-primary; primary-secondary school, and transition to work/adulthood). In addition, results may pave the way for further investigations of genetic and nongenetic mechanisms underlying IQ characteristics and associations with psychotic illness in 22q11DS, with implications that may extend to other high-impact genetic variants and to the general population.

Supplementary material. To view supplementary material for this article, please visit http://doi.org/10.1017/S0033291726105224.

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