

**Caption for Fig. DS1** Cognitive development in children with 22q11.2 deletion syndrome (22q11.2DS) relative to control siblings.

The thick lines represent the cognitive trajectories (derived from linear mixed models) for children with 22q11.2DS and control siblings separately (see statistical analysis aim 1). Each thin line represents one individual's specific cognitive trajectory. (a) Developmental trajectories of standardised IQ scores; (b) developmental trajectories of raw IQ subtest scores. For all IQ subtests, raw scores represent the number of points scored for correct responses. (c) Developmental trajectories of raw neurocognitive test scores. Number of participants as in Table 1.. Processing speed raw score is in five-choice reaction time milliseconds. Set shifting ability is the number of perseverative errors on the Wisconsin Card Sorting Test. Spatial planning is the number of problems solved on the stockings of the Cambridge task. Sustained attention raw score is between 0 and 1 and represents the participant's ability to discriminate target stimuli from distractor stimuli. Visual attention is the number of correct responses on a match-to-sample task. Spatial working memory (SWM) raw score is the number of errors on the Cambridge Neuropsychological Test Automated Battery (CANTAB) SWM task. FSIQ, full-score IQ; VIQ, verbal IQ, PIQ, performance IQ.

Fig DS1(a) Developmental trajectories of IQ standardised scores

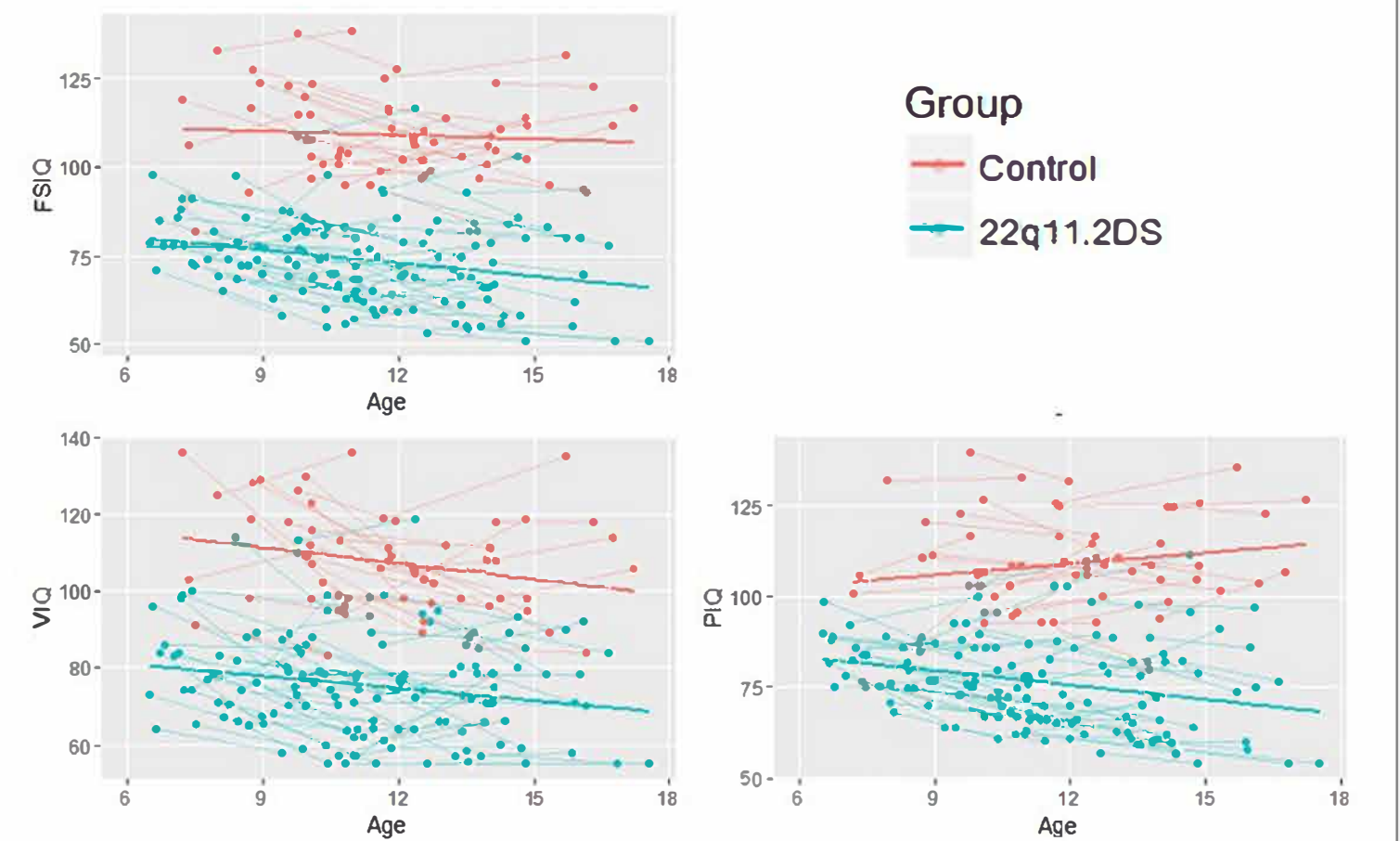


Fig DS1(b) Developmental trajectories of IQ subtest raw scores

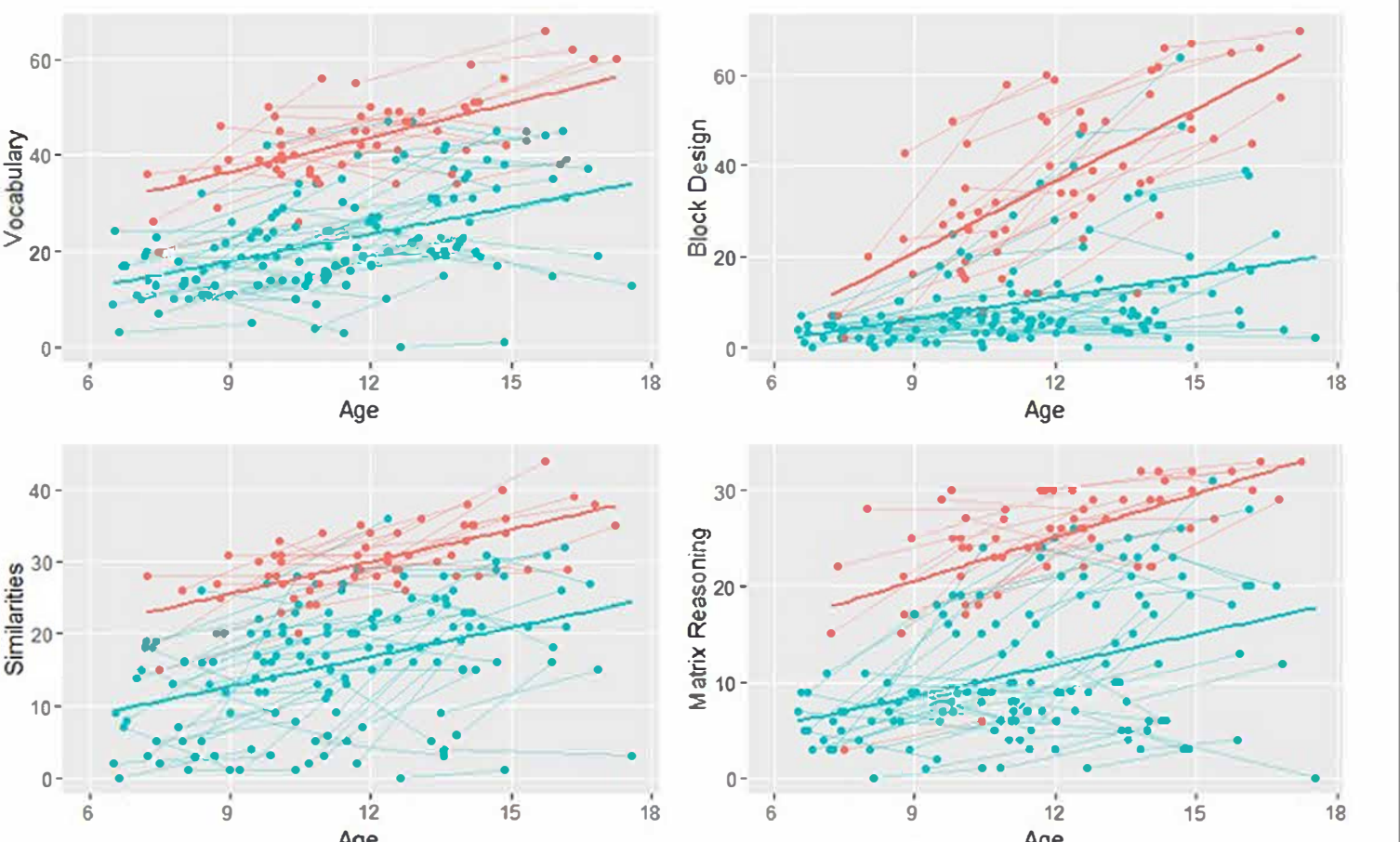
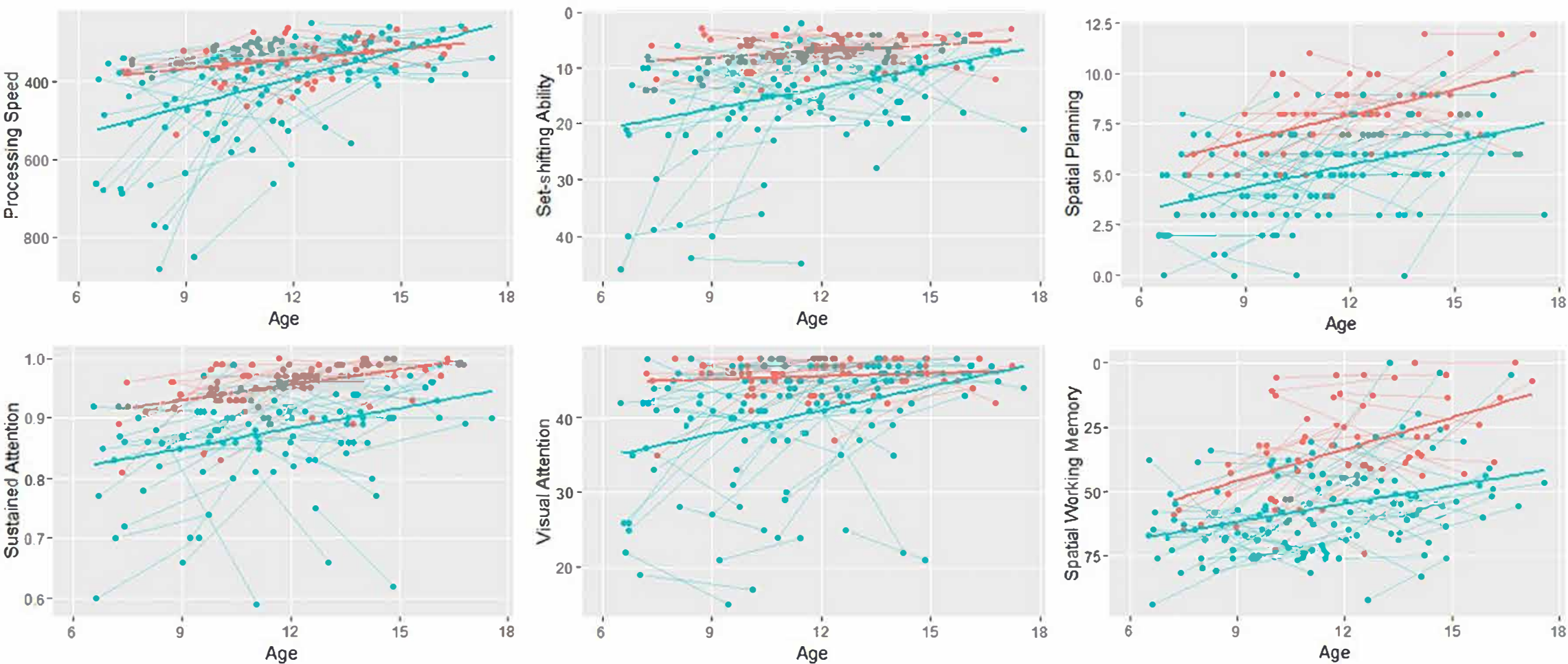


Fig DS1(c) Developmental trajectories of neurocognitive raw scores



**Table DS1:** Sample characteristics associated with reassessment

	22q11.2DS			Controls		
	Reassessed	Not reassessed	p-value*	Reassessed	Not reassessed	p-value*
N	75	27	-	33	16	-
Gender (% male)	58.7	40.7	0.121	51.5	43.8	0.762
Age mean (SD)	9.9(2.4)	10.1(2.0)	0.780	10.6(2.0)	10.9(2.1)	0.629
Full Scale IQ	75.6(12.1)	80.4(13.6)	0.108	106.2(15.8)	110.5(13.2)	0.335

\*p-value: Fisher's exact test was conducted for the gender analysis, Independent t-test was conducted for the age and Full Scale IQ analysis.

**Table DS2:** Psychiatric disorder in children with 22q11.2DS and control siblings

	22q11.2DS		Controls	
	T1 %(n)	T2 %(n)	T1 %(n)	T2 %(n)
Any DSM-IV-TR Psychiatric Disorder	53%(40)	48%(36)	9%(3)	9%(3)
Any Anxiety Disorder	35%(26)	27%(20)	0%(0)	6%(2)
Agoraphobia	8%(6)	11%(8)	0%(0)	0%(0)
Generalised Anxiety Disorder	8%(6)	16%(12)	0%(0)	0%(0)
OCD	3%(2)	0%(0)	0%(0)	0%(0)
Panic Disorder	3%(2)	3%(2)	0%(0)	7%(2)
Separation Anxiety Disorder	5%(4)	7%(5)	0%(0)	0%(0)
Specific Phobia	17%(13)	9%(7)	0%(0)	3%(1)
Social Phobia	21%(16)	16%(12)	0%(0)	3%(1)
Any Mood Disorder	3%(2)	5%(4)	0%(0)	3%(1)
Bipolar Disorder	0%(0)	0%(0)	0%(0)	0%(0)
Dysthymic Disorder	3%(2)	4%(3)	0%(0)	3%(1)
Major Depressive Disorder	0%(0)	1%(1)	0%(0)	0%(0)
ADHD	37%(28)	21%(16)	3%(1)	3%(1)
Conduct disorder	0%(0)	1%(1)	0%(0)	0%(0)
Oppositional Defiance Disorder	17%(13)	15%(11)	3%(1)	3%(1)
Any Psychotic disorder	0%(0)	0%(0)	0%(0)	0%(0)
Selective Mutism	4%(3)	4%(3)	3%(1)	3%(1)
Tic Disorder	5%(4)	3%(2)	0%(0)	0%(0)
Trichillomania	0%(0)	0%(0)	0%(0)	0%(0)
ASD screening (SCQ)	29%(22)	38%(26)	0%(0)	0%(0)

Psychiatric symptomatology, (last 3 months), was assessed at both times using the Child and Adolescent Psychiatric Assessment (CAPA)<sup>1</sup> by means of semi-structured interview with the primary carer (parent CAPA). Children aged  $\geq 11$  years completed a self-report semi-structured interview on

anxiety and mood (child CAPA). Criteria were applied to establish DSM-IV-TR<sup>2</sup> diagnosis. Autism Spectrum Disorder (ASD) traits were assessed using the Social Communication Questionnaire (SCQ)<sup>3</sup>, which was completed by the primary carer. Total scores can range from 0 to 39. In our analysis we used the recommended<sup>4</sup> score of 15 or higher as indicating probable ASD.

**Table DS3:** Linear mixed models results

	22q11.2DS n	Control n	Change per year in 22q11.2DS (95%CI)	Change per year in controls (95%CI)	Divergence in 22q11.2DS relative to controls (95%CI)
Standardised scores					
<b>FSIQ</b>	67	31	-1.4 IQ(-2.2,-0.5)	-0.4(-1.7,0.8)	1.0 IQ(-0.6,2.4)
<b>VIQ</b>	67	31	-1.3 VIQ(-2.3,-0.2)	-0.9(-2.5,0.7)	0.4 VIQ(-1.4,2.2)
<b>PIQ</b>	68	31	-1.3 PIQ(-2.1,-0.5)	0.8(-0.4,2.0)	2.1 PIQ(0.7,3.5)
Raw scores					
<b>Vocabulary</b>	67	31	1.7(1.1,2.3)	1.8(0.8,2.8)	0.1(-1.1,1.2)
<b>Similarities</b>	67	31	1.2(0.6,1.8)	1.7(0.9,2.6)	0.5(-0.5,1.5)
<b>Block Design</b>	68	31	1.6(0.9,2.3)	4.5(3.4,5.6)	2.8(1.5,4.2)
<b>Matrix Reasoning</b>	68	31	1.0(0.6,1.5)	1.6(0.9,2.2)	0.5(-0.3,1.4)
<b>Processing Speed</b>	64	30	-23.3(-34.4,-12.3)	-1.6(-16.2,13.0)	21.7(3.8,39.5)
<b>Sustained Attention</b>	58	29	0.01(0.00,0.02)	0.00(-0.01,0.01)	-0.01(-0.02,0.01)
<b>Spatial Planning</b>	63	30	0.3(0.1,0.4)	0.3(0.1,0.6)	0.1(-4.6,0.4)
<b>Spatial Working Memory</b>	68	31	-1.8(-3.1,-0.4)	-3.9(-6.0,-1.8)	-2.1(-4.6,0.4)
<b>Set-shifting Ability</b>	64	30	-1.1(-1.7,-0.4)	-0.4(-1.3,0.5)	0.7(-0.5,1.8)
<b>Visual Attention</b>	65	31	1.2(0.6,1.7)	0.5(-0.3,1.3)	0.6(-1.6,0.3)

Change per year was derived from the fixed effect of age on cognitive score in our linear mixed models. This represents the average change per year in cognitive score for children with 22q11.2DS (column 4) and control siblings (column 5). Column 6 represents the difference in average change per year between children with 22q11.2DS and control siblings. This was estimated with the fixed interaction effect (interaction term) of age by group on cognitive score for processing speed, spatial working memory and set-shifting ability a higher score represents worse performance so a negative change in raw score reflected increased performance for these tasks. See statistical analysis aim 1 for full methodology description.

**Table DS4:** Percentage of children showing cognitive deterioration

Cognitive measure	n (22q11.2DS, Control)	Raw score decrease			Reliable cognitive deterioration		
		22q11.2DS raw score decrease % (n)	Controls raw score decrease % (n)	Fishers exact p-value	22q11.2DS reliable cognitive deterioration % (n)	Control reliable cognitive deterioration % (n)	Fishers exact p-value
Vocabulary	67,31	23.9(16)	29.0(9)	0.623	0.0(0)	0.0(0)	-
Similarities	67,31	20.9(14)	9.7(3)	0.253	0.0(0)	0.0(0)	-
Block design	68,31	13.2(9)	3.2(1)	0.165	0.0(0)	0.0(0)	-
Matrix reasoning	68,31	25.0(17)	12.9(4)	0.197	0.0(0)	0.0(0)	-
Processing speed	64,30	34.4(22)	26.7(8)	0.488	12.5(8)	3.3(1)	0.263
Sustained attention	58,29	32.8(19)	24.1(7)	0.465	5.2(3)	0.0(0)	0.548
Spatial planning	63,30	23.8(15)	26.7(8)	0.800	1.6(1)	0.0(0)	0.999
Spatial memory	68,31	36.8(25)	25.8(8)	0.360	1.5(1)	0.0(0)	0.999
Visual attention	65,31	30.8(20)	22.6(7)	0.473	13.8(9)	6.5(2)	0.494
Set-shifting ability	64,30	37.5(24)	30.0(9)	0.643	0.0(0)	0.0(0)	-

Raw score decrease was defined as a negative change in raw score between T1 and T2 (<0), reliable cognitive deterioration was defined using cut-off based upon reliable change indices (see statistical analysis Aim 2). Each individual was classified using these criteria and then prevalence was calculated and compared.

**Table DS5:** Mean deficit in 22q11.2DS relative to sibling controls

Cognitive measure	n		Contrast: Controls - 22q11.2DS			
	Controls	22q11.2DS	Mean deficit z-score	95% CI lower bound	95% CI upper bound	p
<b>FSIQ</b>	31	67	-2.4 (-35.6 IQ points)	-2.6 (-39.7 IQ points)	-2.1 (-31.4 IQ points)	<0.001
<b>VIQ</b>	31	67	-2.1 (-32.2 IQ points)	-2.4 (-36.7 IQ points)	-1.8 (-27.7 IQ points)	<0.001
<b>PIQ</b>	31	68	-2.2 (-32.5 IQ points)	-2.4 (-32.5 IQ points)	-1.9 (-32.5 IQ points)	<0.001
<b>Vocabulary</b>	31	67	-2.3	-2.6	-2.0	<0.001
<b>Similarities</b>	31	67	-2.0	-2.3	-1.6	<0.001
<b>Block design</b>	31	68	-2.0	-2.3	-1.7	<0.001
<b>Matrix reasoning</b>	31	68	-2.1	-2.4	-1.9	<0.001
<b>Processing Speed</b>	30	64	-0.6	-1.0	-0.2	0.002
<b>Sustained Attention</b>	29	58	-2.0	-2.4	-1.6	<0.001
<b>Spatial Planning</b>	30	63	-1.3	-1.5	-1.1	<0.001
<b>Spatial Memory</b>	31	68	-1.1	-1.4	-0.7	<0.001
<b>Set-shifting Ability</b>	30	64	-1.7	-2.2	-1.3	<0.001

Mean deficit z-score is the age adjusted z-score of children with 22q11.2DS subtracted from the mean performance of controls. These values are plotted in Figure 2A. See statistical analysis aim 1 for full methodology description.

### Supplementary material references

1. Angold A, Prendergast M, Cox A, Harrington R, Simonoff E, Rutter M. The child and adolescent psychiatric assessment (CAPA). *Psychological medicine*. 1995;25(04):739-753.
2. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, text revision (DSM-IV-TR)*: American Psychiatric Association; 2000.
3. Rutter M, Bailey A, Lord C. *The social communication questionnaire: Manual*: Western Psychological Services; 2003.
4. Berument SK, Rutter M, Lord C, Pickles A, Bailey A. Autism screening questionnaire: diagnostic validity. *British Journal of Psychiatry*. Nov 1999;175.