

**Developmental Changes in the Cognitive and Educational Profiles of Children and
Adolescents with 22q11.2 Deletion Syndrome**

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Abstract

Background:22q11.2 deletion syndrome(22q11DS)is the most common microdeletion syndrome in humans.The presence of learning difficulty is reported in the majority of individuals with 22q11DS, but there is considerable heterogeneity in cognitive and educational profiles and in the age-related changes.**Method:**We assessed verbal, non-verbal and spatial abilities,and educational attainment of 18 children and adolescents with 22q11DS at two time points five years apart. **Results:**There was a decline in full-scale IQ, with a sharper decline in verbal than non-verbal skills whereas spatial abilities remained stable over time. Individual profile analysis revealed discrepancies between full-scale IQ and reading skills, suggestive of 'hyperlexia',for more than two thirds of participants. **Conclusions:**The relative strength in verbal ability observed in 22q11DS is more apparent when children are younger and a more even cognitive profile is observed in older children and adolescents. Educational attainments keep pace with development, and literacy skills are globally higher than might be expected from full-scale IQ.

Keywords: 22q11.2 deletion syndrome; Educational attainment; Cognitive profile; Literacy; Longitudinal study

Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS) is the most common genetic deletion syndrome with an estimated incidence of 1:1600-1:2000 live births (Shprintzen,2008). It shows a highly variable clinical presentation, including serious medical concerns (e.g.,cardiac malformations), psychiatric problems including psychosis, and cognitive impairments (see Philip & Bassett,2011 for a review). Some degree of learning difficulty is also reported in the majority of individuals with 22q11DS, but there is considerable heterogeneity.

Verbal skills are usually considered an area of strength in 22q11DS (De Smedt et al., 2007; Moss et al., 1999). However, this is not observed in all individuals, and characterizing the syndrome as a non-verbal learning disability is simplistic (Schoch et al.,2014). Moreover, the cognitive profile of children with 22q11DS can change over time; specifically, a negative correlation between age and IQ has been reported, with a stronger decline in verbal than non-verbal abilities with age (Duijff et al., 2012, 2013). This decline has been the subject of many recent studies, because of the evidence that loss of cognitive skills precedes the emergence of psychosis, affecting approximately 25% of individuals with 22q11DS (Vorstman et al., 2015).

Considering educational attainment, Moss et al.(1999) examined the learning profile of children with 22q11DS in 16 children aged 6-15 years. While reading and spelling attainments were within the normal range, mathematical skills were weaker, findings replicated in several studies of children of different ages (e.g., Bearden et al.,2001; De Smedt et al., 2002, 2007). As Wang et al.(2000) noted, this psycho-educational profile of impaired numeracy relative to literacy skills is perhaps unsurprising, given that visuospatial short-term memory, known to be weak in 22q11DS (Bearden et al., 2001; Sobin et al., 2005; Wang et al., 2000), is widely regarded as contributing to arithmetic processing in typical development

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(e.g., Venneri et al.,2003).

Changes in the learning profile of children with 22q11DS over time have rarely been investigated. Hooper et al.(2013) found no changes in the academic achievement (reading, spelling, mathematics) of a group of children and adolescents with 22q11DS, over 3.5 years; Antshel et al.(2010) found no significant change in mathematical ability but a significant improvement in reading. More information regarding the change over time in reading, spelling and mathematics in 22q11DS is required if the educational needs of these children and young people are to be adequately addressed. Indeed, providing adequate assessment of needs is the first step for implementing targeted interventions, not only to promote and maintain educational attainments but also to ensure personal wellbeing (e.g., Gilman & Huebner, 2006).

The aim of the present study was to investigate possible changes with development in cognitive functioning and basic learning skills in a sample of children with 22q11DS who were followed over a 5-year period. Although an age-related decline in standard scores might be expected because of a slower rate of development compared to typically developing individuals, a change in the profile of strengths and weaknesses in individuals with 22q11DS would be clinically significant. Previous studies (e.g., Vorstman et al.,2015) have primarily focused on the decline in cognitive abilities as a precursor to the onset of psychosis in 22q11DS and educational attainments have rarely been measured longitudinally. Most previous studies have used the Wechsler Intelligence Scale for Children (Wechsler,2003) which allows for the assessment of verbal and non-verbal IQ, but the Performance IQ measure confounds spatial and more general non-verbal reasoning skills. In the present study, the British Ability Scales (BAS-II; Elliott et al.,1997) allowed us to consider non-verbal skills involving non-verbal abstract and quantitative reasoning separately from spatial skills.

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We predicted that verbal skills would be stronger than non-verbal abilities and some decline in IQ scores would be observed over time, consistent with previous studies (e.g., De Smedt et al., 2007; Vorstman et al., 2015). We were particularly interested in the development of spatial skills, not previously studied. We also considered whether there would be changes over time in basic attainments accounted for by changes in underlying cognitive skills or alternatively whether these would be preserved (e.g., word reading in Down syndrome; Verucci et al., 2006), as suggested by Hooper et al.'s (2013) results.

Methods

Participants

Eighteen children (12 females) with 22q11DS were recruited to the study via an advertisement displayed on a support forum for parents of children with 22q11DS. None of the participants were on medication that could affect their cognitive performance, or were experiencing psychotic symptoms at the time of testing. At the first testing point (T1) their age range was 6.42-17.33 years (mean=9.87, SD=3.50); at T2 they were 11.58-22.25 years old (mean=15.07, SD=3.39). Given the large spread of ages, the group was divided at the median into a younger and an older sample for some analyses. There were 9 children younger than 8.5 years at T1 (7 females, T1 mean=7.25, SD=.69; T2 mean=12.59, SD=.71) and 9 who were older (mean=12.50, SD=3.17; T2 mean=17.55, SD=3.18).

Instruments

Participants completed an assessment battery with co-normed ability and achievement scales, the BAS-II (Elliott et al., 1997), providing standard scores (mean=100; SD=15). The tasks' reliabilities reported were provided by the battery's manual (Elliott et al., 1997).

General Conceptual Ability (GCA). The British Ability Scales provide ability score for

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verbal, spatial and non-verbal domains and these together translate into a general cognitive ability score, described as 'general conceptual ability' ($\alpha=.96$). The Verbal cluster ($\alpha=.93$) comprises Word Definitions, measuring expressive vocabulary, and Similarities, assessing verbal reasoning; the Non-verbal Reasoning cluster ($\alpha=.92$) comprises Matrices, measuring inductive reasoning and Quantitative Reasoning, assessing the identification and application of rules governing quantitative relationships; the Spatial cluster ($\alpha=.96$) comprises Recall of Designs, assessing short-term recall of visual-spatial patterns, and Pattern Construction, evaluating spatial visualization. GCA, equivalent to full-scale IQ, was also measured.

Educational attainments. Basic reading was assessed with the BAS-II Word reading ($\alpha=.94$) which requires the child to read aloud a series of single words (regular and irregular) increasing in difficulty. Similarly, Spelling ($\alpha=.92$) requires the child to write words of increasing difficulty. Arithmetic skills were assessed using Number skills ($\alpha=.91$), a written test of arithmetic including writing digits and simple calculations, complex problems, fractions and algebra.

Procedure

Ethical clearance for the study was obtained from the University of York Ethics Committee. T1 testing was conducted in the child's school or home, in two testing sessions. At T2, the majority of participants were visited at home but four chose to travel to the University to attend the testing session. At both testing points, tasks were administered and scored by trained doctoral students who were also qualified as developmental psychologists and supervised by a clinical psychologist. Scores were extrapolated for the young adults whose chronological age exceeded the typical norms for the standardized tests at T2 ($n=4$): their standard scores were based on the norms obtained by youth from 17.5 to 18 years old,

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that is the oldest normative sample included in the BAS-II.

Results

Table 1 shows the T1 and T2 descriptives for cognitive and achievement scales.

At T1 the characteristic profile of better verbal than non-verbal reasoning abilities was observed in the sample. It is also notable that attainment scores were higher than might be expected from GCA for literacy skills, less so for arithmetic skills. Analysis of the individual profiles revealed that a high proportion were achieving considerably higher than expected based on IQ, as showed by a score discrepancy of clinical relevance (≥ 15 standard scores). For reading at both times, about 75% of the younger and 65% of the older sample could be defined as 'hyperlexic' on this basis, and 50-56% of each group were similarly advanced in spelling. The proportion showing discrepancies for arithmetic was smaller, but again some 28% showed 'exceptional' performance in this domain.

Repeated measures ANOVAs showed a significant decline in GCA between T1 and T2 ($F(1,17)=9.085, p<.01, d=.50$). Examining cluster scores, there was a significant overall effect of Time (Pillai's Trace=.541, $F(3,15)=5.899, p<0.01$) which was significant for Verbal ($F(1,17)=18.775, p<.01, d=.86$) and Non-verbal reasoning ($F(1,17)=6.254, p<.05, d=.34$), but not for Spatial abilities ($F(1,17)=.044, p>.05, d=.04$). Given the reported relationship between decline in cognitive abilities and age, these analyses were also run adding the between subject factor Age. The absence of significant main effects of Age ($F(3,14)=1.173, p>.05$), or of significant interactions Time*Age ($F(3,14)=.792, p>.05$) for BAS-II cluster scores or GCA

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Table 1

Descriptive Statistics showing the Cognitive and Educational Profile of participants at Time 1 and Time 2

	Time 1							Time 2						
	N	Mean	SD	Min	Max	Skewness (SE = .536)	Kurtosis (SE = 1.038)	N	Mean	SD	Min	Max	Skewness (SE = .536)	Kurtosis (SE = 1.038)
IQ scales														
Verbal	18	86.44	13.11	60	108	-.410	-.600	18	73.67	16.56	52	102	.452	-1.323
Non-verbal reasoning	18	74.67	17.62	49	104	-.062	-.943	18	68.61	18.19	49	109	.739	-.300
Spatial	18	71.89	15.74	47	112	.696	1.145	18	71.28	15.99	47	105	.436	-.164
GCA	18	73.94	15.12	47	106	.101	-.129	18	65.72	17.80	39	97	.229	-1.231
Achievement scales														
Word reading	17	91.88	21.17	55	131	.222*	-.917§	18	89.18	20.53	55	130	.413	-.527
Spelling	16	90.53	17.07	63	120	-.145°	-.982^	16	85.20	17.66	60	112	-.241°	-1.419^
Number skills	18	80.58	19.86	55	114	.423	-1.269	18	76.79	20.84	55	115	.464	-1.350

SD=standard deviation; GCA=General Conceptual Ability; SE = standard error

* SE = .550 ; °SE = .564; § SE = 1.063; ^ SE = 1.091

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(Age: $F(1,16)=.799, p>.05$; Time*Age: $F(1,16)=2.625, p>.05$), indicates a similar decline in younger and older children.

Turning to attainment tests, there was no significant change in standard scores over time (Pillai's Trace=.256, $F(1,12)=1.145, p>.05$). Neither the scores for Word reading ($F(1,12)=.613, p>.05, d=.13$), Spelling ($F(1,12)=3.742, p>.05, d=.31$), nor Number skills ($F(1,12)=1.915, p>.05, d=.19$) changed between T1 and T2. However, a significant Time*Age interaction ($F(1,11)=5.904, p<.05$) was found for the Word reading: although still performing within the average range, the younger children showed a significant decline in this task between T1 and T2 (from 101.25 to 92.75; $p<.05, d=.43$), whereas older participants showed a slight and non-significant increase in their decoding skills (from 83.56 to 86; $p>.05, d=.12$).

The above analyses treat the group with 22q11.2 altogether. However, the mean scores mask heterogeneity. In a final set of analyses, we examined the individual data in order to identify the proportion of children showing a clinically significant decline in IQ or attainments scores over time (discrepancy ≥ 15 standard scores; Table 2). Overall, around half of children showed a significant decline in verbal and around one third in non-verbal abilities; the proportion of children showing a decline in the other abilities was lower.

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Table 2

Percentage and number of participants showing a clinically significant decline of at least 15 standard scores between T1 and T2, separate for young (< 8.5 years old at T1) and old (> 8.5 years old at T1) participants.

	Young	Old	Total
	n = 9	n = 9	N = 18
Verbal	66.7 % (n = 6)	33.3 % (n = 3)	50.0 % (n = 9)
Non-verbal reasoning	44.4 % (n = 4)	22.2% (n = 2)	33.3 % (n = 6)
Spatial	11.1 % (n = 1)	11.1 % (n = 1)	11.1 % (n = 2)
GCA	33.3 % (n = 3)	11.1 % (n = 1)	22.2 % (n = 4)
Word reading	25.0 % (n = 2)	0 % (n = 0)	11.8 % (n = 2)
Spelling	25.0 % (n = 2)	16.7 % (n = 1)	21.4 % (n = 3)
Number skills	22.2 % (n = 2)	22.2 % (n = 2)	22.2 % (n = 4)

GCA=General Conceptual Ability

Discussion

This study investigated changes over time in the cognitive and educational profile of children and adolescents with 22q11DS, considering separately verbal, non-verbal reasoning, and spatial abilities, as well as basic learning skills (word reading, spelling and number skills).

Consistent with previous studies (Duijff et al., 2012, 2013), between T1 and T2 we found GCA, analogous to the full-scale IQ measured by other cognitive batteries, to decline with age. More specifically, there was a decline in verbal ability of large effect size, sharper

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than the moderate decline in non-verbal reasoning. Furthermore, it is noteworthy that scores for spatial tasks remained stable over time. Thus, in the five years between the two test phases, verbal ability had dropped from the age appropriate range to below average and it was now in line with non-verbal reasoning and spatial abilities. This phenomenon, sometimes described as “growing into deficit”, was observed to the same extent in younger and older children and does not therefore seem to be restricted to a particular phase of development. However, when we analyzed the profiles of individual children a more mixed picture emerged: half of children showed a significant decline in the verbal domain, whereas half of the sample remained stable. Thus, despite the significant decrease in mean scores highlighted by the first group of analysis, only the 22.2% of children showed a significant decline in GCA.

Turning to achievement tests, it is first important to note that discrepancies between general conceptual ability and literacy skills, suggestive of hyperlexia, were common. This assumption replicates and extends findings from other studies showing impaired reading comprehension in individuals with 22q11.2 (e.g., Antshel et al., 2014). A discrepancy was also observed for number skills. Second, a small proportion of children (11- 22%) showed a relative decline in basic attainments over time, mainly younger children. These profiles suggest the relative preservation of basic achievement skills in individuals with 22q11.2, in particular in literacy abilities.

Although at first pass the individuals in this sample appeared to be developing at the expected rate in word reading, analysis of younger and older children separately showed somewhat slower than expected gains in reading during the middle school years. It could be that this is a reflection of lesser classroom input on basic reading skills as children move from the early to the later primary years. Performance in arithmetic, perhaps a skill less emphasized

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at home and in school, was consistently weaker at both time points than reading.

The main findings of our study suggest that the relative strength in verbal ability observed in 22q11DS may be more apparent when children are younger, and similarly reading develops more quickly in this developmental phase. Later a flatter profile is observed, as also reported by Antshel et al.(2008). Furthermore, the present study indicates that spatial abilities though deficient are stable over time, whereas non-verbal reasoning skills, also poor at T1, significantly decrease. Notwithstanding this, the educational attainments of the sample appeared to keep pace with development, a caveat being the relative decline in reading skills for younger children noted above. It is plausible that this decline, where it occurs, relates to the decline also observed in verbal skills: it is well established that there is a reciprocal interaction between learning to read and the growth of vocabulary (Krashen, 1989; Ouellette, 2006), and the often reported ‘Matthew effect’ in reading suggests that better readers go on to show greater growth in vocabulary and other verbal skills (Stanovich,1986).

In summary, the present study provides evidence that the cognitive decline observed in individuals with 22q11DS is not just a “simple” slower rate of development compared to typically developing individuals. Rather, it is the result of a change in their profile of cognitive strengths and weaknesses thereby underlining the importance of monitoring multiple, discrete domains of cognition across the school years, for identifying deficits that may benefit from special tutoring and targeted interventions. Since not all domains of cognition were affected and many of the test scores fell within the low-normal range, it is likely that some children with 22q11DS could benefit from extra attention to their particular deficits to allow them to ‘keep up’ with their peers, while others are already excelling.

A limitation of the present study was its small sample size and the wide age range of participants. Although a control group would strengthen the results, the use of tests with well-

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established norms allowed reliable considerations. Indeed, the use of extrapolated standard scores for the four young adults who were older than 18 at T2, could have partially influenced the results, showing better performances than the ones that would be obtained administering tests for adults. It is also possible that the recruitment of children from families who volunteered for the study led to bias in the findings of attainment tests since it is undoubtedly the case that these children were well supported.

While further research addressing the longitudinal outcomes of children with 22q11DS is needed, in particular relating the growth of educational attainments over time, we suggest that the findings of this study are important from educational perspectives. 22q11DS is sometimes classified as a non-verbal learning difficulty. However, here we demonstrate that the cognitive profile is heterogeneous and not stable across time, suggesting regular monitoring of cognitive skills in this population is warranted.

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