Developmental trajectories in cognitive development in 22q11 deletion syndrome

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Factors influencing development

“Environment”

Parenting

Maturation

Cultural background

School, education

“Genes”
Del22q11.2

Time/development
Every person with 22q11 DS is unique!
In 22q11 DS...

- MEDICAL CONCERNS
- DEVELOPMENTAL/BEHAVIOURAL CONCERNS

BALANCE
Developmental Phenotypic Transitions regarding cognitive development in del22q11

12-24 m.
Mild to moderate delays in all areas of development:
- Gross/ fine motor
- General cognition
- Speech/language

Gerdes et al. (1999)
Swillen et al. (1999; 2001)

3-6y
Mild to moderate delays in all areas of development:
- Gross/ fine motor
- General cognition (DD, pre-arithmetic skills, visual-perceptual skills)
- Speech/language

7-10/12y
Shyness/withdrawn
Frustration
Social-emotional development: less interactive play, fearful, impulsive

From early adolescence on
Early studies on cognitive development and intelligence in children with 22q11 DS

- Golding-Kushner et al. (1985)
- Swillen et al. (1997; 1999)
- Moss et al. (1999)
- Woodin et al. (2001)

- IQ scores ranging from borderline to moderately intellectual disability
- No association between IQ and CHD (Swillen et al. *JMG*, 1997)
- IQ in familial deletion < IQ in ‘de novo’ deletion (Swillen et al. *JMG*, 1997)
Cognitive shift in 22q11 DS

General population

% van de mensen
0 Intelligentiequotiënt 70 80 100 130 IQ

del22q11

7-10/12y
Intelligence in 22q11 DS (de novo vs. familial deletion)

Early studies on intelligence in 22q11 DS

• important first steps towards understanding the cognitive outcome in 22q11.2 DS and the within syndrome variability in cognitive performance (similar to the variability in the 22q11 DS physical phenotype)

• BUT they were limited by
  o small sample sizes
  o the use of different measures for intelligence
Intellectual abilities in a large sample of children with Velo–Cardio–Facial Syndrome: an update

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² Centre for Human Genetics, University of Leuven, Belgium
³ Pediatric Cardiology, University Hospital Gasthuisberg of Leuven, Belgium
⁴ Faculty of Kinesiology and Rehabilitation Sciences, University of Leuven, Belgium
Cognitive profile (n = 103)

- Mean TIQ 73.48 (SD 11.73) (range 50-109)
- 75% VIQ > PIQ
  - 25% PIQ > VIQ
- Clinical discrepancy (>15 IQ points)?
  - 23/103 = 22.33% (most VIQ > PIQ)
- Lower PIQ due to poor visual-spatial and visuo-motor skills and problems with speed (slow working)
Cognitive challenges in 22q11

- problems with abstract thinking, problem-solving
- problems with integrating new information
- academic problems: **arithmetics and reading comprehension**
- poor attention and concentration, (ADD; problems with starting, initiating,…)
- deficits in visual-perceptual abilities

**BUT:**
- good (technical) reading skills and good auditory memory

(Swillen et al., *Child Neuropsychology*, 1999; 2005; Desmedt et al., 2007; 2008)
What does this mean for learning?

- Appropriate diagnosis → appropriate education + support
  - Mainstream + support (speech, motor, cognitive, play, social skills)
  - Special education
- Stimulation and adaptation
- Encouragement of development of social and daily living skills
- If major concerns about social/emotional/peer-related issues → referral to child psychiatrist

What does this mean for learning?
<table>
<thead>
<tr>
<th>Deletion</th>
<th>De novo (n = 92)</th>
<th>Familial (n = 11)</th>
<th>( p )</th>
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<tbody>
<tr>
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<td>74.50 (11.69)</td>
<td>65.00 (8.45)</td>
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<td>VIQ</td>
<td>79.79 (13.91)</td>
<td>69.27 (11.53)</td>
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<td>PIQ</td>
<td>73.42 (10.89)</td>
<td>66.09 (8.84)</td>
<td>0.03</td>
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<tr>
<td>Sex</td>
<td>Female (n = 47)</td>
<td>Male (n = 56)</td>
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<tr>
<td>FSIQ</td>
<td>73.19 (10.40)</td>
<td>73.73 (12.84)</td>
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<tr>
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<td>78.87 (12.27)</td>
<td>78.50 (15.43)</td>
<td>0.89</td>
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<tr>
<td>PIQ</td>
<td>72.28 (10.38)</td>
<td>72.95 (11.39)</td>
<td>0.76</td>
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<tr>
<td>CHD</td>
<td>Yes (n = 55)</td>
<td>No (n = 48)</td>
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<tr>
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<td>73.56 (10.77)</td>
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<td>Psychiatric</td>
<td>Non-ADHD (n = 76)</td>
<td>ADHD (n = 27)</td>
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<td>FSIQ</td>
<td>73.32 (12.32)</td>
<td>73.96 (10.10)</td>
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<tr>
<td>VIQ</td>
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<td>79.70 (11.76)</td>
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<tr>
<td>PIQ</td>
<td>72.97 (11.18)</td>
<td>71.70 (10.19)</td>
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<td></td>
<td>Non-ASD (n = 84)</td>
<td>ASD (n = 19)</td>
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<td>FSIQ</td>
<td>74.56 (11.83)</td>
<td>68.74 (10.26)</td>
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<tr>
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<td>79.32 (14.51)</td>
<td>75.79 (11.43)</td>
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</tr>
<tr>
<td>PIQ</td>
<td>73.71 (10.90)</td>
<td>67.89 (9.78)</td>
<td>0.03</td>
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</table>

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CHD, congenital heart defect; FSIQ, full-scale IQ; PIQ, performance IQ; SD, standard deviation; VIQ, verbal IQ.
The neuropsychology of 22q11 deletion syndrome. A neuropsychiatric study of 100 individuals

Lena Niklasson\textsuperscript{a,b,*}, Christopher Gillberg\textsuperscript{a,b}

\textbf{Research in Developmental Disabilities 31 (2010)}
Possible factors that contribute to wide variability in intelligence in 22q11 DS?

• *De novo versus familial deletion* (Swillen et al., 1997; 2007)
• Gender differences? No/yes (Swillen et al., 2007; Antshel et al., 2008)
• No effect of congenital heart defect (Swillen et al., 2007)
• No effect psychiatric diagnosis (Vorstman et al., 2006; Niklasson et al., 2010)
• Effect of SES (Ousley et al., 2012), parental IQ and siblings IQ (Kates et al., 2014)

• Size of deletion? (A-D, A-B, A-C, B-C, B-D)
• Role of genes in DGCR? TBX1, COMT, PRODH, CKRL,…
• Modifying genes?
• Other environmental influences (therapy/remediation,…)?
Cognitive development in children with 22q11.2 deletion syndrome

Sasja N. Duijff, Petra W. J. Klaassen, Henriette F. N. Swanenburg de Veye, Frits A. Beemer, Gerben Sinnema and Jacob A. S. Vorstman
Developmental Trajectories in 22q11.2 Deletion

ANN SWILLEN AND DONNA MCDONALD-MCGINN

Chromosome 22q11.2 deletion syndrome (22q11.2DS), a neurogenetic condition, is the most common microdeletion syndrome affecting 1 in 2,000–4,000 live births and involving haploinsufficiency of ~50 genes resulting in a multisystem disorder. Phenotypic expression is highly variable and ranges from severe life-threatening conditions to only a few associated features. Most common medical problems include: congenital heart disease, in particular conotruncal anomalies; palatal abnormalities, most frequently velopharyngeal incompetence (VPI); immunodeficiency; hypocalcemia due to hypoparathyroidism; gentoomenary anomalies; severe feeding/gastrointestinal differences; and subtle dysmorphic facial features. The neurocognitive profile is also highly variable, both between individuals and during the course of development. From infancy onward, motor delays (often with hypotonia) and speech/language deficits are commonly observed. During the preschool and primary school ages, learning difficulties are very common. The majority of patients with 22q11.2DS have an intellectual level that falls in the borderline range (IQ 70–84), and about one-third have mild to moderate intellectual disability. More severe levels of intellectual disability are uncommon in children and adolescents but are more frequent in adults. Individuals with 22q11.2DS are at an increased risk for developing several psychiatric disorders including attention deficit with hyperactivity disorder (ADHD), autism spectrum disorder (ASD), anxiety and mood disorders, and psychotic disorders and schizophrenia. In this review, we will focus on the developmental phenotypic transitions regarding cognitive development in 22q11.2DS from early preschool to adulthood, and on the changing behavioral/psychiatric phenotype across age, on a background of frequently complex medical conditions. © 2015 Wiley Periodicals, Inc.
Divergent cognitive trajectories

12-24 m.
- Mild to moderate delays in all areas of development:
  - Gross/fine motor
  - General cognition
  - Speech/language

3-6 y
- Mild to moderate delays in all areas of development:
  - Gross/fine motor
  - General cognition
  - Speech/language

7-10/12 y
- Wide variability in cognitive development
  - Mean FSIQ around 70; In a subgroup, VIQ > PIQ but also VIQ-PIQ or VIQ < PIQ
  - Divergent cognitive trajectories

From early adolescence on
- Divergent cognitive trajectories:
  - Relative stable IQ trajectory
  - “Growing into deficit”
  - Cognitive decline
  - Verbal decline >> psychosis

Gothelf et al. 2007; 2009
Kates et al., 2009
Vorstman et al. JAMA, 2015

Swillen et al., 1997, 1999;
Desmedt & Swillen, 2007
Duijff et al., 2012
What does this mean for practice and management (learning)?

- no standards for advise/intervention
- USE RECENT COGNITIVE/NEUROPSYCHOLOGICAL ASSESSMENT!
- individualized educational plan (IEP)
- remedial teaching (arithmetics, reading comprehension) or special needs school
- structured and quite learning environment
- be aware of medical problems (hearing, cardiac, fatigue,….)
- be aware of slower tempo
- if visual-perceptual problems are present:
  - adaptation of material, and visual training: learn visual strategies
What does this mean for learning/school?

• NO STANDARDS FOR ADVICE/INTERVENTION
  individualized educational plan (IEP)

• USE RECENT COGNITIVE/NEUROPSYCHOLOGICAL ASSESSMENT!

• remedial teaching and support (arithmetics, reading comprehension) or special needs school

• structured and quite learning environment

• be aware of medical problems (hearing, cardiac, fatigue, ….)

• be aware of slower tempo

• if visual-perceptual problems are present:
  o adaptation of material, and visual training: learn visual strategies
Learning problems increase with age

“Stable trajectory”

“Growing into deficit”

In subgroup, absolute decline $\rightarrow$ verbal decline $\gg$
Psychiatric disorders in 22q11 DS: from childhood to adulthood

3-6y

Shyness/withdrawn
Frustration
Social-emotional development: less interactive play, fearful, impulsive

Developmental disorders (ADHD, ASD)
Anxieties

7-10/12y

From early adolescence on

Psychiatric Disorders From Childhood to Adulthood in 22q11.2 Deletion Syndrome: Results From the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome

SCHNEIDER, DEBBANÉ, BASSETT, ET AL.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Children (6–12 Years)</th>
<th>Adolescents (13–17 Years)</th>
<th>Emerging Adults (18–25 Years)</th>
<th>Young Adults (26–35 Years)</th>
<th>Mature Adults (≥36 Years)</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
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<tr>
<td>Any schizophrenia spectrum disorder&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9/456</td>
<td>1.97</td>
<td>35/346</td>
<td>10.12</td>
<td>76/323</td>
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<tr>
<td>Schizophrenia</td>
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<td>13/342</td>
<td>3.80</td>
<td>5/291</td>
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<td>Schizoaffective disorder</td>
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<td>5/291</td>
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<td>Schizophreniform disorder</td>
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<td>1/289</td>
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<td>3/285</td>
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<td>Brief psychotic disorder</td>
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<td>4/289</td>
<td>1.38</td>
<td>1/288</td>
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<td>Psychotic disorder not otherwise specified</td>
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<td>1.75</td>
<td>14/346</td>
<td>4.05</td>
<td>29/323</td>
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<td>Delusional disorder</td>
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<td>0/346</td>
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<td>155/435</td>
<td>35.63</td>
<td>97/286</td>
<td>33.92</td>
<td>71/295</td>
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<td>Separation anxiety disorder&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>6.33</td>
<td>4/299</td>
<td>1.34</td>
<td>2/113</td>
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<td>Specific phobia&lt;sup&gt;d&lt;/sup&gt;</td>
<td>95/433</td>
<td>21.94</td>
<td>48/282</td>
<td>17.02</td>
<td>19/263</td>
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<td>Social phobia&lt;sup&gt;e&lt;/sup&gt;</td>
<td>45/435</td>
<td>10.34</td>
<td>28/286</td>
<td>9.79</td>
<td>14/295</td>
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<td>Panic disorder&lt;sup&gt;f&lt;/sup&gt;</td>
<td>4/333</td>
<td>1.20</td>
<td>2/231</td>
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<td>17/270</td>
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<td>Posttraumatic stress disorder</td>
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<td>3/222</td>
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<td>Obsessive-compulsive disorder</td>
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<td>17/286</td>
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<td>1/286</td>
<td>0.34</td>
<td>2/295</td>
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<td>Any mood disorder</td>
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<td>41/346</td>
<td>11.85</td>
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<td>8.96</td>
<td>25/232</td>
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<td>Dysthymia&lt;sup&gt;h&lt;/sup&gt;</td>
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<td>1.10</td>
<td>8/346</td>
<td>2.31</td>
<td>16/320</td>
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<td>4/346</td>
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<td>Substance-related disorder (substance abuse and dependence)</td>
<td>0/300</td>
<td>0.00</td>
<td>1/221</td>
<td>0.45</td>
<td>7/278</td>
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</table>

<sup>a</sup> Significant increase with age ($\chi^2=214.70, df=4, p<0.001$).
<sup>b</sup> Significant decrease with age ($\chi^2=57.13, df=4, p<0.001$).
<sup>c</sup> Significant decrease with age ($\chi^2=13.67, df=4, p=0.008$).
<sup>d</sup> Significant increase with age ($\chi^2=16.66, df=4, p=0.005$).
<sup>e</sup> Significant decrease with age ($\chi^2=24.57, df=4, p<0.001$).
<sup>f</sup> Significant decrease with age ($\chi^2=23.35, df=4, p=0.001$).
<sup>g</sup> Significant increase with age ($\chi^2=97.88, df=4, p<0.001$).
<sup>h</sup> Significant difference across age groups ($\chi^2=4.59, df=1, p=0.034$).
<sup>i</sup> Significant difference across age groups ($\chi^2=13.19, df=1, p<0.001$) and between adolescents and adults ($\chi^2=4.59, df=1, p=0.034$).
<sup>j</sup> Significant difference across age groups ($\chi^2=10.07, df=2, p=0.007$).
Psychiatric disorders in 22q11 DS: from childhood to adulthood

3-6y
- Shyness/withdrawn
- Frustration
- Social-emotional development: less interactive play, fearful, impulsive

Developmental disorders (ADHD, ASD)
Anxieties

7-10/12y

From early adolescence on
- Approximately 25-30% of individuals with a 22q11 DS will develop a form of psychosis spectrum disorders

- Anxiety disorders
- Mood disorders
Psychiatric disorders in 22q11 DS: from childhood to adulthood

3-6y

- Shyness/withdrawn
- Frustration
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Developmental disorders (ADHD, ASD)
Anxieties

7-10/12y

From early adolescence on

Approximately 25-30% of individuals with a 22q11 DS will develop a form of psychosis
spectrum disorders

Anxiety disorders
Mood disorders
N=829
IQ (Wechsler) data

N=411
≥2 IQ measurements
AND
Psychiatric assessment

Without psychotic disorder (n=355)

With psychotic disorder (n=56)
Overall cumulative IQ decline (FSIQ, VIQ, PIQ) in 388 individuals with 22q11DS
Longitudinal studies on intelligence

• “Growing into deficit”
  In subgroup, cognitive decline verbal decline >>  (Duijff et al., 2012)

• \textit{psychosis} (catechol-O-methyltransferase low-activity allele (COMT(L)) as a risk factor for decline in prefrontal cortical volume and cognition, as well as for the consequent development of psychotic symptoms during adolescence)  
  (Gothelf et al. 2005; 2009) (Kates et al., 2009)

• Very low functioning group of adults (“dementia”)  (Evers et al., 2011)
The importance of understanding cognitive trajectories: the case of 22q11.2 deletion syndrome

Ann Swillen a,b,c

Purpose of review
The 22q11.2 deletion syndrome (velo-cardio-facial syndrome or DiGeorge syndrome) is the most common known contiguous gene deletion syndrome, and is associated with neurodevelopmental problems and diverse neuropsychiatric disorders across the life span. In this review, we discuss the wide variability in intelligence, the developmental phenotypic transitions regarding cognitive development (intelligence) from preschool to adolescence, and the importance of understanding these cognitive trajectories in 22q11.2 deletion syndrome for care/management and research.

Recent findings
Longitudinal data on the cognitive development of children and adolescents with 22q11.2 deletion syndrome reveal divergent cognitive trajectories. A decline in verbal intelligence quotient precedes the onset of psychosis in 22q11.2 deletion syndrome.

Summary
Understanding these cognitive trajectories is important since it can guide clinicians to develop adequate support, tailored remediation, and psychiatric care and individualized follow-up.

Keywords
22q11.2 deletion syndrome, divergent cognitive trajectories, variability in cognitive abilities
KEY POINTS

- There is a wide variability in cognitive abilities in individuals with 22q11.2 deletion syndrome.
- Divergent cognitive trajectories occur already from primary school age onwards.
- A decline in VIQ precedes the onset of psychosis in 22q11.2 deletion syndrome.
- More knowledge of the developmental trajectories in 22q11.2 deletion syndrome will help to identify the profiles of clinical needs and may guide intervention and treatment decisions.
Persons with 22q11 DS present a distinctive but dynamic and developing cognitive, behavioural, social and psychiatric phenotype.

Wide variability and divergent cognitive trajectories (Swillen & Mc Donald-McGinn, 2015)

A decline in verbal IQ precedes the onset of psychosis in 22q11DS (Gothelf, 2009; Kates et al., 2009, Vorstman et al., 2015)

Dynamic interaction between genes – environment

Need more information on the whole cognitive trajectory (childhood to adulthood) in 22q11 DS. Longitudinal studies are important as a means of elucidating the cognitive changes in individuals with the syndrome throughout the lifespan.

Need for studies regarding risk/protective factors and environmental factors.
Thank you

All participants and families

All colleagues and friends

All members and co-workers of multidisciplinary 22q11 DS team @

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