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

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Every person with 22q11 DS is unique !

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In 22q11 DS…

MEDICAL CONCERNS

DEVELOPMENTAL/ BEHAVIOURAL CONCERNS

BALANCE

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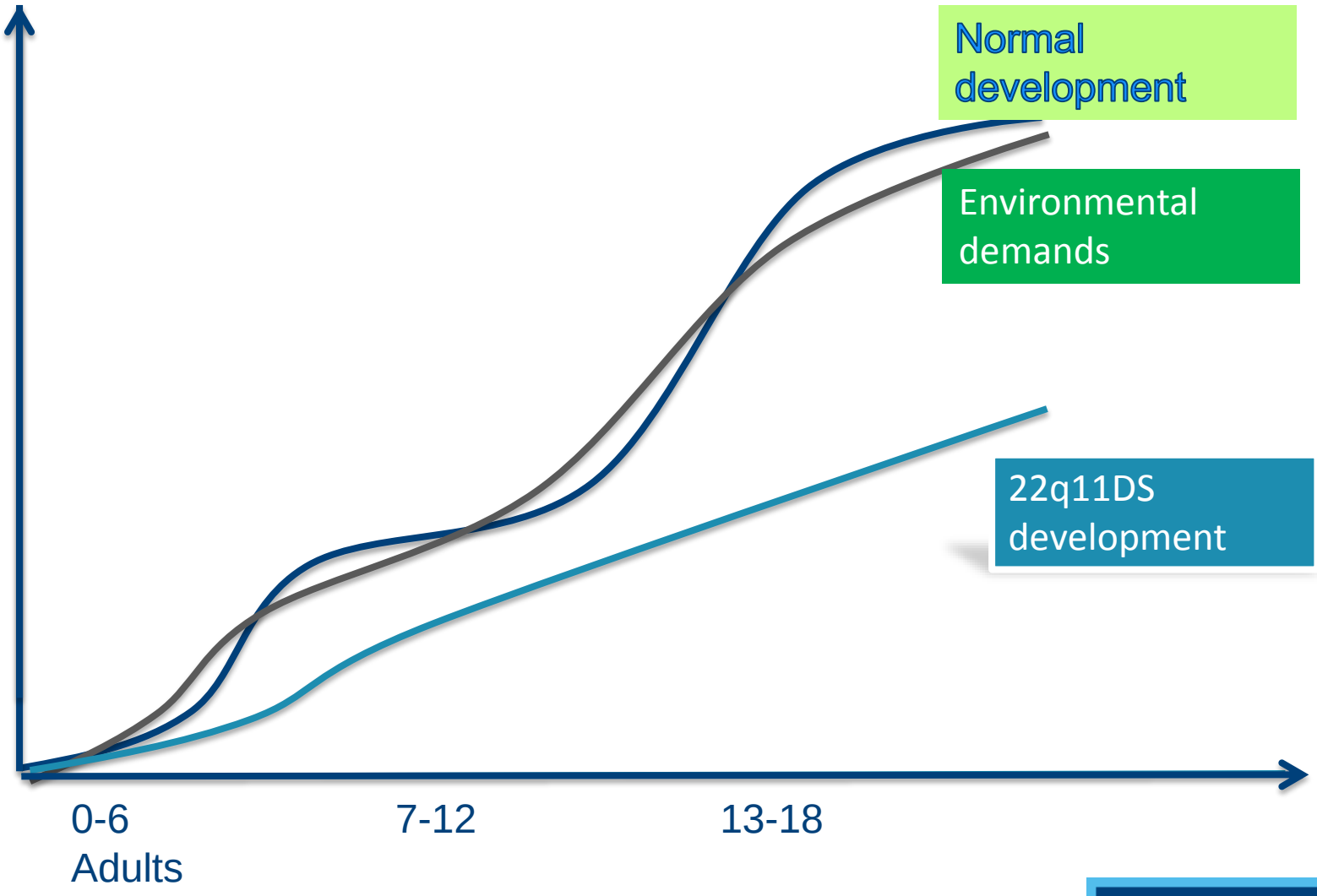

Normal development
Environmental demands
22q11DS development
0-6
Adults
7-12
13-18

Developmental Phenotypic Transitions regarding cognitive development in del22q11

12-24 m.	3-6y	7- 10/12y	**From early adolescence on**

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)

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

Shyness/withdrawn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

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

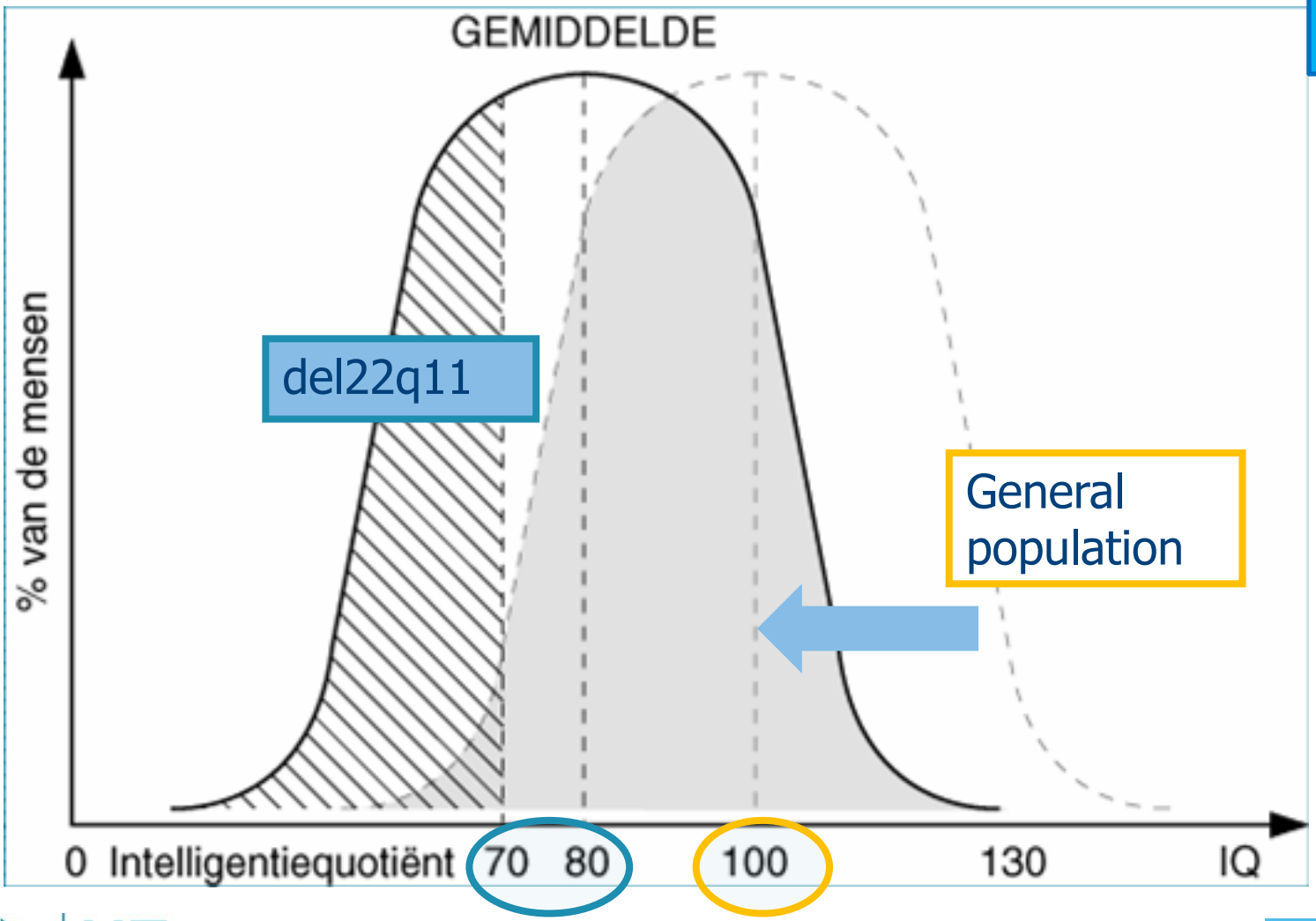
- Golding-Kushner et al. (1985)
- Swillen et al. (1997; 1999)
- Moss et al. (1999)
- Woodin et al. (2001)

7- 10/12y

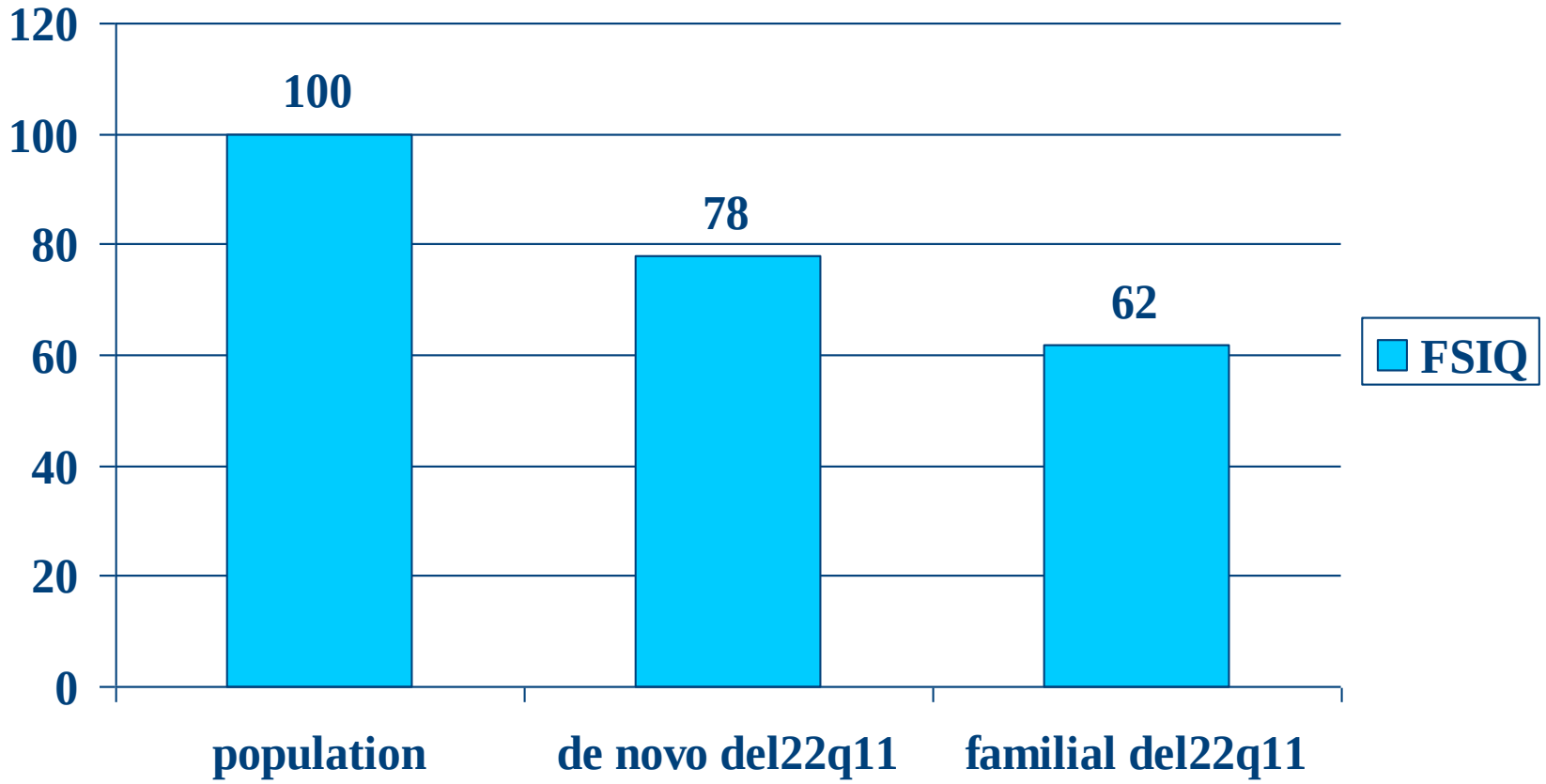
- IQ scores ranging from borderline to moderately intellectual disability
- No association between IQ and CHD
  (Swillen et al. *JMG*, 1997)
- IQ in familial deletion < IQ in 'de novo' deletion
  (Swillen et al. *JMG*, 1997)

Cognitive shift in 22q11 DS

7- 10/12y



Intelligence in 22q11 DS (de novo vs. familial deletion)



Swillen et al, 1997, *Journal of Medical Genetics,* 34: 453-458

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
  - small sample sizes
  - the use of different measures for intelligence

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VOLUME 51 PART 9 pp 666–670 SEPTEMBER 2007

Intellectual abilities in a large sample of children with Velo–Cardio–Facial Syndrome: an update

B. De Smedt,[1,2] K. Devriendt,[2] J.-P. Fryns,[2] A. Vogels,[2] M. Gewillig[3] & A. Swillen[2,4]

1 *Centre for Disability, Special Needs Education and Child Care, University of Leuven, Belgium*
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4 *Faculty of Kinesiology and Rehabilitation Sciences, University of Leuven, Belgium*

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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)

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What does this mean for learning ?

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

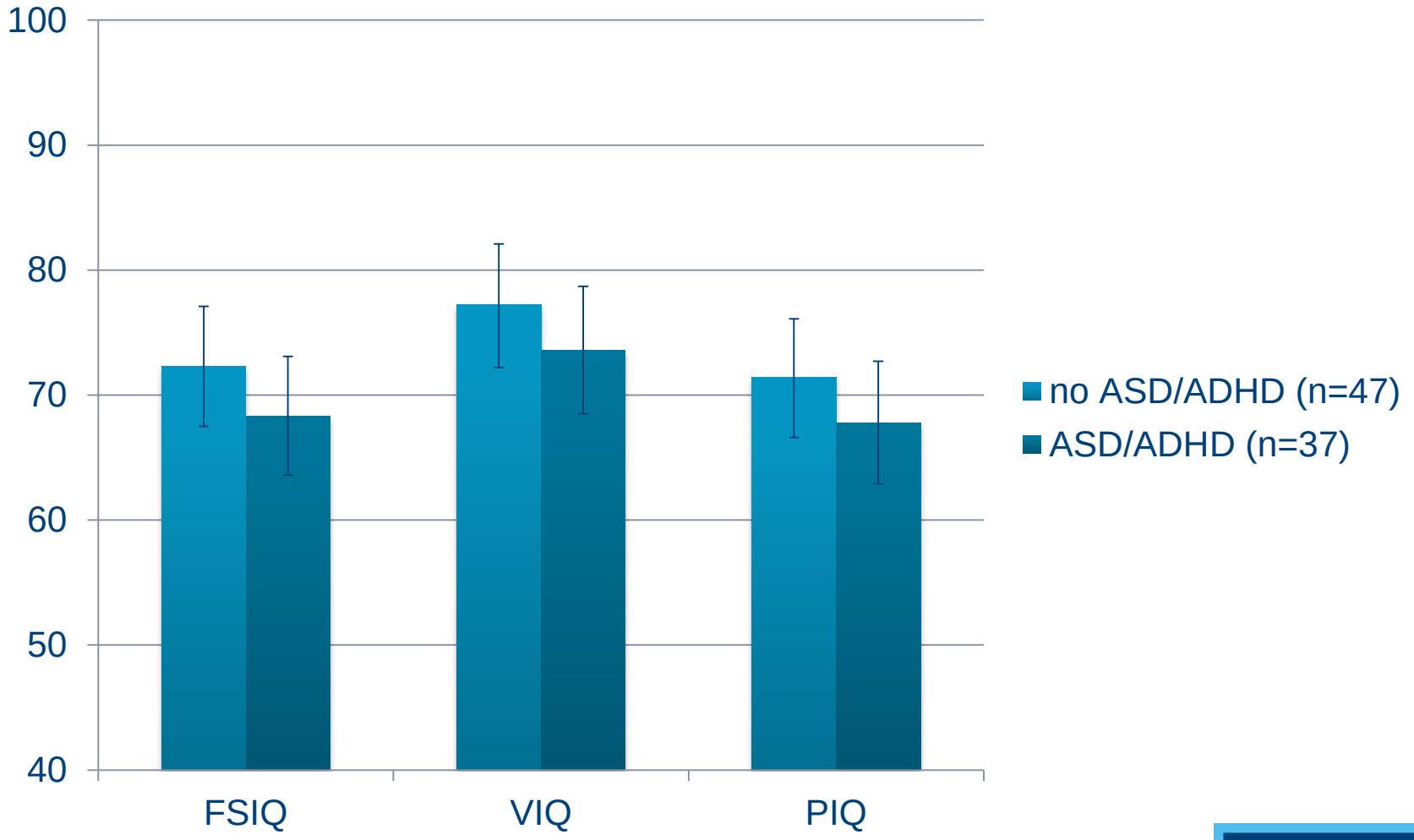
Table 1 Group means (SD)

			P
Deletion	*De novo* ($n = 92$)	Familial ($n = 11$)	
FSIQ	74.50 (11.69)	65.00 (8.45)	0.01
VIQ	79.79 (13.91)	69.27 (11.53)	0.02
PIQ	73.42 (10.89)	66.09 (8.84)	0.03
Sex	Female ($n = 47$)	Male ($n = 56$)	
FSIQ	73.19 (10.40)	73.73 (12.84)	0.82
VIQ	78.87 (12.27)	78.50 (15.43)	0.89
PIQ	72.28 (10.38)	72.95 (11.39)	0.76
CHD	Yes ($n = 55$)	No ($n = 48$)	
FSIQ	74.38 (11.84)	72.46 (11.65)	0.41
VIQ	79.05 (14.23)	78.23 (13.89)	0.77
PIQ	73.56 (10.77)	71.58 (11.05)	0.36
Psychiatric	Non-ADHD ($n = 76$)	ADHD ($n = 27$)	
FSIQ	73.32 (12.32)	73.96 (10.10)	0.81
VIQ	78.30 (14.78)	79.70 (11.76)	0.66
PIQ	72.97 (11.18)	71.70 (10.19)	0.61
	Non-ASD ($n = 84$)	ASD ($n = 19$)	
FSIQ	74.56 (11.83)	68.74 (10.26)	0.05
VIQ	79.32 (14.51)	75.79 (11.43)	0.32
PIQ	73.71 (10.90)	67.89 (9.78)	0.03

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 [a,b,*], Christopher Gillberg [a,b]



Research in Developmental Disabilities 31 (2010)

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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,…) ?

BJPsych | The British Journal of Psychiatry (2012)
200, 462–468. doi: 10.1192/bjp.bp.111.097139

UMC Utrecht

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

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American Journal of Medical Genetics Part C (Seminars in Medical Genetics)

ARTICLE

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; genitourinary 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.

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Divergent cognitive trajectories

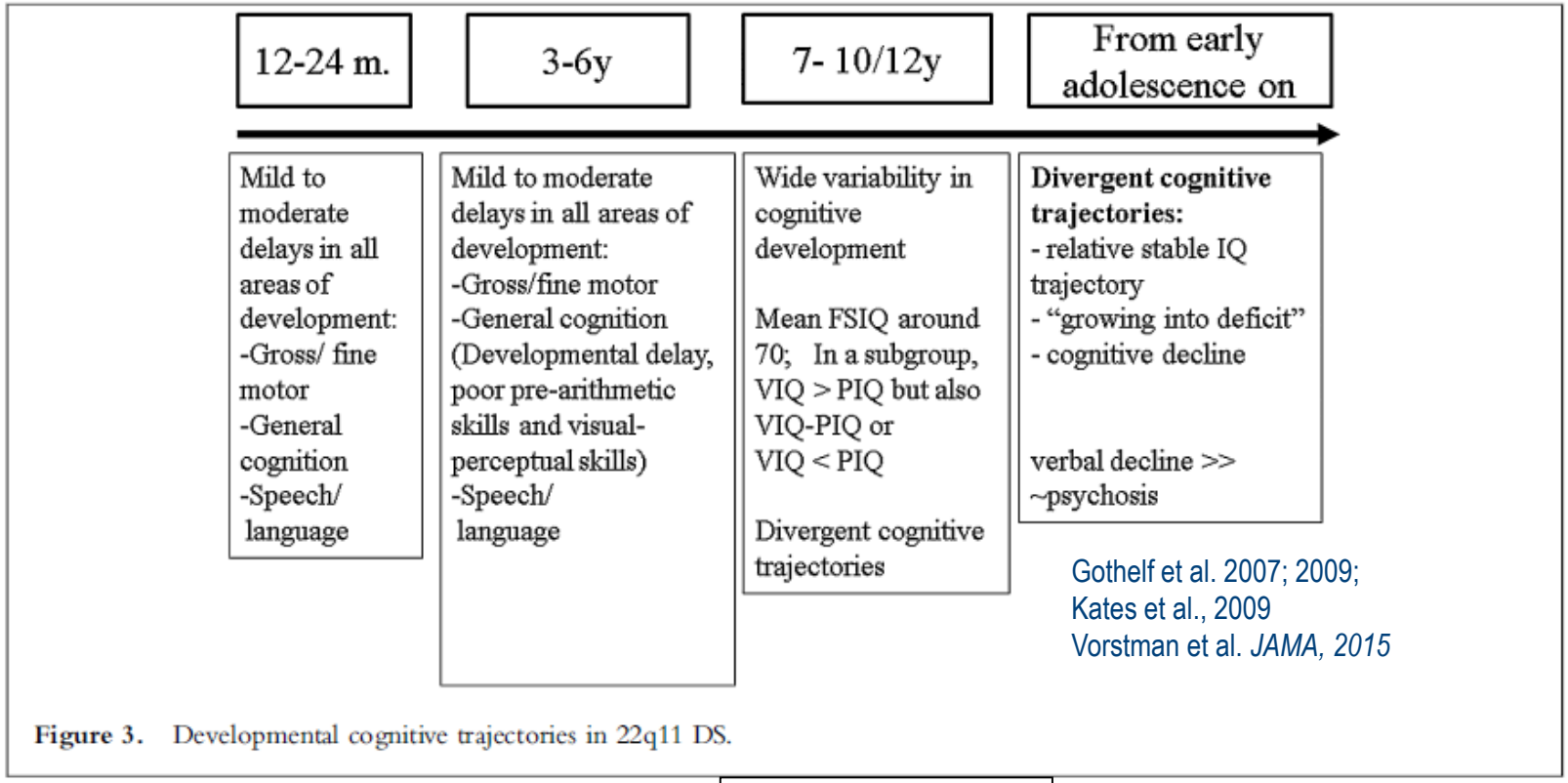

Figure 3. Developmental cognitive trajectories in 22q11 DS.

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

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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 !

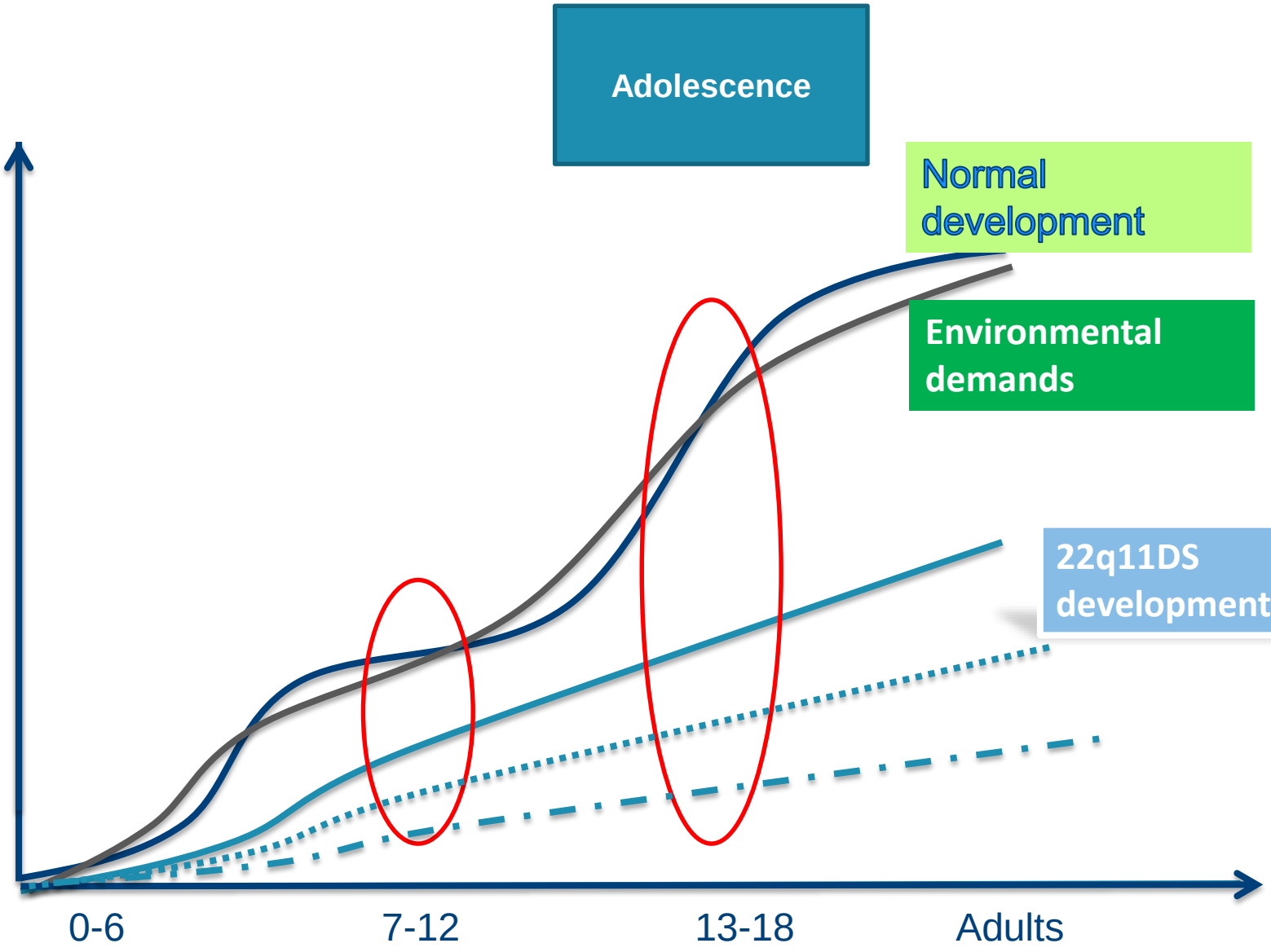
- remedial teaching and support (arithmetics, reading comprehension) or special needs school
- structured and quite learning environment
- be aware of medical problems (hearing, cardiac, fatigue,….)
- be aware of slower tempo

- if visual-perceptual problems are present:
  - adaptation of material, and visual training: learn visual strategies

Cognitive and educational challenges from early adolescence on (13-18y)

- Learning problems increase with age

- “Stable trajectory”
- “Growing into deficit”
- In subgroup, absolute decline → verbal decline >>


Adolescence
Normal development
Environmental demands
22q11DS development
0-6
7-12
13-18
Adults

Psychiatric disorders in 22q11 DS: from childhood to adulthood

3-6y

7- 10/12y

From early adolescence on

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

Developmental disorders (ADHD,ASD)
Anxieties

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.

(Am J Psychiatry 2014; 171:627–639)

TABLE 2. Prevalence of DSM-IV-TR Psychiatric Disorders in Five Age Groups of Subjects With 22q11.2 Deletion Syndrome

Diagnosis	Children and Adolescents				Adults					
	Children (6–12 Years)		Adolescents (13–17 Years)		Emerging Adults (18–25 Years)		Young Adults (26–35 Years)		Mature Adults (≥36 Years)	
	N	%	N	%	N	%	N	%	N	%
Any schizophrenia spectrum disorder[a]	9/456	1.97	35/346	10.12	76/323	23.53	62/150	41.33	53/127	41.73
Schizophrenia	1/456	0.22	13/342	3.80	36/291	12.37	37/132	28.03	32/106	30.19
Schizoaffective disorder	0/456	0.00	3/342	0.88	5/291	1.72	10/132	7.58	4/106	3.77
Schizophreniform disorder	0/259	0.00	1/289	0.34	3/285	1.05	0/127	0.00	0/89	0.00
Brief psychotic disorder	0/259	0.00	4/289	1.38	1/288	0.35	1/131	0.76	0/106	0.00
Psychotic disorder not otherwise specified	8/456	1.75	14/346	4.05	29/323	8.98	14/150	9.33	17/126	13.49
Delusional disorder	0/456	0.00	0/346	0.00	2/323	0.62	0/150	0.00	0/127	0.00
Any anxiety disorder[b]	155/435	35.63	97/286	33.92	71/295	24.07	37/149	24.83	35/127	27.56
Separation anxiety disorder[c]	25/395	6.33	4/259	1.54	2/113	1.77	0/28	0.00	0/20	0.00
Specific phobia[d]	95/433	21.94	48/282	17.02	19/263	7.22	5/131	3.82	3/106	2.83
Social phobia[e]	45/435	10.34	28/286	9.79	14/295	4.75	4/149	2.68	1/127	0.79
Panic disorder[f]	4/333	1.20	2/231	0.87	17/270	6.30	12/137	8.76	17/118	14.41
Posttraumatic stress disorder	1/274	0.36	3/222	1.35	2/240	0.83	0/109	0.00	2/73	2.74
Obsessive-compulsive disorder	24/435	5.52	17/286	5.94	15/295	5.08	8/149	5.37	8/127	6.30
Generalized anxiety disorder	36/435	8.28	30/286	10.49	29/295	9.83	18/148	12.16	14/127	11.02
Anxiety disorder not otherwise specified	1/435	0.23	1/286	0.34	2/295	0.68	1/149	0.67	0/127	0.00
Any mood disorder	15/456	3.29	41/346	11.85	59/323	18.27	22/150	14.67	26/127	20.47
Major depressive disorder[g]	10/456	2.19	31/346	8.96	35/323	10.84	18/150	12.00	20/127	15.75
Dysthymia[h]	5/456	1.10	8/346	2.31	16/320	5.00	2/145	1.38	1/110	0.91
Bipolar disorder or (hypo)manic episode in children	0/318	0.00	2/317	0.32	6/320	1.88	3/150	2.00	5/127	3.94
Mood disorder not otherwise specified	0/456	0.00	4/346	1.16	7/323	2.17	0/150	0.00	2/127	1.57
Substance-related disorder (substance abuse and dependence)	0/300	0.00	1/221	0.45	7/278	2.52	9/142	6.34	5/110	4.55

	Children (6–12 Years)		Adolescents (13–17 Years)		Adults (≥18 years)	
	N	%	N	%	N	%
ADHD[j]	161/434	37.10	63/264	23.86	29/186	15.59
Autism spectrum disorders[j]	12/94	12.77	43/162	26.54	47/292	16.10
Any disruptive disorder[k]	57/400	14.25	25/229	10.92	9/127	7.09
Oppositional defiant disorder	57/400	14.25	25/229	14.79	7/115	6.09
Conduct disorder	0/316	0.00	0/180	0.00	2/138	1.45

[a] Significant increase with age (χ^2=214.70, df=4, p<0.001).
[b] Significant decrease with age (χ^2=15.49, df=4, p=0.004).
[c] Significant decrease with age (χ^2=13.67, df=4, p=0.008).
[d] Significant decrease with age (χ^2=57.13, df=4, p<0.001).
[e] Significant decrease with age (χ^2=24.57, df=4, p<0.001).
[f] Significant increase with age (χ^2=47.35, df=4, p<0.001).
[g] Significant increase with age (χ^2=37.88, df=4, p<0.001).
[h] Significant difference across age groups (χ^2=14.66, df=4, p=0.05).
[i] Significant difference between children and adolescents (χ^2=13.19, df=1, p<0.001) and between adolescents and adults (χ^2=4.59, df=1, p=0.04).
[j] Significant difference across age groups (χ^2=10.07, df=2, p=0.007).

Psychiatric disorders in 22q11 DS: from childhood to adulthood

3-6y

7- 10/12y

From early adolescence on

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

Developmental disorders (ADHD, ASD)
Anxieties

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

Anxiety disorders
Mood disorders

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Psychiatric disorders in 22q11 DS: from childhood to adulthood

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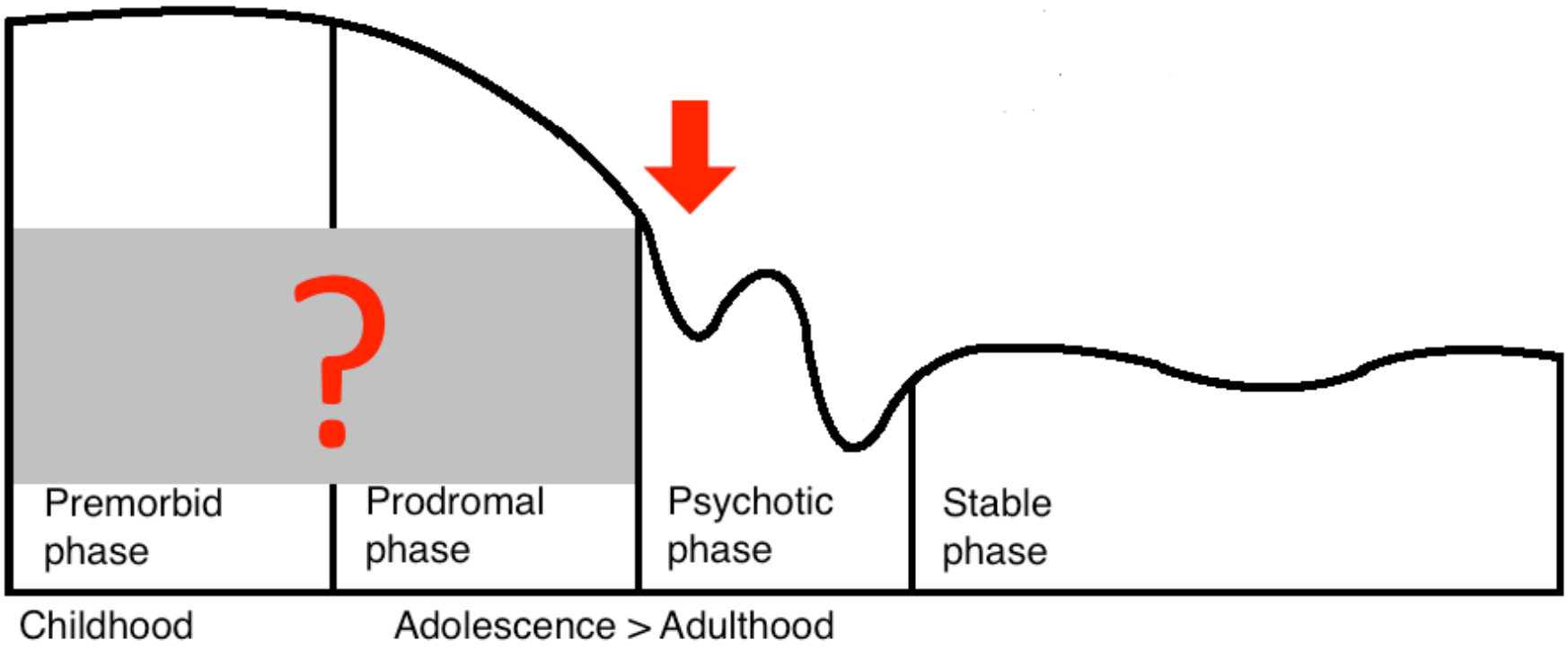
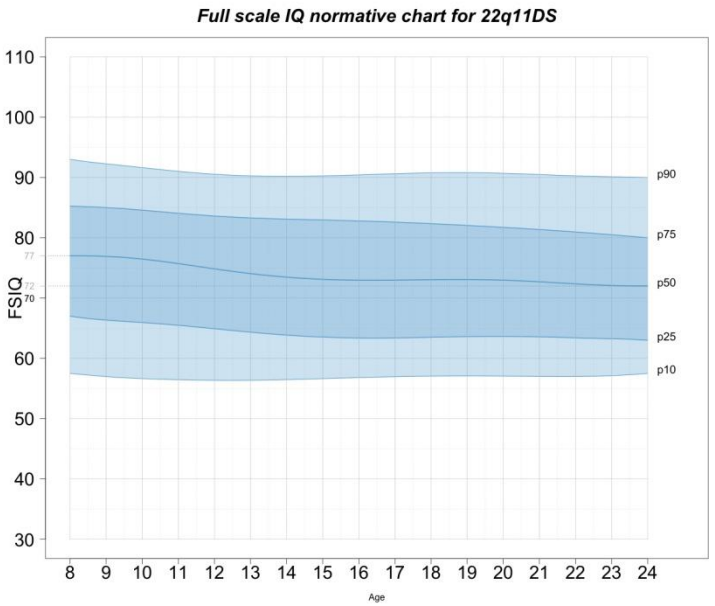


Courtesy J. Vorstman

22q IBBC
International 22q11.2 Brain Behavior Consortium

N=829

IQ (Wechsler) data



N=411
≥2 IQ measurements

AND
Psychiatric assessment

Without psychotic disorder (n=355)

With psychotic disorder (n=56)

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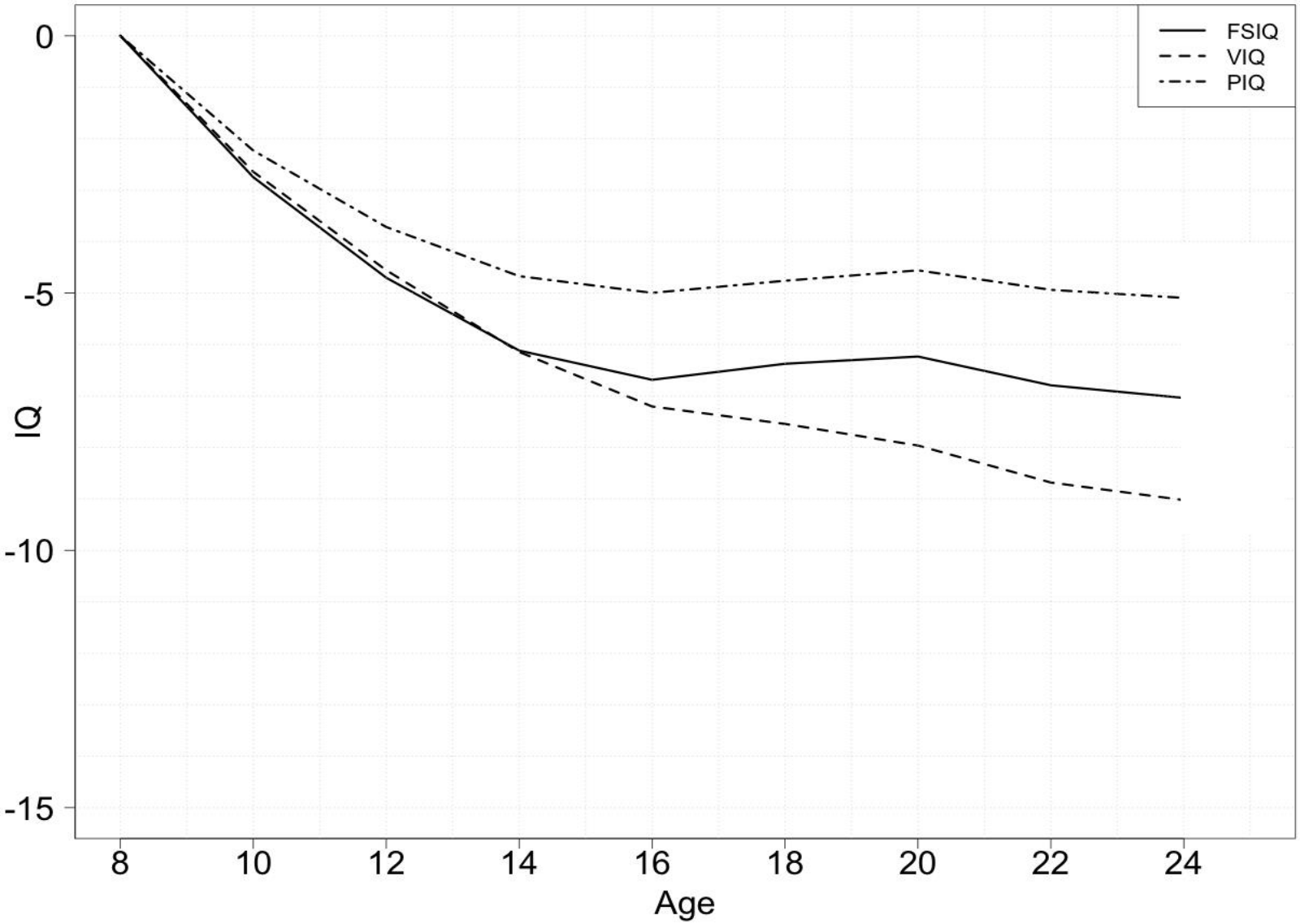
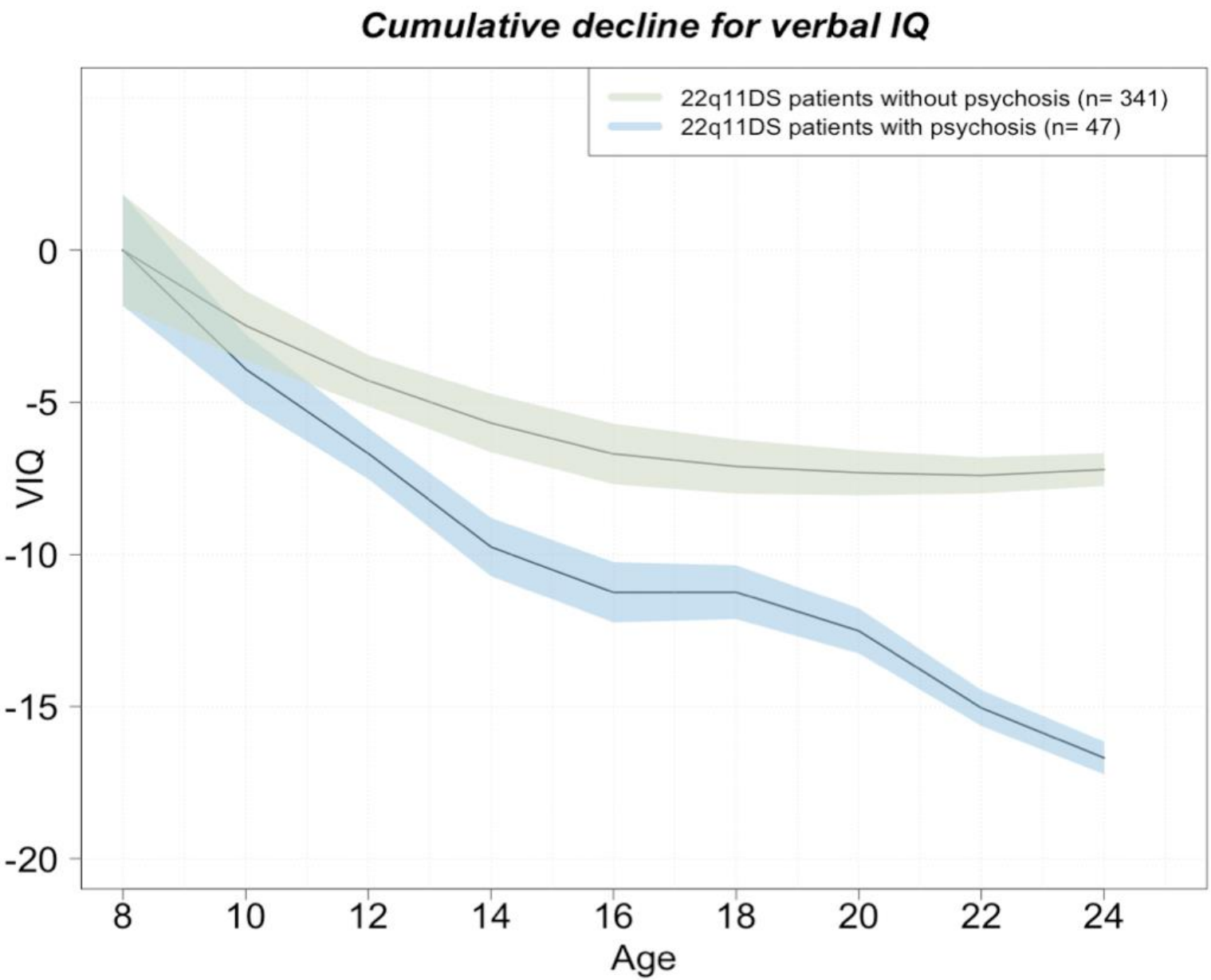
Overall cumulative IQ decline (FSIQ, VIQ, PIQ) in 388 individuals with 22q11DS




Cumulative decline for verbal IQ
22q11DS patients without psychosis (n= 341)
22q11DS patients with psychosis (n= 47)
0
-5
-10
-15
-20
VIQ
8
10
12
14
16
18
20
22
24
Age

Longitudinal studies on intelligence

From primary school/ early adolescence on

- "Growing into deficit"
- In subgroup, cognitive decline
  verbal decline >> (Duijff et al., 2012)
- ~ 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)

REVIEW

CURRENT OPINION

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.

Summary

- 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

22q IBBC
International 22q11.2 Brain Behavior Consortium

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

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NATIONAL INSTITUTES OF HEALTH

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