22q11 Deletion Syndrome across development

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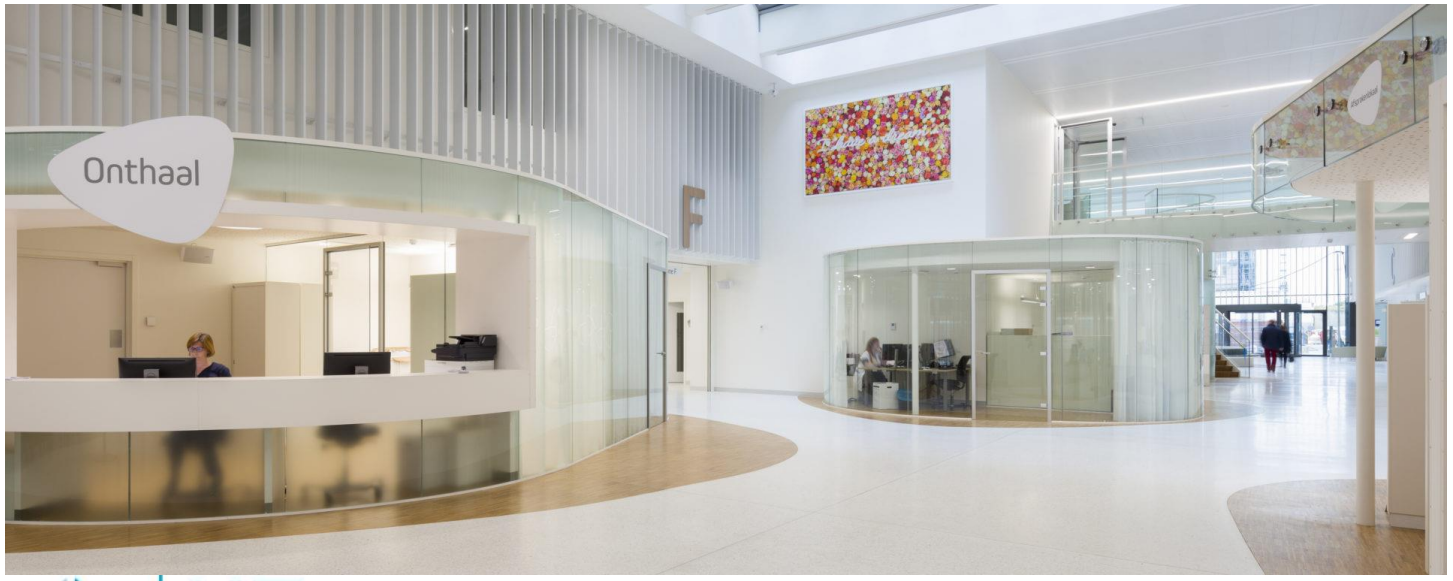

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Multidisciplinary care (the Leuven model)

- **Holistic focus (interaction body and mind + person and context)**
- **Early assessment of patient needs & psycho-education**
- **Multidisciplinary** consultations & meetings
- **Coordination and continuation of perzonalized care**
- **Anticipatory guidance and longitudinal follow-up**

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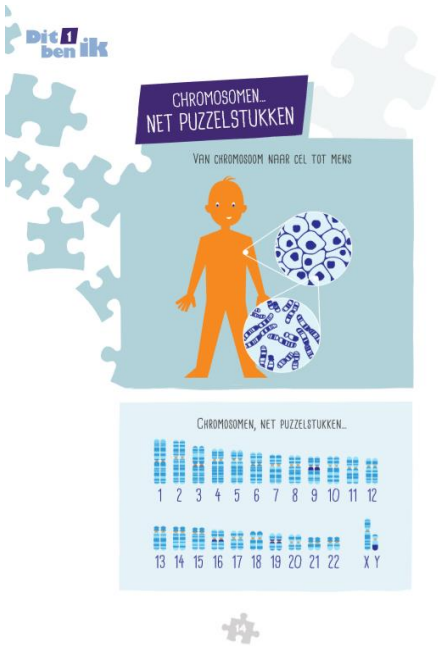
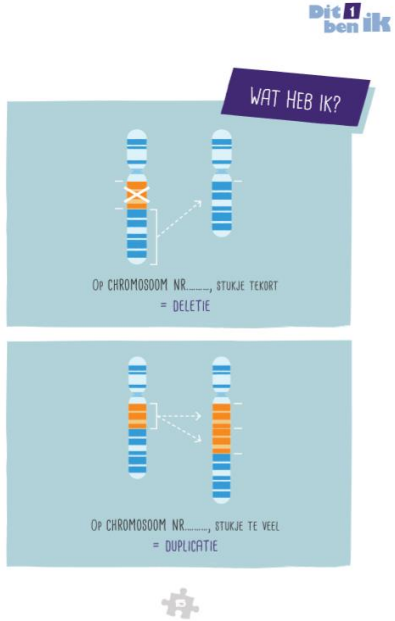
Early diagnosis and assessment of needs is an opportunity

- to start, organize and coordinate the personalized & multidisciplinary care for child and parents
- for (psycho)-education: inform and explain

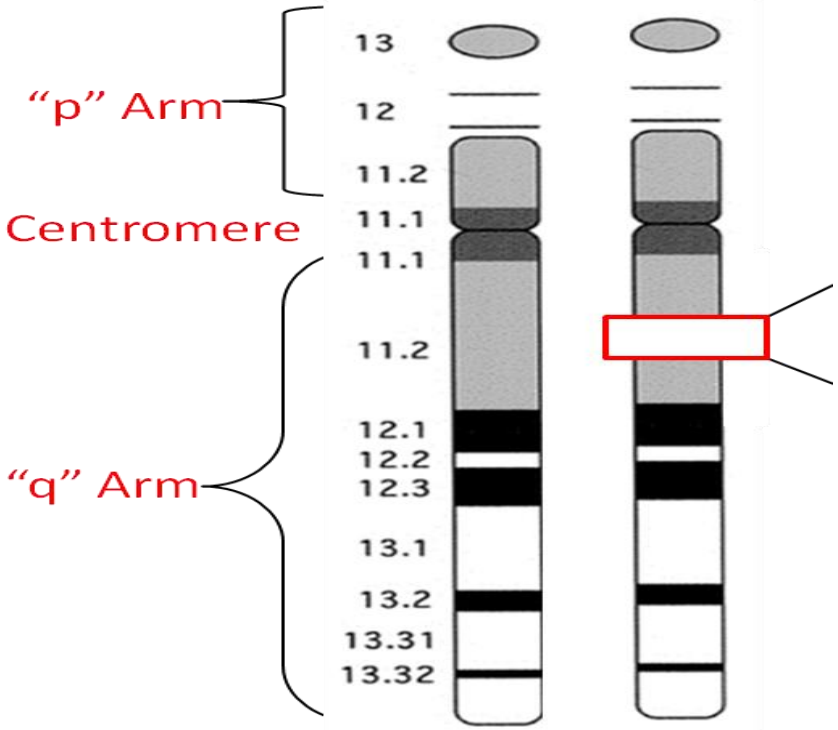




https://www.thegeneticpuzzle.eu

- to anticipate and manage the medical, psychosocial and educational needs

Chromosome 22



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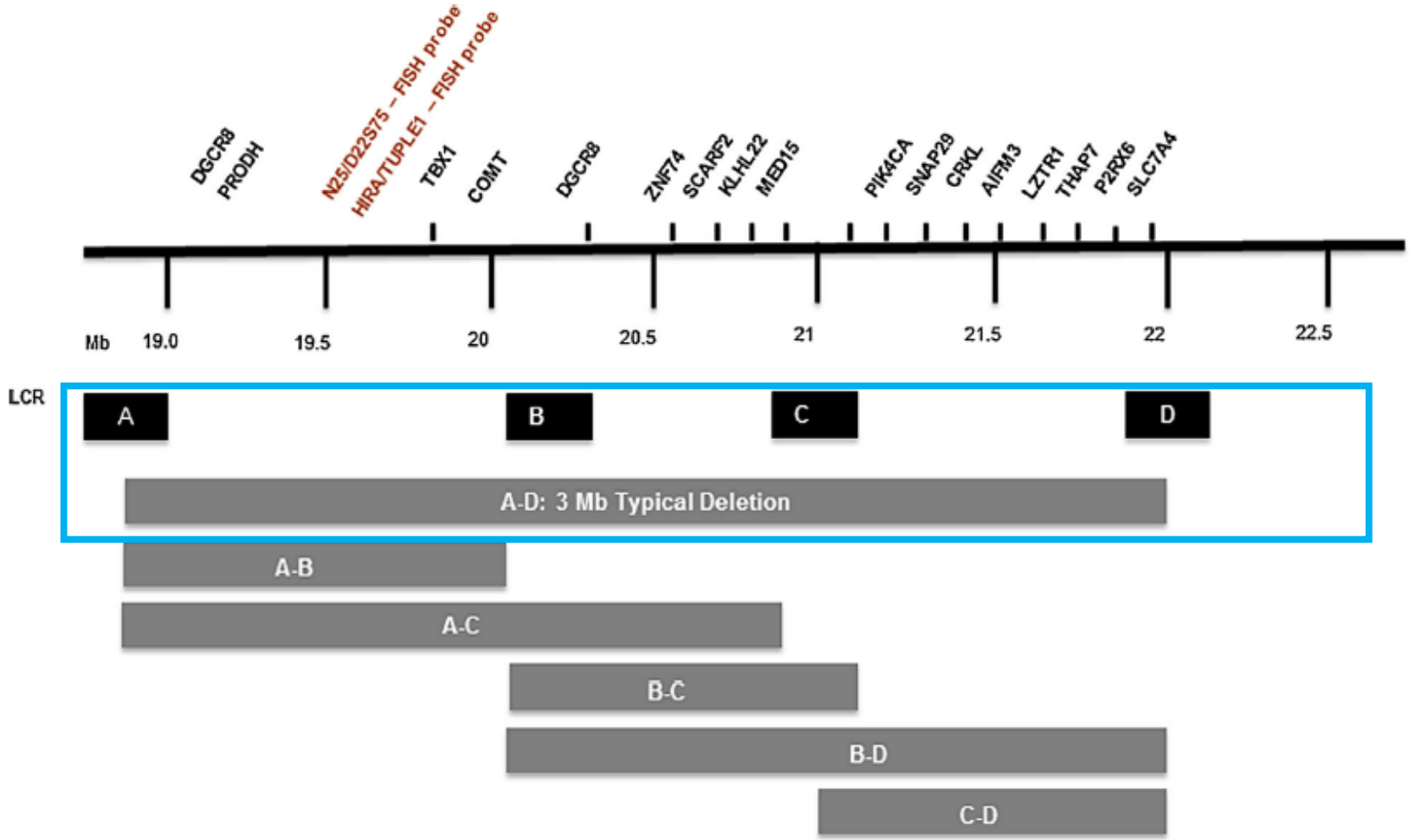


Figure 1. Low copy repeats, represented here as A, B, C, and D, bracket the 22q11.2 deletion and define the breakpoints with the standard ~3Mb 22q11.2 deletion extending from A–D. Atypical nested deletions include A–B, A–C, B–C, B–D, and C–D. Notable genes within the deleted regions of chromosome 22q11.2 include *PRODH*, *TBX1* and *COMT* within A–B and *SNAP 29* and *CRKL1* within C–D. Note that FISH probes D22S75 (N25) and HIRA (TUPLE1) are located within A–B and would be present in those patients with nested deletions excluding the A–B region.

Risk factors

Genes

Environment

Del22q11.2

Development
(cognition and behavior)

Protective factors

Time/development itself

MEDICAL CONCERNS

DEVELOPMENTAL/ BEHAVIORAL CONCERNS

In 22q11 DS…

DEVELOPMENTAL/ BEHAVIORAL CONCERNS

MEDICAL CONCERNS

In 22q11 DS…

MEDICAL CONCERNS

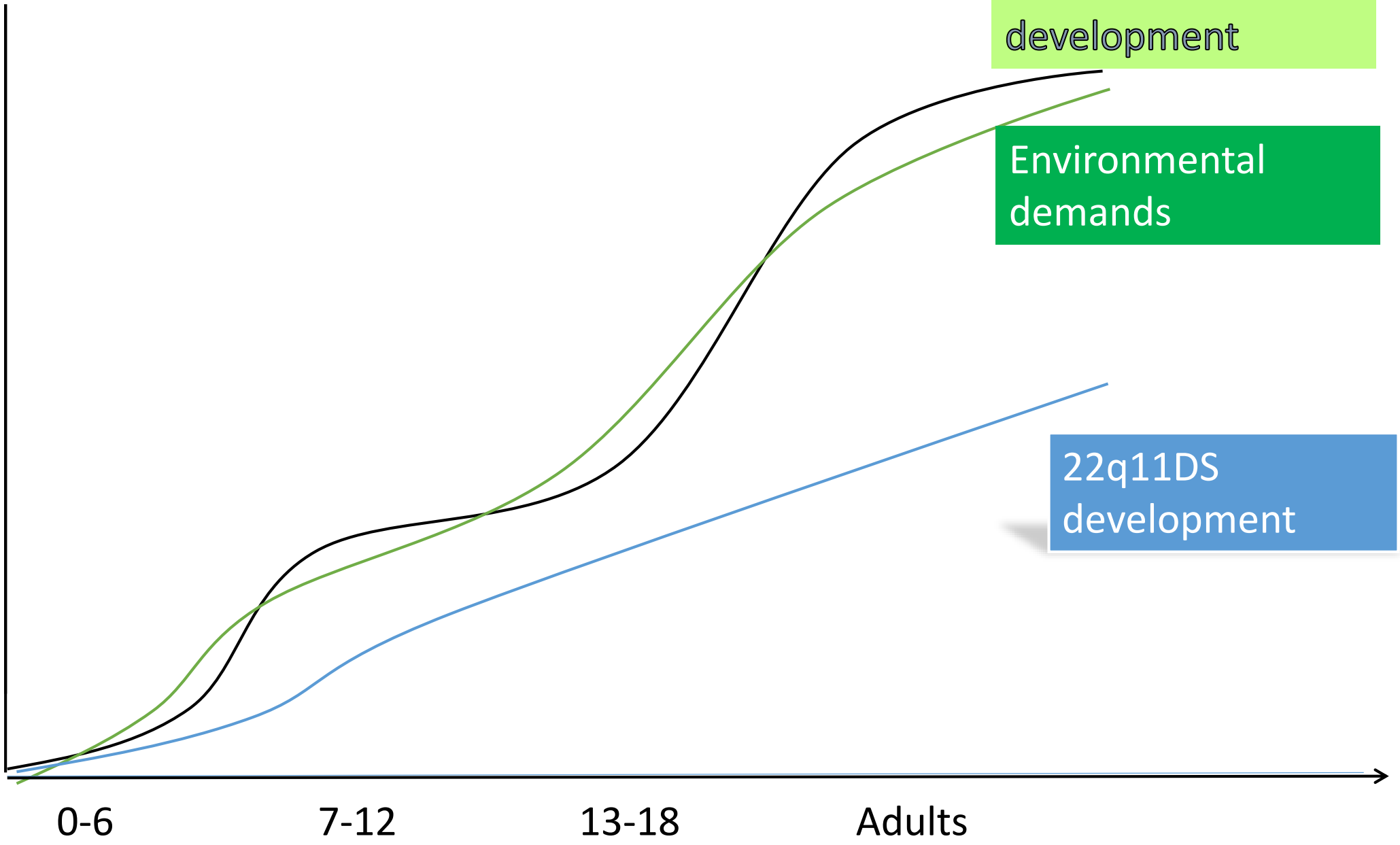
DEVELOPMENTAL/ BEHAVIORAL CONCERNS

In 22q11 DS…

Outline

- 1. Babies, toddlers and preschoolers (0-6y)
  - Medical/developmental concerns/needs
- 2. Primary school (6-12y)
  - Cognitive and educational challenges
- 3. Adolescence (13-18y)
  - Cognitive and educational challenges

1. Babies, toddlers and preschoolers (0-6 y)



Babies/infants with 22q11 DS (0-1y)

MEDICAL CONCERNS

Heart
Feeding
Low calcium
Immune system
Low muscle tone
Constipation

DEVELOPMENTAL CONCERNS

Slow growth and weight gain
Hypotonia/motor delay
Speech and language delay

Toddlers with 22q11 DS (1-2y)

MEDICAL CONCERNS

Heart
Feeding/hypernasal speech
Recurrent infections
Low muscle tone
Constipation
Audiogram @ 18m

DEVELOPMENTAL CONCERNS

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

Infants & toddlers with 22q11 DS (0-3y)

- Investigations/Diagnosis
  - Psychomotor assessment (BSID-II, PMDS-2) at 1y and 2y
  - Speech/language assessment (at 2y; check hearing !)

- **Guidance/support**
- Early intervention (preferably guidance @ home)
  - Physiotherapy/occupational therapy
  - Speech/language therapy (communication !)

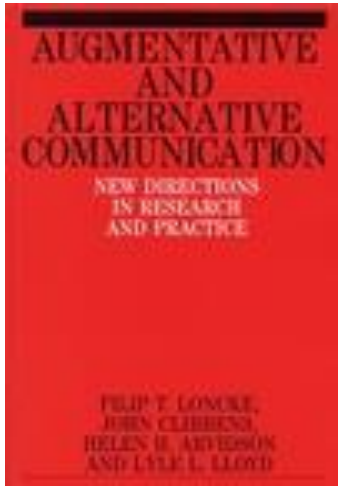
Physiotherapy and occupational therapy

Language therapy
“TOTAL COMMUNICATION APPROACH”

Augmentative and alternative communication (AAC)

e.g. SMOG/SWSS (Speaking With Support of Signs)

Filip Loncke (University of Gent, University of Virginia)



Preschoolers with 22q11 (3-6 y)

MEDICAL CONCERNS

Surgical correction of VPI
Kidney problems/urinary tract problems
Recurrent ear infections
Low muscle tone
Eye problems **(eye exam @ 3 !)**
Sleep problems !

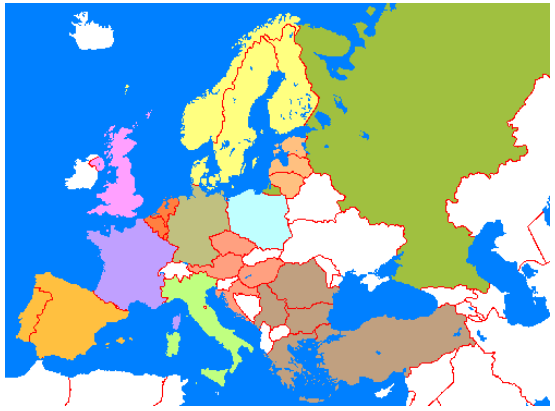
DEVELOPMENTAL CONCERNS

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

Good visual-perceptual processing and visual-spatial insight are important for:

- Motor skills

- Academic skills: pre-arithmetic skills, mathematics, geography,



- Daily living skills

- Social communication skills

Visual-perceptual skills in 22q11 DS:

- need more time to process visual information

- problems with recognizing objects when presented in unconventional way

Conventional

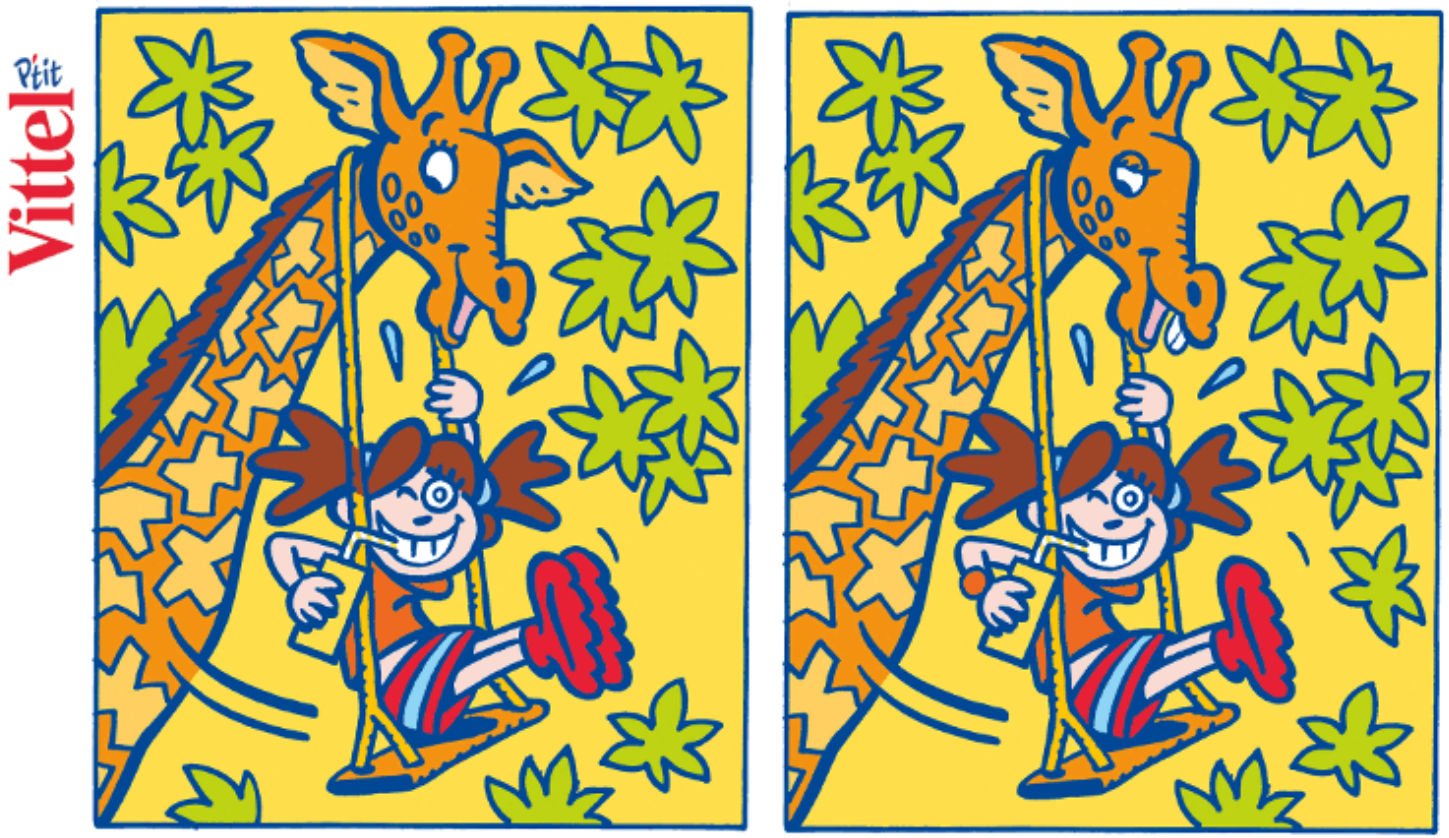
Unconventional

“worm, maggot”

“ear of an elephant”

Visual-perceptual skills in 22q11 DS:

- Problems in tasks with many visual stimuli (complex visual)

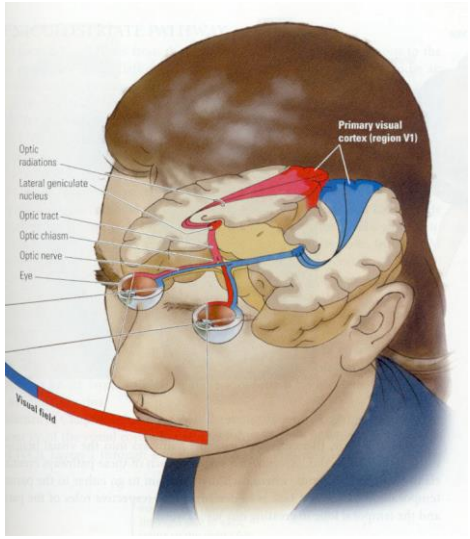


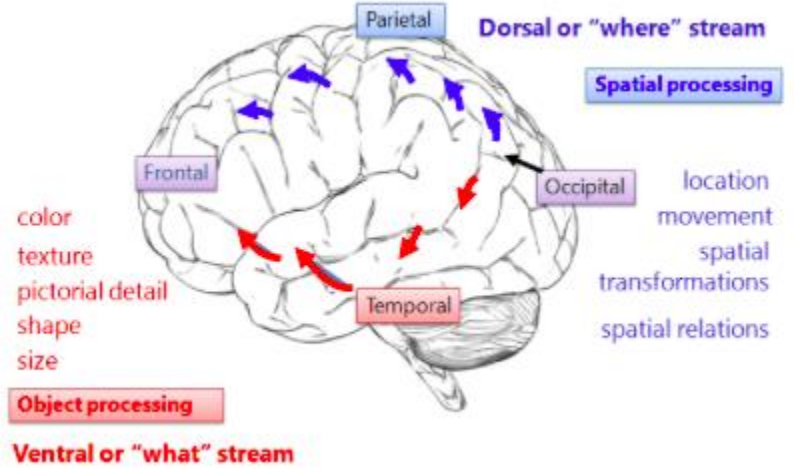
Visual perceptual problems in 22q11 DS

(both in children with problems with vision, and in children with normal vision)

- Need **more time for visual information processing**
- **Misinterpretation of objects** (presented in **unconventional way)**
- Problems with **visuo-motor integration**
- Problems with **spatial insight, spatial orientation, perceptual organization**

➡ Cortical visual impairment (CVI) = visual perception disorder caused by a lesion in the brain





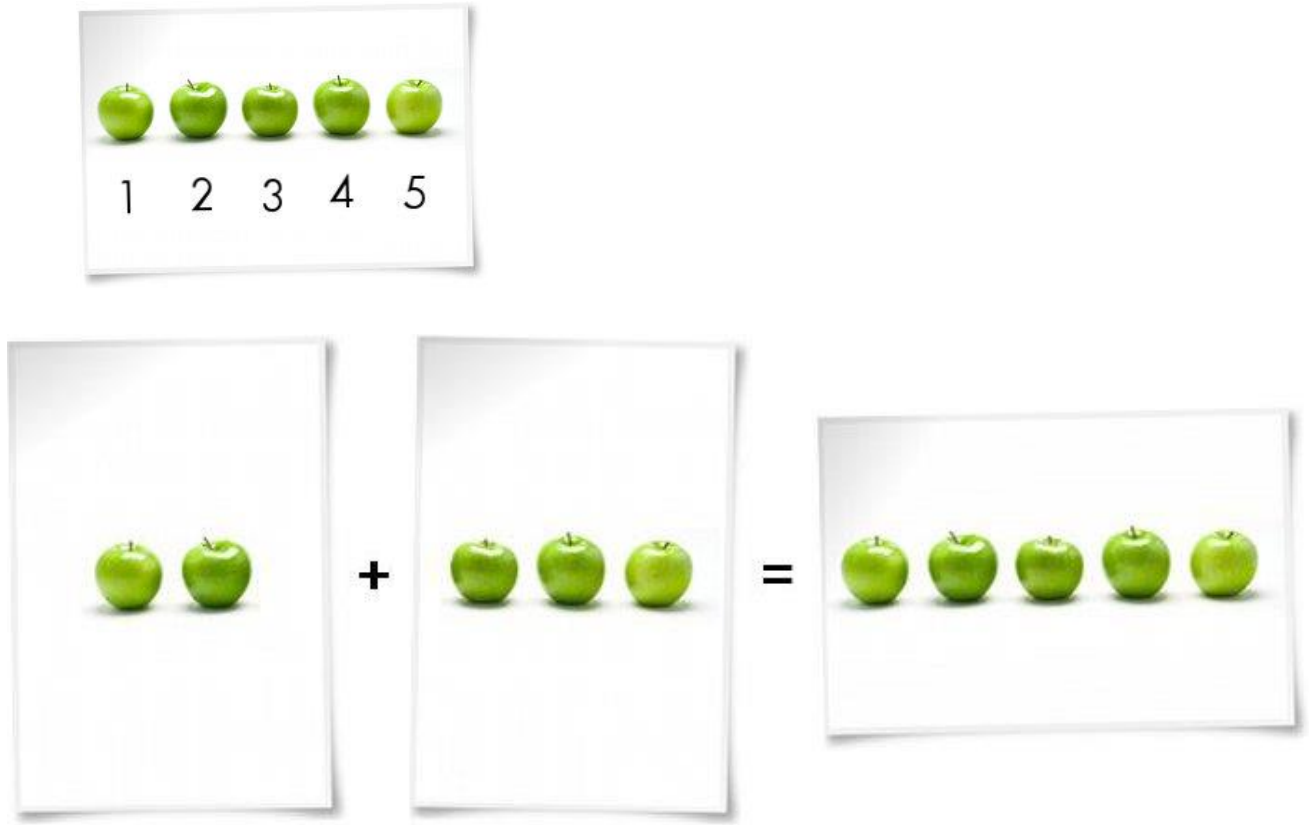
Recommendations

- Eye exam from age 3 on (to exclude or diagnose vision problem)
- Be alert for signals of visual perceptual problems
- Observe visual perception: at home, in class, during play etc…

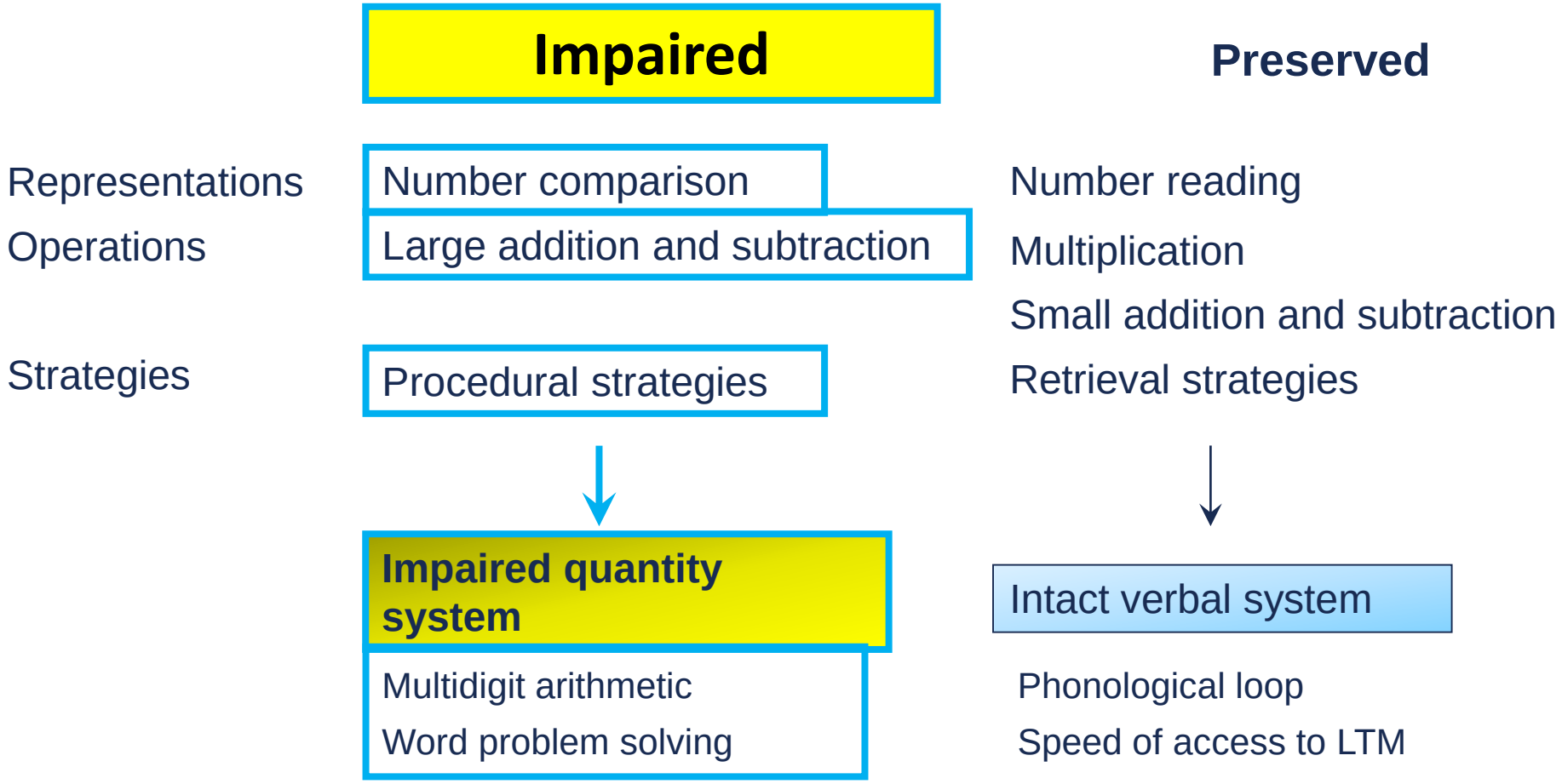
- In case there are several elements present suggestive of visual-perceptual problems:
  - Specific CVI- assessment (CVI= cortical visual impairment) from 4 years on

Pre-arithmetic skills and mathematics in 22q11.2 DS

- Problems with number sense, awareness of “amount”



In 22q11DS:



De Smedt & Swillen, 2009, *Cortex*

Preschoolers with del22q11 (3-6 y)

- **Guidance/support/ Remediation**

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

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RESEARCH REVIEW

WILEY AMERICAN JOURNAL OF medical genetics PART A

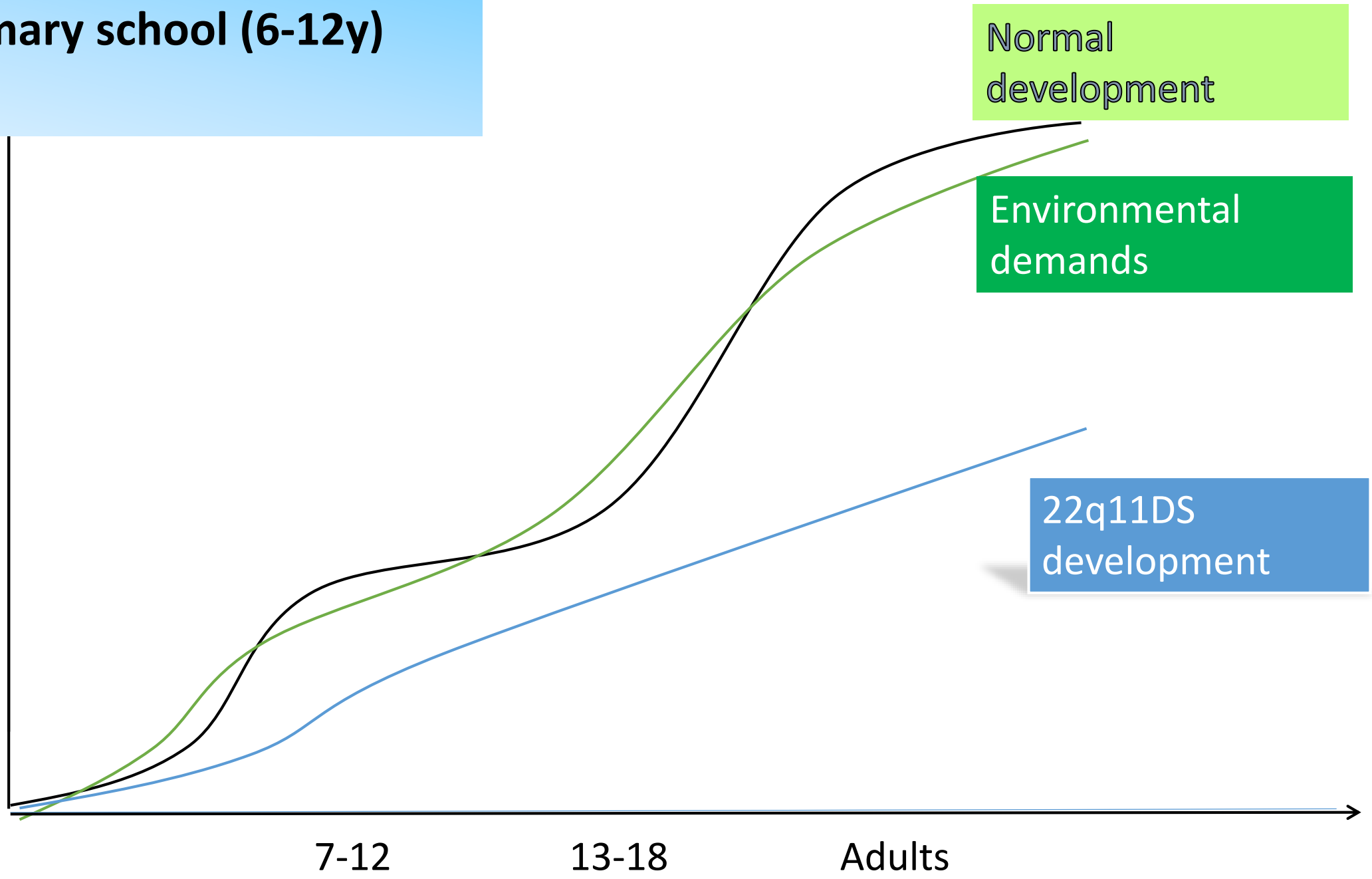
Neurodevelopmental outcome in 22q11.2 deletion syndrome and management

Ann Swillen[1] | Edward Moss[2] | Sasja Duijff[3]

TABLE 1 Treatment recommendations for improving neurodevelopmental outcome in 22q11 DS during infancy and early childhood (0–6y)

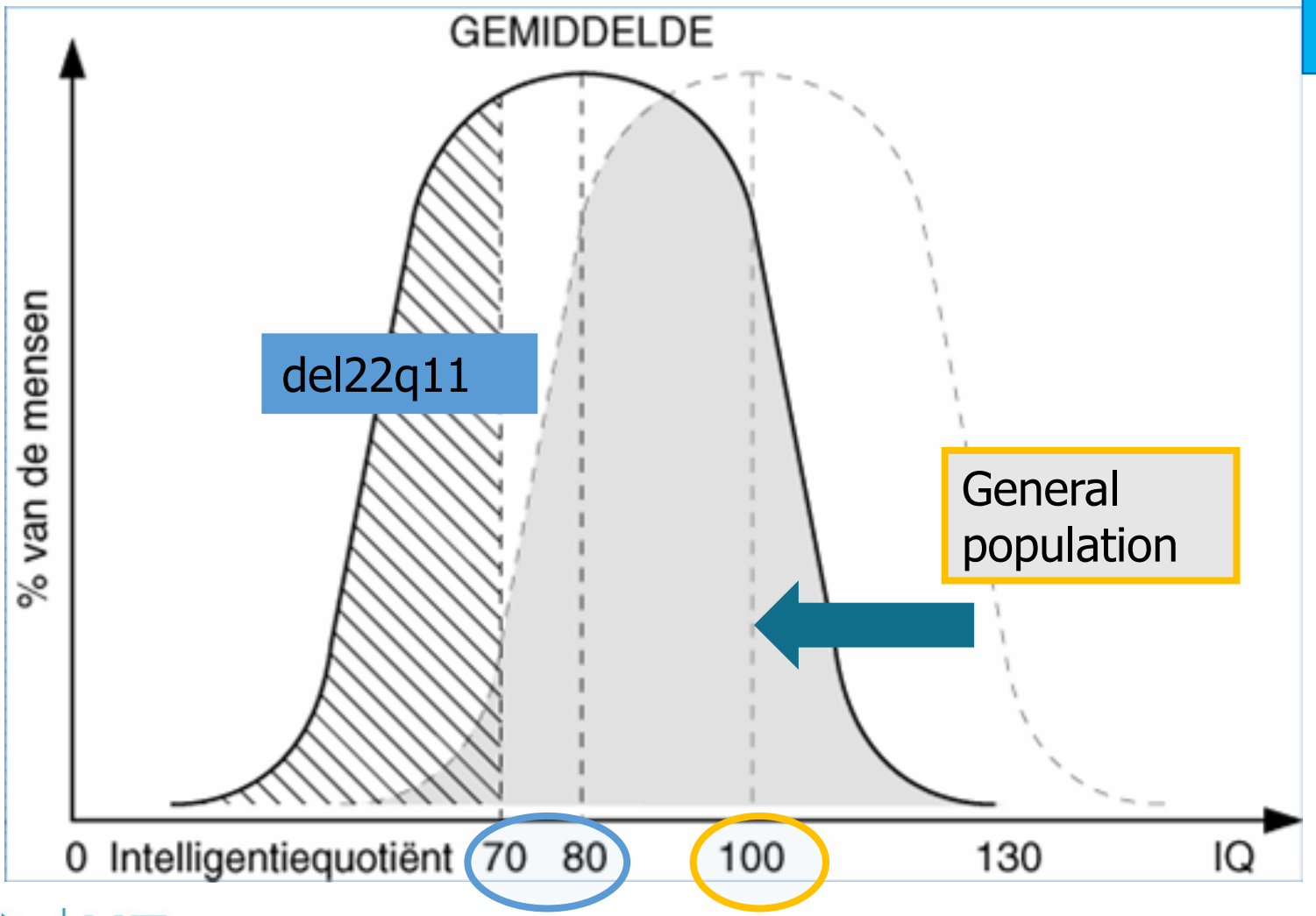
Developmental area	Developmental features	Treatment recommendations
Motor development	Hypotonia and neuromotor deficits	Physiotherapy, occupational therapy, and sensory integration therapy from early age on
Feeding	Poor sucking, nasal reflux, and oral motor coordination problems	Medical guidance/monitoring of feeding problems Feeding advice (feeding specialist with expertise in 22q11 DS)
Speech and language	Impaired speech and language development, hypernasality, high-pitched voice, and compensatory speech	Speech and language therapy, total communication approach (verbal, non-verbal, and sign language in combination with oral speech) (Solot et al., 2001) In the case of severe hypernasality, a pharyngoplasty is sometimes required
Neurodevelopment/ Cognitive development	Varying degree of impairment (from borderline development to mild–moderate ID)	Educational monitoring Early childhood specialist Anticipatory guidance
Social–emotional development and social skills	Emotionally reactive Problems with regulation of emotion and behavior Socially withdrawn, poor peer relations, self-directed behavior Social anxiety and general anxieties	Provide a secure and highly structured environment Infant mental health intervention Play therapy (structured play to promote social play) Structured (social) group experience
Attention	Easily distracted, impulsiveness	Structured (learning) environment Environment free from stimuli Use visual aids to improve sustained attention (sand timer; time-timer, etc.)

2. Primary school (6-12y)



Cognitive shift in 22q11 DS

7- 10/12y



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Cognitive profile (n =103) (4-16y)

- 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/perception and visuo-motor skills and problems with speed (slow working)

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.

Divergent Developmental/ cognitive trajectories

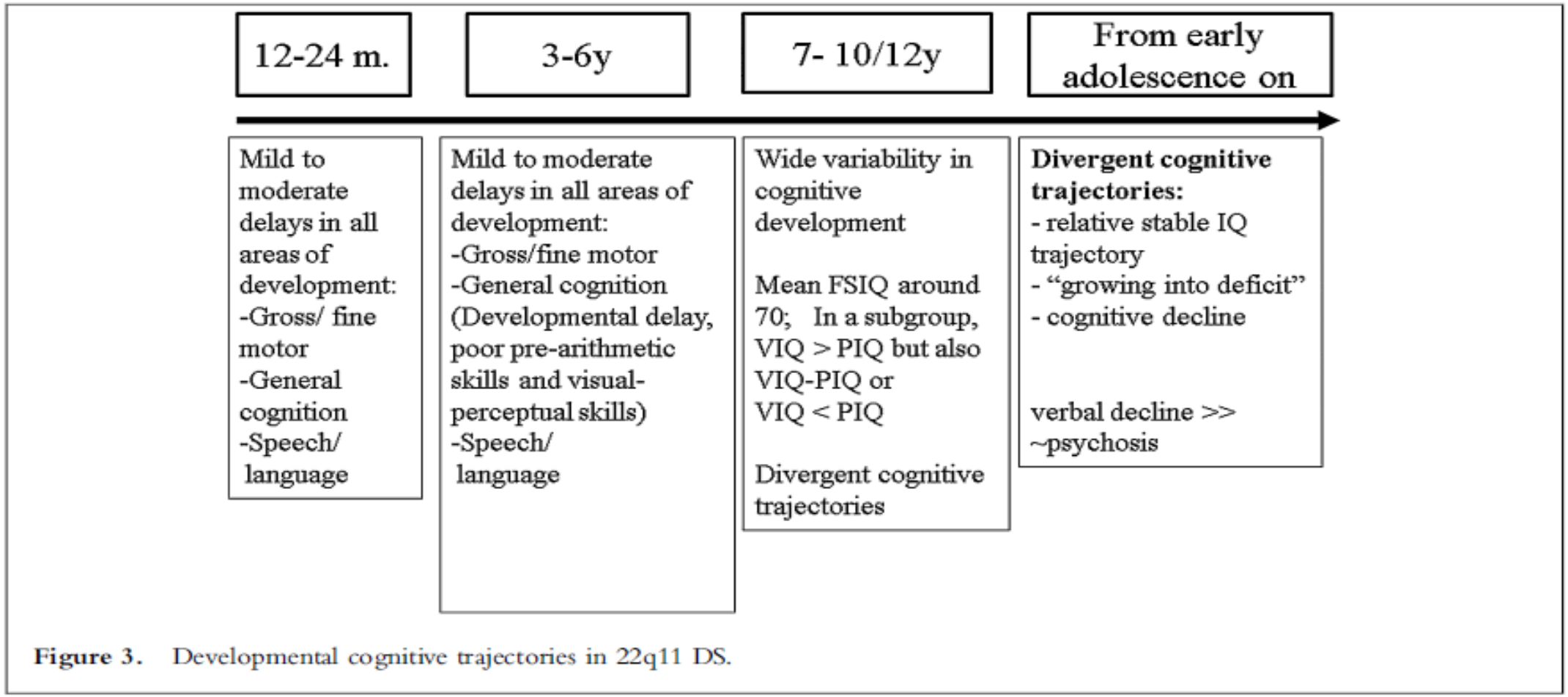
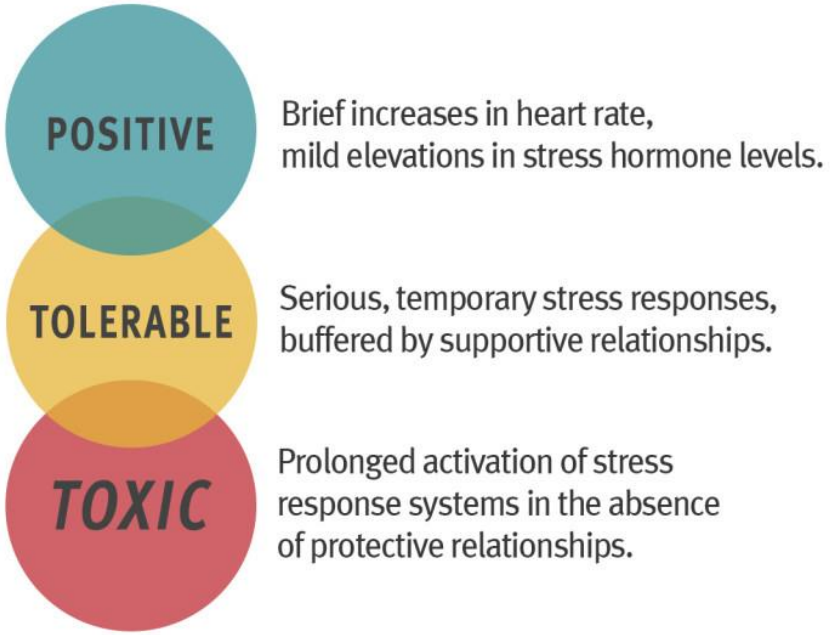


Figure 3. Developmental cognitive trajectories in 22q11 DS.

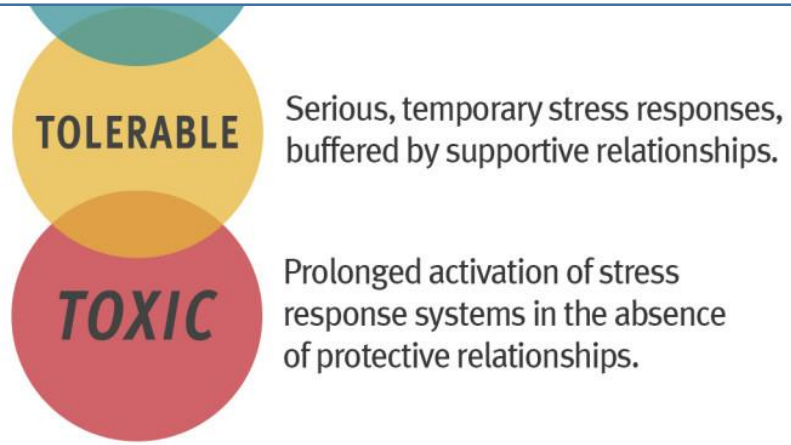
Sensitivity to stimuli and stress

Typically developping people



Individuals with 22q11 DS have a higher sensitivity for stimuli (overwhelmed/under-/; hyper-/hypo-; and for stress)

22q11 DS



Cognitive & social emotional challenges in 22q11 DS (7-12 y)

- academic problems: arithmetics and reading comprehension
- good (technical) reading skills and good verbal (STM) memory but problems with verbal comprehension

- problems with abstract thinking/ problem-solving
- poor attention and concentration (ADD)
- problems with starting, initiating,…
- deficits in visual-perceptual abilities
- social communication challenges/ ASD

(Swillen et al., *Child Neuropsychology*, 1999; 2005; Desmedt & Swillen , 2007; 2008)

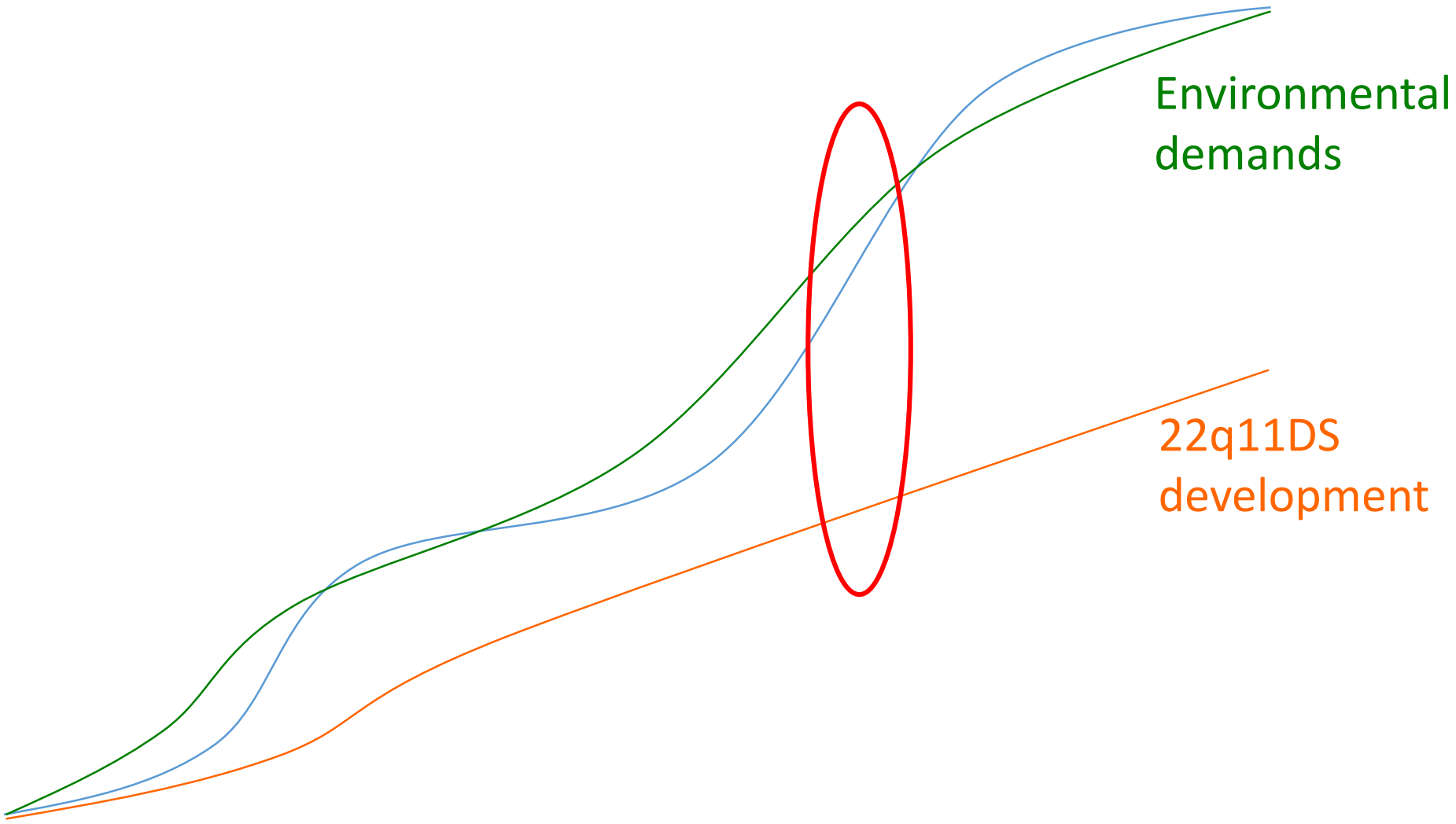
Practice and management (learning)

- 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

3. from early adolescence on (13-18y)



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

- **Learning problems increase with age**

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

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

ARTICLE

Developmental Trajectories in 22q11.2 Deletion

ANN SWILLEN AND DONNA McDONALD-McGINN

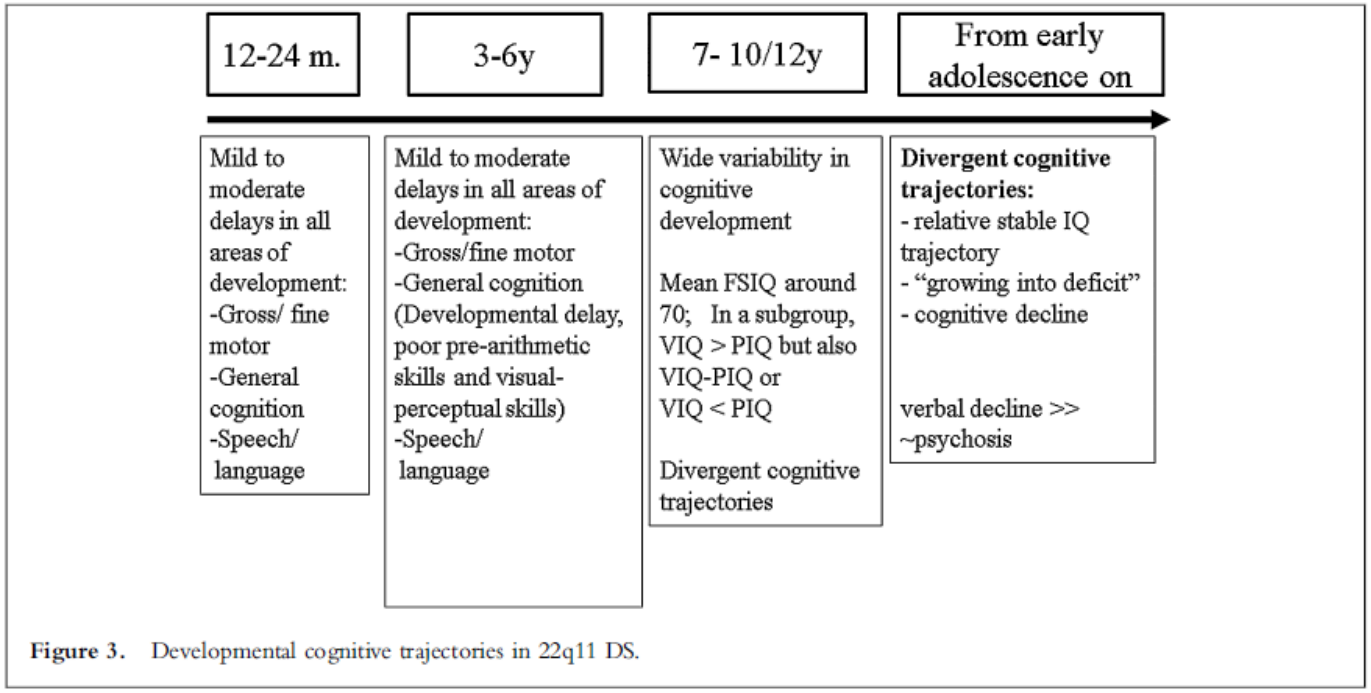
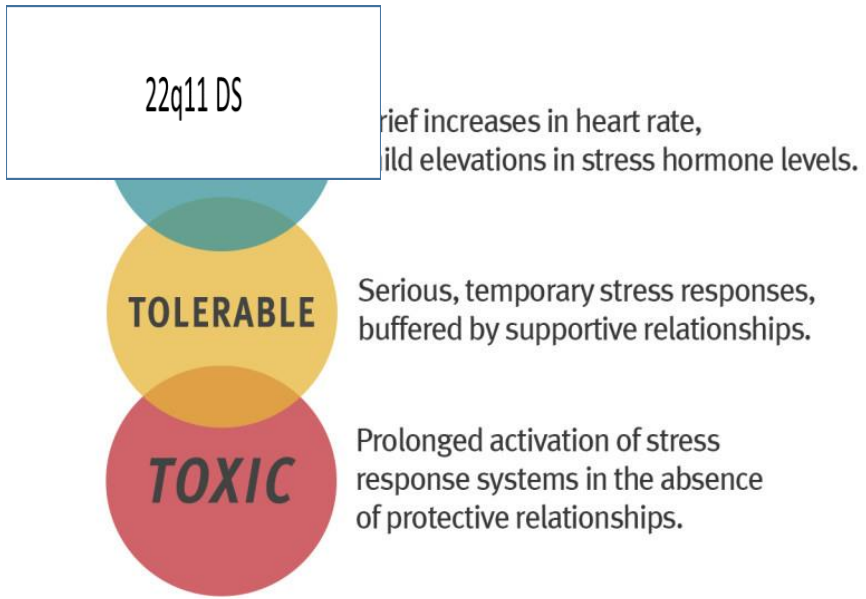
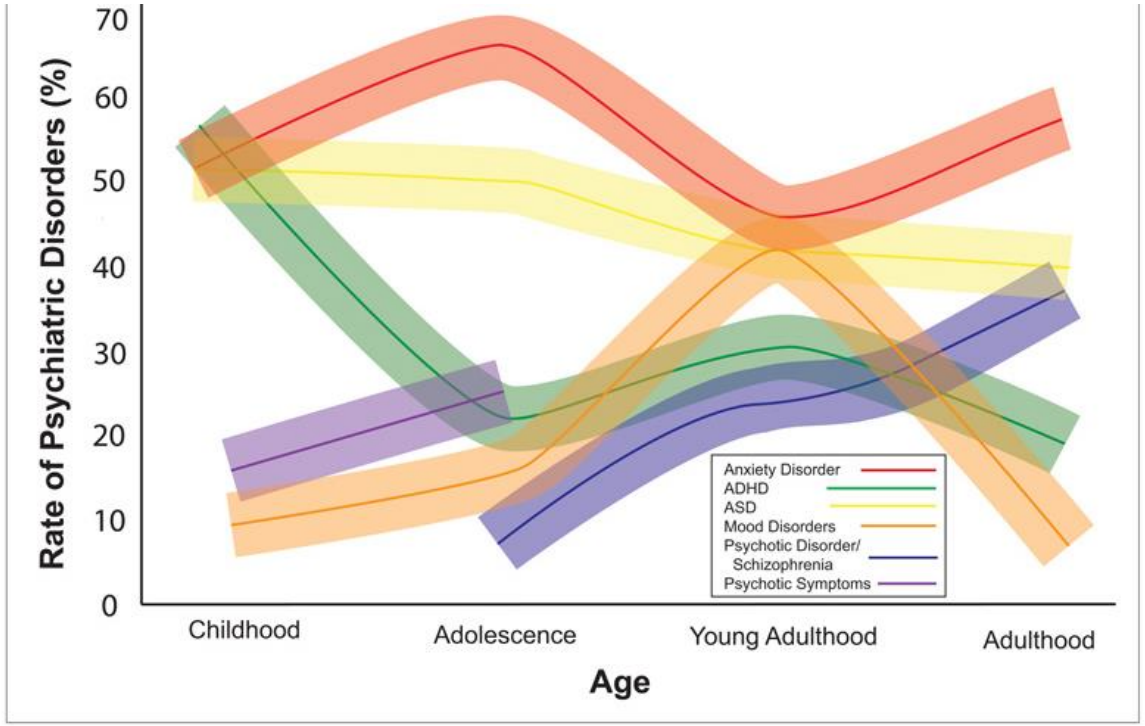


Figure 3. Developmental cognitive trajectories in 22q11 DS.

4. Risk for psychiatric disorders in 22q11 DS

Individuals with 22q11 DS have a higher sensitivity for stimuli (overwhelmed/under-/; hyper-/hypo-; and for stress)

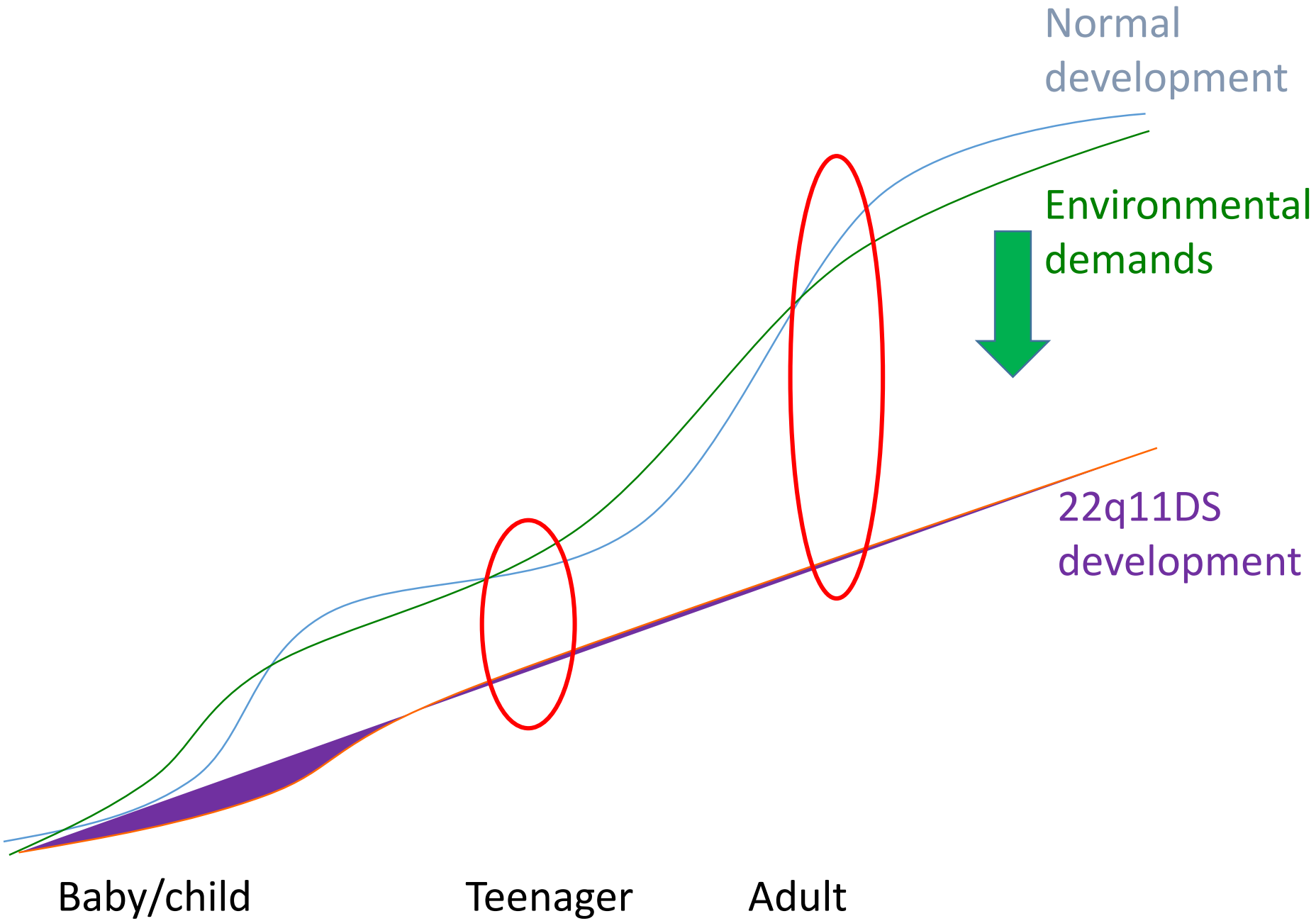




Jonas R, Montojo C, Bearden C. The 22q11.2 Deletion Syndrome as a Window into Complex Neuropsychiatric Disorders Over the Lifespan. Biological Psychiatry. 2014;75(5):351-360.

Recommendations and support for adolescents

- Offer **structure and security**
- « **Match** » **abilities – school/work environment**
- **Be alert for and pay attention regarding bullying**
- School
  - **Psychoeducation** teachers/pupils
  - Adapt curriculum/ extra support, facilities; part-time school (cfr. fatigue)
- Work:
  - **Psychoeducation**
  - Part-time jobs ! (cfr. fatigue, medical problems)
  - Jobcoach
  - Volunteers'work


Normal development
Environmental demands
22q11DS development
Baby/child
Teenager
Adult

Psycho-social challenges (13-18y, 18+)

- Psycho-socially:
  - Shy, withdrawn behaviour
  - Emotional vulnerable and emotionally labile
  - Social and communication impairments:
    - Poor relations with peers
    - Poor verbal and non-verbal communication

Dependent

Poor self-concept

Not confident

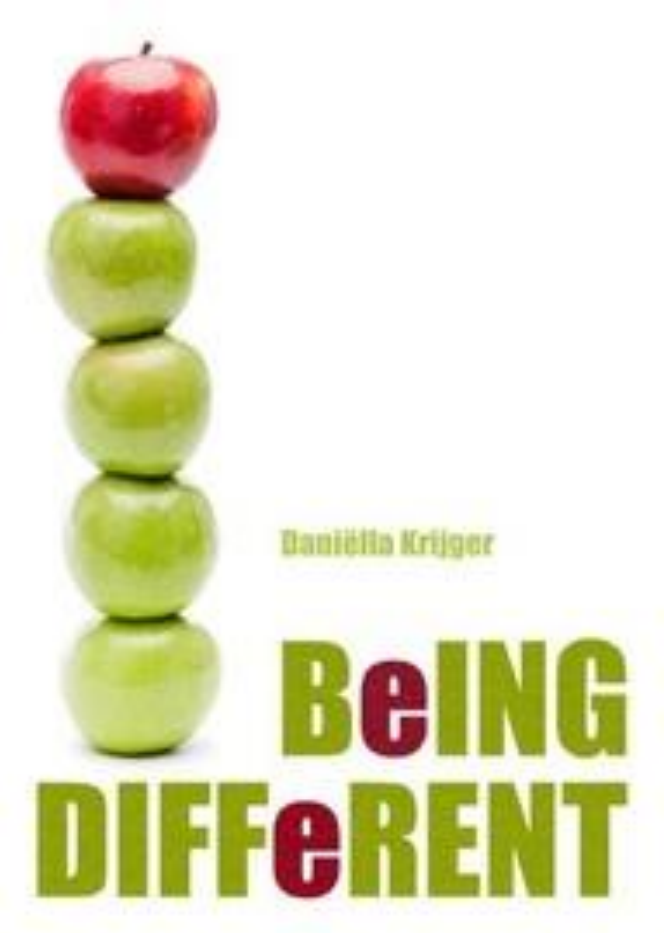
Support for teenagers

- **Talk** to your child/teenager, **explain (psycho-education !)**
- Encourage the development of a **REALISTIC self-concept** (= crucial !)
- **Encourage and practice social skills**
- Encourage and **practice daily living skills** (including basic safety skills)
- **Hobby** ! (music, sport, photography, animals (pets/horses/dogs,….)
- Contact with other teenagers/young adults with 22q11 DS
- Find an **appropriate educational/vocational track**
  - (normal) school/workcircuit + support
  - special school/sheltered work
  - written information about the needs/ necessary adaptations,……

…..

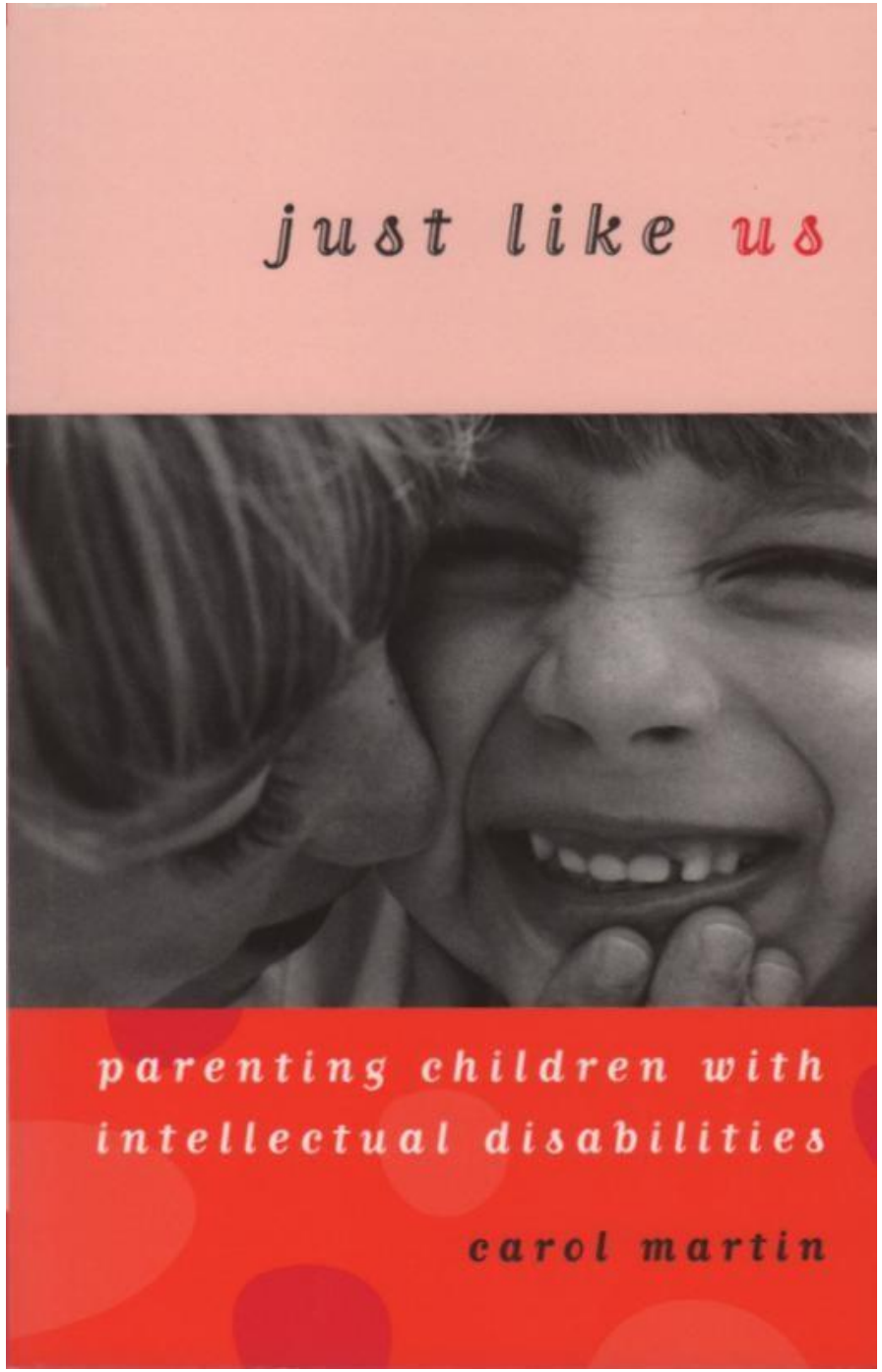
Support for parents

- Support in working through attitudes, feelings and uncertainties about their child's abilities/disabilities
- Support parents in acceptance of the disability and limitations of their child ("develop a realistic and adequate image")
- **provide parents knowledge on "puberty/adolescence" and "p/a in del22q11DS"**
- encourage parents to foster more skills of independence according to their children/adolescent's developmental level
- Importance of sexual education for their children (sexuality in a healthy and protective way)
- Information on resources, legal issues (guardianships, ….)



Growing up with impairments

http://www.hoezoanders.nl/



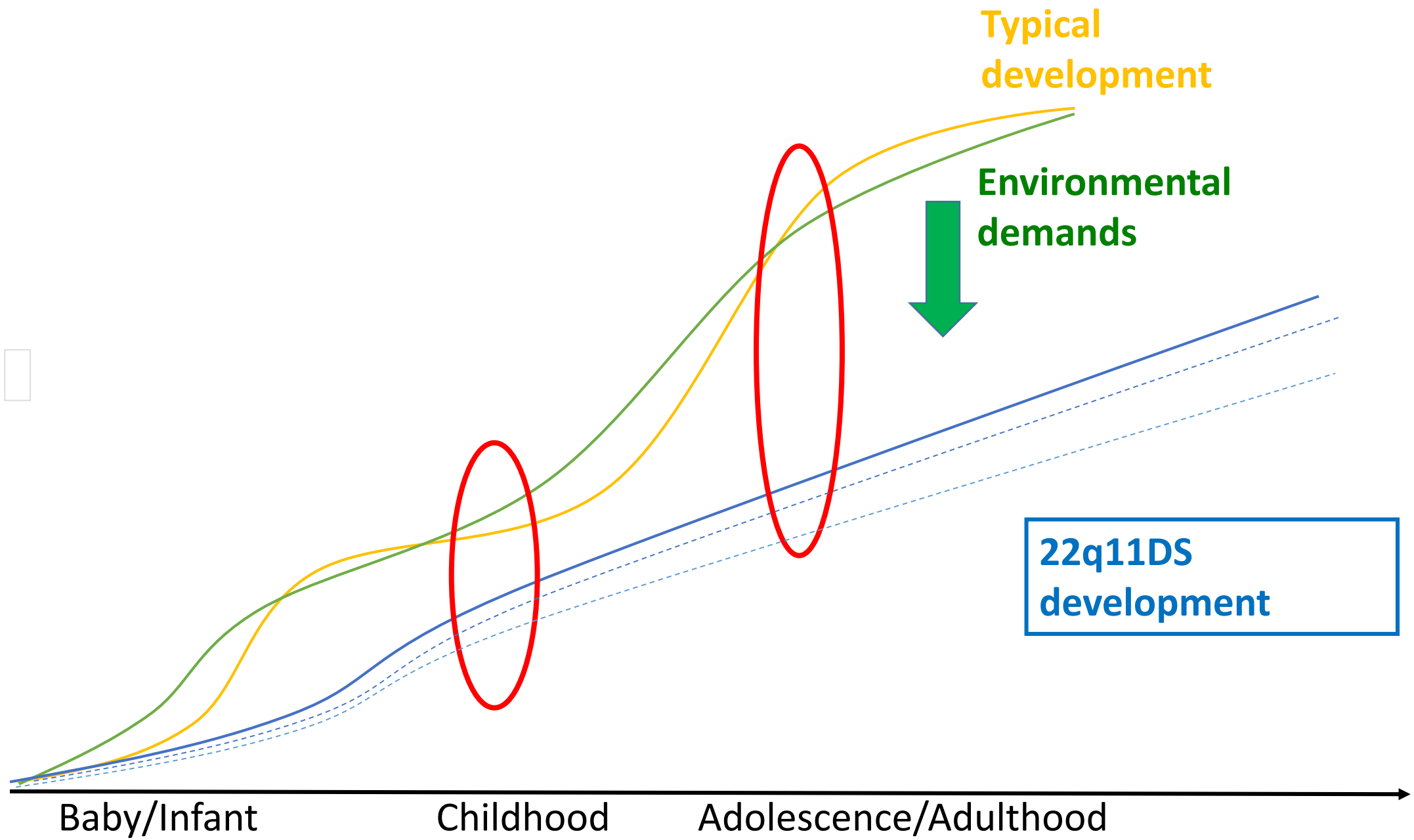
Conclusion:

From infant to adult with 22q11 deletion (22q11 DS):

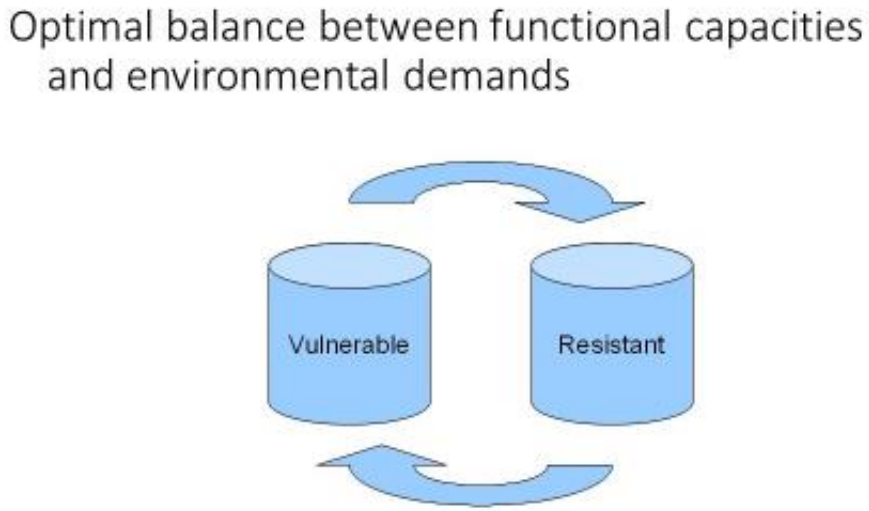
→ **wide variability**

* medical features (clinical phenotype)

* cognitive, behavioural/social-emotional features (behavioural phenotype)


Typical development
Environmental demands
22q11DS development
Baby/Infant
Childhood
Adolescence/Adulthood

- The care = personalized care



- Information & psycho-education, follow-up, support and a coordinated care by a multidisciplinary expert network/team are indispensable.

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https://www.kuleuven.be/labbehaviourandneurodevelopment

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LABORATORY FOR BEHAVIOUR AND NEURODEVELOPMENT

Understanding Neurodevelopment in 22Q and other CNV's

A major concern of families of patients with a rare disease is the risk of developing a developmental disorder including intellectual disability (ID) and psychopathology. Developmental disorders (DD) are broadly defined as cognitive and/or behavioral conditions that have early onset in childhood and include language disorders, intellectual disability, motor disorders or autism spectrum disorders. In a subgroup of patients, these rare diseases are caused by rare recurrent Copy Number variations (CNV's). Psychopathology in CNVs encompasses emotional, perceptual, motor, behavioral and social disruptions in domains that cut across traditional diagnostic categories Rare developmental disorders collectively mean an important physical, psychological and socio-economic burden to patients, families, and society. The multi-system nature of many rare recurrent CNVs requires a multidisciplinary clinical care and research approach.

Team leader

Ann Swillen is professor at the Department of Human Genetics, KU Leuven and at the Department of Rehabilitation Sciences, KU Leuven (University of Leuven, Belgium).

Trained as an educational psychologist, she is also affiliated to CME-UZ (the clinical unit of the Department of Human genetics), an international centre of excellence in the field of clinical and molecular genetics.

She has more than 25 years of experience and expertise in clinical follow-up and research of neurodevelopmental disorders such as intellectual disability (ID), developmental delay (DD) and autism spectrum disorders (ASD) in children, adolescents and adults with pathogenic Copy Number Variants (CNV's) such as microdeletions and - duplications (22q11.2 deletions and duplications, 16p deletions and duplications, 22q13 deletions, etc.) resulting in more than 100 scientific papers on neurodevelopmental disorders and behaviors in CNV's. She teaches courses on" Developmental Psychology" and on "Psychopathology in children and adolescents" . She has obtained funding(from FWO, NIH, Lejeune Foundation, Marguerite Delacroix Foundation, KBS,…, and supervised over 7 PhD students, of which 2 of them became independent professors.

KU Leuven 22q11 DS/Vecarfa Fund

Ann Swillen is holder of the 22q11 DS/Vecarfa fund at the KU Leuven, in order to raise awareness and multidisciplinary care and guidance for families with 22q11 DS.

Deletie syndroom 22q11.2

'Samen leggen we de puzzel'

Upcoming meetings

June 23 - 26: International 22q11 DS research meeting in Croatia

Questions ?

ann.swillen@uzleuven.be

Partnership & team spirit between clinicians and researchers

Thank you patients and families, clinicians and researchers of multidisciplinary 22q11 DS team/lab @

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