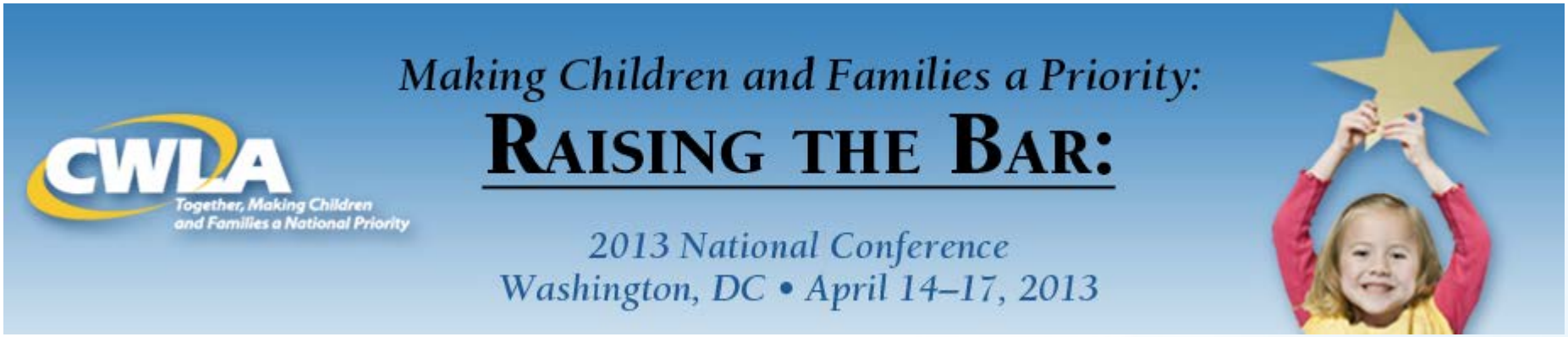
Early Detection of Childhood Schizophrenia: What This Might Mean for Our Work

April 17, 2013



Michel Maziade, M.D., FRCPC, C.Q.

Canada Research Chair in the Genetics of Neuropsychiatric Disorders,
Full professor of Psychiatry, Faculty of Medicine, U. Laval
Director, Centre de recherche Université Laval Robert-Giffard

Centre de santé et de services sociaux de Québec-Nord

UNIVERSITÉ LAVAL

Institut universitaire en santé mentale de Québec

“What is a child. An experiment. A fresh attempt to produce the just man made perfect: that is, to make humanity divine”

George Bernard Shaw

One Way to “Raise the Bar”

There is only one way to “raise the bar” in our individual practice to help children

- **Turning toward evidence-based interventions is the first necessary step**

The Child Seen Under A Very Particular Angle

- Angle of Science of Neurodevelopment

- From the standpoint of major psychiatric disorders
  - Schizophrenia
  - Bipolar disorder (manic-depressive illness)
  - Major depression

DSM-IV

SCHIZOPHRENIA

Symptoms

- Delusions
- Hallucinations
- Disorganized speech
- Social withdrawal
- Persistence of symptoms for at least six months

BIPOLAR DISORDER

Symptoms

- Manic episode
  - Abnormally elevated or irritable mood
  - Inflated self-esteem or grandiosity
  - Reduced need of sleep
  - Distractibility
  - Flight of ideas
  - Increase in goal-directed activity
  - Impairment in social functioning

Children May Be Disadvantaged in Two Ways

- **They may suffer from having a parent affected by one of these diseases**
- **They may be themselves at high risk of developing the disease**

Our Challenge

- **4% of the general population:**
  - **prevalence of schizophrenia, bipolar disorder and recurrent depression**

- **16 millions of people in North America**
- **40 million in the G7 nations**

} **Will develop the disease in young adulthood**

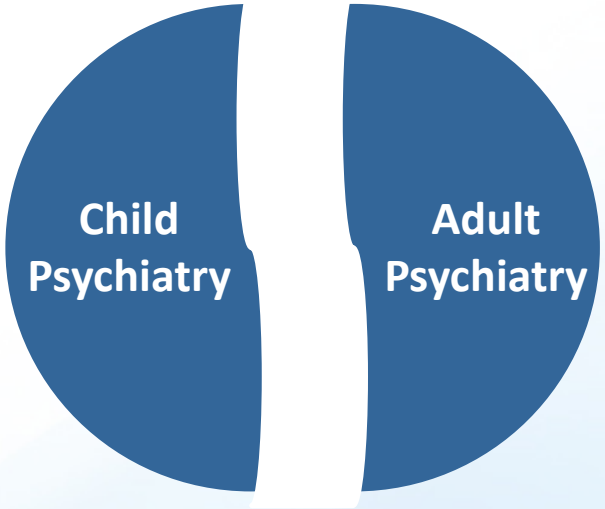
- **Health costs:**
  - **Annual Total Direct and Indirect Costs of Serious Mental Illness > 317 billions / year in the US (source NIMH website)**
  - **Mental health direct costs = 57,5 Billion $/ year in the US**
  - **Overall costs for schizophrenia alone ~ 62 Billion $ in the US**
    - **Direct costs for schizophrenia alone ~ 7 Billion $ in the US**

Schizophrenia Is A Child

- **40+ millions of today's two year-olds will be affected by schizophrenia or bipolar disorder by 2035-2065**
- **What do we all do about this fact?**
- **It is a neurodevelopmental brain disorder**
  - **Early genetic and environmental hits in the child development will deliver their full impact in young adulthood**

Barriers to Overcome

- **Barriers are legal and administrative**
  - **Little transition between child mental healthcare and adult mental healthcare**
- **Barriers also exist in the mind of the healthcare givers**
  - **Child professionnals do not talk to adult professionals**
  - **Children of a bipolar parent are taken care independently from the affected parent**



- **50% of youths at risk already have psychopathologies warranting a consultation (ADHD, substance abuse, etc.)** Maziade et al. 2008

- **Healthy children of an affected parent carry anomalies that adult patients carry**

What This Presentation Aims At

- **Influencing your decisions at work**
- **Influencing also your mind and attitude at work**
  - **Concrete actions could be taken based on current knowledge, evidence-based medicine and social studies**
- **There is something to do that is not done**

Plan of the Presentation

- Progress in neurodevelopmental precursors or endophenotypes in schizophrenia and mood disorders
  - Presence in adult patients and in children at risk
  - Neurocognitive and physiological
  - Precede disease onset by many years

- Our genetic and developmental findings in the Eastern Quebec Study

- Risk endophenotypes can be traced in developmental trajectories
  - The form of the trajectory matters

- Toward a definition of the “At-risk syndrome” in childhood
  - Early common roots for schizophrenia, bipolar disorder and depression
  - Design of risk and prevention studies
  - Elaboration of decision trees to identify children at risk
  - Normalizing risk trajectories

Advantages of Endophenotype Research in Developmental Psychopathology

- **A basic observation**
  - **The deficits expressed in endophenotypes that adult patients display – the children at genetic risk carry them**
    - **Risk endophenotype**
    - **Neurodevelopmental endophenotype**

- **Risk endophenotypes help to define an "At-risk syndrome" in childhood**
  - **Patterns of combinations (correlations) among endophenotypes**

- **Risk endophenotypes amenable to the tracing of a trajectory**

Research Program in Psychiatric Genetics

Institut universitaire en santé mentale de Québec

Marc-André Roy, M.D.
Psychiatry

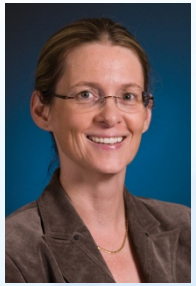
Thomas Paccalet, Ph. D.
Coordinator

Michel Maziade, M.D.
Psychiatrist

Chantal Mérette, Ph. D.
Biostatistics

Alexandre Bureau, Ph. D.
Biostatistics

Nancie Rouleau, Ph. D.
Neuropsychology



Nathalie Gingras, M.D.
Psychiatrist

Elsa Gilbert, Ph. D.
Neuropsychology

Marc Hébert, Ph. D.
Electroretinography

Nicolas Berthelot, Ph. D.
Psychology

Yvon Chagnon, Ph. D.
Molecular Biology

6 Facts
From the Past 10 Years of Research in Major Psychiatric Disorders

1. **Major psychiatric disorders are brain disorders**

   - Genetic vulnerability -- [not sufficient]

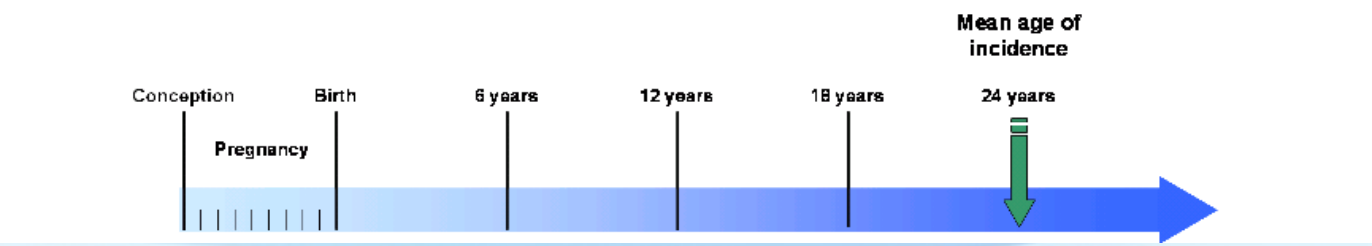
   - Environmental factors hit the genetic vulnerability

2. **These brain disorders are childhood disorders**

   - Neurodevelopmental disorders

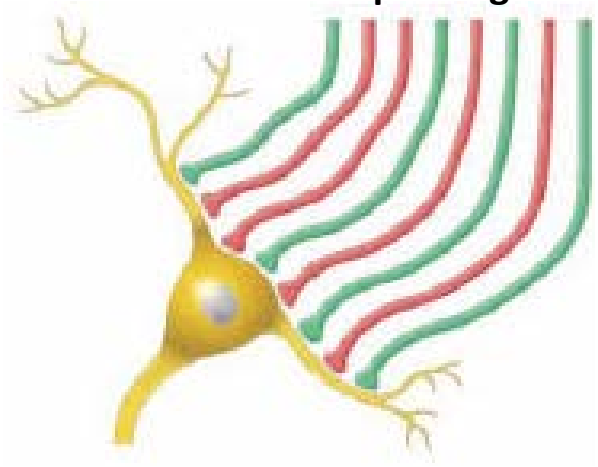
   - Gene-environment interplays along a trajectory from pregnancy to late adolescence

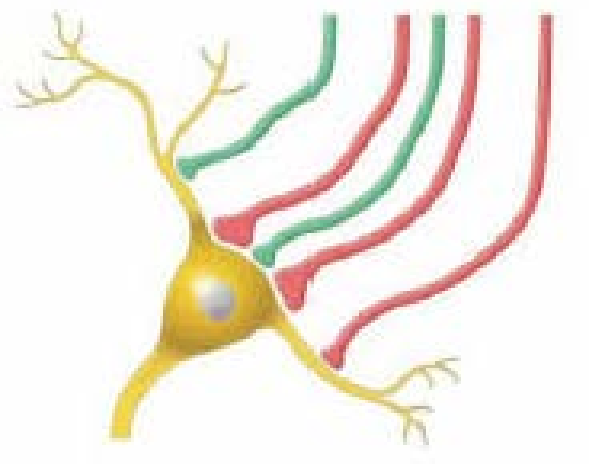
   - Due to subtle alterations of neurogenesis / synaptogenesis



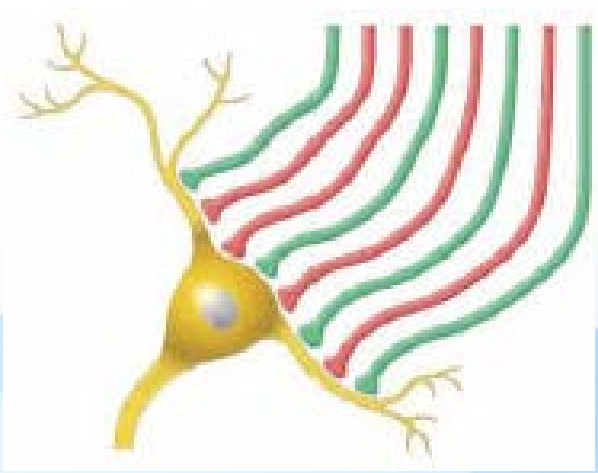
Helathy children

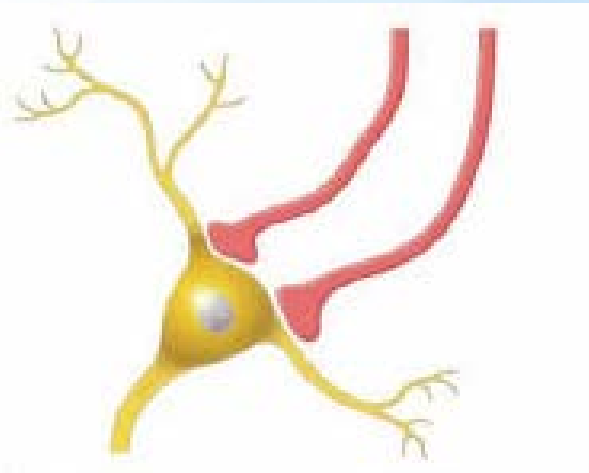
Before pruning





At-risk children





Evidence That Genes Are Involved

- Single gene effects are unlikely to be sufficient

Table 2 Top genome-wide association results for schizophrenia

SNP	Chr.	Mb	Alleles	Frequency	*P* (GC-adjusted *P*)	OR (95% CI)
					5.72×10^{-7} (6.52×10^{-6})	1.14 (1.08–1.19)
rs1625579	1p21.3[a]	98.3	TG	0.80	**2.65×10^{-6}** (n.a.)	1.11 (1.07–1.16)
					1.59×10^{-11} (6.87×10^{-10})	1.12 (1.09–1.16)
					3.09×10^{-6} (2.60×10^{-5})	1.22 (1.13–1.30)
rs17662626	2q32.3[a]	193.7	AG	0.91	**1.70×10^{-3}** (n.a.)	1.16 (1.06–1.27)
					4.65×10^{-8} (1.25×10^{-6})	1.20 (1.13–1.26)
					4.30×10^{-11} (2.76×10^{-9})	1.18 (1.13–1.23)
rs2021722	6p21.3-p22.1	30.3	CT	0.78	**1.55×10^{-3}** (n.a.)	1.10 (1.03–1.17)
					2.18×10^{-12} (2.88×10^{-10})	1.15 (1.11–1.19)
					3.84×10^{-7} (4.71×10^{-6})	1.14 (1.09–1.19)
rs10503253	8p23.2[a]	4.2	AC	0.19	**7.60×10^{-3}** (n.a.)	1.08 (1.01–1.14)
					4.14×10^{-8} (8.98×10^{-7})	1.11 (1.07–1.15)
					1.45×10^{-8} (3.22×10^{-7})	1.16 (1.11–1.21)
rs7004633	8q21.3[a]	89.8	GA	0.18	**0.011** (n.a.)	1.05 (1.01–1.10)
					2.75×10^{-8} (7.03×10^{-7})	1.10 (1.07–1.14)
					1.58×10^{-7} (2.27×10^{-6})	1.11 (1.07–1.15)
rs7914558	10q24.32[a]	104.8	GA	0.59	**1.07×10^{-3}** (n.a.)	1.08 (1.03–1.13)
					1.82×10^{-9} (3.11×10^{-8})	1.10 (1.07–1.13)
					2.23×10^{-8} (4.58×10^{-7})	1.22 (1.15–1.29)
rs11191580	10q24.33[a]	104.9	TC	0.91	**5.09×10^{-3}** (n.a.)	1.09 (1.02–1.16)
					1.11×10^{-8} (3.72×10^{-7})	1.15 (1.10–1.20)
					2.91×10^{-8} (5.69×10^{-7})	1.20 (1.13–1.26)
rs548181	11q24.2	125.0	GA	0.88	0.068 (n.a.)	1.04 (0.98–1.11)
					8.87×10^{-7} (1.74×10^{-5})	1.11 (1.07–1.16)
					1.00×10^{-6} (1.03×10^{-5})	1.10 (1.06–1.14)
rs12966547	18q21.2	50.9	GA	0.58	**2.29×10^{-5}** (n.a.)	1.08 (1.04–1.12)
					2.60×10^{-10} (5.99×10^{-9})	1.09 (1.06–1.12)
					2.35×10^{-8} (4.78×10^{-7})	1.40 (1.28–1.52)
rs17512836	18q21.2	51.3	CT	0.02	0.085 (n.a.)	1.08 (0.96–1.20)
					1.05×10^{-6} (2.86×10^{-5})	1.23 (1.14–1.31)

From the Schizophrenia Psychiatric Genome-Wide Association Study Consortium, Nature Genetics, 2011

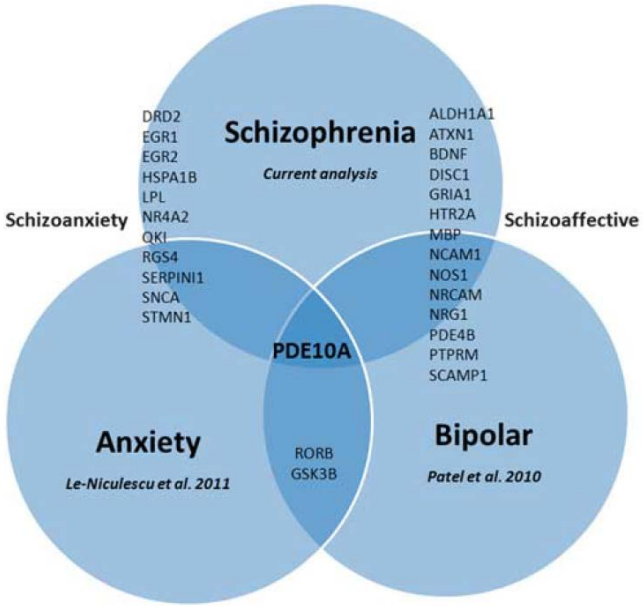


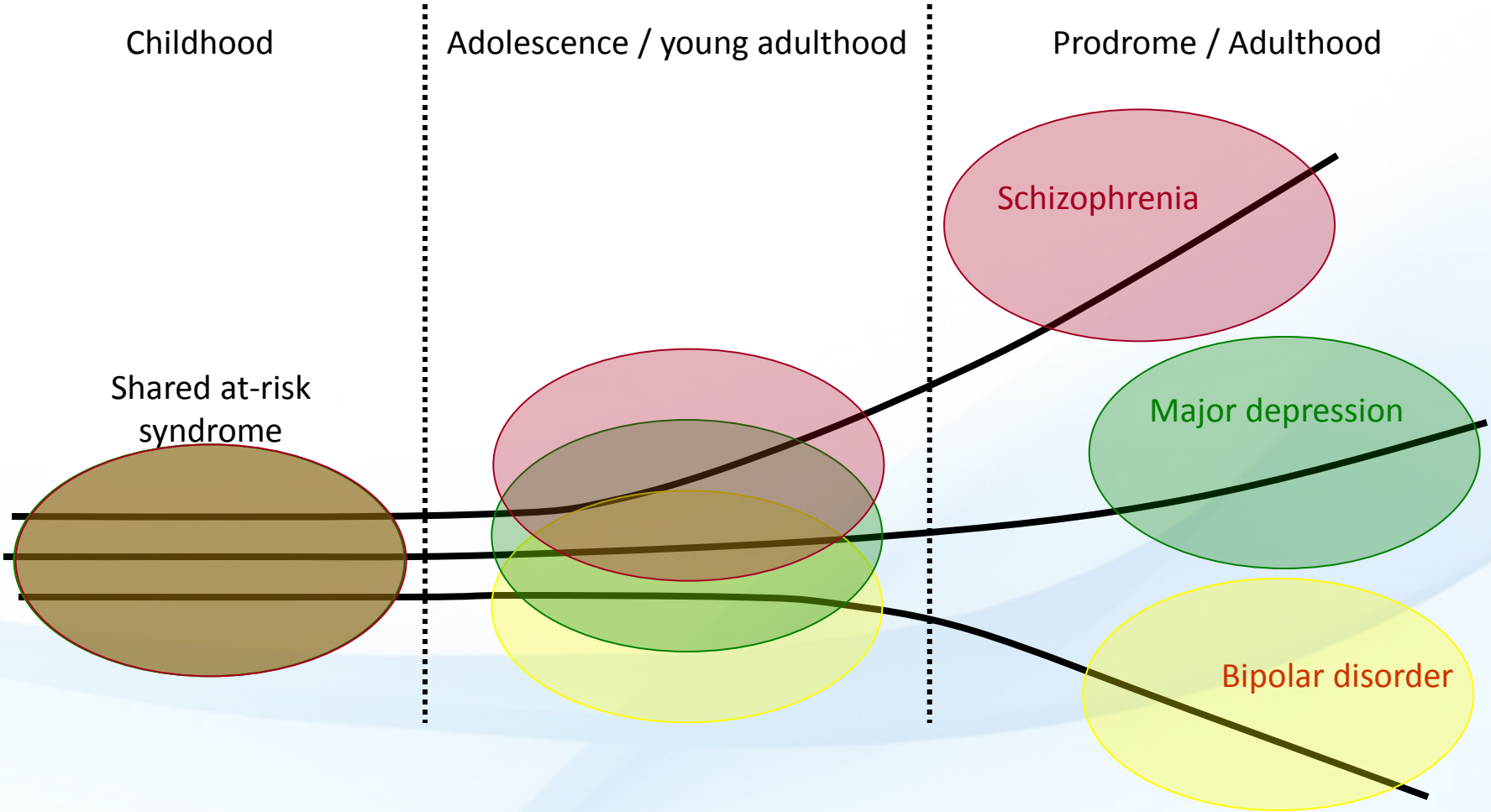
Figure 8. Genetic overlap among psychiatric disorders.

From Ayalew et al., Mol Psychiatry, 2012

3. Schizophrenia, bipolar disorder and recurrent depression are the same disorder

- They share several causative mechanisms

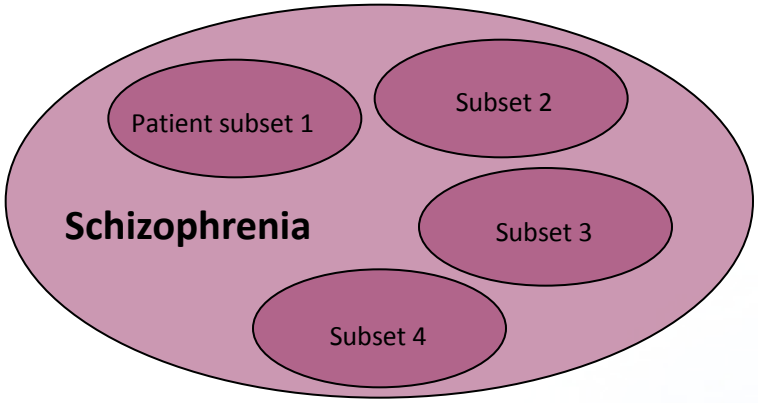
- Particularly in their childhood determinants



4. Heterogeneity

- Schizophrenia is not a unitary concept:

- Made of several different diseases
- Roots in the developmental trajectory in childhood

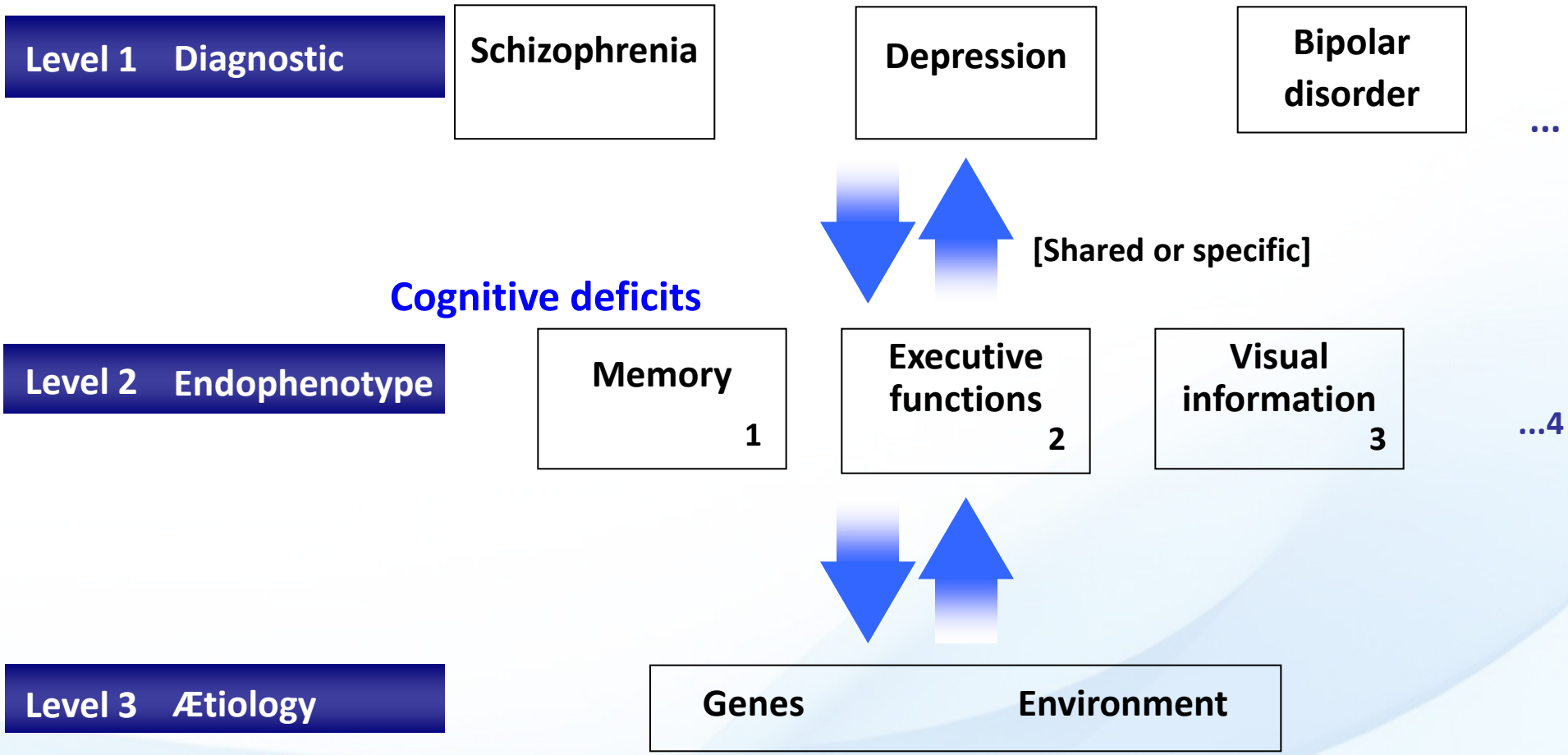


- The consequence:

- The exact brain dysfunctions are still indefinable
- All the developped treatments are symptom-oriented – not curative

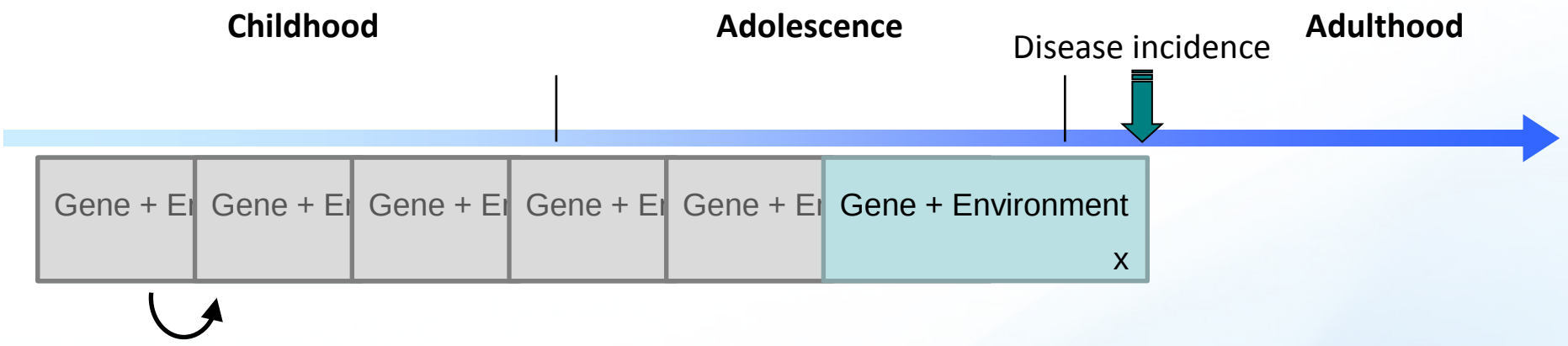
5. The sooner the treatment – the better the outcome

6. Need to Break Down the Diagnosis in components



Neurodevelopment: Different Meanings

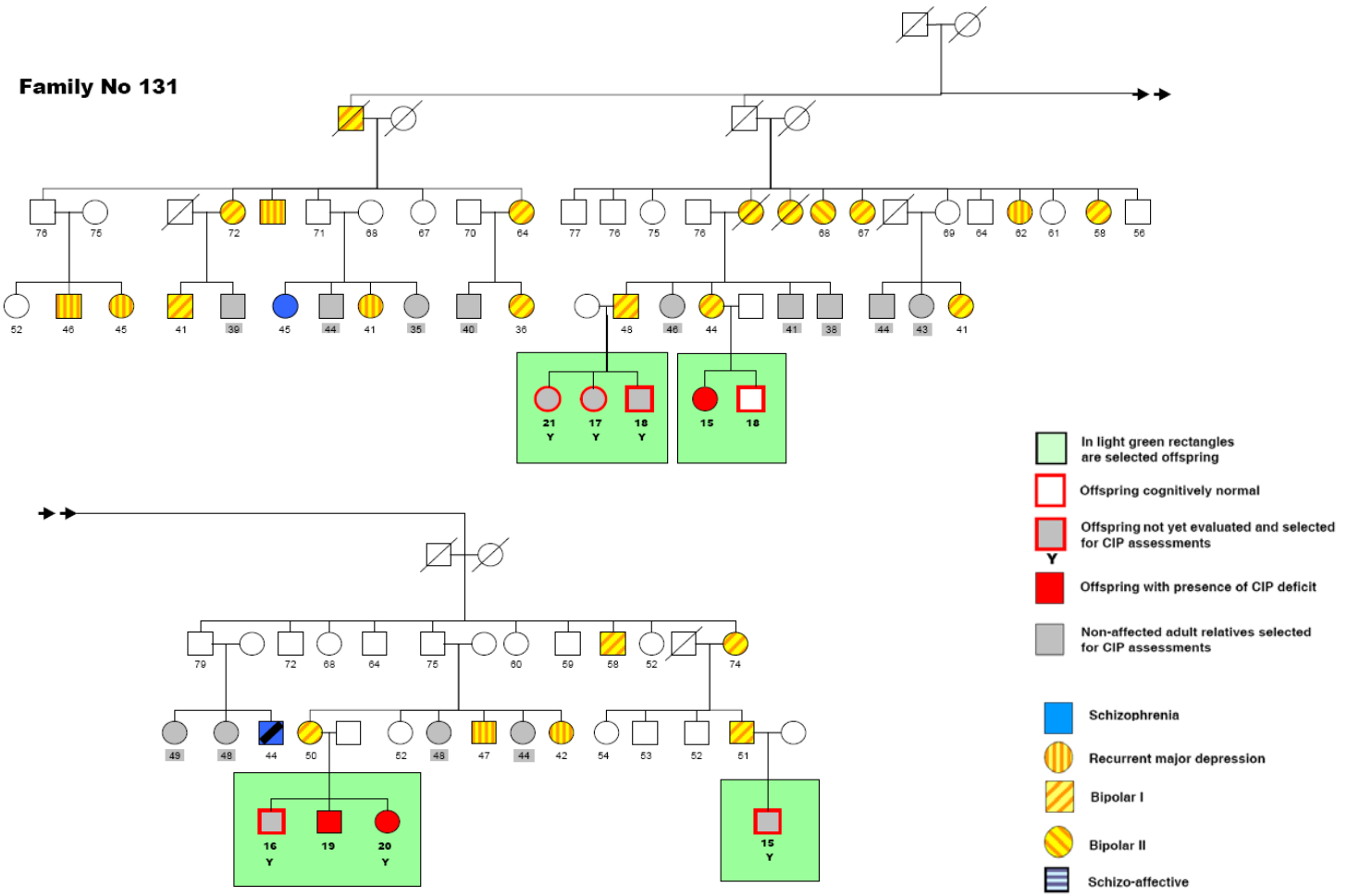
- **To a developmental psychopathologist:**
  - **Gene / Environment / and… Past development** (Sroufe, 2009)



  - **Dysfunction of specific brain microcircuits – Defect of neurogenesis/synaptogenesis**
  - **In a particular timing (sensitive window)**
  - **A hierarchical integration – cumulative G/E events – Past events impact later inputs**

Our Sample: 48 Kindreds From Eastern Quebec Multiaffected Families

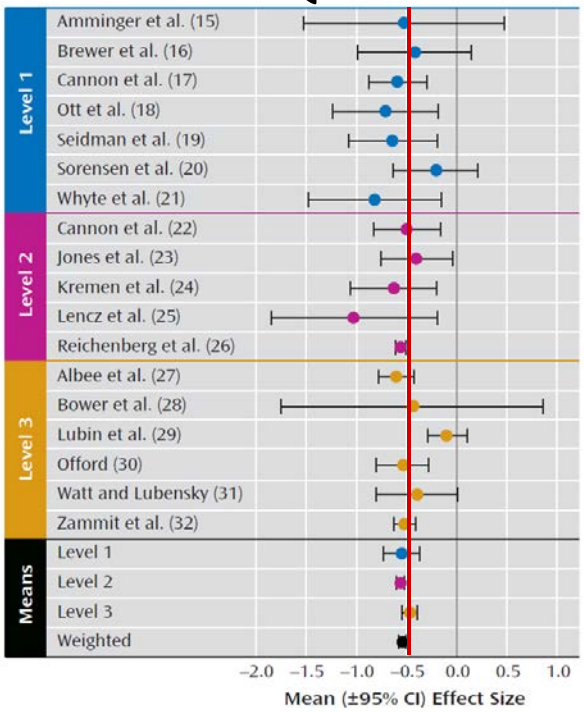
Example of family:



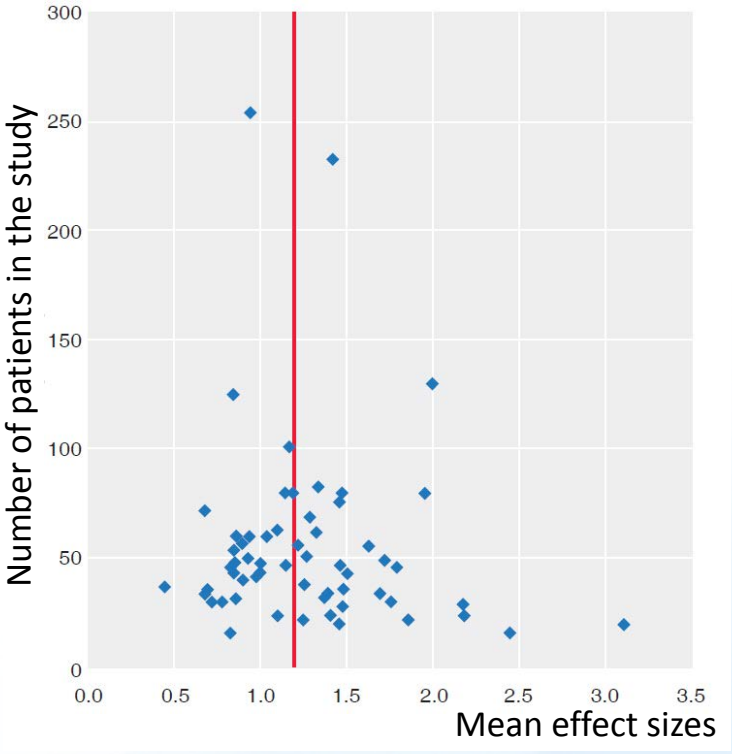
Maziade et al. Am J Psychiatry, 1992
Maziade et al., Mol Psychiatry, 2005

Cognitive Deficits Are Present in Schizophrenia and Relatives

IQ



Memory



Mean effect sizes observed in IQ in patients (in comparison to healthy controls):

ES = -0.5
Middle to large effect sizes

Adapted from *Woodberry et al. 2008, Am J Psychiatry* (meta-analysis of 18 studies)

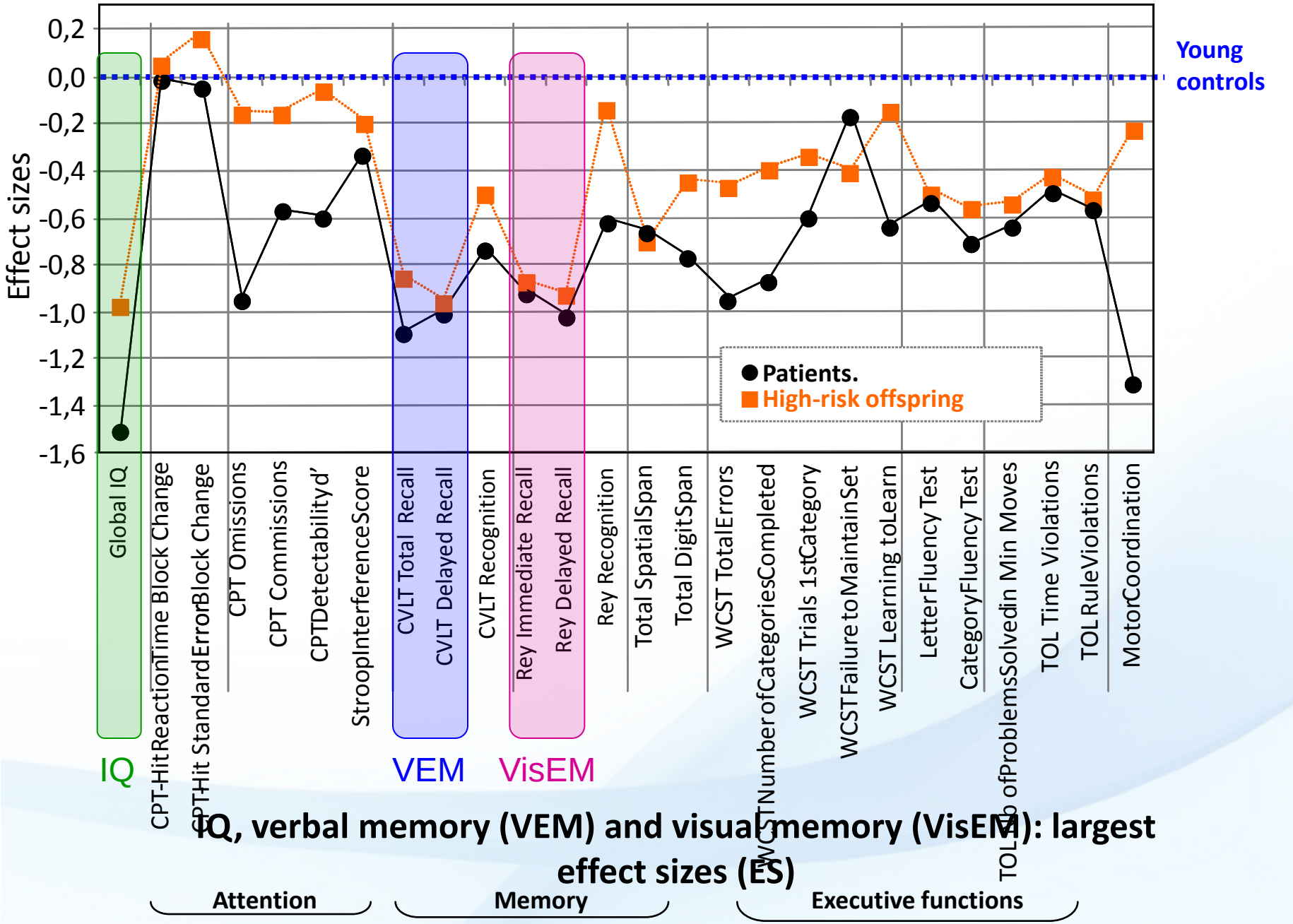
Mean effect sizes observed in memory in patients (in comparison to healthy controls):

ES = -1,3
Large effect sizes

Adapted from *Aleman et al. 1999, Am J Psychiatry* (meta-analysis of 60 studies; each point represents one study)

Cognitive Deficits Precede Disease Onset

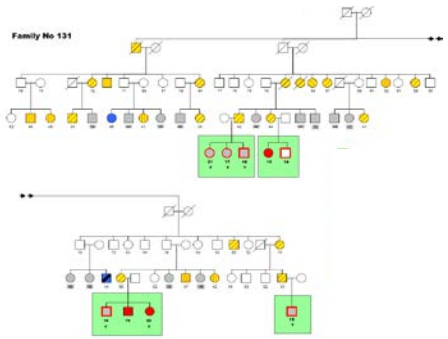
Maziade et al.
Schiz Bull; 2009, 35(5):919-30
Schiz Bull; 2011, 37(6):1218-28



IQ, verbal memory (VEM) and visual memory (VisEM): largest effect sizes (ES)

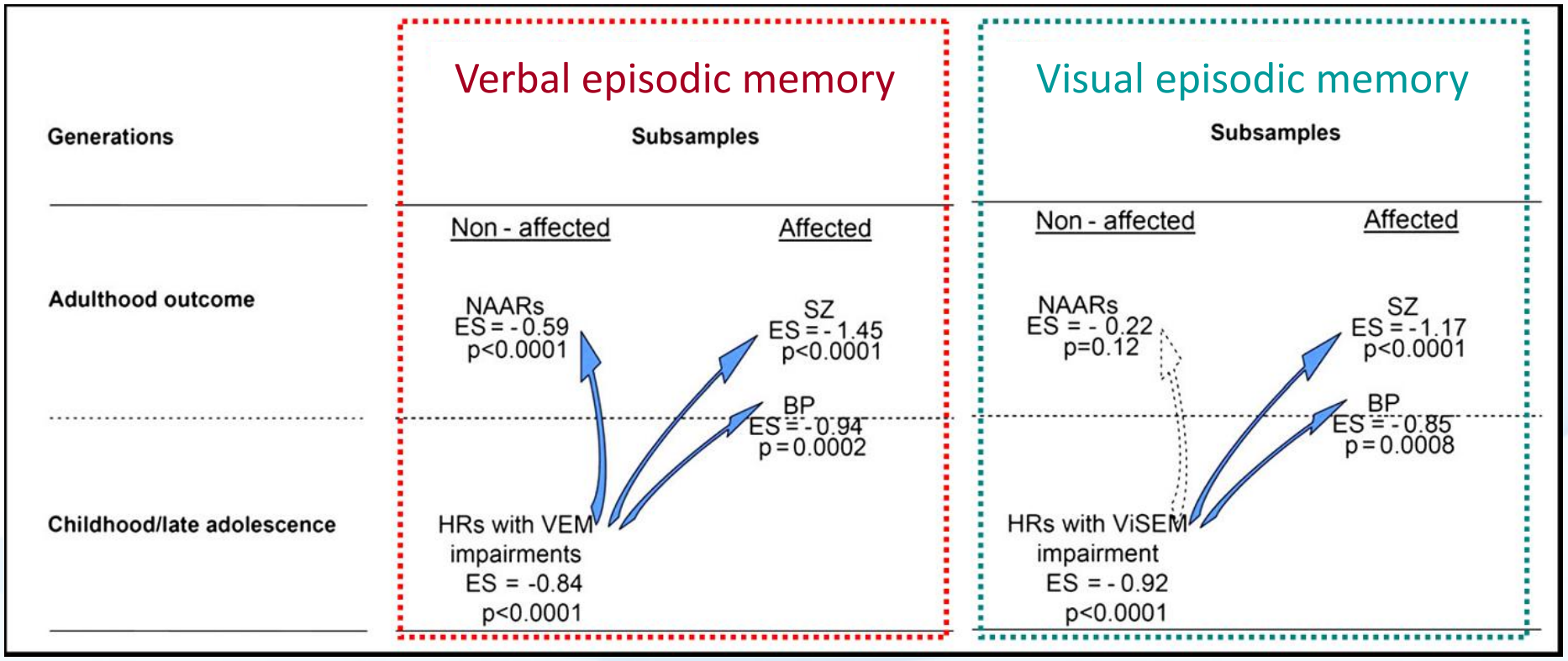
Cognition as a Neurodevelopmental Marker

Visual episodic memory - more specific to patient status

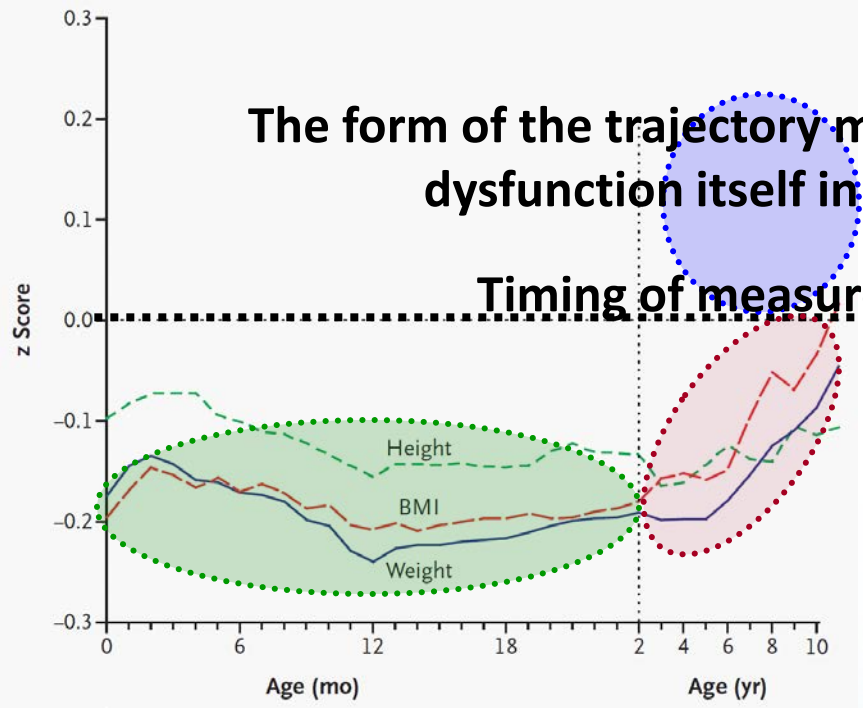


High-risk offspring (HRs)
Non-affected adult relatives (NAARs)
Patients (SZ or BP)

Maziade et al.
Schiz Bull; 2009, 35(5):919-30
Schiz Bull; 2011, 37(6):1218-28



The Form of the Trajectory: A Key to Understand the Disease



From *Barker et al., N Engl J Med, 2005*

The form of the trajectory might be as important as the dysfunction itself in the life of a subject

Timing of measurement is crucial

Risk of heart disease in adulthood:

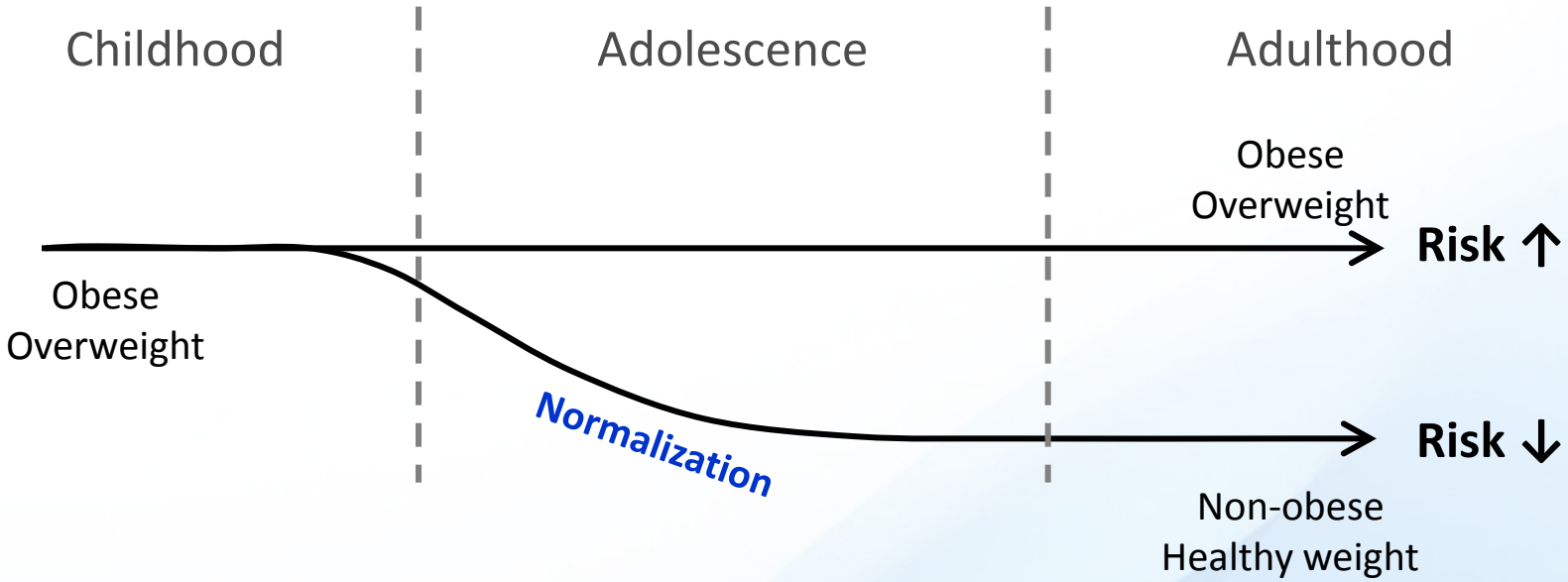
Risk does not come from a low weight from birth to 2 years old

Risk does not come from an abnormal weight gain after age 2

Risk comes from a rapid (although normal) weight gain within a specific period

The Form of the Trajectory of Risk Endophenotypes Matters

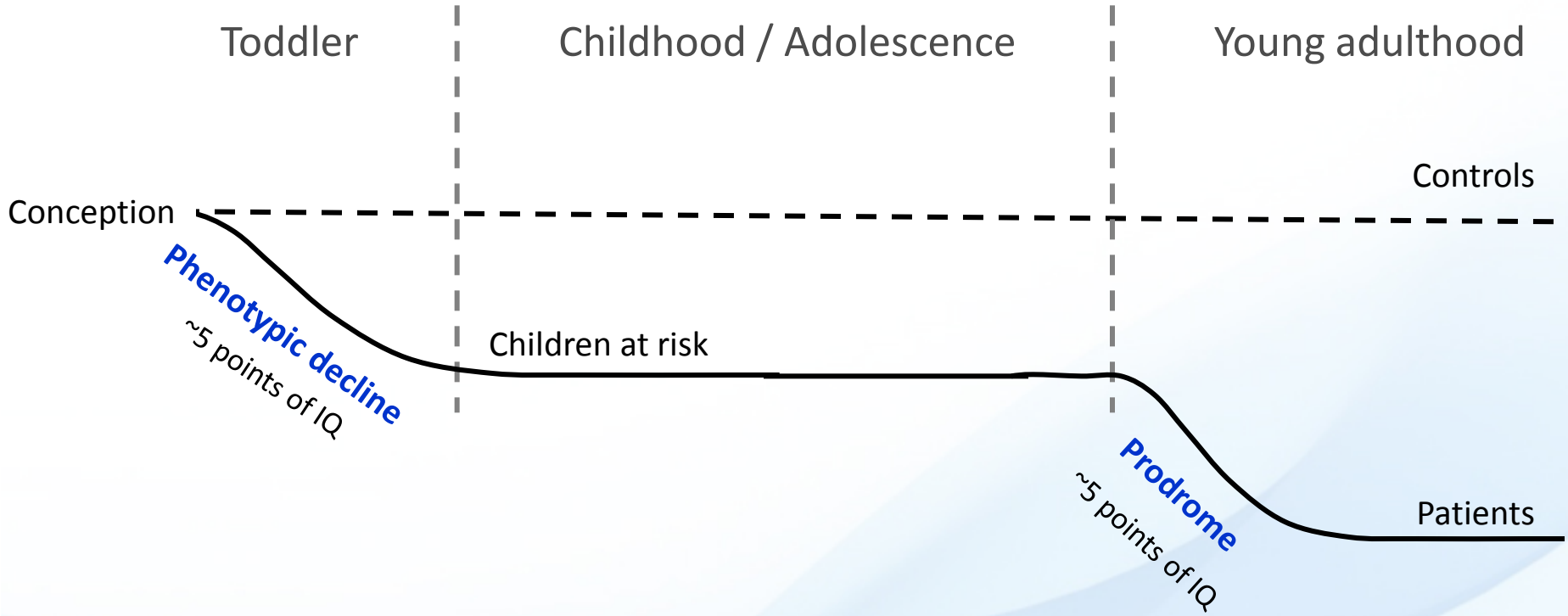
Cardiovascular disease risk: trajectory from childhood to adulthood



From *Juonala et al., N Engl J Med 365; 20, 2011*

IQ Trajectory in Children At Risk of Schizophrenia

3 stages toward the disease



Statistical Analysis

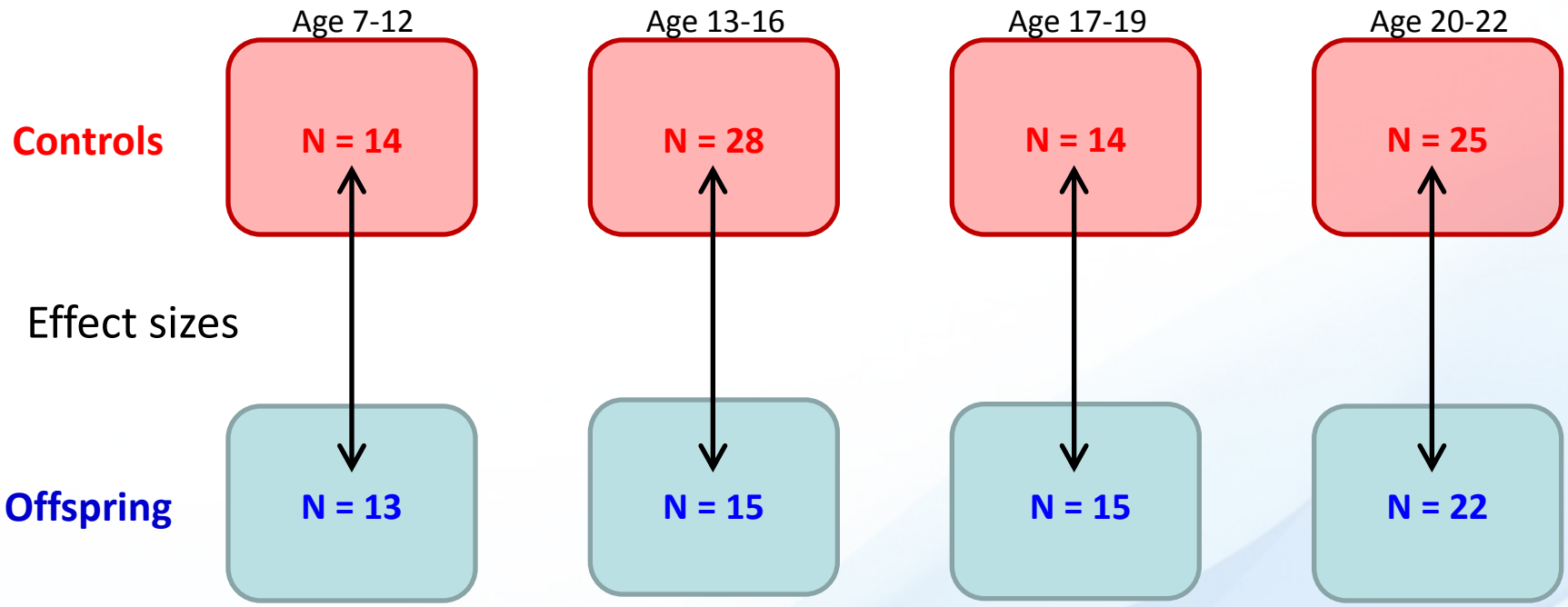
Cross-sectional trajectories *Thomas et al. J Speech Lang Hear Res 2009, Maziade et al. PLoS ONE 2011*

1. Dividing samples of offspring and controls by age periods

	Age 7-12	Age 13-16	Age 17-19	Age 20-22
Controls	**N = 14**	**N = 28**	**N = 14**	**N = 25**
Offspring	**N = 13**	**N = 15**	**N = 15**	**N = 22**

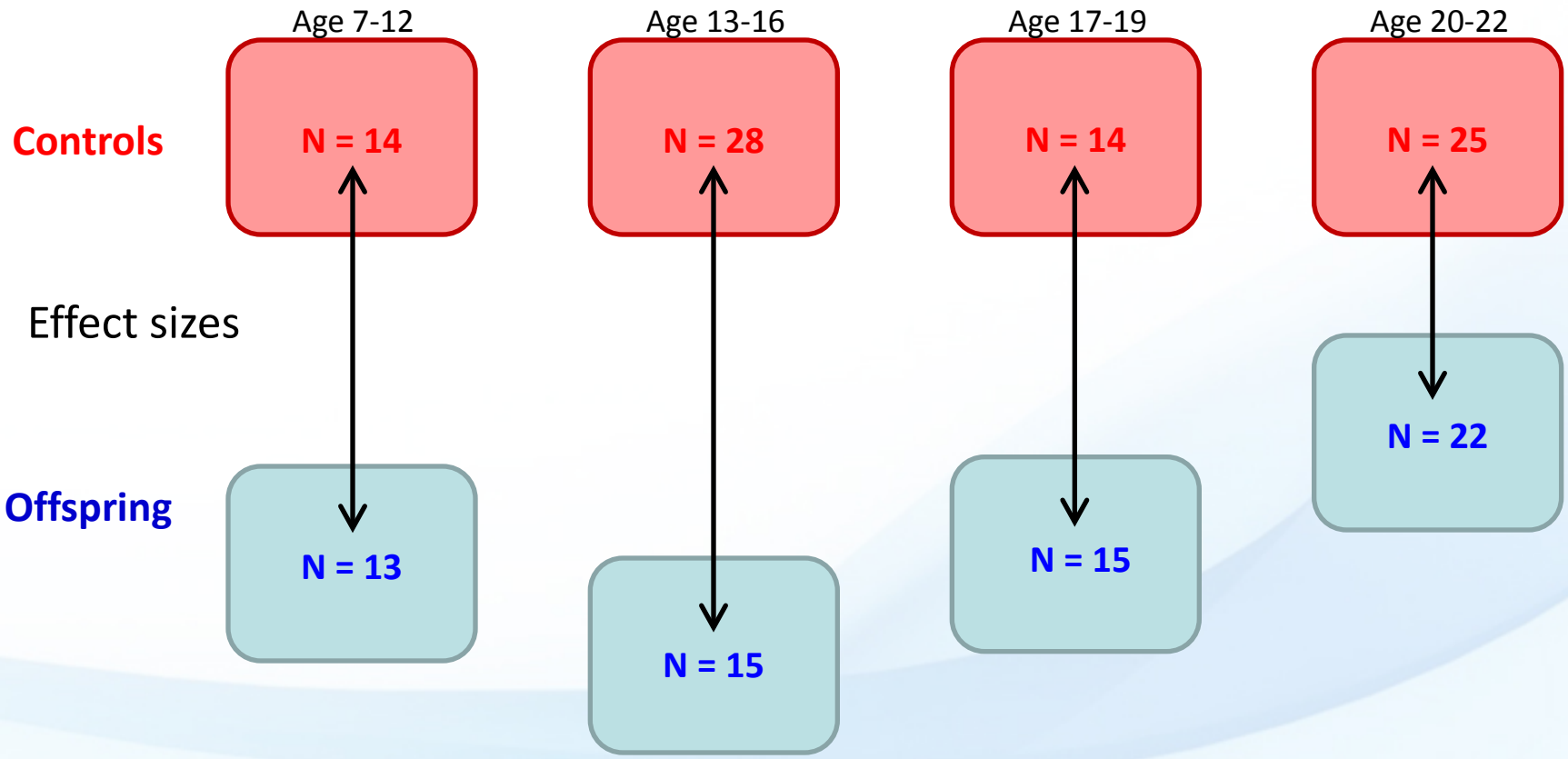
Statistical Analysis

2. Testing the difference (effect sizes) between controls and offspring at each age period



Statistical Analysis

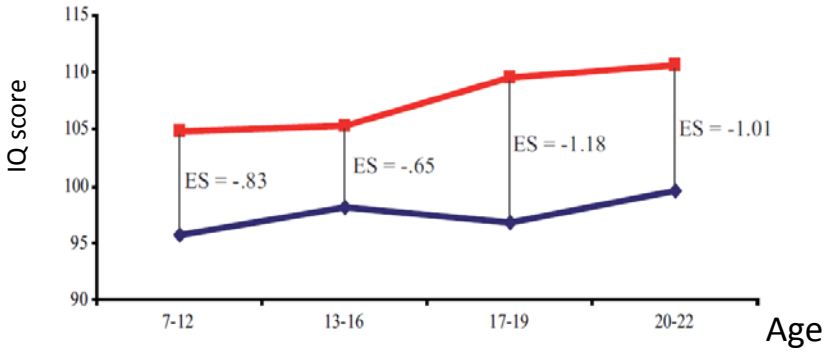
3. Computing the *Group x Age Periods* interaction term to test whether the cognitive differences between offspring and controls differed across the age periods



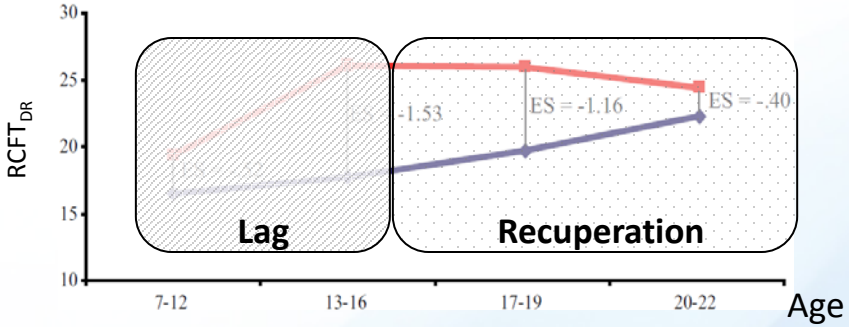
Three Shapes of Trajectories:
-- Early stable deficit -- Recuperation – Late-onset lag

Maziade et al. PLoS ONE 2011

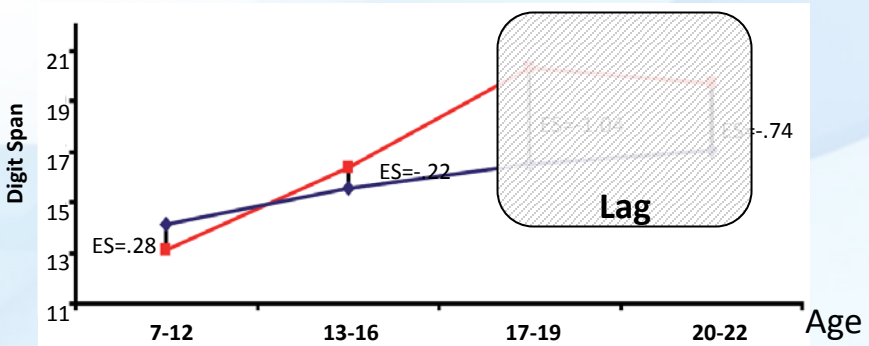
Early stable deficit: IQ



Recuperation : Visual memory



Late-onset lag: Working memory



- **The brain dysfunctions, such as cognitive deficits, that the adult patients have**

- **The children at risk display them in primary school**

Combined Versus Isolated Risk Endophenotypes

High frequency in the population of carriers of <u>only one anomaly</u>

Lower frequency in the population of carriers with a <u>combination of anomalies</u>

Numerous high-risk offspring in our study carried multiple risk endophenotypes

Many non-affected adult relatives (NAARs) carry multiple endophenotypes and do not develop the disease

	Number of cognitive deficits	
	0 or 1 deficit	2 or more deficits
Patients in % (n)	26% (n=13)	74% (n=37)
NAARs in % (n)	75% (n=75)	25% (n=25)
Healthy Controls in % (n)	91% (n=181)	9% (n=19)

$\chi^2 = 93.8$, df = 2, $p < 0.0001$

	Number of cognitive deficits	
	0 or 1 deficit	2 or more deficits
High-risk offspring in % (n)	63% (n=43)	37% (n=25)
Young controls in % (n)	86% (n=88)	14% (n=14)

$\chi^2 = 12.25$, df = 1, $p = 0.0005$

5 cognitive functions:

1) Verbal episodic memory; 2) Visual episodic memory; 3) Speed of processing;
4) Executive functions (Problem solving); 5) Motor coordination.

Deficit: performance < percentile 16th.

Summary on Neurocognitive Risk Endophenotypes in children at risk

- Several cognitive impairments present in patients are also detected in childhood
- Children at risk have combinations of anomalies
- Neurocognitive impairments are amenable to the tracing of developmental trajectories
- Cognitive deficits in different domains have different trajectories
  - The timing of expression along the trajectory varies

Summary (continued)

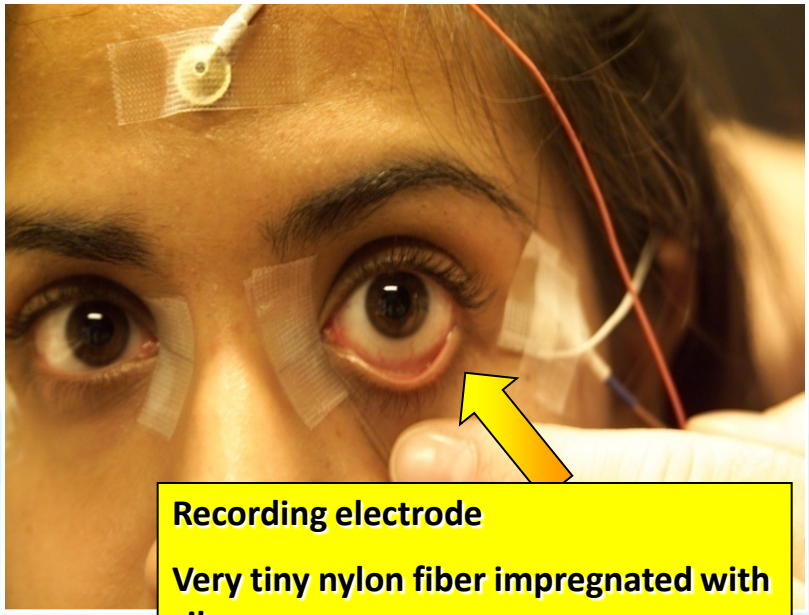
- The need to target the right dysfunction at the right time
- Modifiable by severe environmental adversity
- The form of the trajectory may have a meaning in itself
- Combined vs isolated endophenotypes may have different meaning

Two additional markers of risk of major psychiatric disorders in children of an affected parent

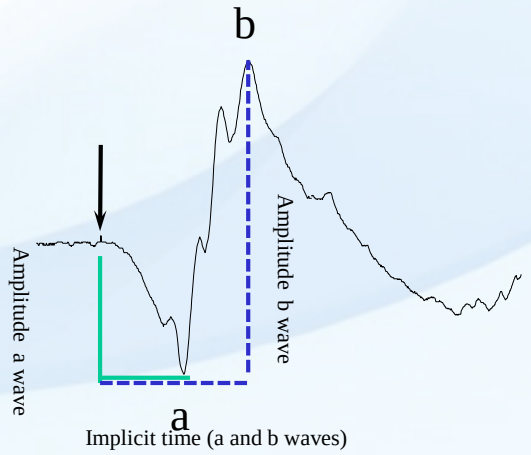
- **Electroretinography (ERG)**
- **Attenuated symptoms of psychosis**

Retina: An Accessible Extension of the Brain

Professor Marc Hébert, PhD



- ERG is similar to EKG or EEG but at the level of the eye.
- Bio-potential generated by the retina in response to standardized light stimulation.
- Non invasive technique.
- Allows the assessment of cones (used for day vision) and rods (used for night vision), separately.



Developmental Stability of Physiological Endophenotypes
– Retinal Response to Light Stimuli Assessment by Electroretinography (ERG)

- Developmental stability: some electroretinographical anomalies are detected in childhood
  |Can be included in the definition of the child « at-risk syndrome »|

- Some are detected after disease onset

Child at risk status

b-wave amplitude of rods

a-wave amplitude of cones

Hébert et al. Biol Psych, 2010

Adult patient status

___ XXXX of cones

___ XXXX of rods

___ XXXX of cones

(publication pending, embargo)

Attenuated Symptoms of Psychosis in Childhood

- **Attenuated symptoms in 5% of children in the general population**:

  Polanczyk et al., Arch Gen Psychiatry, 2010; Schreier et al., Arch Gen Psychiatry, 2009; Welham et al., Psychol Med, 2009; Dominguez et al. Schiz Bull, 2011

  - Correlates of AtS are similar to those of adult schizophrenia:
    - Positive familial history
    - Cognitive deficits and lower IQ
    - Diminished social functionning (GAS)

- **A degree of persistence of AtS across childhood and adolescence**

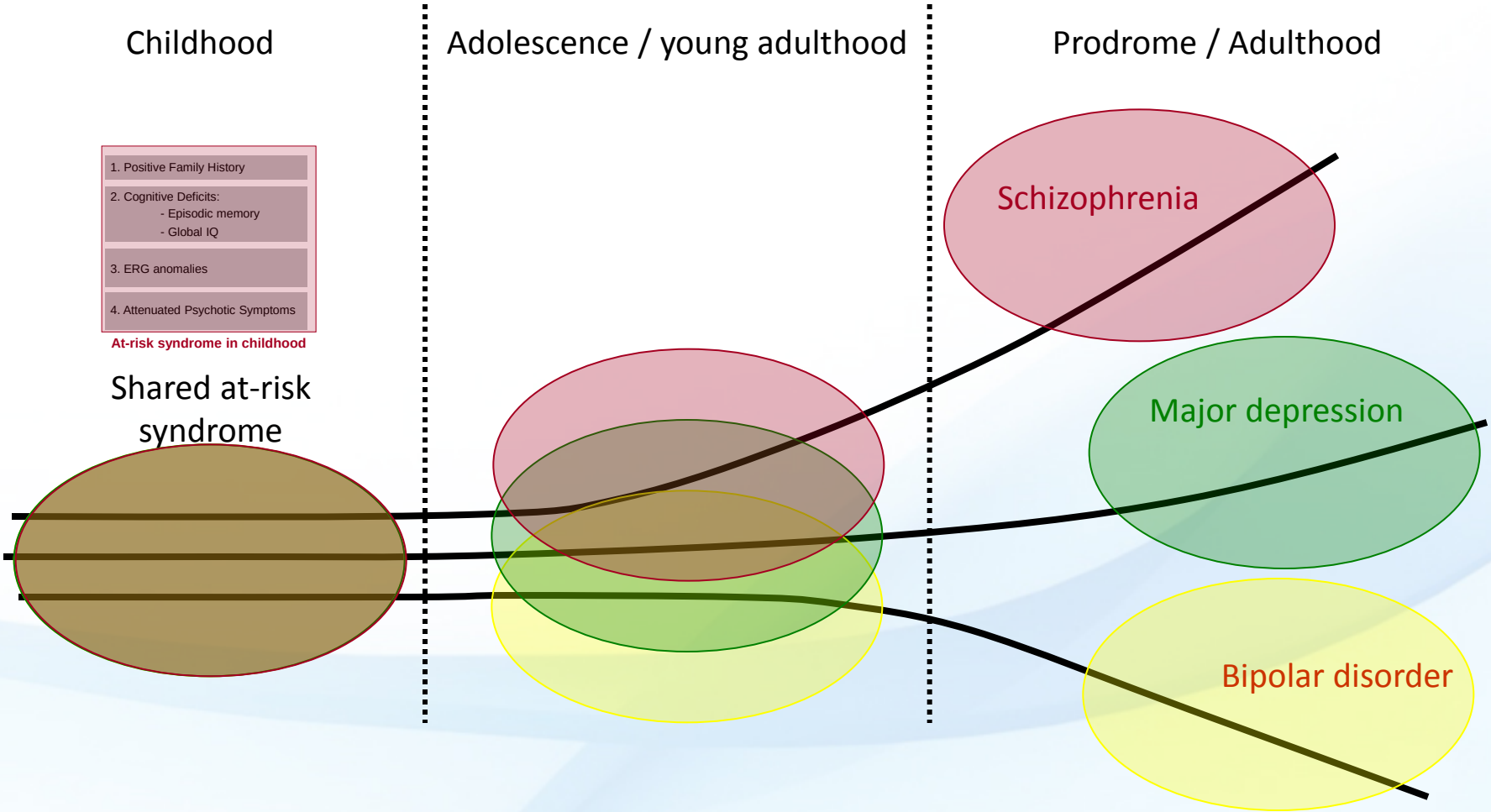
  - Under the effect of environmental adversities:
    - Victimization
    - Trauma
    - Urbanicity
    - Cannabis

  - Predicts later psychosis at age 25

Common Roots of Schizophrenia, Bipolar Disorder and Recurrent Depression

- They share several causative mechanisms

- Particularly in their childhood determinants and <u>syndrome at risk</u>



Three Desirable Preventive Goals

1. **Delay the age of onset by many years**

2. **Alleviate disease severity in the individuals who will develop the disease**

3. **Prevent the occurrence of the disease.**

- **50% of youths at risk already have psychopathologies warranting a consultation (ADHD, substance abuse, etc.)** Maziade et al. 2008

- **The child/adult barrier in health services**
  - **Child healthcare professionals do not talk to adult healthcare professionals**
- **Children of a bipolar parent are taken care independently of the affected parent**

How Can We Provide Better Help?
Screening and Early Intervention in Youths at risk

- **Let us start with children who live in affected families**
  - **Focusing on population already more at risk**
- **Let us treat children who already have a disorder**
  - **Youths already seeking help or not even detected in the community**
- **Let us try to normalize the risk endophenotypes in children from affected families**
  - **Even though we still do not know if this will prevent schizophrenia**
  - **Will provide at least improvement in quality of life and social adaptation**
    - **(improvement of memory, reduction of attenuated symptoms)**

Thank You For Your Kind Attention