

# Updates in Autism

## -Risk factors and red flags

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# Outline

- Basics
- Early clinical “at risk” children
- Genetic risk
- Environmental and parental risk factors
- Risk for poor outcomes (or predictors of good outcome)

# How Common are ASDs?

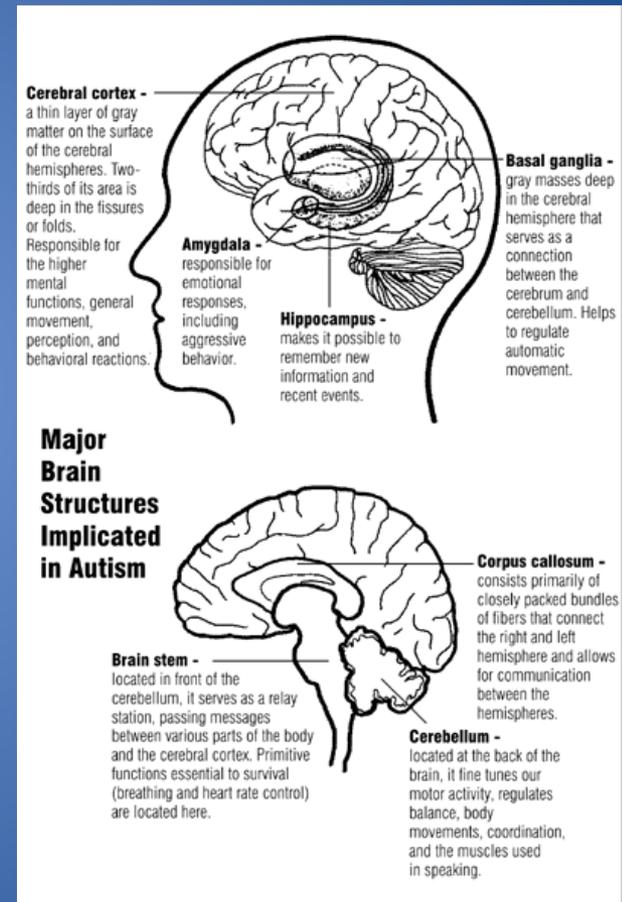
Estimates suggest that there are 1 in 100 people with an ASD and many of these also have a learning disability

Four times as many boys as girls have an ASD in the group with LD and there may be ten times as many boys as girls in the high-ability group

Baird, G. *et al*, *Lancet*, 2006

# How common are ASD's

- At lower end of ID
  - Much overlap
  - Diagnosis contentious
- At higher end
  - Overlap with “normalcy” so great, diagnosis often a matter of expediency



# Early diagnosis (Red flags)

- Evidence that behavioral signs of ASD can be detected by 1 year.
  - Risk markers extend from atypical social communication to motor delays
  - Unusual *trajectories* of language and cognitive skills
- A combined behavioral and biomarker approach may help with early detection of ASD

Zwaigenbaum *et al Brain Beh Res*, 2013

- **Social communication**
  - Lack of orientation to name
  - Lack of social smile
  - Lack or orientation to adults
  - Decreased flexibility in disengaging visual attention
  - Poor joint attention
- **Language-cognitive**
  - Language delay
  - “slowed” developmental trajectory  
12-24months

- **Repetitive behaviours and restricted interests**
  - Less obvious <12 months
  - Some increase in repetitive actions with objects 12-24 months
  - Atypical visuo-motor exploration of objects
- **Motor**
  - Definite motor delays
  - Not easily distinguishable from other children with dev delay



# Milestones of speech

2-4 months – cooing

6-9 months – babbling,  
“gaga” (conversational)

10-12 months- “mama”

18 months – 10 Nouns, jargon

2 years – telegraphic twos

3 years – plurals, name, age, sex

# Language red flags

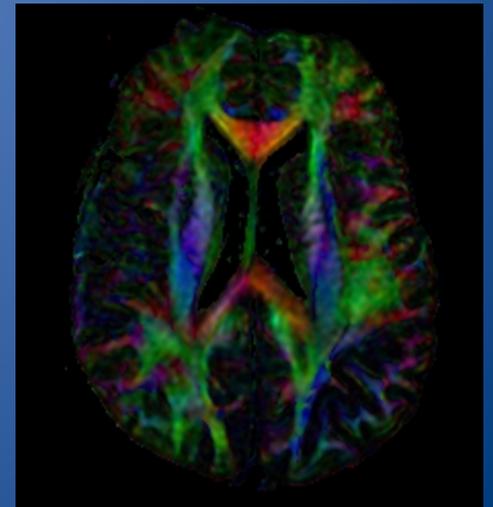
No words by 18 months

No communicative gestures

No joining of words by 2 years

Unintelligible speech, echolalia at 3 years

Absence of imitation and symbolic play at 2-3 years



# Genetic risk

- ASD has strong genetic basis (>90% heritability)
- 1-2% of the population
- large number of genes implicated,
  - incl inherited genes and spontaneous mutations, not classically inherited
- some comorbid genes (ASD, ADHD, schizophrenia)
- Concordance 92% in MZ twins and 10% in DZ pairs
- 10-20% in younger siblings

Jeste *et al* Nat Rev Neurology, 2014

# Specific genetic syndromes

- Tuberous sclerosis
- NF1
- Fragile X
- Rett's syndrome
- CDKL5
- Angelman's syndrome
- *Not all Autism is related to a specific syndrome, but these better understood disorders may provide the key to understanding mechanisms of disease*

# Parental age

- Swedish cohort, 417 303 children born 1984–2003. ASD case status (n=4746)
- Advancing parental age increased the risk of offspring ASD
- Risk of ASD was greater for older mothers, as compared with older fathers
- Increased risk of offspring ASD due to advancing paternal age was evident only in mothers <35 years
- Advancing maternal age increased risk of offspring ASD regardless of paternal age.
- Advancing parental age was more strongly associated with ASD with ID vs ASD without ID

Idring *et al*, *IJE*, 2014

# Parental age-mechanisms

- Frequently proposed to underlie paternal age effects are increased rates of de novo mutations and epigenetic alternations with increasing age
- Increased rates of genomic alternations with increasing maternal age proposed to underlie maternal age effects

# Maternal age -mechanisms

- Exposure environmental factors reported to increase risk of ASD
  - cumulative exposure air pollution or
  - medications
- Perinatal and obstetric complications present at a higher rate in older mothers have been shown to increase risk of ASD
- With increasing age, mothers may be increasingly subjected to other factors associated with ASD
  - autoimmunity,
  - metabolic conditions
  - nutritional deficiencies.

# Environmental risk factors- Perinatal

- Perinatal factors
  - 12%-13% of ASDs among children born in large US cohort attributable to the underlying pathways leading to PTB, SGA, and/or CD
  - globally represents suboptimal perinatal environment
- However, prenatal and neonatal ASD risk studies need to better define complications associated with systemic inflammation that alters brain development
  - maternal infections
  - hypertension
  - chemical exposures (environmental, illicit, and prescribed)
  - diabetes
  - nutrition
  - psychological stress
  - neonatal infections
  - oxygen therapies
  - medications,

Schieve *et al*, *Ann of Epid*, 2014  
Hofheimer *et al*, *J Pediatrics*, 2014

# Environmental risk factors-other

- Toxins
  - Systematic review
  - Prenatal exposure: pesticides, solvents, air pollutants
  - Childhood exposure: pesticides, toxic waste sites, phthalates, air pollutants and heavy metals
  - Primarily retrospective
- Medication
  - antidepressants

Rossignol *et al*, *Transl Psychiatry*, 2014

Andrade, *J Clin Psychiatry*, 2013

- Infections
  - Previous associations with viral infections
  - Large cohort in California
  - Association between inpatient infections and esp bacterial infections (esp UTI's)
  - No specific infection identified

*Zerbo et al, J Autism Dev Disord, 2013*

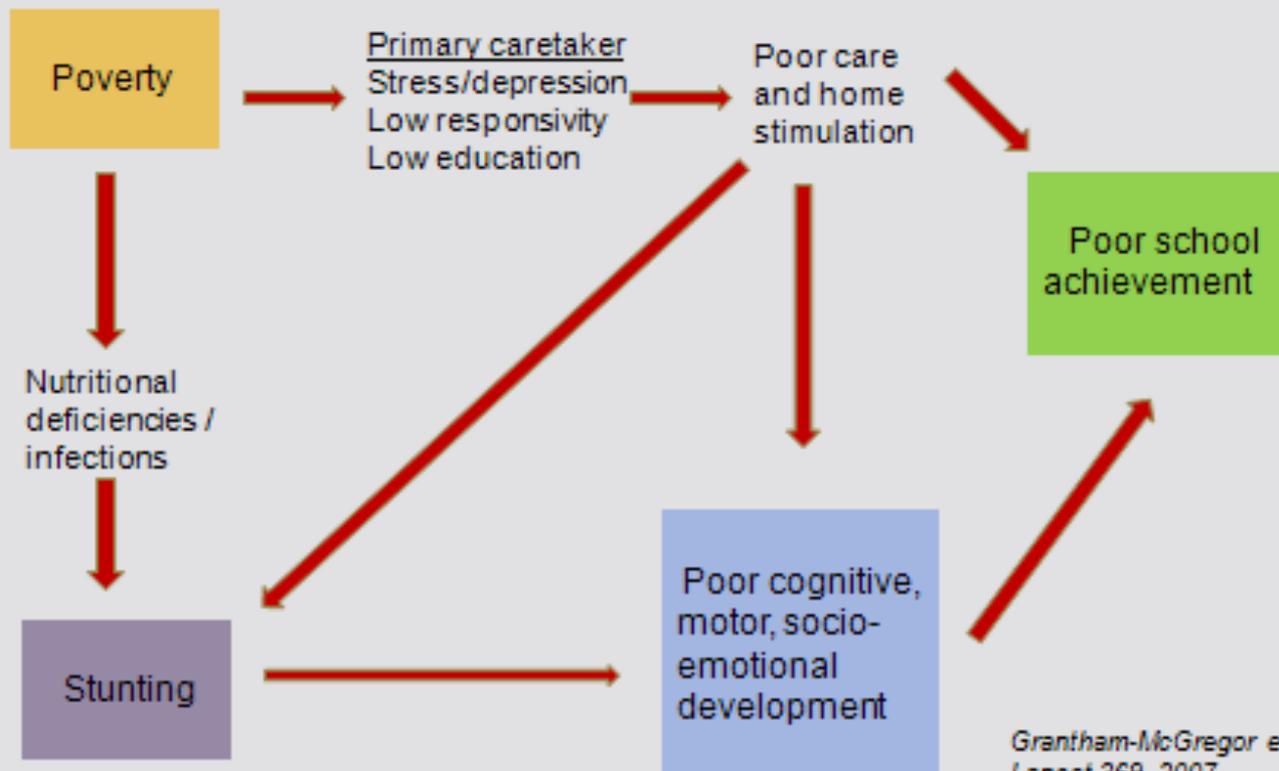
- At least in a subset of children, complex interactions between genetic factors and certain environmental factors may act synergistically or in parallel during critical periods of neurodevelopment, in a manner that increases the likelihood of developing ASD

# Risk factors for intellectual disability in SA

- *Context of poverty and preventability*
  - Child growth stunting (nutritional)
  - Ill-health
  - Substance abuse
  - Cultural and social factors



## Relations between poverty, stunting, child development and school achievement

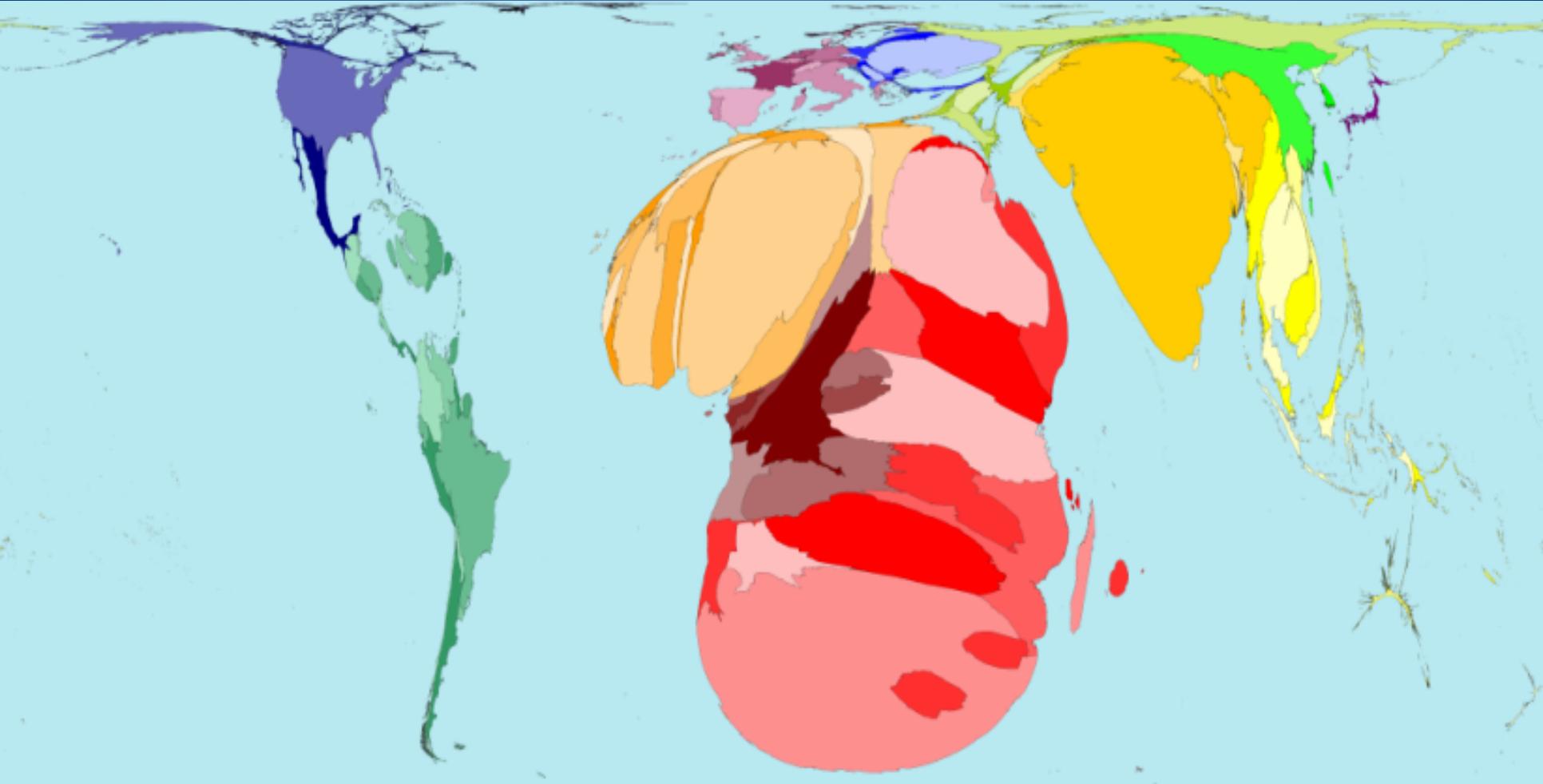


*Grantham-McGregor et al  
Lancet 369, 2007*

- Early childhood is a critical time in human development
- Factors effecting development relate to each other in complex ways during particular periods and across time
- Millions of children across this continent are at additional risk for poor outcomes as a result of biological disadvantage

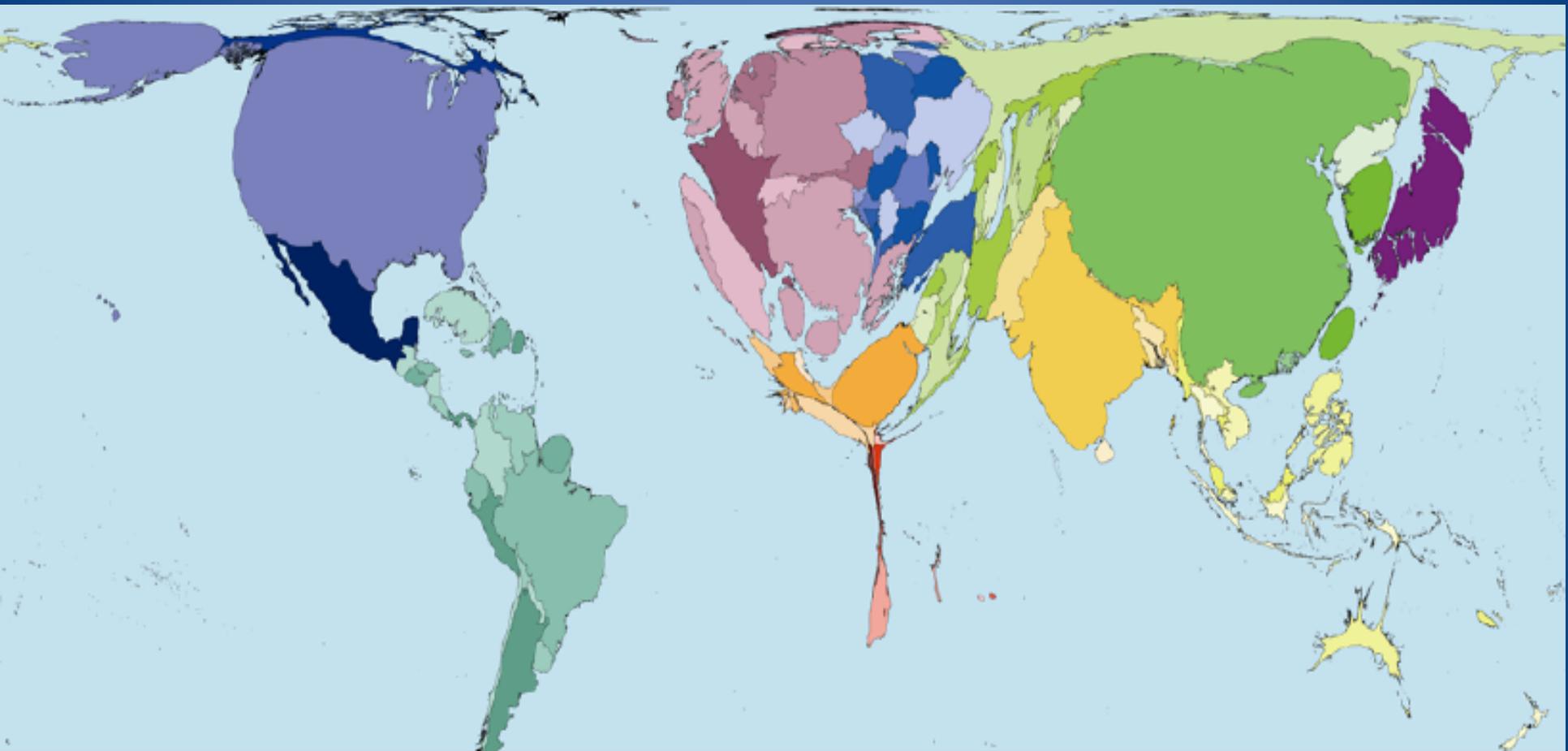


# HIV/AIDS burden



**Africa has two thirds of the world's people living with HIV/AIDS**

# Physician density in countries



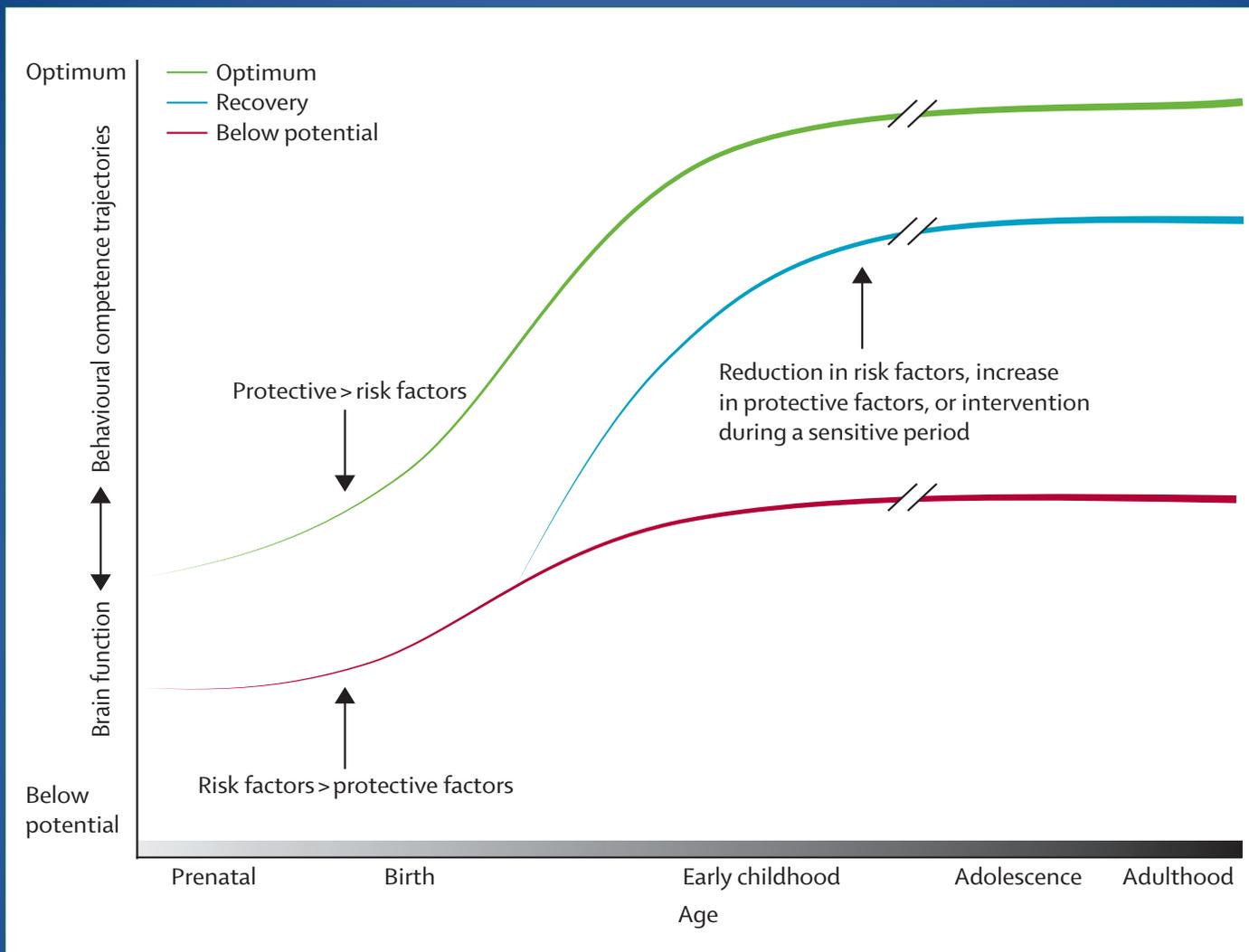
**The INVERSE CARE LAW: Those who need care the most are the least likely to receive it (Tudor-Hart 1971)**

Distribution of GMFCS levels in children with CP		
GMFCS level	Canada N=332	SA (Red Cross) N=270
I	68%	31%
II		
III		
IV	32%	69%
V		

- Clinic vs community samples
- Access to medical care
  - Are child care workers identifying problems?
  - Are health care workers recognising autism?
- Access to interventions

# Predictors of good outcome

- Educational placement
- Years of schooling, intensity of treatment
- Early language development and IQ
- Performance on non-verbal tests
- Presence of useful speech by age 5
- Presence of additional skills or interests
- Degree of support offered by families, educational, employment, and social services



**Figure 2: Differing trajectories of brain and behavioural development as a function of exposure to risk and protective factors**

The cumulative effect is illustrated by the progressive strengthening (darker lines) of the trajectories over time.

- **All interventions expensive**
- Realistic about needing to consider the needs of children over their life-time
- Early intervention is <4 years and the earlier the better.

# Take home message

- Autism is a significant developmental disability in SA and in Africa
  - Real prevalence?
  - Aetiological differences/vulnerabilities?
  - Barriers to recognition?
  - Culturally/economically appropriate models for diagnosis and intervention?