

Disturbi del Neurosviluppo Autism Spectrum Disorders (ASD)

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autism the great modern health concern

Autism spectrum disorders (ASDs) are a group of developmental disabilities that can cause significant social, communication and behavioral challenges. People with **ASDs** handle information in their brain differently than other people. **ASDs** are "spectrum disorders." That means **ASDs** affect each person differently, and can range from very mild to severe. There are three different types of **ASDs**: **Autistic Disorder** (also called "classic" autism), **Asperger Syndrome** and **Pervasive Developmental Disorder – Not Otherwise Specified (PPD-NOS)** (also called "atypical autism")

1980 1 : 1200

Autistic Disorder

What most people think of when hearing the word "autism." People with autistic disorder usually have significant language delays, social and communication challenges and unusual behaviors and interests.

Asperger Syndrome

Usually have some milder symptoms of autistic disorder. They might have social challenges and unusual behaviors and interests. However, typically do not have problems with language or intellectual disability.

Pervasive Developmental Disorder

The symptoms might cause only social and communication challenges. People with PDD-NOS usually have fewer and milder symptoms than those with autistic disorder.

2002 1 : 150

2006 1 : 110



2014 1 : 65

meaning

1%
of the population of children
aged 3-17 have an ASD

with



ASDs 4 to 7 times more likely
to occur in **BOYS** than in **GIRLS**



2008 1 : 88

There is no medical test to diagnose ASDs, doctors look at the child's behavior and development to make a diagnosis.



About half of parents of children with ASD notice
their child's unusual behaviors by age 18 months



about four-fifths notice
by age 24 months

A person with an ASD might:

Not respond to their name by 12 months | Avoid eye contact and want to be alone | Have delayed speech and language skills
Repeat words or phrases over and over (echolalia) | Give unrelated answers to questions | Get upset by minor changes

2014 1 : 65

ASDs are the fastest-growing
developmental disability

1,148%
growth rate

with

10-17%
annual growth

Reports of autism cases per 1,000 children



Lifetime cost to care for
an individual with an ASD
Estimated from recent studies

\$3.2m

with

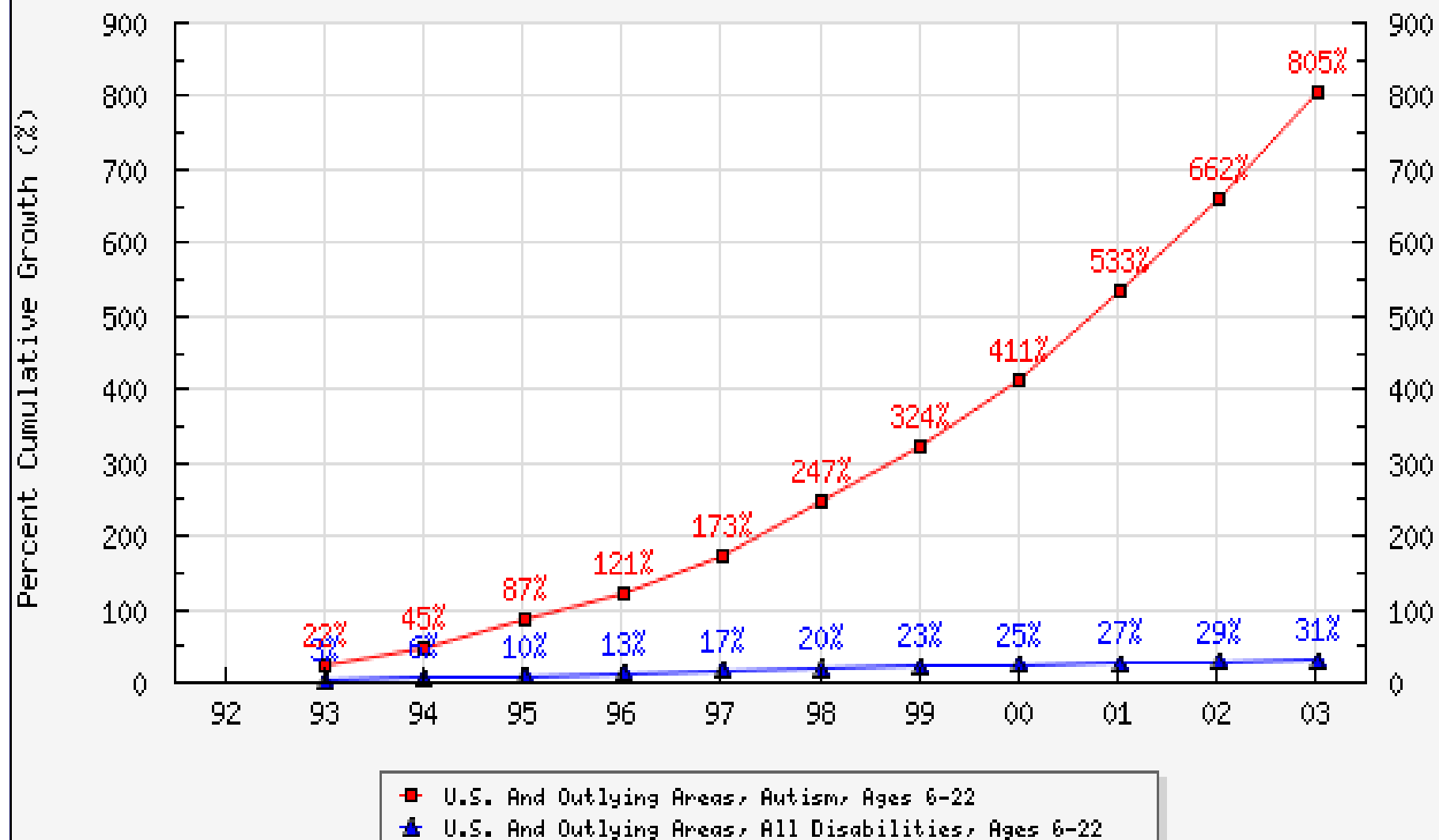
\$4,110-\$6,200 per year

of medical expenditures for
an individual with an ASD
than one without

Autism Spectrum Disorders

Incidence Cumulative Growth

[U.S. School Years 1992 - 2003]



Graph Source: www.fightingautism.org

Data Source: www.ideadata.org and www.cdc.gov/nchs/

The Increased Prevalence of ASDs

The increased prevalence of ASD is probably due to :

1. Broading of the concept
2. Increased early detection by paediatricians/teachers
3. Increased recognition and refinements of diagnostic instruments
4. Advanced paternal and maternal age
5. Potential effects of environmental toxins

Neurobiology of ASDs

- Heterogeneous set of developmental disorders
- High reliable diagnostic measures (ADI, ADOS)
- No biologic diagnostic test
- Strongly genetic ; $M > F$
- No cure

Natural history of ASDs

- Symptoms change with age
- Improve with early intensive intervention (↑ synaptogenesis). Evidence: low-moderate
- Chronic, lifelong disorders
- Lifetime cost for ASDs with intellectual disability: £ 1.2 million

DSM IV

Distinction among ASD clinical subtypes:

- Autistic disorder
- Asperger disorder
- Pervasive developmental disorder not otherwise specified

- Inconsistent over time
- Variable across sites
- Associated with severity of language deficit and intellectual impairment rather than ASD features

DSM 5

Two symptom dimensions:

- Social communication deficits (SCD)
- Fixed interests and repetitive behaviors (FIRB)

Each individual with ASD will be dimensionally described with these two domains, using a severity gradient

The SCD and FIRB symptom dimensions can be used to stratify children with ASD into more homogeneous subgroups

Age at diagnosis of ASDs

- Early signs and other developmental differences were reported in the first year of age among children who later developed ASDs
- A reliable diagnosis of ASDs can be achieved by 20 months
- Parent's suspicion: 18-30 months
- The age of first diagnosis is around 36/48 months

Gap between age at first symptoms and age at referral

> 1 year

Early symptoms

| AGE | SOCIAL INTERACTION | COMUNICATION | STEREOTYPED BEHAVIORS |
|---------------------|---|---|--|
| 6-12 MONTHS | <ul style="list-style-type: none"> ❖ Poor eye contact ❖ Deficit of social smiling ❖ Limited affective range and social reciprocity | <ul style="list-style-type: none"> ❖ Poor vocalizations ❖ Limited use of facial expression | Restricted interests |
| 9-14 MONTHS | <ul style="list-style-type: none"> ❖ Failure to respond to name ❖ Deficit of visual attention ❖ Failure to show things to others and to share interest | <ul style="list-style-type: none"> ❖ Delay of expressive/receptive language ❖ Absence/poor pointing | <ul style="list-style-type: none"> ❖ Repetitive patterns of play ❖ Motor stereotypies |
| 18-24 MONTHS | <ul style="list-style-type: none"> ❖ Failure in imitation ❖ Absence of interest for others children ❖ Poor reactivity to others' emotions ❖ Limited range of facial expressions | <ul style="list-style-type: none"> ❖ Delay of expressive/receptive language ❖ No coordination between eye contact and verbal communication ❖ Echolalia | <ul style="list-style-type: none"> ❖ Restricted interests and repetitive activities ❖ Impoverished stereotyped play ❖ Interest in specific visual stimuli ❖ Hand and finger mannerisms |

Neurobiology of Autism

Developmental Genes Abnormalities



Abnormal brain growth / development



Anatomical and functional abnormalities

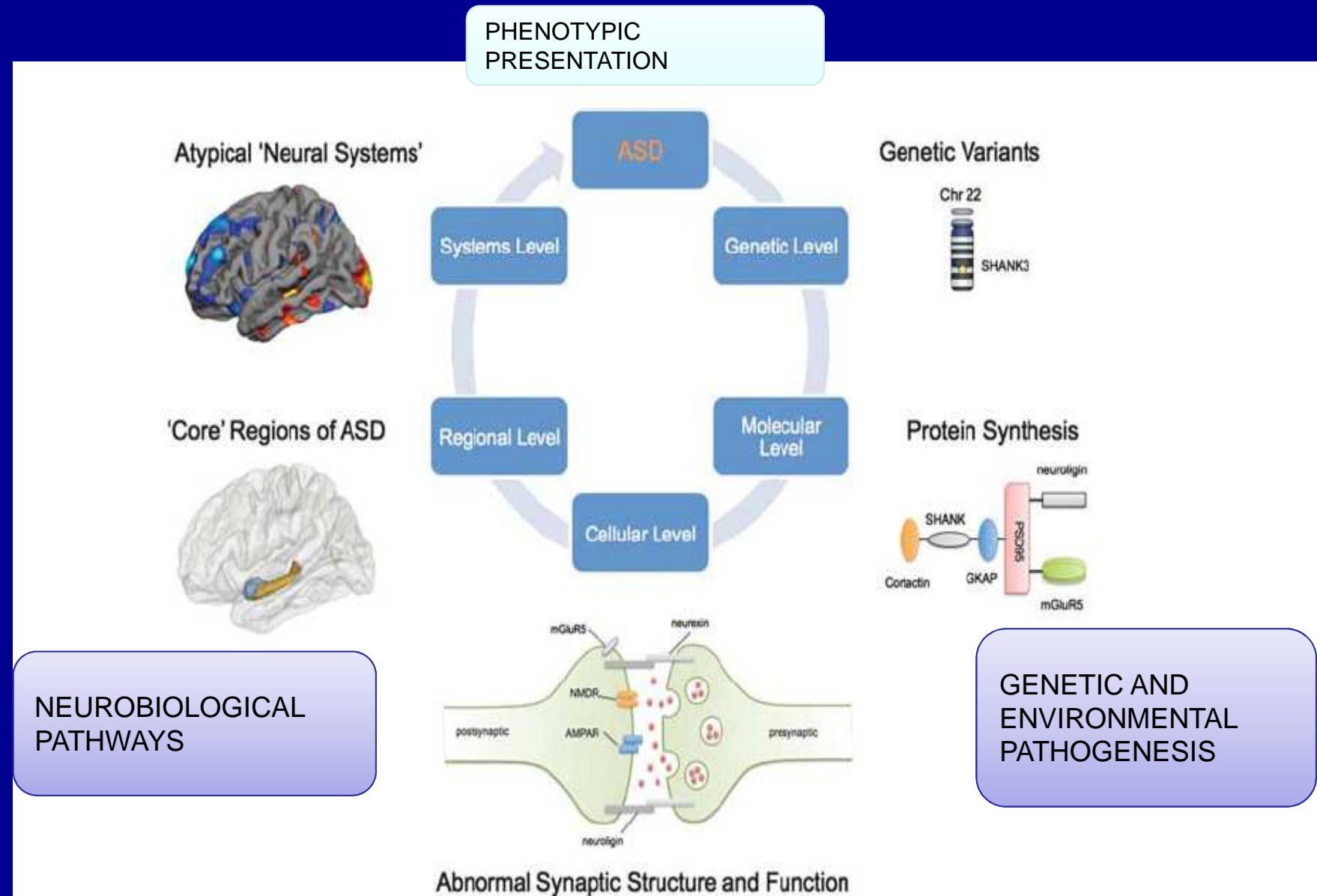


Cognitive and neurological impairment



Behavioral problems

Autism Spectrum Disorders are heterogeneous set of developmental disorders in term of:



Current understanding of the causes of ASDs



20 % known

-5% syndromic

-5% chromosomal abnormalities

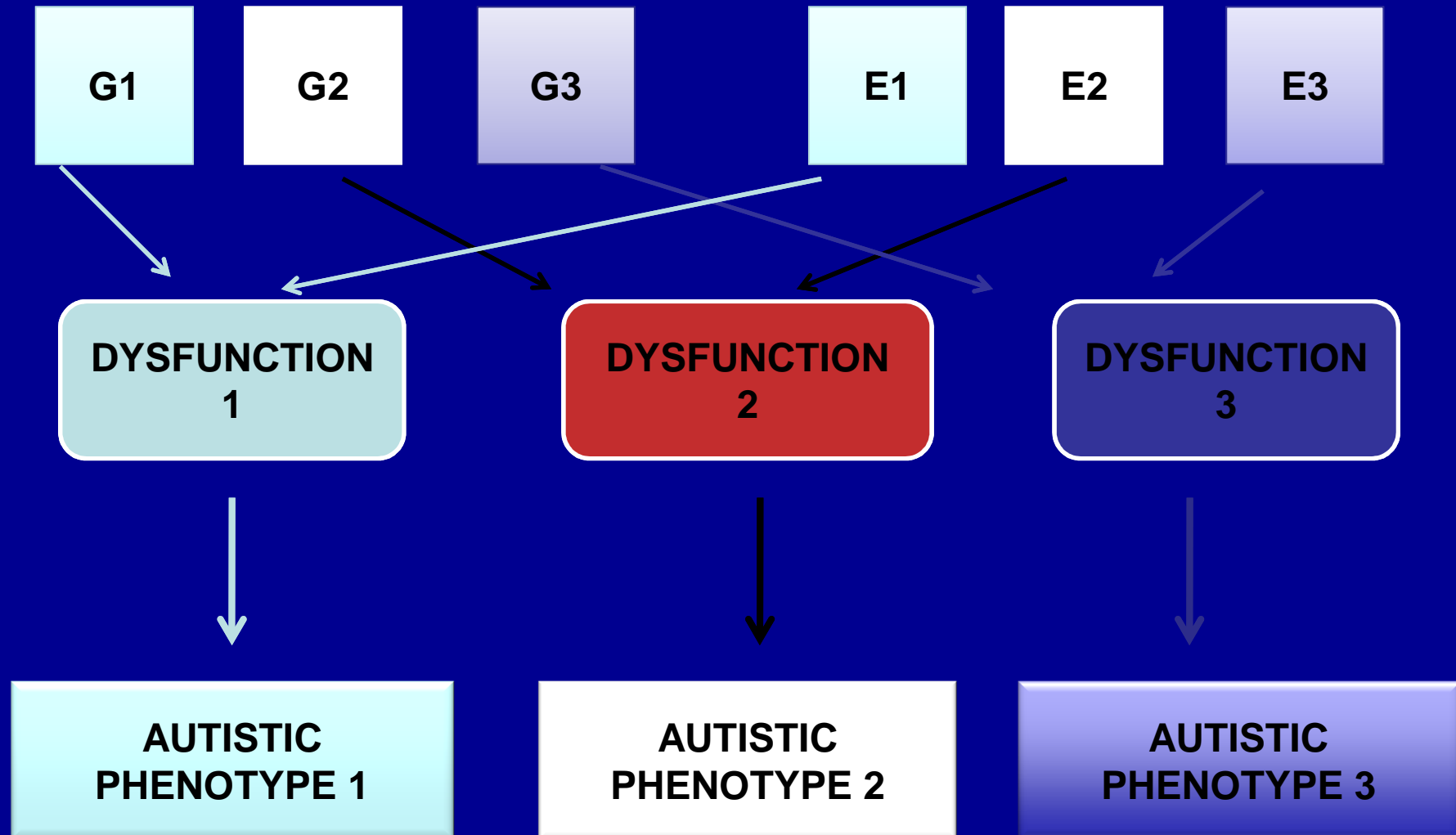
-10 % submicr del/dupl

80% unknown

Epigenetic Risk Factors in Autism

- Daily smoking in early pregnancy
- Small for gestational age
- Lower optimality at birth
- Pre-postnatal infections
- Environmental toxicity
- No association with MMR vaccination

Causal and clinical heterogeneity in ASD



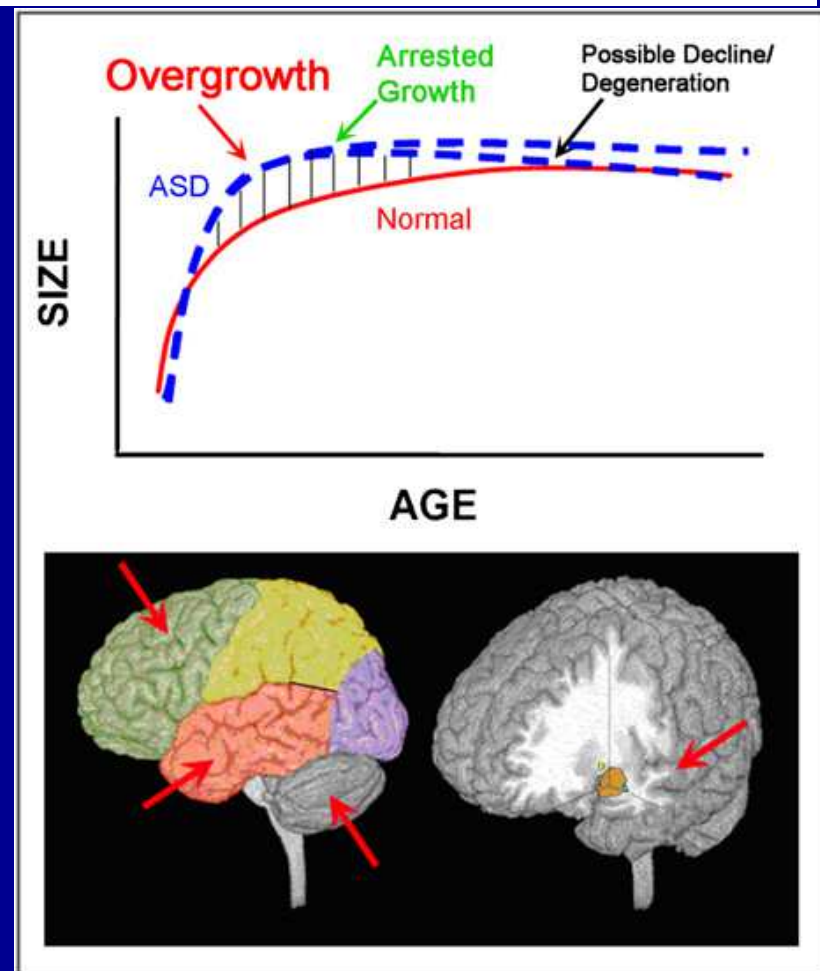
Identifying multiple pathogenetic components to assess their association with biological endophenotypes.

Table 1. Principal Component Structure of Autism Spectrum Disorders [From Sacco et al., 2010]

| I: Circadian and sensory dysfunction | II: Immune dysfunction | III: Neurodevelopmental delay | IV: Stereotypic behavior |
|---------------------------------------|--|--|-------------------------------|
| Sleep disorders | History of allergies in the patient | Level of verbal language development | Verbal and vocal stereotypies |
| Self-injurious behaviors | History of any allergic and/or immune disease in the family | Age at verbal language development | Motor stereotypies |
| Hyperactivity | History of any infectious disease at autism onset | Age at nonverbal language development | Age at first social smile |
| Decreased pain sensitivity | Obstetric complications or recurrent abortions in the mother | Age at walking | |
| Age at nonverbal language development | Pregnancy duration | Age at acquisition of bladder control at night | |
| Level of verbal language development | | | |

Mapping Early Brain Development in Autism

- ❑ Model of early brain overgrowth, followed by arrest of growth in autistic children.
- ❑ Macrocephaly observed in 14-34% of autistic children.
- ❑ Sites of regional overgrowth in ASD include frontal and temporal cortices, cerebellum, and amygdala.



Courchesne et al. 2007

Syndromic autism: causes and pathogenetic pathways

Arianna Benvenuto, Romina Moavero, Riccardo Alessandrelli, Barbara Manzi, Paolo Curatolo

| Gene | Chromosome | Functions | CNS abnormalities | Clinical phenotypes |
|----------------------------------|---------------|--|--|---|
| <i>NGL3</i> ^[60,61] | Xq13.1 | Synaptic transmission, differentiation of synaptic contacts | Synaptic or dendritic changes | Autism with motor tics, mild to severe autism, PDD-NOS |
| <i>NGL4</i> ^[60,61] | Xp22.3 | | | |
| <i>SHANK3</i> ^[11,62] | 22q13 | Master organizer of postsynaptic density at glutamatergic synapses | Synaptic or dendritic changes | Multiple developmental delays, dysmorphic features, autism with severe language and social deficits |
| <i>MAPK3</i> ^[63] | 16p11.2 | Cell to cell signaling and postsynaptic density | Synaptic or dendritic changes | - |
| <i>OXTR</i> ^[64] | 3p25-26 | Oxytocin receptor, mediator of affiliative behavior | Abnormalities of neurotransmitters | - |
| <i>CNTNAP2</i> ^[24] | 7q35 | Contactin associated protein-like 2 | Restricted pattern of expression: frontal and anterior temporal lobes, striatum, and dorsal thalamus | Seizures, developmental language delay, autism |
| <i>GADI</i> ^[65] | 2q31 | Catalyzes the production of GABA from glutamate | - | - |
| <i>CADMI</i> ^[66] | 11q23 | Synaptic cell adhesion molecule promoting the formation of presynaptic terminals and inducing the functional synapse | Loss of cell adhesion functions on the cell surface with impairment of the synaptogenic pathway | Impairment of social behavior, ASD |
| <i>MCPHI</i> ^[67] | 8p23.1-8p23.2 | Microcephalin | - | Speech delay, learning difficulties |
| <i>PTEN</i> ^[68,69] | 10q23 | Regulation of cellular proliferation/differentiation | Abnormalities in brain growth | Macrocephaly, autism and developmental delay |

Low functioning Autism with unknown causes

≥ 6 dysmorphic features
(including minor anomalies, growth abnormalities, abnormal head size for age)

Progressive microcephaly,
Movement/balance disorders

Frequent laughter/smiling,
Abnormal sleep/wake cycles, Seizures,
severe hypotonia

FISH AS/PWS, UPD ch. 15,
UBE3A mutations or FISH ch. 15 with proximal probes

Inv/dup 15 syndrome

Severe speech delay,
long and narrow face with high nasal bridge
and short philtrum
+/- MCA

aCGH

3q29 microdeletion syndrome

Mild unspecific dysmorphisms/
normal appearance

-Hypotonia
- Seizures/ EEG abnormalities
- Psychiatric problems
- MCA

Targeted FISH analysis
(metaphase and /or interphase) or MLPA

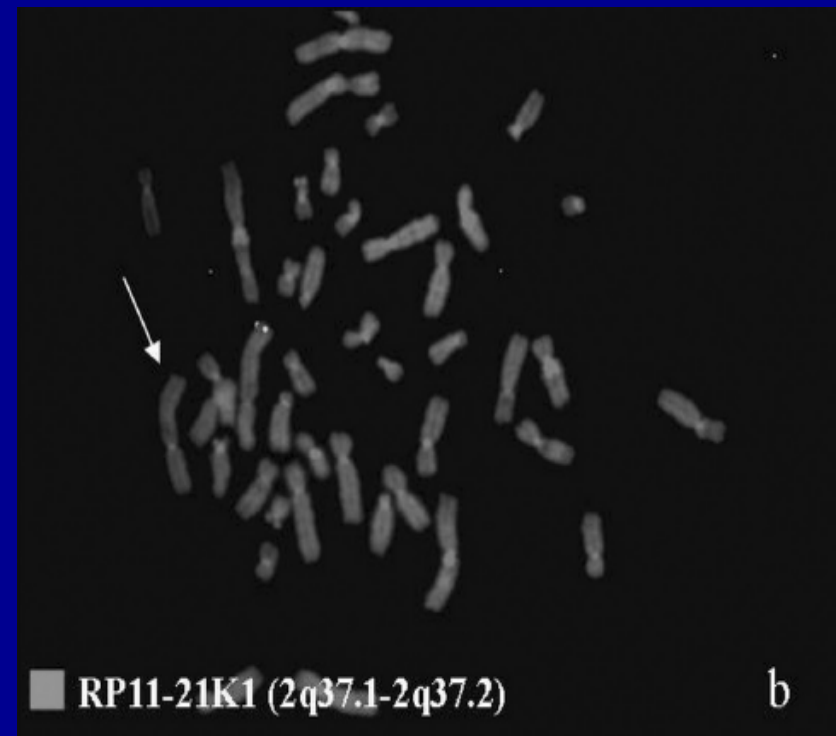
aCGH

Pathogenic CNVs

-1q21.1 del/dup
-2q37 del
-15q11-13 del/dup
-16p11.2 del/dup
-17p11.2 dup
-22q11.2 del/dup
-22q13.3 del

Deletion 2q37: An Identifiable Clinical Syndrome With Mental Retardation and Autism

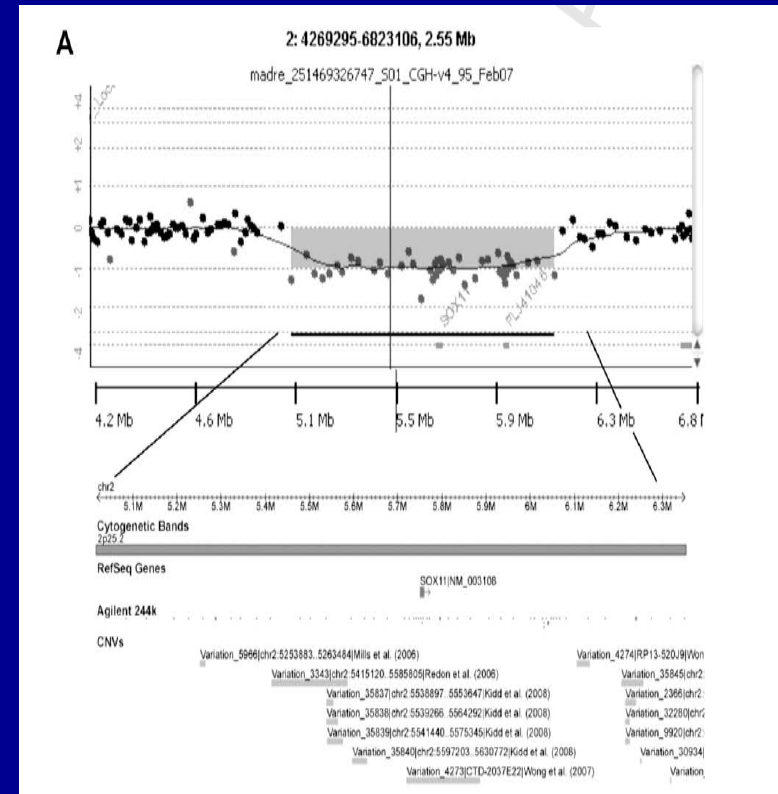
Cinzia Galasso, MD, Adriana Lo-Castro, MD, Cristina Lalli, MD, Anna Maria Nardone, Francesca Gullotta, and Paolo Curatolo, MD



Journal of Child Neurology 2008

Deletion 2p25.2: A cryptic chromosome abnormality in a patient with autism and mental retardation detected using aCGH

Adriana Lo-Castro^{a,*}, Grazia Giana^a, Marco Fichera^b, Lucia Castiglia^b, Lucia Grillo^b, Sebastiano Antonino Musumeci^b, Cinzia Galasso^a, Paolo Curatolo^a



European Journal of Medical Genetics, 2008

Autism and Metabolic Diseases

Barbara Manzi, MD, Anna Livia Loizzo, MD, Grazia Giana, MD,
and Paolo Curatolo MD

- Phenylketonuria
- Biotinidase deficiency
- Ceroid lipofuscinosis (infantile NCL)
- Mucopolysaccharidosis (S. Filippo Syndrome)
- Histidinemia
- Straight Chain Acyl CoA oxidase deficiency
- SSADH deficiency
- Purine metabolic disorders (ALD)
- Cerebral Creatinine Deficiency
- Inborn Errors of cholesterol biosynthesis
- Pyrimidine metabolism disorders

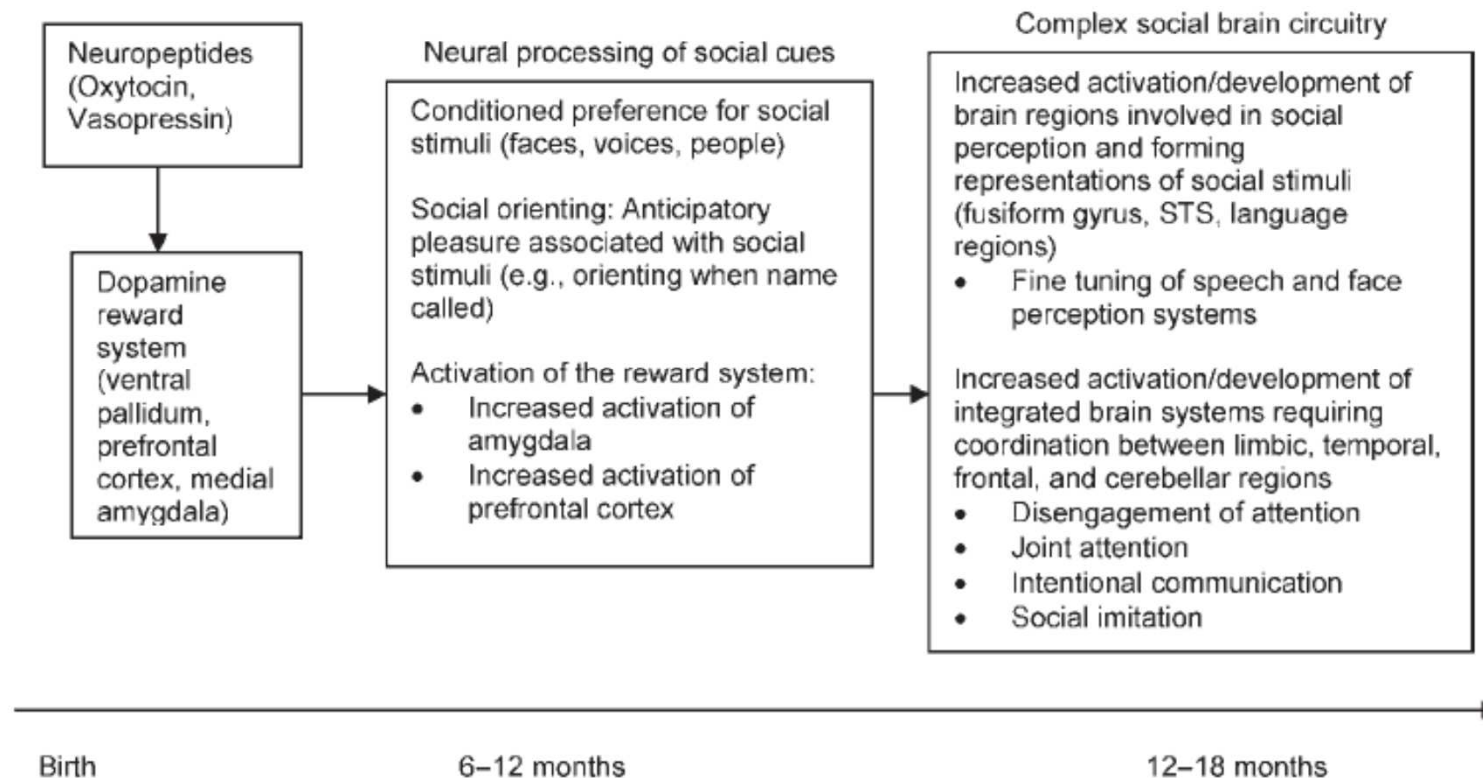
AUTISTIC REGRESSION WITH EPILEPTIFORM EEG

- ✓ Approximately 20% of ASD children appear to have relatively normal development during the first 12-24 months and subsequent global regression in language, play, social behaviour
- ✓ Age at regression: <3 years
- ✓ Gender ratio M/F: 4:1
- ✓ Seizure disorders: infrequent-varies from mild to refractory
- ✓ EEG findings: predominantly focal spikes, infrequent and intermittent

Management of ASDs

- ❖ Understand the core features
- ❖ Complete clinical assessment
 - ❖ Focus on target symptoms
- ❖ Coordinate behavioral and pharmacologic objectives
- ❖ Comprehensive treatment plan

Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder



Early critical periods in the development of SYNAPTOGENESIS and brain functions

Formation of new synapses following stimulation..

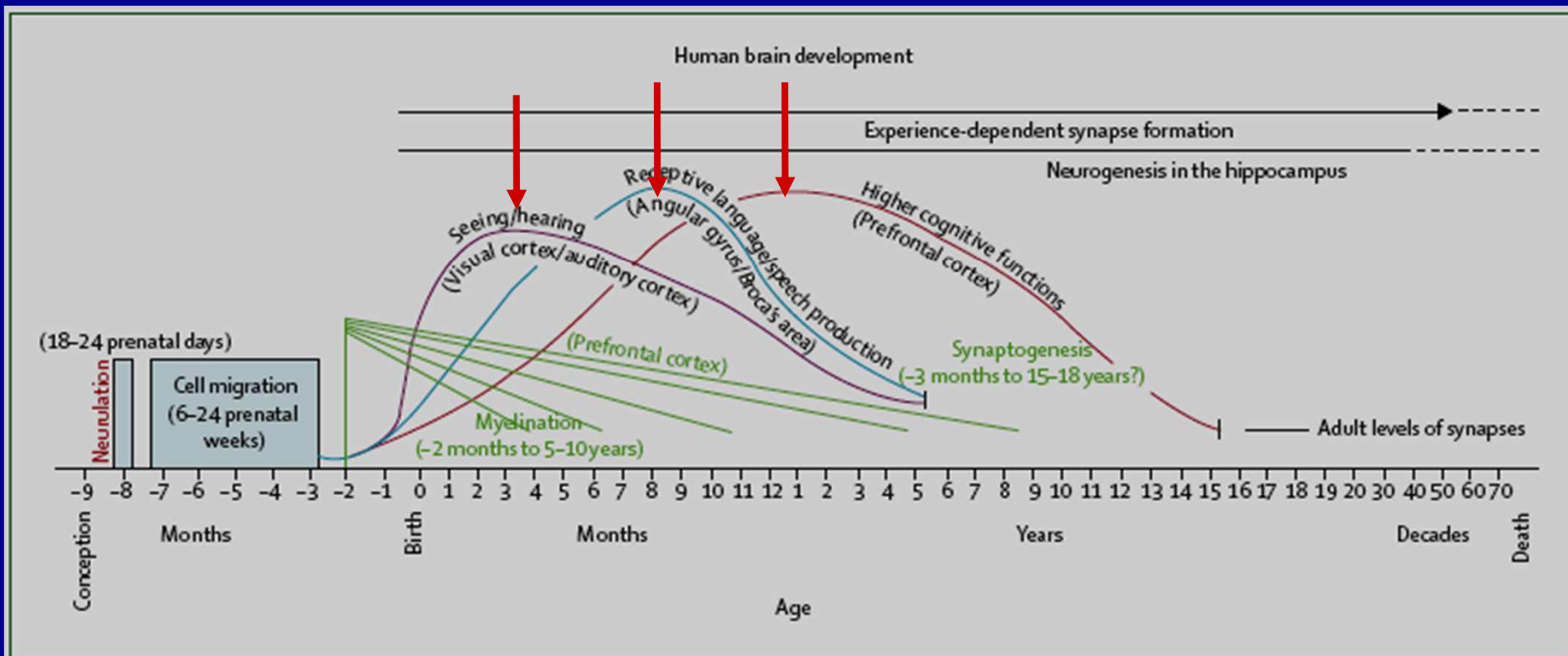


Figure 1: Human brain development

Reproduced with permission of authors and American Psychological Association[®] (Thompson RA, Nelson CA. Developmental science and the media: early brain development. *Am Psychol* 2001; 56: 5-15).

Biological basis of early intervention

Enriched environments, experience-dependent plasticity and disorders of the nervous system

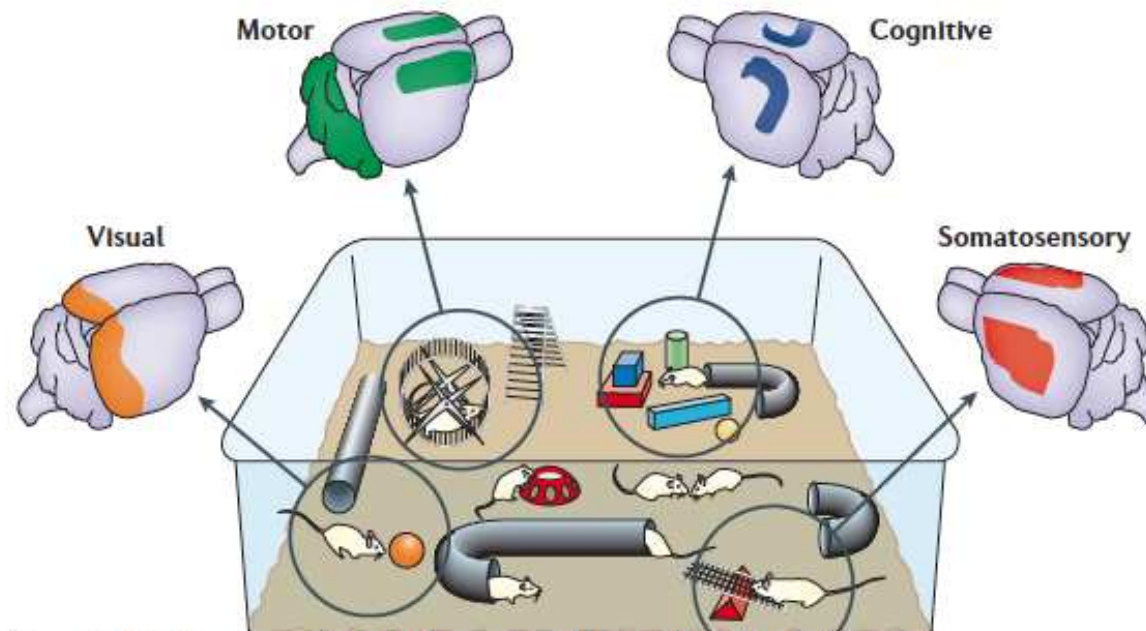
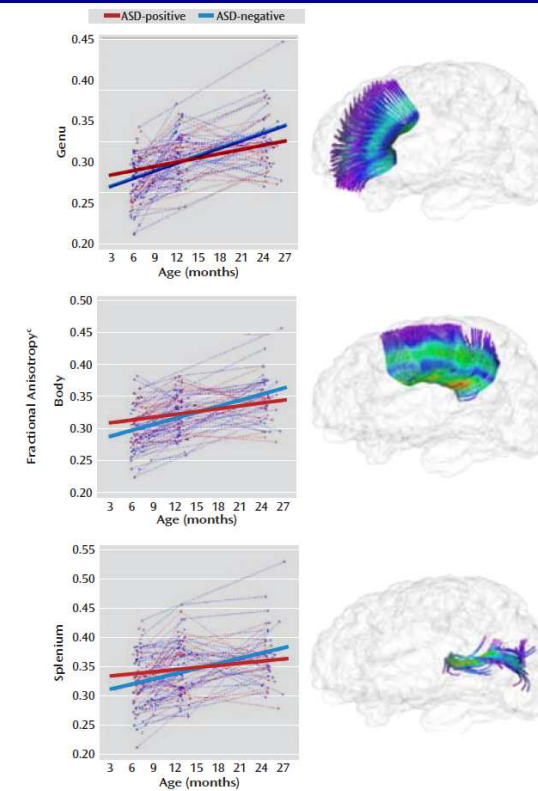
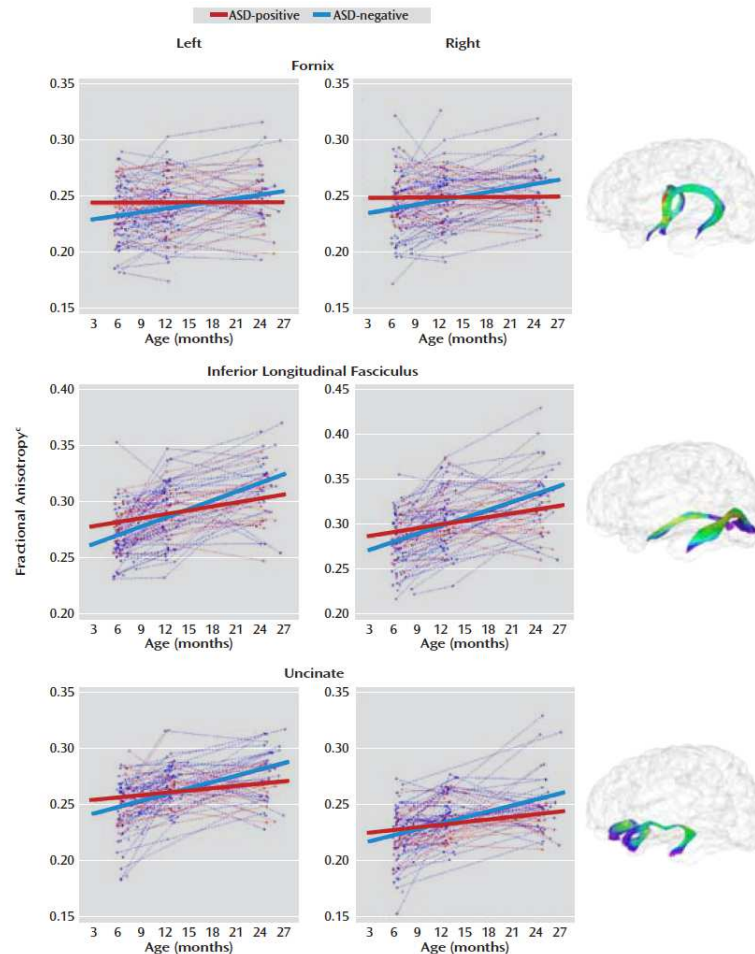


Figure 1 | Environmental enrichment and the effects of enhanced sensory,

Biological basis of early intervention

Differences in White Matter Fiber Tract Development Present From 6 to 24 Months in Infants With Autism



Wolff J. J. et al. *Am J P sychiatry*

2012.

Six Developmental Trajectories Characterize Children With Autism

❑ Significant heterogeneity also in the developmental trajectories of children with autism.

❑ Children with less severity of symptoms and high functioning at first diagnosis tended to improve more rapidly than those severely affected.

❑ Among young children with severe autism, those most likely to “bloom” are those without intellectual disability and with more educated, nonminority mothers

❑ Moreover, children from different classes would have a differential response to treatment

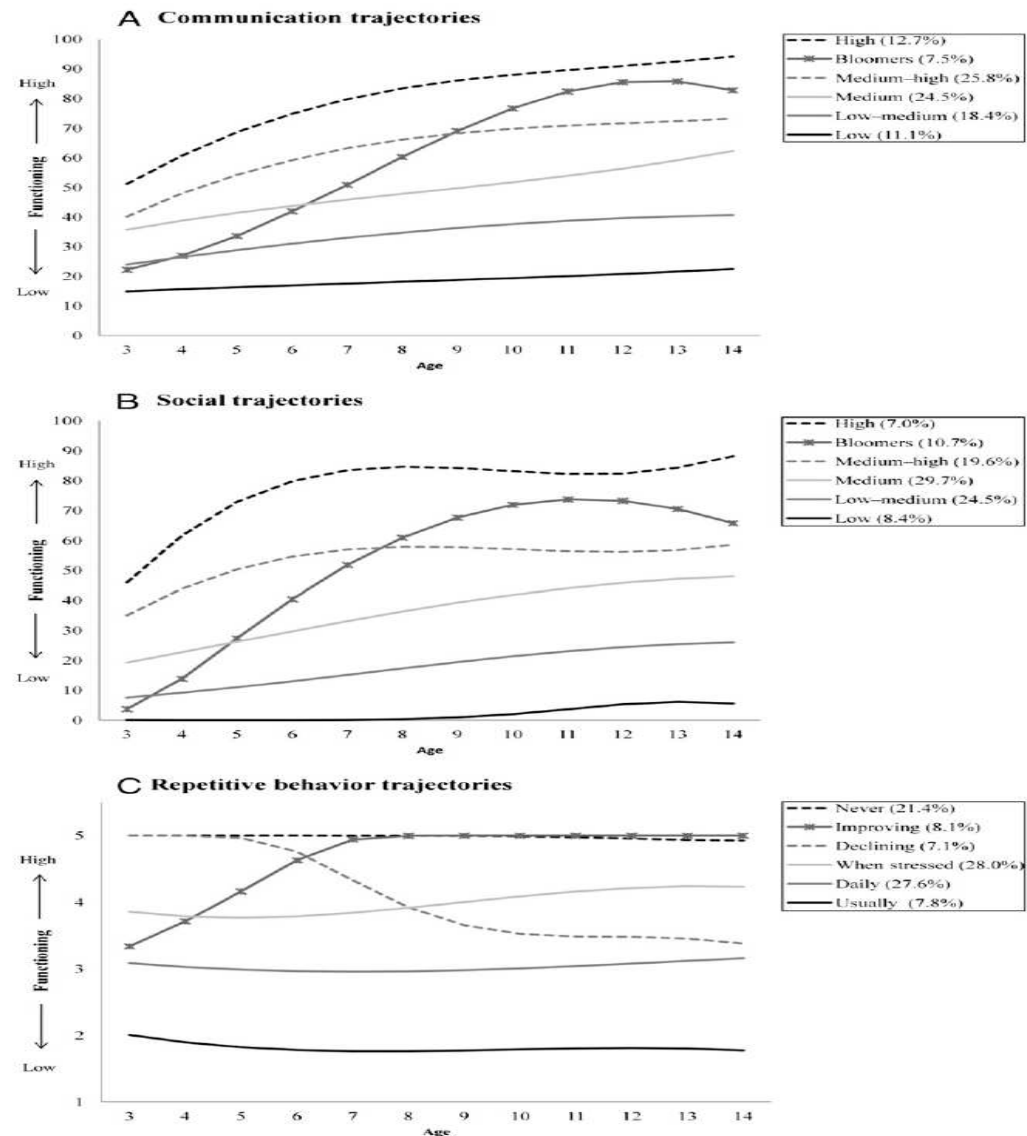


FIGURE 1
(A) Modeled communication, (B) social, and (C) repetitive behavior symptom trajectories based on CDER scores by age.

An Italian Prospective Study on Autism Treatment: The Earlier, the Better?

Giacomo Vivanti¹, Barbara Manzi², Arianna Benvenuto², Barbara Battan² and Paolo Curatolo^{2*}

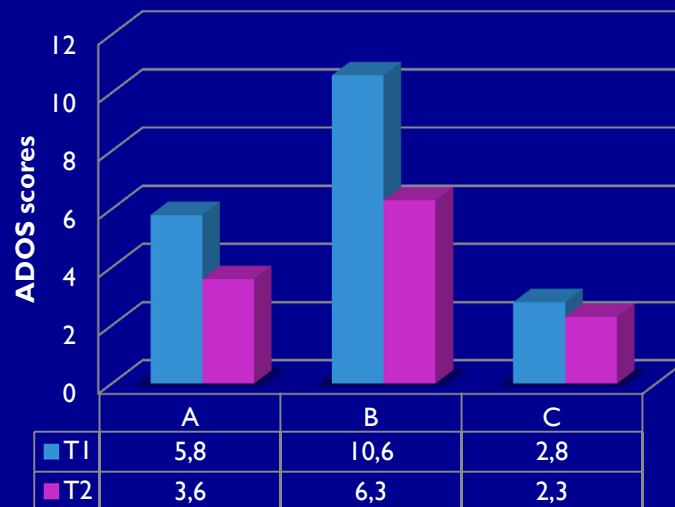
¹Olga Tennison Autism Research Centre, School of Psychological Science, La Trobe University, Melbourne, Australia

²Pediatric Neurology Unit, Tor Vergata University, Rome, Italy

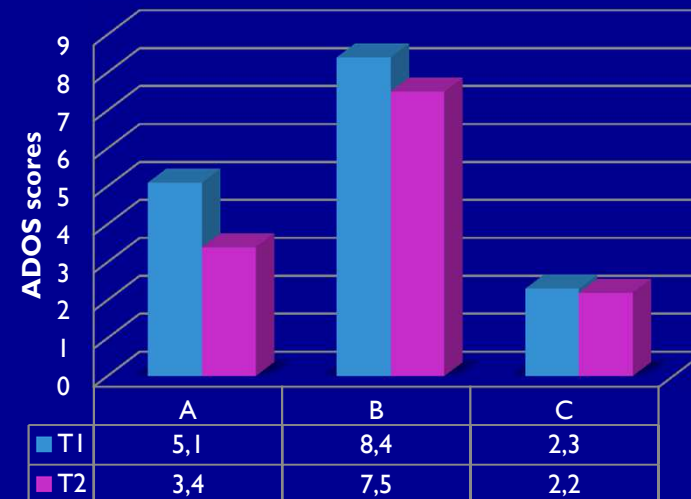
Results

Results

ADOS items (ET)



ADOS items (LT)



Very early intervention in infants at high risk for ASD

- The importance of early identification of ASD is built on the premise that earlier treatment might ameliorate the disabling effects of ASD due to the greater plasticity of younger neural systems.
- It is crucial to identify predictive clinical markers in the 6–9 month period, before developmental delay and autism behaviors appear
- Studies on longitudinal trajectories of high-risk groups have demonstrated that the development of infants later diagnosed with ASD begins to diverge from a typical trajectory between 6 and 12 months of age.

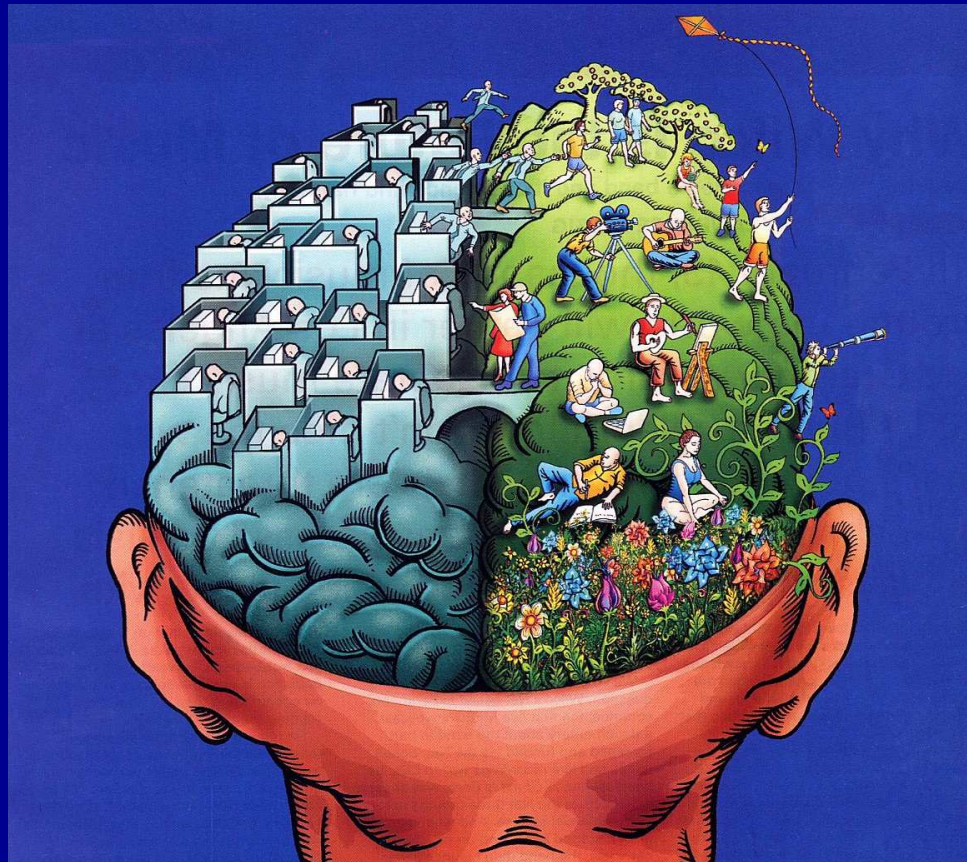
“Best Practices for Early Diagnosis and Intervention in ASD: an Italian-Israeli Consensus Conference”

Open Questions

- ❖ Can we identify early biomarkers and/or risk factors to improve the diagnosis of ASD?**
- ❖ Can earlier recognition improve the long term outcome in some children with ASD?**
- ❖ What is the significance of the high heterogeneity of the early phenotypic expression ?**
- ❖ How to individualize treatment protocols?**
- ❖ How can coordination of care in infancy and early childhood be improved?**
- ❖ How does early intervention influence the neurodevelopment of children with ASD?**
- ❖ How can early intensive treatment help a genetic disorder?**

EARLY
INTERVENTION

CHANGES IN
DEVELOPMENTAL TRAJECTORIES



CHANGES IN
BRAIN ARCHITECTURE



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U.O.C Neuropsichiatria Infantile

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Dott.ssa Monica Terribili
Dott.ssa Arianna Benvenuto

Dott.ssa Barbara Battan
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Medical conditions affect the outcome of early intervention in preschool children with autism spectrum disorders

Mats Anders Eriksson • Joakim Westerlund •
Åsa Hedvall • Per Åmark • Christopher Gillberg •
Elisabeth Fernell

OBJECT: explore the frequency of genetic and other medical conditions, including epilepsy, in a representative group of preschool children with an early diagnosis of ASDs and to relate outcome to co-existing medical findings.

PARTICIPANTS: 208 children, 20–54-month-old with a diagnosis of ASD. 18 % had a significant medical or genetic condition.

RESULTS: Children with any medical/genetic condition, including epilepsy, as well as children with a history of regression had significantly lower VABS-II scores at the 2-years follow-up.

Brief Report: Predictors of Outcomes in the Early Start Denver Model Delivered in a Group Setting

Giacomo Vivanti • Cheryl Dissanayake •
Cynthia Zierhut • Sally J. Rogers •
Victorian ASELCC Team

OBJECT: provide preliminary data on the characteristics of children who are more responsive to a specific EIBI model, the ESDM, being implemented in a community-based setting.

PARTICIPANTS: comprised 21 children aged 1 year 10 months to 4 years 10 months (average = 38 months, SD = 11.5) diagnosed with an ASD.

RESULTS: children with more advanced skills in functional use of objects, goal understanding and imitation made the best developmental gains after 1 year of treatment. Cognitive abilities, social attention, intensity of the treatment and chronological age were not associated with treatment gains

The effects of intellectual functioning and autism severity on outcome of early behavioral intervention for children with autism

Esther Ben-Itzhak^{a,*}, Ditz A. Zachor^b

OBJECT: Assess the relation between pre-intervention variables (cognition, socialization and communication) to outcome in young children with autism.

PARTICIPANTS: 25 children with ASD, aged 20–32 month were enrolled in intensive behavior intervention. The children were divided into groups based on their IQ scores and on the severity of their social interaction and communication deficits.

RESULTS: Significant progress was noted in all developmental-behavioral domains after 1 year of intervention. Children with higher initial cognitive levels and children with fewer measured early social interaction deficits showed better acquisition of skills in receptive language, expressive language and play skills.