

The Importance of Standardized Early Screening from a Biological and Basic Science Perspective

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*Autism Center of Excellence at:
www.autism-center.ucsd.edu*

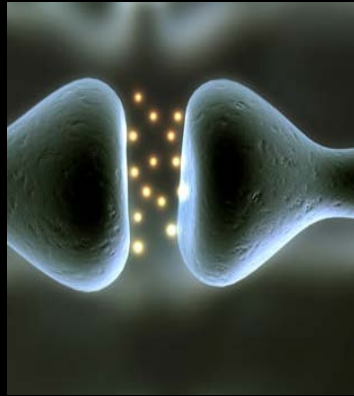


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SCHOOL OF MEDICINE

Early Enrichment, Animal Models, and Brain Plasticity

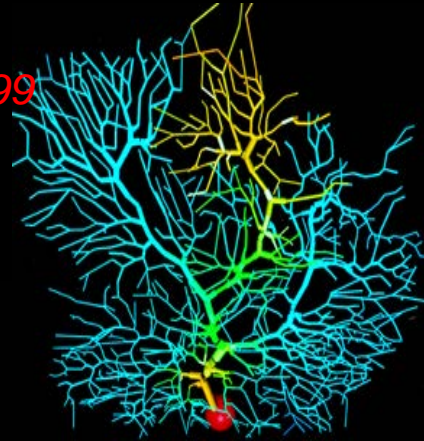
SYNAPSES

Rampon et al., 2000
Turner et al., 2003
Greenough
and Chang, Review

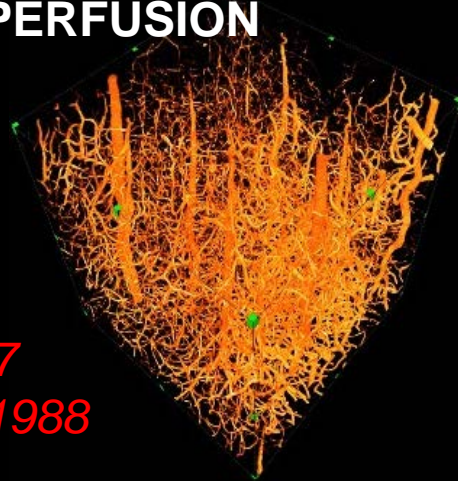


DENDRITIC BRANCHING

Nilsson et al., 1999
Greenough et al., 1986

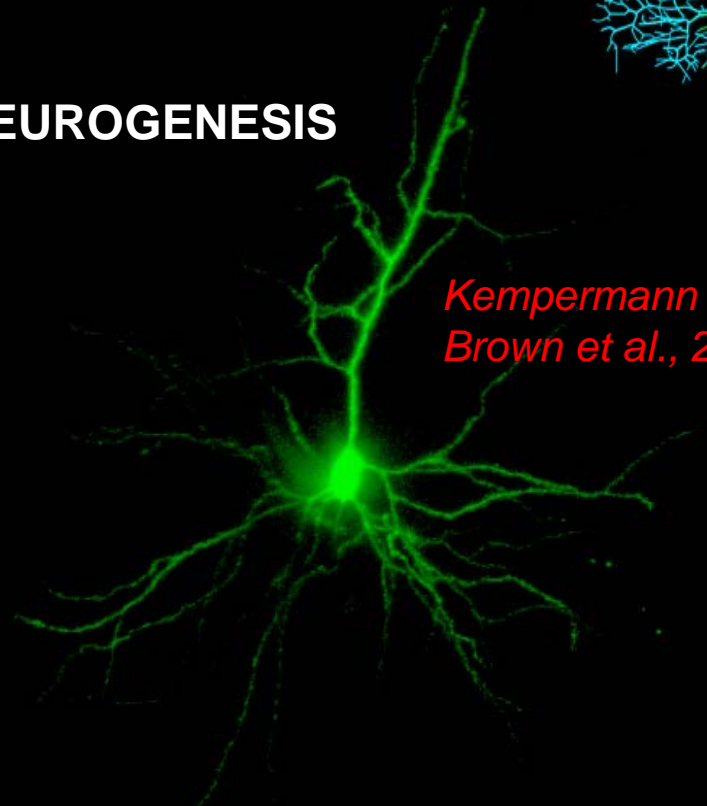


CAPILLARY PERFUSION

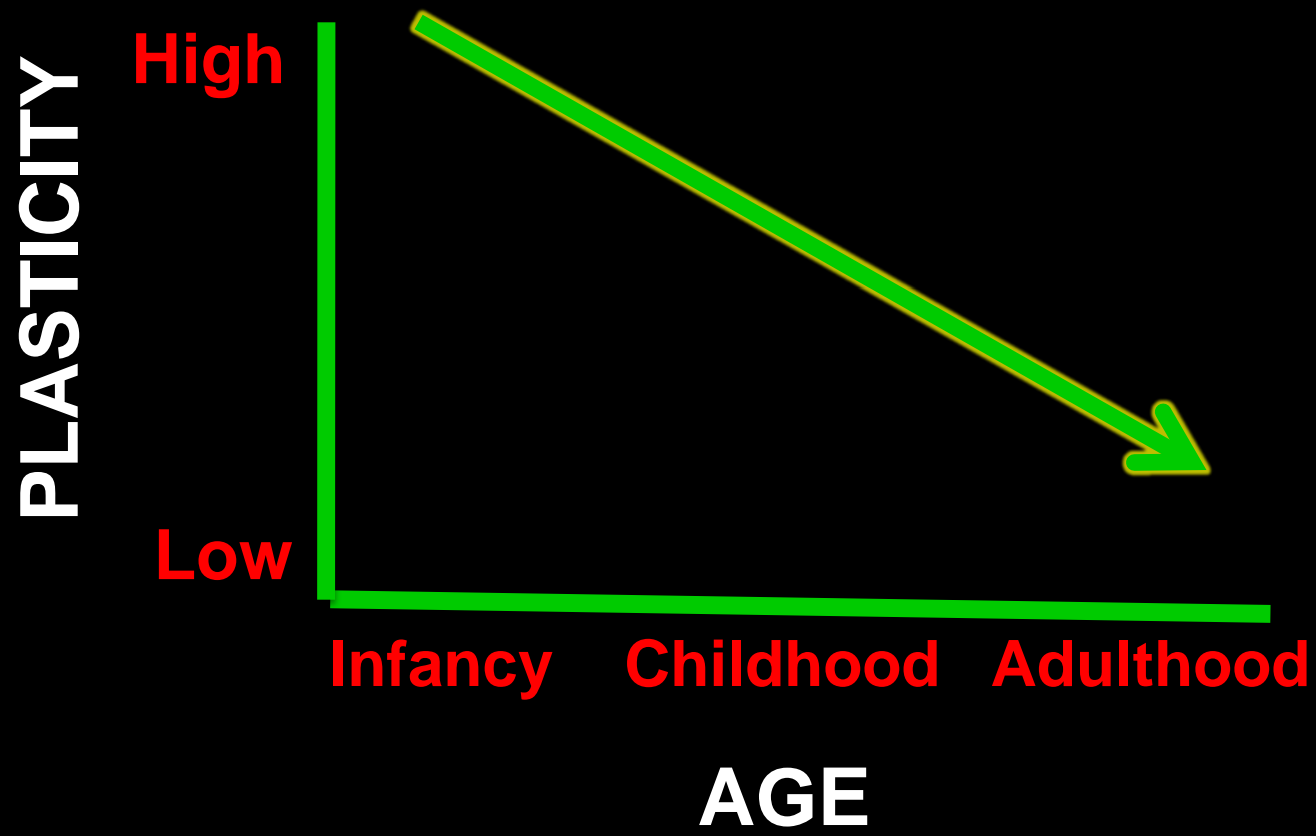


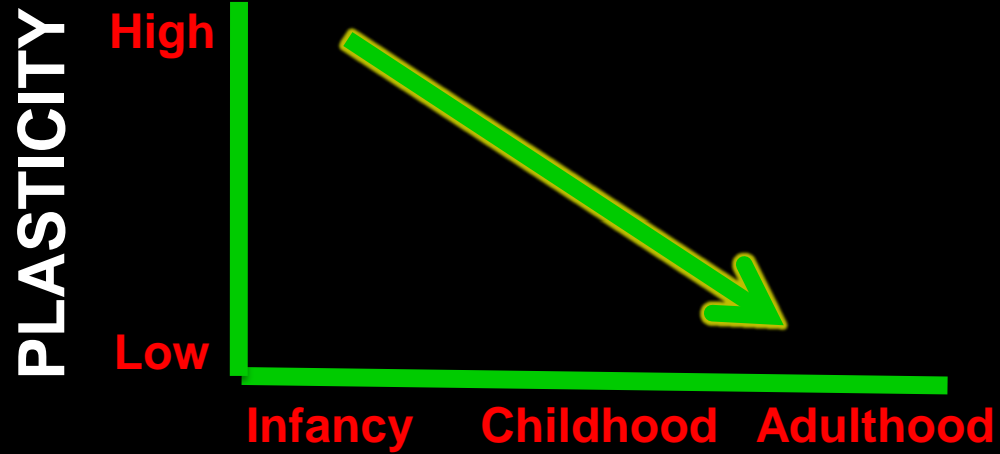
NEUROGENESIS

Kempermann et al, 1997
Brown et al., 2003

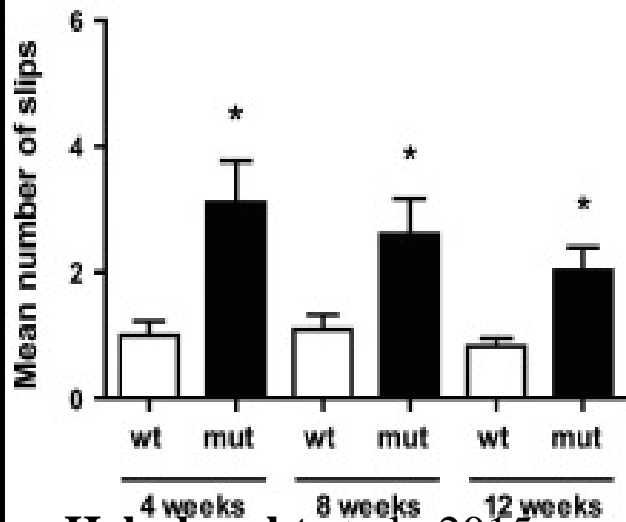


Black et al., 1987
Sirevaag et al., 1988





Normal
Housing
(No Enrichment)
:Rat with
mutation slips
more



CRITICAL PERIODS:

Lessons from Bucharest Early Intervention Project

Nelson et al., *Science*, (2007)

SUBJECTS

- 136 infants abandoned at birth in Bucharest, Romania and institutionalized
- 68 Foster Care (FCG)
- 68 Remained Institutionalized (IG)
- 72 Never Institutionalized (NIG) reared at Home with Biological Parents

Results: Bucharest Early Intervention Project

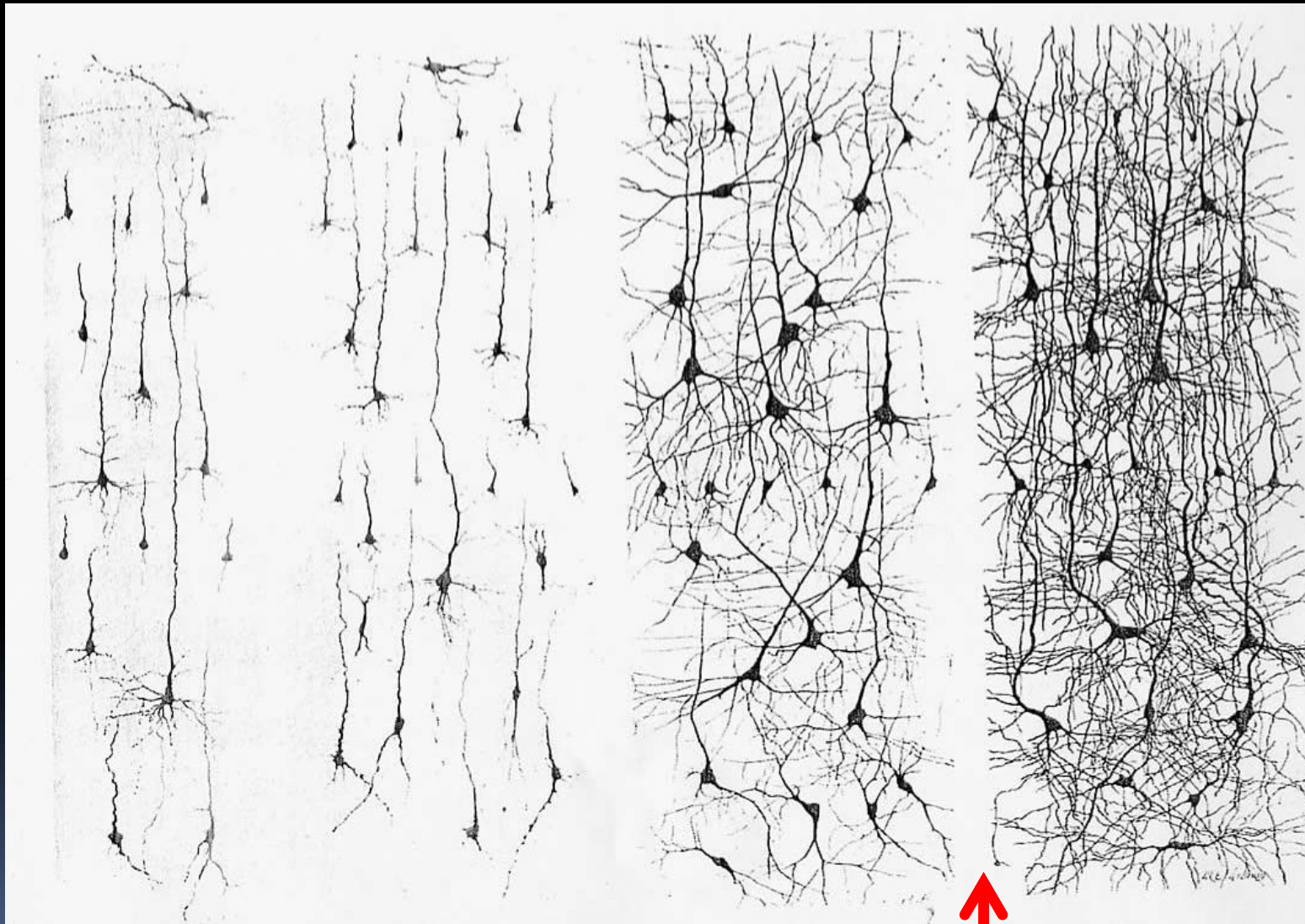
GROUP MEAN D.Q.

Institution (IG)- 42 mo	77.1
Foster Care Group- 42 mo	85.6
Never Institutionalized (NIG) 42 mo	103.4

Foster Care DQ at 42 months BY AGE OF PLACEMENT

AGE AT PLACEMENT	N	MEAN D.Q.
0-18	14	94.9
18-24	16	89.0
24-30	22	80.1
30+	9	79.7

Human Frontal Cortex Neural Development & Circuit Formation (Conel J.L. 1939)



newborn

1 month

6 months

2 years

3-4 years

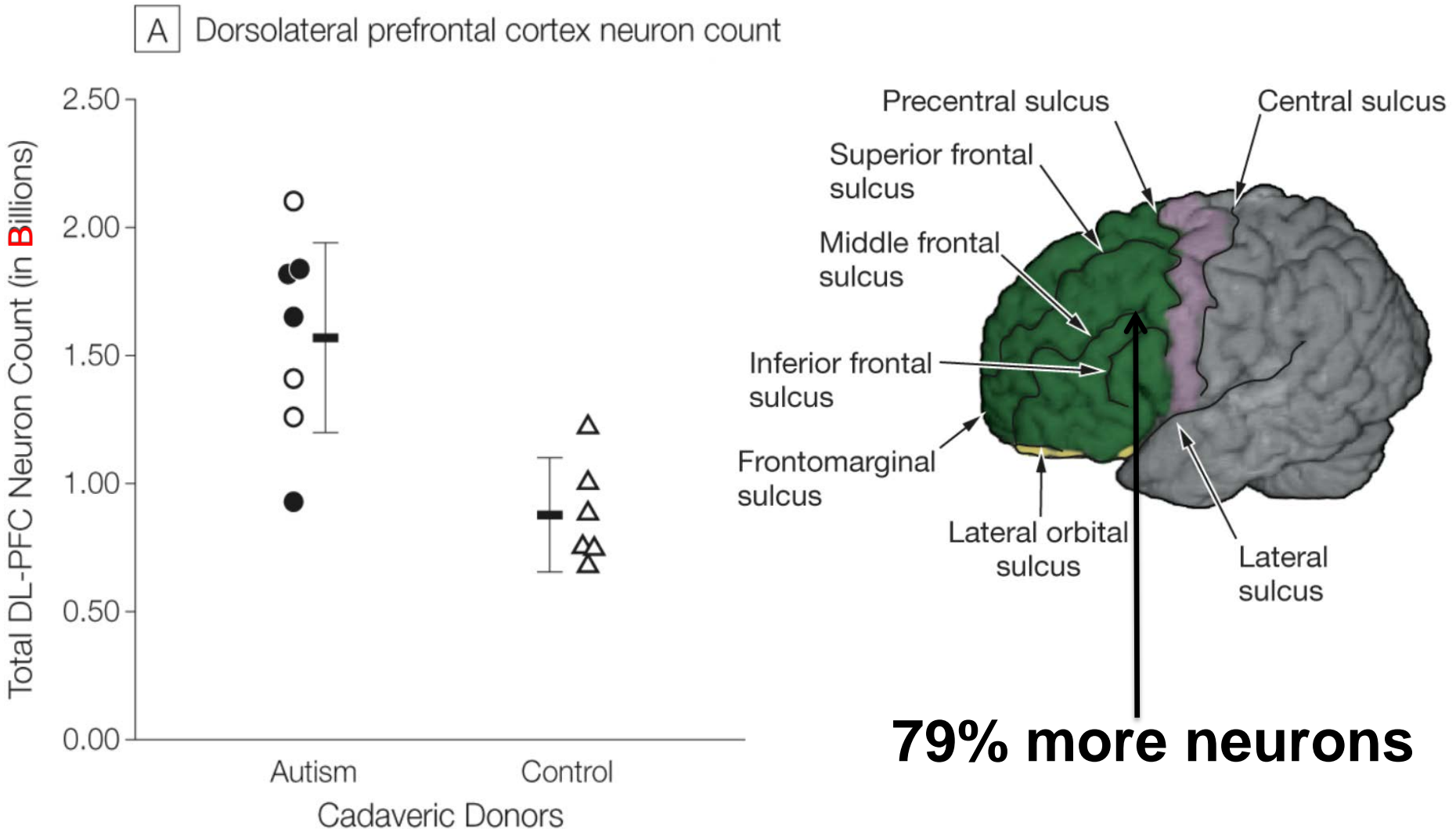
Autism
Diagnosis

Point #1:

**The Human Brain Undergoes
Massive and Rapid Changes During
the First Few Years of Life:**

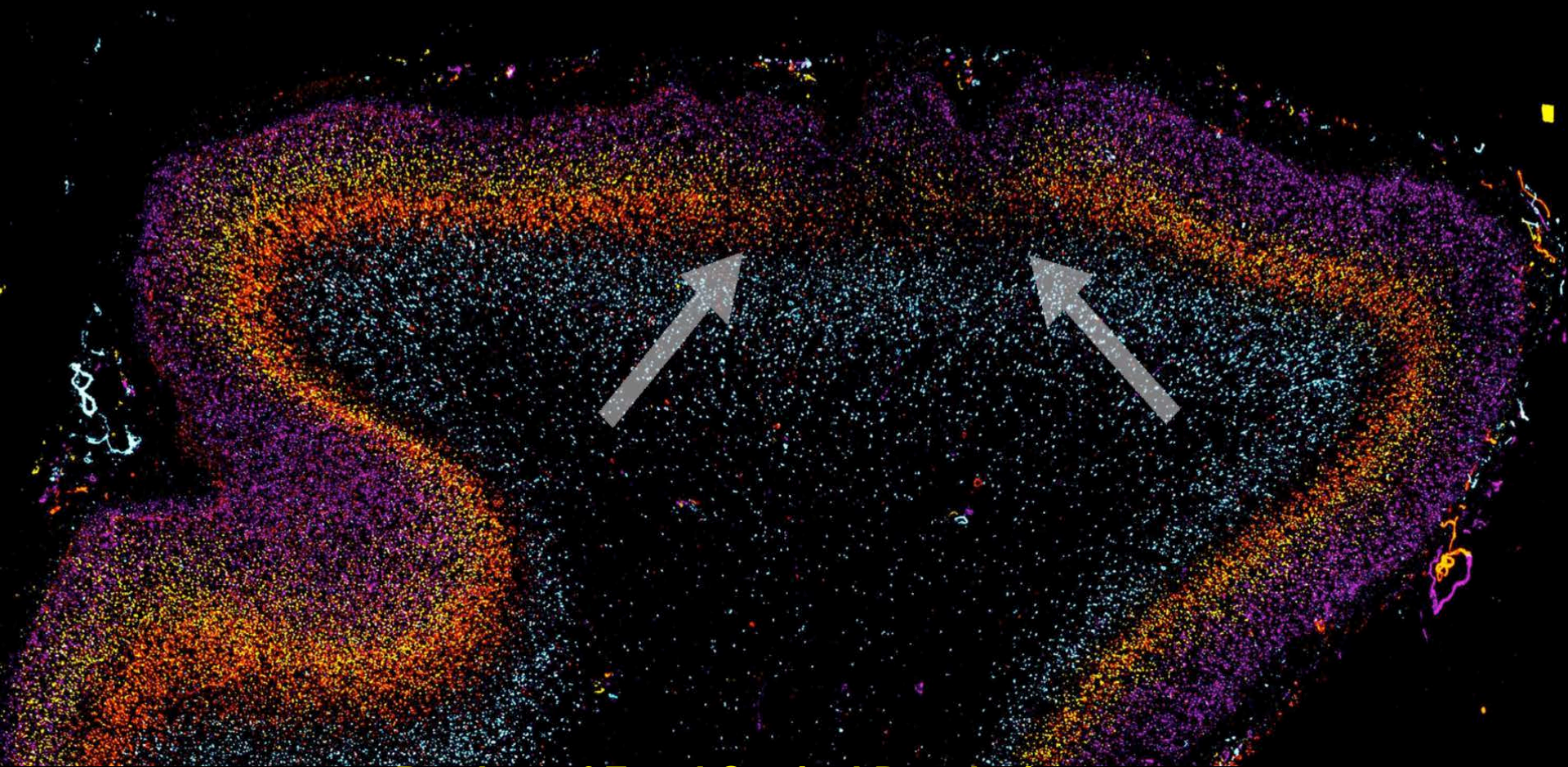
**Can we take the chance to miss this
window?**

When Does Autism Begin?



When Does Autism Begin?

We identified regions of tissue with abnormal labeling across multiple layers in autistic cortex



**Patches of Focal Cortical Dysplasia:
Abnormal Laminar Organization, Migration Defects and Clusters of
Disoriented Cells**

Stoner et al., NEJM, 2013

Point #2:
**Biologically, autism most
likely begins in the womb**

**Should we wait years to start
treatment?**

Studying Autism Prospectively: The 1Yr Well-Baby Check-Up Approach – GET SET Early Model

Pierce, et al., (2011) J. Pediatrics

1-Yr. Check-Up Approach



Rationale:

Administer a broad-band CSBS screen to detect *all* cases of delay at 12-months at routine pediatric check up → a % of cases will end up with ASD.

- **Network of 170 Peds**
- **60,000 Screened to date**
- **Average age Tx Start: 17 months**

Early Biomarkers of ASD Can Not Be Discovered Without Early Detected Cohorts from General Population

- **Eye Tracking Based**

*Eye Gaze Fixation
Patterns*

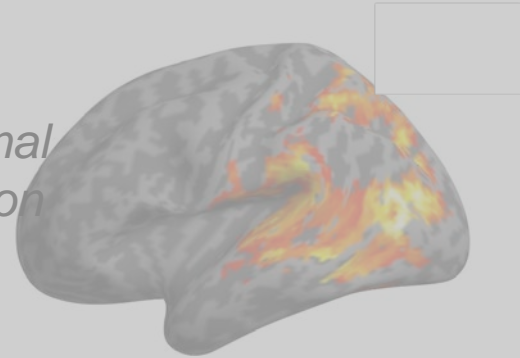


Geo Pref Test

- **Neuroimaging Based**

EEG: Bosl et al., 2011, *BMC Medicine*
fMRI: Lombardo et al., 2015, *Neuron*

*Functional
Activation
Map*



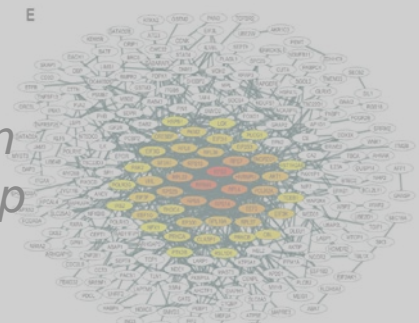
- **Blood Based**

DNA

RNA

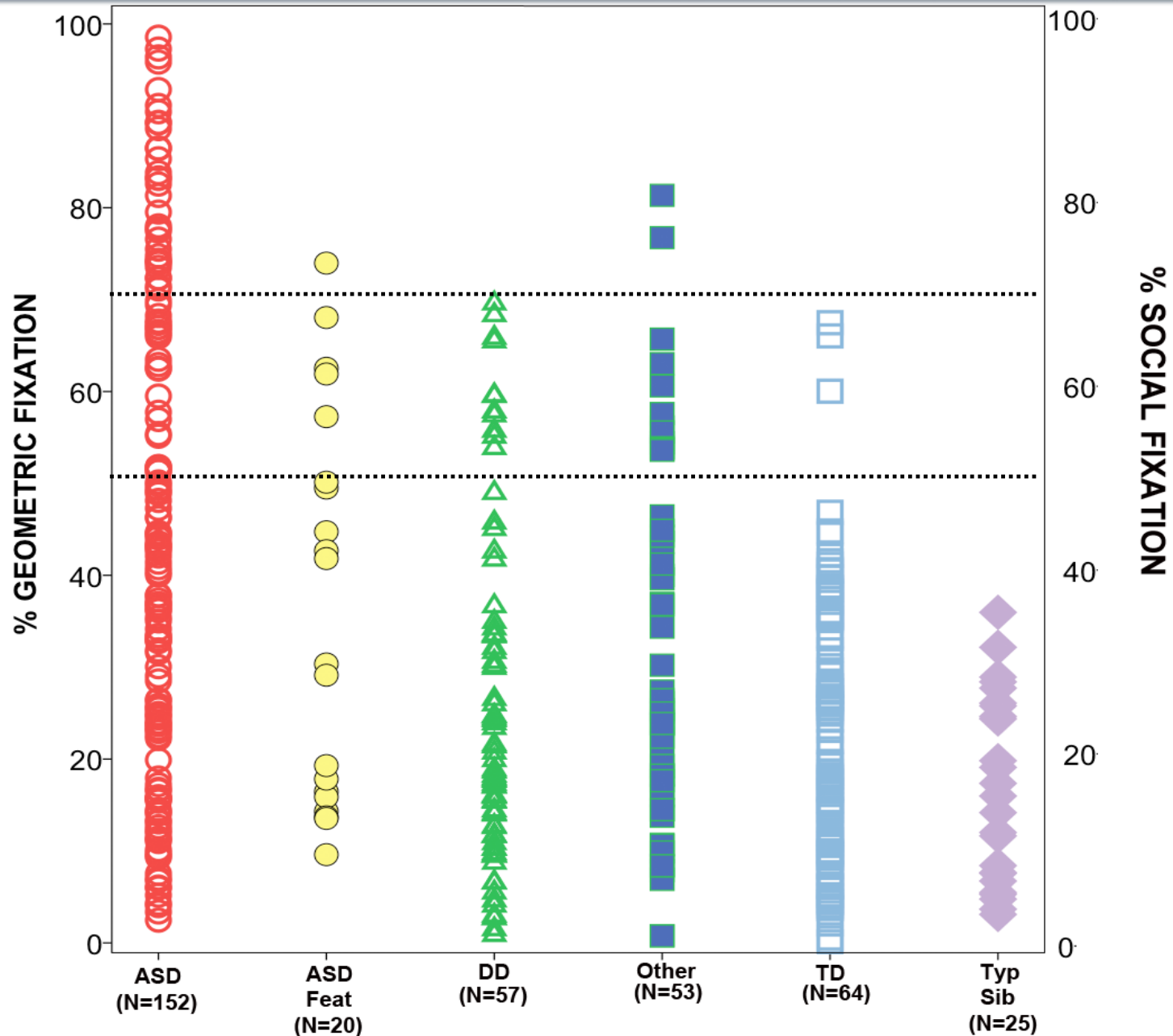
Proteomics

*Protein-Protein
Interaction map*



Pramparo et al., 2015

N=444 From a Screened Cohort

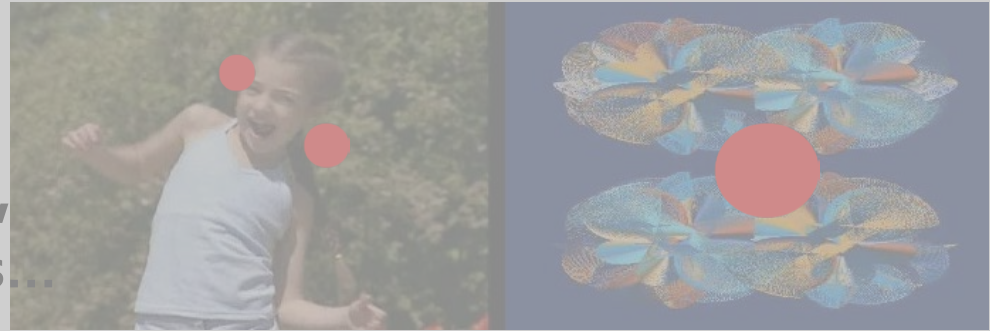


Early Biomarkers of ASD Can Not Be Discovered Without Early Detected Cohorts from General Population

- **Eye Tracking Based**

N=444, specificity for ASD 98%,
12 months, 13 months, 14 months...

Pierce et al., 2015, *Biological Psychiatry*

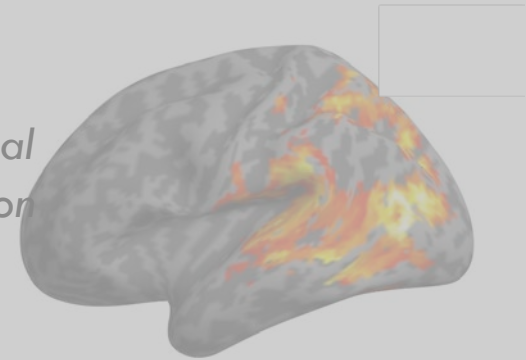


Geo Pref Test

- **Neuroimaging Based**

fMRI: Lombardo et al., 2015, *Neuron*

Functional
Activation
Map



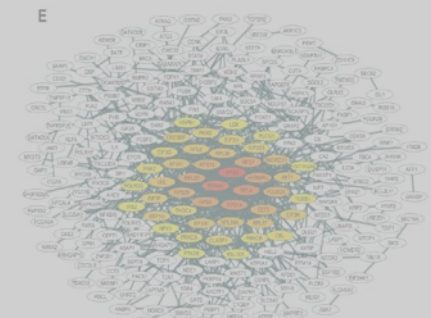
- **Blood Based**

DNA

RNA

Proteomics

Protein-Protein
Interaction map



Pramparo et al., 2015

Screened Cohorts Reveal Biomarkers of Prognosis

N=103

TYPICAL

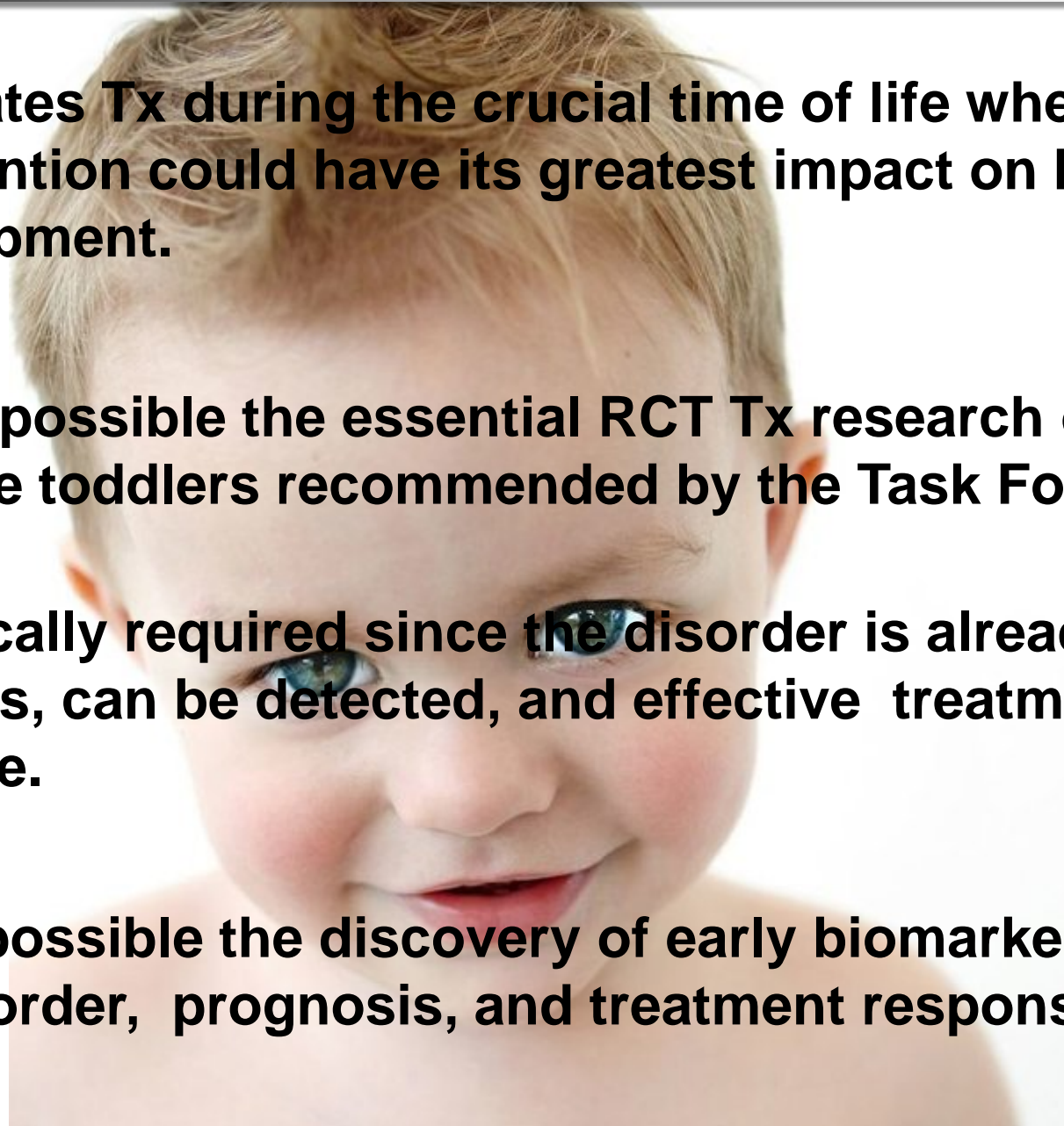
*Lombardo
et al., (2015)
Neuron*

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Point #3:

**Standard of Care Screening
Facilitates Important
Discoveries Regarding Early
ASD**

THE BENEFITS OF EARLY SCREENING

- 
- 1. Facilitates Tx during the crucial time of life when intervention could have its greatest impact on brain development.**
 - 2. Makes possible the essential RCT Tx research of screen positive toddlers recommended by the Task Force.**
 - 3. Is ethically required since the disorder is already in progress, can be detected, and effective treatments available.**
 - 4. Makes possible the discovery of early biomarkers of the disorder, prognosis, and treatment responsiveness**