



# A longitudinal analysis of Autism Spectrum Disorder The <sup>Ups</sup> and <sub>Downs</sub>

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# Disclosures

- Grant/Research Support:

NIH, The Simons Foundation, The Dana Foundation, Stemina Biomarker Discovery

- Scientific Advisory Board Member:

Stemina Biomarker Discovery, Axial Therapeutics

# Outline of Talk

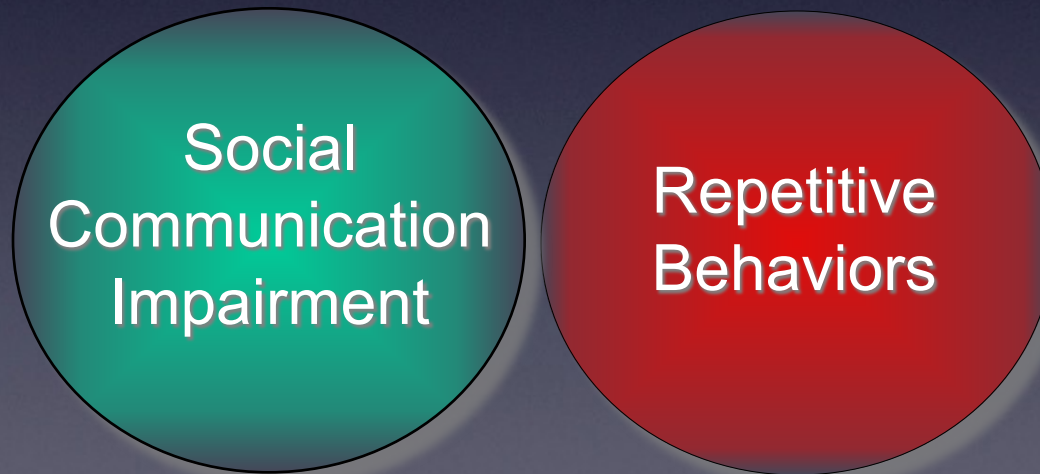
- Some basics about Autism Spectrum Disorder
- An overview of magnetic resonance imaging studies from the MIND Institute. Efforts to define “Neurophenotypes”
- Evidence for behavioral change over childhood
- Anxiety in autism and the amygdala

# What is Autism?

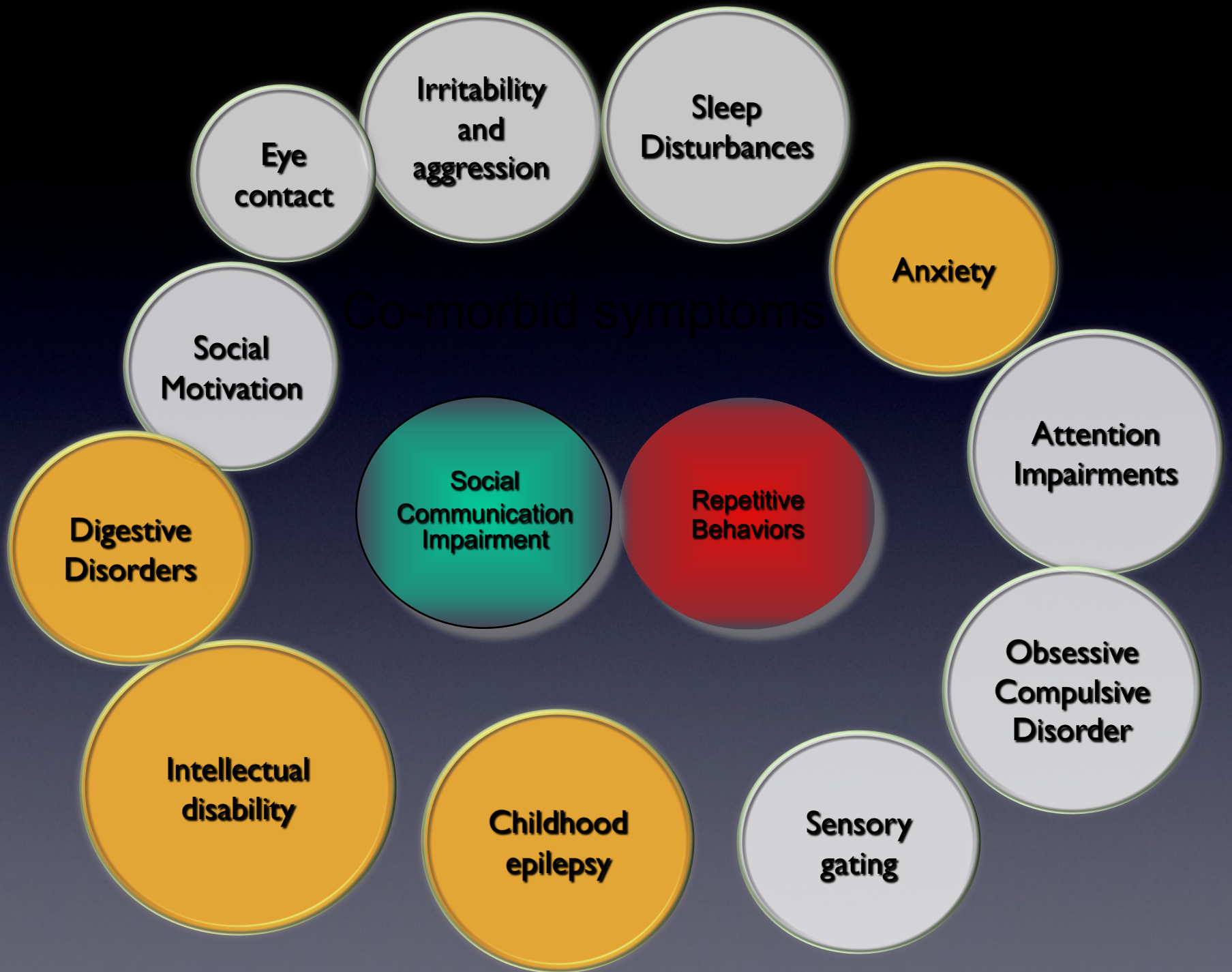


# What is Autism?

## DSM-5 Diagnostic Criteria for Autism Spectrum Disorder



Co-morbid symptoms



# What is Autism?

Male:female ratio = 4:1

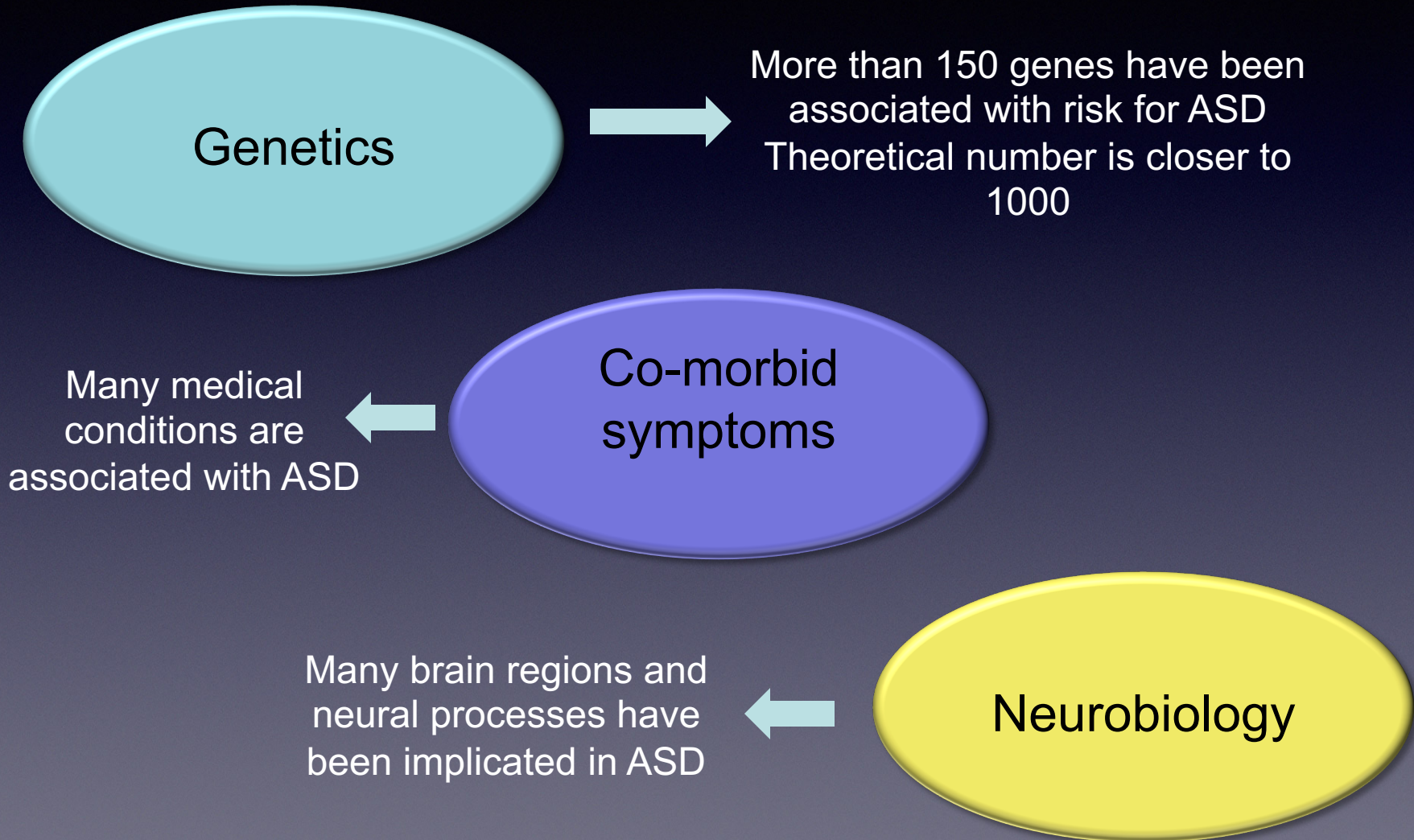


# Heterogeneity in Autism Spectrum Disorder

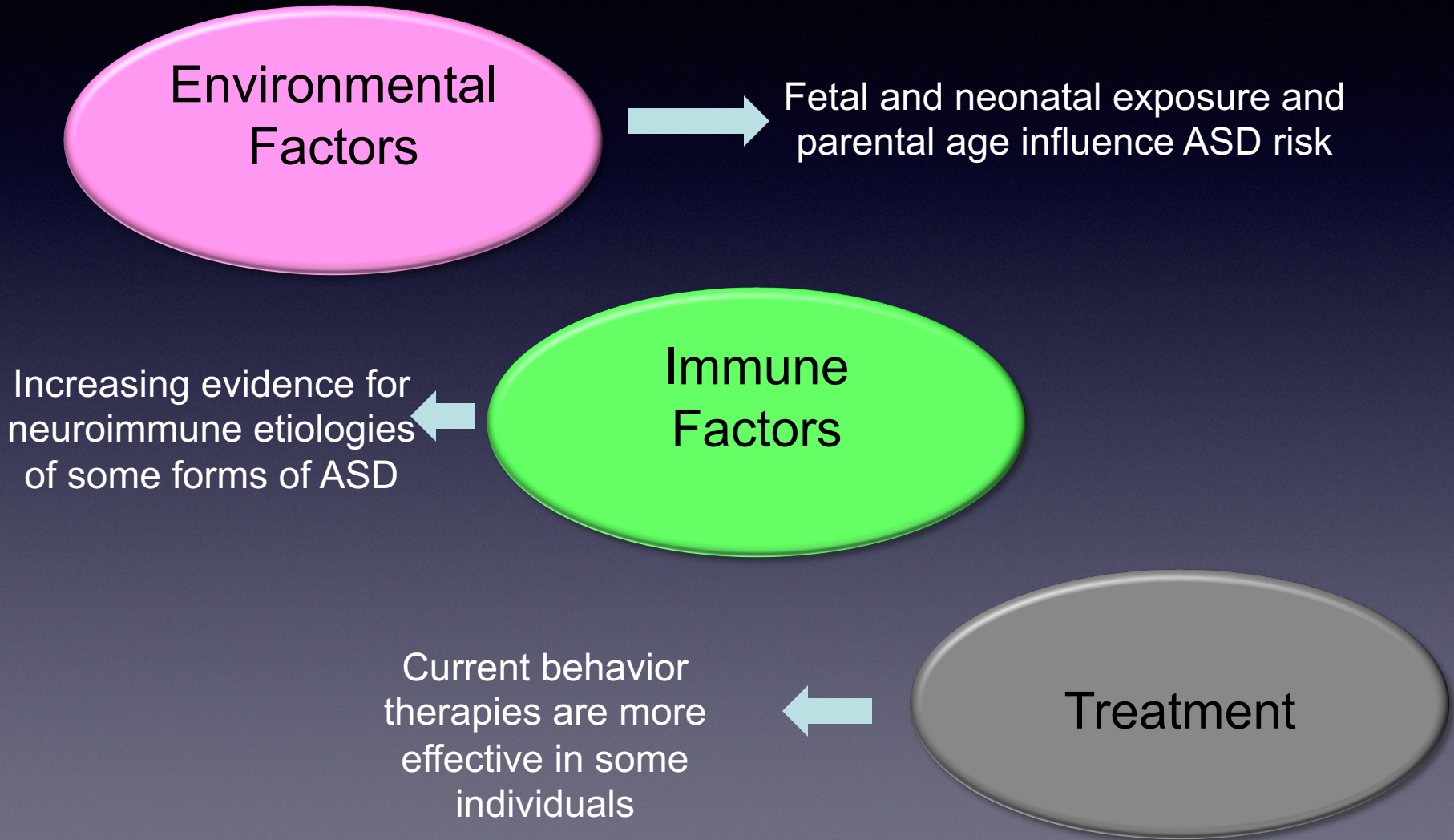
A major impediment to early diagnosis, biological understanding and more effective treatment of autism spectrum disorder is the enormous **heterogeneity** of virtually all of its features.



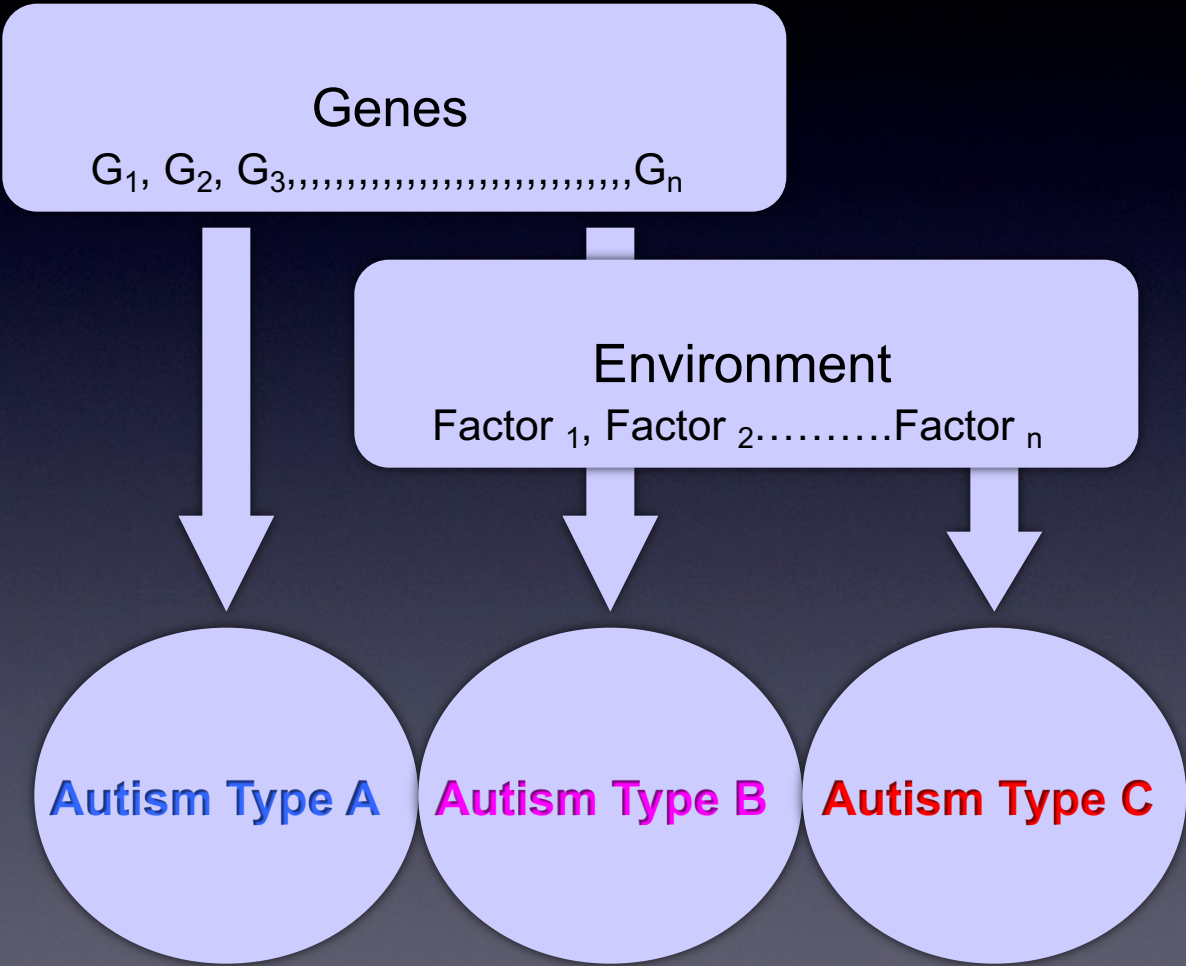
# Heterogeneity in Autism Spectrum Disorder



# Heterogeneity in Autism Spectrum Disorder



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# Heterogeneity in Autism Spectrum Disorder

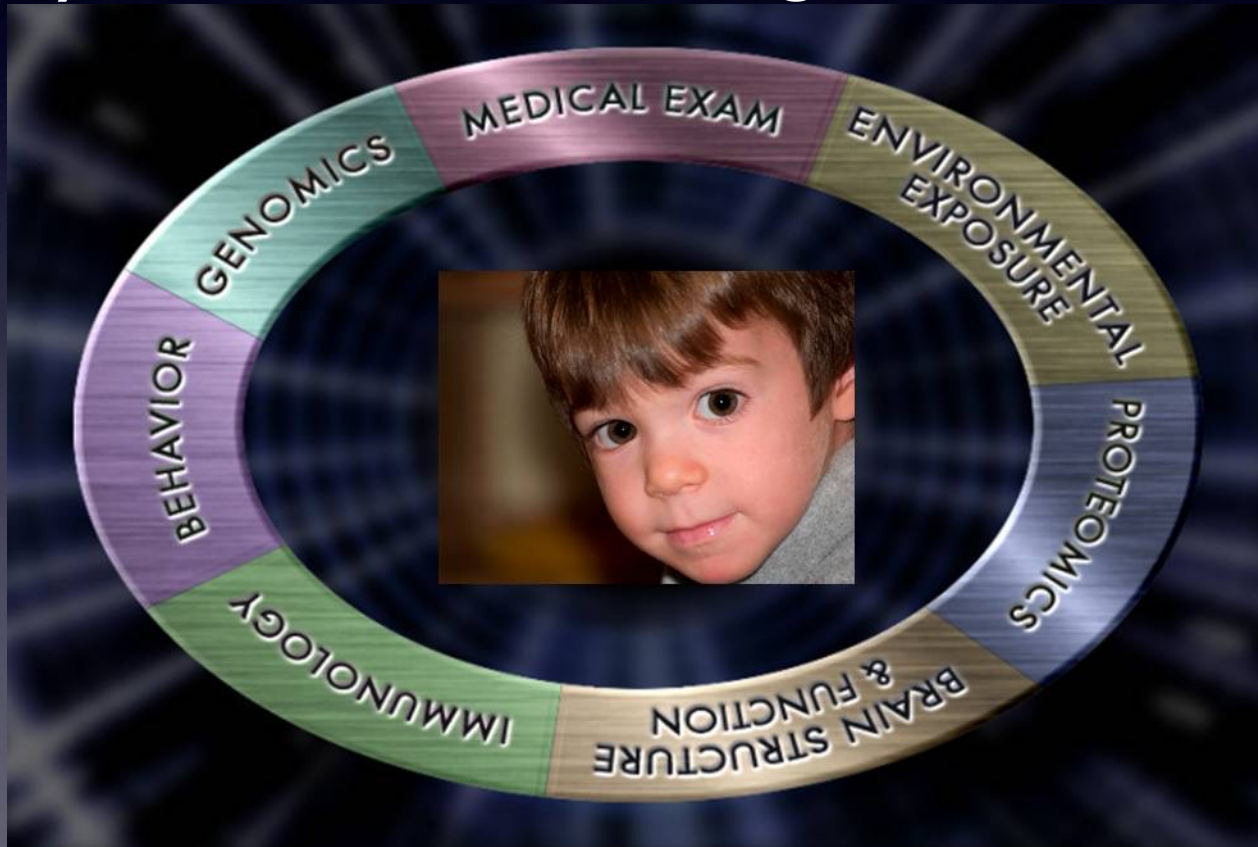
There are many causes of  
autism and many types of  
autism

AutismS not Autism

# Autism Phenome Project

Large-scale multidisciplinary project aimed at identifying subtypes of autism

2 to 3.5 year old children, longitudinal assessments



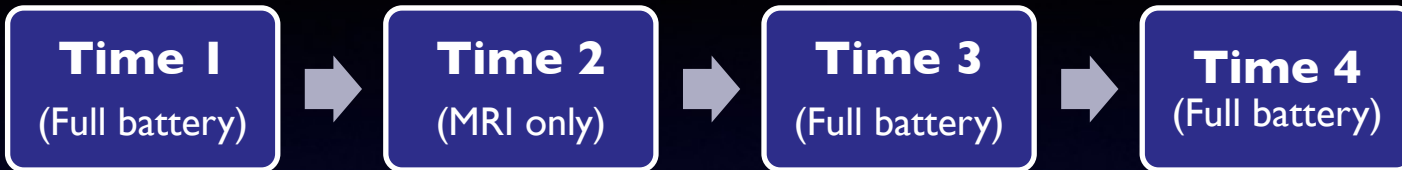
# Autism Phenome Project

- Children are recruited between 2 and 3 1/2 years of age.
- Study includes all children with autism with very few exclusions.
  - Both boys and girls are included.
- Age-matched typically developing children serve as controls.

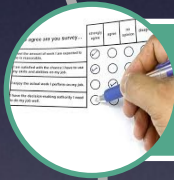
# Autism Phenome Project

- The study is longitudinal - children return to the MIND Institute annually for further testing.
- Blood samples are obtained from subjects, siblings and from parents.

# Comprehensive Study Protocol



Neurological (MRI)



Behavioral (assessments & questionnaires)



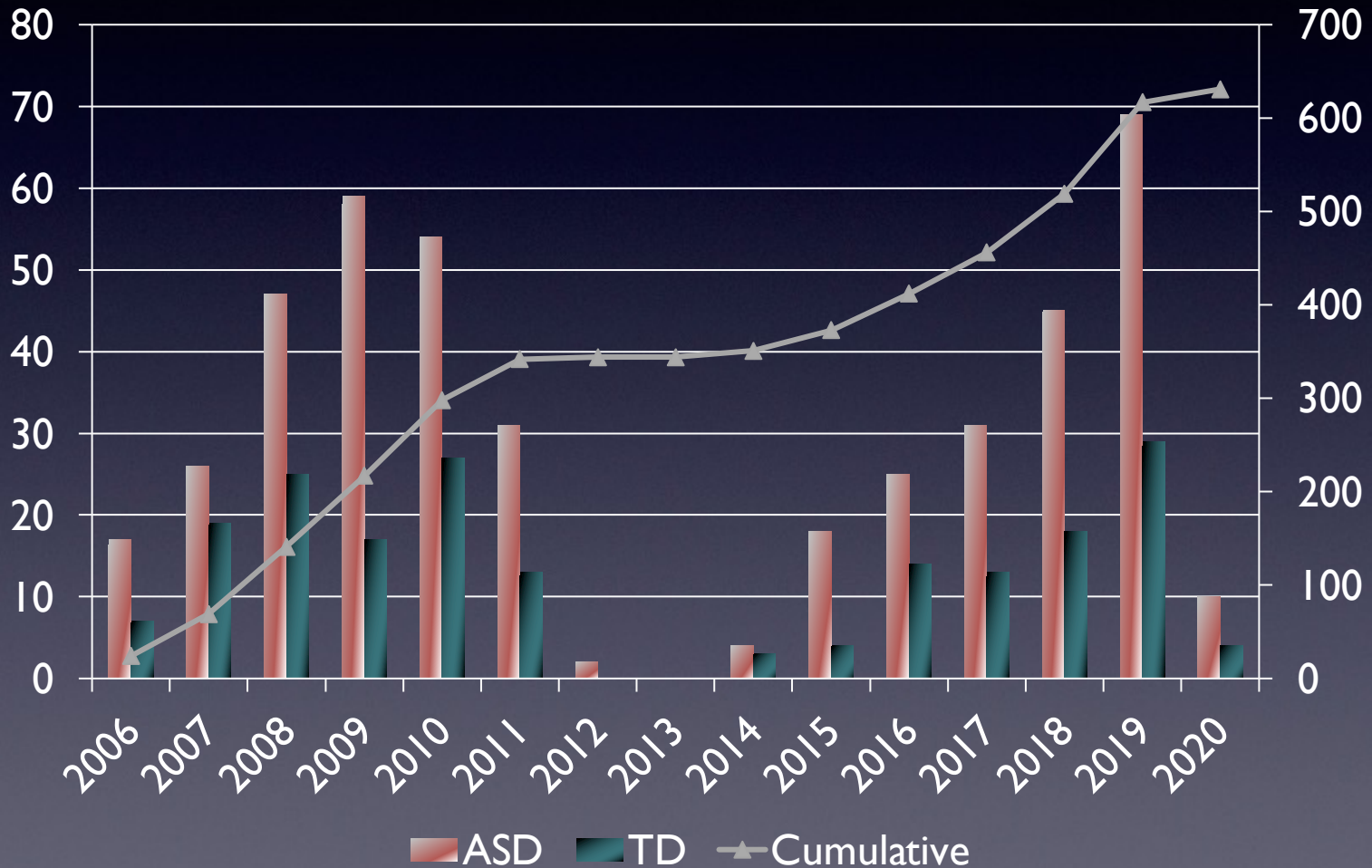
Medical (exam, history, & records)



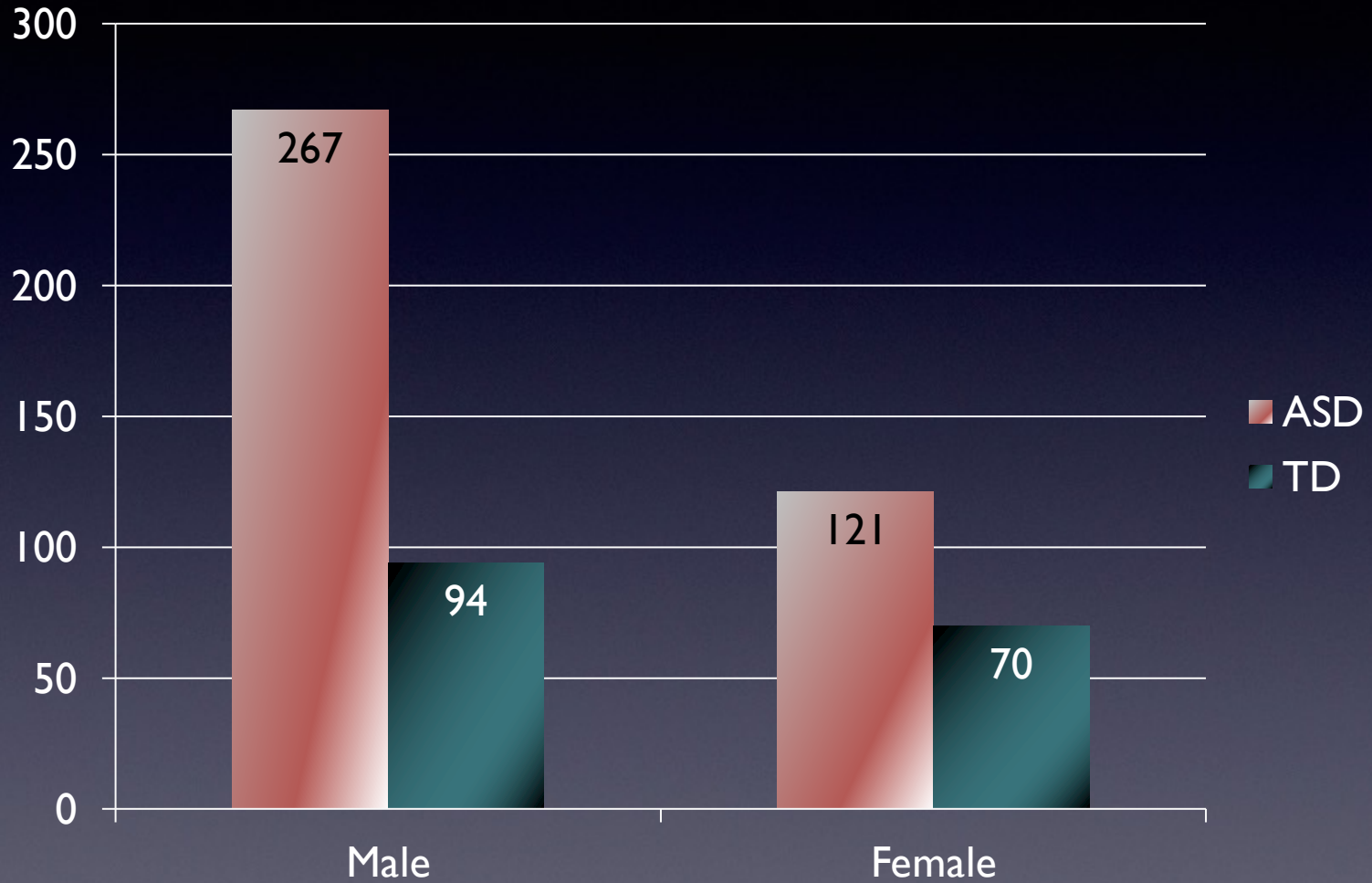
Biological (blood)



# Number of Families Participating



# Male and Female Participants

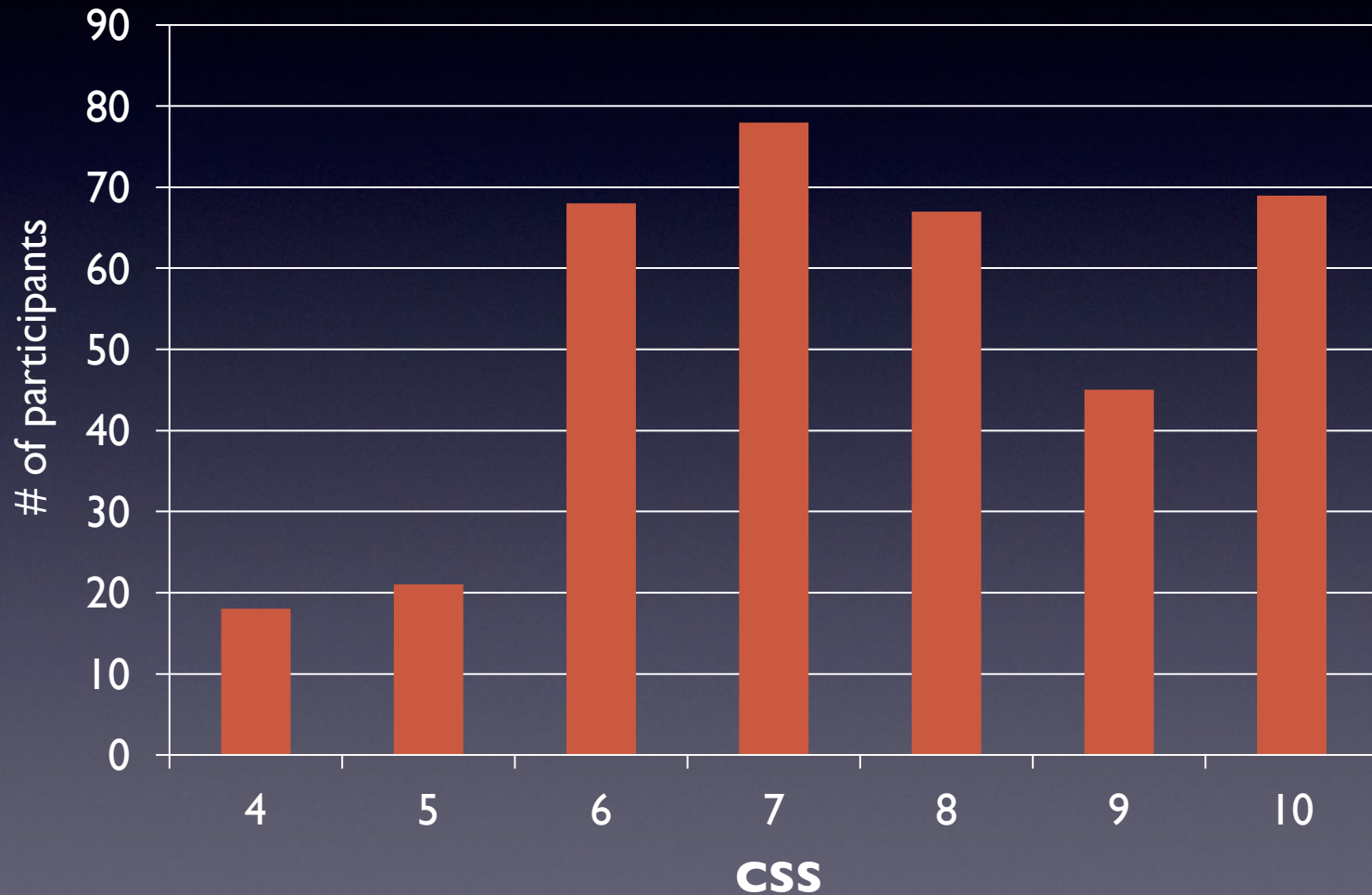


# ADOS Calibrated Severity Scores

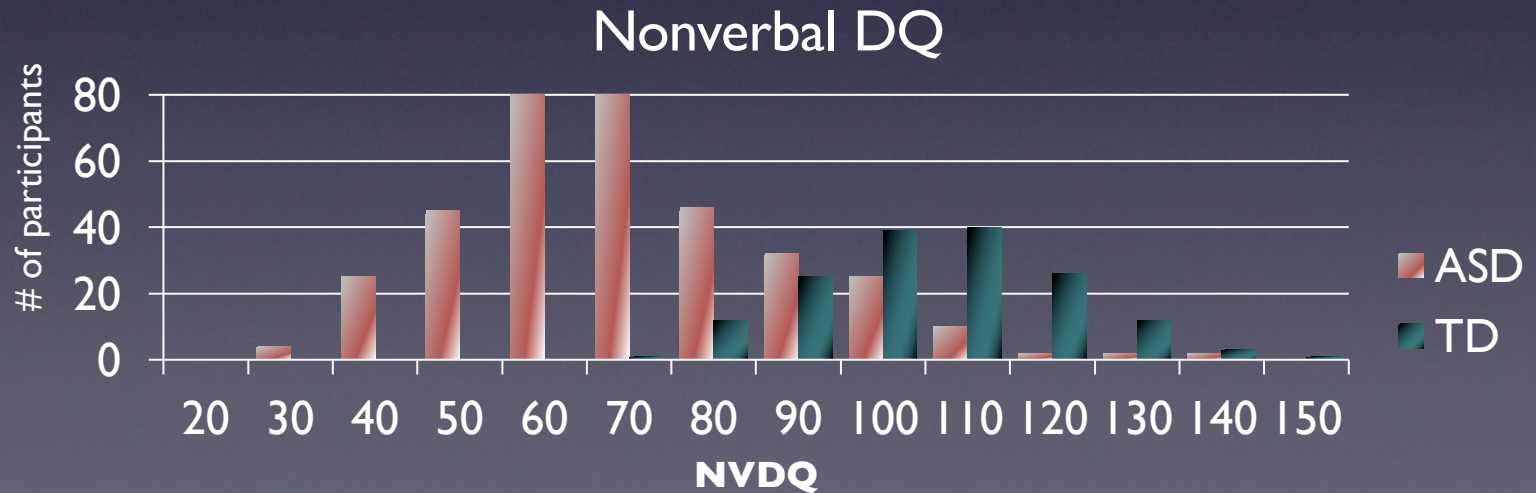
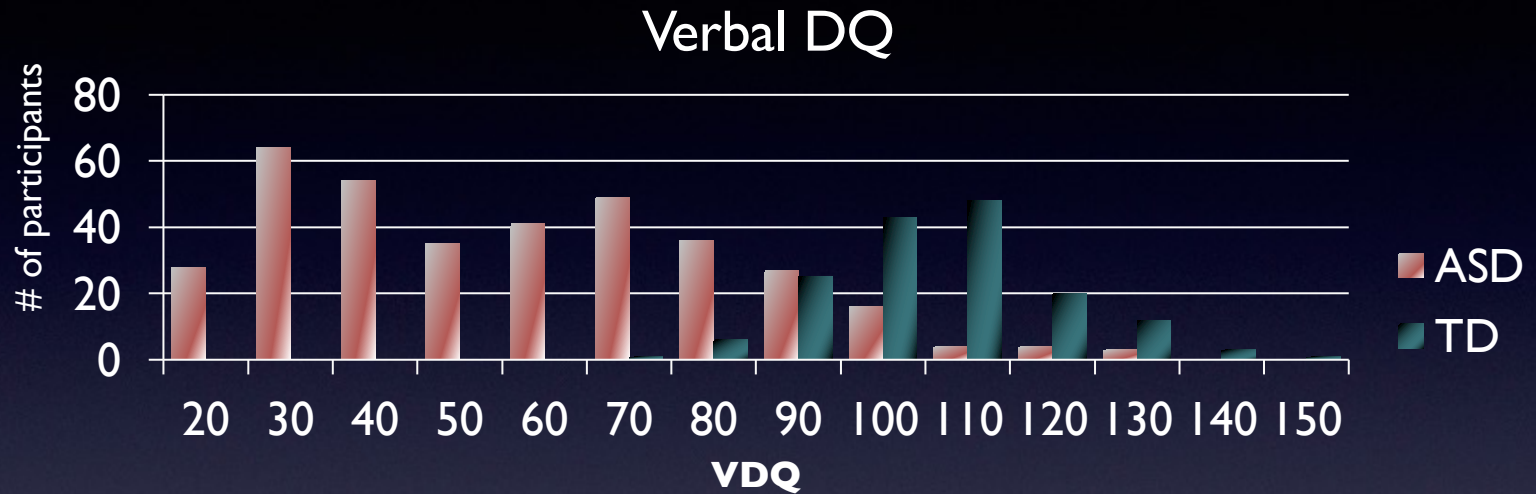
Decreased Severity



Increased Severity



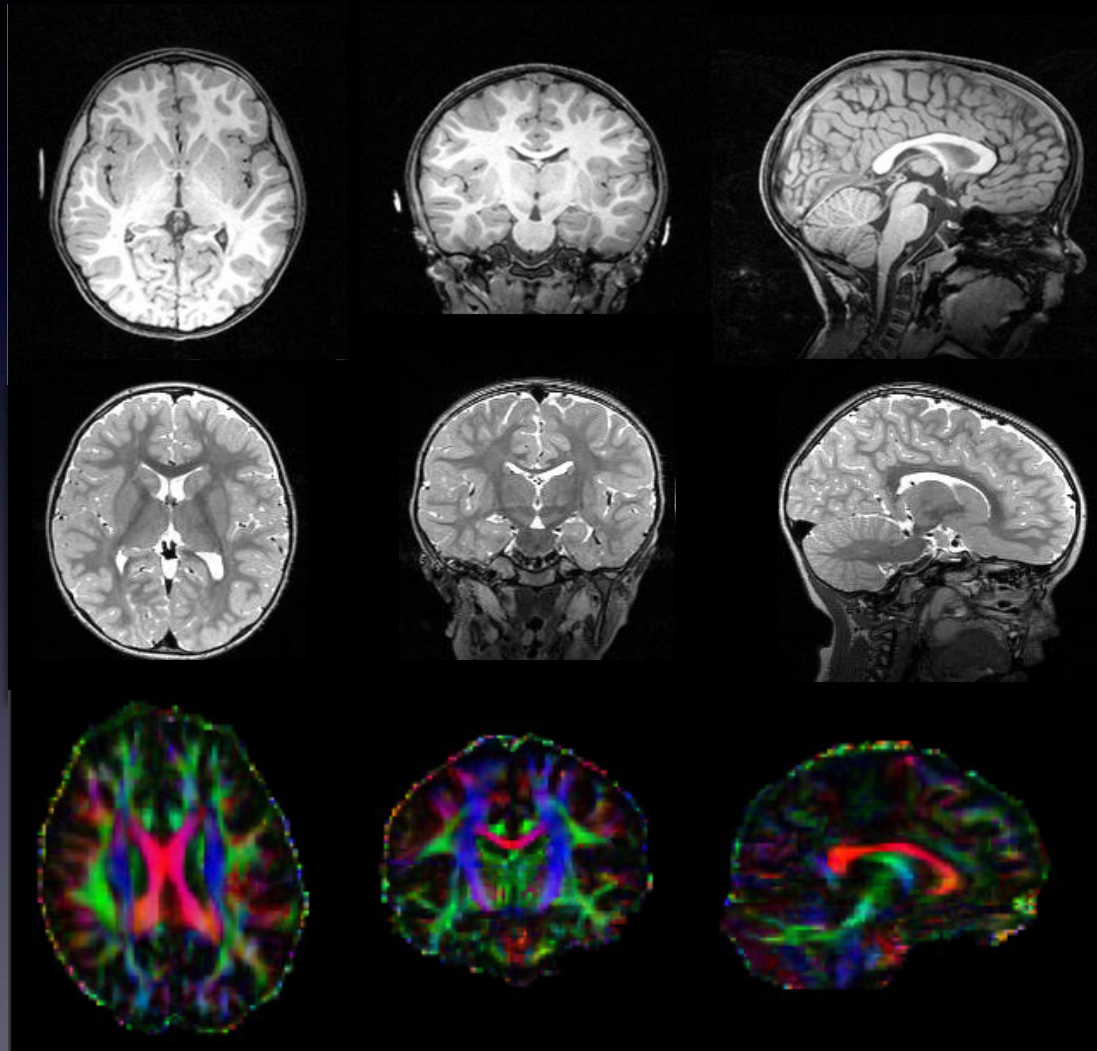
# Mullen Developmental Scores



# Brain Development in ASD

Magnetic resonance imaging  
may provide evidence to help define different  
types of ASD

# Brain Findings



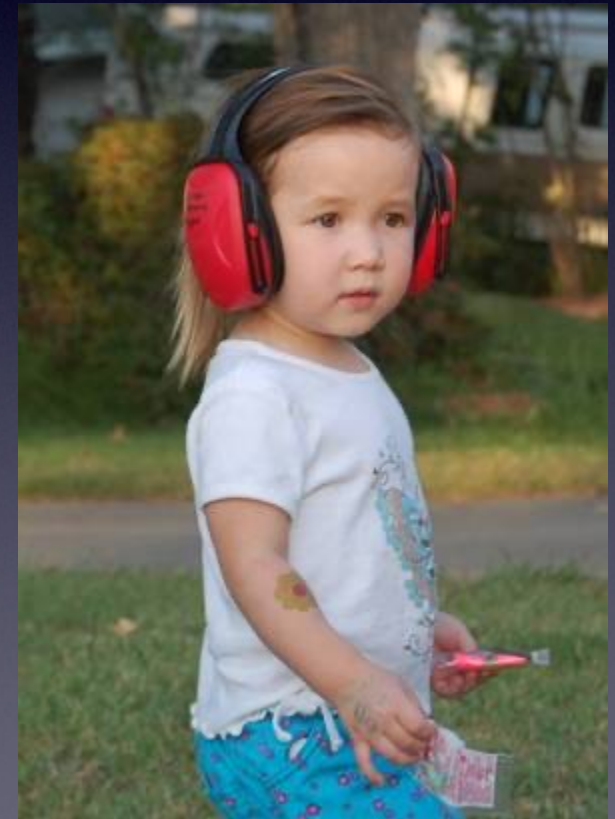
Christine Wu Nordahl

# MRI of Young Children

## Thomas the Train Mock Session



## MRI Practice Kit



# MRI of Young Children

## MRI Practice Kit





# Child-friendly scanning environment

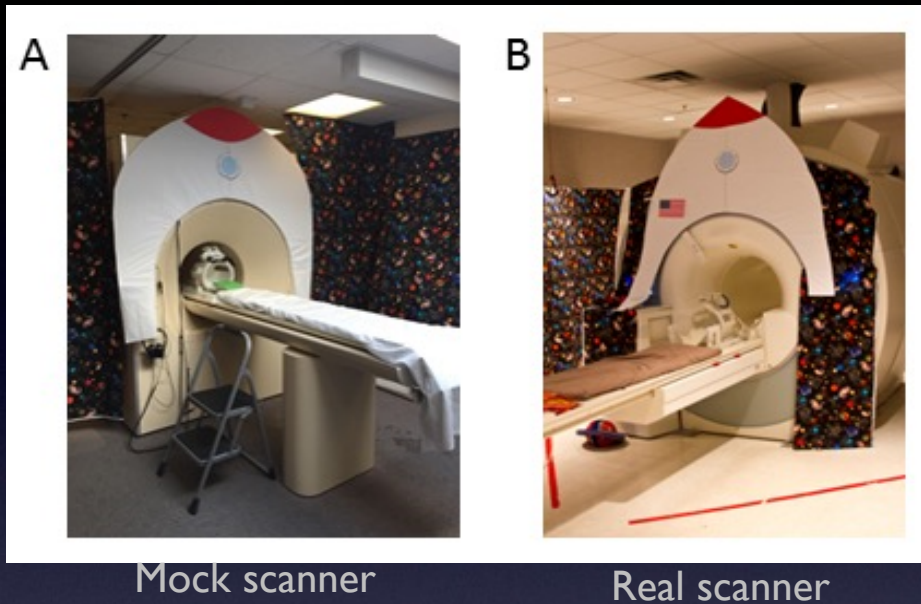
Before



After



# Pediatric MRI scans (9-12 years): Inclusion of severely affected



## The Real Key to Success – Utilizing principles of applied behavior analysis

- Pre-visit consultation with parents for preferred videos, best reinforcers, challenging behaviors
- Series of mock visits: Shaping - pairing, choices, reinforcement, first ... then, peer models
- Flexibility, patience, teamwork

Head motion



Weighted blanket



Visual Timer



YouTube



Webinar: Christine Wu Nordahl  
reveals new autism brain-imaging  
strategies

30 JANUARY 2019

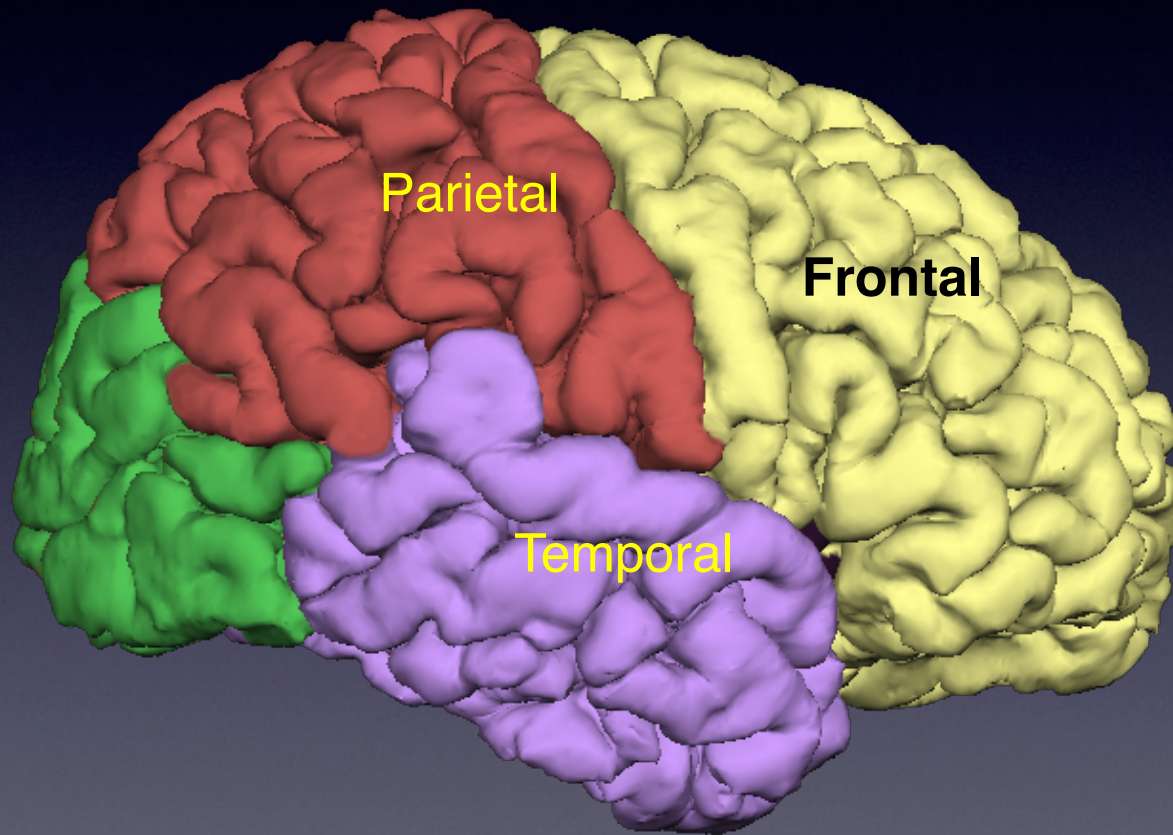
(Nordahl et al, 2016)

# MRI Scanning Success

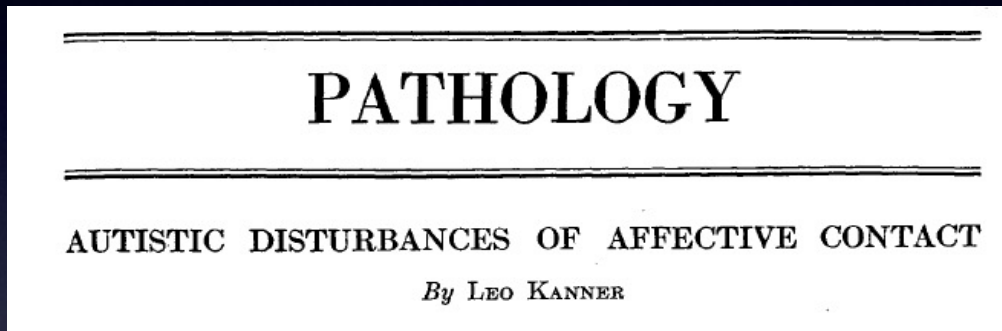


|              | <b>Time 1</b><br>(38 mos) |    | <b>Time 2</b><br>(51 mos) |    | <b>Time 3</b><br>(64 mos) |    | <b>Time 4</b><br>(11 yrs) |    |
|--------------|---------------------------|----|---------------------------|----|---------------------------|----|---------------------------|----|
|              | M                         | F  | M                         | F  | M                         | F  | M                         | F  |
| ASD          | 208                       | 97 | 120                       | 51 | 79                        | 42 | 75                        | 21 |
| TD           | 76                        | 61 | 54                        | 46 | 44                        | 35 | 42                        | 26 |
| <b>Total</b> | <b>442</b>                |    | <b>271</b>                |    | <b>200</b>                |    | <b>164</b>                |    |
| Success Rate | 89%                       |    | 89%                       |    | 89%                       |    | 91%                       |    |

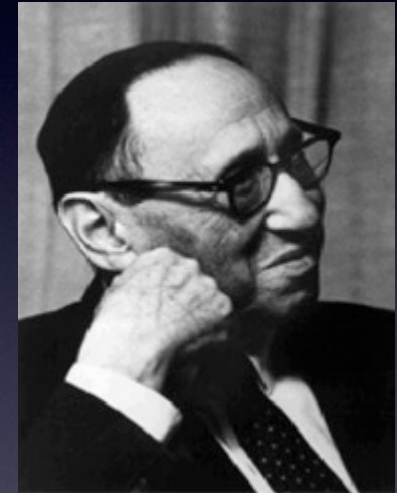
# Total Brain Measurements



# Big Brains and Autism



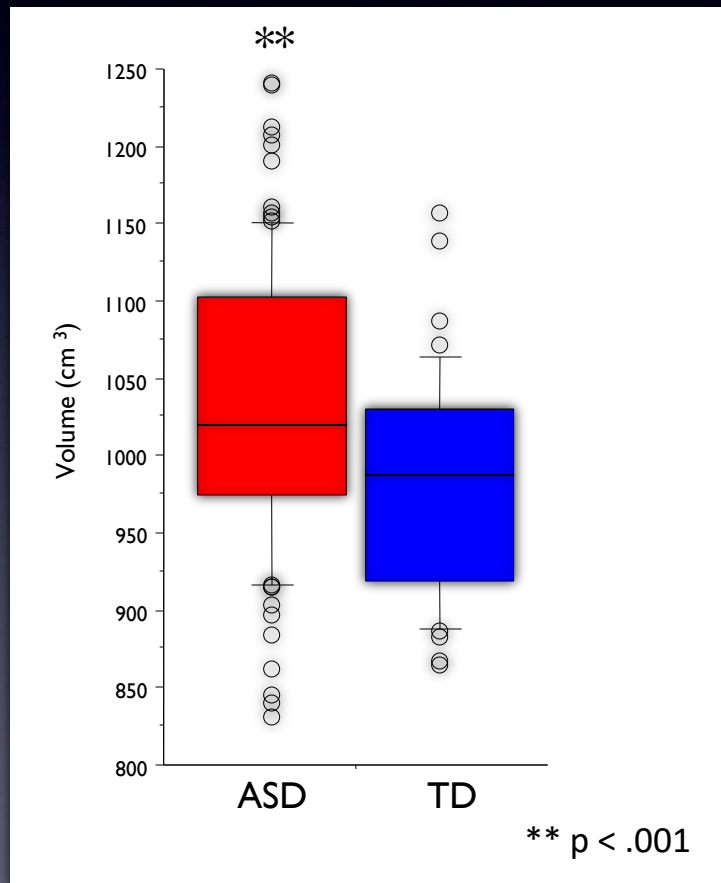
“Physically, the children were essentially normal. Five had relatively large heads”



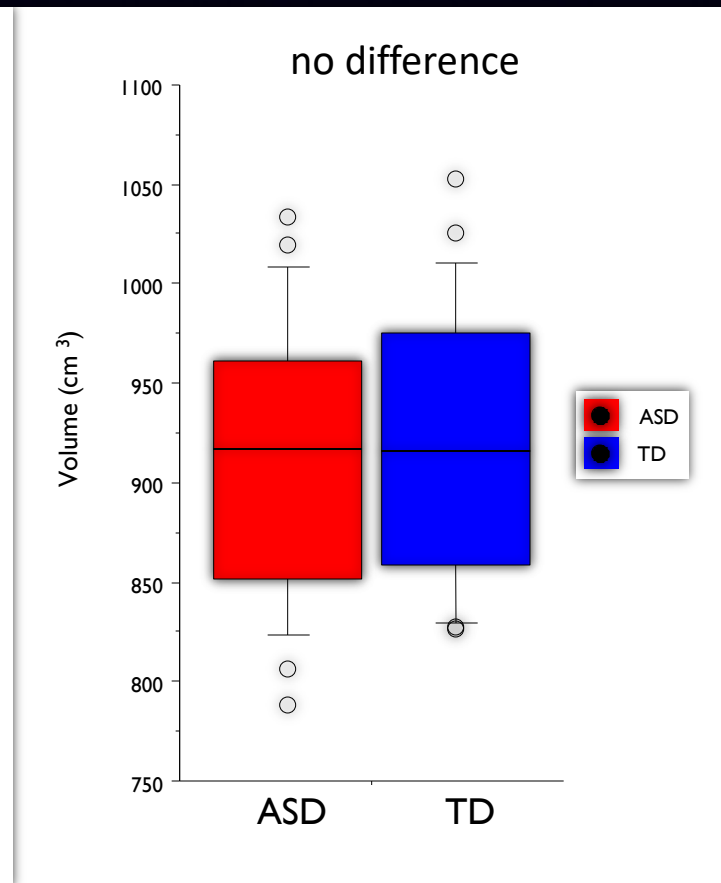
Leo Kanner (1943)

# Total cerebral volume (TCV) is enlarged by 6% in boys with ASD

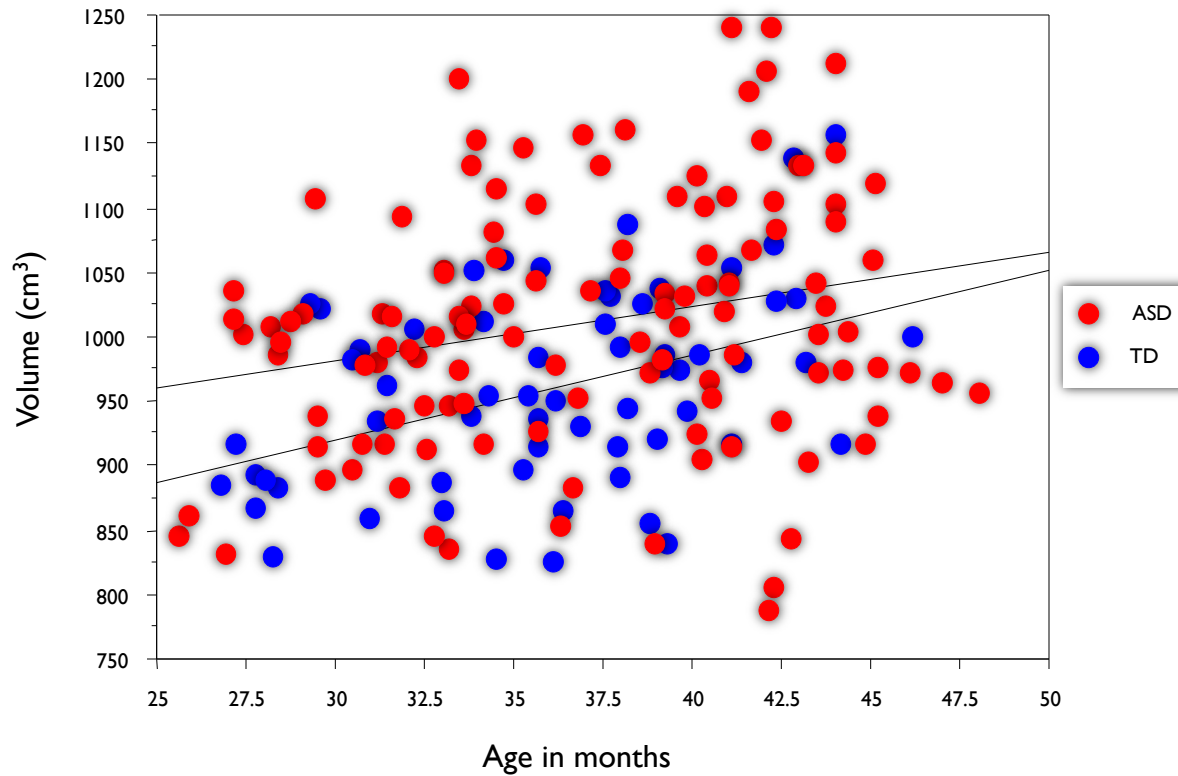
BOYS



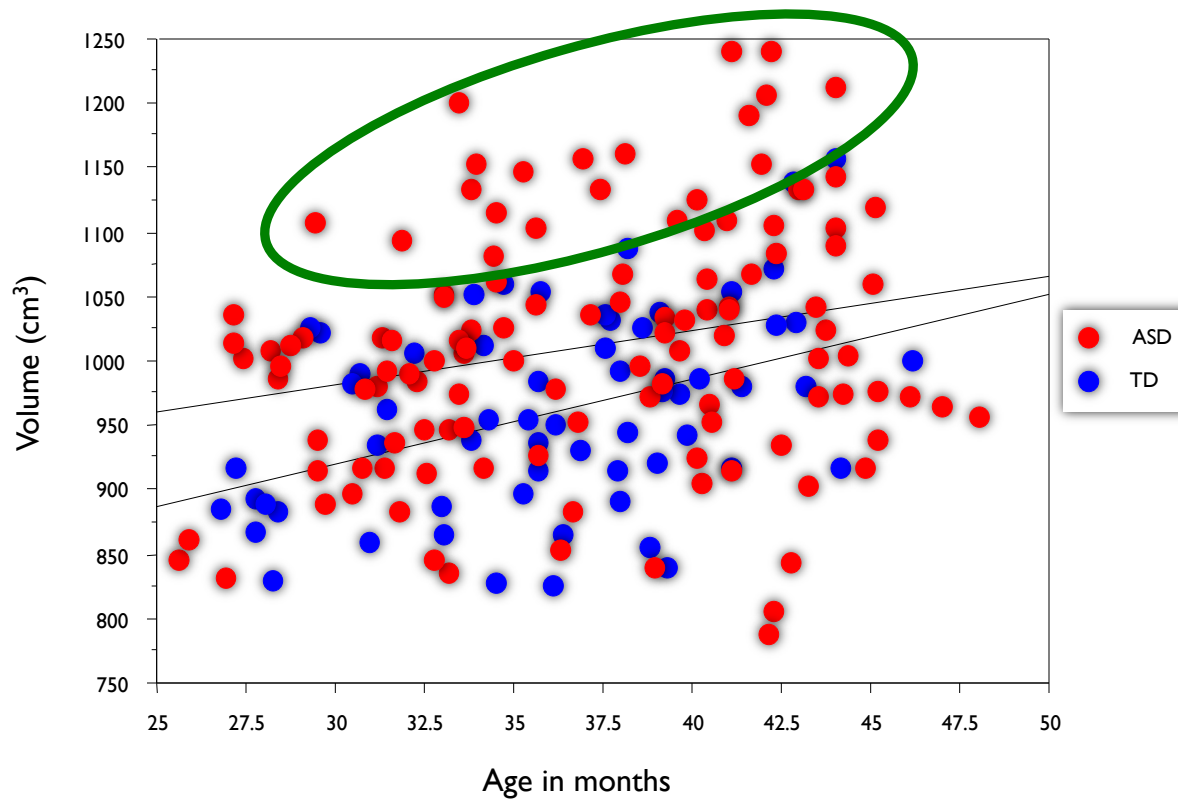
GIRLS



# Total brain size is extremely variable in ASD

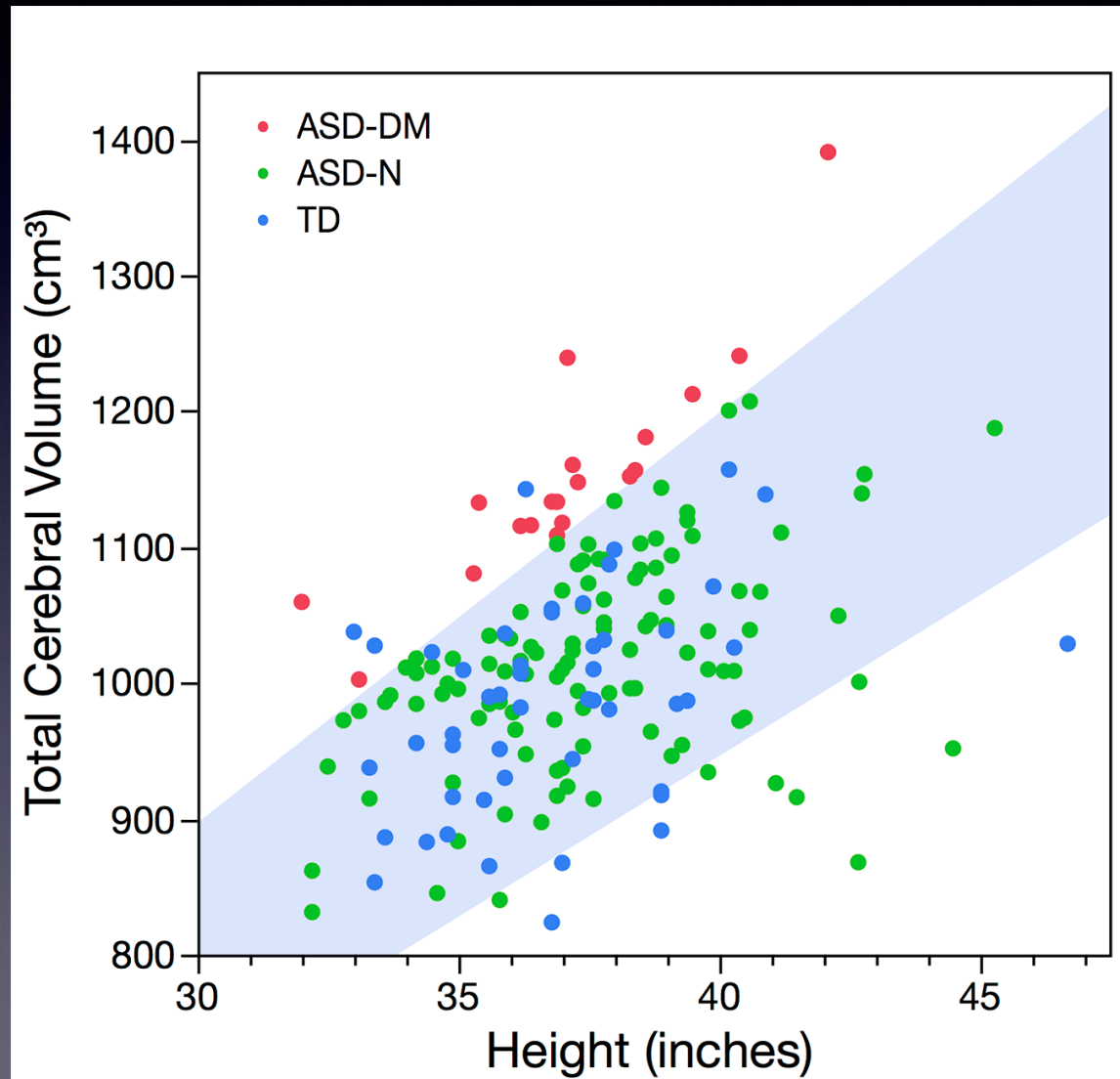


# Total brain size is extremely variable in ASD





# Distribution of Brain Size/Height for Boys in APP



## Disproportionate Megalencephaly (ASD-DM)

Disproportionate Megalencephaly (ASD-DM)  
i.e. the ratio of brain volume to height is 1.5  
standard deviations above control mean

# Disproportionate Megalencephaly (ASD-DM)

## Boys

85%

15%



Typical Child  
Age 31 months  
TCV 981.96

Autism  
Normal brain size  
Age 32 months  
TCV 984.57

Autism  
Megalencephaly  
Age 30 months  
TCV 1180.98

# More surface area of the cortex But not thicker cortex



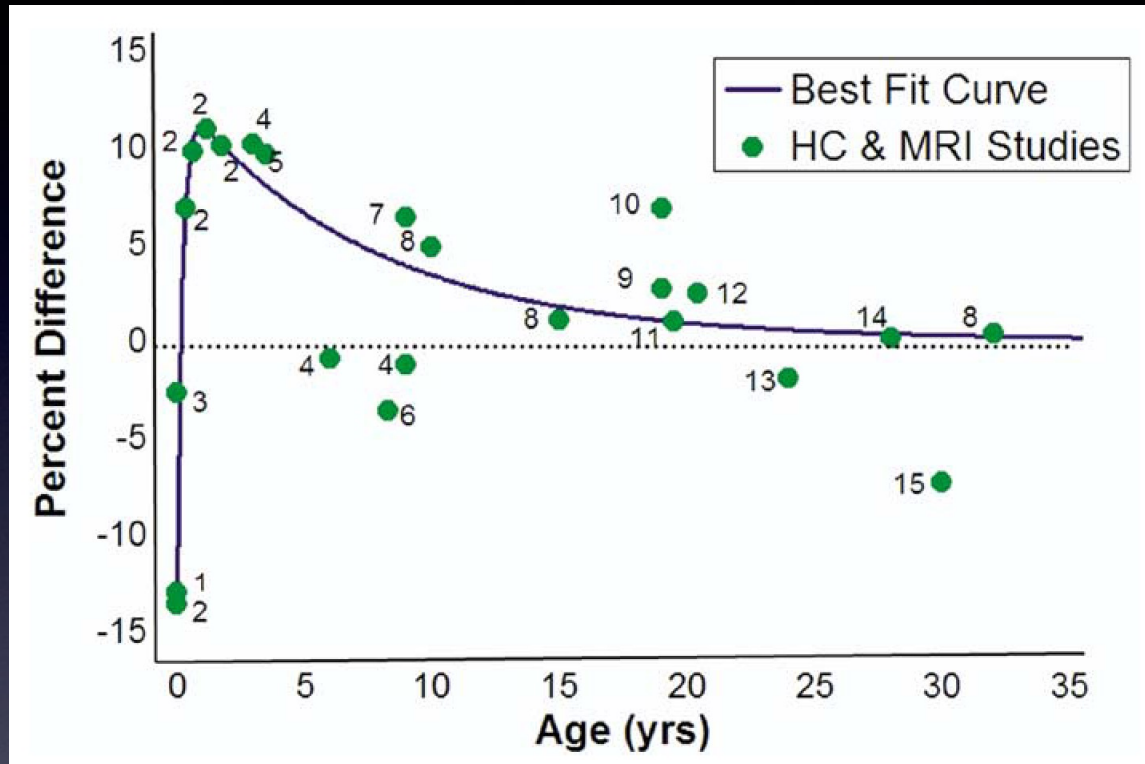
Typical Child  
Age 31 months  
TCV 981.96

Autism  
Normal brain size  
Age 32 months  
TCV 984.57

Autism  
Megalencephaly  
Age 30 months  
TCV 1180.98

# Questions Related to Outcome

- Do early neurophenotypes persist into middle childhood? Do ASD-DM boys continue to have big brains as they get older?
- Do early neurophenotypes predict different patterns of autism severity, cognitive function and co-morbid syndromes? Does it matter if you have the big brain form of ASD versus ASD with a typical size brain?



Elizabeth Redcay , Eric Courchesne

When Is the Brain Enlarged in Autism? A Meta-Analysis of All Brain Size Reports

Biological Psychiatry, Volume 58, Issue 1, 2005, 1 - 9

## RESEARCH ARTICLE

# Persistence of Megalencephaly in a Subgroup of Young Boys With Autism Spectrum Disorder

Lauren E. Libero, Christine W. Nordahl, Deana D. Li, Emilio Ferrer, Sally J. Rogers, and David G. Amaral

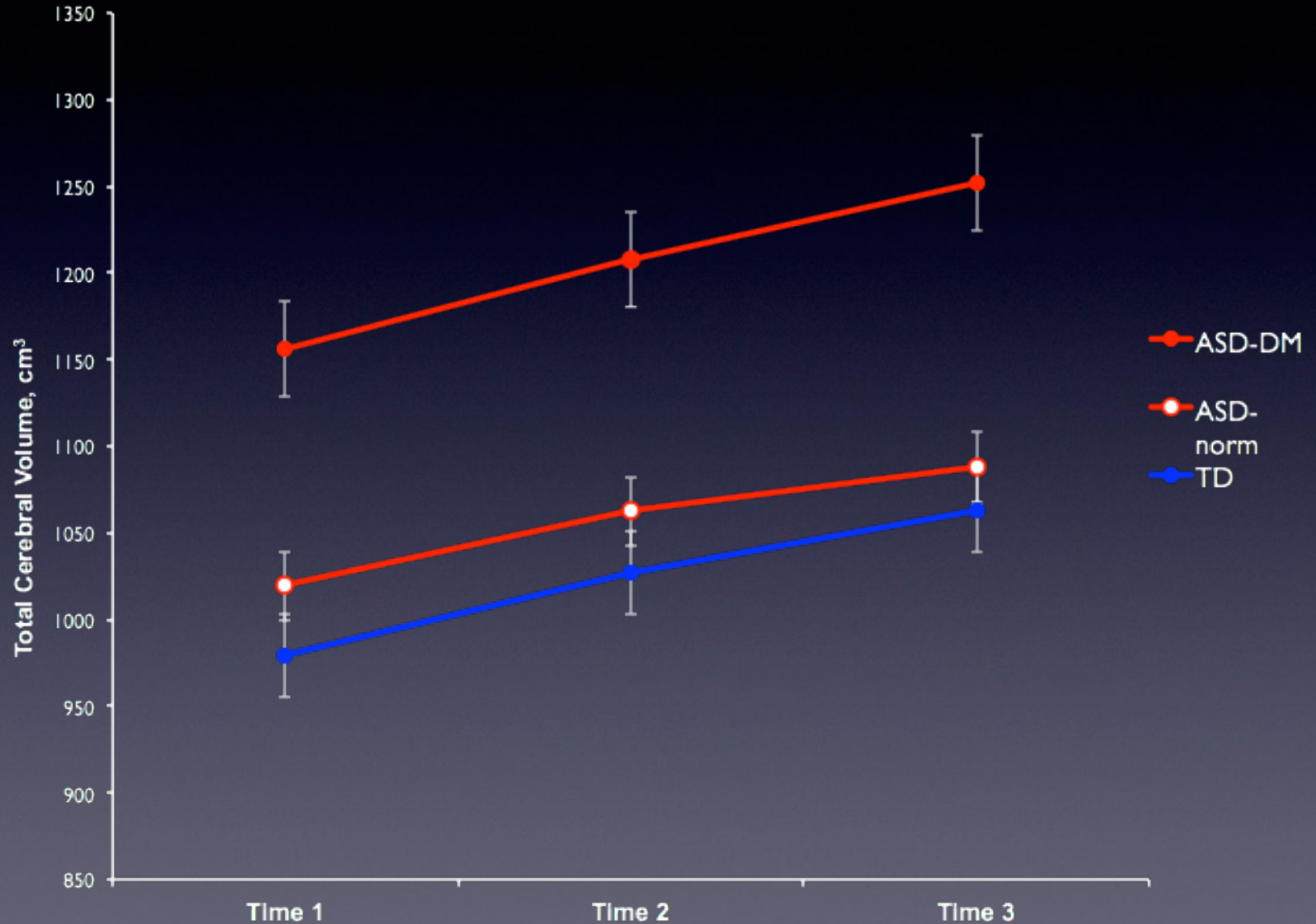
A recurring finding in autism spectrum disorder research is that head and brain growth is disproportionate to body growth in early childhood. Nordahl et al. (2011) demonstrated that this occurs in approximately 15% of boys with autism. While the literature suggests that brain growth normalizes at older ages, this has never been evaluated in a longitudinal study. The current study evaluated head circumference and total cerebral volume in 129 male children with autism and 49 age-matched, typically developing controls. We determined whether 3-year-old boys with brain size disproportionate to height (which we call disproportionate megalencephaly) demonstrated an abnormal trajectory whether they maintained an enlarged brain at 5 years of age. Findings were based on head circumference data collected around 3, 4, and 5 years of age and head circumference data from medical records. Boys with autism had enlarged brains while 110 had brain sizes in the normal range. Boys with megalencephaly had greater total cerebral, gray matter, and white matter volumes from birth to 5 years of age than normal sized brains and typically developing boys, but no differences in head circumference. Although head circumference did not differ between groups at birth, it was significantly greater in the disproportionate megalencephaly group around 2 years. These data suggest that there is a subgroup of boys with autism who have a disproportionately large head and body size and that this continues until at least 5 years of age. *Autism Research*, Wiley Periodicals, Inc.



Lauren Libero

Autism Research 9: 1169–1182, 2016

# Mean Total Cerebral Volume: 3-6 years





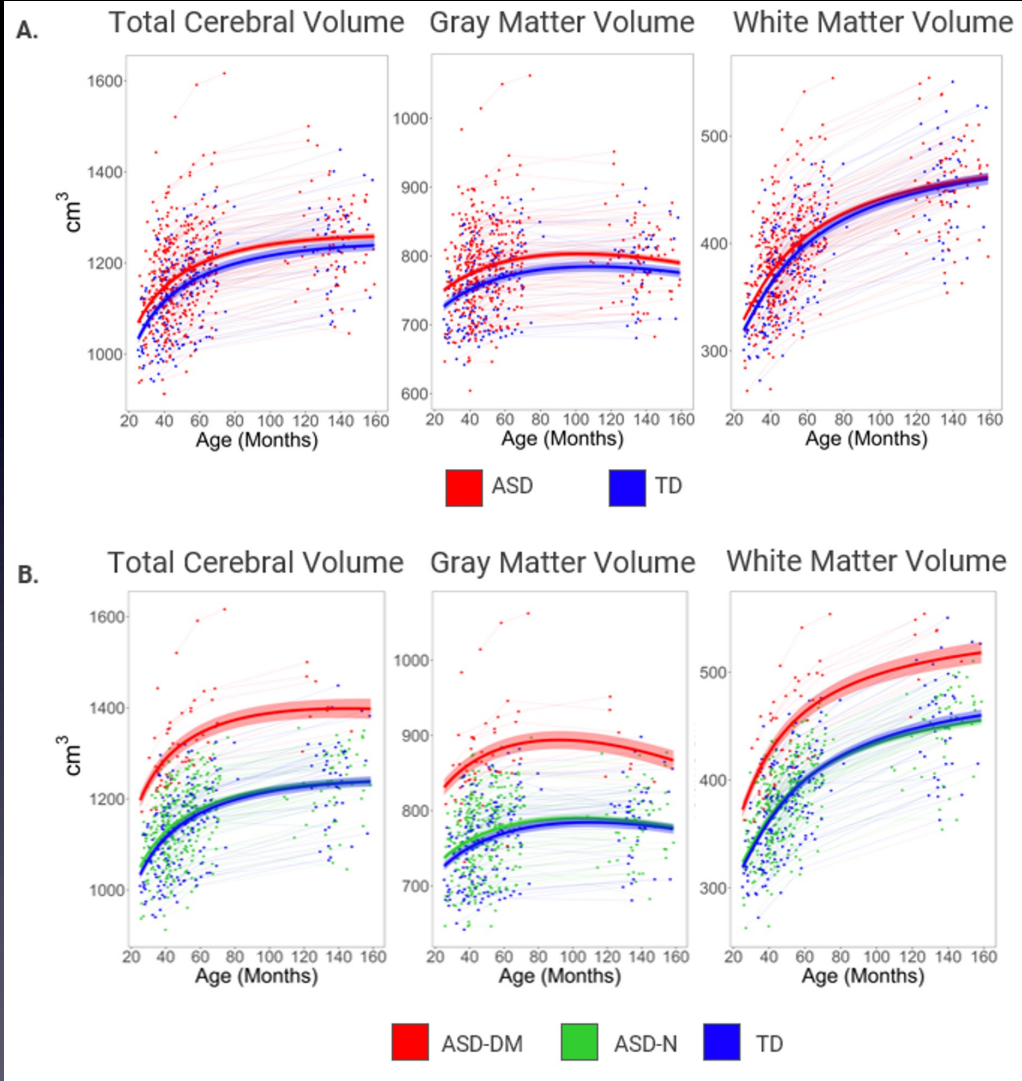
## Longitudinal Evaluation of Cerebral Growth Across Childhood in Boys and Girls With Autism Spectrum Disorder

Joshua K. Lee, Derek S. Andrews, Sally Ozonoff, Marjorie Solomon, Sally Rogers, David G. Amaral, and Christine Wu Nordahl

286 © 2020 Society of Biological Psychiatry.  
Biological Psychiatry September 1, 2021; 90:286–294 [www.sobp.org/journal](http://www.sobp.org/journal)



Joshua Lee, Ph.D.



# Are there behavioral, cognitive or biomedical differences between ASD-N and ASD-DM?

## COMMENTARY

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### In Pursuit of Neurophenotypes: The Consequences of Having Autism and a Big Brain

David G. Amaral, Deana Li, Lauren Libero, Marjorie Solomon, Judy Van de Water, Ann Mastergeorge, Letitia Naigles, Sally Rogers, and Christine Wu Nordahl

***Autism Res* 2017, 10: 711–722.**

IQ  
in ASD-N and ASD-DM boys

Time 1  
(~3 years)

Time 3  
(~6 years)

ASD-N

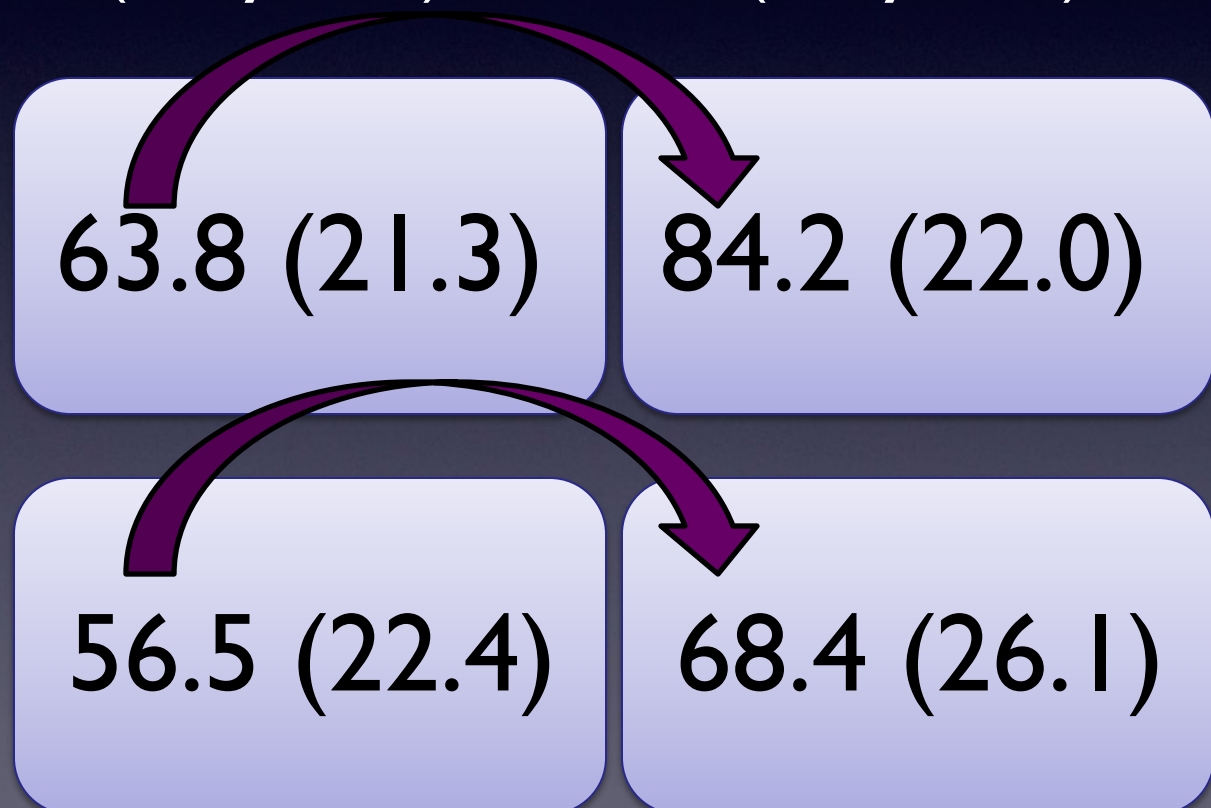
63.8 (21.3)

84.2 (22.0)

ASD-DM

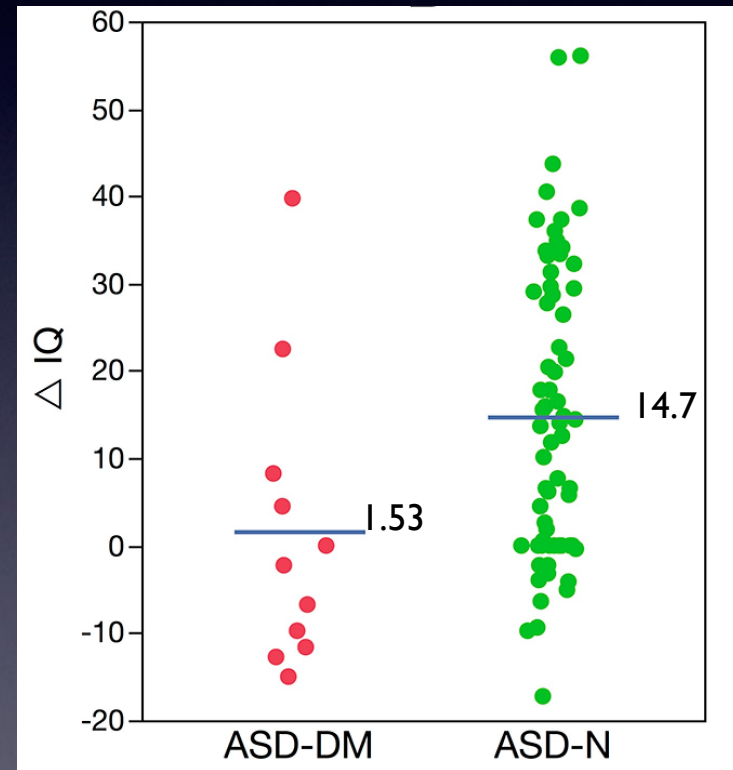
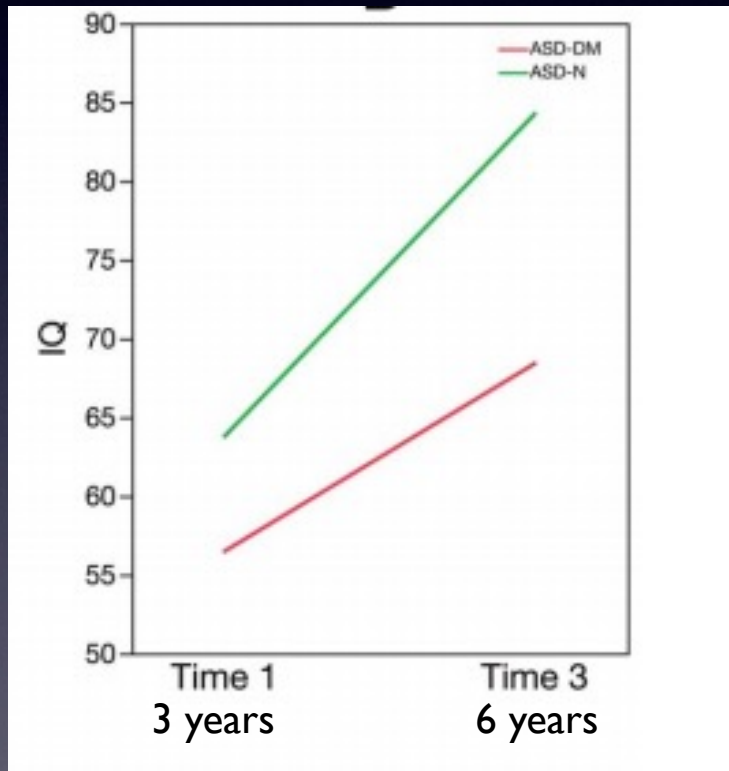
56.5 (22.4)

68.4 (26.1)

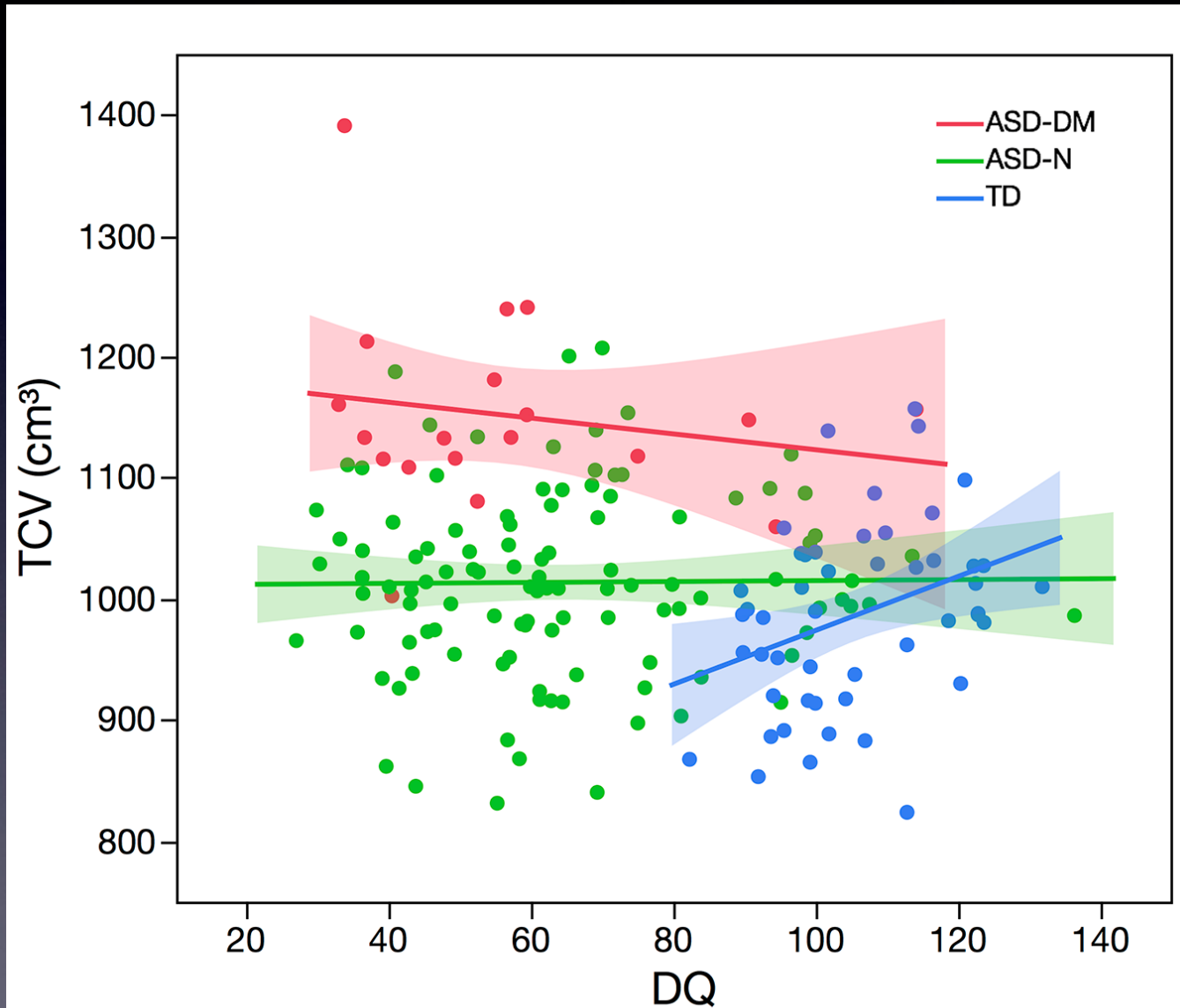


# Disproportionate megalencephaly subgroup: Behavioral findings

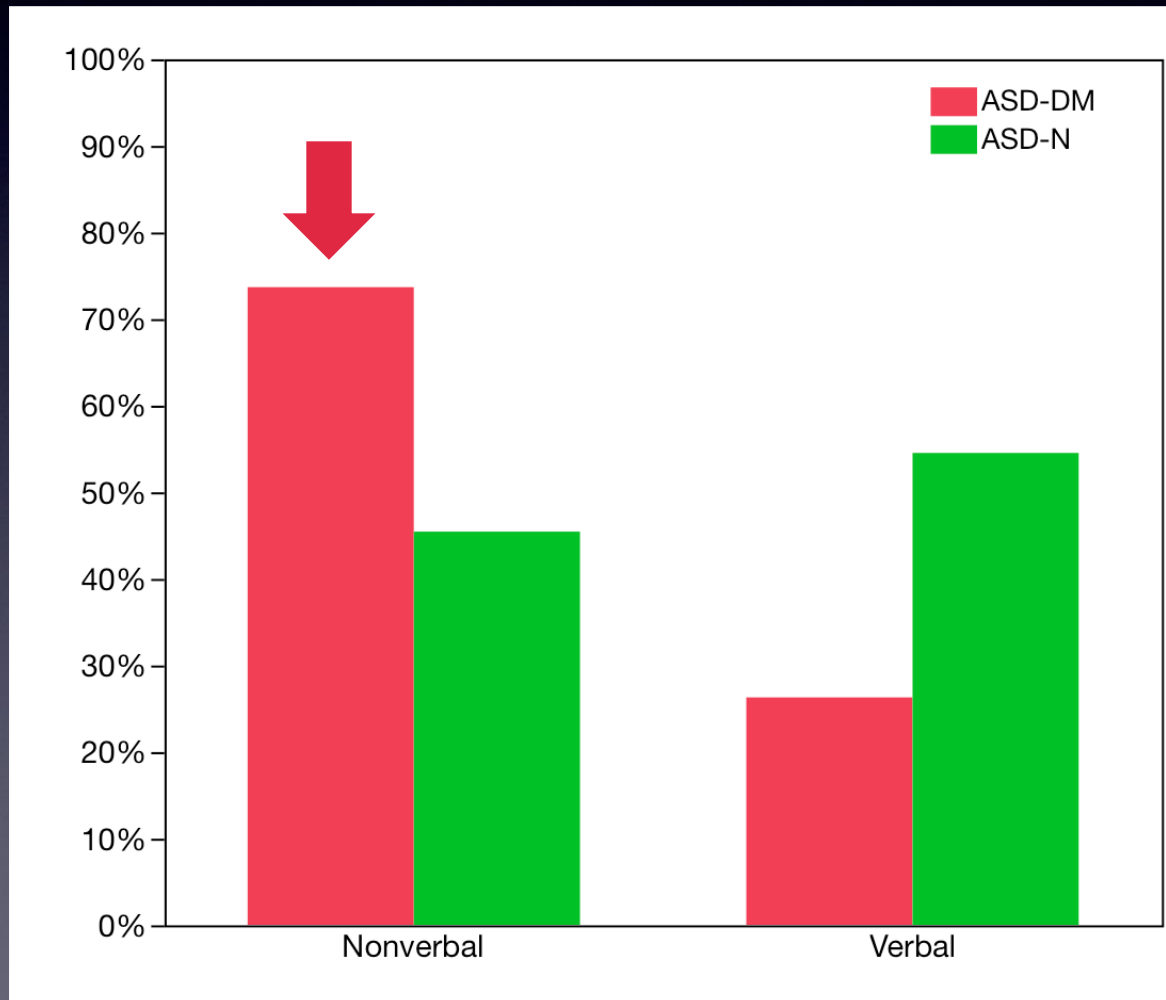
As a group – ASD-DM fewer gains in IQ from 3 to 6 years of age



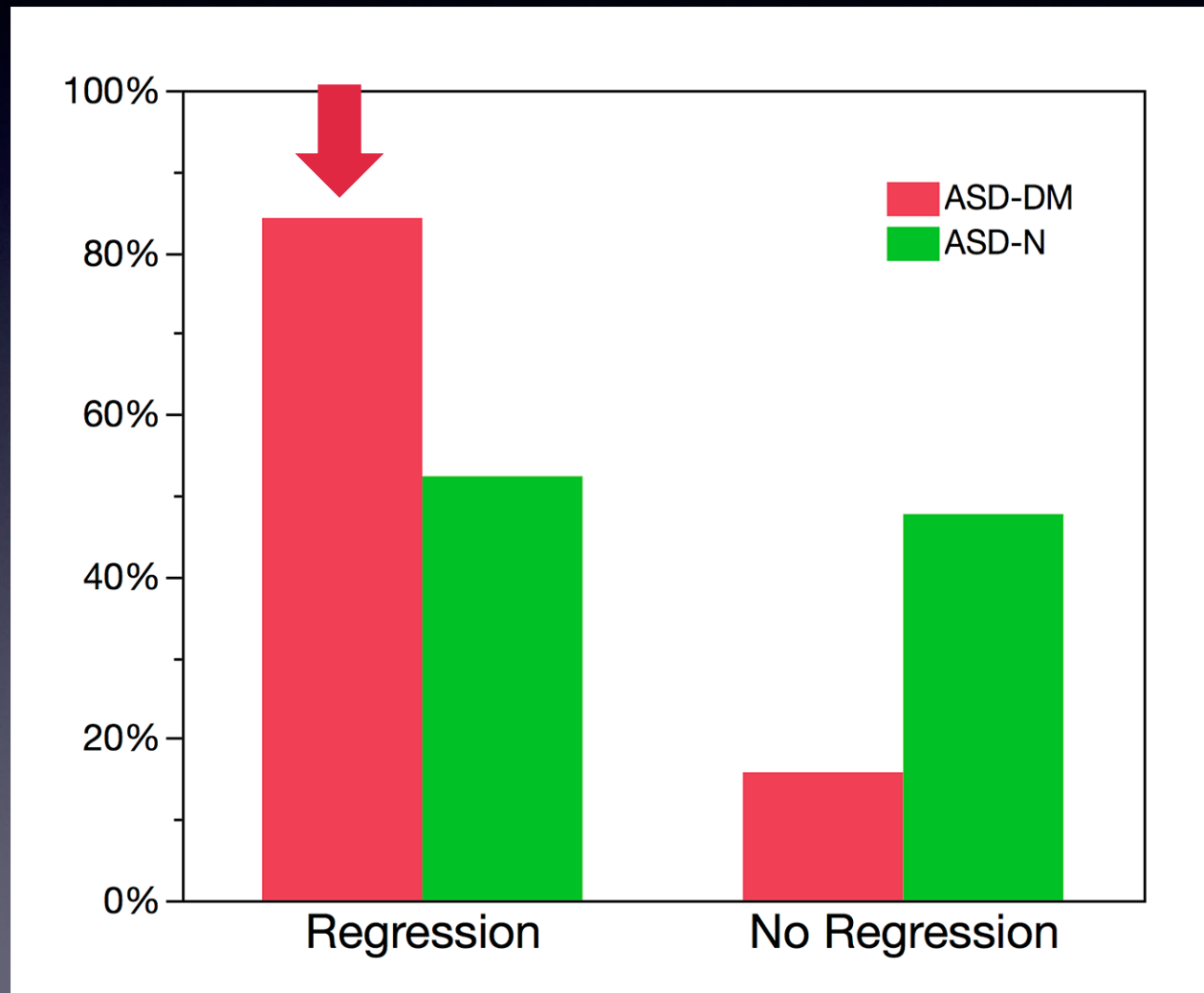
# Relationship between IQ and brain size in ASD-DM, ASD-N and TD Boys



# Relationship between language and brain size in ASD-DM and ASD-N Boys



# Relationship between regression and brain size in ASD-DM and ASD-N Boys





# Conclusion

Boys with the large brain form of ASD have greater deficits and a more difficult prognosis.

# Center for the Development of Phenotype-Based Treatments of Autism Spectrum Disorder



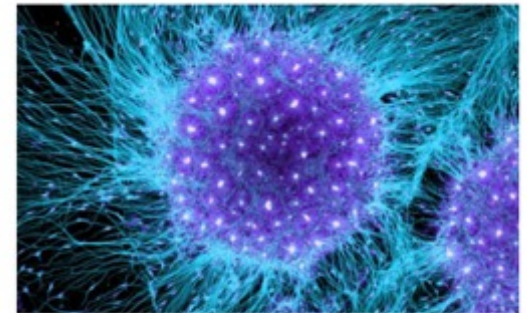
## STAAR

Specifying and Treating  
Anxiety in Autism Research



## BRAIN

Brain Research in Autism  
Investigating  
Neurophenotypes



## SC2BC

Stem Cells to Brain Cells

NICHD P50 HD093079

# Is ASD Stable throughout life?

THE JOURNAL OF CHILD  
PSYCHOLOGY AND PSYCHIATRY



*Journal of Child Psychology and Psychiatry* 54:2 (2013), pp 195–205

doi:10.1111/jcpp.12037

## Optimal outcome in individuals with a history of autism

**Deborah Fein,<sup>1,6</sup> Marianne Barton,<sup>1</sup> Inge-Marie Eigsti,<sup>1</sup> Elizabeth Kelley,<sup>2</sup> Letitia Naigles,<sup>1</sup> Robert T. Schultz,<sup>3</sup> Michael Stevens,<sup>4</sup> Molly Helt,<sup>1</sup> Alyssa Orinstein,<sup>1</sup> Michael Rosenthal,<sup>5</sup> Eva Troyb,<sup>1</sup> and Katherine Tyson<sup>1</sup>**

<sup>1</sup>Department of Psychology, University of Connecticut, Storrs, CT, USA; <sup>2</sup>Department of Psychology, Queens University, Kingston, ON, Canada; <sup>3</sup>Center for Autism Research, Children's Hospital of Philadelphia, PA, USA; <sup>4</sup>Institute of Living, Hartford Hospital, Hartford, CT, USA; <sup>5</sup>Child Mind Institute, NY, USA; <sup>6</sup>Department of Pediatrics, University of Connecticut, Farmington, CT, USA



# Is ASD Stable throughout life?

## Six Developmental Trajectories Characterize Children With Autism



**WHAT'S KNOWN ON THIS SUBJECT:** Autism is widely considered a heterogeneous disorder in terms of etiology and phenotype. Although autism is usually a lifelong disorder, little is known about the rate or timing of how children develop regarding their communication and social functioning.



**WHAT THIS STUDY ADDS:** Utilizing annual evaluations for a large population of children with autism, we describe the 6 most common trajectories from diagnosis through age 14 years. Trajectories revealed considerable variation, and high socioeconomic status children were more likely to experience rapid improvement.

**AUTHORS:** Christine Fountain, PhD, Alix S. Winter, BA, and Peter S. Bearman, PhD

*Paul F. Lazarsfeld Center for the Social Sciences, Columbia University, New York, New York*

### **KEY WORDS**

autistic disorder, longitudinal outcomes, trajectory models

### **ABBREVIATIONS**

BIC—Bayesian Information Criterion

CDER—Client Development Evaluation Report

DDS—Department of Developmental Services

HF—high-functioning

LF—low-functioning

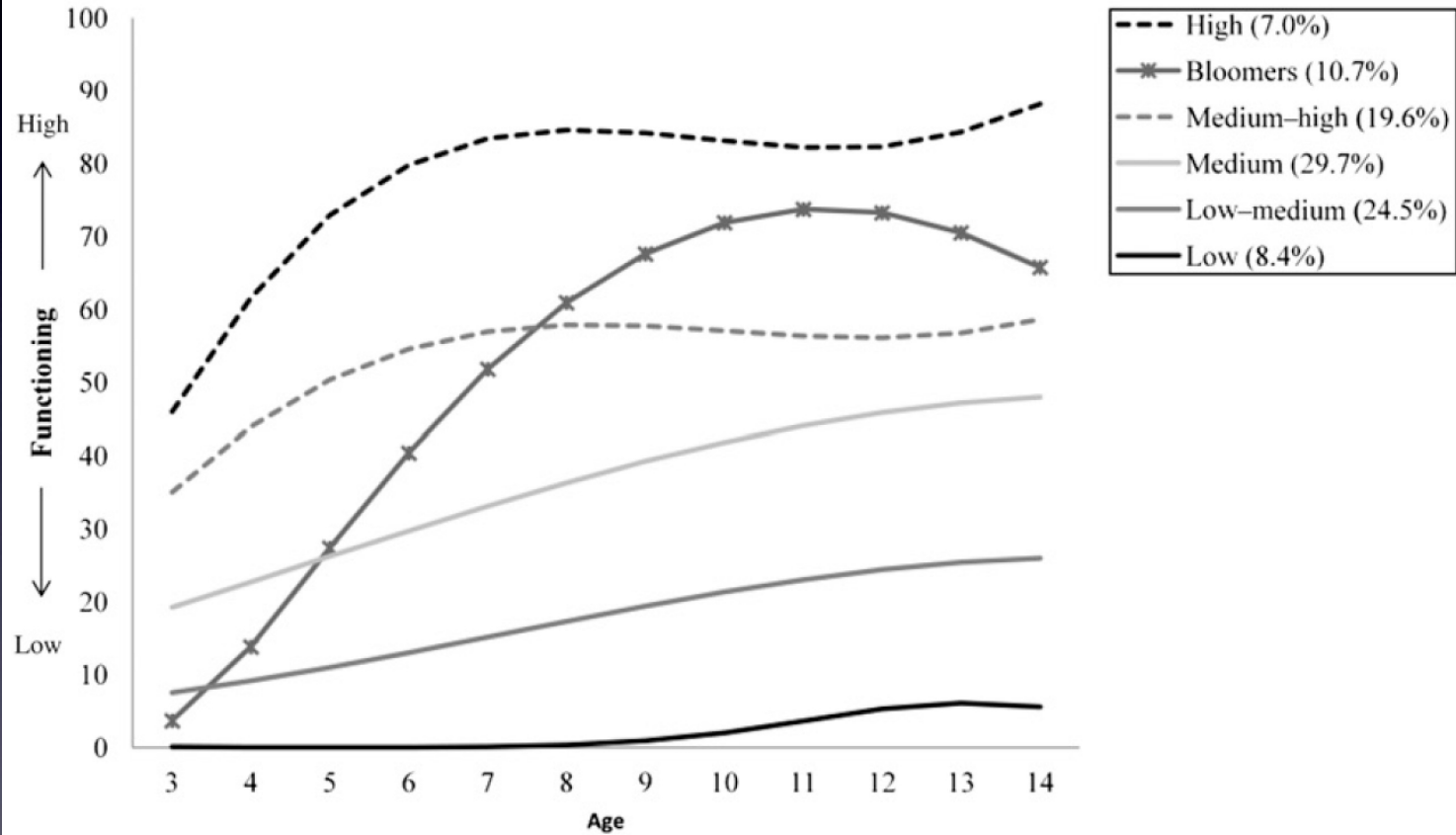
OR—odds ratio

RR—relative risk

*Pediatrics* 2012;129:e1112–e1120

# Changes in Social Ability

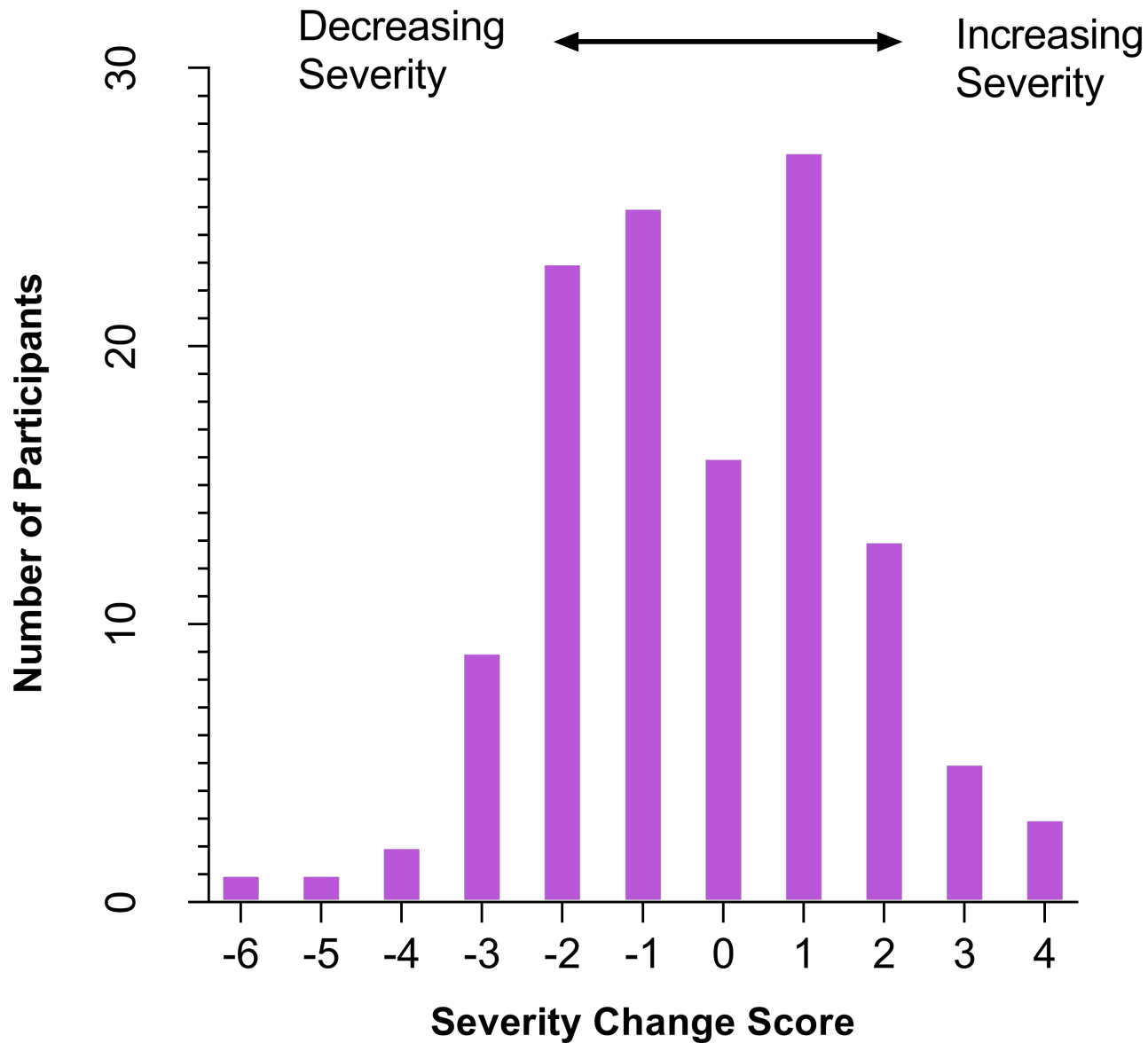
**B Social trajectories**



# How does Autism Severity change over time?

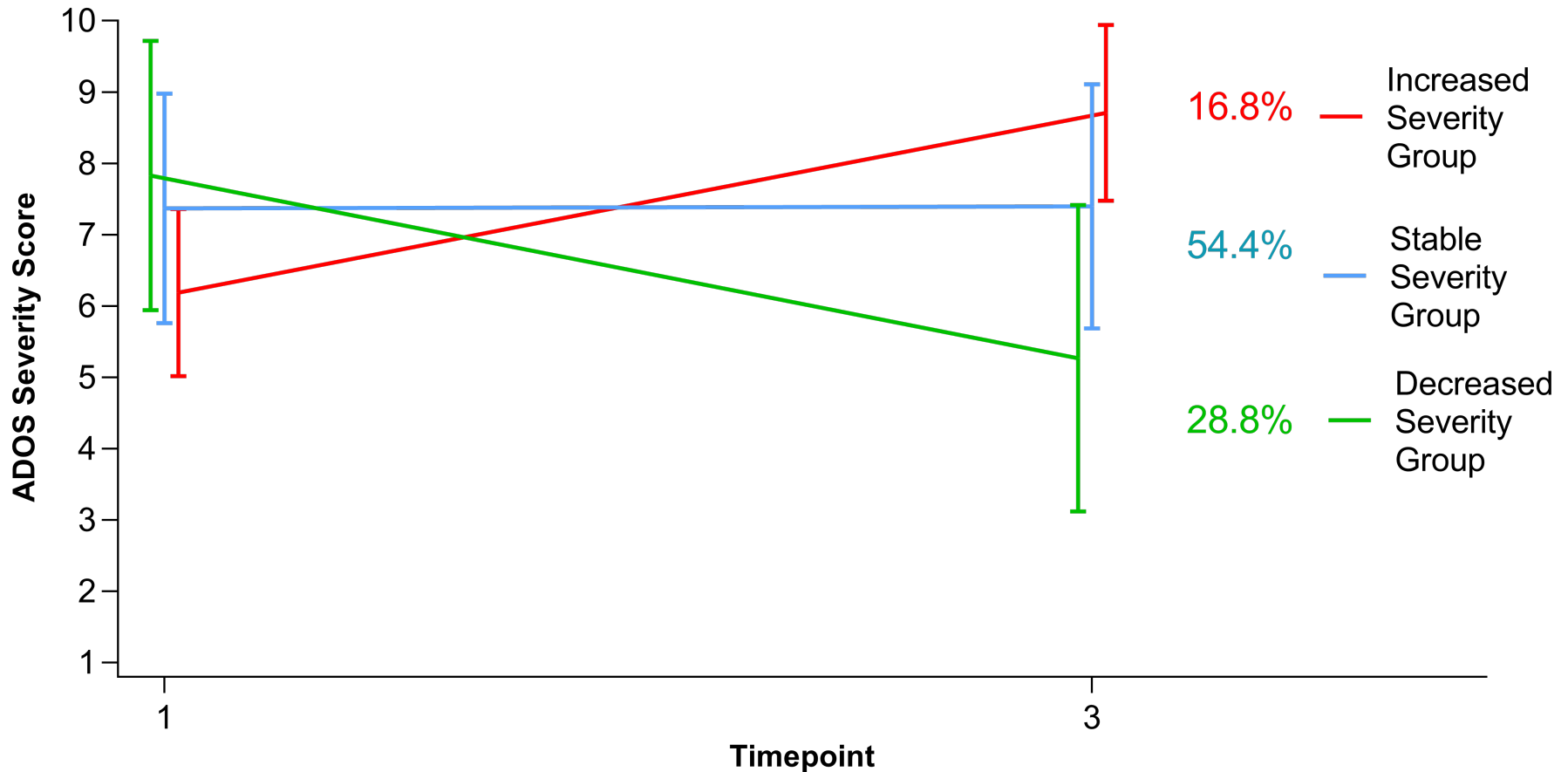
- Autism Severity is difficult to measure
  - One strategy is to use a Calibrated Comparison Score based on the ADOS (Gotham et al 2009)
- 1-10 scale with 10 being most severe

# Range of severity change - APP subjects



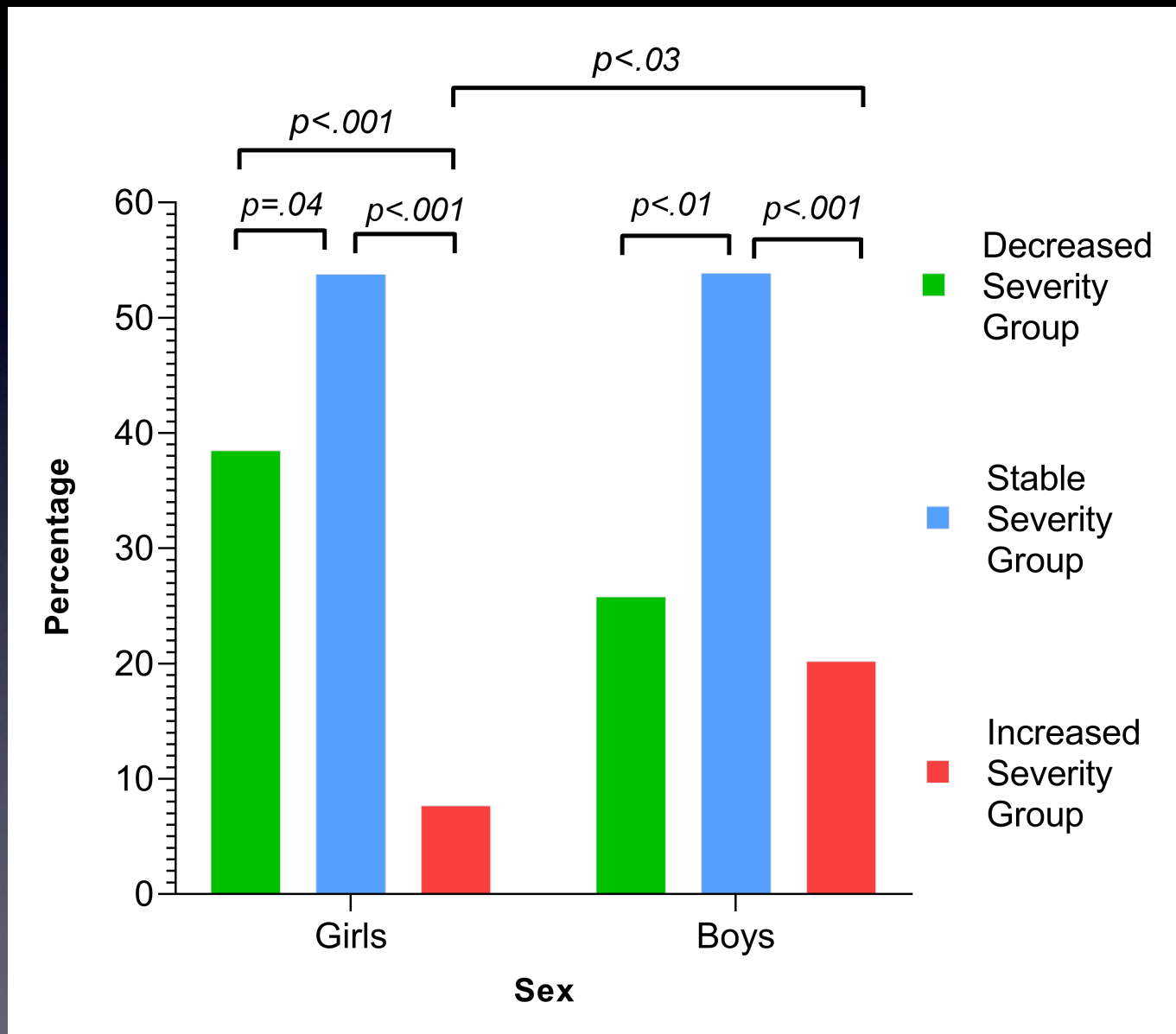
Einat Waizbard Bartov

# Trajectories of ASD Severity

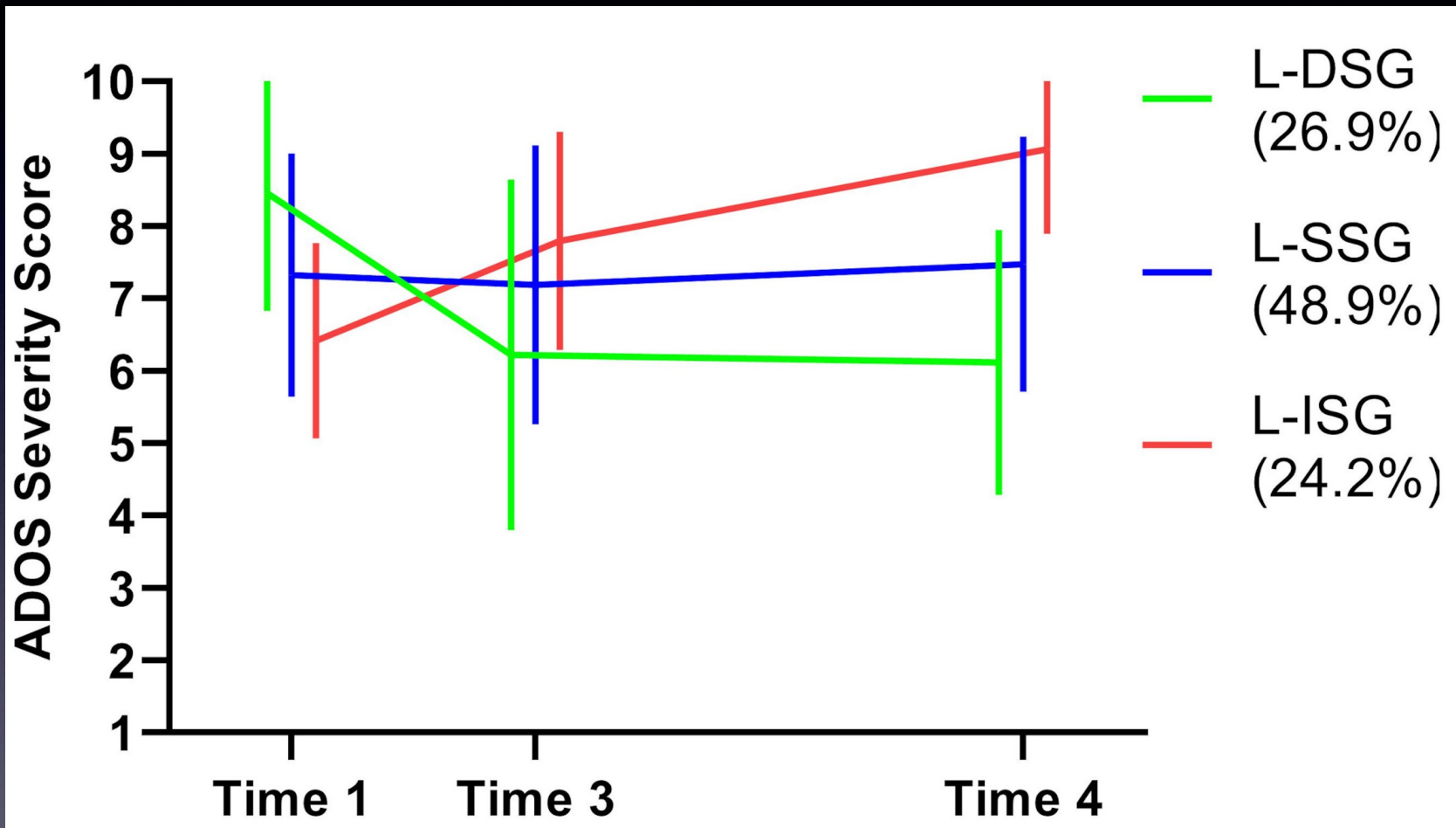




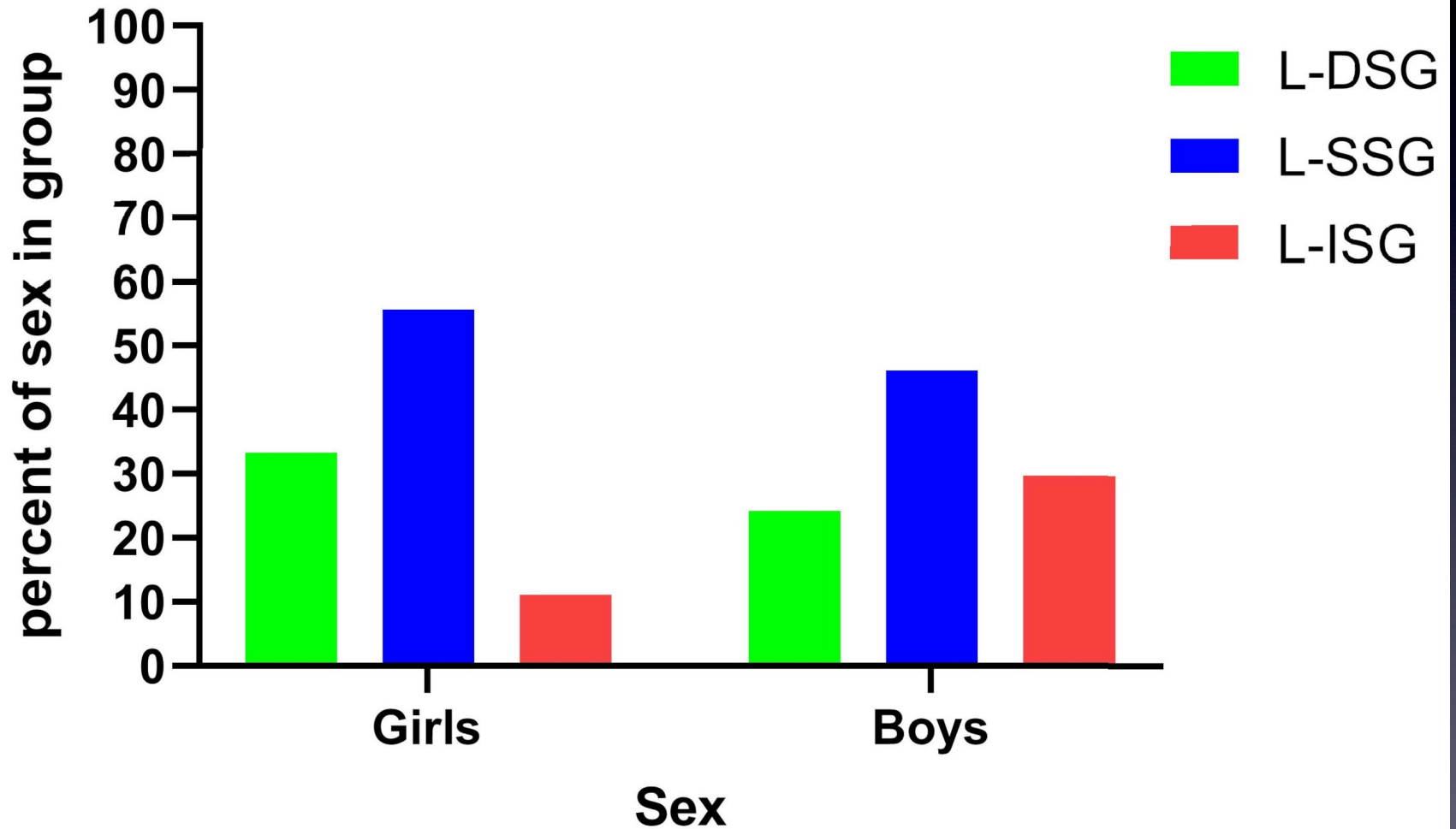
# Sex Differences of ASD Severity



# Trajectories of ASD Severity





# Trajectories of ASD Severity



# How does IQ change over time?

## RESEARCH ARTICLE

### What will My Child's Future Hold? Phenotypes of Intellectual Development in 2–8-Year-Olds with Autism Spectrum Disorder

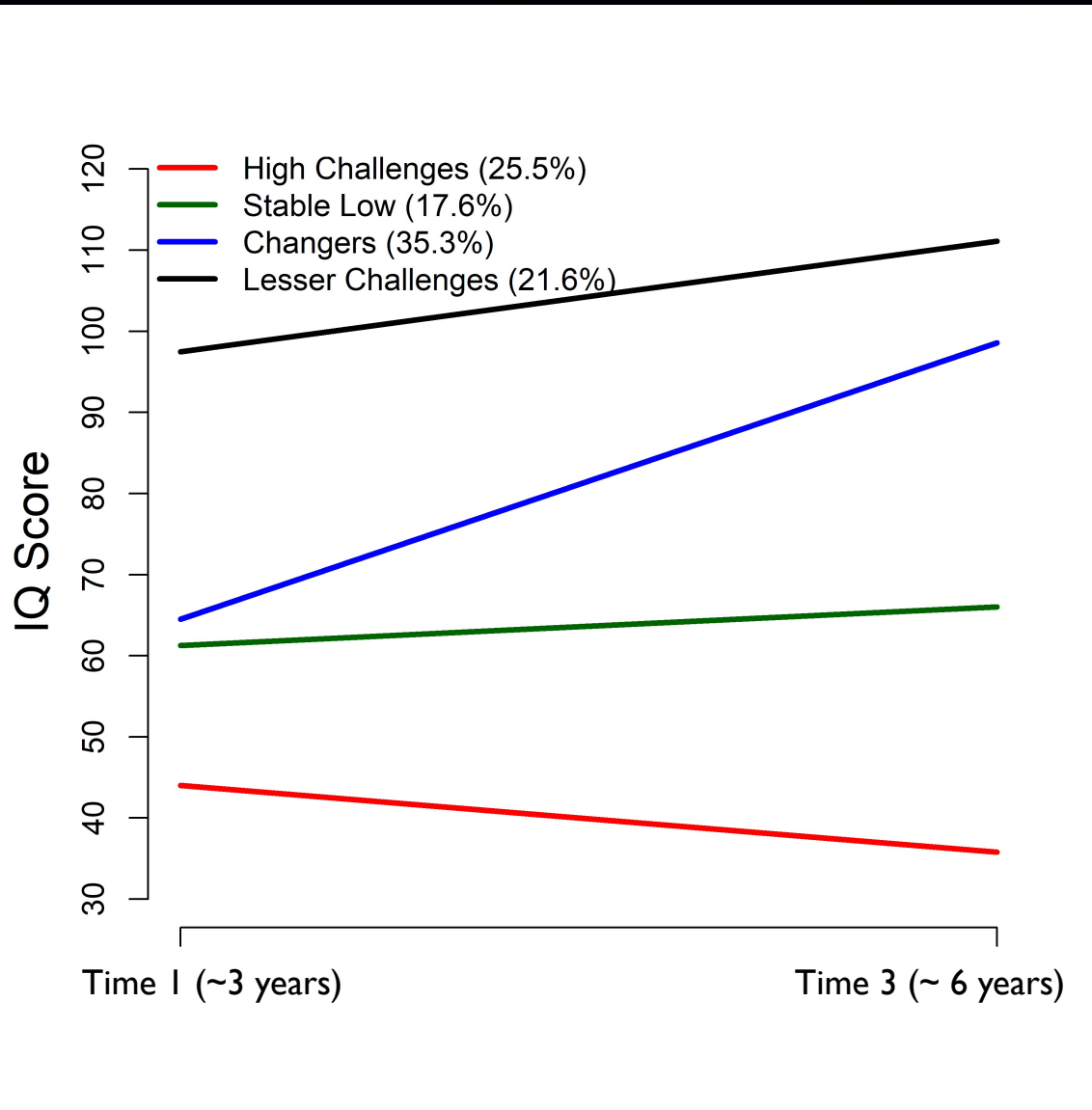
Marjorie Solomon , Ana-Maria Iosif , Vanessa P. Reinhardt, Lauren E. Libero, Christine W. Nordahl, Sally Ozonoff, Sally J. Rogers, and David G. Amaral

*Autism Res* 2018, 11: 121–132.



Marjorie Solomon Friedman

# Trajectories of IQ



# Are there Associations with Behavioral Intervention?

NO - Those doing more poorly got more intervention

Between T1 and T3 68%-83% received ABA  
(This means between 15 and 18 weekly hours of ABA).

# Anxiety in Autism

“This summer [1937] we brought him to a playground slide and on the first afternoon when the other children were sliding on it he would not get about it, and when we put him up to slide down it he seemed horrorstruck. The next morning when nobody was present, however, he walked out, climbed the ladder, and slid down and he has slid on it frequently since, but slides only when no other child is present to join him in sliding.”

Case 1, “Donald”

“He frets when the bread is put in the oven to be made into toast, and is afraid it will get burned and be hurt. He is upset when the sun sets. He is upset because the moon does not always appear in the sky at night.”

Case 8, “Alfred”

*Autistic Disturbances of Affective Contact* by Leo  
Kanner, 1943

# Anxiety in Autism

JOURNAL OF CLINICAL CHILD & ADOLESCENT PSYCHOLOGY  
<https://doi.org/10.1080/15374416.2019.1703712>

 **Routledge**  
Taylor & Francis Group



## Clinically Significant Anxiety in Children with Autism Spectrum Disorder and Varied Intellectual Functioning

Connor M. Kerns<sup>a</sup>, Breanna Winder-Patel<sup>b</sup>, Ana Maria Iosif<sup>c,d</sup>, Christine Wu Nordahl<sup>b,d</sup>, Brianna Heath<sup>b,d</sup>, Marjorie Solomon<sup>b,d</sup>, and David G. Amaral<sup>b,d</sup>

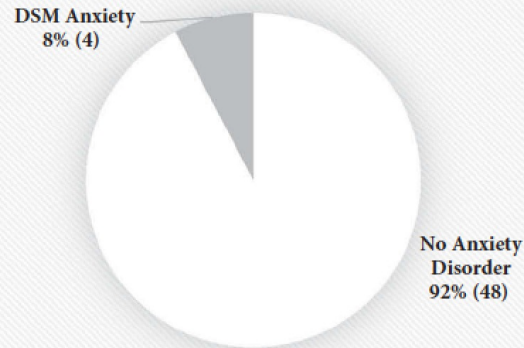
<sup>a</sup>Department of Psychology, University of British Columbia; <sup>b</sup>The MIND Institute, UC Davis; <sup>c</sup>Division of Biostatistics, Department of Public Health Sciences, University of California; <sup>d</sup>Department of Psychiatry and Behavioral Sciences, UC Davis



Connor Kerns, Ph.D.

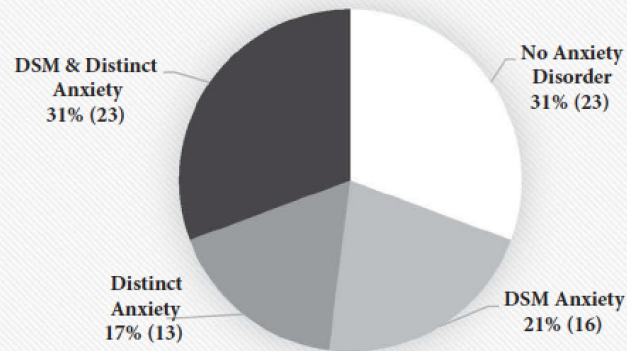


a. Rates (%[n]) of Clinically Significant Anxiety (Including Phobias) in TD Group (N=52)



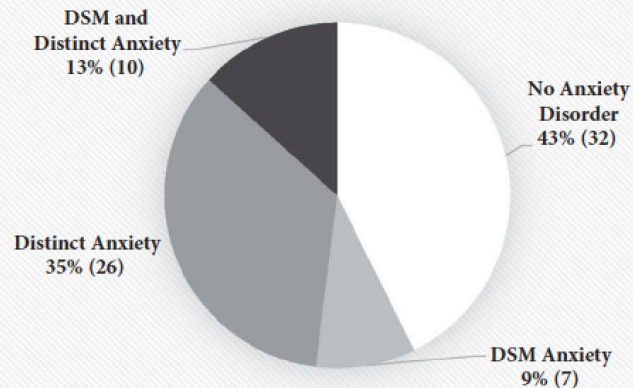
8%

b. Rates (%[n]) of Clinically Significant Anxiety (Including Phobias) in ASD Group (N=75)



69%

c. Rates (%[n]) of Clinically Anxiety (Excluding Phobias) in ASD Group (N=75)



57%

# Anxiety and the Amygdala

NEW RESEARCH

## Functional Connectivity of the Amygdala Is Disrupted in Preschool-Aged Children With Autism Spectrum Disorder

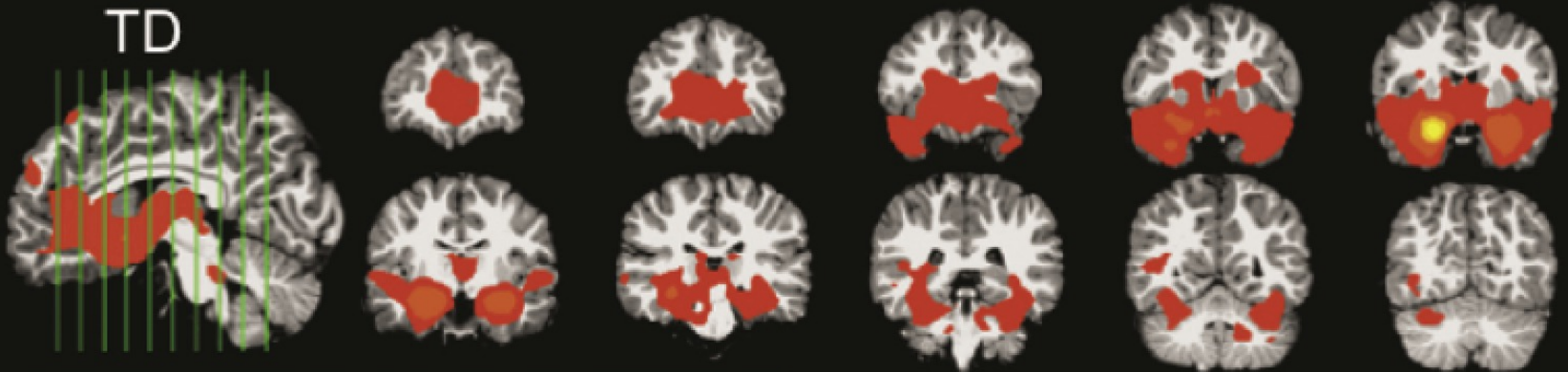
Mark D. Shen, PhD, Deana D. Li, MPH, Christopher L. Keown, MS, Aaron Lee, BS,  
Ryan T. Johnson, PhD, Kathleen Angkustsiri, MD, Sally J. Rogers, PhD, Ralph-Axel Müller, PhD,  
David G. Amaral, PhD, Christine Wu Nordahl, PhD

J Am Acad Child Adolesc Psychiatry 2016;55(9):817–824.

Connectivity with Right Amygdala

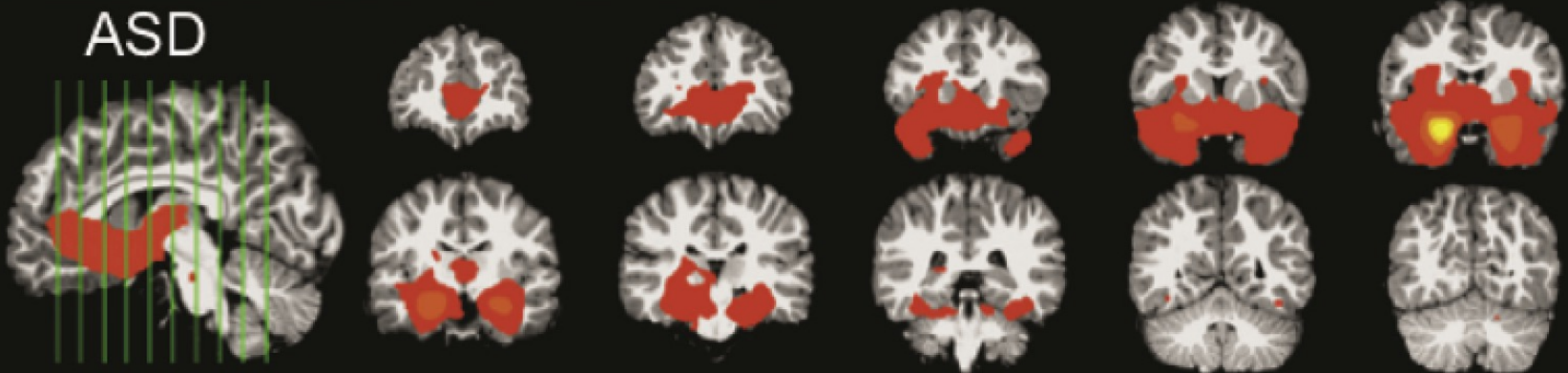
D

TD



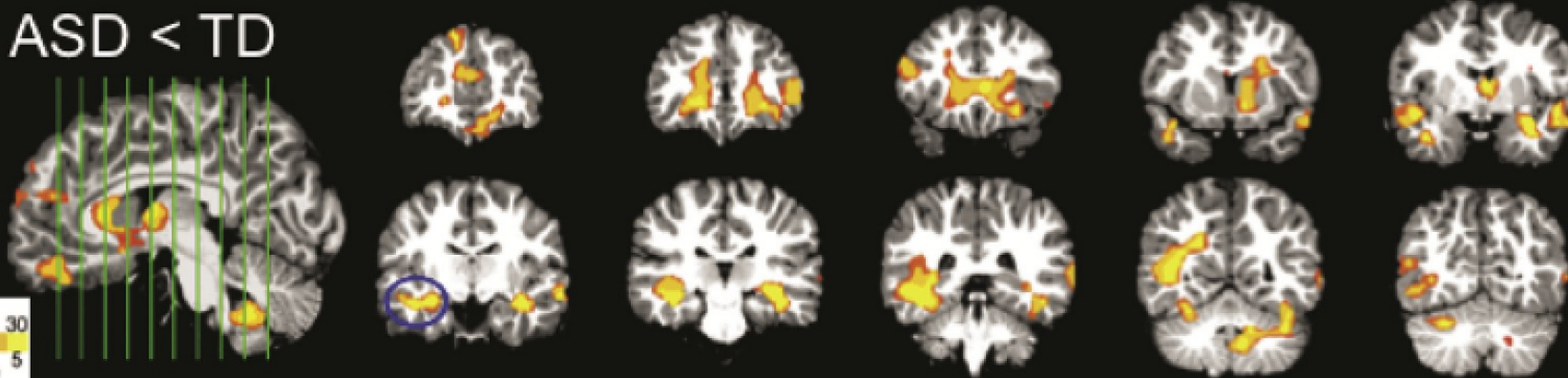
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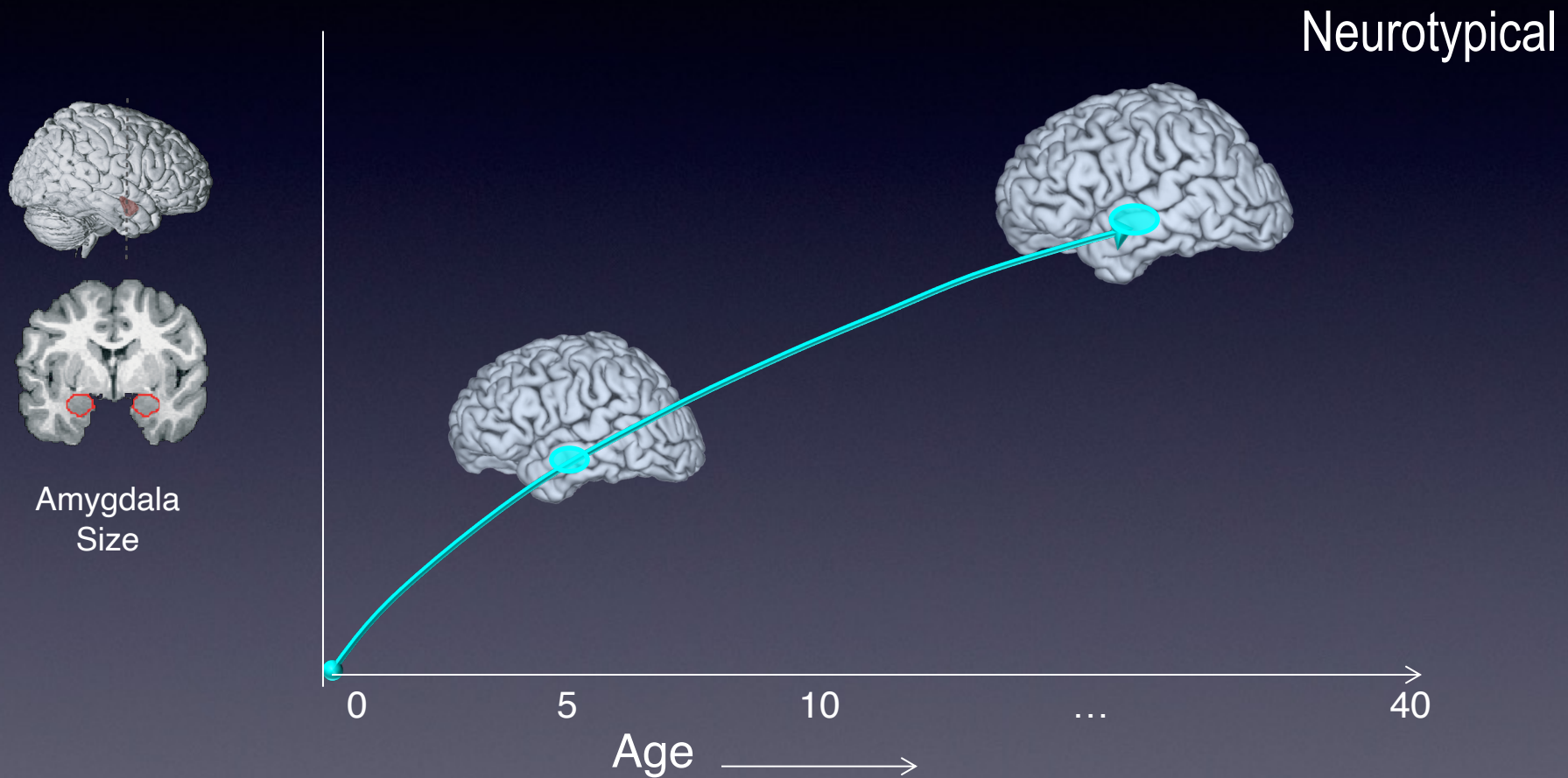


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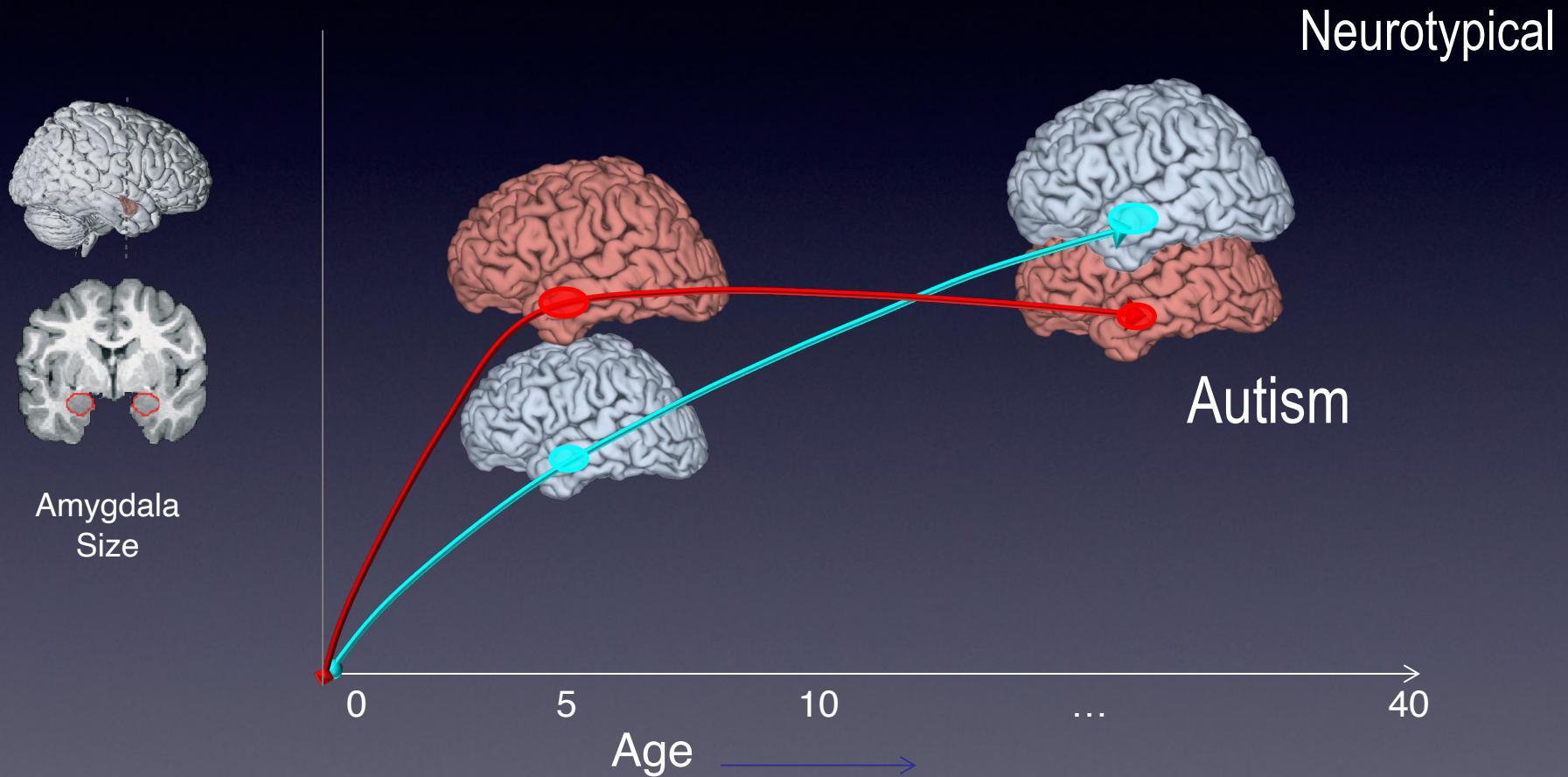
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# Amygdala continues to grow in typical development



# Amygdala grows too large too quickly in ASD



# Postmortem studies of the amygdala

## Neuron numbers increase in the human amygdala from birth to adulthood, but not in autism

Thomas A. Avino<sup>a</sup>, Nicole Barger<sup>a</sup>, Martha V. Vargas<sup>a</sup>, Erin L. Carlson<sup>a</sup>, David G. Amaral<sup>a,b,c</sup>, Melissa D. Bauman<sup>a,b</sup>, and Cynthia M. Schumann<sup>a,1</sup>

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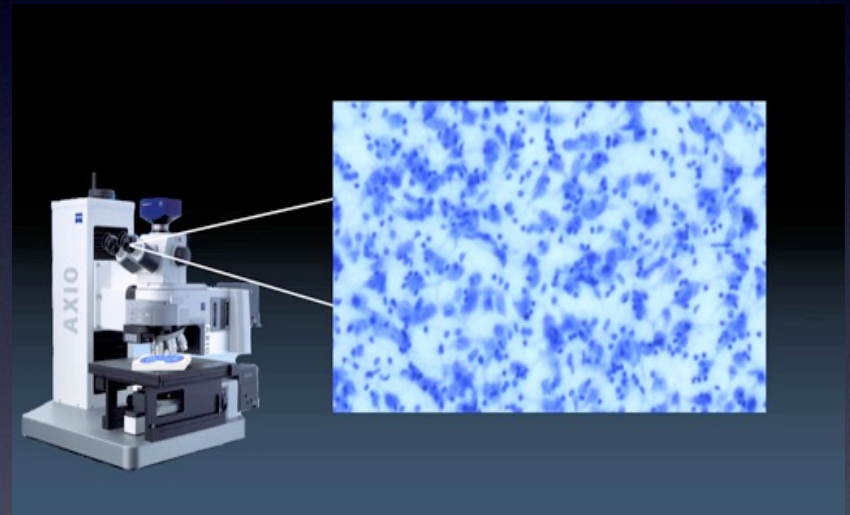
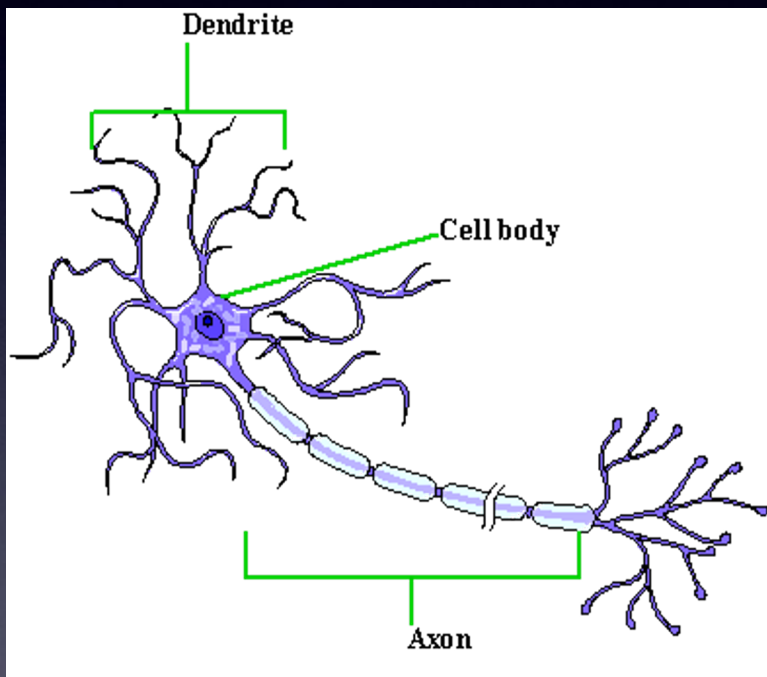


Thomas Avino, Ph.D.

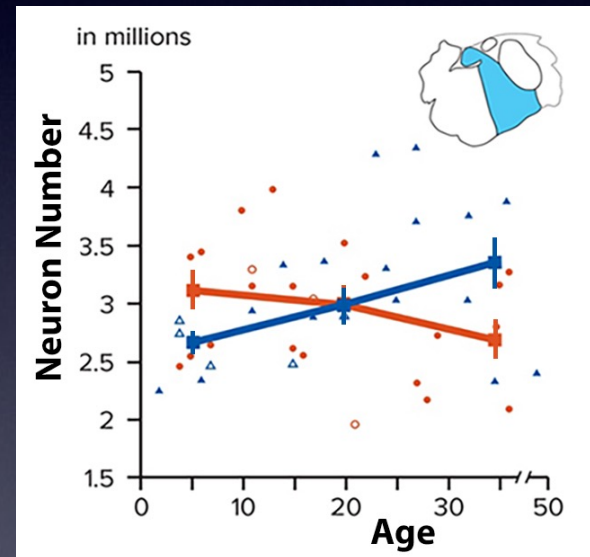
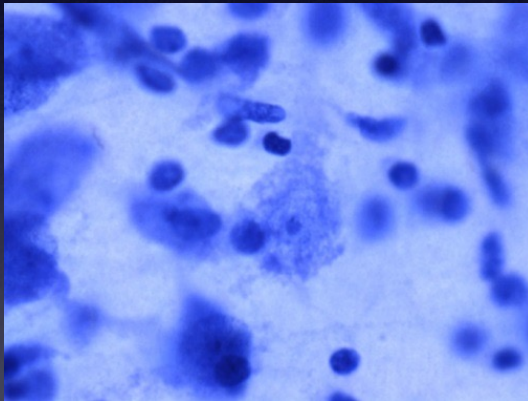


Cynthia Schumann, Ph.D.

How do the number of neurons change throughout the human lifespan? How is it different in ASD?



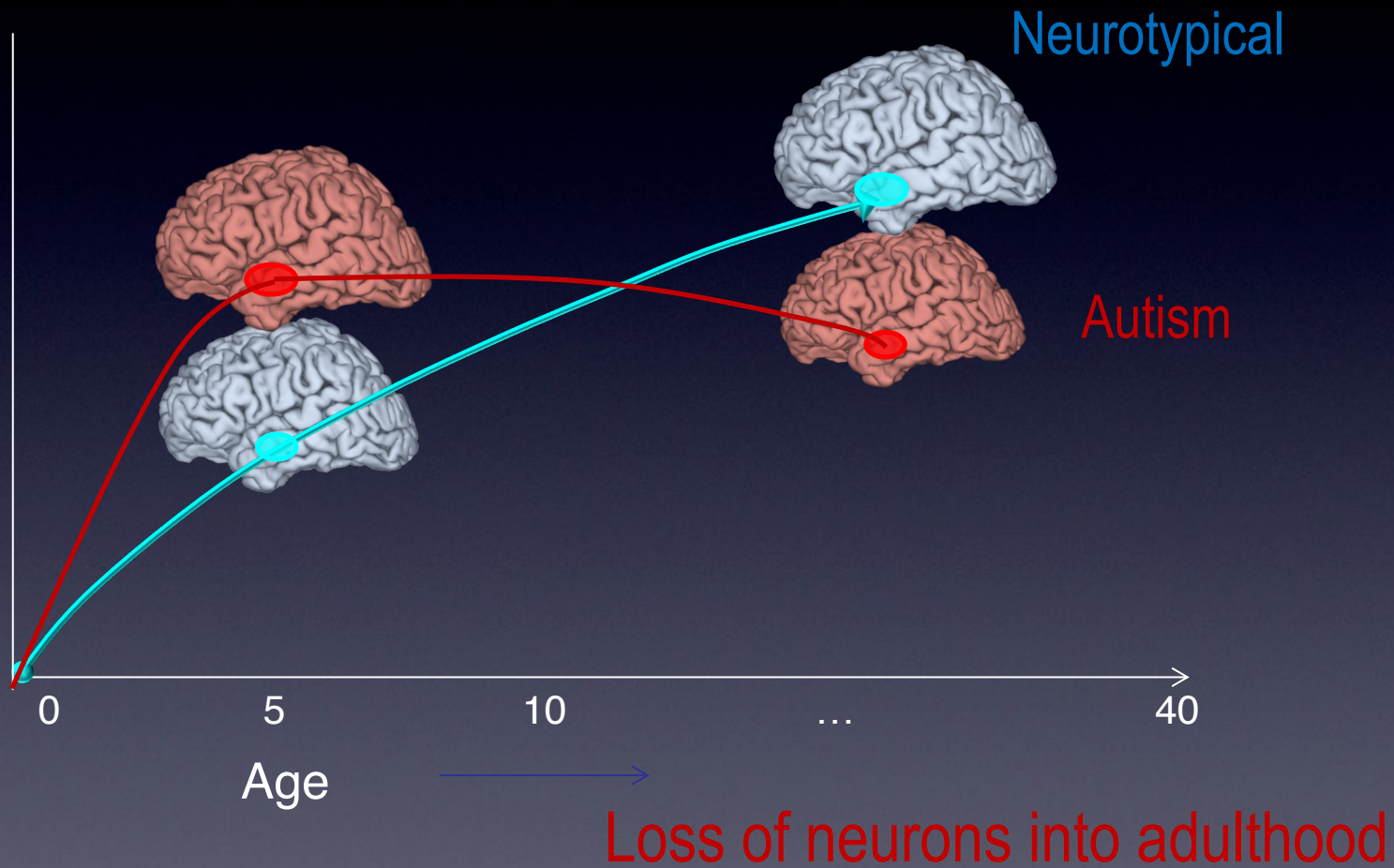
There are more amygdala neurons in children with ASD, but fewer amygdala neurons in adults with ASD



Avino et al., 2018 PNAS



# Too many amygdala neurons in children with ASD



# Overall Conclusions

- The big brain form of ASD is seen mainly in males and predicts a more difficult cognitive and behavioral trajectory
- Autism is not necessarily a lifelong disorder
- There are different trajectories of autism severity and cognitive development
- The biological basis for the different trajectories is just beginning to become clear.

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