Neuroimaging the Full Spectrum of Autism

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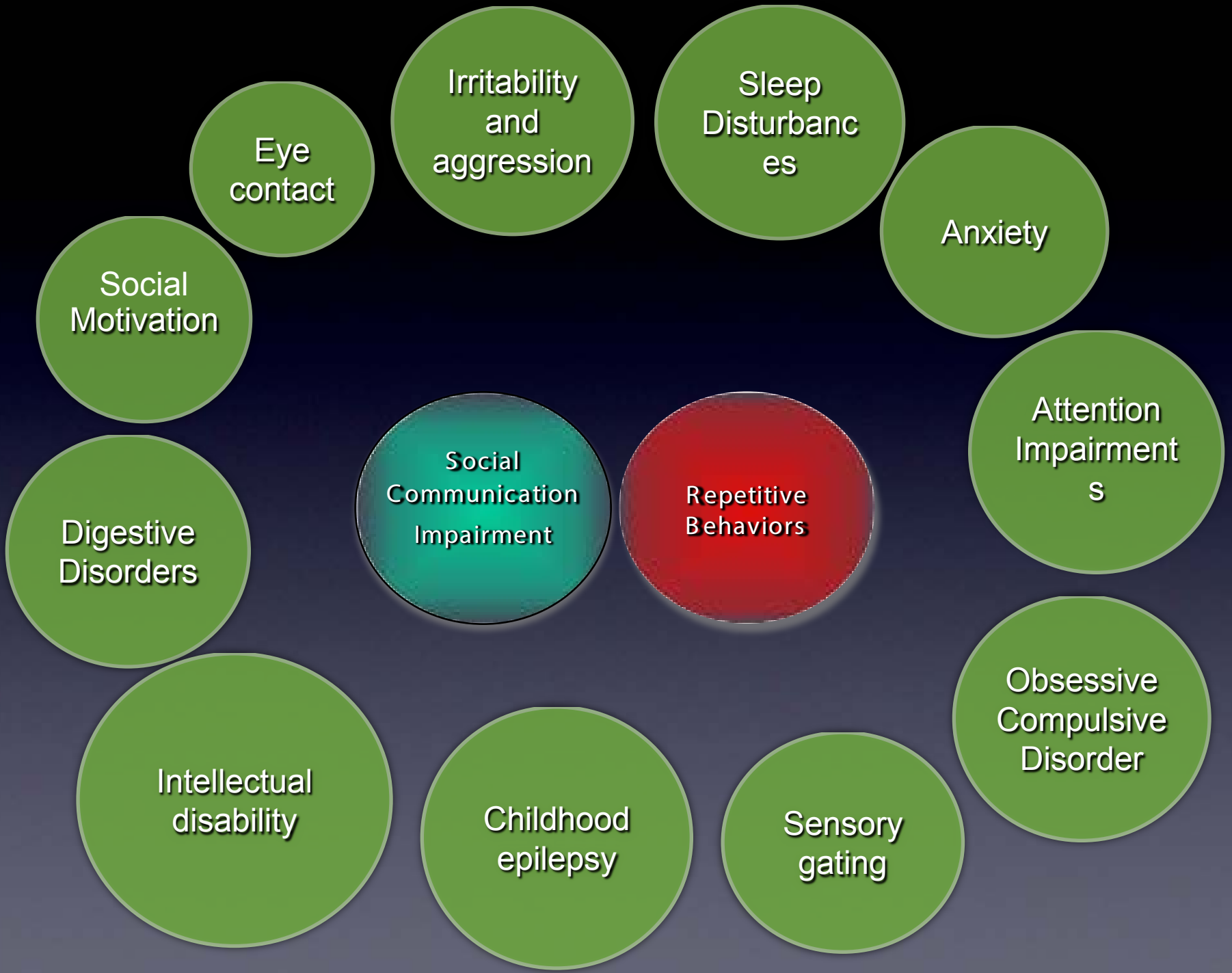
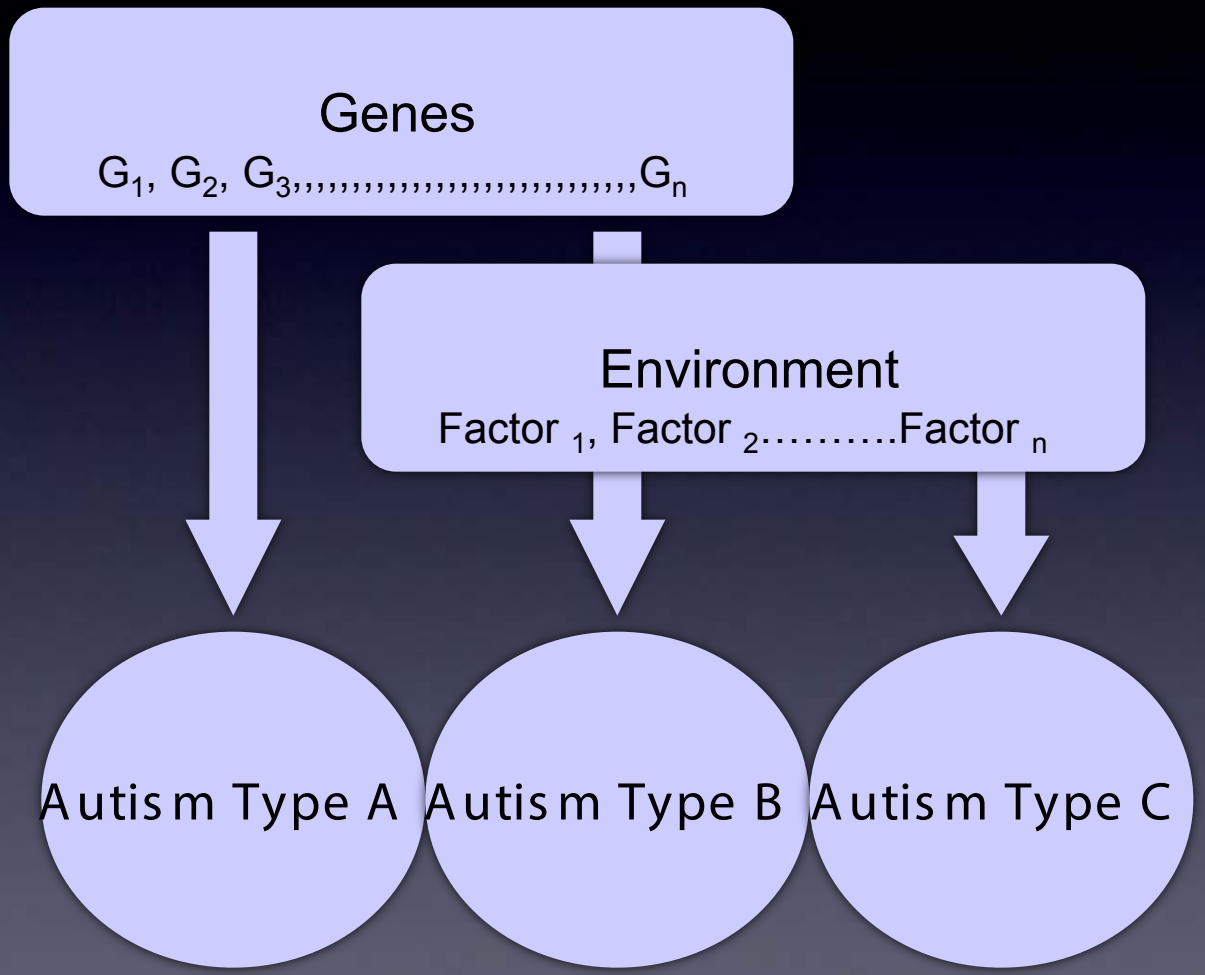

Irritability and aggression
Sleep Disturbances
Eye contact
Anxiety
Social Motivation
Attention Impairments
Social Communication Impairment
Repetitive Behaviors
Digestive Disorders
Obsessive Compulsive Disorder
Intellectual disability
Childhood epilepsy
Sensory gating

Heterogeneity of Causes?



Heterogeneity of Causes?

There are many causes of autism and many types of autism?

Autism**S** not Autism

Heterogeneity of Causes?

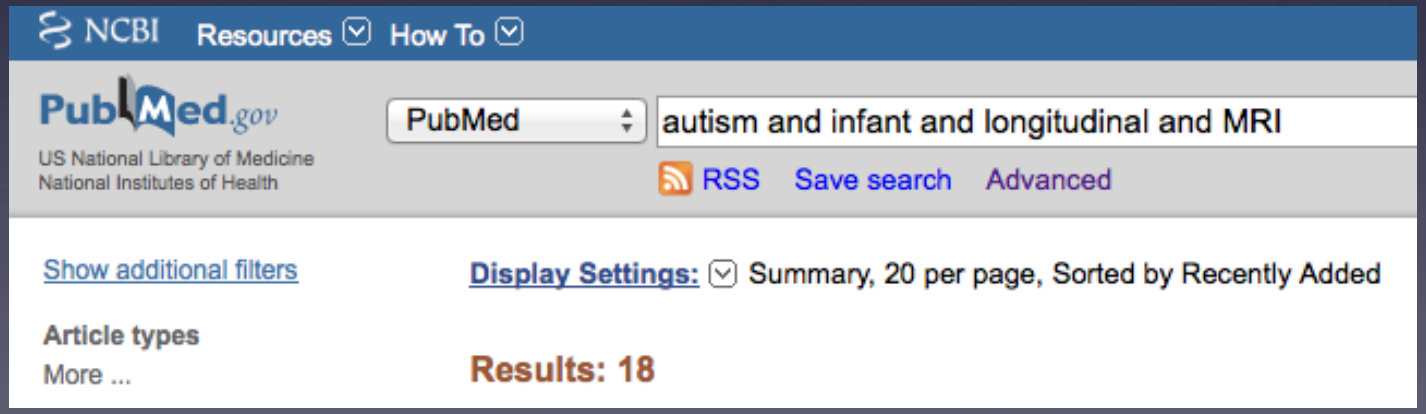
Magnetic resonance imaging may provide evidence to help define different types of ASD

MRI of Autism Spectrum Disorder Weaknesses of Earlier Studies

- Small sample sizes (dozens instead of hundreds)
- Heterogeneous samples
- Cross-sectional
- Focus on older and higher functioning individuals

There is a scarcity of large-scale, longitudinal neuroimaging studies of infants at all severity levels of autism spectrum disorder

Autism is a neurodevelopmental disorder



Only a small number of papers have focused on children under age 5

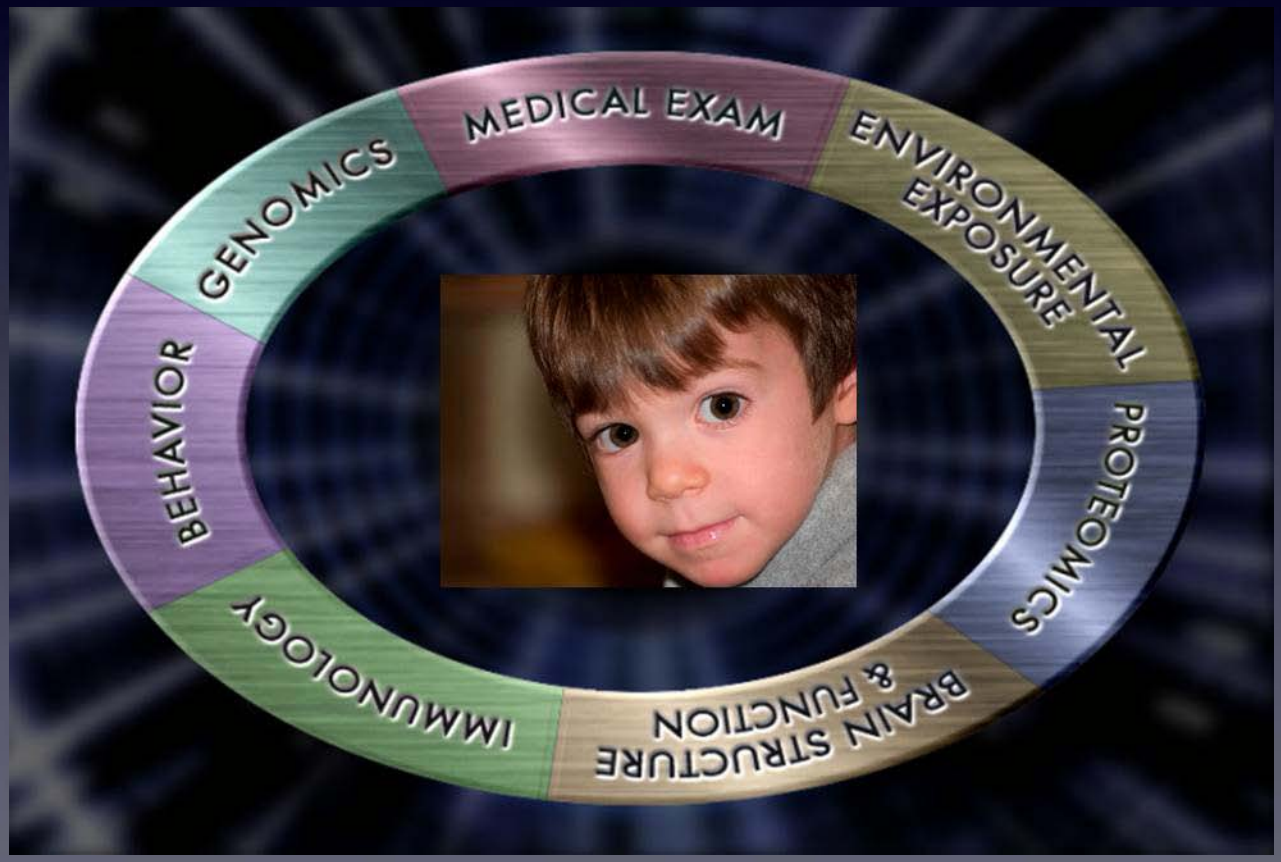
Overarching Hypothesis:

When you study the brains of young children with ASD using MRI, you will see different neurophenotypes.

Autism Phenome Project

Large-scale multidisciplinary project aimed at identifying subtypes of autism

2 to 3.5 year old children, longitudinal assessments



The MIND Institute
Autism Phenome Project (APP)

- Children are recruited between 2 and 3 1/2 years of age.

- Study includes all children with autism with very few exclusions.

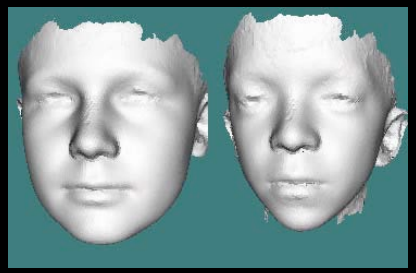
- Both boys and girls are included.

- Age-matched typically developing children serve as controls.

The MIND Institute
Autism Phenome Project (APP)

- The study is longitudinal - children return to the MIND Institute annually for further testing.

- Blood samples are obtained from subjects, siblings and from parents.



Visit 1: Diagnostic Confirmation, Cognitive Testing

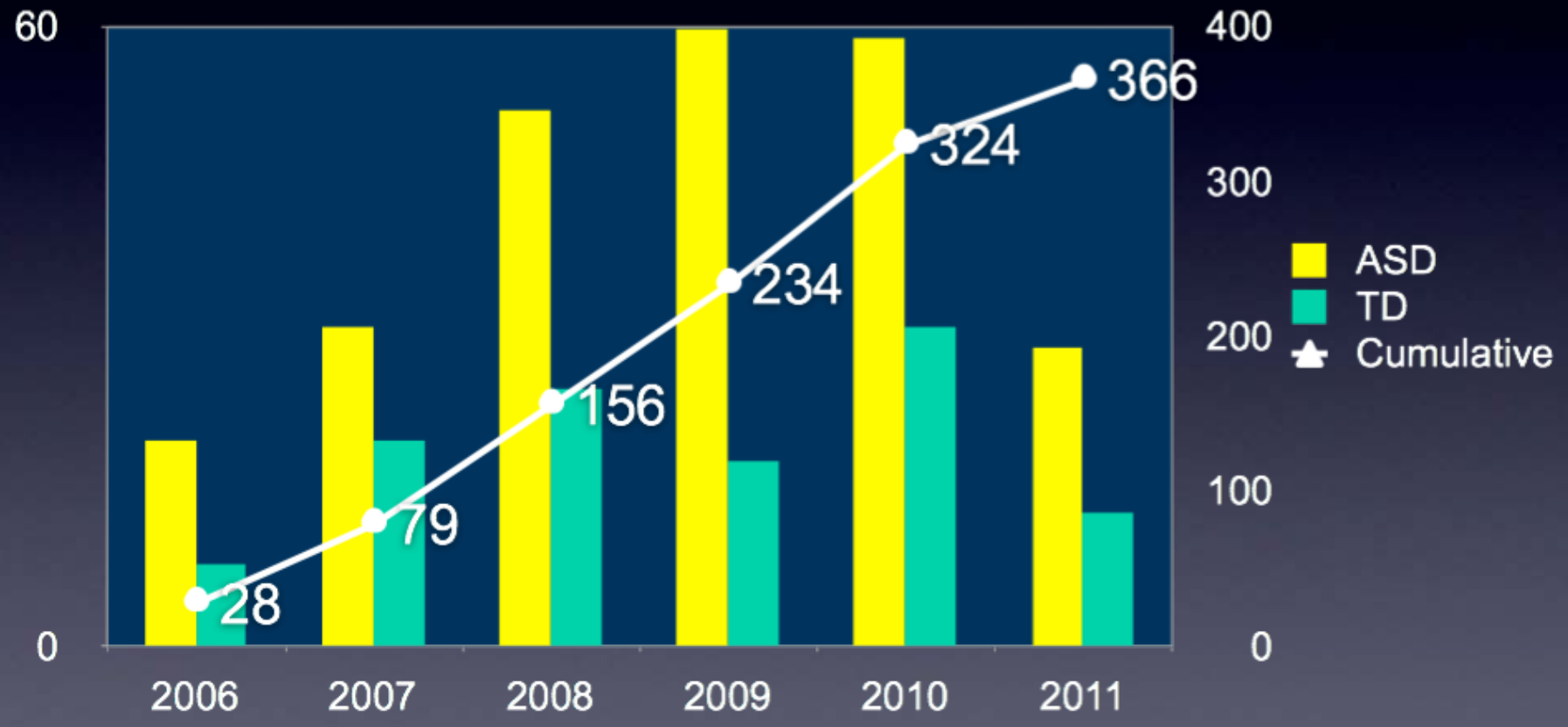
Visit 2: Language Assessment, Imitation, Handedness

Visit 3: Medical Exam, 3-D Photograph, Vitals Measurement and Blood Draw

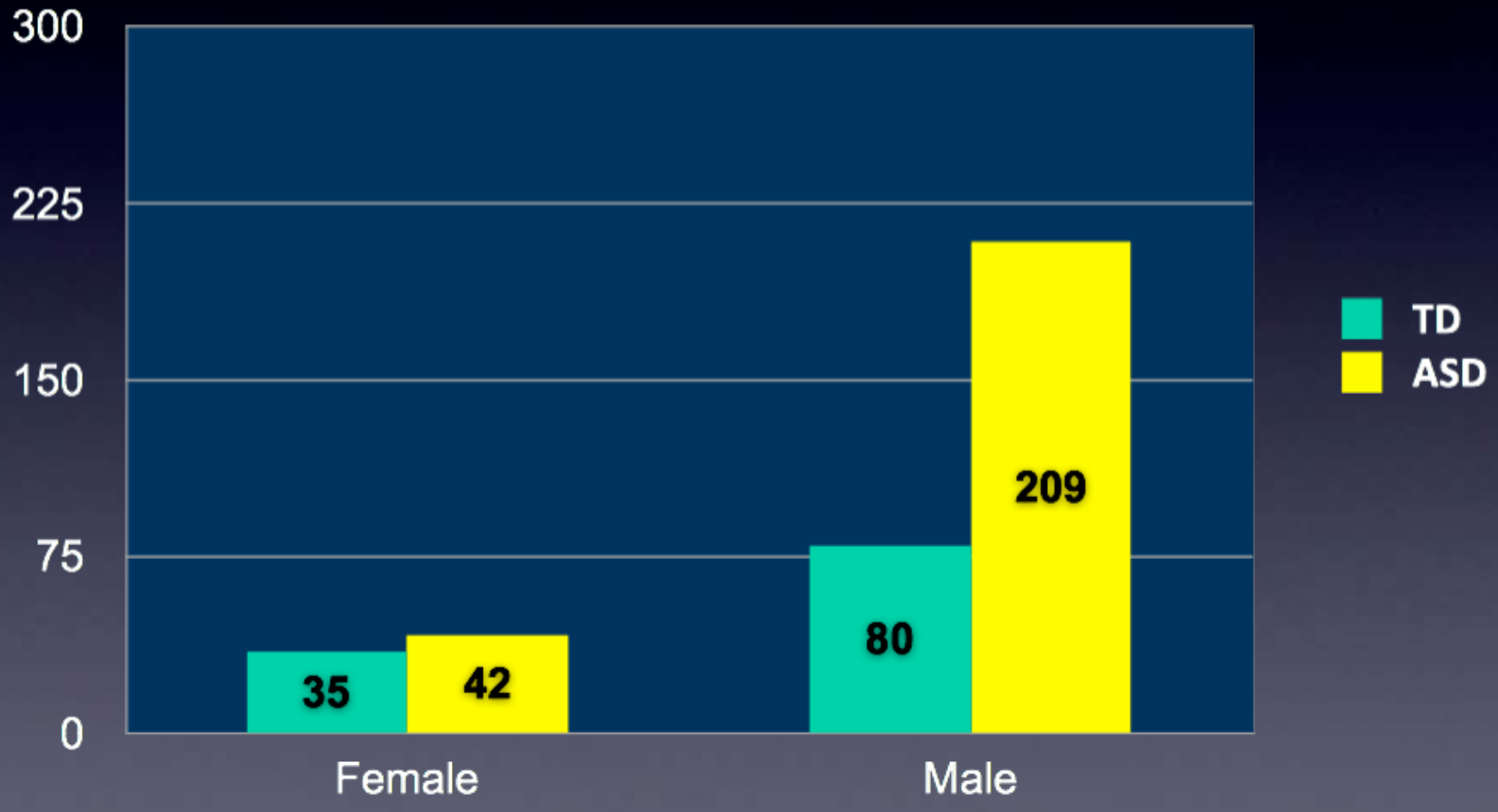
Visit 4: Nighttime MRI

Visit 5: EEG/ERP

Autism Phenome Project Background
Number of Families Participating



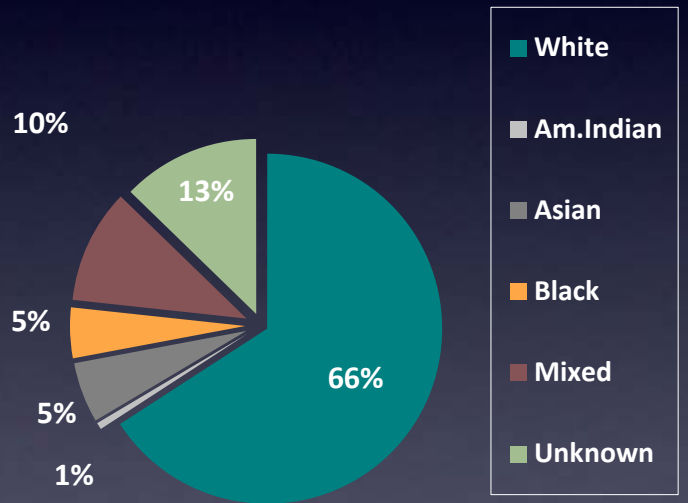
Autism Phenome Project Background Male and Female Participants



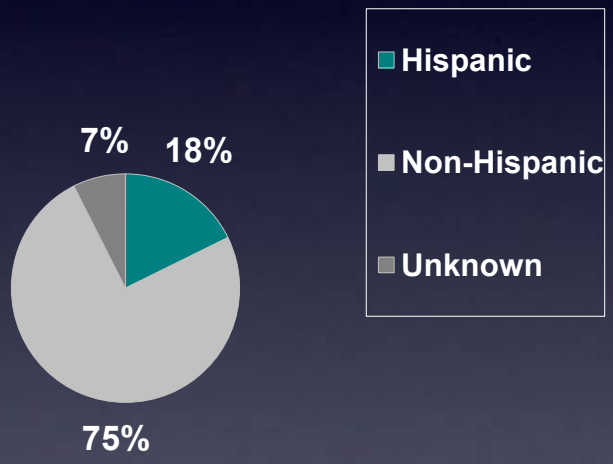
Autism Phenome Project Background Age at Entry into Study

	Male		Female	
	ASD	**TD**	**ASD**	**TD**
N	209	80	42	35
Average Age (yrs)	2.97	2.86	3.05	2.89
Std Dev	0.50	0.55	0.43	0.56

Autism Phenome Project Background

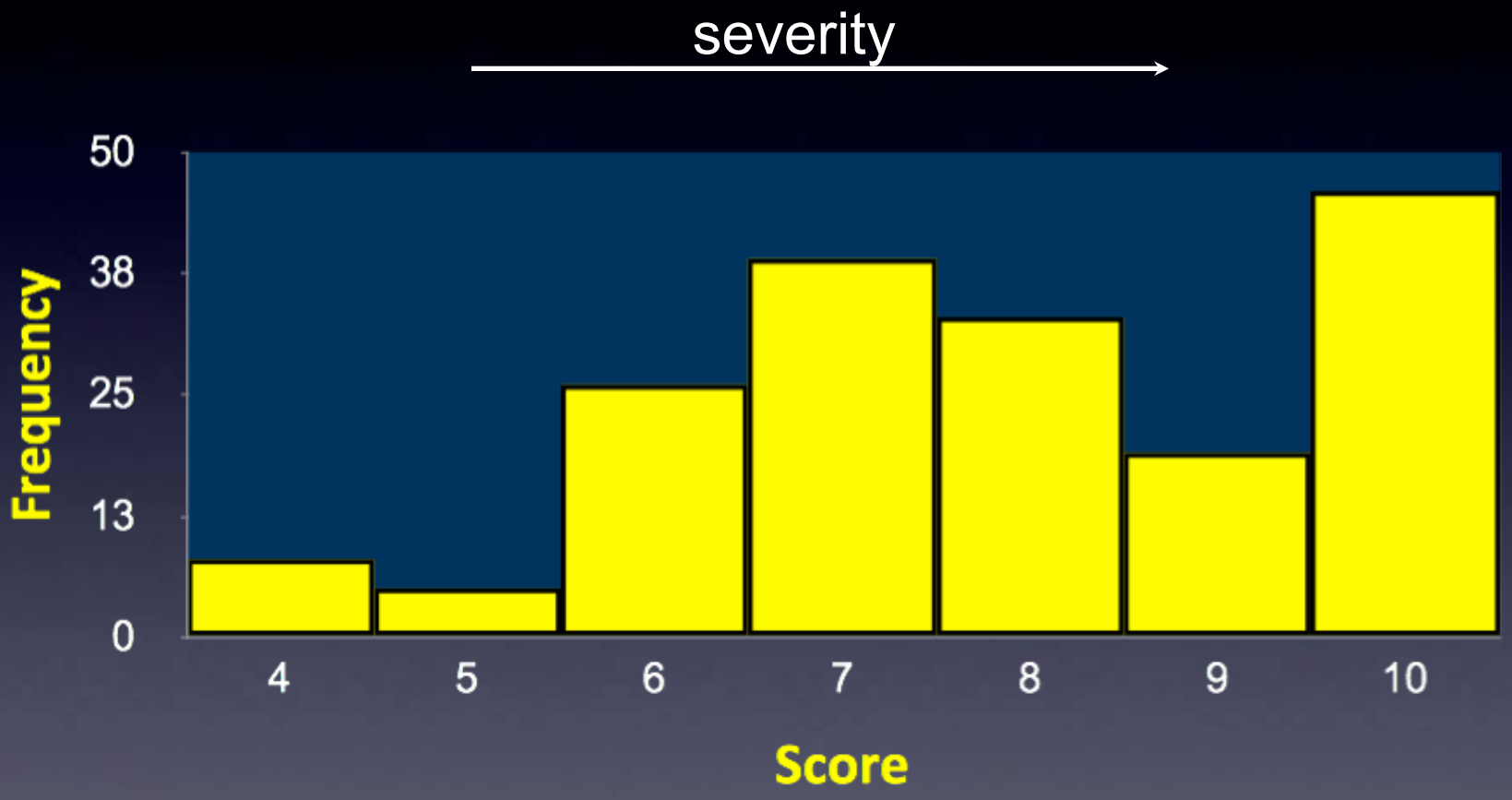


Race

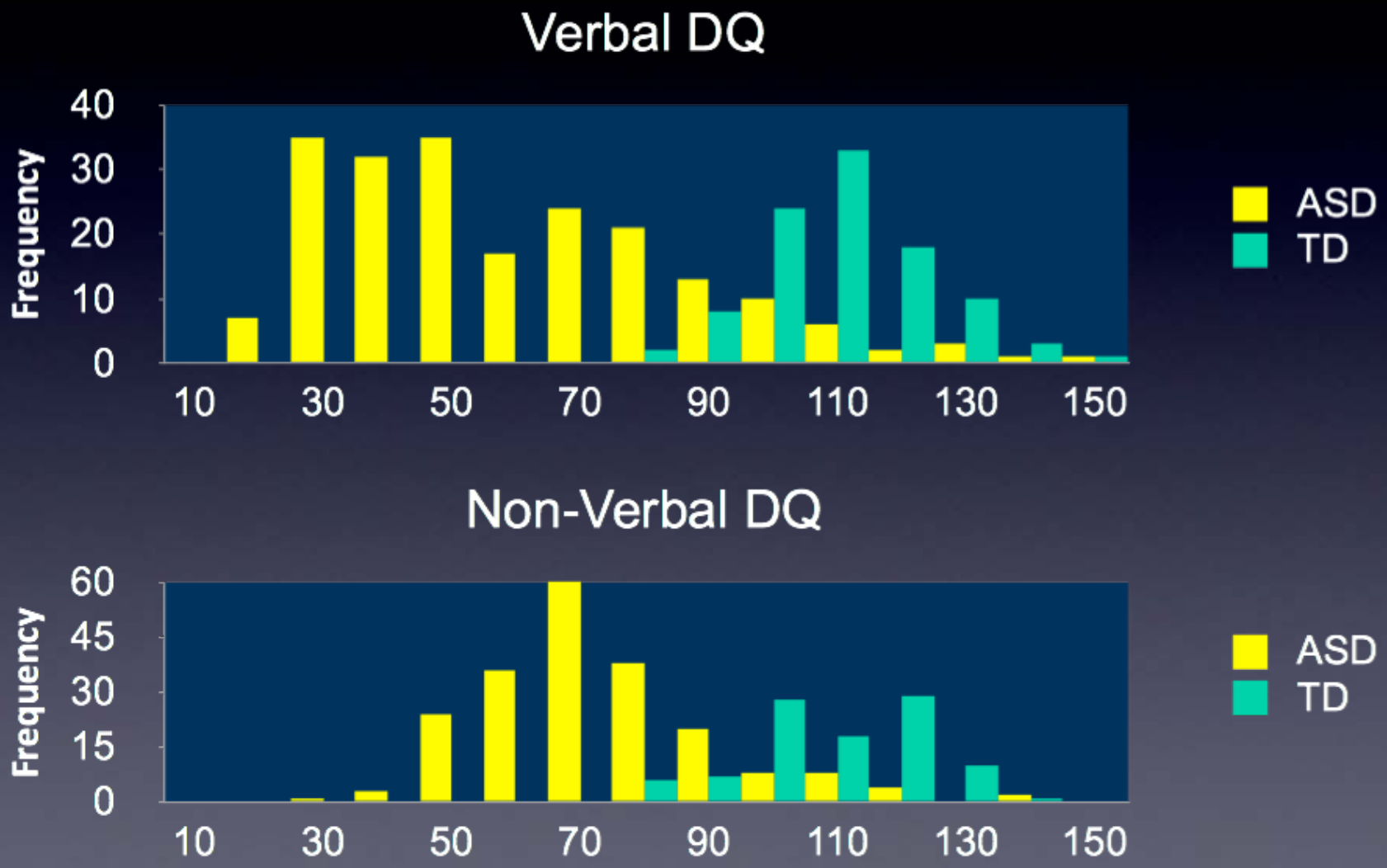


Ethnicity

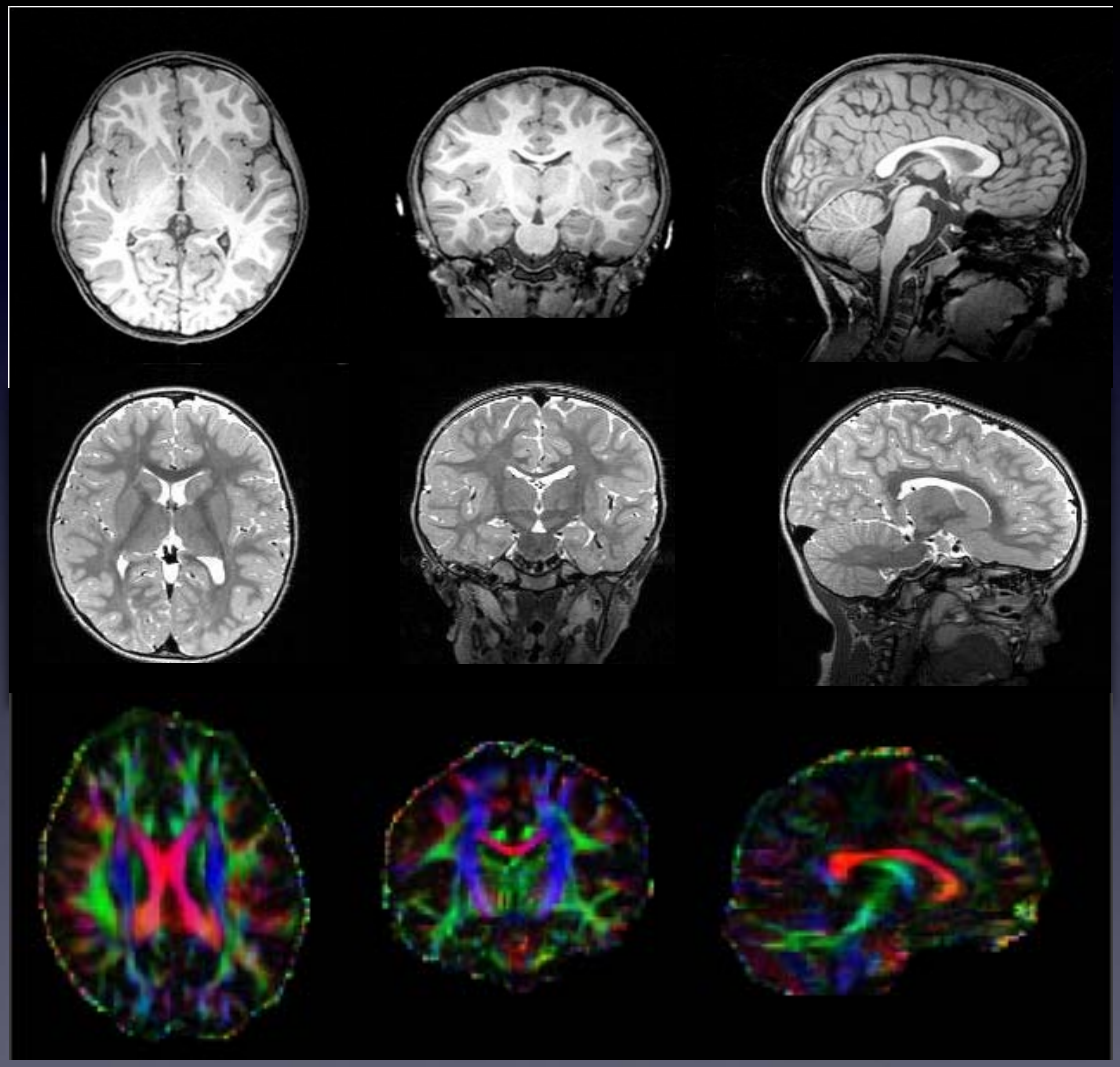
Autism Severity Score



Developmental Quotient



Brain Findings



MRI of Young Children

Thomas the Train Mock Session

MRI Practice Kit

MRI of Young Children

MRI Practice Kit

Child-friendly scanning environment

Before

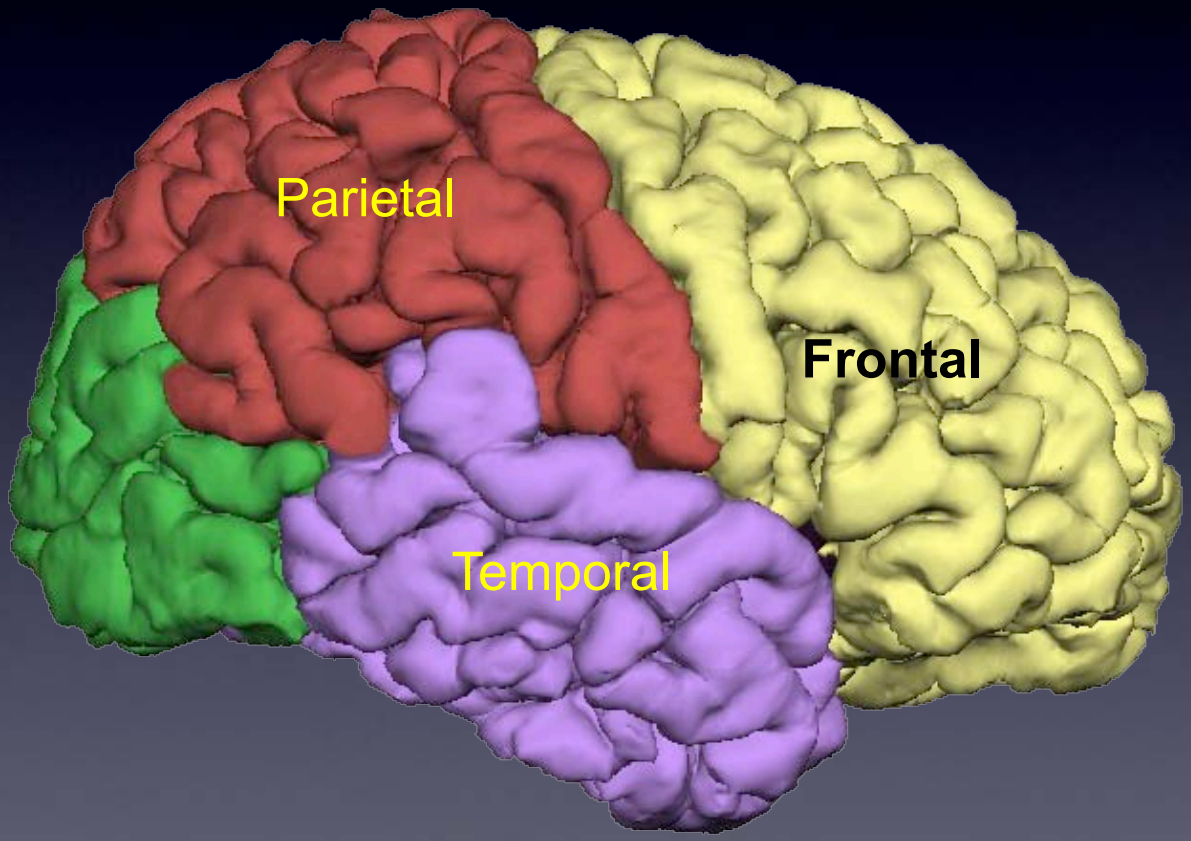
After

Christine Nordahl, Ph.D
and
MRI Team

Subjects and Success

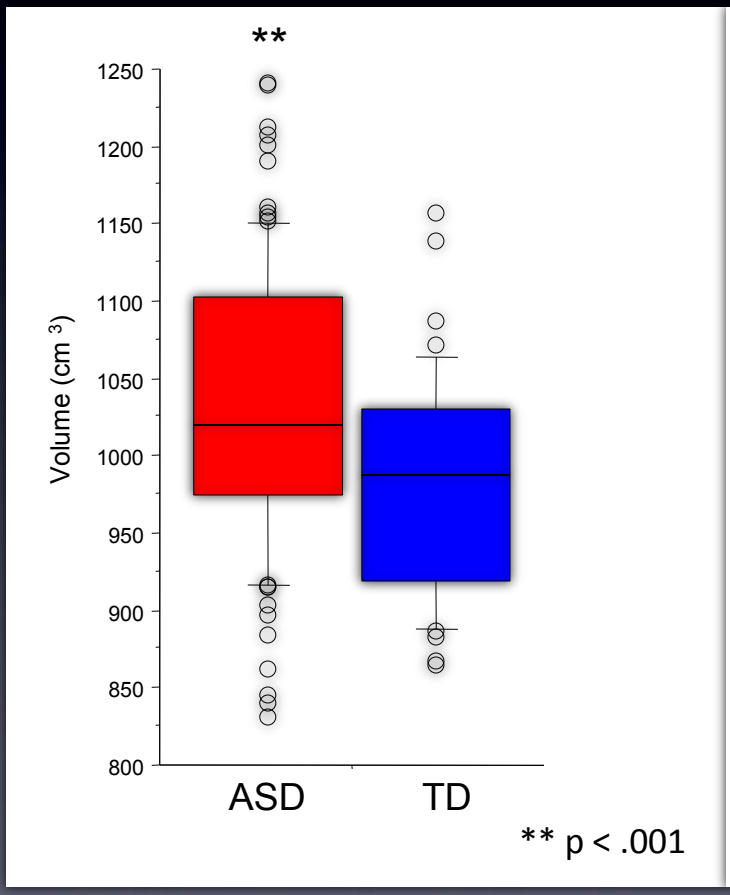
	Time 1 38 months		Time 2 51 months		Time 3 64 months	
	M	F	M	F	M	F
ASD	155	34	97	21	68	15
TD	59	31	48	25	39	20
Total	279		191		142	
Success Rate	88%		91%		88%	
Attrition			19%		21%	

Total Brain Measurements

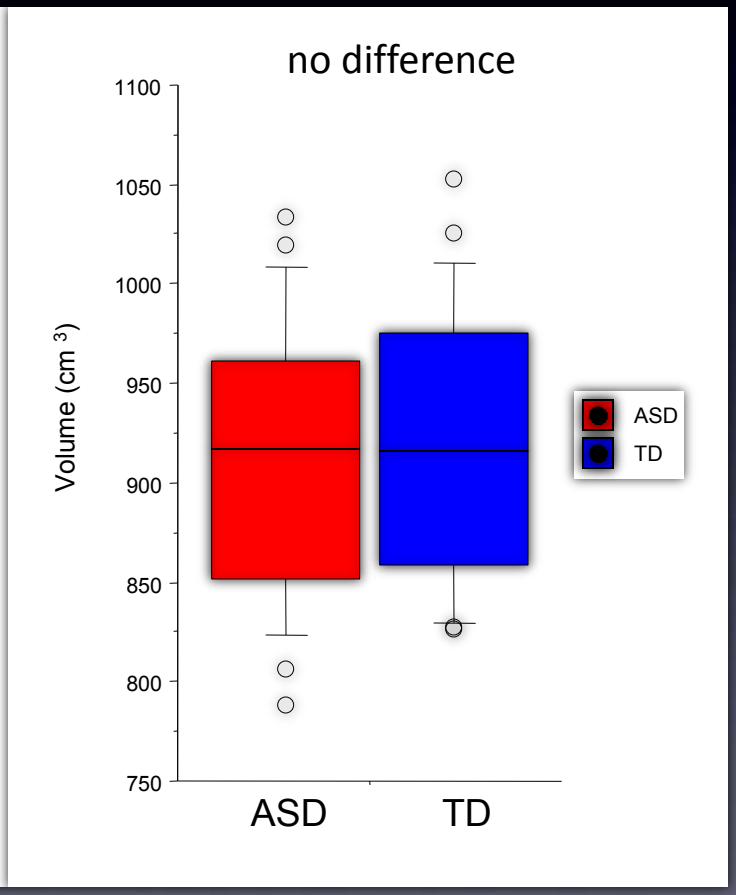


Total cerebral volume (TCV) is enlarged by 6% in boys with ASD

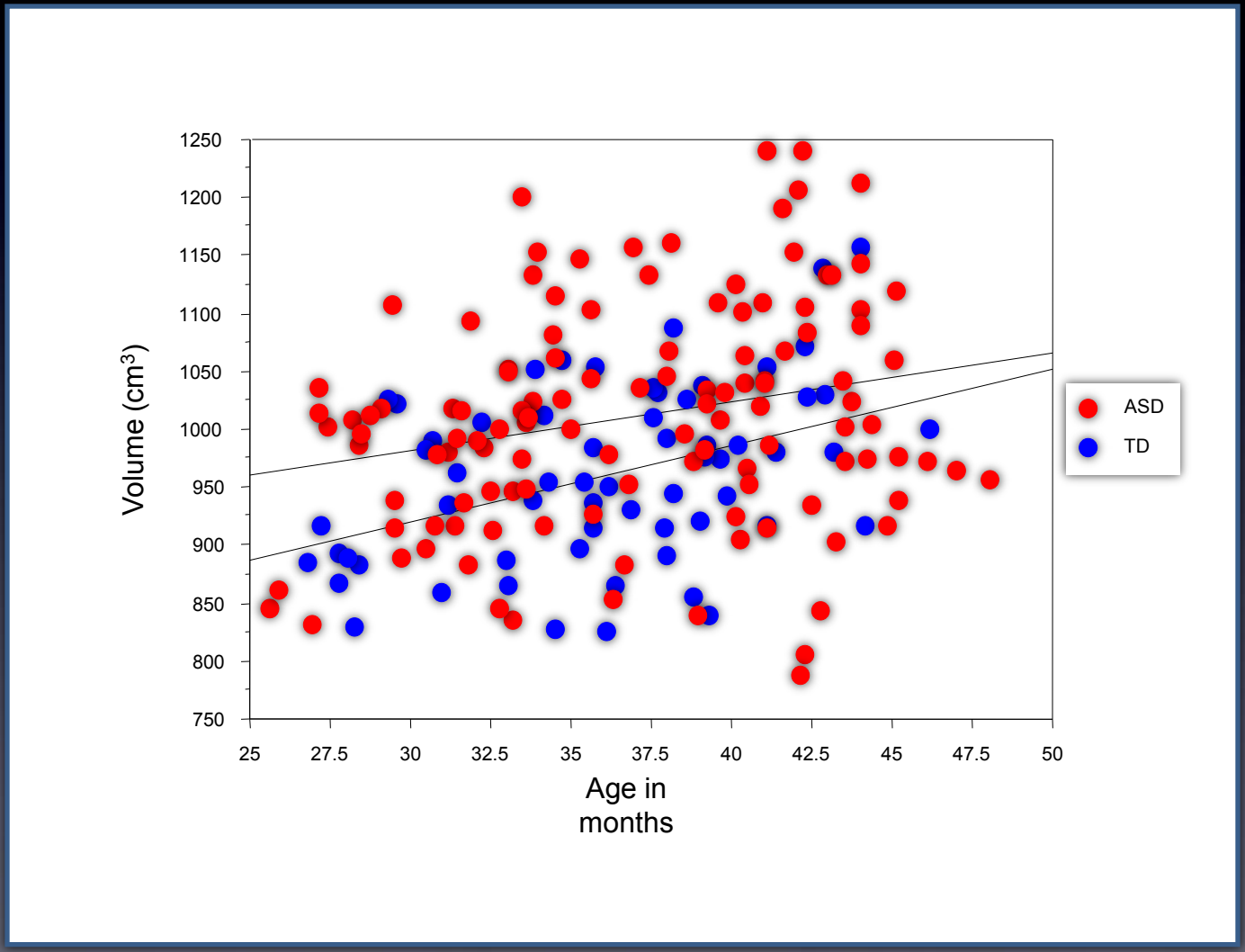
BOYS



GIRLS



Total brain size is extremely variable in ASD



Autism Onset and Brain Size

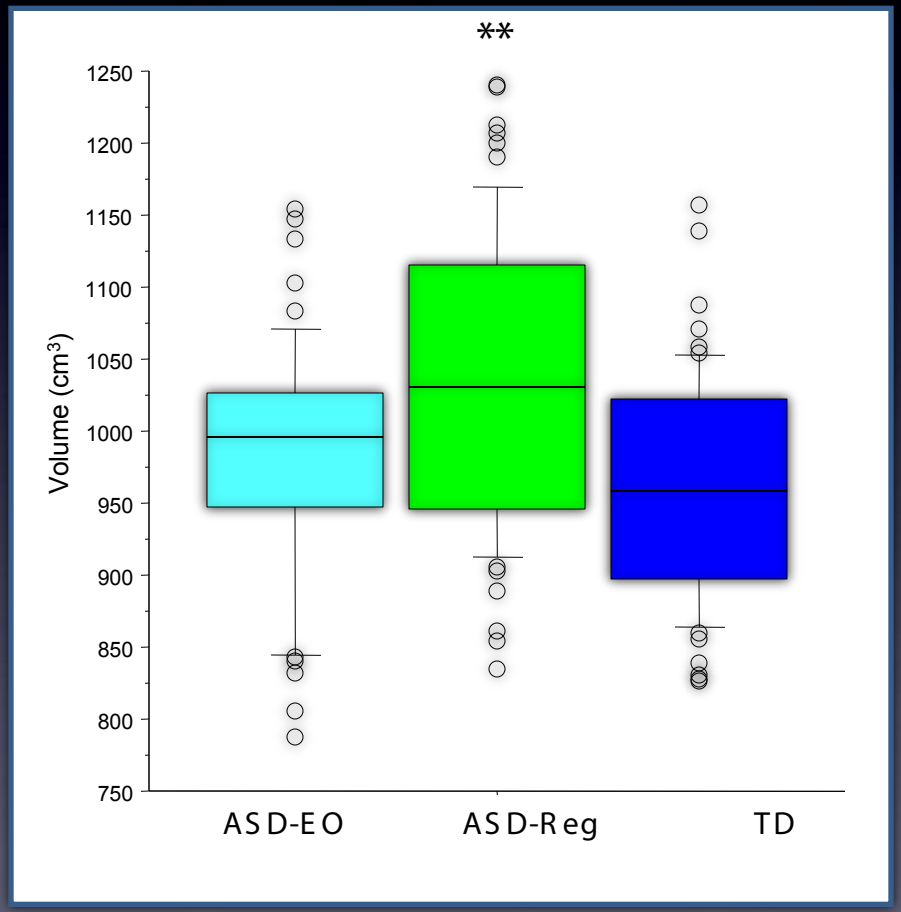
Onset status is based on parent report on ADI-R

Early Onset = 47%

Regression = 53%

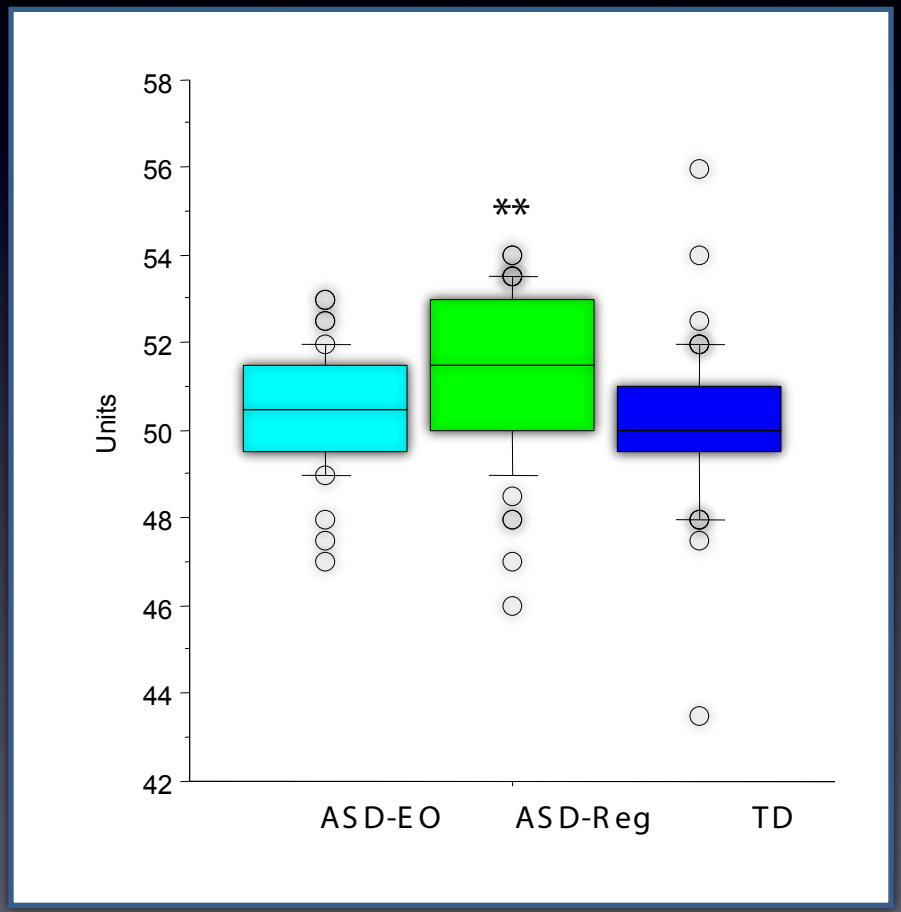
ASD children who regressed have enlarged brains

Total Cerebral Volume



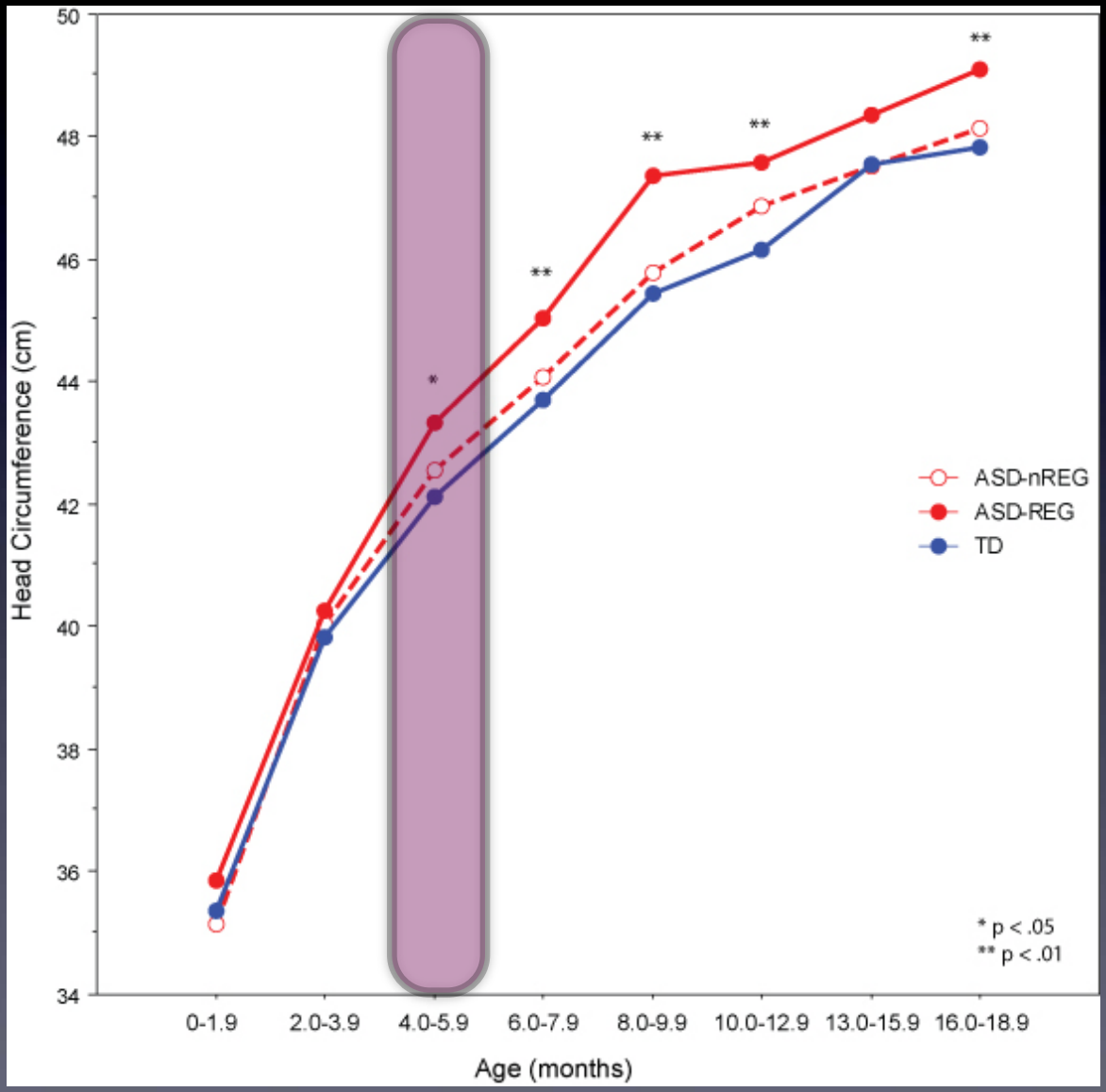
ANCOVA – age, DQ, gender as covariates
** p < .01

Head Circumference



ANCOVA – age as covariate
** p < .01 ASD-Reg > TD & ASD-EO

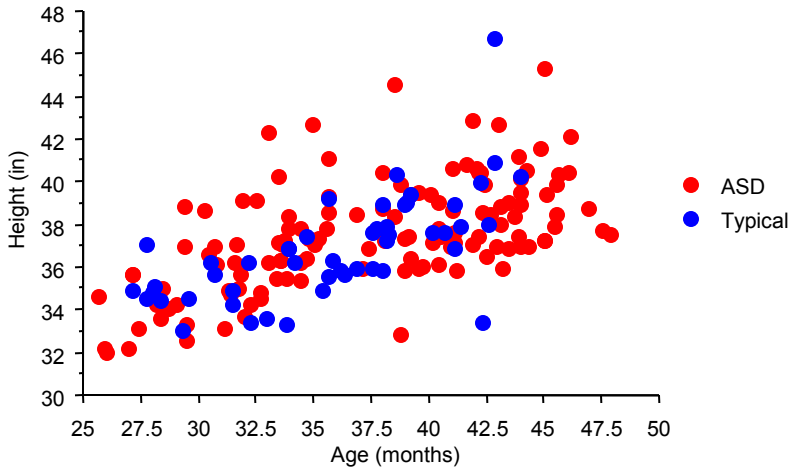
Retrospective head circumference shows divergence at 4-6 months

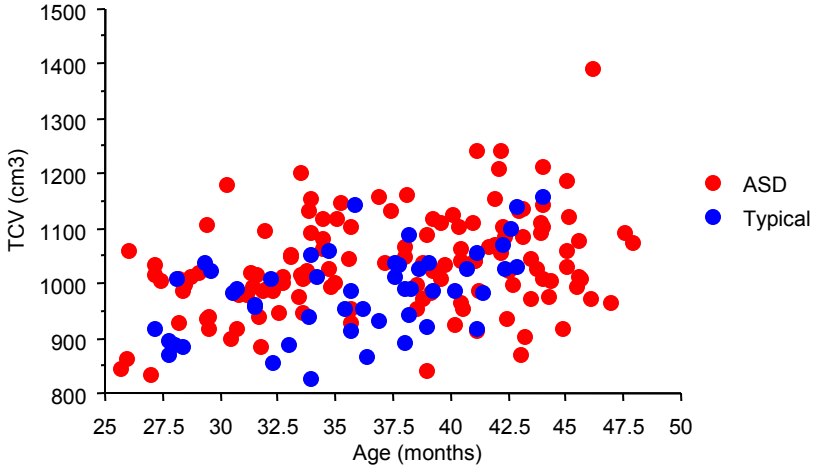


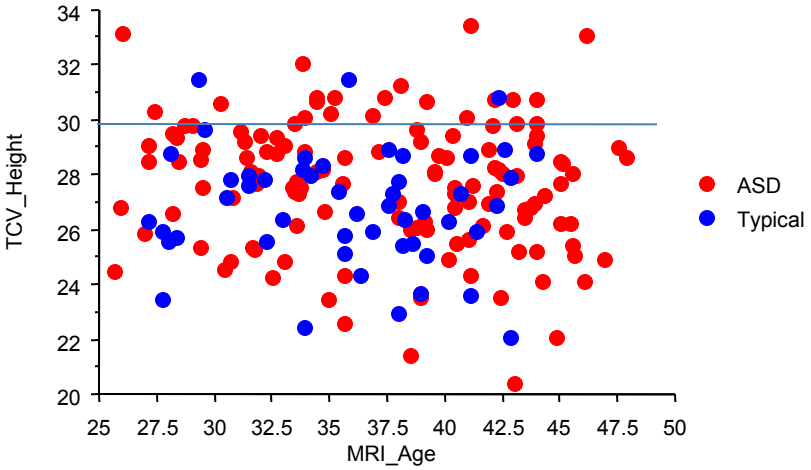
Surface rendering of children's brains

Typical Child	Autism	Autism
Age 31 months	Early Onset	Regression
TCV 981.96	Age 32 months	Age 30 months
	TCV 984.57	TCV 1180.98

Relationship of Total Cerebral Volume to Height





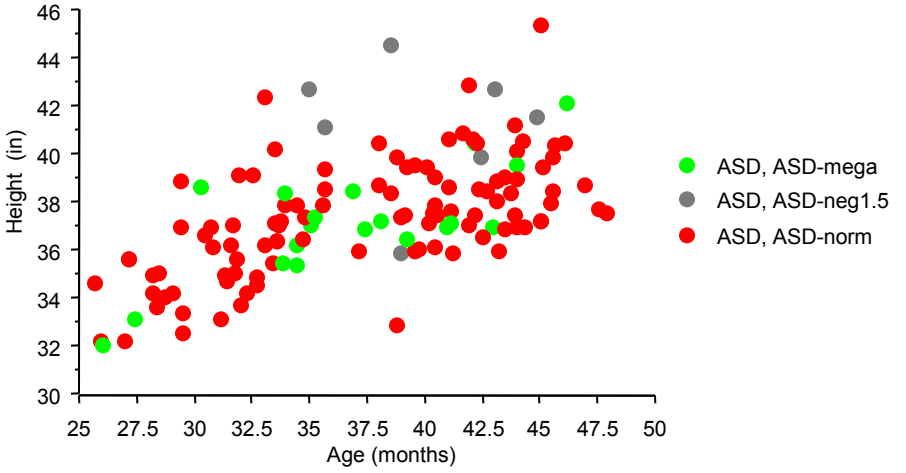


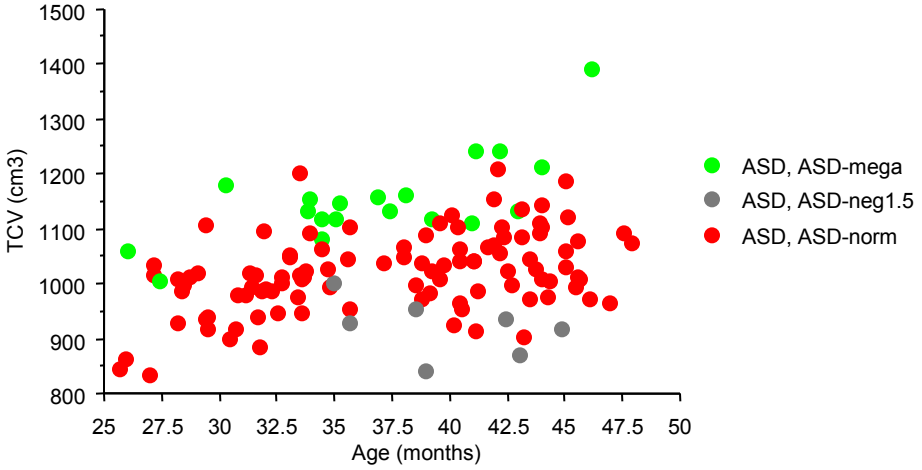
50 TD males
Mean TCV/height ratio 26.8, sd 2.11.
Cutoff for DM is 29.97

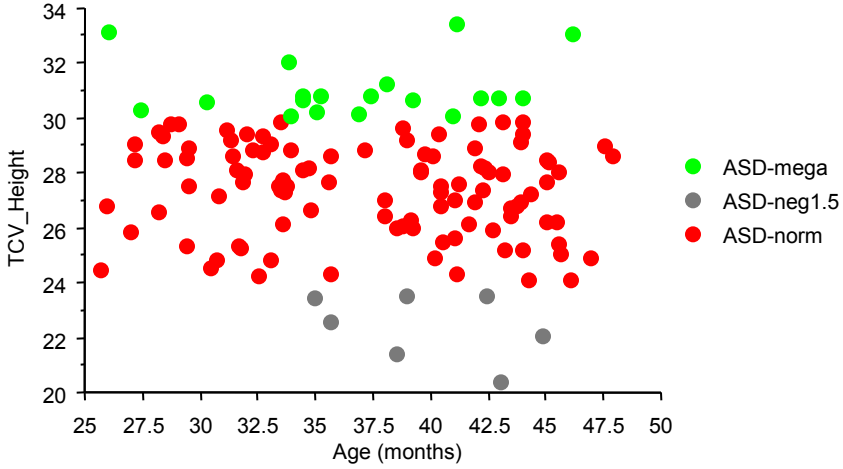
130 ASD males
Mean TCV/height ratio 27.6
19/130 ASD-DM (14.6%)
7/130 ASD-micro (5.4%)

On average, ASD kids are not taller than Typical kids

Relationship of Total Cerebral Volume to Height ASD only







– illustrates where the
Mega subgroups fall on height and TCV

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

This accounts for 15% of our male, ASD cohort

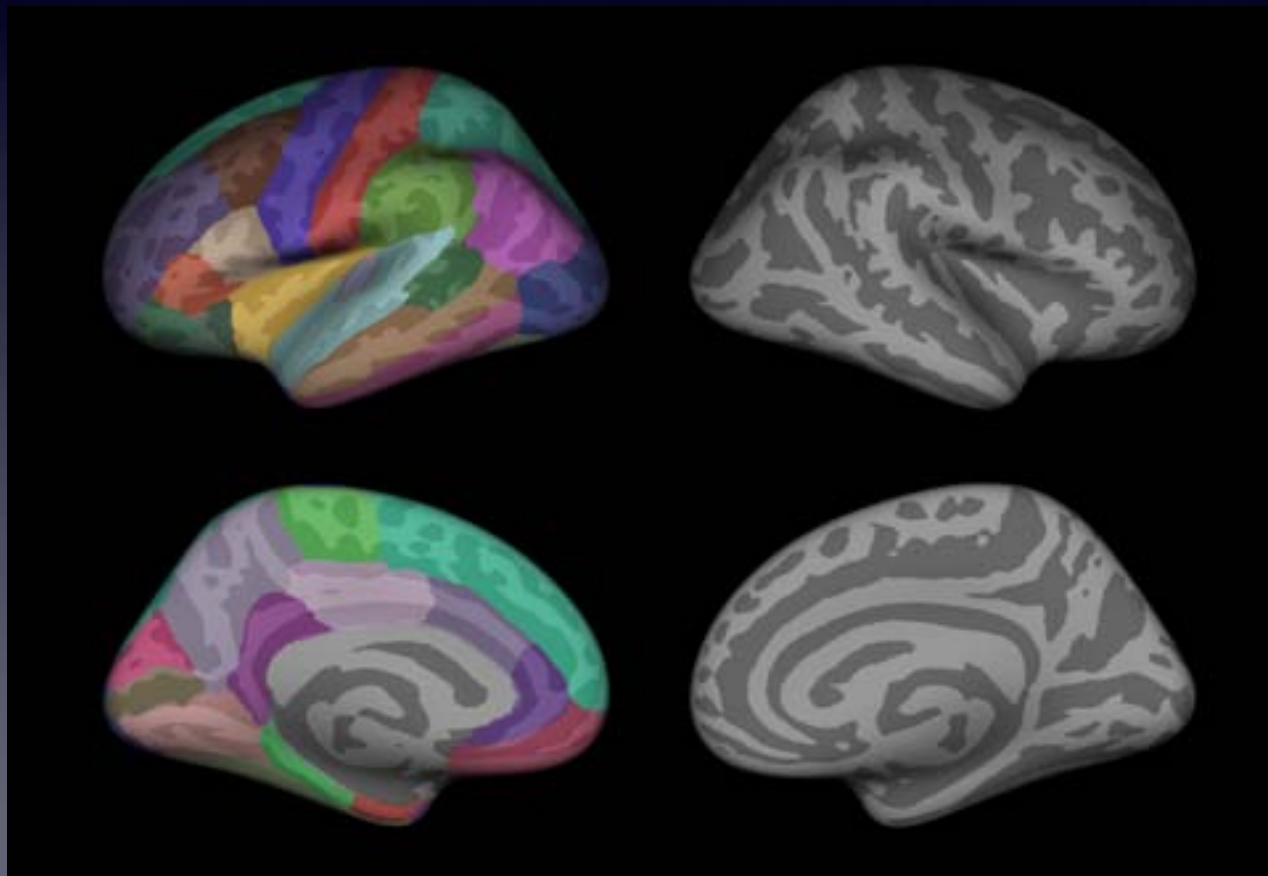
Is the cortex of the brain thicker?

or

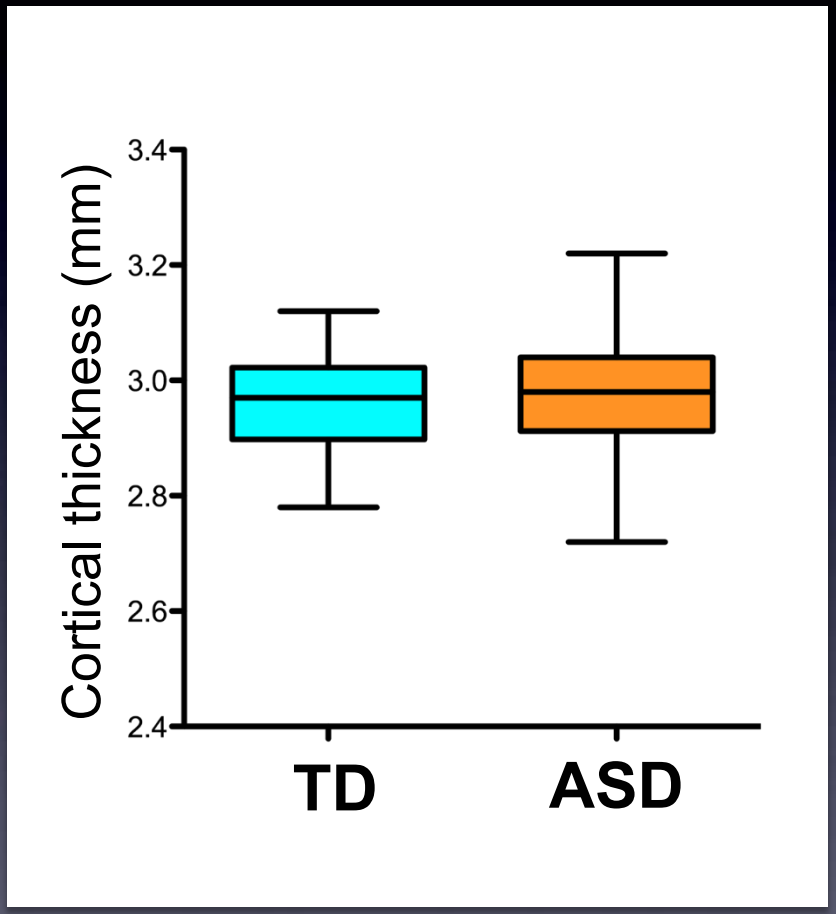
Is there more surface area?

Visualization in Freesurfer

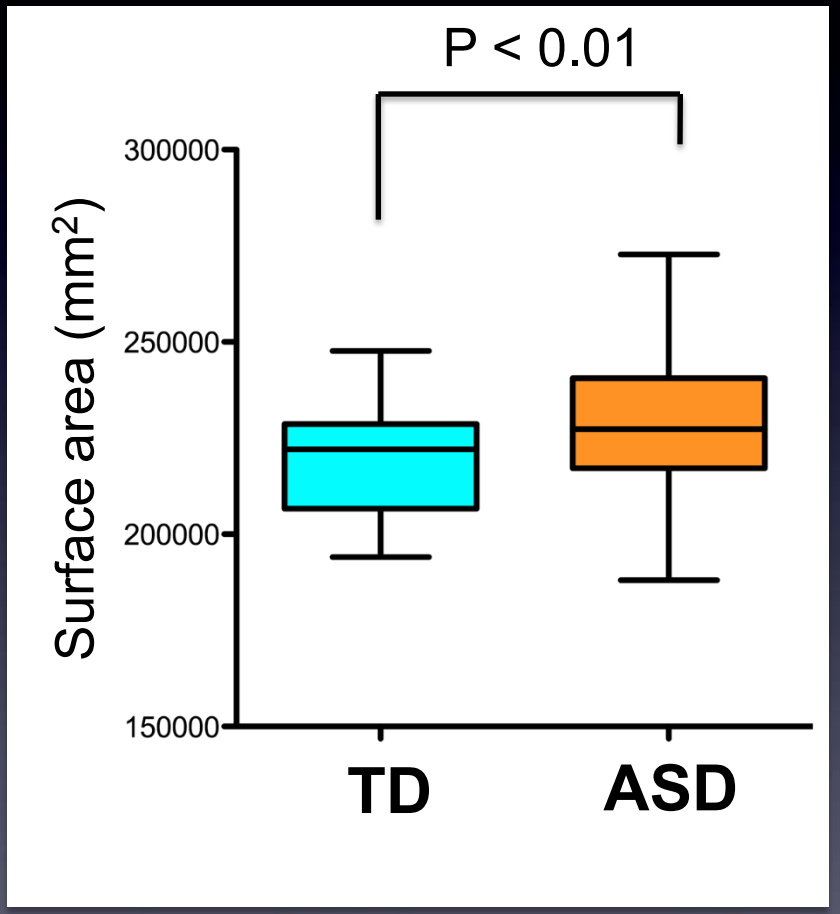
dark grey = sulci; light grey = gyri



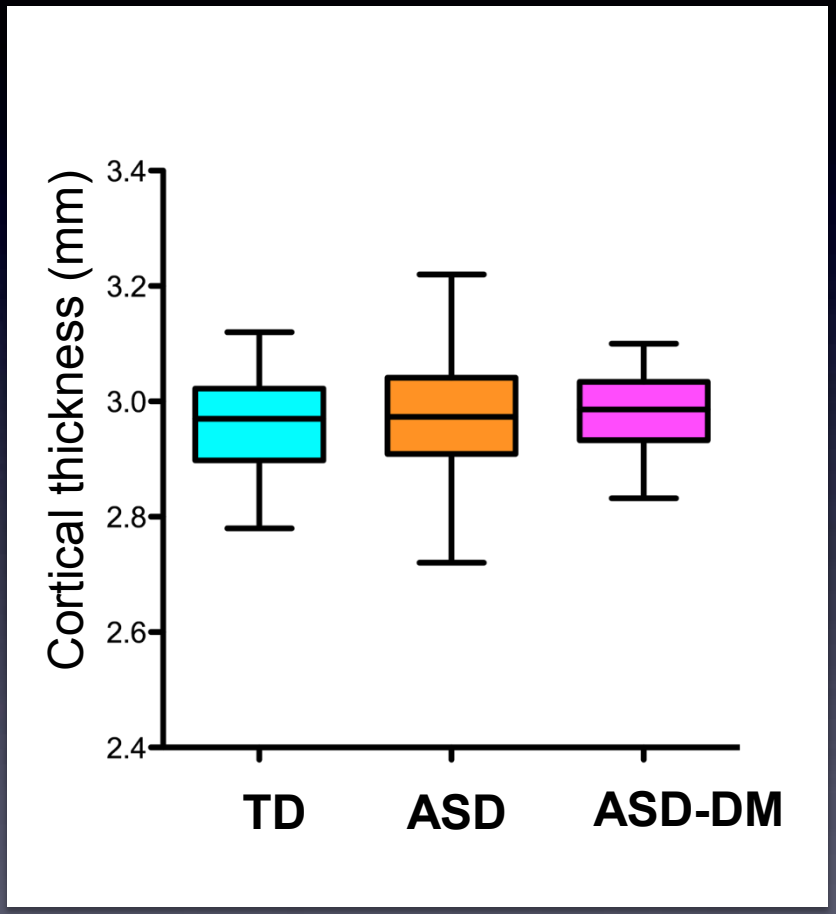
Average of cortical thickness of whole brain



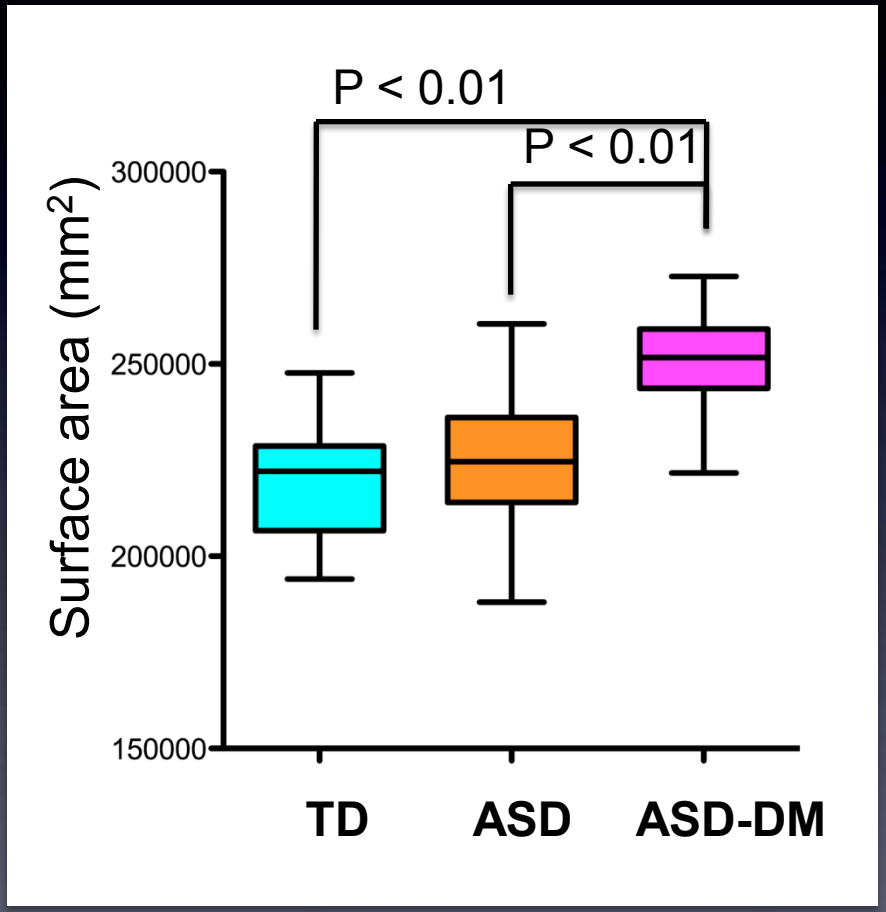
Cortical surface area of whole brain

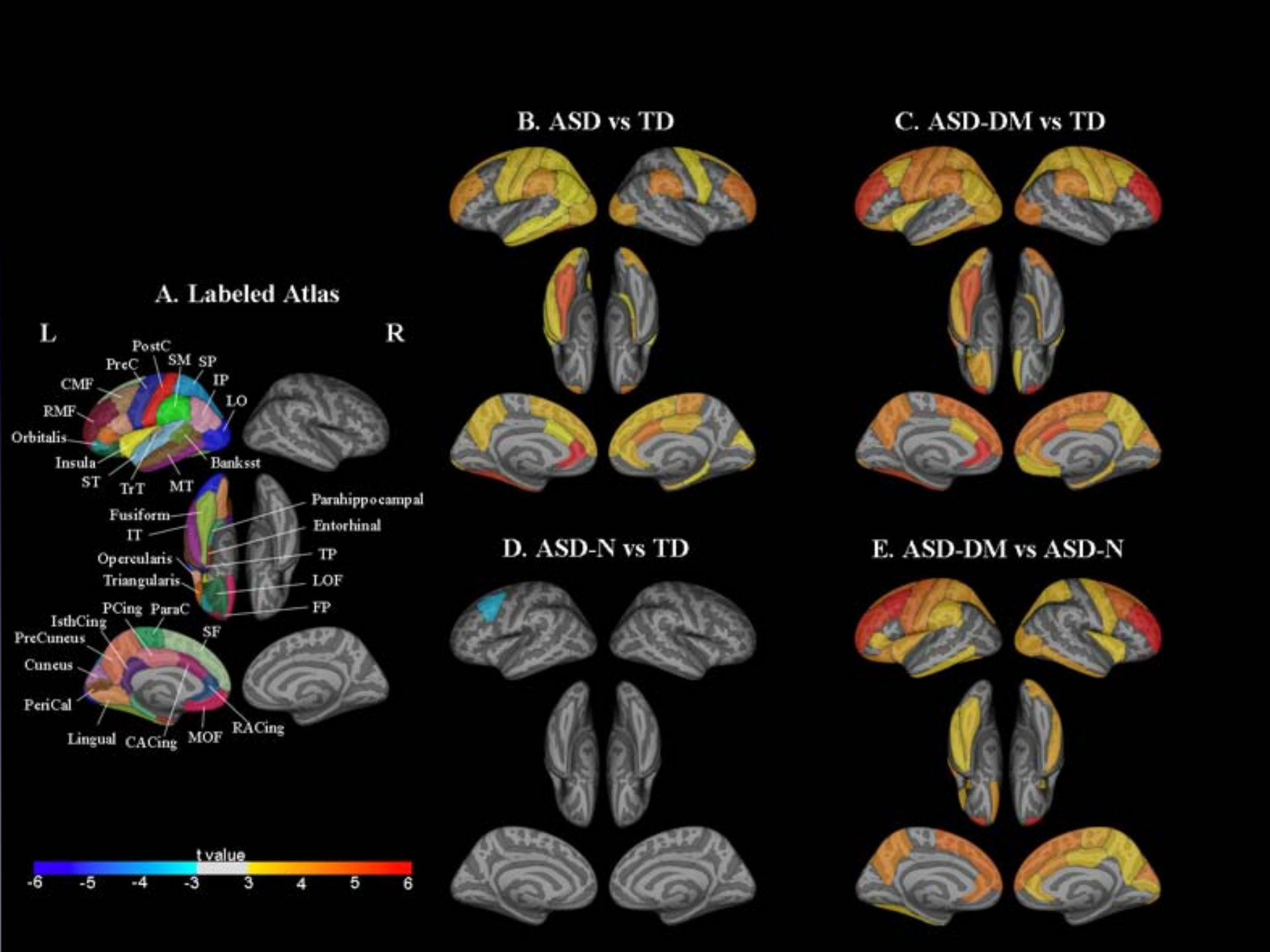


Average of cortical thickness of whole brain

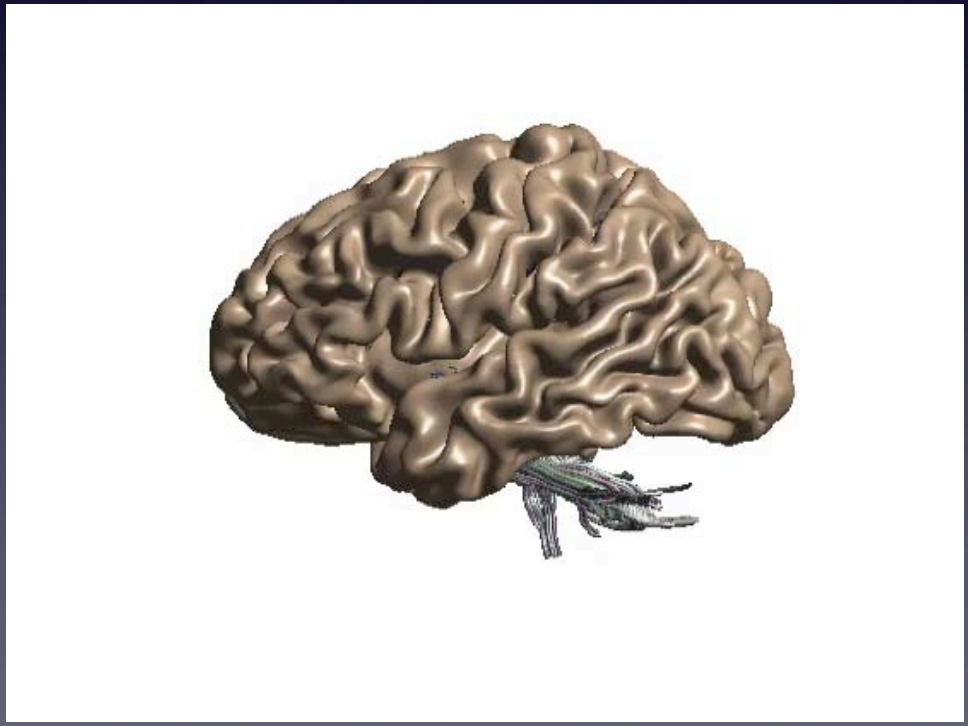


Cortical surface area of whole brain

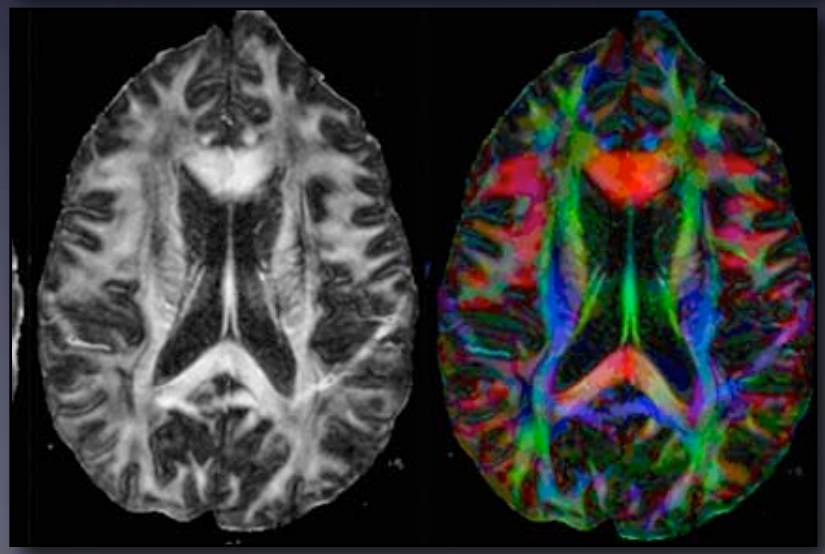



A. Labeled Atlas
L
R
PostC
PreC
SM
SP
IP
LO
CMF
RMF
Orbitalis
Insula
ST
TrT
MT
Banksst
Parahippocampal
Fusiform
Entorhinal
IT
Opercularis
TP
Triangularis
LOF
FP
PCing
ParaC
IsthCing
SF
PreCuneus
Cuneus
PeriCal
Lingual
CACing
MOF
RACing
t value
-6
-5
-4
-3
3
4
5
6
B. ASD vs TD
C. ASD-DM vs TD
D. ASD-N vs TD
E. ASD-DM vs ASD-N

Is there evidence for different fiber connection alterations in the megalencephalic brains?



DTI Tractography



- Parallel bundles of fibers have high anisotropy
- White-matter can be isolated and investigated
- Fiber pathways can be reconstructed with good anatomic validity

NeuroImage 88 (2014) 143–154

Contents lists available at ScienceDirect

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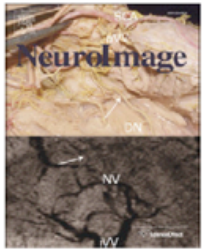
journal homepage: www.elsevier.com/locate/ynimg

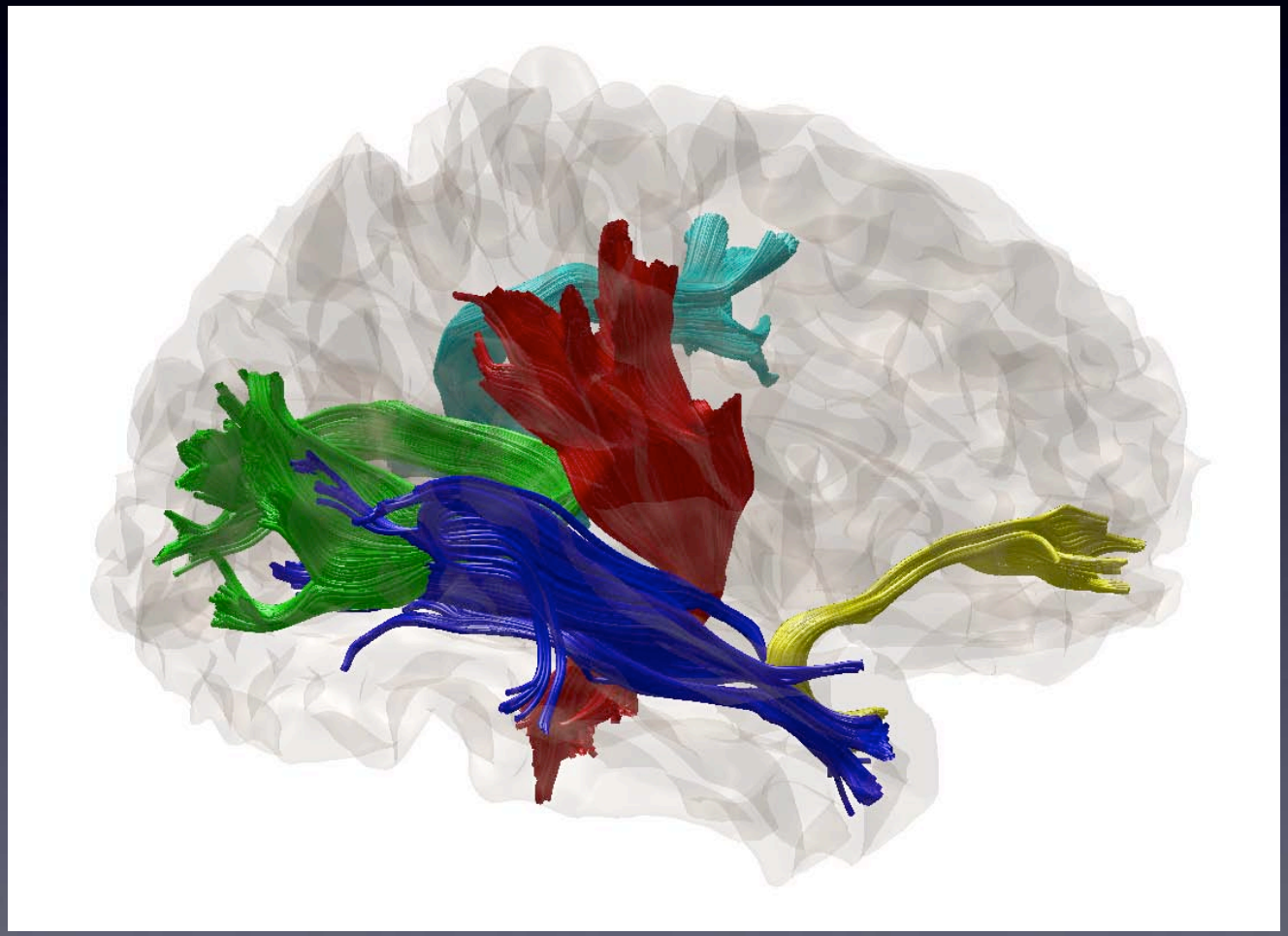


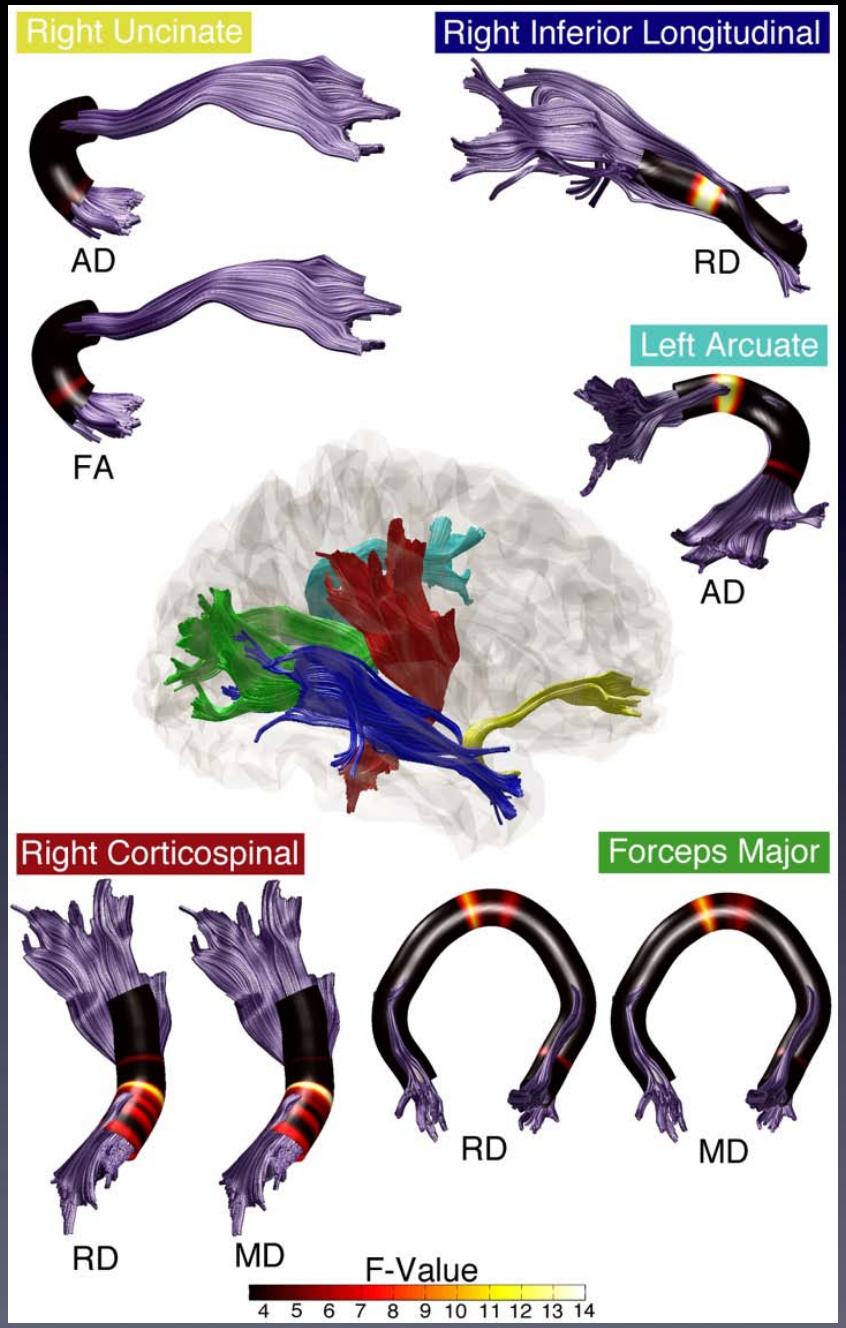
Diffusion properties of major white matter tracts in young, typically developing children

Ryan T. Johnson [a], Jason D. Yeatman [b], Brian A. Wandell [b], Michael H. Buonocore [c], David G. Amaral [a], Christine Wu Nordahl [a,*]

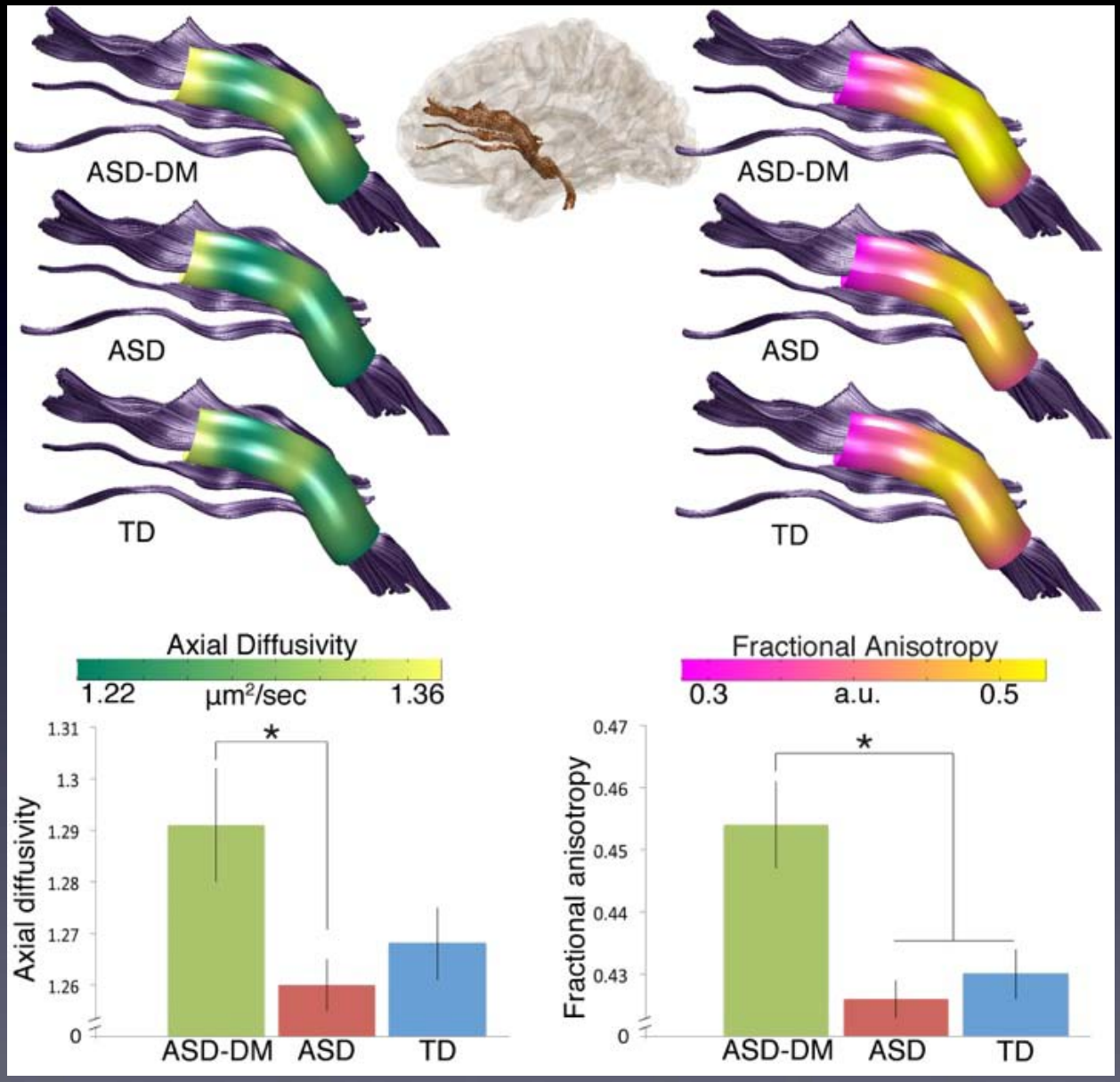
[a] M.I.N.D. Institute, Department of Psychiatry and Behavioral Sciences, University of California at Davis, 2825 50th Street, Sacramento, CA 95817, USA
[b] Department of Psychology, Jordan Hall, Stanford University, 450 Serra Mall, Stanford, CA 94305, USA
[c] Department of Radiology, UC Davis School of Medicine, University of California, Sacramento, CA 95817, USA

White Matter Abnormalities in Boys with ASD

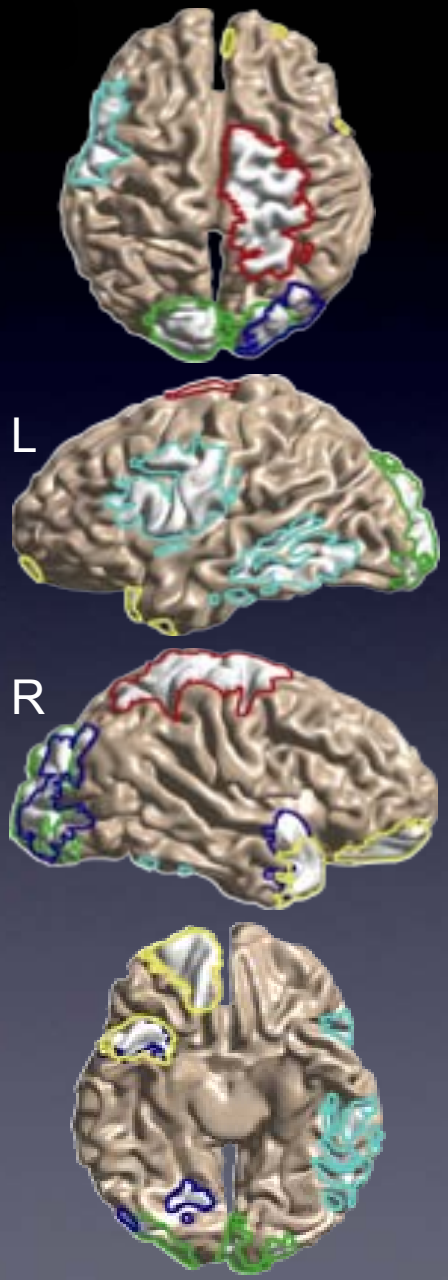



Right Uncinate
AD
FA
Right Inferior Longitudinal
RD
Left Arcuate
AD
Right Corticospinal
RD
MD
Forceps Major
RD
MD
F-Value
4 5 6 7 8 9 10 11 12 13 14

Anterior Thalamic Radiation

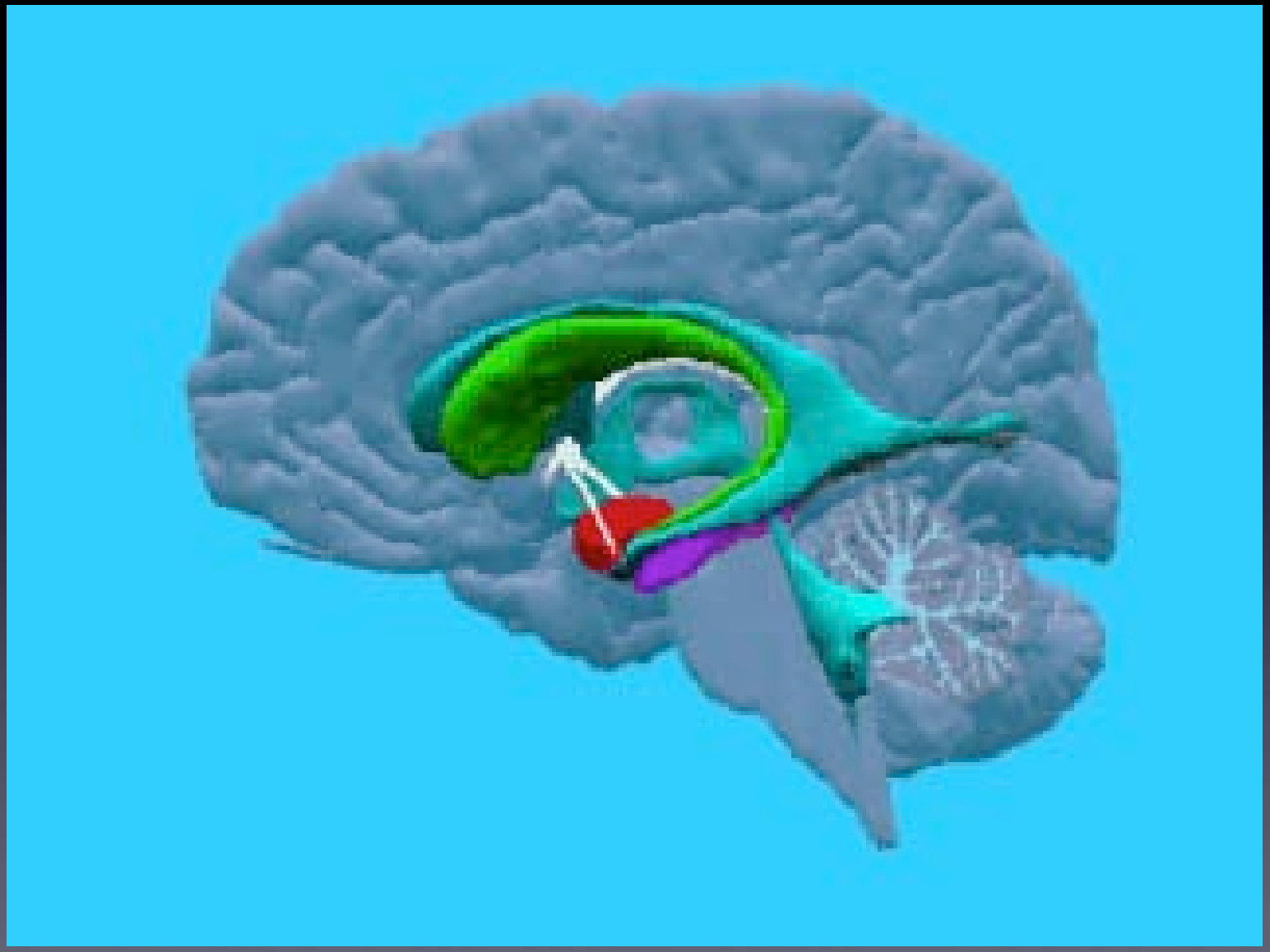


Fiber Tract Abnormalities in ASD males



Domain	Tracts Implicated
Social Communication	
Reception of Facial Communication	Uncinate fasciculus
Reception of Non-Facial Communication	Inferior longitudinal fasciculus
Production of Non-Facial Communication	Arcuate fasciculus, Inferior longitudinal fasciculus
Perception and Understanding of Self	
Agency	Inferior longitudinal fasciculi, Corticospinal tract
Self-Knowledge	Uncinate fasciculus
Perception and Understanding of Others	
Animacy Perception	Inferior longitudinal fasciculus
Action Perception	Corticospinal tract
Understanding Mental States	Uncinate fasciculus, Inferior longitudinal fasciculus
Positive Valence Systems	
Repetitive/Stereotypic/Compulsive Behaviors	Uncinate fasciculus
Cognitive Systems	
Language	Arcuate fasciculus

The Amygdala



Amygdala growth relative to TCV

- 40% of boys with ASD have an abnormally rapid growth of the amygdala
- 20% of boys with ASD have an abnormally slow growth of the amygdala
- 40% of boys with ASD have a normal growth rate of the amygdala

Questions Related to Outcome

- Do early neurophenotypes persist into middle childhood?
- Do early neurophenotypes predict different patterns of autism severity, cognitive function and co-morbid syndromes?
- Is there a pattern of early brain organization that is associated with optimal outcome?

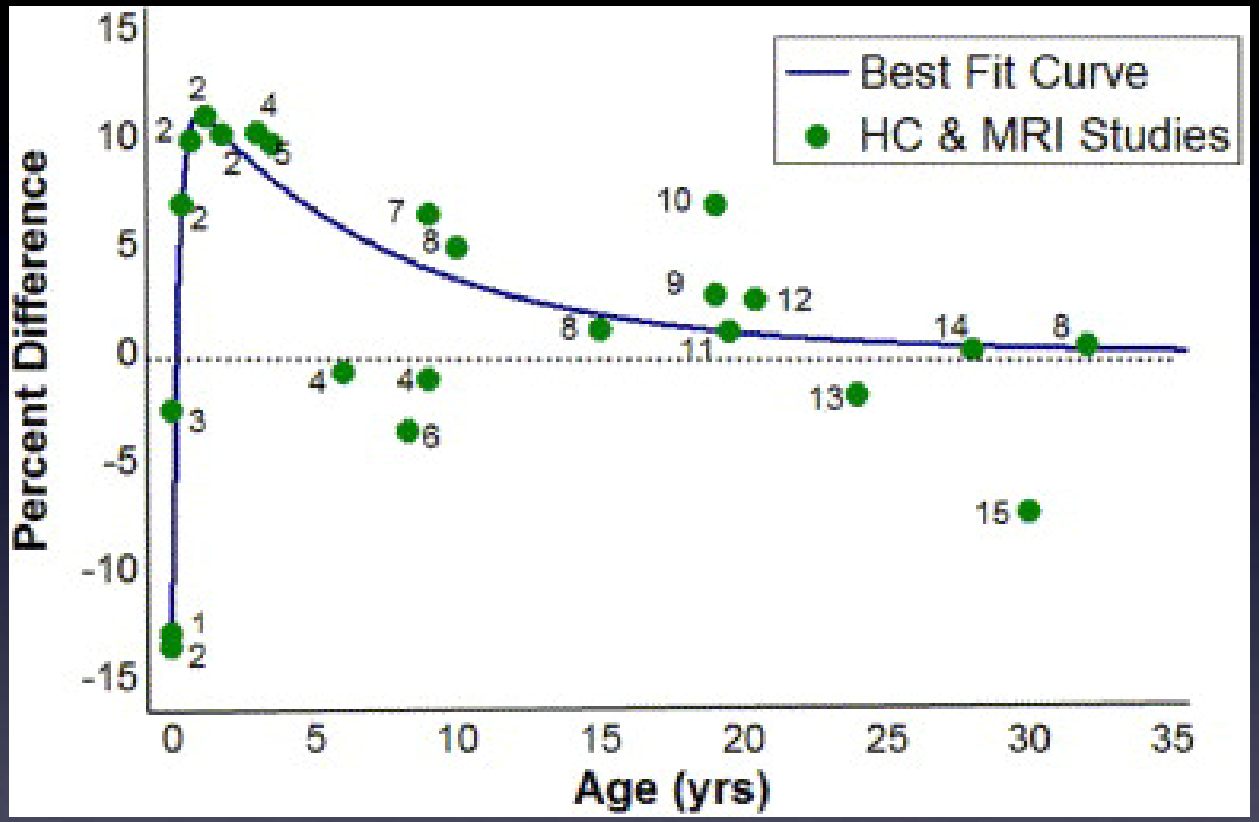


Figure 1 HC and MRI percent difference (%Diff) by age. %Diff values from all HC and MRI studies are plotted by the mean age of the study. The best fitted curve shows the most rapid rates of increased deviation from normal brain size in autism within first ...

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

Some low IQ

Few low IQ

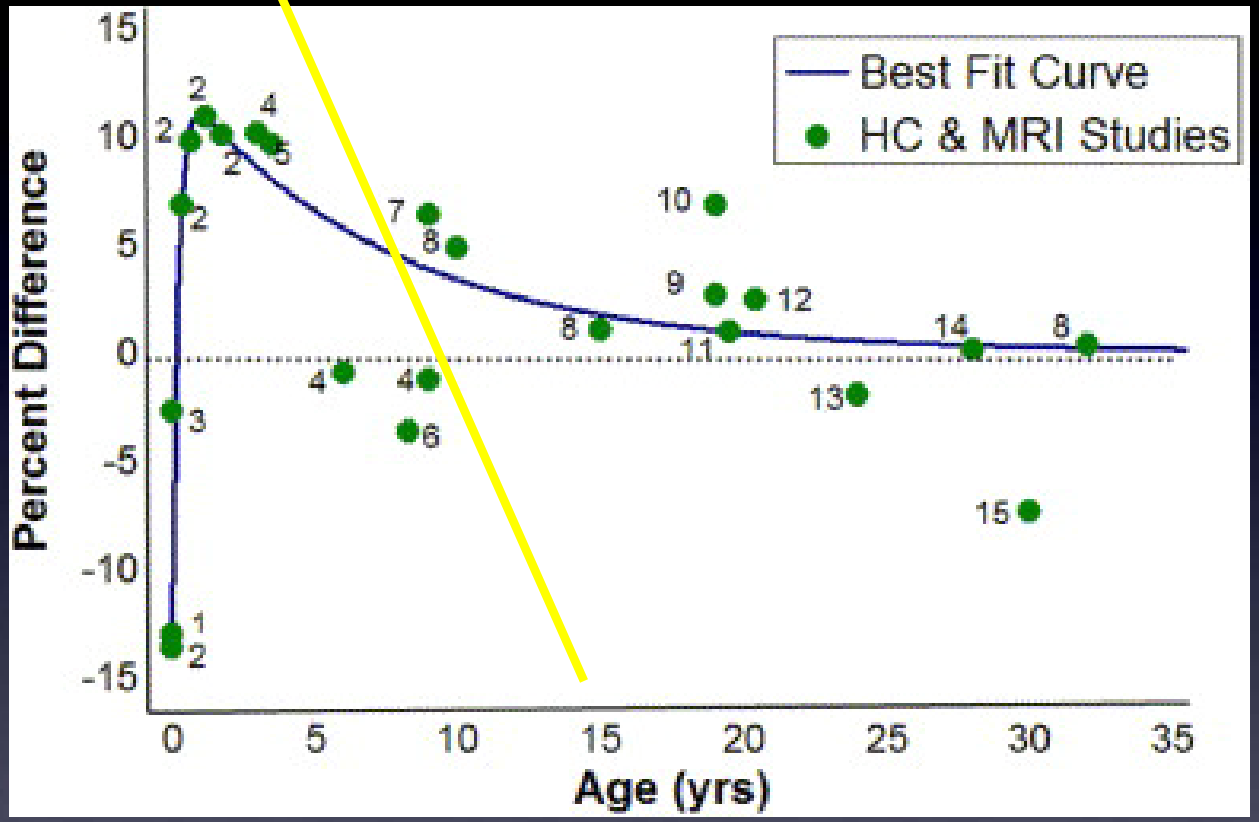


Figure 1 HC and MRI percent difference (%Diff) by age. %Diff values from all HC and MRI studies are plotted by the mean age of the study. The best fitted curve shows the most rapid rates of increased deviation from normal brain size in autism within first ...

Elizabeth Redcay , Eric Courchesne

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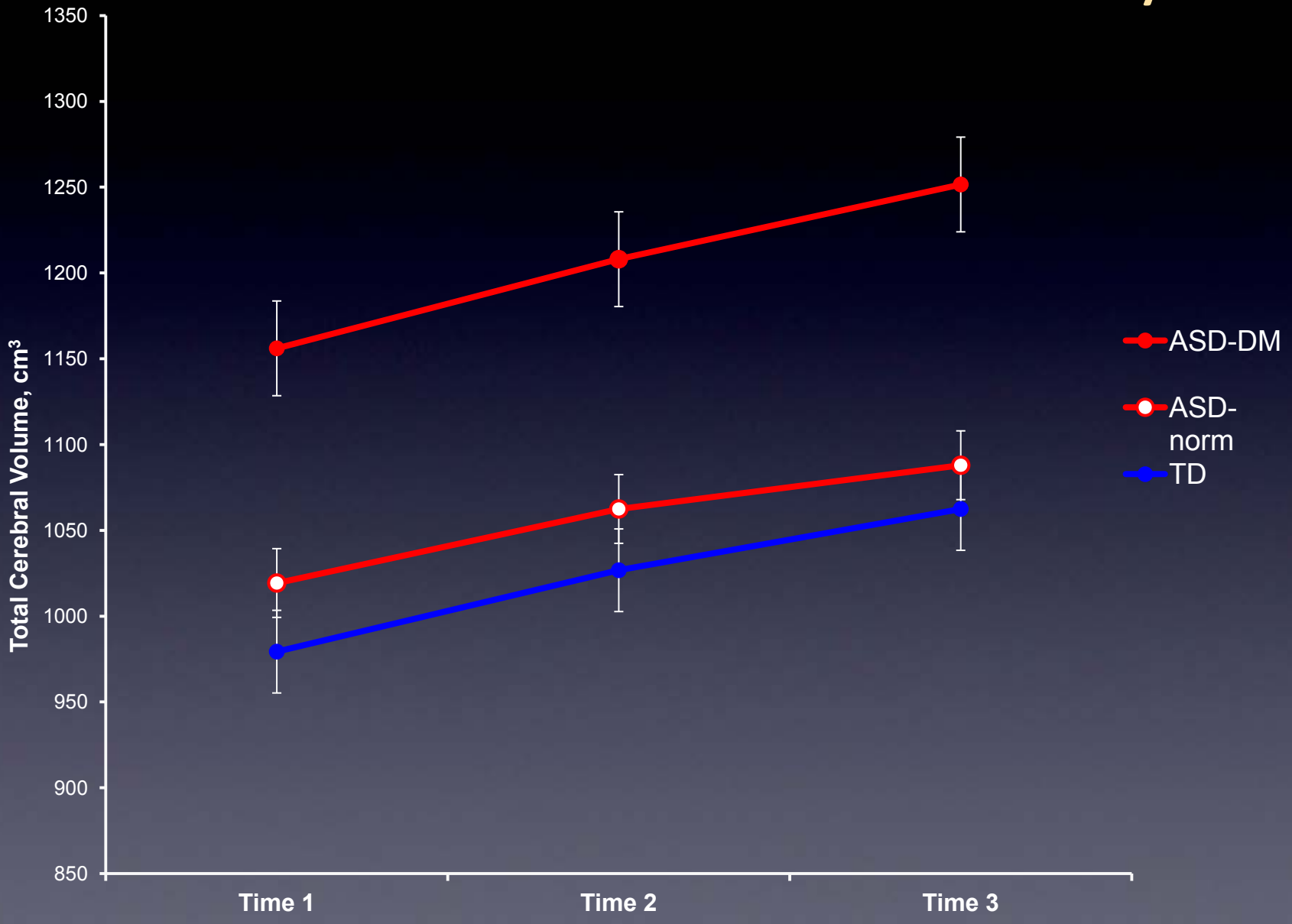
Mean Total Cerebral Volume: 3-6 years



IACC 2009 Strategic Plan

Question 2: How Can I Understand What is Happening?

Research Opportunity

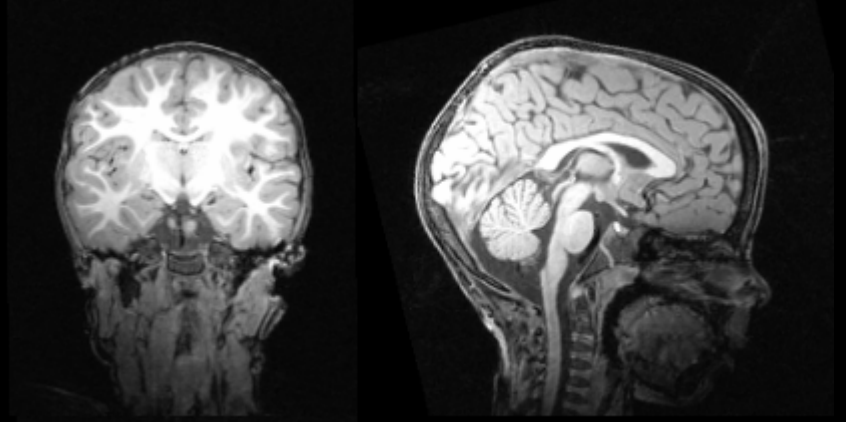
Multi-disciplinary, longitudinal, biobehavioral studies of children, youths, and adults beginning during infancy that characterize neurodevelopmental and medical developmental trajectories across the multiple axes of ASD phenotype and identify ASD risk factors, subgroups, co-occurring symptoms, and potential biological targets for intervention.

Subject NB

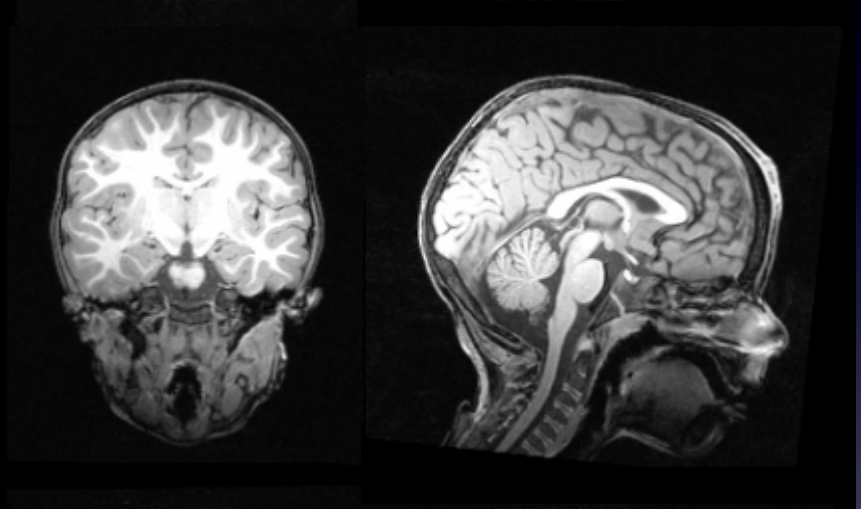
- 9 year old male
- I.Q. 41
- ADOS Total Score 19
- Non-verbal
- Self injurious behavior
- Aggression

NB scans

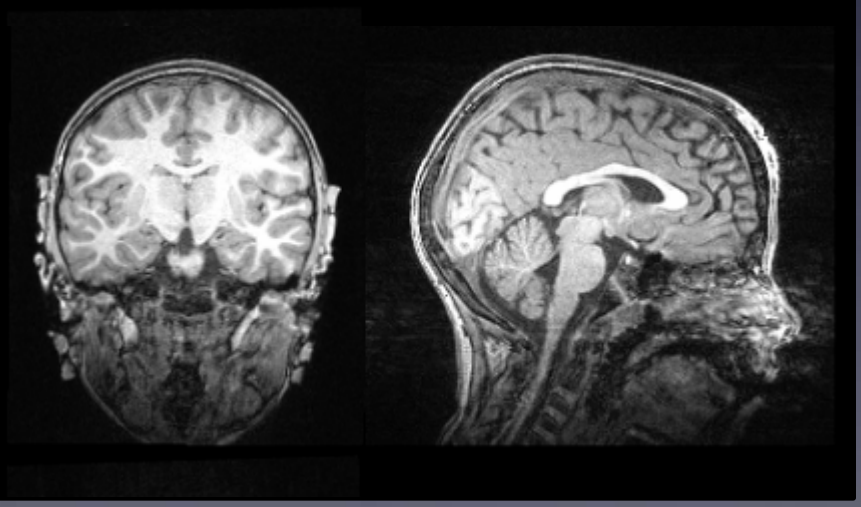
Time 1
Age 3.7 years



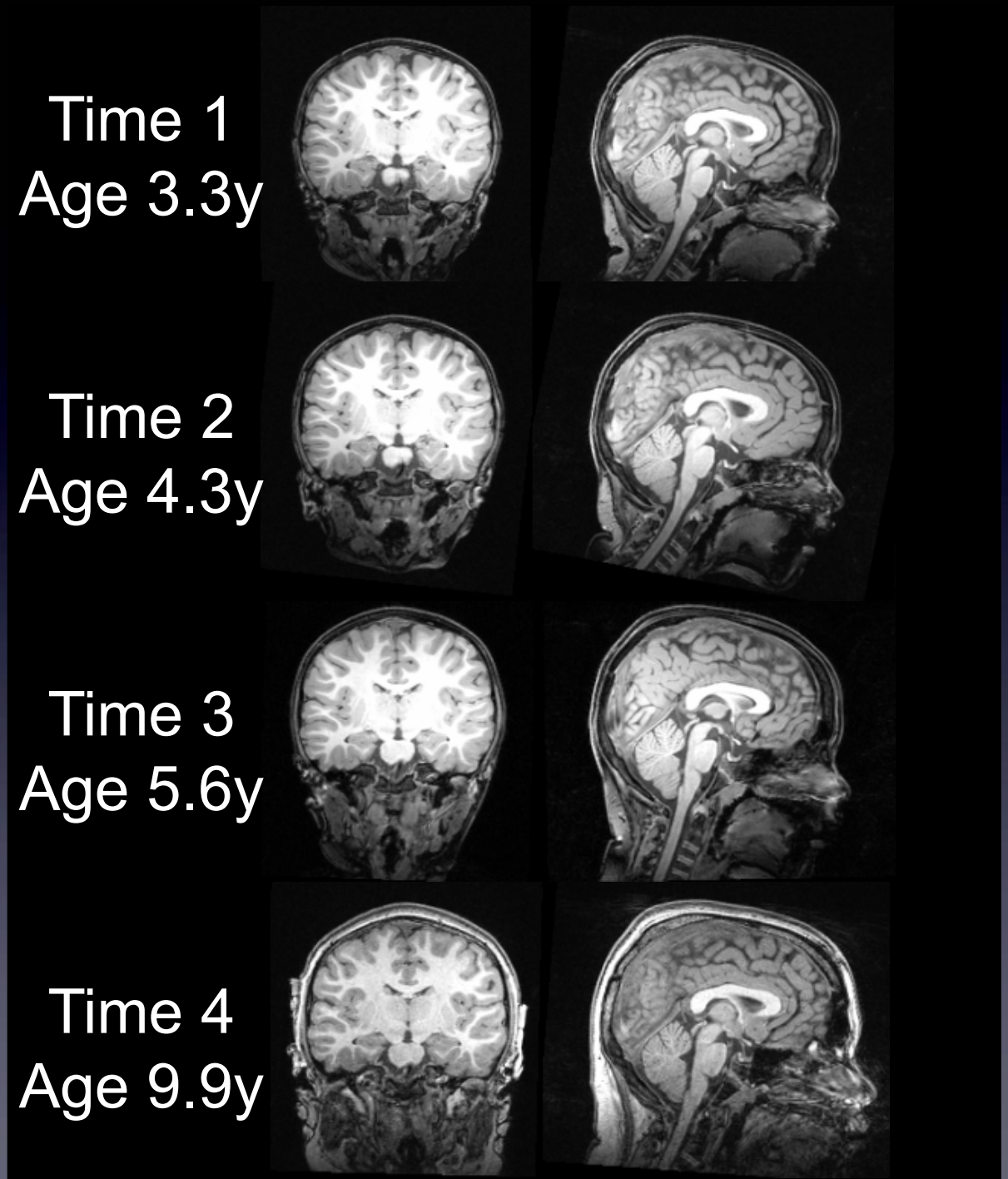
Time 2
Age 4.7 years

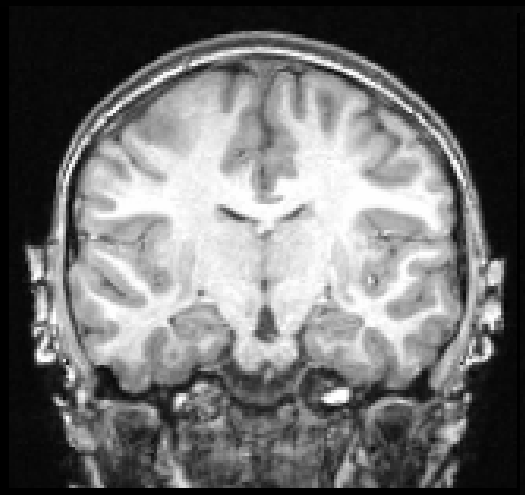


Time 4
Age 9.7 years



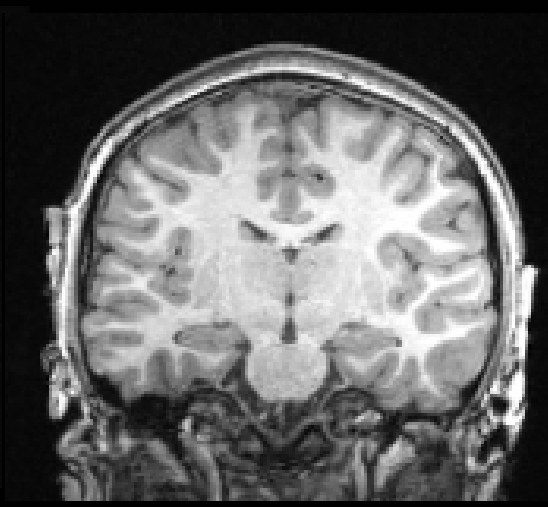
ACL





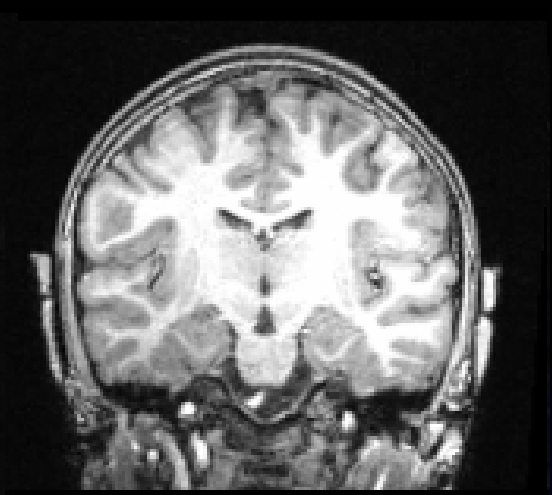
Age 12 y, male
IQ 58, ADOS total 16

LP



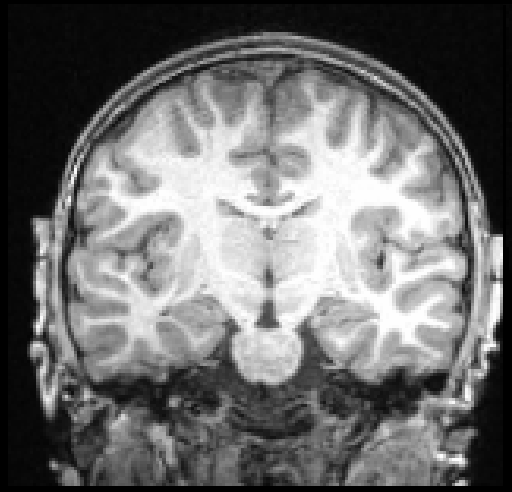
Age 9 y, male
IQ 49, ADOS total 17

ACL



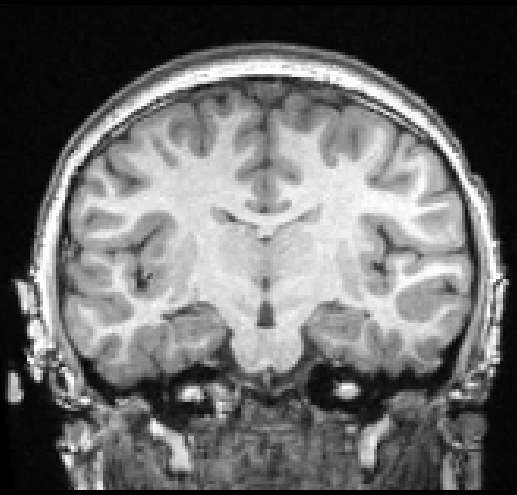
Age 9 y, female
IQ 42, ADOS total 17

OC



Age 10 y, male
IQ 41, ADOS total 19

NB



Age 10 y, male
IQ 52, ADOS total 17

XC

Age 9 y, female
IQ 41, ADOS total 23

NS

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  - The NIH
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