Infant Brain Imaging Study Network

an NIH Autism Centers of Excellence (ACE) Network

University of North Carolina
University of Washington
Washington University in St. Louis
Children's Hospital of Philadelphia
Montreal Neurological Institute
University of Utah
University of Alberta

Principal Investigator: Joe Piven

Carolina Institute for Developmental Disabilities

University of North Carolina

IACC Meeting
Washington, D.C.
April 2011

IBIS (Infant Brain Imaging Study) Network

NIH Autism Center of Excellence (www.ibis-network.org)

"A Longitudinal MRI Study of Infants at Risk for Autism"

Infant Siblings

of

Older Autistic Children

6 months → 12 months → 24 months

Rationale for the IBIS Network:

(1) onset of brain overgrowth

and

(2) onset of autistic behavior

both appear to occur in the latter part of the first year of life in autistic individuals

Studies Reporting Increased **Brain Volume** (5-10%) in Autism

MRI Studies	Brain Volume	Subject Age
Piven et al. (1992)	increased mid-sagittal area	18 - 53 yrs
Piven et al (1995)	increased total brain volume	14 – 29 yrs
Hazlett et al (2005)	increased total brain volume (N=51)	2 yrs
Courchesne et al (2001)	increased cerebral. gray and white	2 – 4 yrs only
Sparks et al (2002)	increased total cerebral	3-4 yrs
Aylward et al (2002)	increased TBV (HFA)	under 12 yrs
Lotspeich et al (2004)	increased cerebral gray (N=52)	7 – 18 yr
Herbert et al (2004)	increased (radiate) white matter (N=13)	~ 9 yrs
Palmen et al (2005)	increased TBV, cerebral gray (N=21)	7 – 15 yrs
Schultz et al (unpub)	increased TBV, GM, WM (N=117)	7-36 yrs
Hyde et al, (2008)	increased gray vol (VBM + cortical thick)	young adults
Freitag et al, (2009)	increased TBV, GM and WM (N=15) HFA	adol/adult
Hardan et al, (2006)	increased TBV, gray/cortical thick 17 HFA	children
Schuman et al (2010)	increased cerebral gray and white	2-5 yrs

Increased Brain Volume Noted **by Two Years of Age**

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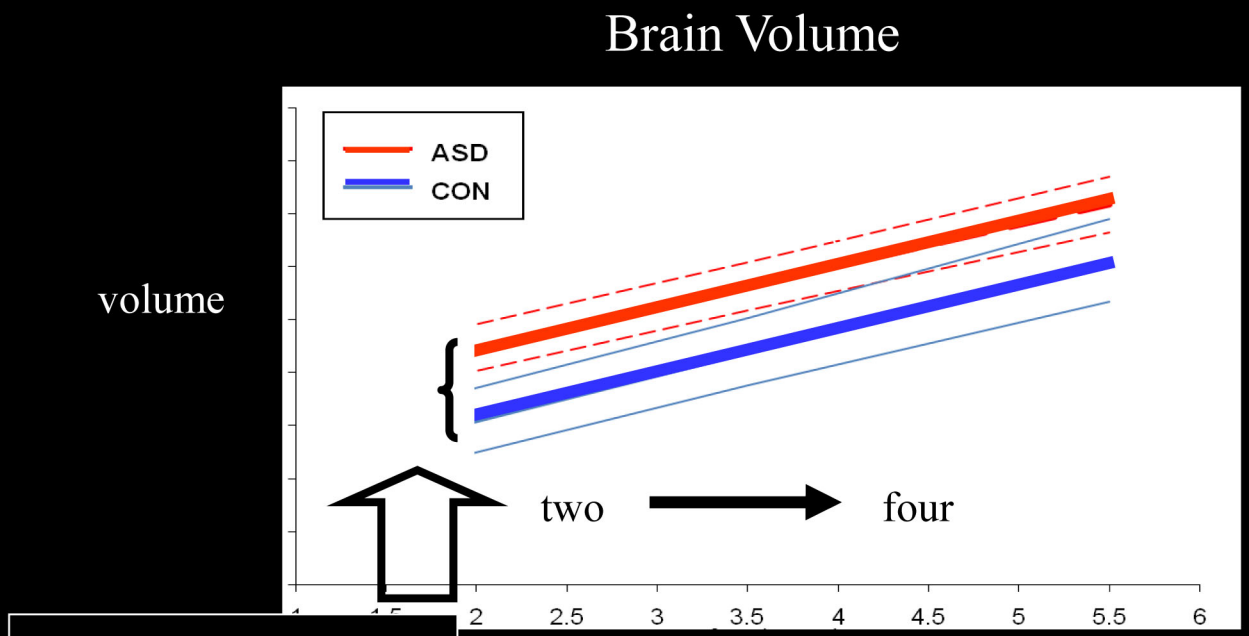
Parallel Growth Trajectories in Autism and Controls from Age 2 to 4

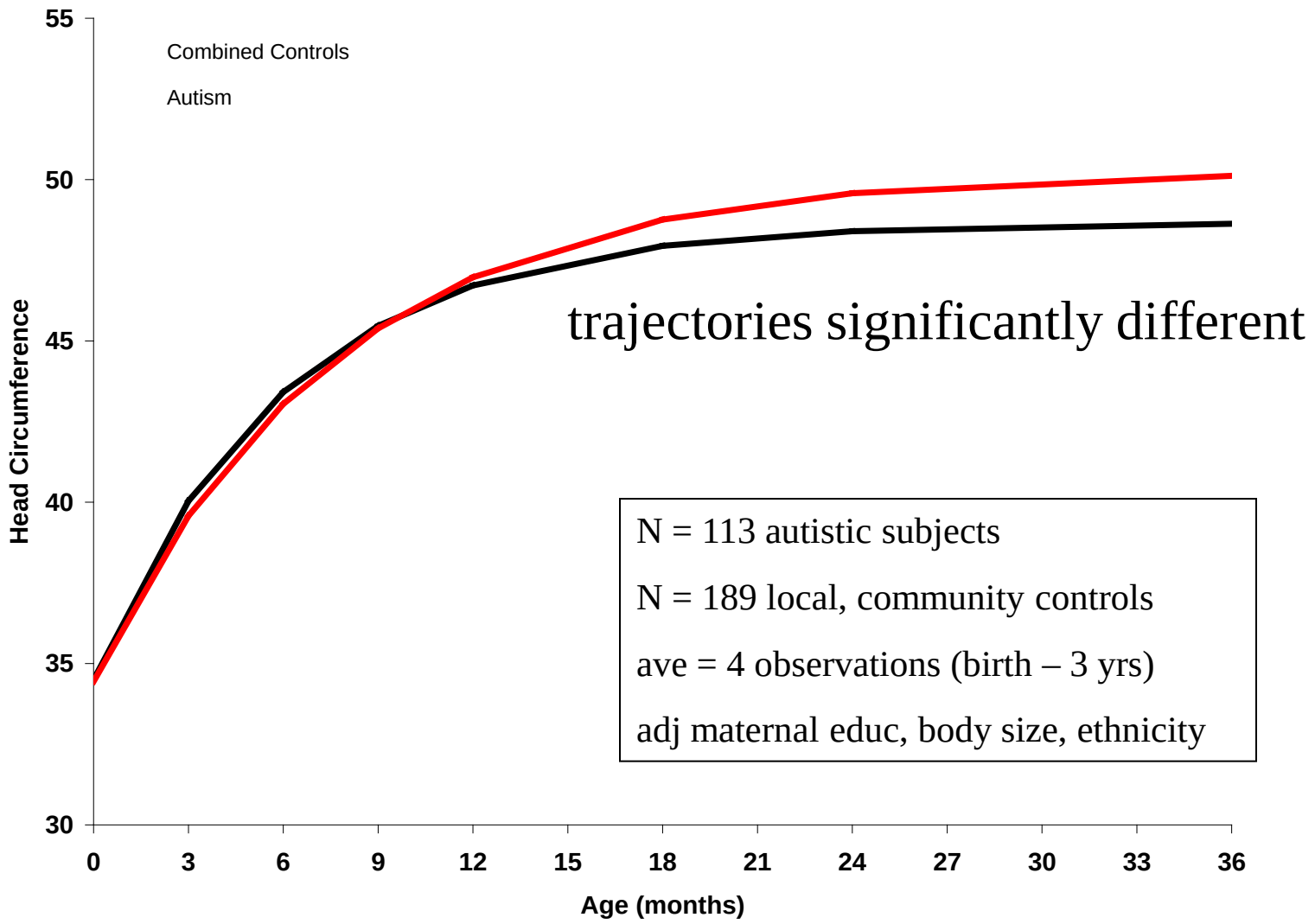


suggests an increased rate of brain growth prior to age 2

Hazlett et al (in press)

The Timing of Brain Overgrowth: Clues from Head Circumference

(Hazlett et al., 2005)



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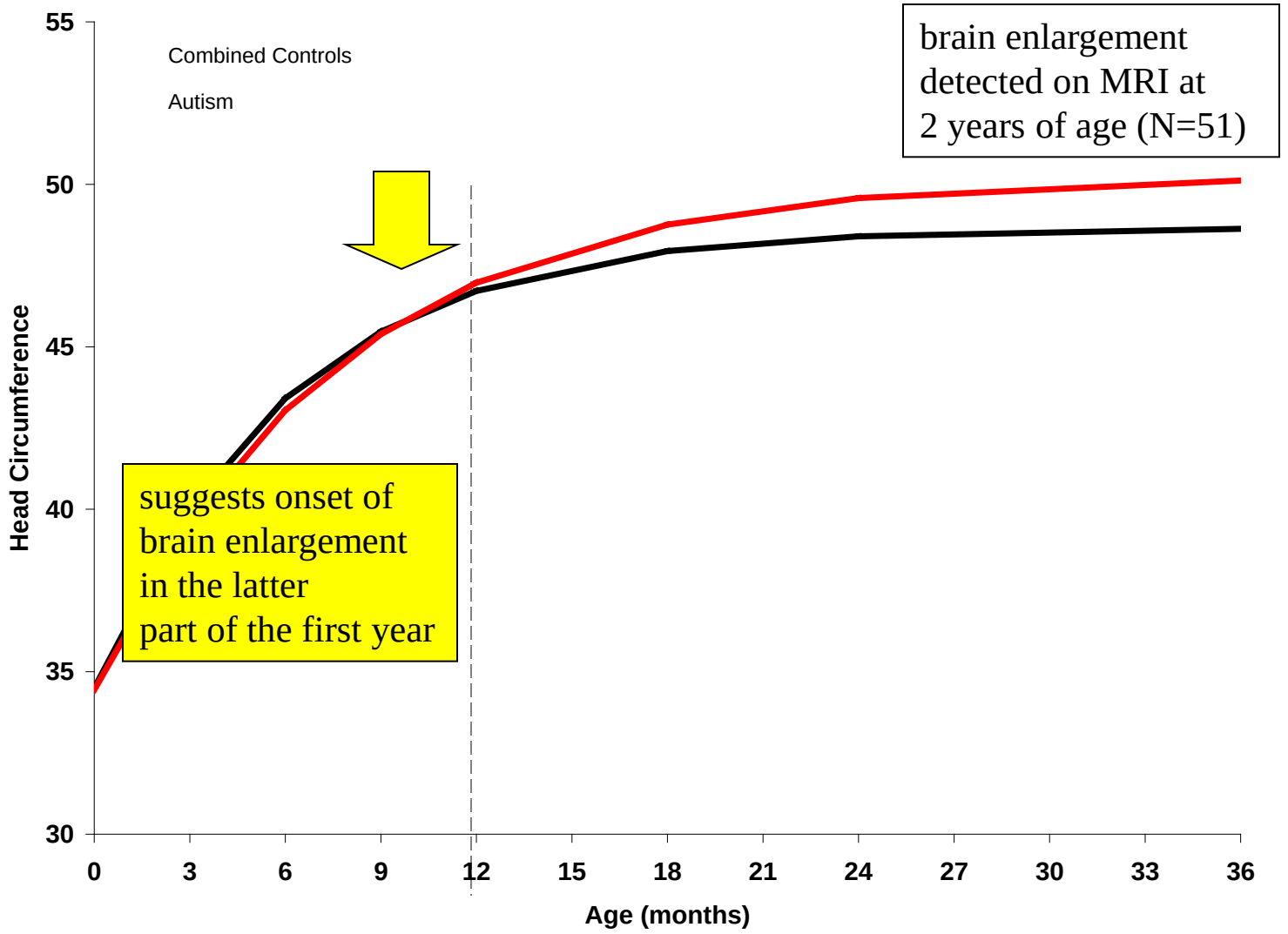

Brain Overgrowth in Autism

there is direct evidence for an increased rate of brain growth in autism occuring before age 2 (MRI)

and

indirect evidence that the onset of this overgrowth is in the latter part of the first year of life. (head circumference)

Rationale for the IBIS Network:

(1) onset of brain overgrowth

and

(2) onset of autistic behavior

both appear to occur in the latter part of the first year of life in autistic individuals

‘Baby Sibs’ or ‘Infant Sibs’ Studies a New Autism Research Paradigm

- autism is a genetic disorder (twin, family, molecular).

‘Baby Sibs’ or ‘Infant Sibs’ Studies a New Autism Research Paradigm

- autism is a genetic disorder (twin, family, molecular).

- risk of having a 2nd child with autism (or, recurrence risk) is 10-20 times higher than risk in the general population.

risk: general population risk ~ 1%

recurrence risk ~ 10-20%

Canadian 'Infant Sib' Study

Zwaigenbaum, Bryson, Roberts, Brian, Szatmari (2005)

- **10** of 74 infant siblings (of older autistic children) met criteria for an Autism Spectrum Disorder at age 36-48 months (recurrence =13.5%)

- examined at 6, 12 and 18 months with

Autism Observation Scale for Infants (AOSI) Bryson et al. (2008)

- **visual tracking**
- **disengagement of attention**
- **response to name**
- **social babbling**
- **eye contact**
- **social smiling**
- **social anticipation (peek-a-boo)**
- **social interest and affect**
- **response to change in facial emotion**
- **imitation**
- **coordination of eye gaze and action**
- **reactivity**
- **transitions between activities**
- **motor behavior**
- **atypical motor behaviors**
- **atypical sensory behaviors**
- **engagement**
- **social referencing**

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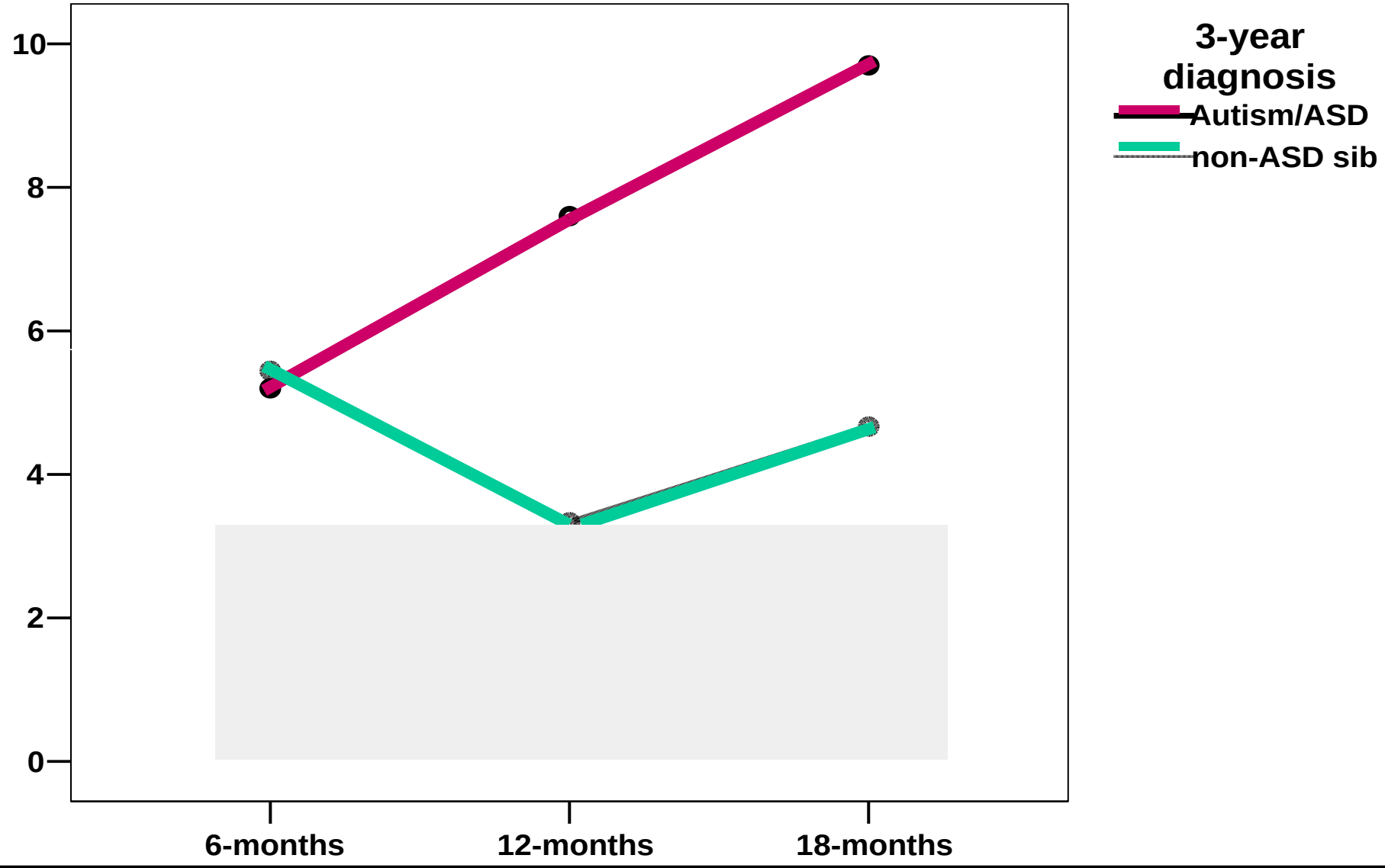
Autism Observation Scale for Infants: Scores ASD and Non ASD Siblings

(Zwaigenbaum et al., 2005)



Children with Autism: Features at 6 months

- subtle differences
  - visual tracking[1]
  - anticipatory responses[1]
  - motor control[1,2]

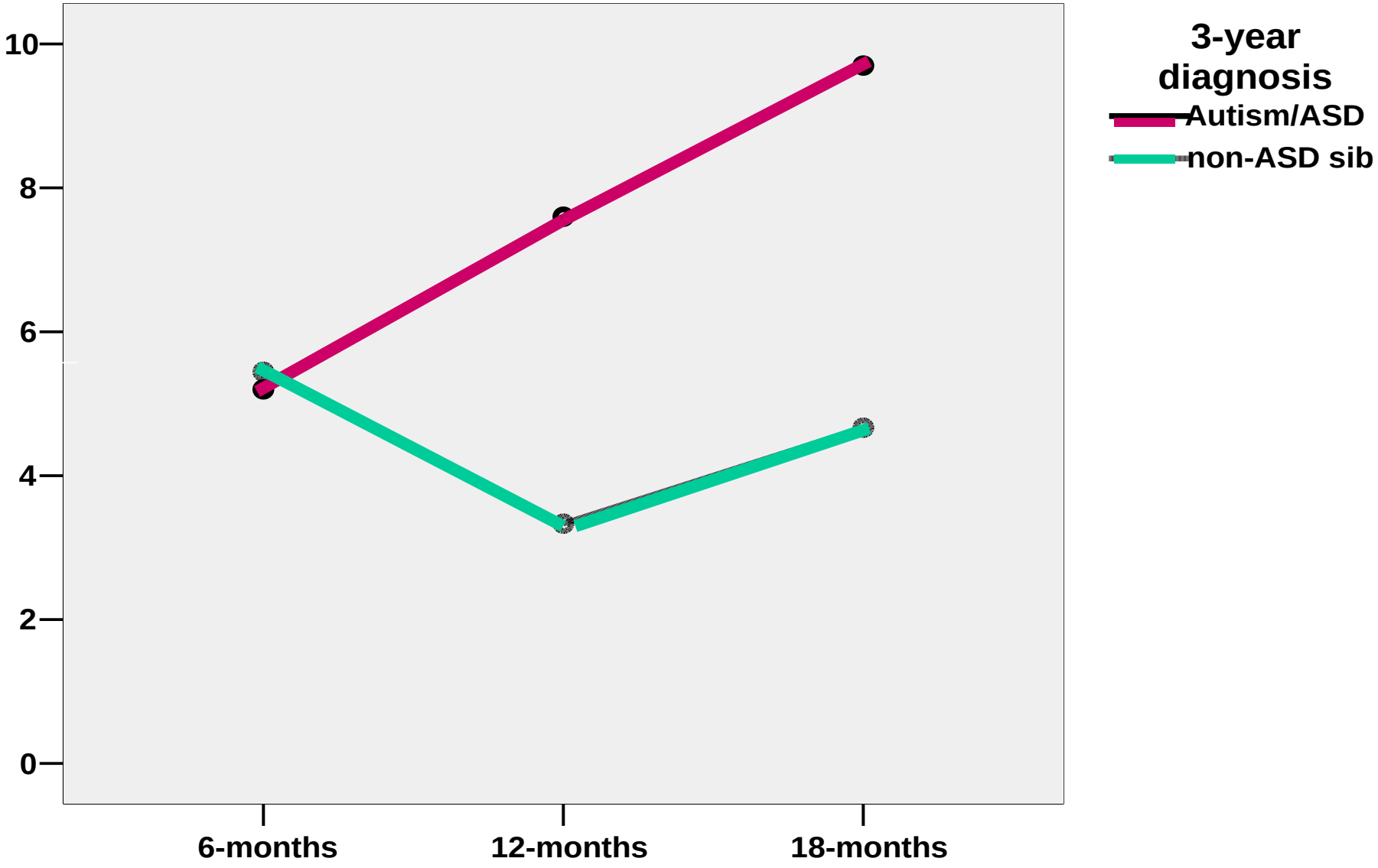
- many typical social behaviors (defining features of autism)
  - eye contact (100%)
  - reciprocal social smiling (88%)
  - social interest and affect (88%)

[1]Sibs-ASD>controls; [2]Sibs-ASD>Sibs-N; $p<.01$

Zwaigenbaum et al., 2005

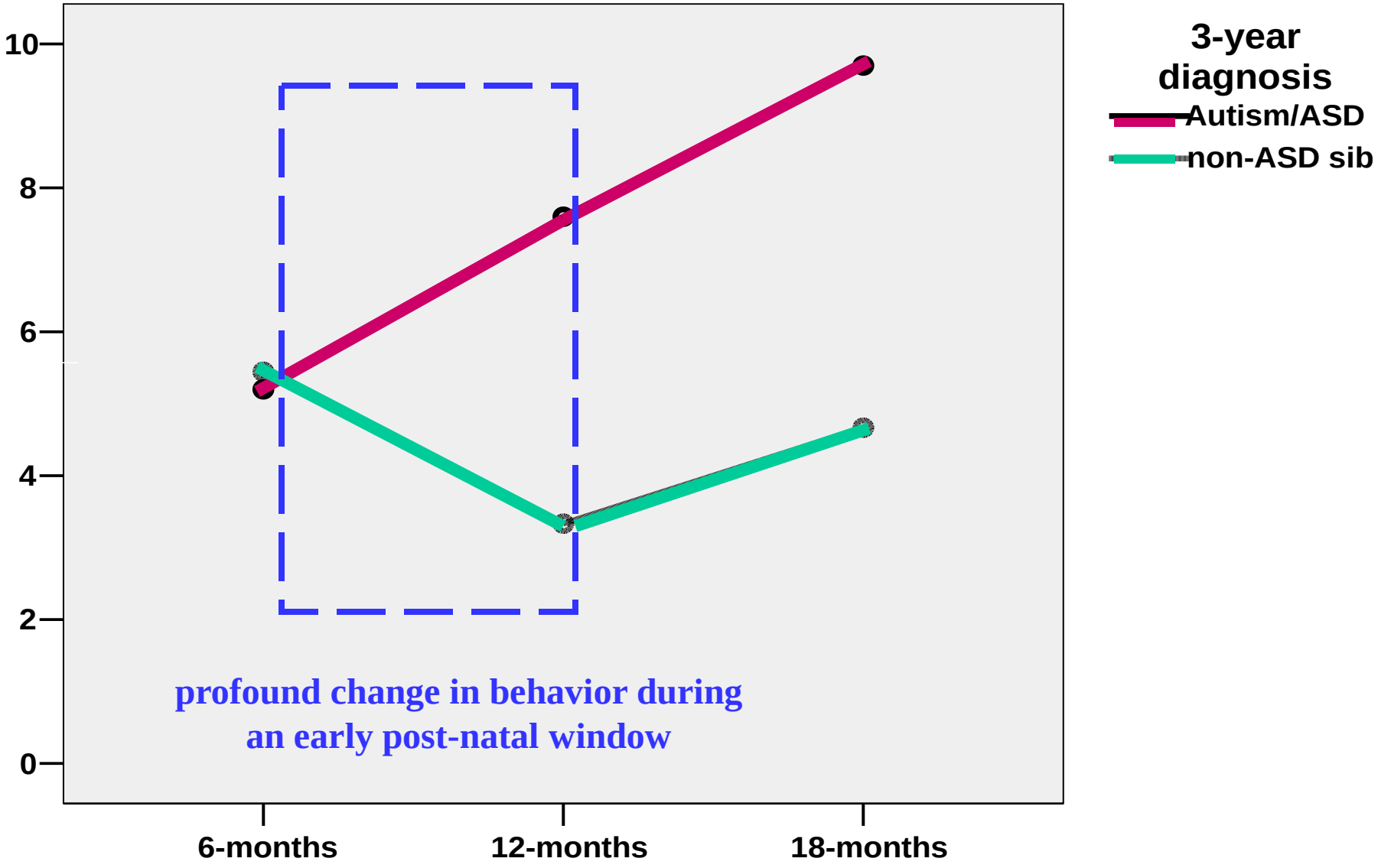
Autism Observation Scale for Infants: Scores ASD and Non ASD Siblings

(Zwaigenbaum et al., 2005)



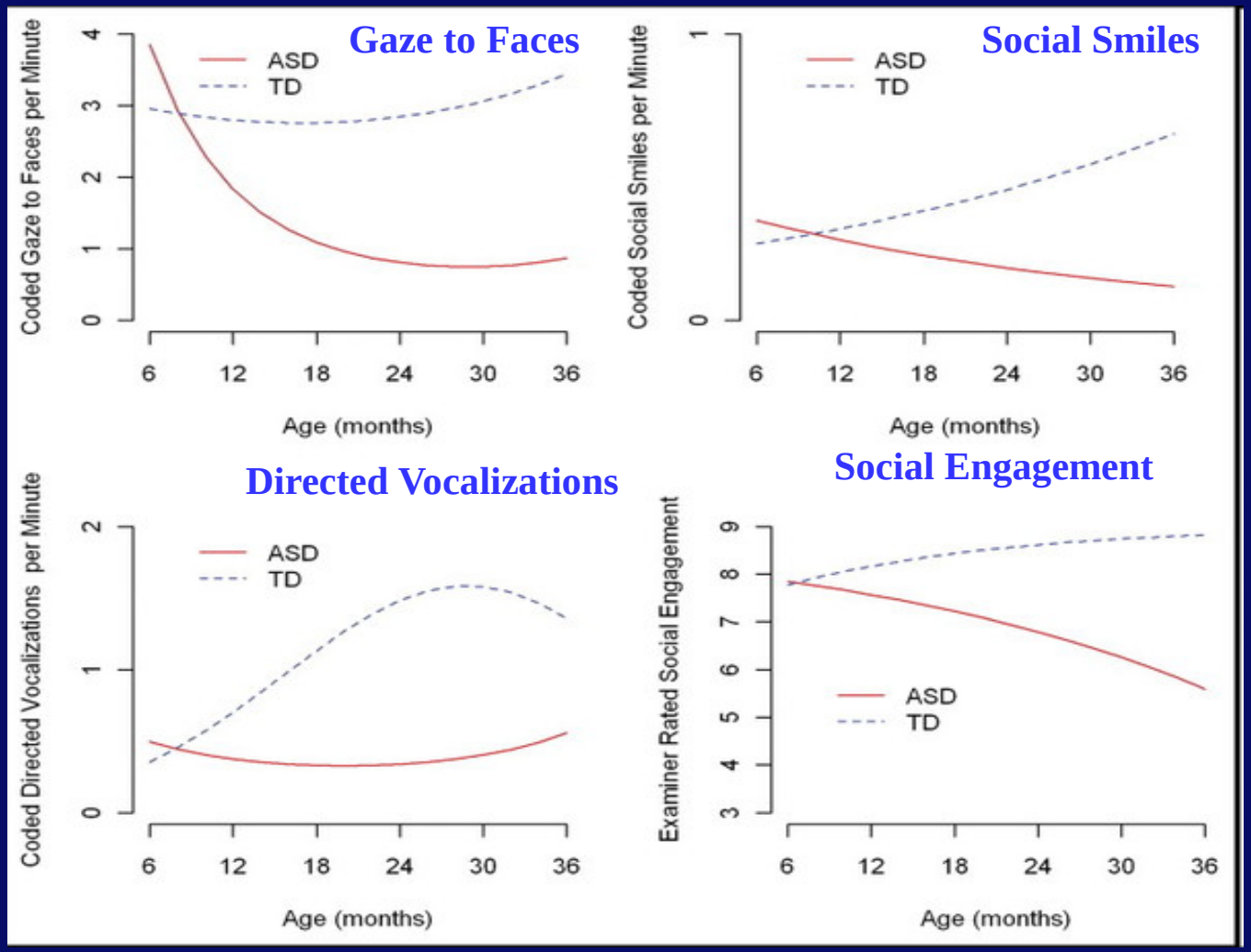
Early Post-natal Onset of Autistic Behavior

(Zwaigenbaum et al., 2005)



A Prospective Study of the Emergence of Early Behavioral Signs of Autism

Ozonoff et al (2010) JAACAP



25 high risk sibs who developed ASD vs. 25 low risk sibs who did not have ASD

differences remain after covarying for developmental level (Mullen)

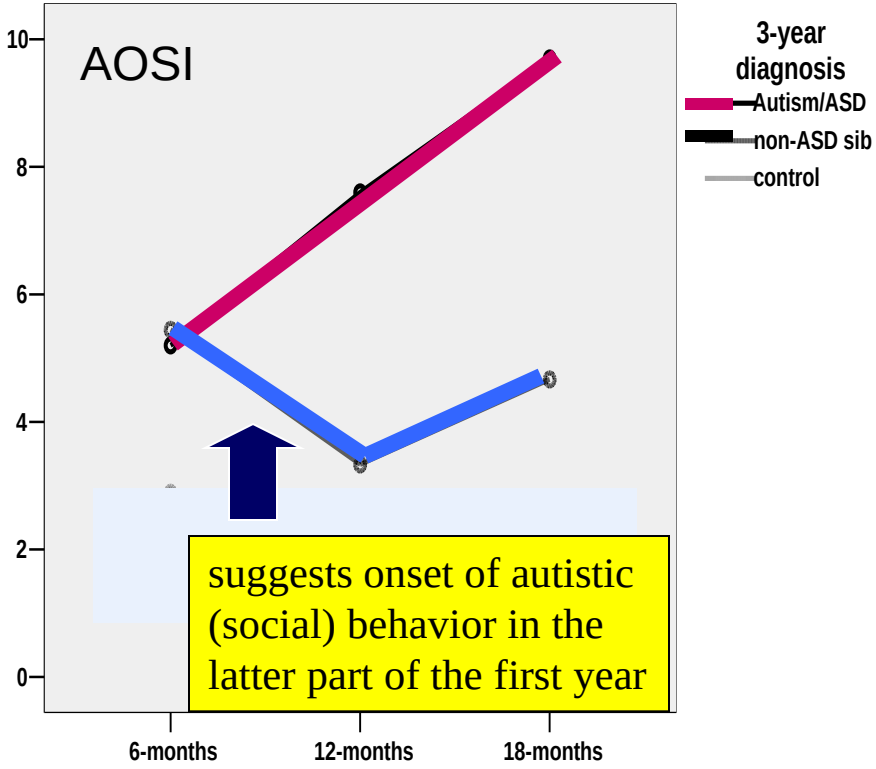
Trajectories for Social Communication Behaviors and Overall Ratings of Social Engagement. ASD = autism spectrum disorders; TD = typically developing children.

The convergence of evidence from infant sib behavioral studies, head circumference studies and MRI studies suggests that:

the onset of autistic behavior is temporally related to the onset of brain enlargement in the latter part of the 1st year

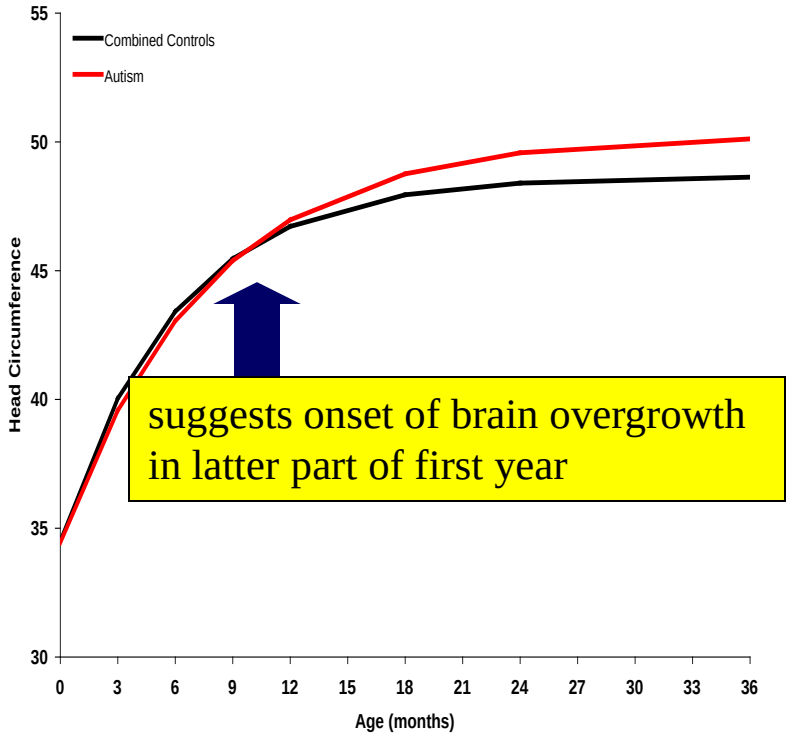
Onset of Autistic Behavior

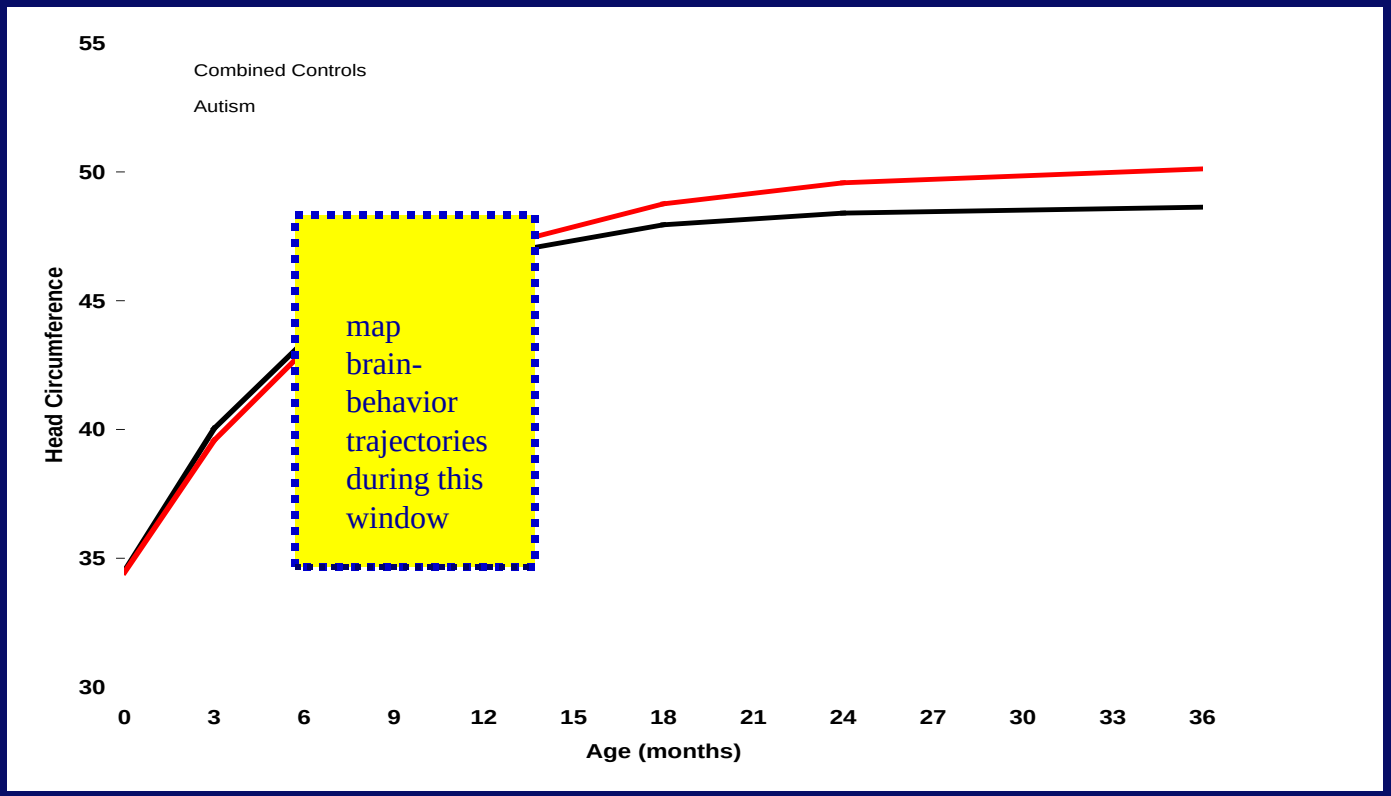
Zwaiggenbaum et al., 2005



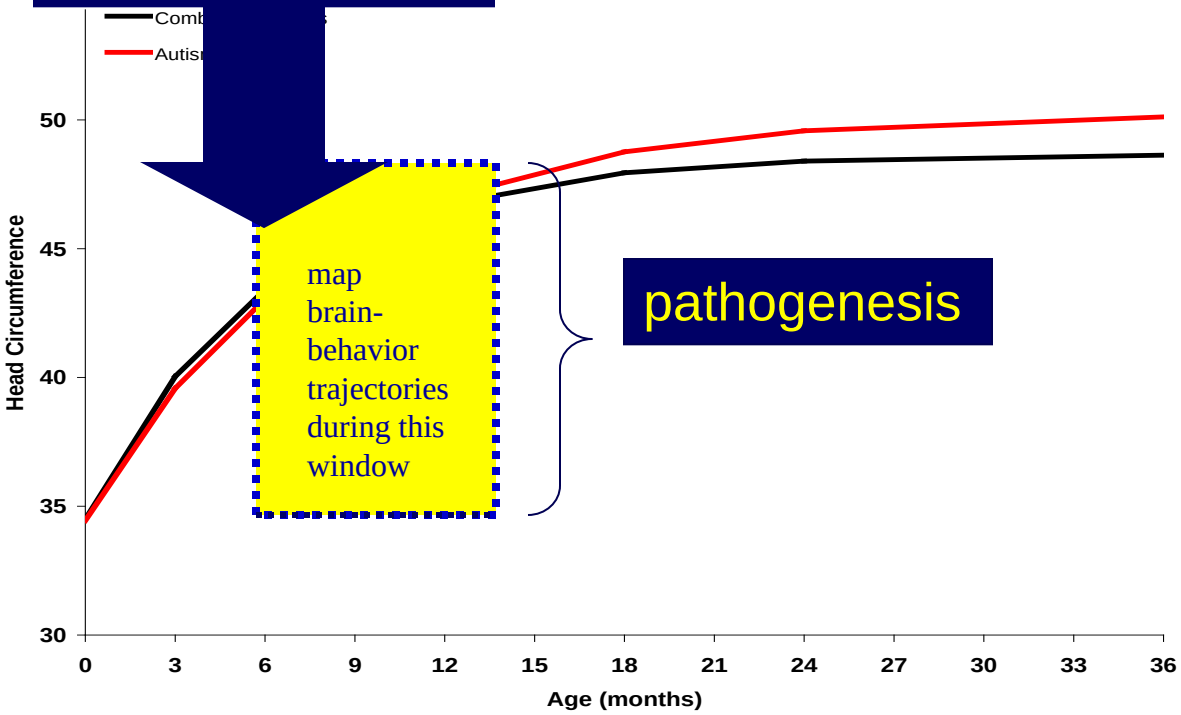
Onset of Brain Enlargement

Hazlett et al 2005

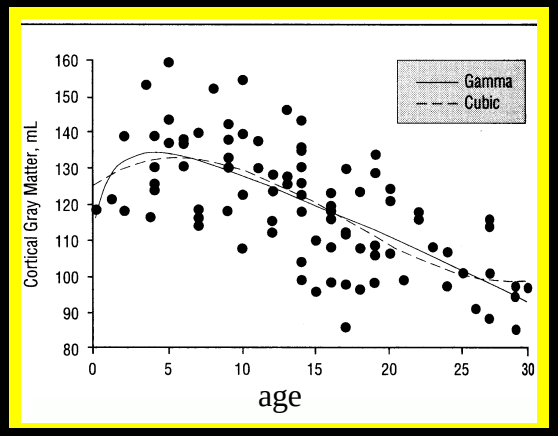



55
50
45
40
35
30
Combined Controls
Autism
Head Circumference
map brain-behavior trajectories during this window
0
3
6
9
12
15
18
21
24
27
30
33
36
Age (months)

prediction ?
intervention ?



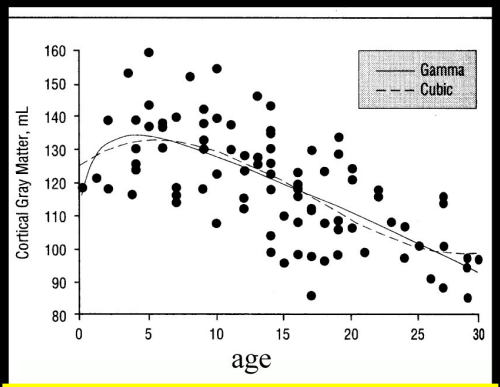
Studying Development



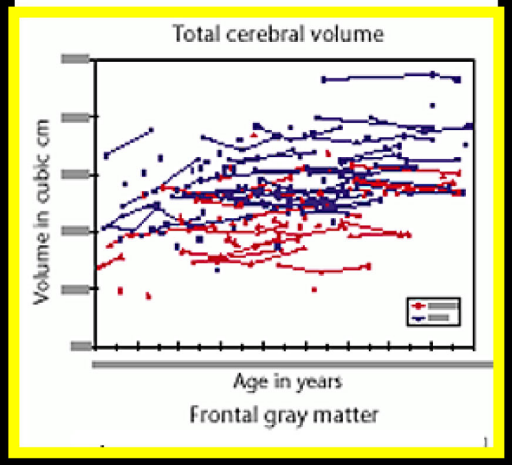
Studying Development

Cross-sectional Study A, B, C, D, E …

Studying Development

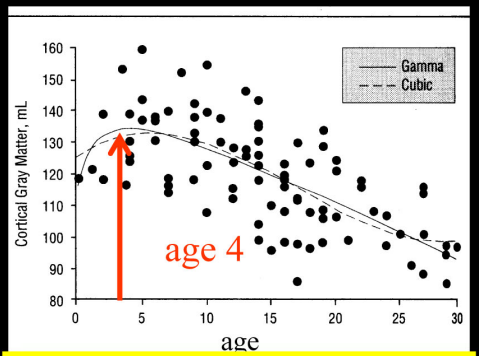


Cross-sectional Study A, B, C, D, E …

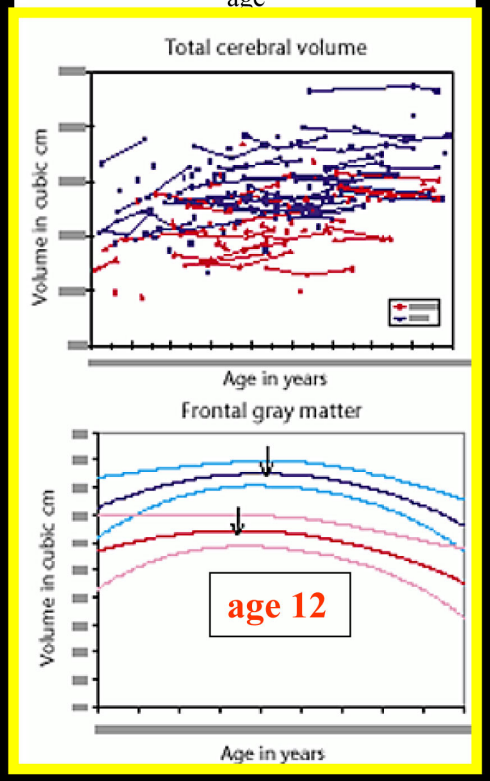


Longitudinal Study $A^1 \rightarrow A^2$; $B^1 \rightarrow B^2 \rightarrow B^3$

Studying Development

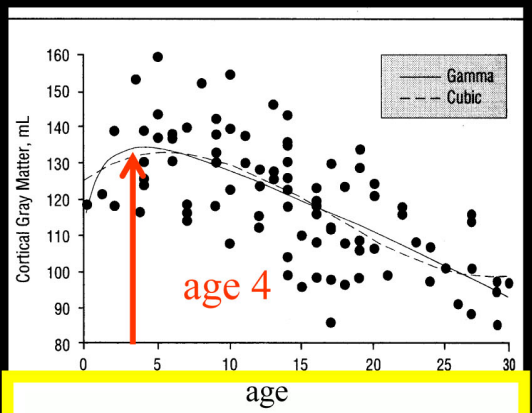


Cross-sectional Study A, B, C, D, E …

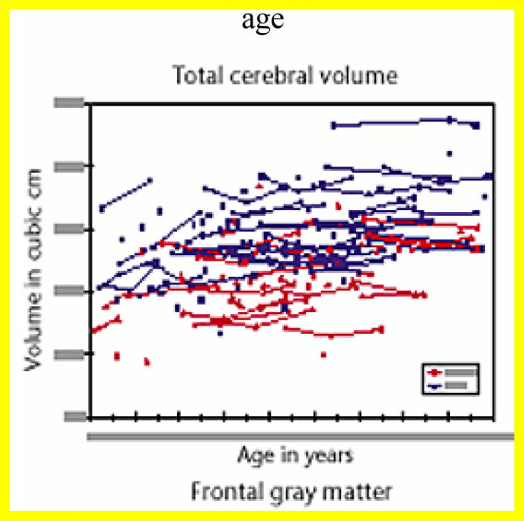


Longitudinal Study A → A; B → B; C → C → C

Studying Development



Cross-sectional Study A, B, C, D, E …



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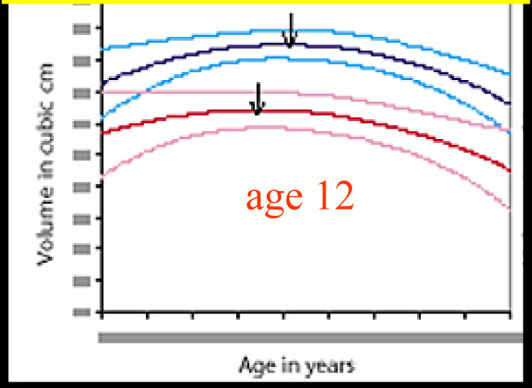
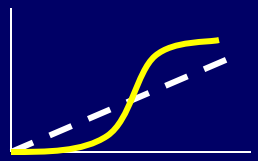
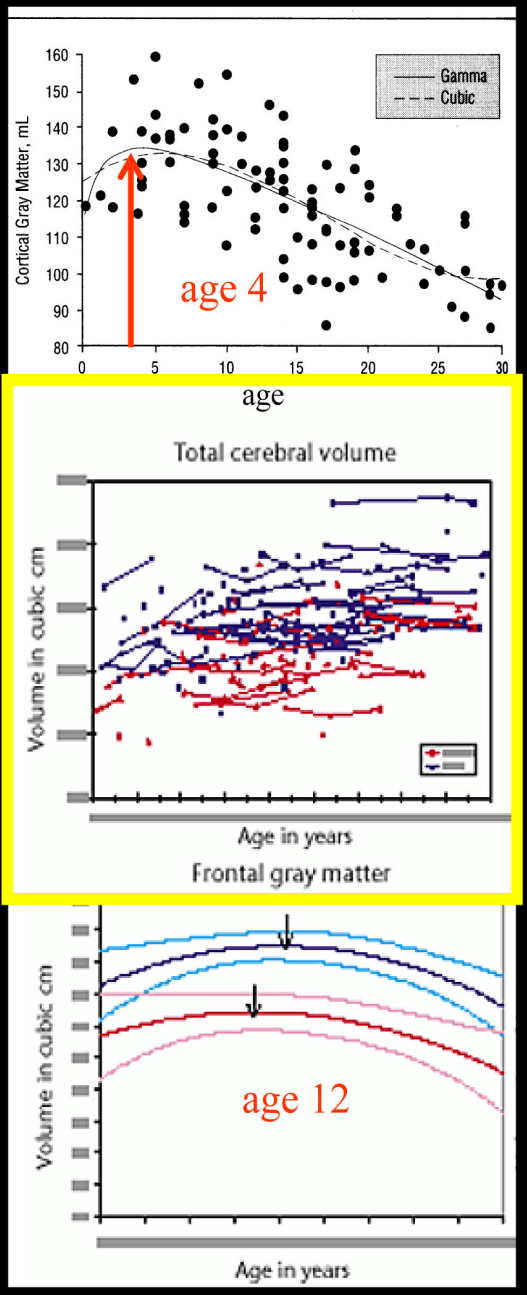


- when you have 'heterogeneity' (apples and oranges),
- and, when you have non-linear development



→ **LONGITUDINAL STUDIES**

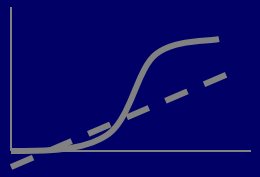
Studying Development



Cross-sectional Study A, B, C, D, E …

Longitudinal Study A → A; B → B; C → C → C

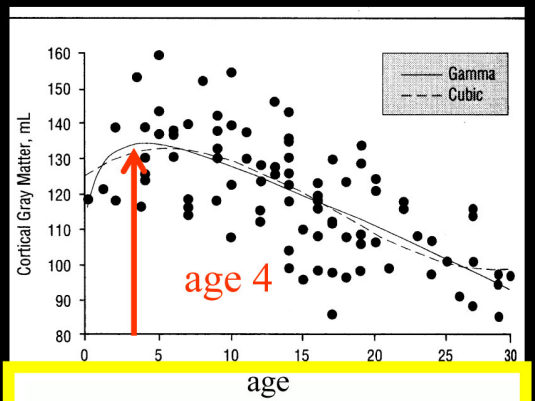
- when you have 'heterogeneity' (apples and oranges),
- and, when you have non-linear development



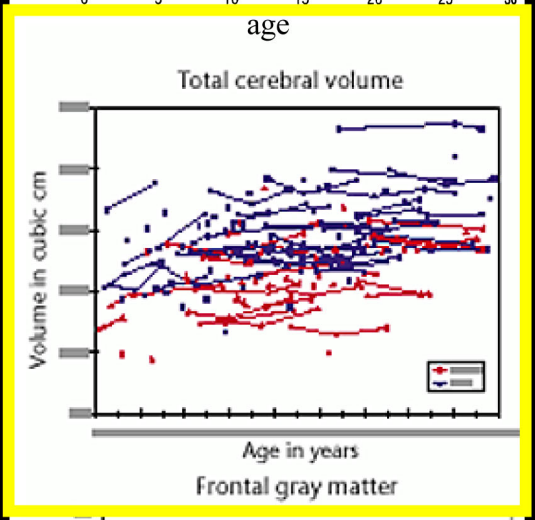
→ **LONGITUDINAL STUDIES**

rather than measure change across different individuals at different ages;
measure change in the same individual over time.

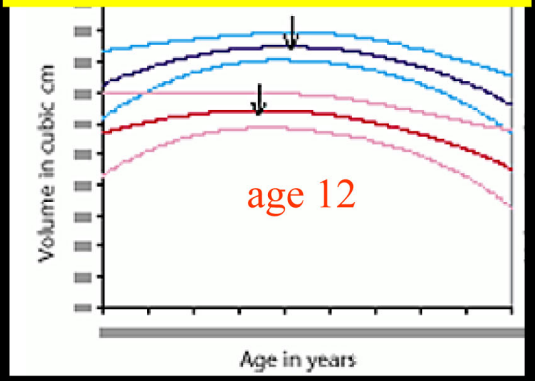
Studying Development



Cross-sectional Study A, B, C, D, E …



Longitudinal Study A → A; B → B; C → C → C



longitudinal studies take a long time and are expensive

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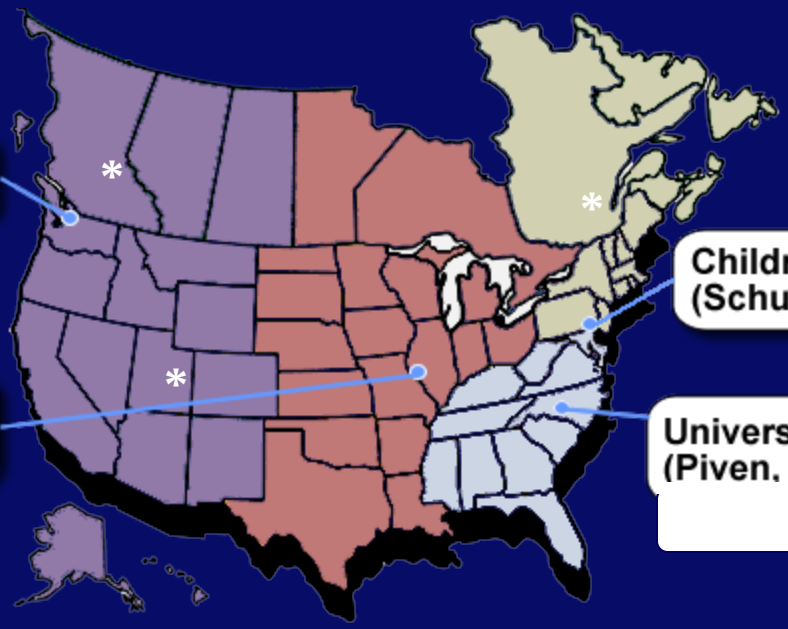

University of Washington
(Dager, Dawson, Estes)

Children's Hospital of Philadelphia
(Schultz, Paterson)

Washington Unviversity
(Botteron, McKinstry, Constantino)

University of North Carolina
(Piven, Hazlett, Styner, Linn, Gu)
Sullivan, Wright

University of Alberta
(Zwaigenbaum) *

Montreal Neurological Institute
(Evans, Collins, Pike) *

University of Utah
(Gerig) *

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400 HIGH RISK infants at 6 months of age

IBIS (Infant Brain Imaging Study) Network

NIH Autism Center of Excellence (www.ibis-network.org)

400 HIGH RISK infants at 6 months of age

+

100 HIGH RISK infants at 12 months of age

500 HIGH RISK infants

IBIS (Infant Brain Imaging Study) Network

NIH Autism Center of Excellence (www.ibis-network.org)

400 HIGH RISK infants at 6 months of age

+

100 HIGH RISK infants at 12 months of age

500 HIGH RISK infants

+

150 LOW RISK controls

IBIS (Infant Brain Imaging Study) Network

NIH Autism Center of Excellence (www.ibis-network.org)

500 HIGH RISK infants

+

150 LOW RISK controls

longitudinal

brain imaging and behavior assessments

6 months → 12 months → 24 months

650 infants

IBIS (Infant Brain Imaging Study) Network

	Final Sample Expected
~ 15 – 20% high risk meet criteria for ASD:	~ 60 – 75*
~ 50% high risk symptomatic/subthreshold	~ 120-140 *
~ 50% high risk asymptomatic:	~ 200 *
low risk controls	~ 150

* after attrition, poor quality scan etc.

IBIS (Infant Brain Imaging Study) Network

	Final Sample Expected
~ 15 – 20% high risk meet criteria for ASD:	~ 60 – 75*
~ 50% high risk symptomatic/subthreshold	~ 120-140 *
~ 50% high risk asymptomatic:	~ 200 *
low risk controls	~ 150
infants with Fragile X Syndrome	36 (PI: Heather Hazlett)

* after attrition, poor quality scan etc.

Progress To Date (3/17/2011)

- 780 scans have been completed
- 266 high risk subjects have been enrolled

High Risk

6 months	217
12 months	225
24 months	126

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- 780 scans have been completed
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High Risk

6 months	**217**
12 months	225
24 months	126

Progress To Date (3/17/2011)

- 780 scans have been completed
- 266 high risk subjects have been enrolled

High Risk

6 months	217
12 months	**225** ← 49
24 months	126

Progress To Date (3/17/2011)

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- 266 high risk subjects have been enrolled

High Risk

6 months	217
12 months	225
24 months	**126**

Progress To Date (3/17/2011)

- 780 scans have been completed
- 266 high risk subjects have been assessed (brain imaging and behavior)
- 104 low risk controls have entered the study

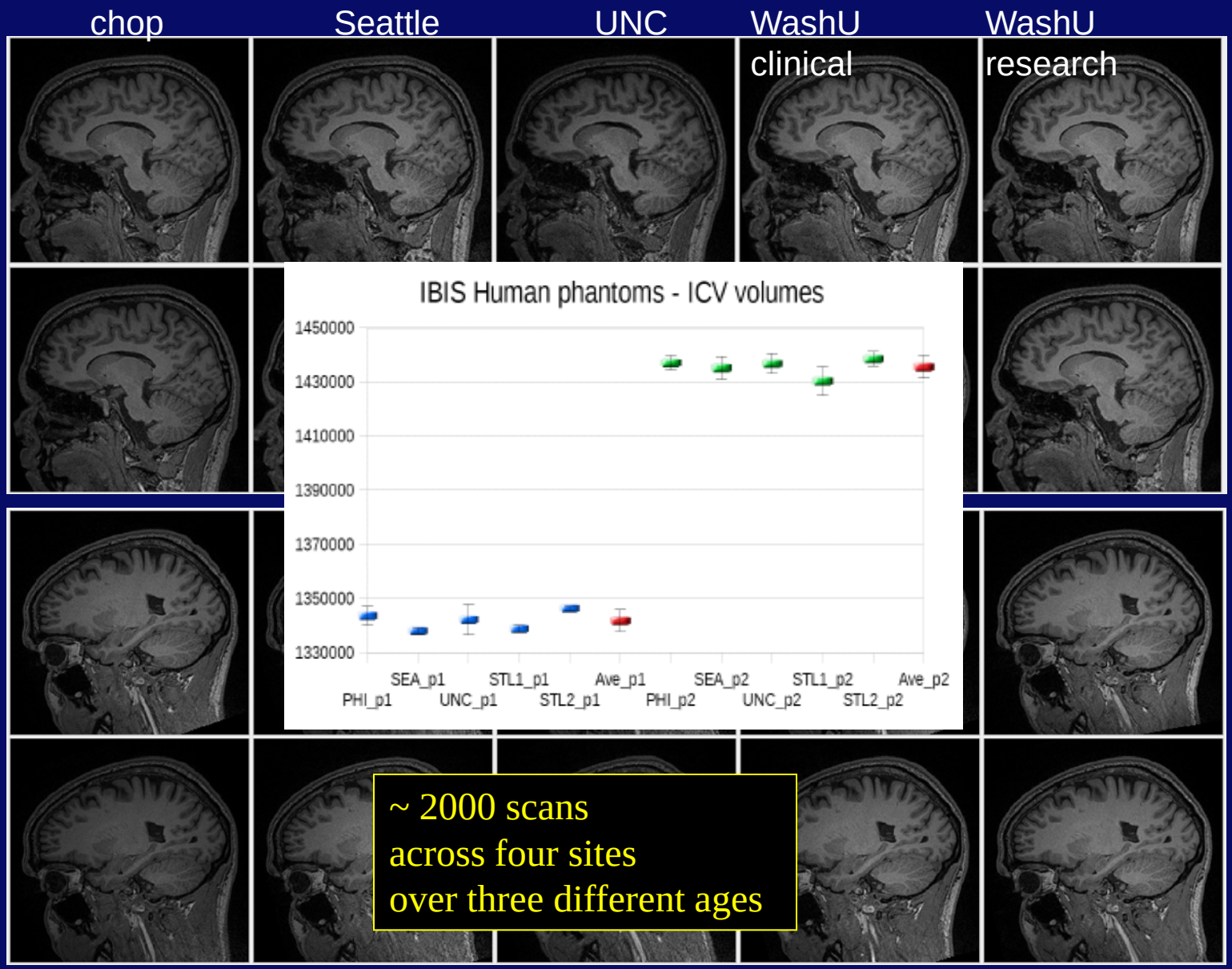
High Risk

6 months	217
12 months	225
24 months	126

Low Risk Controls

6 months	**104**
12 months	74
24 months	34

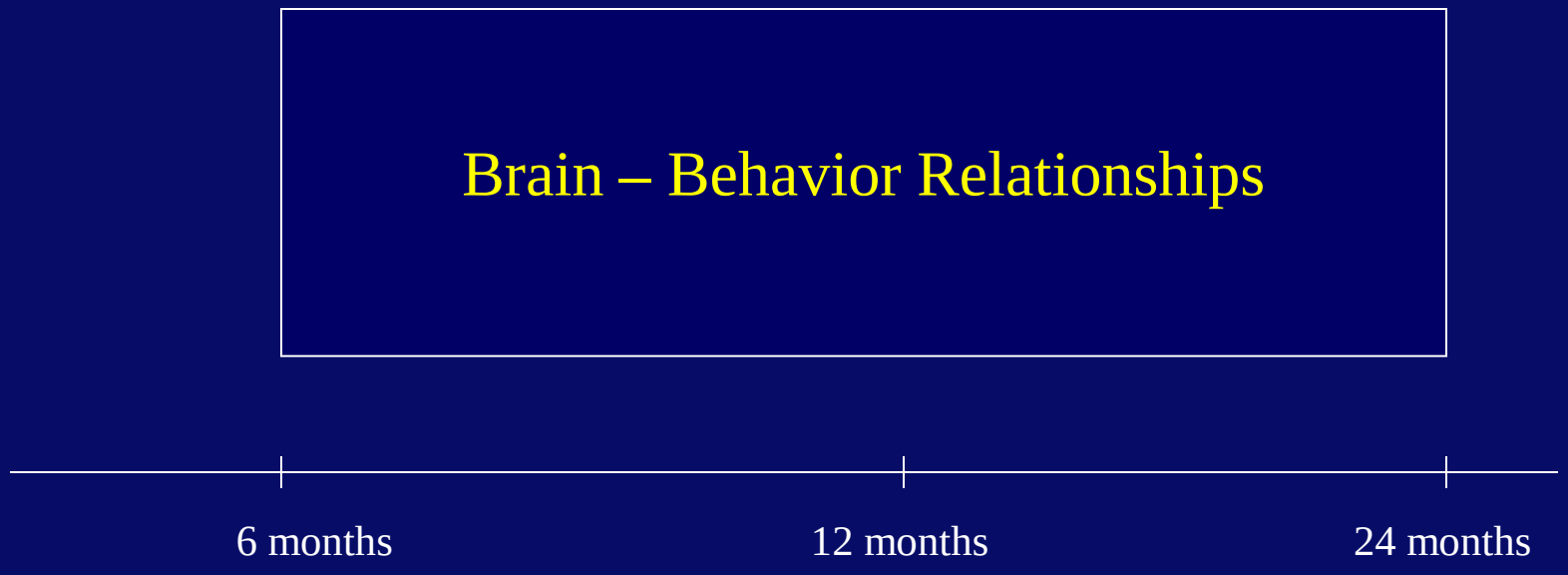
IBIS (Infant Brain Imaging Study) Network: Image Quality Control



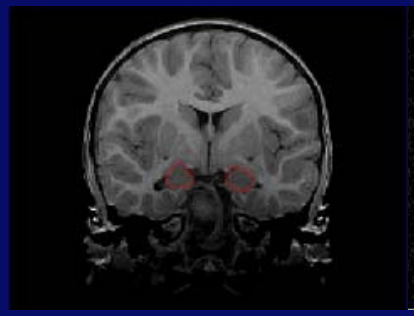
~ 2000 scans
across four sites
over three different ages

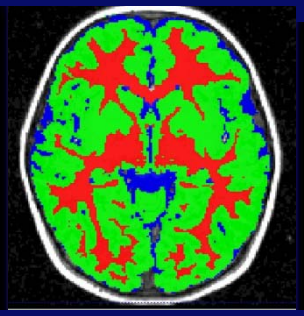
Potential Impact of this Research

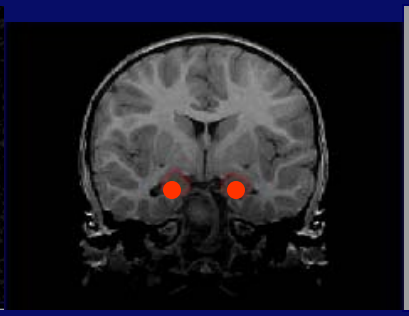
1. What brain changes are associated with behavioral changes during this window ?

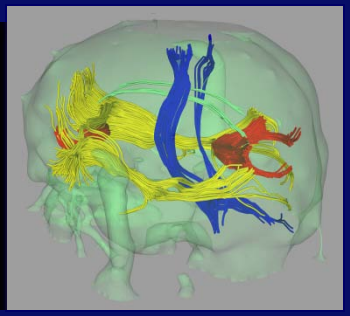


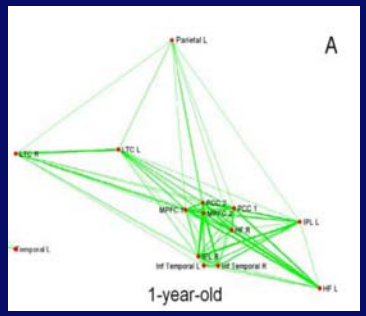
1. What brain changes are associated with behavioral changes during this window ?









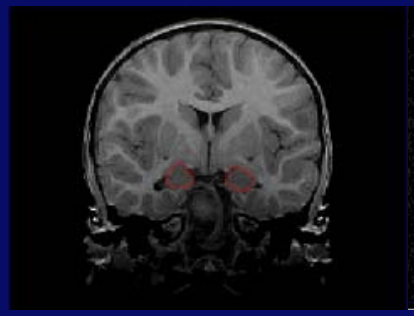


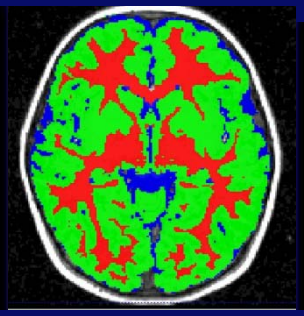
global volume tissue volume substructures neural circuits networks

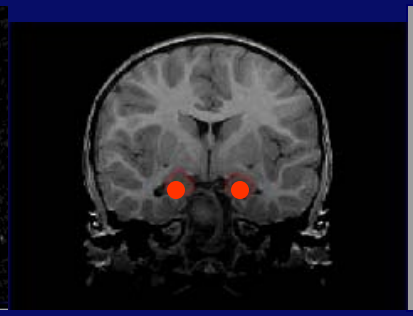
Brain-Behavior Relationships

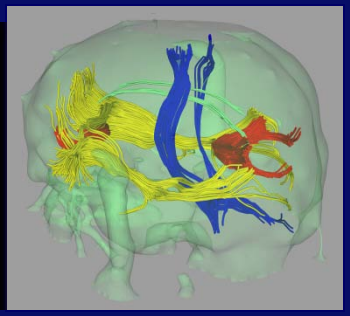
6 months 12 months 24 months

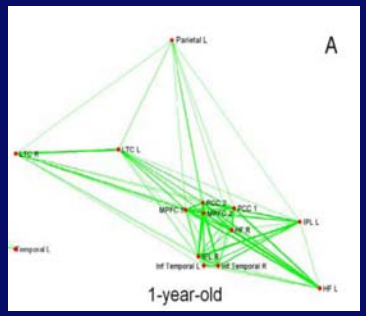
1. What brain changes are associated with behavioral changes during this window ?











global volume tissue volume substructures neural circuits networks

autism

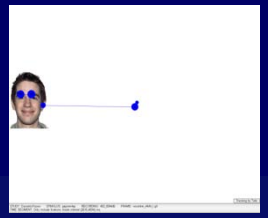
diagnosis

onset

social deficits

social cognition

attention



6 months 12 months 24 months

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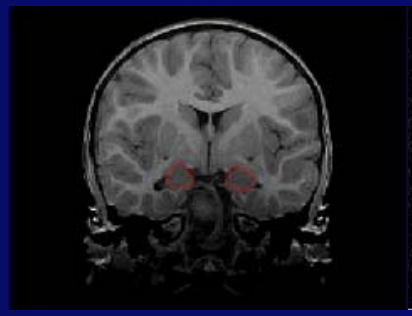
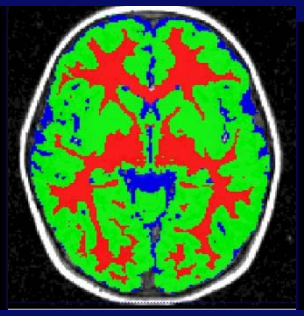
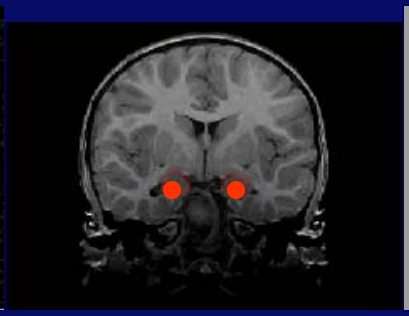
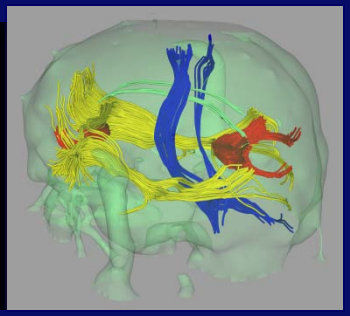
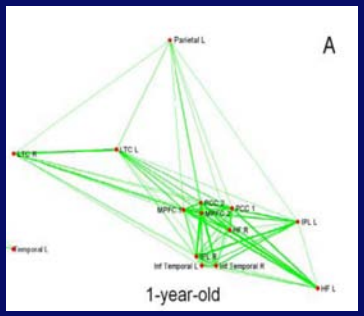






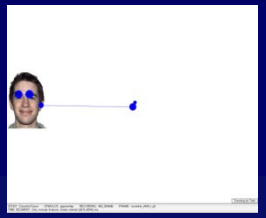
global volume | tissue volume | substructures | neural circuits | networks

autism diagnosis onset

social deficits

social cognition

attention



6 months | 12 months | 24 months

Changes over time will allow us to make inferences about mechanisms.

2. Disease Specific or Associated With Genetic Liability ?

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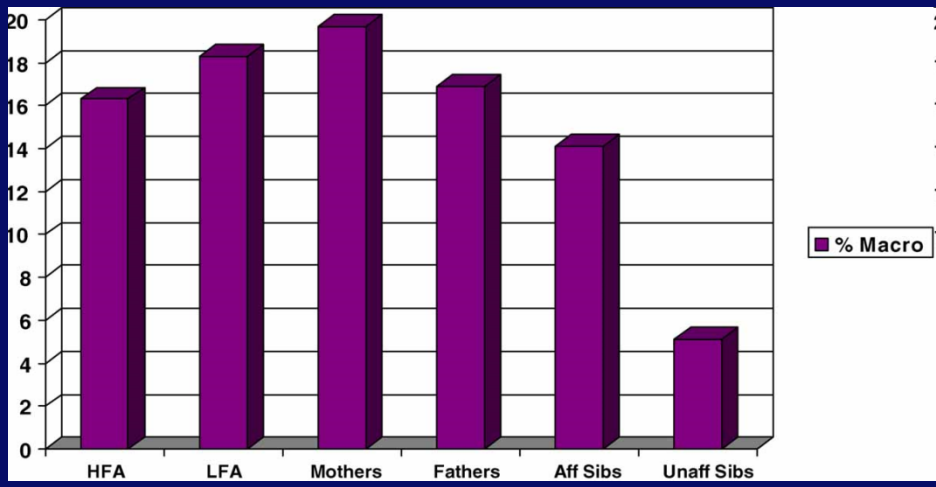
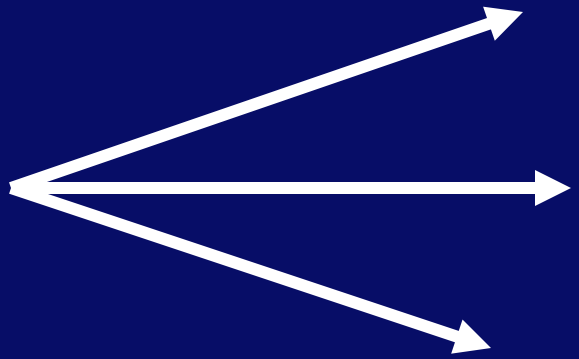


Rate of macrocephaly (percent) in "autism families" (Lainhart et al., 2006)

2. Disease Specific or Associated With Genetic Liability ?

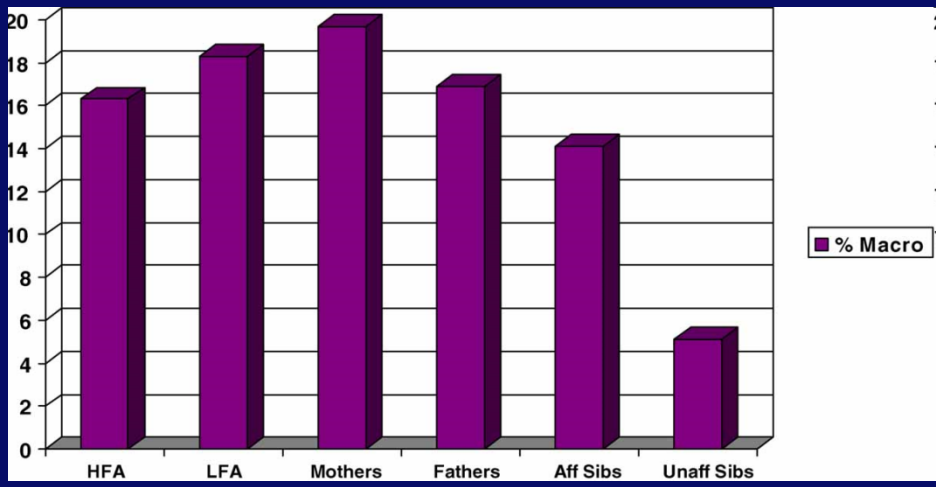
High Risk
Infant Sibs



autism

milder cognitive/behavioral deficits

typical development



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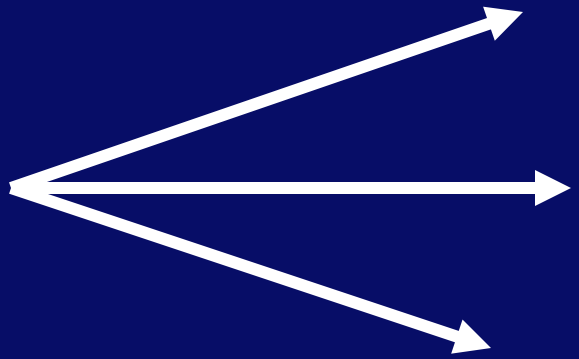
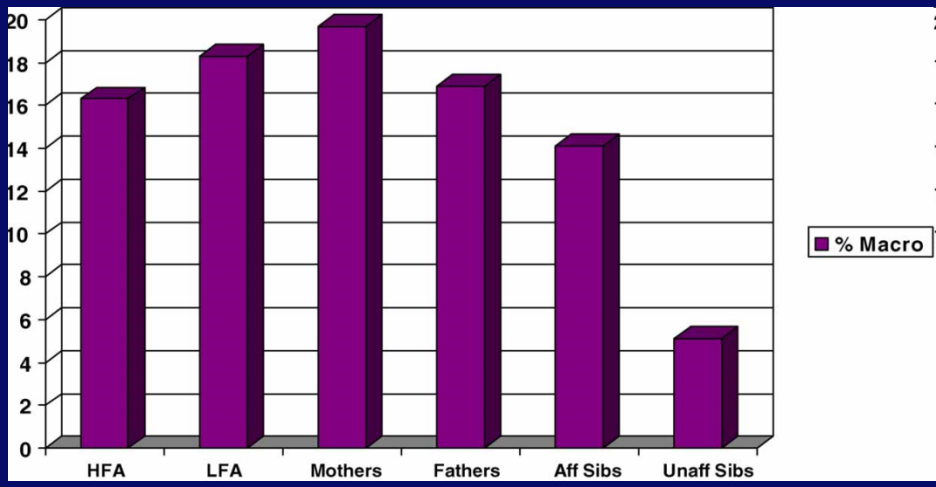


autism

milder cognitive/behavioral deficits

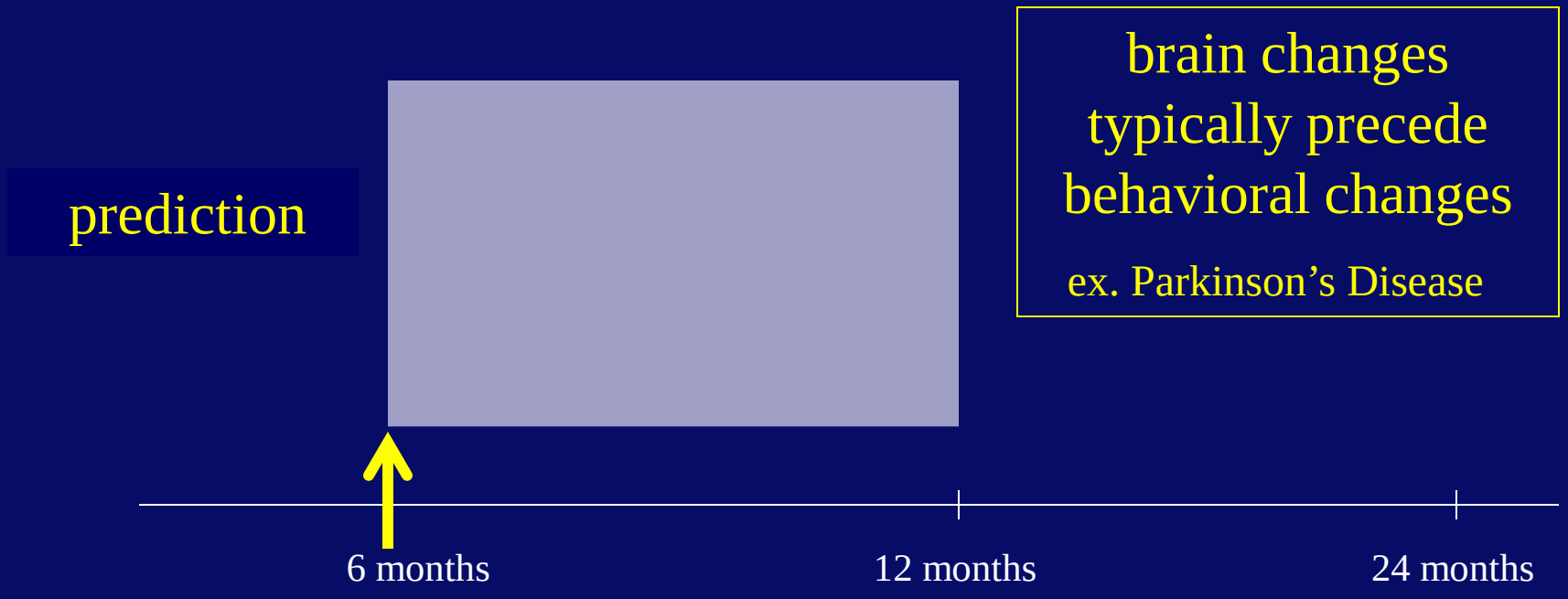
typical development

Which brain changes are specific to the presence of autistic disorder and which ones are associated with genetic liability only (i.e., necessary but not sufficient) ?



Rate of macrocephaly (percent) in "autism families" (Lainhart et al., 2006)

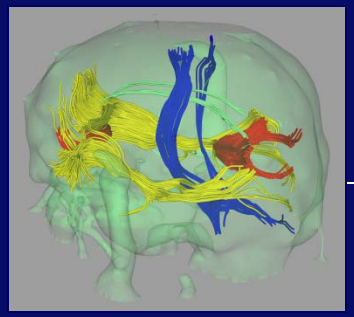
3. Prediction/Early Detection

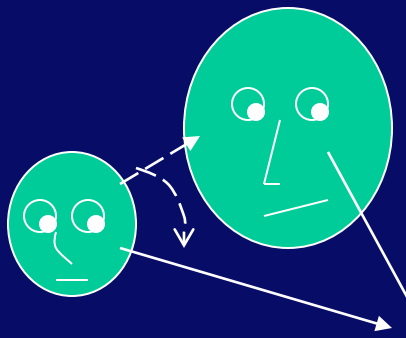


3. Prediction/Early Detection

Hypothesis:

delayed maturation of the uncinate fasciculus predicts abnormal joint attention ?





joint attention

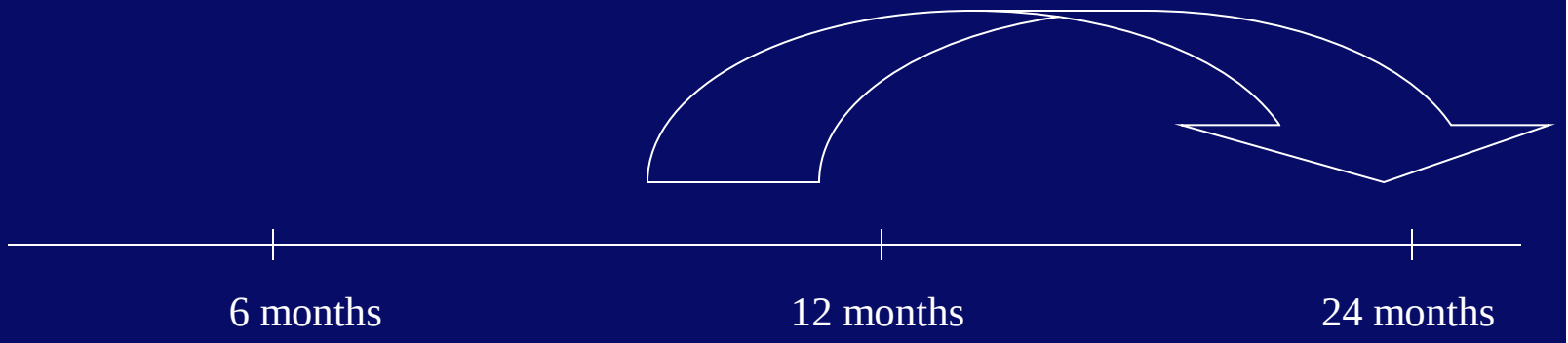
6 months

12 months

24 months

3. Prediction/Early Detection

early brain + behavior trajectories (6, 12 and 18 months)
predicting later diagnosis (24, 36 months)



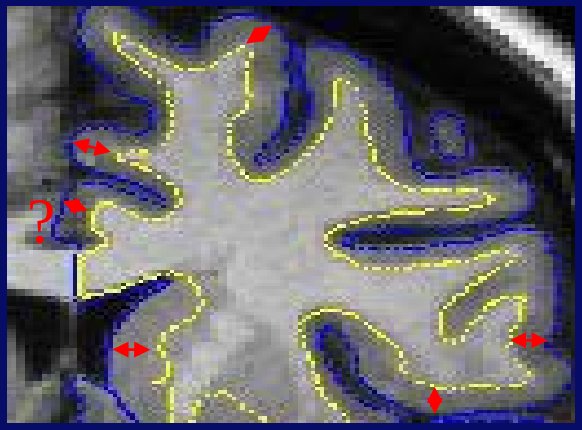
4. Pathogenesis

(Causes/Neurobiological Mechanisms Underlying the Development of Autism)

1. particular brain changes narrow the search for causes

   - cortical overgrowth due to increased surface area (Hazlett et al, in press)

   - suggests proliferation of progenitor cells/ suggests specific genes (e.g., GSK) (Kim et al, 2010)



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2. molecular genetic basis underlying brain and behavior **trajectories**

   - brain-behavior trajectories constitute 'new phenotypes' or definitions of autism
   - Autism Speaks; partnership with NIH EARLI ACE Network
   - DNA →NIMH Genetics Repository
   - candidates and genetic signatures (ex. cancer)

4. Pathogenesis

(Causes/Neurobiological Mechanisms Underlying the Development of Autism)

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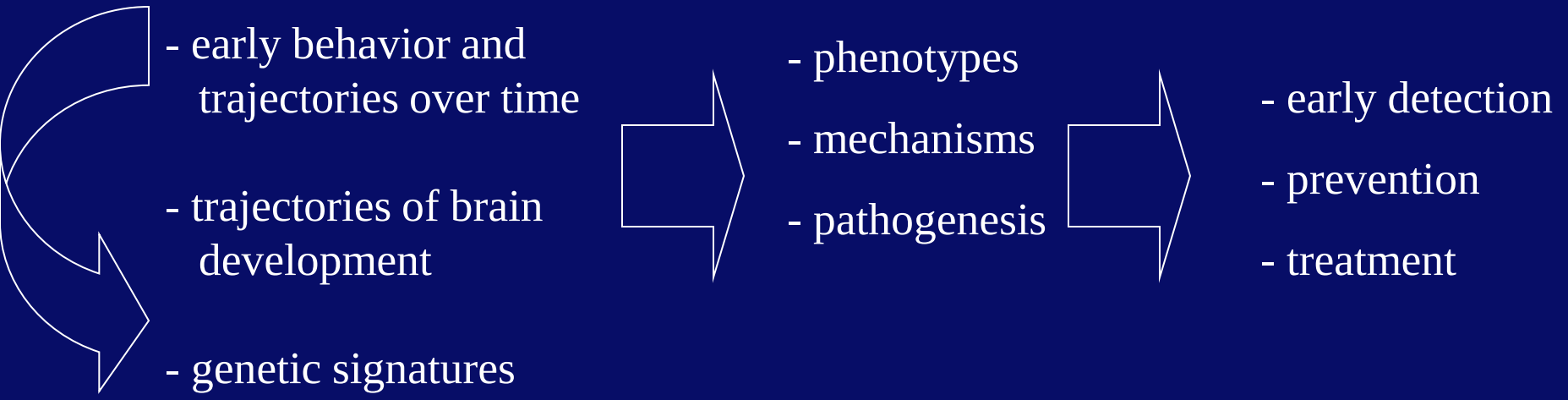
   - candidates and genetic signatures (ex. cancer)

3. contrast with Fragile X (PI: Hazlett Hazlett, UNC)
   same behavior / different brains (Hazlett et al., 2009; Hoeft et al., 2011)
   specific and non-specific effect of background genes (Wassink, in prep)

Impact of Longitudinal Studies of Early Behavior x Brain x Gene Interactions



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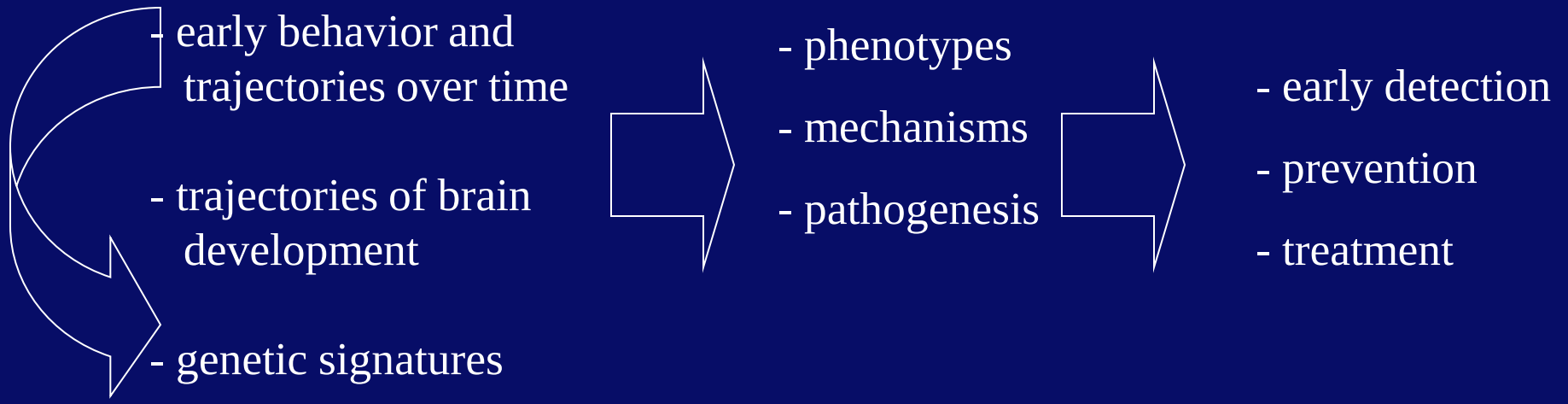

Major understanding of autism will require going beyond single points in time; single brain structures and single genes to predict trajectories of development (particularly around the time of onset of the disorder), to elucidate underlying pathogenetic mechanisms and to develop rational approaches to treatment and prevention.

Acknowledgements

- funding: NICHD
  Autism Speaks
  Simons Foundation
  LENA Foundation
- IBIS Network Collaborators
- and the contribution of participating families

www.ibis-network.org

IBIS (Infant Brain Imaging Study) Network

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- Heather Cody Hazlett
- Martin Styner
- Hongbin Gu
- Jed Elison
- Clement Vachet
- Zhexing Liu
- Chad Chappell

University of Washington
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- Dennis Shaw
- Stephen Dager

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University of Alberta
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