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
“A Longitudinal MRI Study of Infants at Risk for Autism”

Infant Siblings of Older Autistic Children

6 months \(\rightarrow\) 12 months \(\rightarrow\) 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
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**Increased Brain Volume Noted by Two Years of Age**
Parallel Growth Trajectories in Autism and Controls from Age 2 to 4

Brain Volume

- **ASD**
- **CON**

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)

Combined Controls
Autism

 trajectories significantly different

N = 113 autistic subjects
N = 189 local, community controls
ave = 4 observations (birth – 3 yrs)
adj maternal educ, body size, ethnicity
The Timing of Brain Overgrowth: Clues from Head Circumference (Hazlett et al., 2005)

Combined Controls
Autism

Brain enlargement detected on MRI at 2 years of age (N=51)

suggests onset of brain enlargement in the latter part of the first year
Brain Overgrowth in Autism

there is direct evidence for an increased rate of brain growth in autism occurring 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 2\textsuperscript{nd} child with autism (or, recurrence risk) is 10-20 times higher than risk in the general population.

risk: general population risk $\sim 1\%$

recurrence risk $\sim 10-20\%$
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

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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)
profound change in behavior during an early post-natal window

(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)

Gaze to Faces  Social Smiles

Directed Vocalizations  Social Engagement

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.
map brain-behavior trajectories during this window
Head Circumference

Age (months)

30 33 36

0 3 6 9 12 15 18 21 24 27 30 33 36

prediction ?
intervention ?

pathogenesis

map brain-behavior trajectories during this window
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

age 4

age 12
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
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
IBIS (Infant Brain Imaging Study) Network

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

6 months ➔ 12 months ➔ 24 months

650 infants

longitudinal brain imaging and behavior assessments
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**

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<td>infants with Fragile X Syndrome</td>
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* 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

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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

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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?
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- 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
- social deficits
- social cognition
- attention

- diagnosis
- onset

6 months | 12 months | 24 months
1. What brain changes are associated with behavioral changes during this window?

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

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

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

Brain changes typically precede behavioral changes, e.g., Parkinson’s Disease.
3. Prediction/Early Detection

Hypothesis:
delayed maturation of the uncinate fasciculus predicts abnormal joint attention?
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)
4. Pathogenesis

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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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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

- early behavior and trajectories over time
- trajectories of brain development
- genetic signatures

- phenotypes
- mechanisms
- pathogenesis

- early detection
- prevention
- treatment
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

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