Differences in early brain development predict ASD outcome in high risk infants

Heather Cody Hazlett, PhD

Department of Psychiatry & Carolina Institute for Developmental Disabilities
University of North Carolina

Meeting of the Interagency Autism Coordinating Committee
Bethesda, MD
April 2017
Conflicts of Interest

No conflicts of interest

Research funding support:

NIH National Institutes of Health
Turning Discovery Into Health

SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

AUTISM SPEAKS®
Why study early brain development in autism?
Early brain overgrowth

‘infantile autism’
Leo Kanner (1943)

He reported that 5 of the original 11 cases had ‘relatively large heads’
Head Circumference

- Indirect measure of brain
- Increased head circumference in ASD, present during the first 3 years
- Methodological differences in studies
  
  - Prospective/retrospective
  - Samples included/diagnostic criteria
  - Accuracy of measures/QC
  - Normative data
Brain volume increased early in autism

Amaral, Schumann, & Nordahl, 2008
Brain development present in toddlers with ASD

Longitudinal design:

Time1 (~ 2 yrs)
ASD = 59, TD = 38

Time (~ 4-5 yrs)
ASD = 36, TD = 21

Hazlett et al., Am J Psych, 2011
Increased surface area, but not cortical thickness, in a subset of young boys with autism spectrum disorder.


- Autism Phenome Project
- 115 ASD boys (15% DM), 50 TD boys
- Scanned at age 3

- Found ASD group had greater surface area than TD but not in cortical thickness
Birth to Three

- The first two years of life involve rapid brain growth and development
- Brain development is ‘activity dependent’
- Critical periods for development
Typical brain development

Gilmore et al., 2012
Gray matter maturation in 1st year

Overall increase in GM 106%

Gilmore et al., 2012
Gray matter maturation in 2nd year

Overall increase in GM 18%

Gilmore et al., 2012
White matter maturation

Neonate (2 wks)  Infant (1 year)  Adult

Corpus callosum: DTI (FA) along commissural bundles
Can brain differences be used to detect ASD?
IBIS (Infant Brain Imaging Study) Network

NIH Autism Center of Excellence (PI: Joseph Piven)

University of Washington (Dager, Estes)

Washington University (Botteron, McKinstry, Constantino)

Alberta University (Zwaigenbaum)

Montreal Neurological Institute DCC (Evans, Collins, Pike)

University of North Carolina (Piven, Hazlett, Styner, Gu)

New York University (Gerig)

University of Minnesota (Elison, Wolff)

Johns Hopkins University (Fallin, Volk)
Onset of Autistic Behavior and Brain Enlargement in the Latter Part of the First Year of Life

Onset of Autistic Behavior in At-Risk Infant Sibs Between 6-12 months

Zwaigenbaum et al 2005

Onset of Brain Enlargement in Autistic Children before 12 mo.

Hazlett et al 2005

Onset of Autistic Behavior and Brain Enlargement in the Latter Part of the First Year of Life

Onset of Autistic Behavior in At-Risk Infant Sibs Between 6-12 months

Zwaigenbaum et al 2005

Onset of Brain Enlargement in Autistic Children before 12 mo.

Hazlett et al 2005

Onset of Autistic Behavior and Brain Enlargement in the Latter Part of the First Year of Life

Onset of Autistic Behavior in At-Risk Infant Sibs Between 6-12 months

Zwaigenbaum et al 2005

Onset of Brain Enlargement in Autistic Children before 12 mo.

Hazlett et al 2005

Onset of Autistic Behavior and Brain Enlargement in the Latter Part of the First Year of Life

Onset of Autistic Behavior in At-Risk Infant Sibs Between 6-12 months

Zwaigenbaum et al 2005

Onset of Brain Enlargement in Autistic Children before 12 mo.

Hazlett et al 2005

Onset of Autistic Behavior and Brain Enlargement in the Latter Part of the First Year of Life

Onset of Autistic Behavior in At-Risk Infant Sibs Between 6-12 months

Zwaigenbaum et al 2005

Onset of Brain Enlargement in Autistic Children before 12 mo.

Hazlett et al 2005

Onset of Autistic Behavior and Brain Enlargement in the Latter Part of the First Year of Life

Onset of Autistic Behavior in At-Risk Infant Sibs Between 6-12 months

Zwaigenbaum et al 2005

Onset of Brain Enlargement in Autistic Children before 12 mo.

Hazlett et al 2005

Onset of Autistic Behavior and Brain Enlargement in the Latter Part of the First Year of Life

Onset of Autistic Behavior in At-Risk Infant Sibs Between 6-12 months

Zwaigenbaum et al 2005

Onset of Brain Enlargement in Autistic Children before 12 mo.

Hazlett et al 2005

Onset of Autistic Behavior and Brain Enlargement in the Latter Part of the First Year of Life

Onset of Autistic Behavior in At-Risk Infant Sibs Between 6-12 months

Zwaigenbaum et al 2005

Onset of Brain Enlargement in Autistic Children before 12 mo.

Hazlett et al 2005

Onset of Autistic Behavior and Brain Enlargement in the Latter Part of the First Year of Life

Onset of Autistic Behavior in At-Risk Infant Sibs Between 6-12 months

Zwaigenbaum et al 2005

Onset of Brain Enlargement in Autistic Children before 12 mo.

Hazlett et al 2005

Onset of Autistic Behavior and Brain Enlargement in the Latter Part of the First Year of Life

Onset of Autistic Behavior in At-Risk Infant Sibs Between 6-12 months

Zwaigenbaum et al 2005

Onset of Brain Enlargement in Autistic Children before 12 mo.

Hazlett et al 2005
IBIS Network

- Infants at high-risk for autism ("baby sibs") – younger sibling at increased risk (~20%)

- Seen longitudinally at 3, 6, 12, and 24 months with follow up at 36 m

- Developmental & behavioral assessments and MRI
Early brain development in infants at high risk for autism spectrum disorder

Heather Cody Hazlett\textsuperscript{1,2}, Hongbin Gu\textsuperscript{1}, Brent C. Munsel\textsuperscript{3}, Sun Hyung Kim\textsuperscript{1}, Martin Styner\textsuperscript{1}, Jason J. Wolff\textsuperscript{4}, Jed T. Elison\textsuperscript{5}, Meghan R. Swanson\textsuperscript{2}, Hongtu Zhu\textsuperscript{3}, Kelly N. Botteron\textsuperscript{7,8}, D. Louis Collins\textsuperscript{11}, John N. Constantino\textsuperscript{7}, Stephen R. Dager\textsuperscript{8,9}, Annette M. Estes\textsuperscript{9,10}, Alan C. Evans\textsuperscript{11}, Vladimir S. Fonov\textsuperscript{11}, Guido Gerig\textsuperscript{12}, Penelope Kostopoulos\textsuperscript{11}, Robert C. McKinstry\textsuperscript{13}, Juhi Pandey\textsuperscript{14}, Sarah Paterson\textsuperscript{15}, John R. Pruett Jr\textsuperscript{7}, Robert T. Schultz\textsuperscript{14}, Dennis W. Shaw\textsuperscript{8,9}, Lonnie Zwaigenbaum\textsuperscript{16}, Joseph Piven\textsuperscript{1,2} & the IBIS Network*
## Sample

<table>
<thead>
<tr>
<th></th>
<th>LR</th>
<th>HR-neg</th>
<th>HR-ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>117</td>
<td>248</td>
<td>70</td>
</tr>
<tr>
<td><strong>% males</strong></td>
<td>59%</td>
<td>57%</td>
<td>83%</td>
</tr>
<tr>
<td><strong>Maternal age (yrs)</strong></td>
<td>33.2</td>
<td>33.2</td>
<td>33.3</td>
</tr>
<tr>
<td><strong>Birth weight (lbs)</strong></td>
<td>8.0</td>
<td>7.9</td>
<td>7.9</td>
</tr>
<tr>
<td><strong>Gestational age (wks)</strong></td>
<td>39.3</td>
<td>39.1</td>
<td>38.9</td>
</tr>
<tr>
<td><strong>Age at visit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6m</td>
<td>6.7</td>
<td>6.6</td>
<td>6.6</td>
</tr>
<tr>
<td>12m</td>
<td>12.7</td>
<td>12.7</td>
<td>12.7</td>
</tr>
<tr>
<td>24m</td>
<td>24.6</td>
<td>24.7</td>
<td>24.6</td>
</tr>
<tr>
<td><strong>Mullen ELC at 24m</strong></td>
<td>109.7</td>
<td>101.8</td>
<td>79.3</td>
</tr>
<tr>
<td><strong>Vineland ABC at 24m</strong></td>
<td>105.0</td>
<td>101.0</td>
<td>88.1</td>
</tr>
</tbody>
</table>

Note: also saw difference in maternal education
Brain overgrowth in HR-ASD

Hazlett et al., Nature 2017
Trajectory of surface area 6-24m

Hazlett et al., Nature 2017
Regions of SA expansion in HR-ASD

A = middle occipital gyrus & cuneus, B = lingual gyrus, C = inferior temporal gyrus, D = middle frontal gyrus

Hazlett et al., Nature 2017
Brain enlargement associated with behavioral features

TBV growth rate & ADOS severity score

- no relationship at 6-12 month interval
- significant (positive) relationship at 12-24 months (p=0.06)
- relationship with social affect score, not repetitive behavior

Relationship to social behaviors also seen in CSBS

- Social deficits at 24 months related to increased growth rate in TBV from 12-24 months
Could early surface area be a biomarker?
Deep Learning Classification of Cortical Data

Martin Styner, Ph.D. & Brent Munsell, Ph.D.
UNC                              College of Charleston

- predicting clinical best estimate diagnosis at 24 months: high risk-ASD versus high risk-negative
- 6 and 12 month scans
- cortical thickness & surface area; sex, total brain volume
- 78 ROI’s x 2 hemispheres x 2 time points = 608 data points
- divide 179 (34 HR-ASD, 145 HR-neg) into 10 equal parts (folds) each with a HR-ASD/AR-Neg ratio ~ to total sample
- train on 9 parts/folds and test on 1 part/fold; average correct vs incorrect across all 10 folds

Hazlett et al., Nature 2017
### Predicting 24 Month Diagnostic Outcome from 6-12 Month Surface Area

<table>
<thead>
<tr>
<th></th>
<th>ASD (n=34)</th>
<th>Non-ASD (n=145)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive Test (ASD)</strong></td>
<td>True Positive (TP) N=30</td>
<td>False Positive (FP) N=7</td>
<td>PPV = 81%</td>
<td>TP/(TP + FP)</td>
</tr>
<tr>
<td><strong>Negative Test (Non-ASD)</strong></td>
<td>False Negative (FN) N=4</td>
<td>True Negative (TN) N=138</td>
<td>NPV = 97%</td>
<td>TN/(FN + TN)</td>
</tr>
<tr>
<td>Total ASD</td>
<td>sensitivity = 88% TP/ASD</td>
<td>Total non-ASD</td>
<td>specificity = 95% TN/non-ASD</td>
<td></td>
</tr>
</tbody>
</table>

Features correctly classify ~ 8 of 10 (81%) of infants as ASD
Predicting Later Autism from Early Behavior?

PPV = .14
no validation sample

PPV = .50
in a validation sample
Early surface area expansion → Brain overgrowth → Emergence of behavioral features

1\textsuperscript{st} year 2\textsuperscript{nd} year
Summary of findings

brain changes are present as early as 6 months of age (before the appearance of the defining features of autism)

the brain in autism changes over time (age 6 – 24 months) ... during a critical period when autistic behavior is first unfolding
Clues to mechanisms?

Neocortical neurogenesis and the etiology of autism spectrum disorder (2016). Alan Packer (SFARI)

Some ASD risk genes have role in neurodevelopment

Altered neurogenesis?

Neural progenitor cell proliferation?
Other evidence for early brain differences and ASD outcomes?
Neural circuitry at age 6 months associated with later repetitive behavior and sensory features in autism

HR-ASD (N=44); HR-NEG (N=173)
- DTI tracts at 6, 12 and 24 months
- Behavior: RBS-R, SEQ

Genu FA & Cerebellar pathways at 6 months

Repetitive behavior & sensory features at 24 months

- no association between genu/cerebellar tracts and ADOS social affect score

ATR = anterior thalamic radiation; CST = cortico-spinal tract; genu = genu of corpus callosum; MCP = mid-cerebellar peduncle; SCP = superior cerebellar peduncle

Wolff et al, Mol Autism 2017
Examining brain networks

Using functional connectivity at 6 months to predict ASD outcomes at 24 months

Robert Emerson

6 Months of Age

functional connectivity networks from rsMRI
Future directions and next steps

• Explore brain-behavior relationships in cortical and subcortical data

• Multi-modal analyses (e.g., sMRI, DTI, bx)

• Individual profiles and domain based trajectories (e.g., RDoC)

• Incorporate genetics and environmental risk data
Acknowledgements

Research funding support:

NIH - NICHD; NIH – T32 (CI DD); Autism Speaks; Simons Foundation, Foundation of Hope

Many thanks to the participating families!