Infant Brain and Behavior Development in Autism: Relevance to Intervention and Pathogenesis

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Meeting of the Iowa Psychiatric Society
October 2015

‘InfantSibling’ Studies: A New Autism Research Paradigm

risk of having a 2nd child with autism (or, recurrence risk) is ~ 20% (Ozonoff et al, 2010);
~ 20 fold greater than risk in the general population.

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

(Zwaigenbaum et al., 2005)
A Prospective Study of the Emergence of Early Social Behaviors in Autism
Ozonoff et al (2010) JAACAP

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

The defining social deficits seen in autism emerge in the latter part of the first and second years of life

IBIS (Infant Brain Imaging Study) Network
NIH Autism Center of Excellence (www.ibis-network.org)

Aim: To characterize the relationship between brain and behavior changes in autism, from the latter part of the 1st year through the 2nd year of life.

longitudinal brain imaging and behavior assessments

375 HIGH RISK infants + 175 LOW RISK controls

6 months → 12 months → 24 months

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funding from NICHD, NIMH, Autism Speaks, Simons Foundation, LENA Foundation
Longitudinal Behavioral Trajectories: Sample

<table>
<thead>
<tr>
<th>Familial Risk (HR)</th>
<th>DSM IV Autism</th>
<th>ADOS 24 Month Clinical Best Estimate</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>High HR severe</td>
<td>N = 38</td>
<td>Autism Diagnostic Observation Score (ADOS)</td>
<td></td>
</tr>
<tr>
<td>HR moderate</td>
<td>N = 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR Negative</td>
<td>N = 215</td>
<td></td>
<td></td>
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<tr>
<td>Low HR negative</td>
<td>N = 105</td>
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</tbody>
</table>

Estes, Zwaigenbaum, Gu et al., 2015

AOSI (Autism Observation Scale for Infants) Score

- severe = moderate > HR neg = LR
- differences at 12 months

ASD - severe
ASD - moderate
HR negative
LR negative
No ASD

Autism Observe Scale for Infants Score

- severe = moderate > HR neg = LR
- no significant differences at 6 months

• disengagement of attention
• visual tracking
• response to name
• social babbling
• eye contact
• reciprocal social smiling
• social anticipation
• social interest and affect
• response to facial emotion
• imitation
• coordinate eye gaze - action
• reactivity
• transitions
• atypical motor behaviors
• atypical sensory behaviors
• engagement
• social referencing

Mullen Cognitive Development (expert tester)
Vineland Adaptive Behavior (parent report)

- autism = spectrum < HR neg = LR (trajectories)
- significant differences at 12 and 24 months, not 6 months
- significant group x time effect (symptoms unfolding)
Mullen: Gross Motor

- Motor deficits at 6 months
- No change over time

Mullen: Visual Reception (VR)

- Significant differences at 6 months
- VR at 6 months is largely about sensory abilities
- Differences unfold over time

Visual Orienting in Infants at Risk for Autism

Gap Overlap Paradigm

Orienting to salient information in the environment, during infancy, is critical for early cognitive development

How quickly do infants shift or orient their gaze from a central to a peripheral stimulus?
Visual Orienting in Infants at Risk for Autism

at 6 months of age, HR infants later classified with ASD (at 24 months) oriented more slowly to the peripheral stimulus


Brain Volume Doubles in the First Year


Converging Behavioral Findings:

- prodromal period ~ first year;
  - motor – sensory – visual orienting deficits observed
  - but no evidence of the defining features (social deficits)
- defining (social) features unfold during the latter part of the 1st and 2nd year
- declining cognitive abilities and adaptive function 6-24 months
- variability in the trajectory from 6-24 months (individual, group)

SA x CT = Volume

Rationale

- genetic architecture (SA ≠ CT)
- mechanism?

  - surface area - symmetrical proliferation neural progenitor cells

  - surface area but not cortical thickness increased at 2 and 4 years of age in ASD
  - Hazlett et al., 2011
Neuron Number and Size in Prefrontal Cortex of Children With Autism
Courchesne et al., JAMA (2011)

plausible mechanism?

Opposing Brain Differences in 16p11.2 Deletion and Duplication Carriers
J Neuroscience (2014)

The 16p11.2 Deletion Mouse Model of Autism Exhibits Altered Cortical Progenitor Proliferation and Brain Cytarachitecture Linked to the ERK MAPK Pathway
Pucilowska et al., Journal of Neuroscience; February 2015

Cell Reports
Fang et al., 2014
Overproduction of Upper-Layer Neurons in the Neocortex Leads to Autism-like Features in Mice

Differences in White Matter Fiber Tract Development Present From 6 to 24 Months in Infants with Autism
Jason Wolff et al., 2012, Amer J Psychiatry

high risk-ASD vs. high risk-neg

(1) differences by 6 months of age; (2) 6 months ≠ 12 months ≠ 24 months

Predicting Later Autism from Early Behavior?

The First Year Inventory: a longitudinal follow-up of 12-month-old to 3-year-old children
Autism; 2013

PPV = .14
no validation sample

18-Month Predictors of Later Outcomes in Younger Siblings of Children With Autism Spectrum Disorder: A Baby Siblings Research Consortium Study
JAAACP 2014

PPV = .50
in a validation sample

Corpus Callosum (CC) Size from 6-24 Months of Age in Autism
Wolff et al., Brain (in press)

increased area
increased thickness

• most robust increase: anterior 6-12 months
• no difference: 24 months
environmental autism spectrum disorder social-communication deficits, ritualistic-repetitive behavior

environmental autism spectrum disorder social-communication deficits, ritualistic-repetitive behavior

sensory/motor delays Æ social/cognitive deficits atypical visual orienting Æ atypical joint attention

experience dependent neuronal development

birth pre-school

RISK DIAGNOSIS

6 12 24 months

RISK DEVELOPMENT DIAGNOSIS

Ebert and Greenberg, Nature (2013)
Autism spectrum disorder

Differences in parent-child interaction at 12 months in ASD

Ming Wan et al (Jonathan Green Lab) (2012)

Autism Treatment in the First Year of Life: A Pilot Study of Infant Start, a Parent-Implemented Intervention for Symptomatic Infants

Sally Rogers et al (2014)

Infant Brain Imaging Study (IBIS)
Acknowledgements

Many thanks to the participating families!

Research funding support: NICHD; Autism Speaks; Simons Foundation