Infant Brain and Behavior Development in Autism

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Infant Brain Imaging Study (IBIS)
an NIH Autism Center of Excellence
Development During Infancy in Children with Autism

RISK
- environmental
- genetic

DEVELOPMENT

DIAGNOSIS/TREATMENT
- autism spectrum disorder
  - social-communication deficits
  - ritualistic-repetitive behavior

BIRTH

2-3 YEARS
‘Infant Sibling’ Studies: A New Autism Research Paradigm

risk of having a 2\textsuperscript{nd} child with autism (or, recurrence risk) is \sim 20\% 
\sim 20 fold greater than risk in the general population.

Ozonoff et al, 2010
Autism Observation Scale for Infants: Scores ASD and Non ASD Siblings

(Lonnie Zwaiggenbaum et al., 2005)

AOSI
- 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

diagnosis at age 3 years

HR-ASD

HR-NEG
A Pre-Symptomatic Period in the Development of Autism

High risk infant sibling studies have demonstrated that the defining social deficits in autism emerge in the latter part of the first and second years of life.

Ozonoff et al (2010)
A Pre-Symptomatic Period in the Development of Autism

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Ozonoff et al (2010)
Visual Orienting in Infants at High Risk for Autism

How quickly do infants shift or orient their gaze from a central to a peripheral stimulus?

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

Visual Orienting in Infants at High Risk for Autism

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

Emergence of Autistic Social Deficits

Courtesy of Lonnie Zwaigenbaum, M.D.
Cognitive Development in Autism Spectrum Disorder: 6-24 months

High Risk-ASD (N=58); High Risk-non ASD (N=212); Low Risk-Typical (N=109)

Estes et al., 2015
unpublished data, slide not included
A **Pre-Symptomatic Period** in the Development of Autism

High risk infant sibling studies have demonstrated that the defining social deficits in autism emerge in the latter part of the first and second years of life.

Ozonoff et al (2010)
The Timing of Brain Overgrowth: Clues from Head Circumference
(Hazlett et al., 2005)

Brain Volume
(Hazlett et al., 2005, 2011)
Gaze to Faces

The Timing of Brain Overgrowth:
Clues from Head Circumference
(Hazlett et al., 2005)

Brain Volume


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

suggested onset of brain enlargement in the latter part of the first year

(Age (months))

(Head Circumference)

35 40 45 50 55

(Hazlett et al., 2005)
Dramatic Changes Take Place in the Brain of a Child Developing Autism

RISK

- environmental
- genetic

DEVELOPMENT

- brain doubles in size from 2 to 52 weeks


DIAGNOSIS/TREATMENT

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BIRTH 2-3 YEARS
Infant Brain Imaging Study (IBIS) Network
An NIH-funded Autism Center of Excellence (ACE) Network

Study Sites

Philadelphia  Seattle  St. Louis  Chapel Hill
Children’s Hospital of Philadelphia  U Washington  Washington U in St Louis  UNC

400 high and low familial-risk infants assessed at: 6-12-24 months
Infant Brain Imaging Study (IBIS) Network
An NIH-funded Autism Center of Excellence (ACE) Network

Study Sites

- Philadelphia: Children’s Hospital of Philadelphia
- Seattle: U Washington
- St. Louis: Washington U in St Louis
- Chapel Hill: UNC

400 high and low familial-risk infants assessed at: 6-12-24 months

1. **development**
2. **cascading changes in brain and behavior**
3. **mechanisms and therapeutic targets**
4. **prediction: clinical implications**
Diffusion Tensor Imaging (DTI)
Longitudinal DTI (Fractional Anisotropy) in High Risk Infants 
With and Without Autism at 6, 12 and 24 Months


Inferior Longitudinal Fasciculus

12/15 white matter tracts

Jason Wolff
U. Minnesota
The *neural signature* of autism is **change**

*Development itself is the key to understanding developmental disorders*

Annette Karmiloff-Smith (1998)
Increased Brain Volume in Autism

**The Timing of Brain Overgrowth: Clues from Head Circumference**
(Hazlett et al., 2005)

- 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 Volume**
(Hazlett et al., 2005, 2011)

- ASD
- CON

Volume:
- 2 years → 4 years

Age (years):
- 0
- 1.5
- 2
- 2.5
- 3
- 3.5
- 4
- 4.5
- 5
- 5.5
- 6
High Risk-ASD > High Risk-Negative = Low Risk-Typical

increased brain volume growth rate in autism from 12-24 months

High Risk-ASD (N=15); High Risk-Neg (N=91); Low Risk (N=42)
Hazlett et al., Nature (2017)

increased brain volume growth rate was associated with the emergence of autistic social deficits not repetitive behaviors (ADOS; CSBS)
surface area \times \text{cortical thickness} = \text{total brain volume}
Rationale:

- genetic architecture: *surface area* differs from *cortical thickness*
Rationale:

• genetic architecture: **surface area** differs from **cortical thickness**

• mechanism: **neural progenitor cell proliferation** influences cortical surface area
Early Brain Overgrowth in Autism Associated With an Increase in Cortical Surface Area Before Age 2 Years *Arch Gen Psychiatry.* 2011;68(5):467-476

Heather Cody Hazlett, PhD; Michele D. Poe, PhD; Guido Gerig, PhD; Martin Styner, PhD; Chad Chappell, MA; Rachel Gimpel Smith, BA; Clement Vachet, MS; Joseph Piven, MD

**Rationale:**

- **genetic architecture:** surface area differs from cortical thickness
- **mechanism:** neural progenitor cell proliferation
- **surface area not cortical thickness increased at 2 and 4 years of age in ASD (Hazlett et al., 2011)**
increased surface area growth rate in autism from 6-12 months

Heather Hazlett
Nature (2017)

High Risk-ASD (N=15); High Risk-Neg (N=91); Low Risk (N=42)
surface area growth rate most robust in regions of visual cortex

Heather Hazlett
Nature (2017)
Surface area growth rate (6-12 months of age) is significantly associated with brain volume growth rate (12-24 months of age).

Hazlett et al., Nature (2017)
Sequential Changes in Brain and Behavior from 6-12 and 12-24 Months of Age

High Risk-ASD (N=15); High Risk-Neg (N=91); Low Risk (N=42)

Surface Area vs. Age (months)

Total Brain Volume vs. Age (months)

r=0.6

sensori-motor; attention problems

social deficits
Hyper-expansion of cortical surface area from 6-12 Months of Age is a Result of Earlier Changes in Development of Immature Nerve Cells

Cortical surface area expansion is due to development of early (prenatal) neurons (nerve cells or neural progenitor calls) in the brain before birth.

P. Rakic; Nat Rev Neurosci (2009)

When does autism begin?

The Example of Schizophrenia

**Prodrome**

- 10 year old
  - attention deficit hyperactivity
  - learning problems
  - schizoid/schizotypal personality

**Diagnosis**

- 18 year old (schizophrenia)
  - hallucinations
  - delusions
Cascading Series of Brain and Behavior Changes Leading to Autism

increased proliferation of neural progenitor cells

\[\downarrow\]

expansion of cortical surface area (sensory regions)

\[\downarrow\]

disruption of sensory experiences \(\setminus\) attention

\[\downarrow\]

altered experience dependent development ?

\[\downarrow\]

cortical overgrowth

\[\downarrow\]

emergence of autistic social deficits

Piven, Elison, Zylka; Molecular Psychiatry (2018)
Hypothesis: autism may be primarily a disorder of sensorimotor-attention systems in infancy, with the defining features of the disorder emerging secondarily in the 2\textsuperscript{nd} year of life
Increased Extra-axial CSF by Six Months of Age in ASD

Shen et al., Brain 2013
(ASD: N=10)

Shen et al., Biological Psychiatry 2017
(ASD: N=47)
Linking Aberrant CSF Volume to Underlying Mechanisms

continously produced (delivering growth factors) and reabsorbed into brain parenchyma filtering inflammatory cytokines and metabolic byproducts (e.g., β-amyloid)

impact of early CSF physiology on downstream brain development

Linking Aberrant CSF Volume to Underlying Mechanisms

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impact of early CSF physiology on downstream brain development

Earlier and Earlier Identification

DIAGNOSIS/TREATMENT

autism spectrum disorder

social-communication deficits
ritualistic-repetitive behavior

2 years
Presymptomatic Detection: Behavioral Markers

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

Katarzyna Chawarska, no, Frederick Shic, no, Suzanne Maccari, no, Daniel J. Campbell, no, Jessica Brian, no, Rebecca Landa, no, Ted Hutman, no, Charles A. Nelson, no, Sally Ozonoff, no, Helen Tager-Flusberg, no, Gregory S. Young, no, Lanie Zwigenbaum, no, Ira L. Cohen, no, Tony Chaitman, no, Daniel S. Messinger, no, Ami Klin, no, Scott Johnson, no, Susan Bryson, no

PPV = .50

1

2 years

DIAGNOSIS/TREATMENT

autism spectrum disorder

social-communication deficits
ritualistic-repetitive behavior
Brain Changes in the First Year: Pre-symptomatic Detection?

**DIAGNOSIS/TREATMENT**

*autism spectrum disorder*

social-communication deficits
ritualistic-repetitive behavior

<table>
<thead>
<tr>
<th>birth</th>
<th>6 months</th>
<th>1</th>
<th>2 years</th>
</tr>
</thead>
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**Brain Changes in the First Year:**
- **Pre-symptomatic Detection?**

**Brain Imaging:**
- Images of brain changes over time.

**DIAGNOSIS/TREATMENT**

*autism spectrum disorder*

social-communication deficits
ritualistic-repetitive behavior

**Prediction**

birth

12 months

24 months

A positive predictive value (PPV) of 81% means that of those who are positive on the test (brain scan) in the first year, 80% will later meet criteria for ASD.
Robert Emerson et al., (Sci Transl Med, 2017): early connectivity predicts later autism

**fcMRI**

- Accuracy: 97%
- Sensitivity: 82%
- Specificity: 100%
- PPV: 100%

N=59 HR (11 ASD+)

**Prediction**

- Birth
- 6 months
- 2 years

**DIAGNOSIS/TREATMENT**

- Autism spectrum disorder

  - Social-communication deficits
  - Ritualistic-repetitive behavior

**Prediction accuracy:** 97%
**Sensitivity:** 82%
**Specificity:** 100%
**PPV:** 100%
unpublished data, slide not included
Brain Changes Known to Precede Behavior Change in Other Conditions

~ 50 percent loss of dopamine neurons of the brain in Parkinson’s Disease before clinical features are reported.
Three distinct approaches have revealed that brain characteristics detectable on MRI, in the first year of life, accurately predict which individuals will meet criteria for autism at 24 months of age.

- While we have not yet replicated a specific method ...

- we have demonstrated ‘proof of principle’: i.e., replication that early brain features predict later diagnosis.
**IBIS Early Prediction Study**

- **NIMH**
- **250 high risk infants**
- **6 → 24 months of age**
- **5 sites just started**
- **www.ibis-network.org**

<table>
<thead>
<tr>
<th>Who do we need?</th>
<th>What do you get?</th>
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<tbody>
<tr>
<td>- Families who have a child or children with autism and a new baby 6-months of age or younger</td>
<td></td>
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<tr>
<td>- Infants and child with autism must share same mom and dad</td>
<td>- $50 compensation for completion of remote data collection for each timepoint</td>
</tr>
<tr>
<td>- Identify autism earlier</td>
<td>- A detailed results report of your infant’s development</td>
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**What's the point?**
- Earlier identification means earlier intervention and improved outcomes

[Visit www.ibis-network.org](www.ibis-network.org)
Current Practice:  Treatment after Diagnosis

DIAGNOSIS/TREATMENT

autism spectrum disorder

social-communication deficits
ritualistic-repetitive behavior

birth  1  2 years
Pre-symptomatic Detection
Pre-symptomatic Detection and Intervention

• earlier is better
  - plasticity

brain doubles in size from 2 to 52 weeks
Pre-symptomatic Detection and Intervention

- earlier is better
  - plasticity
  - general rule: hypertension $\rightarrow$ stroke
There were small but statistically significant gains, ranging from effect sizes of 0.21 for adaptive behavior to 0.32 for communication. These results are in stark contrast to those reported in prior meta-analyses of university-based clinical trials.
Pre-symptomatic Detection and Intervention

• earlier is better
  • plasticity
  • general rule
• ASD treatment

Outcome for Children Receiving the Early Start Denver Model Before and After 48 Months

Giacomo Vivanti¹ ² ³ · Cheryl Dissanayake² · The Victorian ASELCC Team³
Pre-symptomatic Detection and Intervention

- earlier is better
  - plasticity
  - general rule
  - ASD treatment
  - preclinical studies

**JCI** The Journal of Clinical Investigation

*Ube3a reinstatement identifies distinct developmental windows in a murine Angelman syndrome model*

Sara Silva-Santos, …, Steven A. Kushner, Ype Elgersma

*J Clin Invest.* 2015;125(5):2069-2076. [https://doi.org/10.1172/JCI80554](https://doi.org/10.1172/JCI80554).
Pre-symptomatic Intervention?

Language outcome in autism: Randomized comparison of joint attention and play interventions.

Connie Kasari et al. (JCCP, 2008)
Pre-symptomatic Intervention?

**Language outcome in autism: Randomized comparison of joint attention and play interventions.**

Connie Kasari et al. (JCCP, 2008)
Pre-symptomatic Detection and Intervention: Scalability

• population screening?

phase I screen → phase II MRI

• behavior questionnaire
• eye tracking (Jones and Klin, 2013)
• polygenic risk score?
• EEG (Gabard-Durnam et al., 2019 – Nelson Lab)
• multi-modal
unpublished data, slide not included
Future Directions

• replicate MRI early prediction (→ future presymptomatic treatment studies)

• infancy → school age
  John Pruett (Wash U St Louis), Joe Piven (UNC)

• contrasting disorders (Fragile X, Down Syndrome)
  Kelly Botteron (Wash U St Louis), Heather Hazlett (UNC)

• cost effective markers (population): EEG, eye tracking
  Shafali Jeste (UCLA, Jed Elison (U Minnesota)

• molecular/cellular underpinnings (genetics, induced pluripotent stem cells)
  Dani Fallin (Johns Hopkins), Jason Stein (UNC)

• environmental exposures (air pollution, metals)
  Heather Volk (Johns Hopkins)

• ethical-legal-social implications of pre-symptomatic detection
  Kate McDuffie (U Washington)
Infant Brain Imaging Study (IBIS)

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