Infant Visual Brain Development in Autism

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Outline

• *Who we are* – the IBIS Network

• *What we do* – infant brain imaging

• *What we’ve discovered*
  • Early brain changes
  • Predicting autism from brain scans
  • Findings in the visual system

• *What we’re doing now* – our “Early Prediction” Study
The Infant Brain Imaging Study (IBIS) Network

• The first, and largest, study of brain development during infancy in ASD

• Over 15 years of research in early ASD

• Following initial cohort of ~400 “high likelihood” infants into adolescence

• New data collection under way
  • IBIS-Early Prediction (IBIS-EP)
Autism & the Infant Sibling Study Design

• ASD is highly heritable
• Younger siblings of children with ASD are at ~10x higher likelihood of developing ASD
• Siblings can be followed prospectively to study the development of ASD

Infant Brain Imaging Study Timeline

- Proband
- Sibling
- Mother
- Father

IBIS

6m 12m 24m

- Behavior MRI
- Behavior MRI
- Behavior MRI Diagnosis
Infant MRI: a window into the developing brain
Thousands of successful IBIS scans

- ~90% success rate
- ~1hr to complete the protocol
- Highly trained staff ‘baby whisperers’
Key discoveries:

1. Brain changes are apparent in ASD during infancy, and they precede or coincide with changes in behavior

2. We can use machine learning to predict autism diagnoses from brain scans taken in the first year of life
A cascade of early brain changes

- Increased extra-axial CSF volumes
- Atypical pattern of white matter maturation
- Amygdala overgrowth
- Surface area hyper-expansion
- Brain volume overgrowth

Hazlett 2017; Shen 2022; Wolff 2012, 2017; Lewis 2017
Predicting ASD with high accuracy

Can we use information from brain scans to predict later diagnosis?

- Cortical Surface Features
  - Thickness, Surface area at 6 and 12m
  - n = 179 HL infants

  ASD Prediction
  - PPV 80%
  - 30 of 34 infants correctly identified as later developing ASD

- Functional connectivity
  - at 6m
  - n = 59 HL infants

  ASD Prediction
  - PPV 100%
  - 9 of 11 infants correctly identified as later developing ASD

- MRI significantly outperforms behavioral prediction from first year measures
- First evidence that MRI could be used as a screening tool for a subset of the population
- Critical need to replicate, test the generalizability of the model ➔ goal of our new study

Hazlett et al., Nature, 2017; Emerson et al., Science Translational Medicine, 2017
The visual system

- Interprets what we see, guides where we look

- Understanding visual system development in autism may help us understand early differences in behavior.
Hyper-expansion of visual cortical areas

• Visual areas expand rapidly from 6-12m in infants later diagnosed with autism.

• Top contributors to algorithms that predict diagnosis

Hazlett, Nature, 2017
Amygdala overgrowth in ASD

- Amygdala volume increases from 6-12m in ASD, coinciding with expansion in visual cortical surface area
- Responsible for orienting to salient visual cues, shares direct projections with visual cortex
- Rate of amygdala overgrowth from 6-12m related to degree of social impairment at 2yrs

Shen et al., Am. J. Psych., 2022
Amygdala-visual cortex connectivity at 12m

Weaker connectivity between right amygdala and left visual cortex at 12m in high likelihood infants

Related to lower motor and communication abilities.
Visual orienting delayed in autism, linked to visual white matter pathway

At 6 months of age, infants who later developed autism *oriented more slowly* to the peripheral stimulus.

Orienting associated with a visual white matter pathway, opposite associations in autism infants and controls.

*Elison et al., 2013*
Initiation of joint attention and brain function

At 12 months of age, connectivity between visual and other brain networks were related to the frequency of initiating joint attention.

Eggebrecht et al., 2017
Developmental timeline

Visual-spatial behavior linked to visual system connectivity.

Visual cortical surface area hyper-expands in autism

Amygdala volume overgrowth in autism

Amygdala-visual cortex connectivity weaker in infants with a family history of ASD, linked to behavior

Faster amygdala growth, greater social symptoms

Weaker visual-salience connectivity linked to social impairments at 7-11yrs
Proband autistic traits predict diagnosis in younger siblings

3 out of 4 infants who developed autism had probands with higher than average levels of ASD traits.

Odds Ratio = 2.90, \( p < 0.001 \)
Proband traits are related to sibling brain development

- Higher levels of autistic traits in probands were related to:
  - Weaker functional connectivity in visual networks
  - Larger cortical surface area in visual areas
  - Atypical white matter in visual tracts

Findings converged on cortical regions, fiber pathways, and functional connections involved in visual processing

Robust differential gene expression in visual cortex in ASD

Gandal, Nature, 2022

Girault et al., Am. J. Psych., 2023
Summary

• Differences in visual brain development are apparent during infancy and school-age in autism
• Span multiple aspects of brain development, including structure and function
• May be related to genetics

How does this fit with what we know about behavioral features?
Viewing of social scenes is different in autism

Warren & Jones, 2013

Autism Infant

Control Infant

Less time looking at the eyes, missed opportunities for social learning.

Warren & Jones, 2013
Autism is highly heritable, genetics shape how we view the world around us.

Fraternal Twins
50% shared DNA

Identical Twins
100% shared DNA

Constantino et al., 2017
Visual system: the start of a developmental cascade?

Genetic liability for autism

Differences in the visual system

Altered experience-dependent brain development

Missed opportunities for learning

Core social features of autism
Understanding development helps us identify when and how to intervene
**IBIS Early Prediction (IBIS-EP)**

**Goal:** build the framework for MRI prediction of ASD in high-likelihood families, pave the way for presymptomatic intervention.

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**General Population**
- 1 in 32

**Infant Siblings of children with ASD**
- 1 in 5
- 1st-year-of-life MRI

**Extract Relevant Features**
- 6-12m Surface Area
- 6m EA-CSF and Cortical Complexity
- 6m Functional Connectivity

**Model Building**
- Diagnostic Outcomes
- Continuous Scores

**Model Evaluation**
- Accuracy
- PPV, NPV
- Sensitivity, Specificity
- Mean absolute error
- Correlation

**Model Comparisons**
- 1. Brain Only
- 2. Brain + Behavior
- 3. Behavior Only

**Clinical Significance**
- Identify infants at very-high likelihood for ASD (n≈50)
- Assign infants to targeted, early interventions
- Identify specific domains of vulnerability in non-ASD HL infants (n≈125)

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IBIS-EP Data Collection Overview

What it’s like for the family:
- Two-day visit + travel
- MRI scans during sleep
- Receive assessment reports on their child’s development

Recruit & enroll
n = 250
HL infants

MRI & Clinic
6m Visit

MRI & Clinic
12m Visit

MRI & Clinic
24m Visit

Diagnosis
n≈50 ASD
n≈200 No ASD

autism prodrome

emergence of symptoms

Birth
6m
12m
24m
Beyond IBIS-EP: Building a cohort for scientific discovery

IBIS-EP Cohort

- iPSC Models
- Parent-Infant Dyad
- More to come!
- Compare to genetic syndromes
- DEI Barriers
- ELSI
- EEG/ET
- Home Language
Diverse perspectives in ASD research

• Ethical, legal, and social implications of early prediction

• Identifying, addressing barriers to participation for minority families

• Examining sex differences in autism using unbiased sampling
Project Status

• Currently enrolled ~180 families, looking to recruit an additional 70 families
• ~25% recruited from SPARK Research Match – a huge success!

If you are interested in hearing more about our study, visit our website!
Thank you for your help in making our research possible!