Developmental social neuroscience meets public health challenge: A new system of healthcare delivery for infants and toddlers with autism spectrum disorder

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Thank You

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• The National Institute of Mental Health
• The Marcus Foundation
• The JB Whitehead and Woodruff Foundations
• The Children’s Healthcare of Atlanta Foundation
• The Georgia Research Alliance
  as well as
• The National Institute of Child Health and Human Development
• The Autism Science Foundation

Conflicts of Interest

No conflicts of interest associated with this presentation
Marcus Autism Center at a glance

- >5,000 unique patients/yr
- >3,500 in the community
- Tx: set protocols (x visits)
- > 60% on Medicaid
- ~ 35% minorities/under-served

Clinical Assessment/Diagnosis
- Treatment Programs
- Center/Home/School/Community
- Care Coordination Program
- Educational Outreach Program

Autism and other developmental delays are a Public Health Challenge

- Prevalence: 1:68 autism; 1:10 developmental delays
- Autism Societal Cost/Year in the US: $ 136 billion
- Autism Lifetime Cost of Care Per Child: $ 2.4 - 3.6 million
- Importance of early diagnosis and intervention for lifelong outcome and cost of care
- American Academy of Pediatrics recommends screening for autism at 18 and 24 months
- Autism Median age of diagnosis in US: 4-6 to 5.7 years
- % of primary care providers who routinely screen not known
- <20% of children identified before age 3 years

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The Science of Clinical Care

ASD symptoms RESULT from deviations from normative socialization

Sociality: the evolutionary roots of our social brain
Universal Principle: the Platform for Development of Social Brain

Born to Socially Orient

Reciprocal Social Interaction

Neuroplasticity

WHITE MATTER DEVELOPMENT
Preterm (6 months)  Infant (4 weeks)  Adult (25 years)

H-J Park PhD

The co-creation of social experience

Anthropomorphizing
Anthropomorphizing
Attention to Biological Motion


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Two-year-olds with autism orient to non-social contingencies rather than biological motion

Typically-Developing Children

% of Fixation Time

0 20 40 60 80 100

Typically-Developing Children

Developmentally-Delayed Children

Children with Autism

Preference in Autism Only When Clapping Happens

Physical, rather than social, cues guide looking in toddlers with autism

Audiovisual Synchrony Quantification

Change in Motion * Change in Sound = Audiovisual Synchrony
Patterns of visual fixation to approaching caregiver

How do 2-year-olds with autism watch the face of a caregiver?

Watching a Face…
But Seeing Physical Contingencies?

Looking at Eyes and Mouth As a Function of Audiovisual Synchrony
Social Interaction is the Platform for Brain Development

Brain size doubles in the 1st year of a baby's life, synaptic density quadruples.

(Gilmore et al, 2007; Pfefferbaum et al, 1994; Huttenlocher, 1979; Petanjek et al, 2011)
Derivation of Attentional Funnel
The majority of typically-developing 2-year-olds fixate on the same locations, at the same moments, during 80% of viewing time.
The accrual of missed opportunities for social learning

Divergence Expected by Chance (permutation testing)

ASD vs. TD
p < .001

TD, N=44
ASD, N=22

Scenes of Social Action

Toddlers with Autism

Scenes of Social Interaction

Toddlers with Autism

Toddlers with Autism

Toddlers with Autism

Toddlers with Autism
Assessing Presence of ASD

Quantitative Indices for Assessing Presence of ASD

Presence of ASD: Diagnostic Accuracy

Entire Sample

Training

Testing

Device

Reference

N=326
N=218 training
N=108 testing

Empirical ROC curve
Fitted ROC curve
+/- 95% CI

All ages - external validation

All ages - training

Device

Reference

Time 1

Time 2

Probability of looking at the same locations at the same times as typical control children is significantly correlated with levels of autistic social disability, both contemporaneously and 1.5 years after initial testing.
Quantitative Indices for Assessing Severity of ASD

Translational Opportunities

- High-throughput, low-cost, deployment of universal screening in the community
- Early detection, early intervention, optimal outcome
- Prevention or attenuation of intellectual disability in ASD

Severity of ASD: Prognostic Indicators

Public Health Opportunities

- Support a system that does not have sufficient expert clinicians
- A new, promising view of autism, with universal design implications
- Genetic influence informs modality of early treatment
- Reduce the child, family, health, education, and societal costs of autism
Objectifying and quantifying diagnosis in toddlers: community-viable proxies

- High-throughput, low-cost, deployment of universal screening in the community
- Objective, quantitative measures of risk
- Early detection, early intervention, optimal outcome
- Prevention or attenuation of intellectual disability in ASD

Quantitative Measures of Social Disability

From High-Impact Publication to FDA-registered Clinical Trial of Diagnostic

- Site selection
  - 7 sites confirmed
    - Marcus
    - Seattle Children’s
    - Cincinnati Children’s
    - Southwest Regional Autism Center (Phoenix)
    - UC-San Francisco
    - University of Vermont
    - TREAT Center Toronto

Intended Indication for Use

- The Social Developmental Testing Device is a medical device designed to measure visual attention to social information in the environment relative to normative, age-specific benchmarks.
- These measurements assess
  - presence (primary efficacy outcome) &
  - severity (secondary efficacy outcome) of Autism Spectrum Disorder (ASD) in 16- to 30-month-old children.
A Bioethical Imperative: Access to Early Treatment - Promoting Social Engagement

Reciprocal Social Interaction

New science informing modality of treatment - Genetic influences over social visual engagement

Typically Developing 5-month old baby

5-month-old baby later diagnosed with ASD

How to link these quantifications of behavior to the genetic bases of autism?

Measuring the genetic structure of social visual engagement

Eye tracking assay is under tight genetic control

N=250 TD toddlers, including 166 epidemiologically-ascertained twins, 82 MZ & 84 DZ

Age: 21.3 months (4.26)

Twin-Twin Concordance

MZ ICC: 0.91 (0.85-0.95)

DZ ICC: 0.35 (0.07-0.59)

Non-sibling pair: 0.16 (0.00-0.44)
Concordance in social visual engagement as a function of zygosity.

MZ concordance of looking behavior at timescales of milliseconds

When watching complex social scenes

MZ twins are more likely than DZ twin
- to shift their eyes at the same moment
- in the same direction
- onto the same targets

They are creating their social world of experiences.
The markers of social visual engagement that are most highly heritable...

...are also those that most clearly distinguish typically-developing children from those with autism.
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From reducing age of diagnosis to improving access to early intervention

(National Research Council, 2001)

...so how do we achieve 25 hours per week in which the child is engaged **actively** and **productively** in meaningful activities?

*Less than 20% of children who will need special services in school in the US are identified before the age of 3 years.*

high **Heritability** (eye- & mouth-looking)

+ high **Probability** (shifting eyes at same moments, in same directions, towards same content)

= profound influence on human biological niche construction
Augmenting Access to Early Treatment

Family

Primary Care Physician

Early Intervention Provider

Amy Wetherby, PhD

Jennifer Stapel-Wax, PsyD

Collection of Tools

About Autism
Early Intervention Providers
Primary Care Physicians
Family Collection

Bridging the Gap Between Science and Community Practice

Autism Navigator™ increases the capacity of healthcare and early intervention providers, educators, and families to improve outcomes of children and youth with autism spectrum disorder (ASD).

OUR PARTNERS

Parent-Delivered Early Social Interaction

Wetherby et al., 2014
Treating deviations from normative social engagement: Parent-Delivered Social Interaction

**Pediatrics**

Parent-Implemented Social Intervention for Toddlers With Autism: An RCT

**Goals for Early Treatment:**
Every waking hour in the home and in the community

**Child Behaviors**

**ACTIVE ENGAGEMENT**
1. Emotional Regulation
2. Productivity
3. Social Connectedness
4. Gaze to Face
5. Response to Verbal
6. Directed
7. Flexibility
8. Generative Ideas

**Parent Behaviors**

**TRANSACTIONAL SUPPORTS**
1. Participation & Role
2. Make Activity
3. Follow Child’s Attention
4. Promote Initiations
5. Balance of Turns
6. Support Comprehension
7. Modeling
8. Expectations &

**Everyday Activities**

| Play with Toys | Play with People |
| Blocks, Puzzles, Band box, Playdough, Cars and Trucks, Ball Games, Baby Dolls | Social Games like Peek-a-boo, Rough and Tumble, Songs & Rhymes |

| Meals and Snacks | Caregiving |
| Preparation, Eating, Cleanup | Dressing, Diaper Change, Bath, Washing Hands, Brushing Teeth |

**Book Sharing**

**Family Chores**

**Teaching Strategies & Supports to Promote Active Engagement**

**Supports for better skills**
- Model and expand language and play skills
- Extend activity, child’s roles, & transitions
- Balance demands and supports

**Supports for social reciprocity**
- Natural reinforcers
- Waiting for initiation and balance of turns
- Clear message to ensure comprehension

**Supports for a common agenda**
- Positioning
- Follow child’s attentional focus
- Motivating activity with clear roles & turns
Social Interaction is the Platform for Brain Development

“Our brains become who we are.” (J LeDoux)
Brain structure and function are physical instantiations of lived experience.
Neonates preferentially orient towards stimuli that...

More Preferred

Less Preferred

...sound like caregivers.
...smell like caregivers.

Macfarlane, 1975.


Marcus Autism Center
Neonates preferentially orient towards stimuli that...

- **sound** like caregivers.
- **smell** like caregivers.
- **move** like caregivers.
- **look** like caregivers.

Valenza, Simion, Casali, & Umiltà, 1996.
Farroni et al, 2005.

Typically-Developing 5-Month-Old

- **sound** like caregivers.
- **smell** like caregivers.
- **move** like caregivers.
- **look** like caregivers.

Attention to eyes is present but in decline in 2–6-month-old infants later diagnosed with autism

Warren Jones1,2,3 & Ami Klin1,2,3

In typical development, the processes of normative social interaction are highly conserved phylogenetically16 and lay the foundation for iterative specialization during development17. However, in infancy, these processes may become dysregulated18. Early-emerging normative processes may reveal disruptions in ASD at a very young age19,20.

Deficits in eye contact have been a hallmark of autism1,2 since the condition's initial description3. They are cited widely as a diagnostic criterion for autism spectrum disorders (ASDs) and are among the most highly heritable of psychiatric conditions7.

However, the genetic heterogeneity of ASD—with estimates suggesting as many as three- to five-hundred distinct genes impacting aetiology8—poses a stark challenge for understanding the biology of the condition:

- In the ASD group, we constrained current analyses to males only, 11 of whom had a younger female sibling who was typically developing (all from the low-risk cohort).
- Of the high-risk infants, 12 met criteria for ASD20 (10 males, 2 females, TD eyes 71.25 (27.66) min, ASD eyes 15.74, t = 18.02, P < 0.001, by functional analysis of variance (functional ANOVA)21).

The decrease in the duration of eye fixation on faces12,13 is a result of a divergence from typical development that may begin before the age of three months. In this way, a decreasing trend in eye fixation might be diminished from birth onwards2,3,17.

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Eye-Looking in Typically-Developing Infants and Infants Later Diagnosed with ASD

This decline in eye fixation—rather than outright absence—offers a hypothesis: in the first months of life, this basic mechanism of social interaction may be intact but a divergence from typical development is shared. In this way, the early-emerging normative processes may reveal disruptions in ASD at a very young age19,20.

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First Replication Cohort

TD eyes
ASD1 eyes
ASD2 eyes

Growth Charts

Quantifying Disruption of Early-Emerging, Highly-Conserved Mechanisms of Social Adaptive Action

Our ultimate goal

To make autism an issue of diversity, not of disability