Bringing science to the community: A new system of healthcare delivery for infants & toddlers with autism spectrum disorders

Ami Klin, PhD
Director, Marcus Autism Center, Children’s Healthcare of Atlanta
GRA Eminent Scholar Professor & Chief, Division of Autism, Department of Pediatrics, Emory University School of Medicine
Emory Center for Translational Social Neuroscience
Thank You

• The children and families for their participation
• Warren Jones, my colleagues & students
• The National Institute of Mental Health
• The National Institute of Child Health and Human Development
• The Marcus Foundation
• The Whitehead Foundation
• The Woodruff Foundation
• The Simons Foundation
• The Autism Science Foundation
• Autism Speaks
Conflicts of Interest

No conflicts of interest associated with this presentation
Marcus Autism Center at a glance:
Strategic Plan 2014-2019

- Translation
- Impact
- Clinical Resources

• Science
• Faculty Advancement
• Research Resources

The Science of Clinical Care
Research Enterprise
Strategic Plan 2014-2019

- CAUSES
- TREATMENT
- COMMUNITY-VIABLE SOLUTIONS
- “VALUE PROPOSITION”

**RESEARCH INITIATIVES**

**RESEARCH INFRASTRUCTURE**

- 13 RESEARCH CORES
- 9 INTERNAL, 4 COLLABORATIVE
- RESEARCH ADMINISTRATION
- INFORMATICS
- DATA MANAGEMENT & ANALYSIS

**Concept**

- Diagnosis
- Social Neuroscience
- Neurobiology
- Genetics
- Animal Models
- Psychopharmacology

Strategy for Research Enterprise
Marcus Autism Center,
An NIH Autism Center of Excellence

Social Visual Engagement in Infants (0 to 36 months)

Social Vocal Engagement in Infants (0 to 36 months)

Treatment in Infants & Toddlers (beginning at 12 months)

Social Visual Engagement & Brain Development in a Model System

$ 8.8 m total
Societal Impact of Autism

- Prevalence: 1 : 68  [1:42 in boys]
- Community Disparities
- Societal Cost/Year in the US: $ 136 billion
- Lifetime Cost of Care Per Child: $ 1.4 to 2.4 million

* CDC, 2014; Mandell et al., 2013; 2014*
Challenges and Opportunities: Reducing Age of Diagnosis & Improving Access to Care

- Brain disorder of genetic origins
- Adverse outcomes can be prevented
- Importance of early diagnosis and intervention for lifelong outcome and cost of care
- American Academy of Pediatrics
  - Screening (18 and 24 months), but still low uptake
- Median age of diagnosis in US: 4-6 to 5.7 years
- No Community-viable system of care
- Reimbursement systems NOT in place
First 2 years of life

Jones et al. (2008). Arch Gen Psy, 65(8), 946-54.
Our mission is to transform autism diagnosis and treatment to alter the life course of kids with autism.
Redefining Autism: Preventing costly impact
Developmental Trajectories

Developing Expertise about the Social World

Developing Expertise about the Physical World
Autism Disrupts the Platform for Brain Development

The Brain Becomes Who We Are....

MH Johnson PhD

JE LeDoux PhD

H-J Park PhD
Attention to Biological Motion

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

Ami Klin¹, David J. Lin¹†, Phillip Gorrindo¹†, Gordon Ramsay¹,² & Warren Jones¹,³

Typically developing human infants preferentially attend to biological motion within the first days of life. This ability is highly conserved across species and is believed to be critical for filial attachment and for detection of predators. The neural underpinnings of biological motion perception are overlapping with brain regions involved in perception of basic social signals such as facial expression and gaze direction, and preferential attention to biological motion is seen as a precursor to the capacity for attributing intentions to others. However, in a serendipitous observation, we recently found that an infant with autism failed to recognize point-light displays of biological motion, but was instead highly sensitive to the presence of a non-social, physical motion that occurred within the visual display. This conspecific, looking at others to entreat or avoid interaction, learning by imitation, or directing preferential attention to cues that build on biological motion (such as facial expression and gaze direction).

Notably, many of the same behaviours have also been shown as deficits in children with autism: deficits in social interaction, diminished eye contact and reduced looking at others, problems with imitation, deficits in recognizing facial expressions, and difficulties following another’s gaze. Autism is a lifelong, highly prevalent, and strongly genetic disorder defined by impairments in social and communicative functioning and by pronounced behavioural rigidities. Although the preponderance of evidence points to prenatal factors instantiated in infancy, knowledge of the first two years of life in autism remains underexplored.
Two-year-olds with autism do not exhibit preferential attention to biological motion

But during ‘Pat-a-Cake’…

• A “pat-a-cake” finding led to the hypothesis that children’s visual behavior was being guided by physical, not social contingencies.
Audiovisual Synchrony Quantification

Change in Motion \times \text{Change in Sound} = \text{Audiovisual Synchrony}
audiovisual synchrony, playback at 1/2 speed
Cumulative Audiovisual Synchrony in Point-Light Animations

Relative Audio-Visual Synchrony = Normalized Peak Difference

Clap Location

Max Synchrony

No Synchrony

Pat-a-cake

Feeding
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 properties?
Fixation on Mouth and Eyes as a Function of Audiovisual Synchrony

Jennings Xu

ASD

TD

<table>
<thead>
<tr>
<th></th>
<th>R²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>0.296</td>
<td>0.016</td>
</tr>
<tr>
<td>Mouth</td>
<td>0.302</td>
<td>0.015</td>
</tr>
<tr>
<td>Both</td>
<td>0.685</td>
<td>&lt;1.5e-10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>R²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>0.111</td>
<td>0.164</td>
</tr>
<tr>
<td>Mouth</td>
<td>0.161</td>
<td>0.089</td>
</tr>
<tr>
<td>Both</td>
<td>0.0003</td>
<td>0.919</td>
</tr>
</tbody>
</table>
Growth Charts of Social Engagement
Strategic Plan

Psychopharmacology & Clinical Trials

Behavioral Neuroscience

Animal Models

Neurobiology

Diagnosis & Treatment

Genetics

Marcus Autism Center
Marcus Autism Center, An NIH Autism Center of Excellence

Social Visual Engagement in Infants (0 to 36 months)

Social Vocal Engagement in Infants (0 to 36 months)

Treatment in Infants & Toddlers (beginning at 12 months)

Social Visual Engagement & Brain Development in a Model System
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

Deficits in eye contact have been a hallmark of autism¹·² since the condition's initial description³. They are cited widely as a diagnostic feature⁴ and figure prominently in clinical instruments⁵; however, the early onset of these deficits has not been known. Here we show in a prospective longitudinal study that infants later diagnosed with autism spectrum disorders (ASDs) exhibit mean decline in eye fixation from 2 to 6 months of age, a pattern not observed in infants who do not develop ASD. These observations mark the earliest known indicators of social disability in infancy, but also falsify a prior hypothesis: in the first months of life, this basic mechanism of social adaptive action—eye looking—is not immediately diminished in infants later diagnosed with ASD; instead, eye looking appears to begin at normative levels prior to decline. The timing of decline highlights a narrow developmental window and reveals the early derailment of processes that would otherwise have a key role in canalizing typical social development. Finally, the observation of this decline in eye fixation—rather than outright absence—offers a promising opportunity for early intervention that could build on the apparent preservation of mechanisms subserving reflexive initial orientation towards the eyes.

Autism Spectrum Disorders (ASDs) affect approximately 1 in every 88 individuals⁶. These disorders are lifelong, believed to be congenital, and are among the most highly heritable of psychiatric conditions⁷. However, the genetic heterogeneity of ASD—with estimates suggesting

Data were collected at 10 timepoints: at months 2, 3, 4, 5, 6, 9, 12, 15, 18 and 24. We studied 110 infants, enrolled as risk-based cohorts: n = 59 at high-risk for ASD (full siblings of a child with ASD⁸) and n = 51 at low-risk (without first-, second-, or third-degree relatives with ASD). Diagnostic status was ascertained at 36 months. For details on study design, clinical characterization of participants, and experimental procedures, see Methods and Supplementary Information.

Of the high-risk infants, 12 met criteria for ASD⁹ (10 males, 2 females), indicating a conversion rate of 20.3%⁹. One child from the low-risk cohort was also diagnosed with ASD. Given the small number of girls in the ASD group, we constrained current analyses to males only, 11 ASD (10 from the high-risk cohort and 1 from the low-risk), and 25 typically developing (all from the low-risk cohort).

At each testing session, infants viewed scenes of naturalistic caregiver interaction (Fig. 1a, b) while their visual scanning was measured with eye-tracking equipment. The 36 typically developing and ASD children viewed 2,384 trials of video scenes.

Control comparisons tested for between-group differences in attention to task and completion of procedures. There were no between-group differences in duration of data collected per child (typically developing = 71.25 (27.66) min, ASD = 64.16 (30.77) min, data given as mean (standard deviation), with t₄₅ = 0.685, P = 0.498; two-sample t-test with 34 degrees of freedom, equal variances); or in the distribution of ages at which successful data collection occurred (k = 0.0759, P = 0.906, two-sample Kolmogorov-Smirnov).
Baby’s Gaze May Signal Autism, a Study Finds
By Pam Belluck

Updated, 11:15 a.m. | When and how long a baby looks at other people’s eyes offers the earliest behavioral signs to date of whether a child is likely to develop autism, scientists are reporting.

In a study published Wednesday, researchers using eye-tracking technology found that children who were found to have autism at age 3 looked less at people’s eyes when they were babies than children who did not develop autism. But contrary to what the researchers expected, the

Autism signs 'present in first months' of life
By Helen Briggs
BBC News
Infants
Growth Charts of Social Visual Engagement
(Typically-Developing Children)

Eye Fixation
Children with ASD relative to Typically-Developing Norms

TD, N=25, male, 1637 trials
ASD, N=11, male, 747 trials
Eye Fixation, and Rate of Change in Eye Fixation

Percent fixation vs age (months)

$D_t$ fixation vs age (months)

$D_t$ eyes

Eyes
Eye Fixation, and Rate of Change in Eye Fixation

$F_{1,34} = 11.90, p = .002$

$$D_t$$ fixation:
- TD eyes
- ASD eyes

$$D_t$$:
- TD eyes
- ASD eyes
Children with ASD relative to Typically-Developing Norms

\[ F_{1,34} = 10.60, \ p = .003 \]
Object Fixation
Children with ASD relative to Typically-Developing Norms

$F_{1,34} = 12.08, p = .002$
Figure 3. In children with ASD, growth curves of fixation to eyes during the first 2 years of life are strongly and significantly correlated with outcome measures of symptom severity. Functional Principal Component Analysis (FPCA) was used to extract growth curve components explaining variance in trajectory shape about the population mean.

(A) Population mean for fixation to eyes in children with ASD (red line) plotted with lines indicating direction of individual trajectories having positive principal component one (PC1) scores (line marked by plus signs) or negative PC1 scores (line marked by minus signs).

(B) Correlation of eyes PC1 score (as measure of decline in eye fixation) with ADOS social-affect cluster score at 24 months of age.

(C) Correlation of eyes PC1 score relative to outcome for subsets of the available longitudinal data (2-6 mos vs. outcome at 24 mos; then 2-9 mos; 2-12 mos; etc.). Decline in eye fixation predicts outcome levels at trend levels by 2-9 months ($p = 0.100$), and is statistically significant thereafter ($r = -0.709, p = 0.015$ for 2-12 months).
Growth Charts of Social Engagement to Enable Early Diagnosis

- TD eyes
- ASD eyes

- \( D_t \) TD eyes
- \( D_t \) ASD eyes
Differences Present within the First 6 Months of Life

Figure 4. Developmental differences in visual fixation between 2 and 6 months of age. Boxplots and linear regression lines for eyes fixation (A-C) and mouth fixation (D-F) for typically-developing infants (in blue) and infants with autism (in red). Boxplot vertical lines and lightly shaded regions extend from minimum to maximum values in the data; boxplot boxes and more darkly shaded regions span the 25th to 75th percentiles of the data. When fitted with linear regressions (black lines), data for both ASD and TD groups show significant correlations with chronological age, but these correlations differ significantly between-groups for eyes and body fixations. (G-H) Bivariate correlation functions for eyes fixation in typically-developing infants (G) and infants with autism (H). Note the steep decline in month-to-month correlation in eyes fixation in infants with ASD: at 3 and 4 months of age, there is no longer any positive correlation in month-to-month eyes fixation, and the correlation becomes negative by months 5 and 6 and more negative by subsequent timepoints, indicating increased likelihood of declining eyes fixation. This can be contrasted with the eyes fixation correlation function for TD infants, which remains positively correlated throughout the first 2 years.
Internal Validation

eyes

body

Known Dx LOOCV Known Dx LOOCV

Fixation Time (%)

False positive rate
True positive rate

Internal Validation

eyes

body

Known Dx LOOCV Known Dx LOOCV

Fixation Time (%)

False positive rate
True positive rate
External Validation

![Graph showing change in body fixation and eye fixation for TD and ASD with 6 independent test cases.](image-url)
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
Screening devices in primary care offices?
Developmental Instantiation of a Spectrum of Social Disability: A GLIMPSE INTO SIBLING RESILIENCE (eye fixation)

Outcome x Time:

\[ F = 6.95, \quad p < 0.001 \]
New Scientific Hypotheses

- Genetics: gene expression and methylation studies
- Gene x Environment: alleles more plastic to environmental influences?
- Targeting onset of treatment at these “INFLECTIONABLE” points?
- WILLIAMS SYNDROME
Eye Fixation

Are we wrong? Not one but in fact two curves?

- Reflexive
- Experience Expectant
- Subcortically controlled

- Interactional, Reward-Driven
- Experience Dependent
- Cortically controlled

Eye Fixation Mean

Percent fixation vs. Age (months)

TD eyes
ASD eyes
New Scientific Hypotheses

- Human Developmental Neuroimaging
- Specific developmental timing of cortical-subcortical connectivity
- Non-Human Primate Developmental Neuroimaging
Toddlers
Autism Disrupts the Platform for Brain Development

The Brain Becomes Who We Are....

MH Johnson PhD

JE LeDoux PhD

H-J Park PhD
Improving Access to Early Intervention ....from 5 years to 2 years

(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 with Autism in the US are identified before the age of 3 years”
Augmenting Access to Early Treatment

Family

Early Intervention Provider

Primary Care Physician

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
the Community: Families, Pediatricians, Early Intervention Providers

Course Introduction

Unit 1: Improving Early Detection

Unit 2: Collaborating with Families

Unit 3: Developmental Perspective

Unit 4: Evidence-based Intervention Strategies

Unit 5: Prioritizing Intervention Outcomes

Unit 1: Improving Early Detection

Importance of early detection, defining the core deficits of ASD, finding current information on prevalence and etiology, identifying early red flags of ASD in infants and toddlers

Resume Unit
Everyday Activities

- **Play with Toys**
  - Blocks, Puzzles, Sand box, Playdough, Cars and Trucks, Ball Games, Baby Dolls

- **Play with People**
  - Social Games like Peek-a-boo, Rough and Tumble, Songs & Rhymes

- **Meals and Snacks**
  - Preparation, Eating, Cleanup

- **Caregiving**
  - Dressing, Diaper Change, Bath, Washing Hands, Brushing Teeth

- **Book Sharing**

- **Family Chores**
  - Mailbox, Laundry, Care for Pets, Plants
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
Goals for Early Treatment:

Every wakeful hour in the home and in the community

<table>
<thead>
<tr>
<th>Child Behaviors</th>
<th>Parent Behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACTIVE ENGAGEMENT</strong></td>
<td><strong>TRANSACTIONAL SUPPORTS</strong></td>
</tr>
<tr>
<td>1. Emotional Regulation</td>
<td>1. Participation &amp; Role</td>
</tr>
<tr>
<td>2. Productivity</td>
<td>2. Make Activity Predictable</td>
</tr>
<tr>
<td>3. Social Connectedness</td>
<td>3. Follow Child’s Attention</td>
</tr>
<tr>
<td>4. Gaze to Face</td>
<td>4. Promote Initiations</td>
</tr>
<tr>
<td>5. Response to Verbal Bids</td>
<td>5. Balance of Turns</td>
</tr>
<tr>
<td>7. Flexibility</td>
<td>7. Modeling</td>
</tr>
<tr>
<td>8. Generative Ideas</td>
<td>8. Expectations &amp; Demands</td>
</tr>
</tbody>
</table>
Our ultimate goal

To make autism an issue of diversity, not of disability