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

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Emory Center for Translational Social Neuroscience
Thank You

- The children and families who support our clinical and research activities
- Warren Jones and many wonderful colleagues and students
- 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 Mental Health
- The National Institute of Child Health and Human Development
- The National Science Foundation
- The Simons Foundation
- The Autism Science Foundation
- Autism Speaks
- United Way
- Cox Foundation
Conflicts of Interest

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

- >5,700 unique patients/yr
- Tx: set protocols (x visits)
- > 65% on Medicaid
- ~ 40% minorities/under-served

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

RESEARCH INITIATIVES
- CAUSES
- TREATMENT
- COMMUNITY-VIABLE SOLUTIONS
- IMPLEMENTATION SCIENCE

The Science of Clinical Care
Research Enterprise

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

Strategy for Research Enterprise

Concept

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

RESEARCH INITIATIVES

- Diagnosis & Treatment
- Clinical Trials
- Animal Models
- Genetics
- Neurobiology
- Social Neuroscience
Autism as a Public Health Challenge

• Prevalence: 1 : 68  [1:42 in boys]
• Community Disparities (dx; access)
• Societal Cost/Year in the US: $ 136 billion
• Lifetime Cost of Care Per Child: $ 2.4 million
• Despite strong genetic bases, diagnosis is behavioral, reference standards excellent (ADI-R/ADOS/expert clinician)
• Majority of autism diagnoses in US outside academic medical centers
  ✴ usage of ADI-R and ADOS in fewer than 0.1% and 2.1%, respectively
  ✴ questionnaires/checklists in 30%

CDC, 2014; Peacock et al., 2012; Cidav et al., 2012; Mandell et al., 2013; 2014; Wang et al., 2013; Buescher et al., 2014; Wiggins et al., 2006
Challenges and Opportunities: Reducing Age of Diagnosis & Improving Access to Care

- Brain disorder of genetic origins
- Adverse outcomes can be attenuated
- 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
- 8% of primary care providers routinely screen for ASD
- Median age of diagnosis in US: 4-6 to 5.7 years
- Later still in disadvantaged communities
- No Community-viable system of care
- Reimbursement systems NOT in place

Johnson & Myers, 2007; Dosreis et al., 2006; Heidgerken et al., 2005; Honigfeld et al., 2012; Shattuck et al., 2009; Mandell et al., 2005; 2009
The importance of early identification & treatment: altering the life course of children

FUTURE Age of Diagnosis (Phase II)  
FUTURE Age of Diagnosis (Phase I)  
Average Age of Diagnosis TODAY

Window of Opportunity to Change Autism

ALTERING AUTISM COURSE  
ATTENUATING AUTISM  
PROMOTING LANGUAGE  
REDUCING ASSOCIATED DISABILITIES (language, intellectual, behavioral, medical)

Development (Age)

Positive Outcome

FUTURE
Independent, College, Working, Relationships

BEST SCENARIO
NOW  
Medium level of Supports

TYPICAL NOW
High level of Supports

1 yr  
2 yrs  
3 yrs  
4 yrs  
5 yrs  
6 yrs +
First 2 years of life

No Genetic Determinism

No Brain Determinism

JE LeDoux PhD

Autism Disrupts the Platform for Brain Development

Born to Socially Orient

Reciprocal Social Interaction

Neuroplasticity

WHITE MATTER DEVELOPMENT

Preterm (6 months)  Infant (4 weeks)  Adult (25 years)

H-J Park PhD
Autism:

Unlike in typical development, predispositions to orient to, and engage with people are absent or significantly reduced.
Developmental Trajectories

Developing expertise about the Social World

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

Born to Socially Orient

Reciprocal Social Interaction

Neuroplasticity

WHITE MATTER DEVELOPMENT

Preterm (6month)  Infant (4 weeks)  Adult (25 years)
Attention to Biological Motion
Attention to Biological Motion

Toddler with Autism, 15 months

% Looking Time

INV | UP

[Bar chart with data points]
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 life⁴. This ability is highly conserved across species⁵,⁶ and is believed to be critical for filial attachment and for detection of predators⁷. 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 direction⁸, and preferential attention to biological motion is seen as a precursor to the capacity for attributing intentions to others⁹. However, in a serendipitous observation⁰, 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 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 direction¹). 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 gaze¹². Autism is a lifelong, highly prevalent, and strongly genetic disorder defined by impairments in social and communicative functioning and by pronounced behavioural rigidities¹¹. Although the preponderance of evidence points to prenatal factors instantiated in infancy, knowledge of the first two years of life in
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 * Change in Sound = Audiovisual Synchrony
audiovisual synchrony, playback at 1/2 speed
Cumulative Audiovisual Synchrony in Point-Light Animations

Pat-a-cake

Feeding

Relative Audio-Visual Synchrony = Normalized Peak Difference

Clap Location

Max Synchrony

No Synchrony
Patterns of visual fixation to approaching caregiver

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

Fixation on Mouth and Eyes as a Function of Audiovisual Synchrony

Jennings Xu

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<tr>
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<tr>
<td>Both</td>
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<td>&lt;1.5e-10</td>
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<td>Both</td>
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Growth Charts of Social Engagement
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 autism since the condition’s initial description. They are cited widely as a diagnostic feature and figure prominently in clinical instruments; 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 canalisizing 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 individuals. These disorders are lifelong, believed to be congenital, and are among the most highly heritable of psychiatric conditions. However, the genetic heterogeneity of ASD—with estimates suggesting

Data were collected at 10 time points 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 ASD) 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 ASD (10 males, 2 females), indicating a conversion rate of 20.3%. 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 t₃₄ = 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 = 0.45; Kolmogorov–Smirnov)
Baby’s Gaze May Signal Autism, a Study Finds
By PAMELLA M.

Updated, 6:51 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. That contrasts to what the researchers expected, the

Autism signs 'present in first months' of life
By Helen Briggs
BBC News

SCIENTIFIC AMERICAN
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

Mean and 95% CI for percent fixation by age (months) and $D_t$ fixation by age (months) for eyes.
Eye Fixation, and Rate of Change in Eye Fixation

\[ F_{1,34} = 11.90, p = .002 \]
Body Fixation
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

$$F_{1,34} = 12.08, p = 0.002$$
Decline in Eye Fixation Predicts Severity of Outcome

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 (with r = -0.709, p = 0.015 for 2-12 months).

<table>
<thead>
<tr>
<th>Age Range</th>
<th>r</th>
<th>p</th>
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<tr>
<td>2-6 mos.</td>
<td>-0.415</td>
<td>0.204</td>
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<tr>
<td>2-9 mos.</td>
<td>-0.521</td>
<td>0.100</td>
</tr>
<tr>
<td>2-12 mos.</td>
<td>-0.708</td>
<td>0.015</td>
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<tr>
<td>2-15 mos.</td>
<td>-0.659</td>
<td>0.027</td>
</tr>
<tr>
<td>2-18 mos.</td>
<td>-0.684</td>
<td>0.020</td>
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</tbody>
</table>

Mean ASD fixation on eyes and direction of individual trajectories with positive and negative PC1 scores.
Growth Charts of Social Engagement to Enable Early Diagnosis

- TD eyes
- ASD eyes

**Mean and 95% CI**

**$D_t$ 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.

(B-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.

eyes

body
Internal Validation

eyes

body

Known Dx    LOOCV    Known Dx    LOOCV

False positive rate
True positive rate

E F G H
I J K L

Internal Validation
External Validation

6 Independent Test Cases
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
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

percent fixation vs. age (months)

TD eyes
ASD eyes

mean
95% CI
A Bioethical Imperative: Access to Early Treatment - Promoting Social Engagement

Reciprocal Social Interaction

The Brain Becomes Who We Are....

JE LeDoux PhD
Autism Disrupts the Platform for Brain Development

The Brain Becomes Who We Are....

MH Johnson PhD

JE LeDoux PhD

H-J Park PhD
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.”
Augmenting Access to Early Treatment

Family

Early Intervention Provider

Primary Care Physician

Amy Wetherby, PhD

Jennifer Stapel-Wax, PsyD
Treating deviations from normative social engagement: Parent-Delivered Early Social Interaction

Wetherby et al., 2014
Parent-Implemented Social Intervention for Toddlers With Autism: An RCT

WHAT’S KNOWN ON THIS SUBJECT: Randomized controlled trials (RCTs) of intensive clinician-implemented interventions have demonstrated significant improvements in outcomes of toddlers and preschool children with autism spectrum disorder. RCTs of parent-implemented interventions have demonstrated improvements in parent skills, but generally they have not demonstrated effects on children’s outcomes.

WHAT THIS STUDY ADDS: This RCT found significantly greater improvements with individual home coaching on child outcome measures of social communication, adaptive behavior, and developmental level. These findings support the efficacy of a parent-implemented intervention using little professional time, which increases potential community viability.

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Departments of 1Clinical Sciences, 2Autism Institute, 3School of Communication Sciences and Disorders, and 5Psychology, Florida State University, Tallahassee, Florida; and 6Department of Psychiatry, Weill Cornell Medical College, New York, New York

KEY WORDS
autism, early intervention, toddlers, parent-implemented, outcomes

ABBREVIATIONS
ADOS—Autism Diagnostic Observation Schedule
ASD—autism spectrum disorder
CSBS—Communication and Symbolic Behavior Scales
EI—early intervention
FSI—Frederick Sound bender Index
## Everyday Activities

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<th>Play with Toys</th>
<th>Play with People</th>
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<td>Blocks, Puzzles, Sand box, Playdough, Cars and Trucks, Ball Games, Baby Dolls</td>
<td>Social Games like Peek-a-boo, Rough and Tumble, Songs &amp; Rhymes</td>
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<tr>
<td><strong>Meals and Snacks</strong></td>
<td><strong>Caregiving</strong></td>
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<td>Preparation, Eating, Cleanup</td>
<td>Dressing, Diaper Change, Bath, Washing Hands, Brushing Teeth</td>
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<td><strong>Book Sharing</strong></td>
<td><strong>Family Chores</strong></td>
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<td></td>
<td>Mailbox, Laundry, Care for Pets, Plants</td>
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### Child Behaviors

**ACTIVE ENGAGEMENT**

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

### Parent Behaviors

**TRANSACTIONAL SUPPORTS**

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

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**Goals for Early Treatment:**

*Every waking hour in the home and in the community*
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
Our ultimate goal

To make autism an issue of diversity, not of disability