An attempt at redefining autism for the biological sciences: Implications and translational opportunities

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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
Challenges and Opportunities

• Brain disorder of genetic origins
• Importance of early diagnosis and intervention for lifelong outcome and cost of care
• American Academy of Pediatrics
  – Screening (18 and 24 months)
• Median age of diagnosis in US: 4-6 to 5.7 years
• Missed opportunity for attenuating, maybe preventing the burdens associated with autism

• Community Disparities
• No Community-viable system of care
• Reimbursement systems NOT in place
  – Dx services under reimbursed
  – Tx services un-reimbursed
The Realities of Autism: 
...Changing the nature of autism for children tomorrow

FUTURE by 2017  
FUTURE by 2015

Average Age of Diagnosis: 2013

Window of Opportunity to Change Autism

PREVENT AUTISM  ALLEVIATE AUTISM  PROMOTE LANGUAGE  REDUCE ASSOCIATED DISABILITIES (language, intellectual, behavioral, medical)

Development (Age)

1 yr  2 yrs  3 yrs  4 yrs  5 yrs  6 yrs +

Positive Outcome

FUTURE
Independent, College, Working, Relationships

BEST SCENARIO NOW
Capable of Independence, Medium level of Supports

TYPICAL NOW
Disabled, High level of Supports

Marcus Autism Center

NIH Autism Center of Excellence
The Science of Clinical Care

- The largest and most comprehensive center for CLINICAL CARE in the country (5,712 unique patients seen in 2013; ~ 8 fold larger than leading centers)
  - Clinical Assessment, Medical Care & Treatment Programs
  - Care Coordination and Advocacy
  - Community and Educational Outreach

- Among the most comprehensive hubs of CLINICAL SCIENCE in the country
  - NIH Autism Center of Excellence (one of only 3)
  - genes, neurobiology, brain & behavior, animal modeling
  - behavioral and medical treatments
  - empowerment of families and communities
First 2 years of life

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

Not significantly different from chance, \( p > .05 \)

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

Ami Klin\textsuperscript{1}, David J. Lin\textsuperscript{1}\textsuperscript{†}, Phillip Gorrindo\textsuperscript{1}\textsuperscript{†}, Gordon Ramsay\textsuperscript{1,2} & Warren Jones\textsuperscript{1,3}

Typically developing human infants preferentially attend to biological motion within the first days of life\textsuperscript{1}. This ability is highly conserved across species\textsuperscript{2,3} and is believed to be critical for filial attachment and for detection of predators\textsuperscript{4}. 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\textsuperscript{5}, and preferential attention to biological motion is seen as a precursor to the capacity for attributing intentions to others\textsuperscript{6}. However, in a serendipitous observation\textsuperscript{7}, 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 action target presented within the same 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\textsuperscript{8}).

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\textsuperscript{9}. Autism is a lifelong, highly prevalent, and strongly genetic disorder defined by impairments in social and communicative functioning and by pronounced behavioural rigidities\textsuperscript{10,11}. Although the preponderance of evidence points to prenatal factors instantiated in infancy, knowledge of the first two years of life in autism remains limited. As new genetic and imaging techniques allow us to better understand the developmental trajectory of autism, we will be able to design more effective interventions during critical periods.
A “pat-a-cake” finding led to the hypothesis that children’s visual behavior was being guided by physical, not social contingencies.
Patterns of visual fixation to approaching caregiver

Watching a face ... but seeing physical properties?
Fixation on Mouth and Eyes as a Function of Audiovisual Synchrony

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The Brain Becomes Who We Are....

JE LeDoux PhD
Growth Charts of Social Engagement
Strategic Plan

Diagnosis & Treatment

Psychopharmacology & Clinical Trials

Behavioral Neuroscience

Animal Models

Neurobiology

Genetics
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 Jones, A. Klin

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 within the first 2 to 6 months of life, 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 seems 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 121 children, making it the second most common neurodevelopmental condition following intellectual disability. However, the precise timing of the onset of these deficits is not well understood. While ASDs have been characterized by the absence of eye contact, recent work has suggested that eye contact may occur at some point in the first days of life, but this has not been confirmed by longitudinal studies.

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 cohort: 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 medians (interquartile range) with n = 11 and 25, respectively).
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

age (months)

$D_t$ fixation

$D_t$ eyes

eyes

mean

95% CI
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

$F_{1,34} = 12.08, p = .002$
Growth Charts of Social Engagement to Enable Early Diagnosis

- TD eyes
- ASD eyes

- $D_t$ TD eyes
- $D_t$ ASD eyes

- Mean
- 95% CI

Age (months)

Percent fixation

$D_t$ fixation
Decline in Eye Fixation Predicts Severity of Outcome

A. Fixation Time, Eyes (%) vs Age (in months)

- Mean ASD fixation on eyes
- Direction of individual trajectories with positive PC1 scores
- Direction of individual trajectories with negative PC1 scores

B. Outcome at 24 Months vs PC1 Score

- Linear regression line
- p-value: p = 0.007
Differences Present within the First 6 Months of Life

eyes

body
Internal Validation

eyes

body

Known Dx  LOOCV  Known Dx  LOOCV
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
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
Molecular Genetics

Steve Warren, PhD, FACMG
Mike Zwick, PhD
Jen Mulle, PhD
Peng Jin, PhD
David Cutler, PhD
Eye Fixation
Are we wrong? Not one but in fact two curves?

- Reflexive
- Experience Expectant
- Subcortically controlled

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

<table>
<thead>
<tr>
<th></th>
<th>TD eyes</th>
<th>ASD eyes</th>
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<tr>
<td>percent fixation</td>
<td>mean</td>
<td>95% CI</td>
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<td>age (months)</td>
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<td>3</td>
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<tr>
<td>TD eyes</td>
<td></td>
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<tr>
<td>ASD eyes</td>
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</table>

TD eyes
ASD eyes
New Scientific Hypotheses

• Human Developmental Neuroimaging

• Specific developmental timing of cortical-subcortical connectivity

• Non-Human Primate Developmental Neuroimaging

Longchuan Li, PhD
Sarah Shultz, PhD
Ontogeny & Neural Basis of Social Visual Engagement in Monkeys

Yerkes Field Station, Lawrenceville GA
-> Never separated from mom
-> Remain in social group

Jocelyne Bachevalier, PhD
Xiao Ping Hu, PhD
Lisa Parr, PhD
Ontogeny & Neural Basis of Social Visual Engagement in Monkeys

*In vivo* diffusion MRI data showing major white matter pathways in a 2-week-old *rhesus macaque.*

Jocelyne Bachevalier, PhD

Longchuan Li, PhD
Psychopharmacology & Clinical Trials

• Clinical trials in psychopharmacology, parent training, feeding disorders, severe behavior, skill acquisition

• MAJOR CHALLENGE
• QUANTIFYING Autism
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?
Augmenting Access to Early Treatment

Family

Early Intervention Provider

Primary Care Physician

Amy Wetherby, PhD

Jennifer Stapel-Wax, PsyD
the Community: Families, Pediatricians, Early Intervention Providers

Course Introduction

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

Unit 2: Collaborating with Families

Unit 3: Developmental Perspective

Unit 4: Evidence-based Intervention Strategies

Unit 5: Prioritizing Intervention Outcomes

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Resume Unit
## Everyday Activities

<table>
<thead>
<tr>
<th>Play with Toys</th>
<th>Play with People</th>
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<tbody>
<tr>
<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>
</tr>
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<tr>
<th>Meals and Snacks</th>
<th>Caregiving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation, Eating, Cleanup</td>
<td>Dressing, Diaper Change, Bath, Washing Hands, Brushing Teeth</td>
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<thead>
<tr>
<th>Book Sharing</th>
<th>Family Chores</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mailbox, Laundry, Care for Pets, Plants</td>
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</table>
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 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>
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<tbody>
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<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>
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<tr>
<td>7. Flexibility</td>
<td>7. Modeling</td>
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<tr>
<td>8. Generative Ideas</td>
<td>8. Expectations &amp; Demands</td>
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Our ultimate goal

To make autism
an issue of diversity, not of disability