Developmental social neuroscience meets public health challenge: The next generations of children with autism spectrum disorder

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

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- My wonderful clinical science colleagues, Cheryl Klaiman, Kasia Chawarska, Celine Saulnier and others over the years
- My wonderful colleague investigators, Gordon Ramsay, Sarah Shultz, Longchuan Li, and our wonderful students and trainees over the years

Marcus Autism Center: Addressing the needs of children and families today; building a better future for the next generations

Reciprocal Social Interaction & Early Brain Development

Universal Principle: the Platform for Development of Social Brain

White Matter Development

Neuroplasticity

Preterm (6 months), Infant (6 weeks), Adult (25 years)
Autism:

Unlike in normative development, predispositions to orient to, and engage with people are significantly reduced.

ASD symptoms RESULT from deviations from normative socialization

<table>
<thead>
<tr>
<th>GENETIC LIABILITY</th>
<th>MECHANISMS OF SOCIALIZATION</th>
<th>BEHAVIORAL SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increasingly Refined Social Interaction</td>
<td>Symptom Development</td>
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<td></td>
<td>Tridac Interaction</td>
<td>Symptom Development</td>
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<td></td>
<td>Dyadic Interaction</td>
<td>Symptom Development</td>
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</tbody>
</table>

Attention to Biological Motion

- Toddler with Autism, 15 months:
  - Not significantly different from chance, $p > .05$

Developmental Trajectories

- Developing expertise about the Social World
- Developing expertise about the Physical World
Attention to Biological Motion


Cumulative Audiovisual Synchrony

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

<table>
<thead>
<tr>
<th>Component</th>
<th>F-value</th>
<th>p-value</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>12.87</td>
<td>&lt;0.001</td>
<td>1.56</td>
</tr>
<tr>
<td>Mouth</td>
<td>5.599</td>
<td>&lt;0.006</td>
<td>1.40</td>
</tr>
</tbody>
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**Eye-tracking measures of Social Visual Engagement**


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**Typically-Developing 5-Month-Old**

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Typically-Developing 5-Month-Old

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**Typically-Developing 5-Month-Old**

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The figure shows growth charts for social visual engagement across age in months. The charts compare fixation time percentages and change over time between different groups: typically developing (TD), high-risk ASD1, and high-risk ASD2. The data is collected at 10 time points: months 2, 3, 4, 5, 6, 9, 12, 15, 18, and 24.

First Replication Cohort

The first replication cohort includes 63 TD, 13 ASD2, and 11 ASD1 individuals. The data shows changes in fixation over time (% per month) with mean and 95% CI. The fixation is measured for TD, ASD1, and ASD2 eyes separately.

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

The figure illustrates the decline in attention to eyes from 2 to 6 months in typically developing (TD), ASD1, and ASD2 infants. The data is from a prospective longitudinal study with infants later diagnosed with ASD, and it shows the decline in preferential attention to others' eyes over time. The study uses hierarchical linear modelling (HLM) to analyze the data.

Eye Fixation in the first 6 months of life

The figure shows eye fixation in the first 6 months of life, with markers indicating ASD in the first 6 months of life. It highlights predictive of individual child's diagnostic classification at outcome (24-36 months) and internal and external validation of results.
Decline in eye fixation (2-12 through 2-24 months) predictive of outcome levels of ASD severity at 36 months

Predicts level of disability at outcome

Measuring the genetic structure of social visual engagement

250 toddlers:
- 82 monozygotic twins (41 MZ pairs)
- 84 dizygotic twins (42 DZ pairs)
- 84 non-sibling comparison children (42 non-sib control pairs)
- age 21.3(4.3) months
- non-sibs matched <1 day


The genetic basis of Social Visual Engagement

Concordance in social visual engagement as a function of zygosity.


John Constantino, MD

Marcus Autism Center
Strong genetic influence persists across development.

Twins tested again 15 months later, at 36 months. (N=22 MZ, N=44DZ)

Individual variation in eye-looking is strongly influenced by genetics.

Genetic influence persists whether twins watch the same or different videos.

Presentation order of video stimuli was randomized, so each twin saw separate videos, the majority of which were the same (M(50)=86.4(19.3)% but some of which were different (13.6(19.3)% seen by only one among the pair.)
Genetic influence exerts effects on a moment-by-moment basis.

MZ twins are more likely to...

...move their eyes at the same moments in time.

MZ twins are more likely to...

...move their eyes in the same directions.
MZ twins are more likely to...

...fixate on the *same semantic content* at the *same moments in time*.

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.

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.
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

Hundreds of natural experiments within a 5-minute free viewing video experiment

- In ASD: ~570 divergences in 5 minutes of video  
- ~13,680 divergences in a 2-hour period of real-life social experience  
- 6 hour social exposure/day results in ~15,000,000 divergences over the course of one year of real-life exposure to social environments

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

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
Massive Challenge - Massive Opportunity

- 60,000 children born every year will have autism (1:68); societal cost of autism is $126B/year in US alone; early detection and intervention is a game changer (NIH)
- A cohort of children with autism followed from birth reaching 3 years of age without developmental delays: diversity, not disability
- 700,000 children with autism in schools; annual cost $37B/year; median age of diagnosis of autism in the US: 4.5 - 5.5 years
- 6,600,000 special education children (13% of all students); 9% with autism; 20% language impairment; 12% with developmental delays or intellectual disability
- These are all conditions originating in disrupted early brain development due to genetic, medical or environmental vulnerabilities
- Maybe ~10% are "inevitable"; in ~90%, burdens can be significantly attenuated if not prevented altogether
- Neurodevelopmental Medicine of the 21st century: optimizing outcomes

Developmental Social Neuroscience meets Public Health Opportunities

- We are genetically programmed to be social beings
- This programming is altered in autism
- But social experiences are co-created by environment
- We can engineer these experiences via parent-delivered treatment

Augmenting Access to Early Treatment

- FAMILY
- PRIMARY CARE PHYSICIAN
- EARLY INTERVENTION PROVIDER

Augmenting Access to Early Treatment

- www.autismnavigator.com
- www.firstwordsproject.com
the Community: Families, Pediatricians, Early Intervention Providers

Parent-Delivered Early Social Interaction

Universal design because there is only one platform for early brain development

- For children with complex genetic burden: Autism, Williams syndrome
- For children with compromising medical conditions: Extremely Preterm, Congenital Heart Disease
- For children from disadvantaged backgrounds

Pediatric Medicine of the 21st century: The criticality of Public Health considerations

- Not necessarily curing “diseases”
- BUT OPTIMIZING OUTCOMES
- Universal screening, accessing identification, increasing access to early intervention
- Cost-effective, community-viable
- Value Proposition!
Take Away Messages - 1

• Autism is a massive public health challenge and an enormous public health opportunity
• Children’s lifetime outcomes can be optimized with
  ✦ Early Detection, Access to Diagnostic Services, Access to Early Intervention
• The greatest burdens of autism are not inevitable and be significantly ameliorated
  ✦ Intellectual Disability, Language Disability, Severe Behavior Challenges
• What moves early brain development is reciprocal social engagement, and early experiences shape the trajectories of social and communication skills and social-communicative brain
• Infants & toddlers create their own social environment; these behaviors are under stringent genetic control and disrupted (and diagnostic) in the case of young children with autism

Take Away Messages - 2

• But we can engineer social learning experiences via manipulation of children’s environment - via parent-delivered treatments
• We need cost-effective and community-viable solutions for
  ✦ Universal Screening, Diagnosis, and Early Treatment
• Solutions for screening and diagnosis are not far off
• Solutions for early treatment are being studied at a grand scale right now
• Solutions for optimizing the development of children with autism are relevant to a much broader group of children
• The future of neurodevelopmental medicine is likely to be focused on optimizing the outcome of children born with genetic, medical or environmental challenges rather than on the “cure” of these complex conditions
Our ultimate goal:
To change the narrative of autism

To make autism an issue of diversity, not of disability