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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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
Thank You

- The children and families who support our clinical and research activities
- Warren Jones and many wonderful colleagues and students
- 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

Advocacy
- Training
- Clinical
- Research
- Center-Based Model Program
- Community-Viable Outreach Model
- The Science of Clinical Care
Autism and other developmental delays are a Public Health Challenge

★ Prevalence: 1:59 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: 4-0 to 5.7 years
★ % of primary care providers who routinely screen not known
★ <20% of children identified before age 3 years

CDC, 2014; Peacock et al., 2012; Cidav et al., 2012; Mandell et al., 2015; 2009; 2013; 2014; Wang et al., 2013; Buescher et al., 2014; Wiggins et al., 2006; Shattuck et al., 2009; Honigfeld et al., 2012; Heidgerken et al., 2005; Dosreis et al., 2006; Johnson & Myers, 2007;
ASD symptoms RESULT from deviations from normative socialization

GENETIC  MECHANISMS OF SOCIALIZATION SYMPTOMS  BEHAVIORAL  LIABILITY

First 2 years of life

Development

Dyadic Interaction

Triadic Interaction

Increasingly Refined Social Interaction

Normative Social Development

Development in Autism Spectrum Disorders

Sociability

Universal Principle: the Platform for Development of Social Brain

Born to Socially Orient

Reciprocal Social Interaction

Neuroplasticity

WHITE MATTER DEVELOPMENT

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

H-J Park PhD
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.
FORWARD
IN TIME
Autism Spectrum Disorder
Core Challenges of Older Individuals with Autism Spectrum Disorder

- **SOCIAL SKILLS**: the intangibles, the unstructured, the novel, the implicit, the intuitive, the “common sense”, the mentalistic

- **COMMUNICATION SKILLS**: the informal, the conversational, the reciprocal, the ‘other-directed’, the polite, the ‘untrue’, the ‘chatty’

- **ADAPTIVE SKILLS**: grooming and self-care, domestic chores, ‘survival skills’, living in the community, functioning in bureaucracies, groups and relationships, legal concerns

- **LEARNING SKILLS**: rote & sequential, not conceptual & integrative; learning ABOUT not learning HOW TO

- **ORGANIZATIONAL SKILLS**: repetitive schedules, ‘to do’ lists, planning ahead, learning form feedback, adjusting to variants of situations, recognizing novelty, knowing when and how to seek assistance, breaking down big tasks into stepwise plans

- **OBSTACLES TO ADAPTATION**: anxiety, panic, fears and phobias, depression and despondency, motivational issues, rigidities
Core Challenges

• SOCIAL SKILLS: the intangibles, the unstructured, the novel, the implicit, the intuitive, the “common sense”, the mentalistic

• COMMUNICATION SKILLS: the informal, the conversational, the reciprocal, the ‘other-directed’, the polite, the ‘untrue’, the ‘chatty’

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• OBSTACLES TO ADAPTATION: anxiety, panic, fears and phobias, depression and despondency, motivational issues, rigidities
Self-help: a non-exhaustive list

• Personal hygiene
• Grooming
• Minor or annoying health issues
• Major health issues
• Clothing: purchasing, care, choice, when and how
• Mores and regulations
• The private vs. the public
• Puberty related
• Sexuality
• …
Community and survival skills:  
a non-exhaustive list

• Going to places, transportation
• Emergencies
• Dealing with social annoyances (e.g., panhandlers, manipulators, exploitative companions)
• Dealing with people in position of authority
• POLICE
• Rules, the law, the novel, the unexpected
• The private, the public, the acceptable, the seemingly criminal, the self-incriminating, the poor self-advocate
• The bureaucracies, the forms, the scheduled commitments
• The telemarketers, the soliciting, the “too good to be true’ invitations and offers, ‘junk’ mail, INTERNET
• …
Core Challenges aka Realities

• **SOCIAL SKILLS**: the intangibles, the unstructured, the novel, the implicit, the intuitive, the “common sense”, the mentalistic

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• **OBSTACLES TO ADAPTATION**: anxiety, panic, fears and phobias, depression and despondency, motivational issues, rigidities
Thinking about things and thinking about people
Searching for Social Meaning in Real-life Situations
Looking at People
Adolescents & Adults

It is a social disability
Looking at People Interacting
Typically Developing Viewer

Viewer with Autism
Focus on mouths vs focus on eyes

Klin et al. (2002). Arch Gen Psychiat
Viewer with Autism
Typically Developing Viewer

Klin et al. (2002). *Am J Psychiat*
Tracing the Shape of a Social Triangle

Viewer with Autism
Typically Developing Viewer
Core Challenges aka **Realities**

- **SOCIAL SKILLS**: the intangibles, the unstructured, the novel, the implicit, the intuitive, the “common sense”, the mentalistic
- **COMMUNICATION SKILLS**: the informal, the conversational, the reciprocal, the ‘other-directed’, the polite, the ‘untrue’, the ‘chatty’
- **ADAPTIVE SKILLS**: grooming and self-care, domestic chores, ‘survival skills’, living in the community, functioning in bureaucracies, groups and relationships, legal concerns
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- **OBSTACLES TO ADAPTATION**: anxiety, panic, fears and phobias, depression and despondency, motivational issues, rigidities
Circumscribed interests

• Frequent and highly visible manifestation of the condition
• Monopolizes learning
• Monopolizes thinking
• Monopolizes conversation and relationships
Some examples

- on snakes
- Writings of incarcerated people
- On death and dying
- Religion
- Cul-de-sacs
- Deep-fat-fryers
- Shakespeare’s plays
- Telephone pole insulators

- Pokemon
- Digimon
- Weather
- TV/radio stations
- Electrical fans
- Photographing people
- Computer serial numbers
- Large numbers
- Algebraic equations
Potential for catastrophic consequences

- DANGER!! Interests and repetitive behaviors get caught together (e.g., touching, shoes, fetish)
- DANGER!! Internet, solitary and unmonitored use of computer, pornography on the web
- The dangerous combination of computer technical skills and naivety + lack of street smarts may lead to problems with the law
- Not potential victimizers, but the law often does not make that distinction (mandatory sentences)
Importance for Self-Identity and Self-Esteem

• Circumscribed interest may be important pillar of self-identity
• Very important to take this very seriously
• Examples:
  – Cul de sacs
  – Gaining insight into people through mathematics (e.g., algebraic equations)
BACK
IN TIME
Neonates preferentially orient towards stimuli that...

...sound like caregivers.

DeCasper & Fifer, 1980.
Butterfield & Siperstein, 1970
Eisenberg, 1976.

Shultz et al. (2018). Trends in Cognitive Sciences

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Neonates preferentially orient towards stimuli that...  

More Preferred  

mother's scent  

Less Preferred  

stranger’s scent  

...sound like caregivers.  
...smell like caregivers.
Neonates preferentially orient towards stimuli that...

More Preferred
- biological motion

Less Preferred
- inverted biological motion
- scrambled biological motion

...**sound** like caregivers.
...**smell** like caregivers.
...**move** like caregivers.

Simion, Regolin, & Bulf, 2008.
Shultz et al. (2018). *Trends in Cognitive Sciences*
Neonates preferentially orient towards stimuli that...

...sound like caregivers.
...smell like caregivers.
...move like caregivers.
...look like caregivers.

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

Shultz et al. (2018). *Trends in Cognitive Sciences*
Neonates preferentially orient towards stimuli that...

More Preferred
- mother, engaging
- stranger, eyes open

Less Preferred
- stranger, eyes averted
- stranger, eyes closed

...sound like caregivers.
...smell like caregivers.
...move like caregivers.
...look like caregivers.
...interact like caregivers.

Farroni, Csibra, Simion, & Johnson, 2002.
Sai, 2005.

Shultz et al. (2018). *Trends in Cognitive Sciences*
Unifying Principle in Development: Autism and other conditions

Reciprocal Social Interaction
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

April 1926

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Attention to Biological Motion

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 Children

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

Ami Klin, David J. Lin, Phillip Gorrindo, Gordon Ramsay, & Warren Jones

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, playback at 1/2 speed
Cumulative Audiovisual Synchrony

Relative Audio-Visual Synchrony = Normalized Peak Difference

Clap Location

Pat-a-cake

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

- **Eye:** $F_{2,63} = 12.87, p < .001$
  - $d = 1.56$

- **Mouth:** $F_{2,63} = 5.599, p < .006$
  - $d = 1.40$

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)
Eye-tracking measures of Social Visual Engagement

Typically-Developing 5-Month-Old
Growth Charts: of Social Visual Engagement
Normative Growth Charts of Social Visual Engagement

TD eyes

TD, N=63
5-Month-Old with Autism
Eye-Looking in Typically-Developing Infants and Infants Later Diagnosed with ASD

[Graph showing changes in fixation time and change in fixation percentage per month for typically developing infants.]

TD, N=63

$D_t$ TD eyes

Increasing

Decreasing
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

TD eyes
ASD1 eyes

$D_t$ TD eyes
$D_t$ ASD1 eyes

TD, N=63
ASD1, N=11

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

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**Fixation Time (%)**

- **TD eyes**
- **ASD1 eyes**

**Change in Fixation (%) per Month**

- **D_t TD eyes**
- **D_t ASD1 eyes**

**Data**

- TD, N=63
- ASD1, N=11

First Replication Cohort

- **Fixation Time (%):**
  - TD eyes
  - ASD1 eyes
  - ASD2 eyes

- **Change in Fixation (% per Month):**
  - $D_t$ TD eyes
  - $D_t$ ASD1 eyes
  - $D_t$ ASD2 eyes

**Notes:**
- TD, N=63
- ASD1, N=11
- ASD2, N=13
First Replication Cohort

Fixation Time (%) vs. Age (in months)

Change in Fixation (% per month) vs. Age (in months)

TD, N=63
ASD1, N=11
ASD2, N=13

TD eyes
ASD1 eyes
ASD2 eyes

$D_t$ TD eyes
$D_t$ ASD1 eyes
$D_t$ ASD2 eyes
Eye Fixation in the first 6 months of life

- Markers of ASD in the first 6 months of life
- Predictive of individual child’s diagnostic classification at outcome (24-36 months)
- 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
Growth Charts

Quantifying Disruption of Early-Emerging, Highly-Conserved Mechanisms of Social Adaptive Action
How to link these quantifications of behavior to the genetic bases of autism?

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

Constantino et al.; *Nature*, 2017; 547(7663):340-344
The genetic basis of Social Visual Engagement

Concordance in social visual engagement as a function of zygosity.

DZ males
Constantino & Colleagues
MZ males
Constantino & Colleagues
Social visual engagement when viewing scenes of dyadic caregiver interaction

Concordance in social visual engagement as a function of zygosity.

Constantino et al.; *Nature*, 2017; 547(7663):340-344
Individual variation in eye-looking is strongly influenced by genetics.

Constantino et al.; *Nature*, 2017; 547(7663):340-344
Strong genetic influence persists across development.

Twins tested again 15 months later, at 36 months. (N=22 MZ, N=44DZ)
Strong 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(SD)=86.4(19.3)%) but some of which were different (13.6(19.3)%), seen by only one among the pair.
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(SD)=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 males
Constantino & Colleagues
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…

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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.

Marcus Autism Center
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

Scarr & McCartney, 1983.
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
• 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

• 6,600,00 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
• www.autismnavigator.com
• www.firstwordsproject.com
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
• 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 make autism an issue of diversity, not of disability