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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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

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Marcus Autism Center

Marcus Autism Center at a glance

Children's Healthcare of Atlanta

- Translation
- Impact
- Clinical Resources

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EMORY UNIVERSITY SCHOOL OF MEDICINE

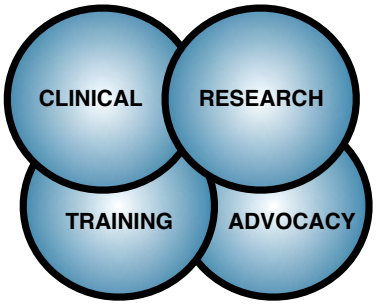
- Science
- Faculty Advancement
- Research Resources

Excellence

- >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

COMMUNITY-VIABLE OUTREACH MODEL



The Science of Clinical Care

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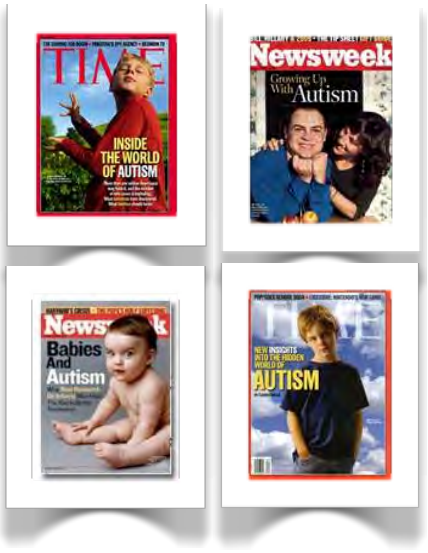
Autism and other developmental delays are a Public Health Challenge



★ 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;

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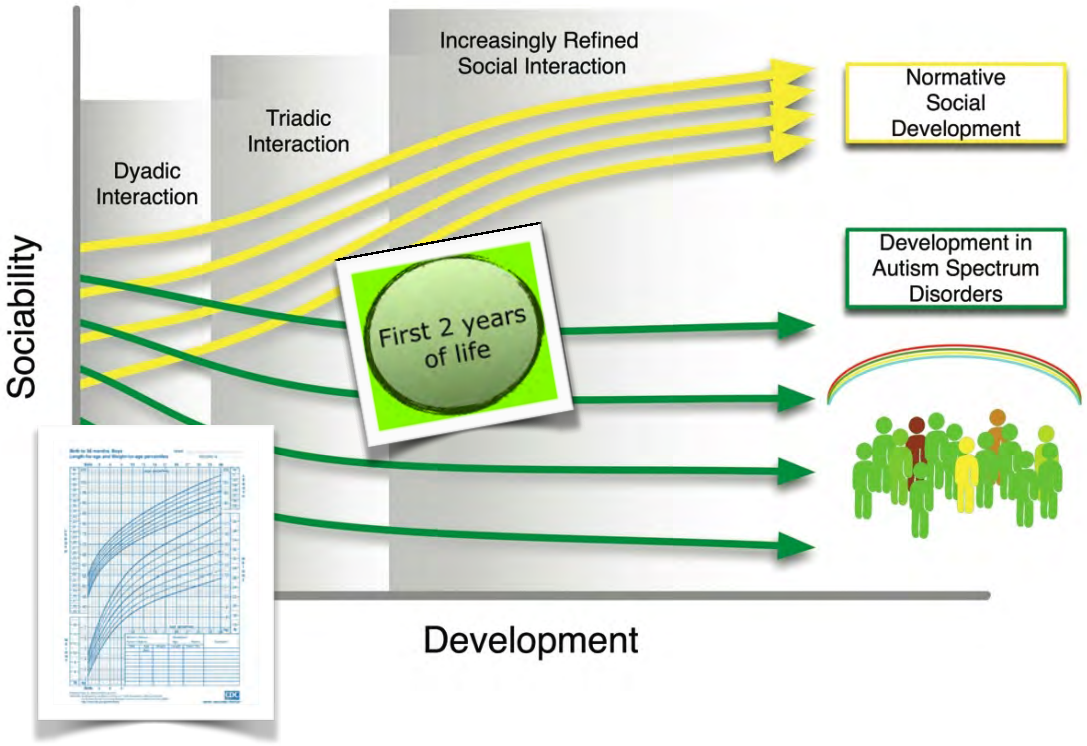
ASD symptoms RESULT from deviations from normative socialization

GENETIC | MECHANISMS OF SOCIALIZATION | BEHAVIORAL SYMPTOMS | LIABILITY



Jones et al. (2008). *Arch Gen Psy;* Klin et al. (2009). *Nature*; Jones & Klin (2009). *J Am Acad of Child Psy;* Jones & Klin (2013). *Nature;* Klin et al. (2014). *Neurosci Biobehav Rev;* Moriuchi et al. (2017). *Am J Psy;* Constantino et al. (2017). *Nature;* Shultz et al. (2018). *TICS.*

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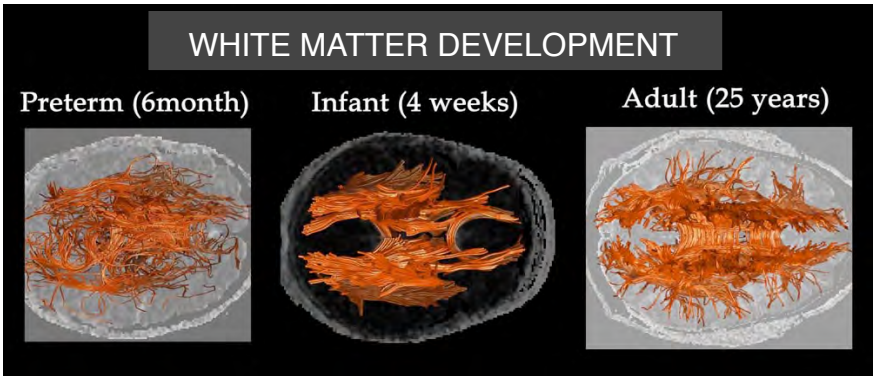
Universal Principle: the Platform for Development of Social Brain

Born to Socially Orient

MH Johnson PhD

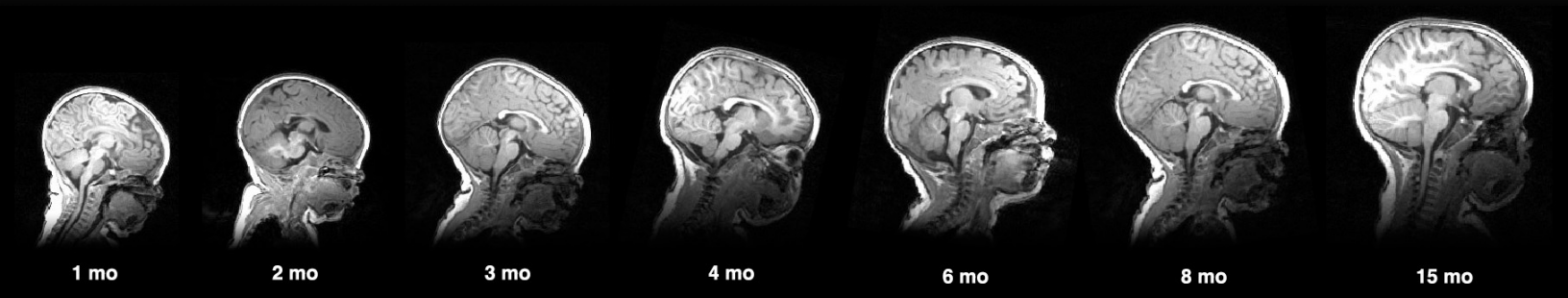
Reciprocal Social Interaction

Neuroplasticity



H-J Park PhD

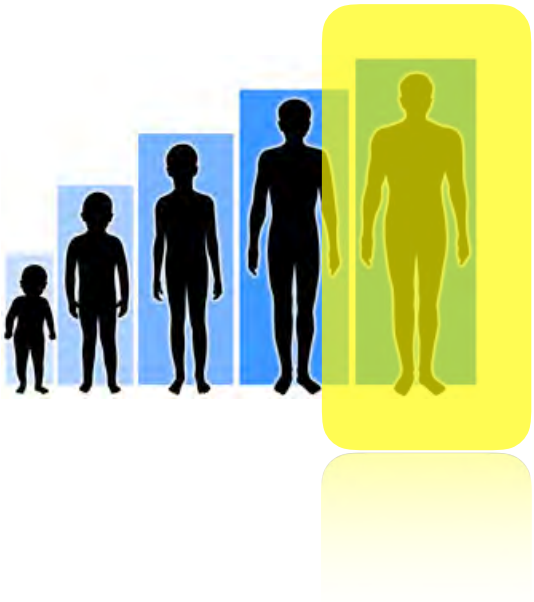
Social Interaction is the Platform for Brain Development



"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

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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
- COMMUNICATION SKILLS: the informal, the conversational, the reciprocal, the 'other-directed', the polite, the 'untrue', the 'chatty'
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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


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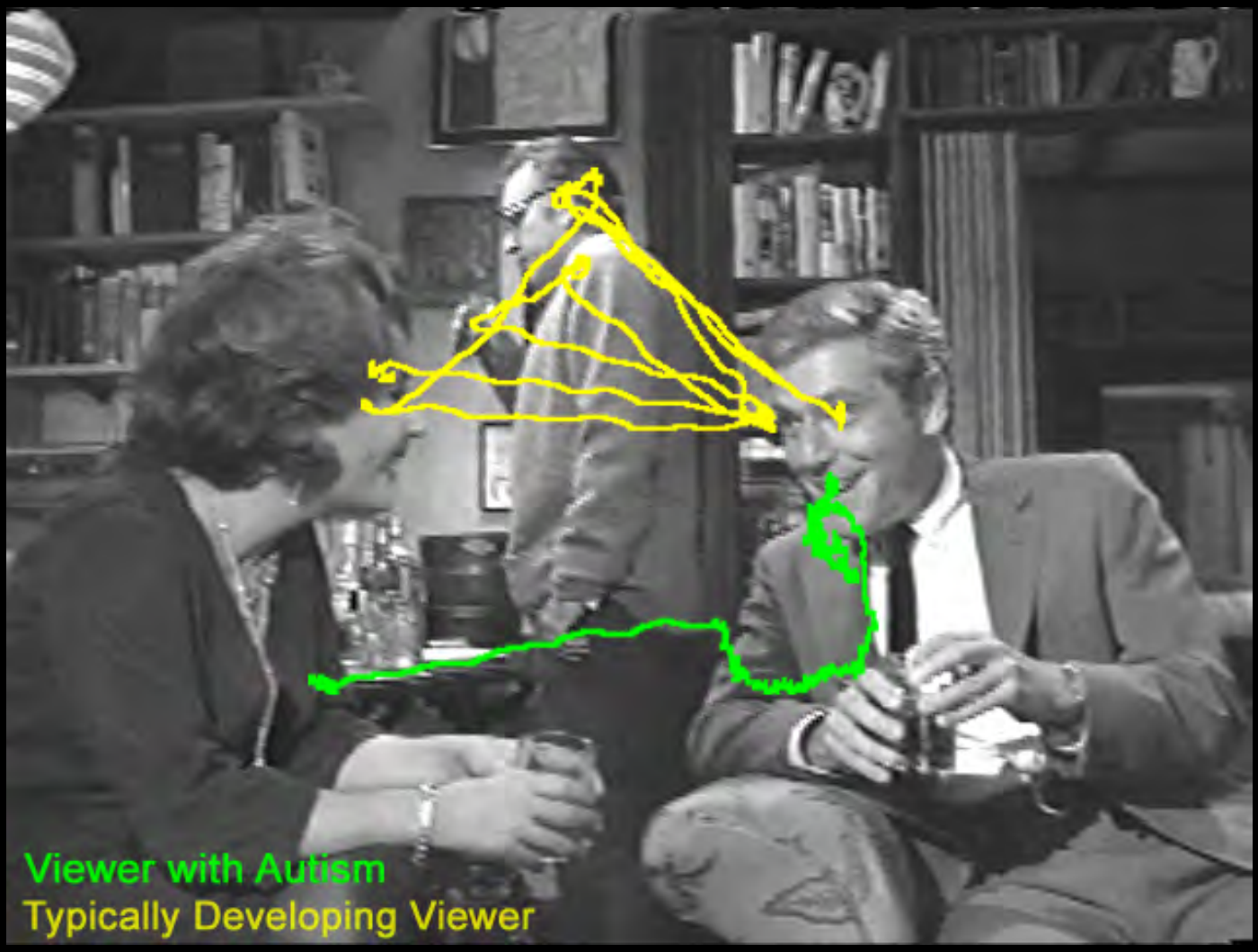
Viewer with Autism
Typically Developing Viewer

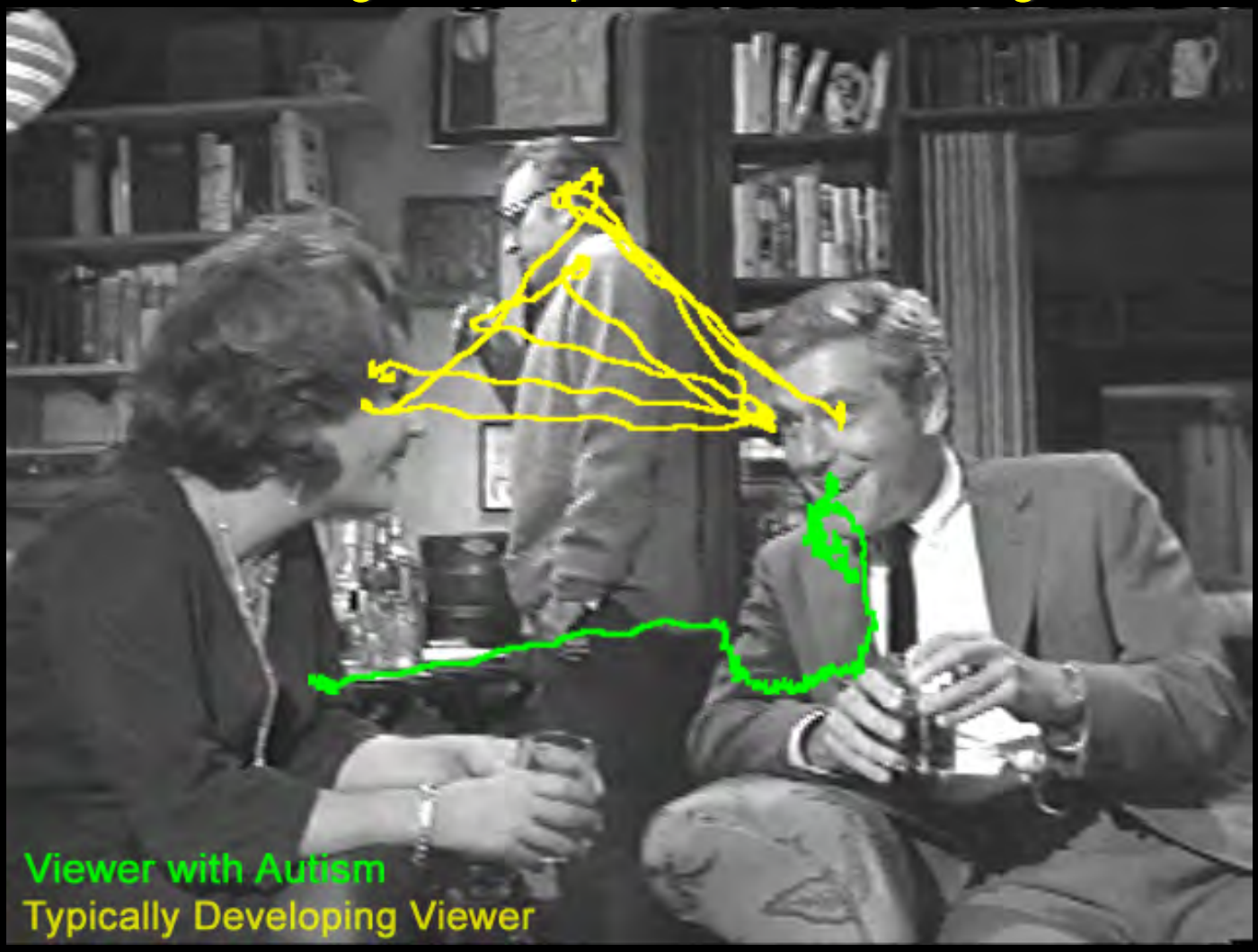
Focus on mouths vs focus on eyes

Klin et al. (2002). *Arch Gen Psychiat*



Klin et al. (2002). *Am J Psychiat*

Tracing the Shape of a Social Triangle



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'
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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

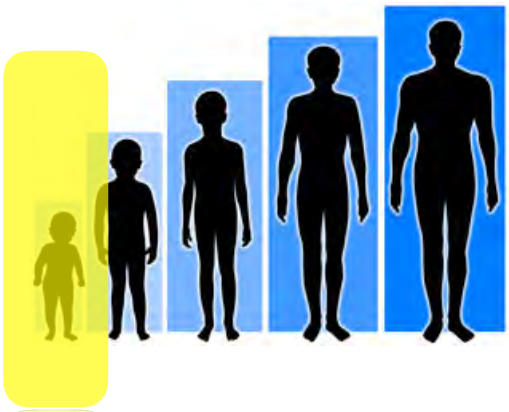
Potential for catastrophic consequences

- 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)

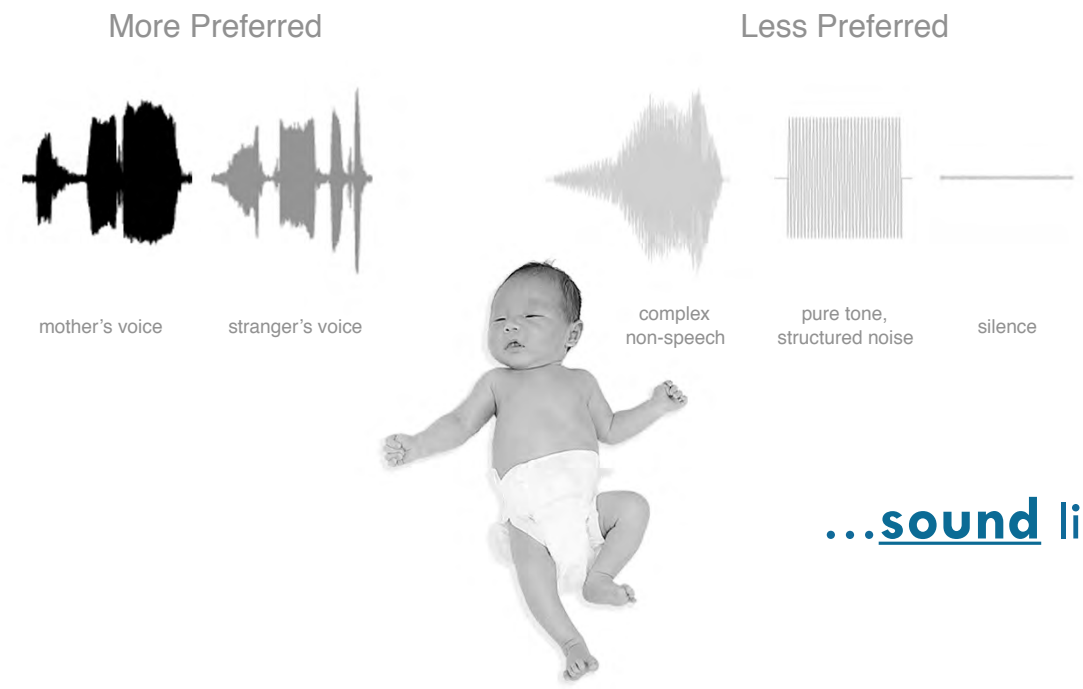
Importance for Self-Identity and Self-Esteem

- 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.
Vouloumanos & Werker, 2007.
Butterfield & Siperstein, 1970
Eisenberg, 1976.

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

Neonates preferentially orient towards stimuli that…

More Preferred

mother's scent

Less Preferred

stranger's scent

…**sound** like caregivers.

…**smell** like caregivers.

Macfarlane, 1975.
Porter & Winberg, 1999.

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

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…

More Preferred

face-like

face-like configural

Less Preferred

face-like, scrambled

face-like, inverted

…**sound** like caregivers.
…**smell** like caregivers.
…**move** like caregivers.
…**look** like caregivers.

Goren, Sarty, & Wu, 1975.
Johnson, Dziurawiec, Ellis, & Morton, 1991.
Simion, Valenza, Umiltà, & Barba, 1998.
Valenza, Simion, Cassia, & Umiltà, 1996.
Farroni et al, 2005.

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.

…**interact** like caregivers.

Bushnell, Sai, & Mullin, 1989.
Simion, Valenza, Umiltà, & Barba, 1998.
Farroni, Csibra, Simion, & Johnson, 2002.
Batki, Baron-Cohen, et al, 2000.
Sai, 1990.
Sai, 2005.
Walton, Bower, & Bower, 1992.

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

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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



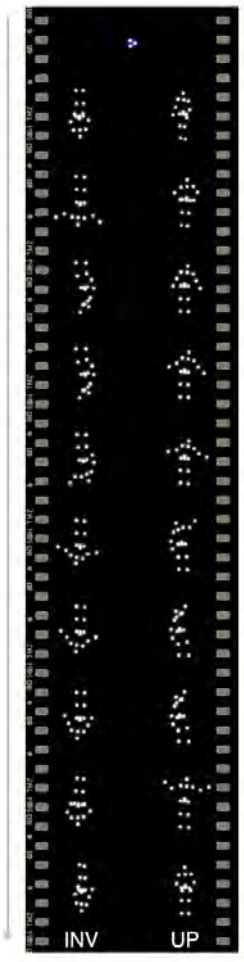


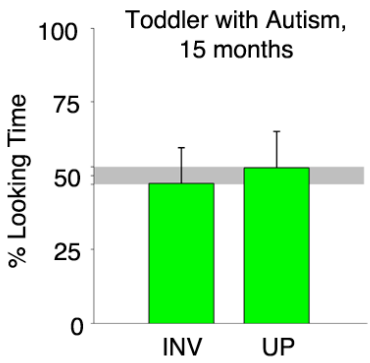

Developing expertise about the Social World



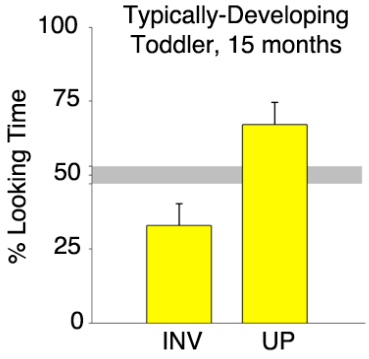

Developing expertise about the Physical World

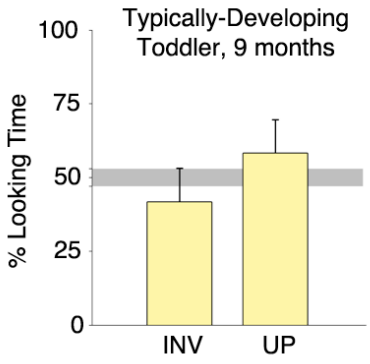
Attention to Biological Motion





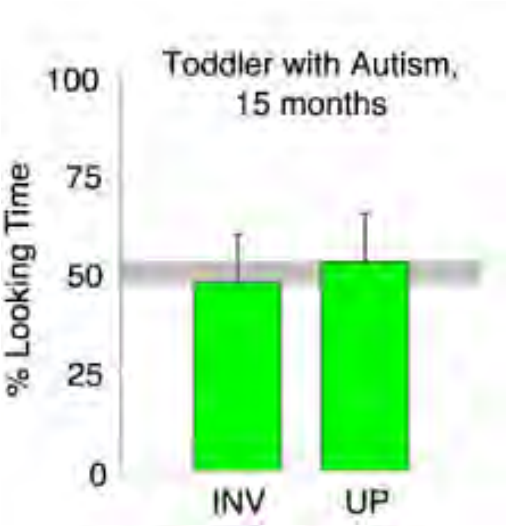
not significantly different from chance, $p > .05$

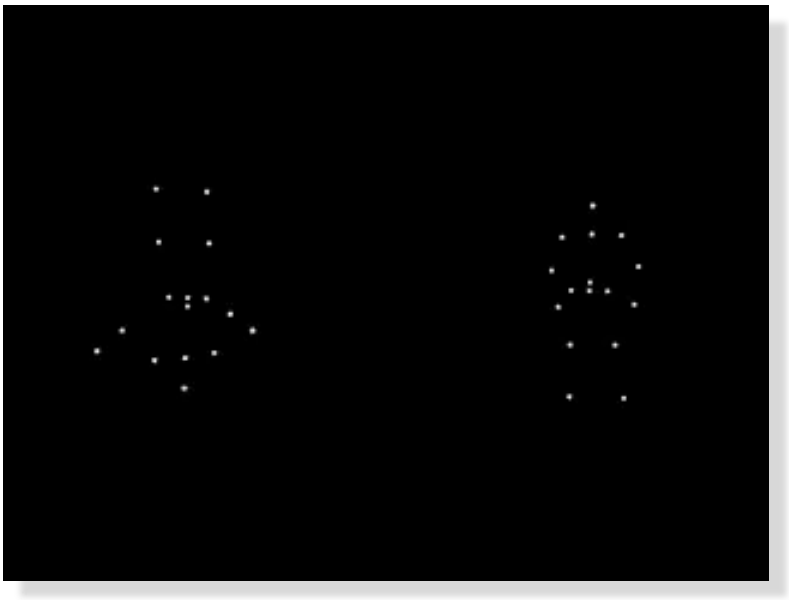




Klin A & Jones W. (2008). *Dev Science*, 1: 40-46.

Attention to Biological Motion





Klin A & Jones W. (2008). *Dev Science*, 1: 40-46.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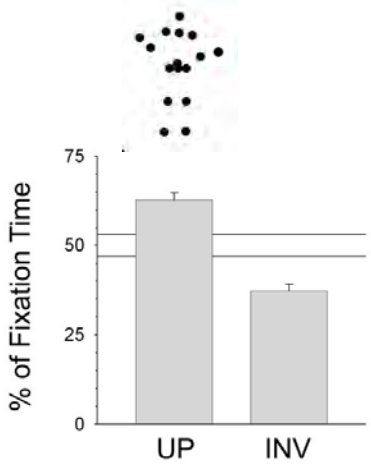
22:17:00:15

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

Ami Klin[1], David J. Lin[1]†, Phillip Gorrindo[1]†, Gordon Ramsay[1,2] & Warren Jones[1,3]



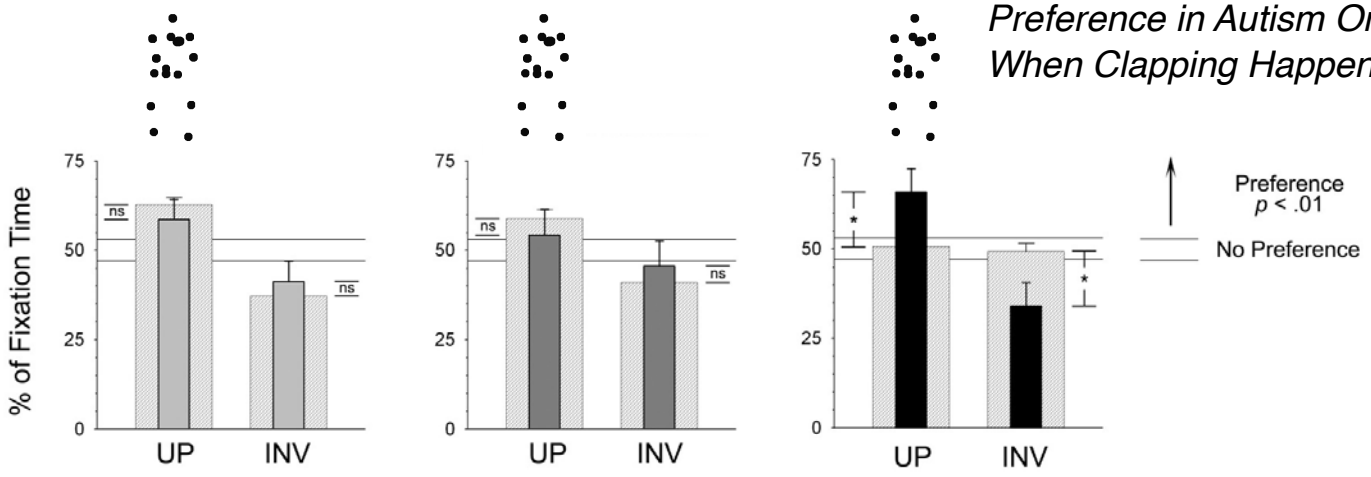
Typically-Developing Children

Klin, Lin, Gorrindo, Ramsay, & Jones, *Nature*, 2009.

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

Ami Klin[1], David J. Lin[1]†, Phillip Gorrindo[1]†, Gordon Ramsay[1,2] & Warren Jones[1,3]

Preference in Autism Only When Clapping Happens



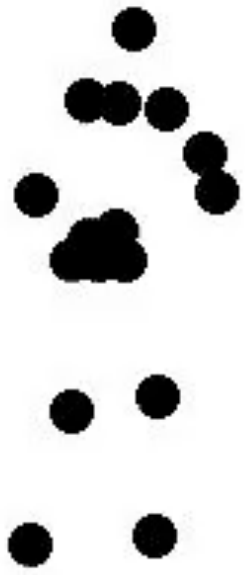
Typically-Developing Children

Developmentally-Delayed Children

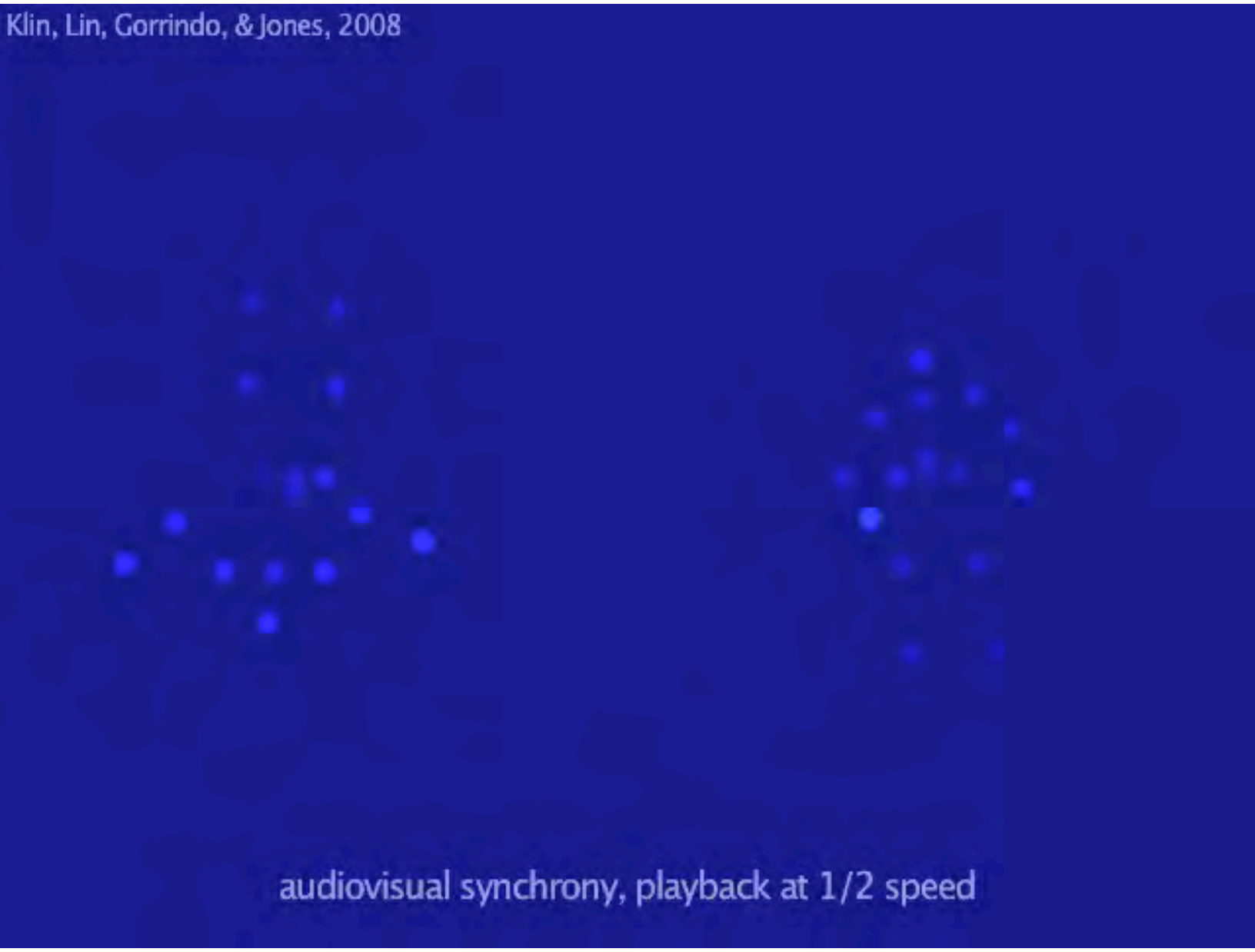
Children with Autism

Klin, Lin, Gorrindo, Ramsay, & Jones, *Nature*, 2009.

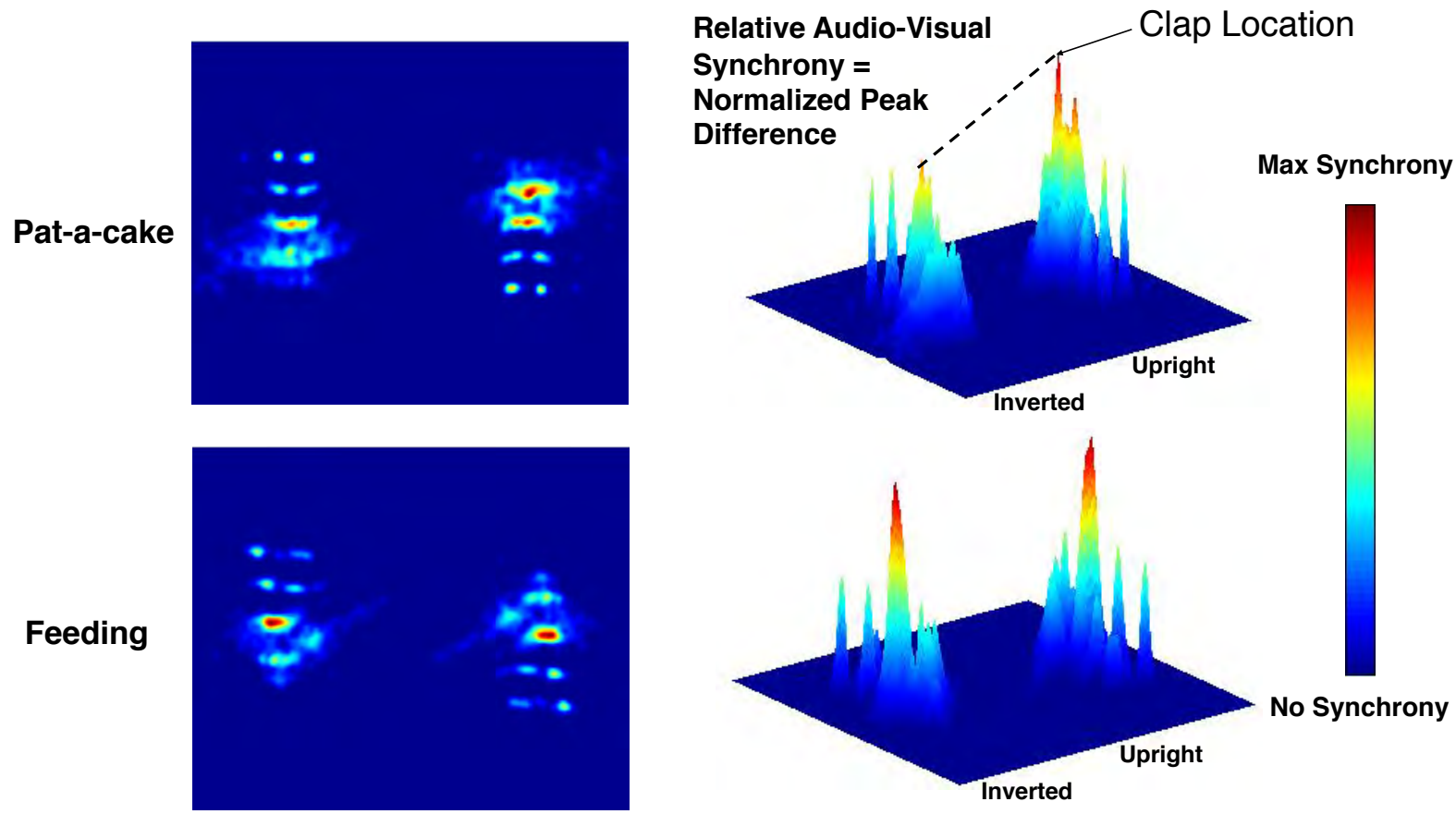
Physical, rather than social, cues guide looking in toddlers with autism

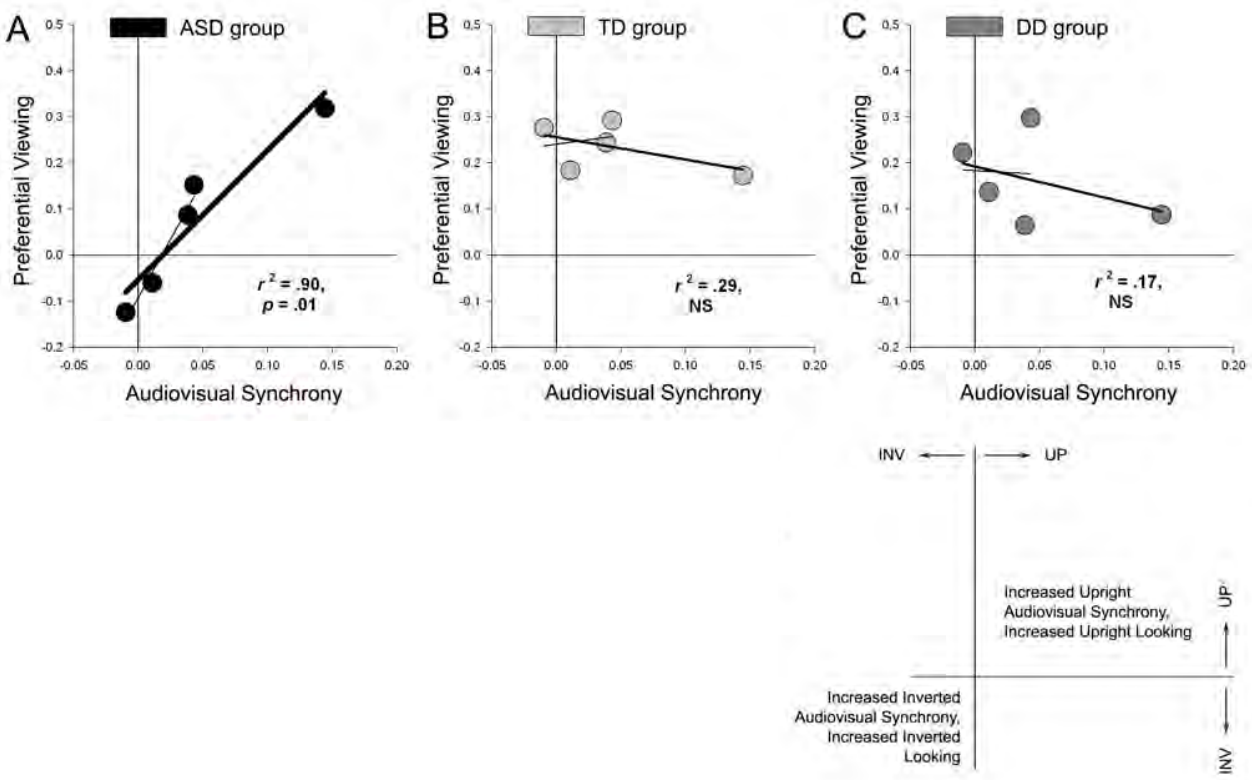


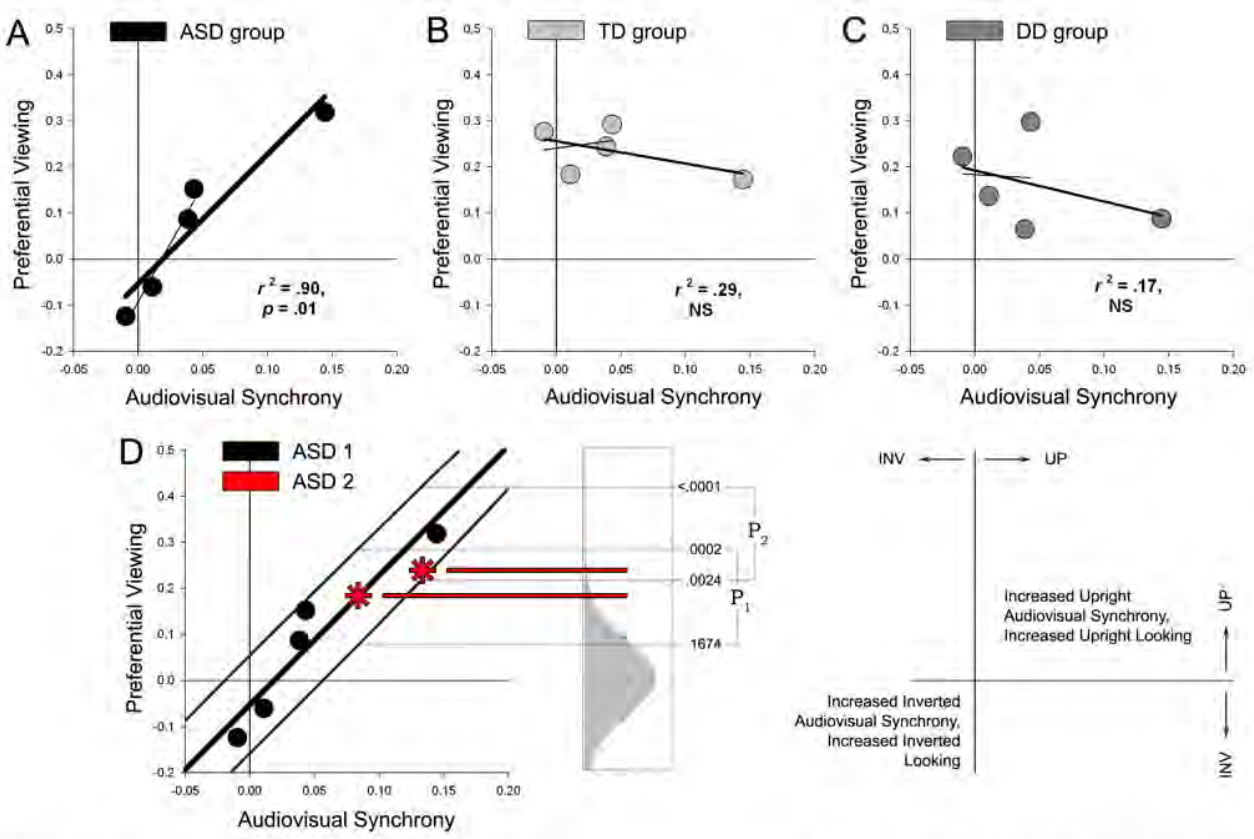
Klin, Lin, Gorrindo, Ramsay, & Jones, *Nature*, 2009.


Klin, Lin, Gorrindo, & Jones, 2008
audiovisual synchrony, playback at 1/2 speed

Cumulative Audiovisual Synchrony




A
ASD group
Preferential Viewing
Audiovisual Synchrony
r 2 = .90,
p = .01
B
TD group
Preferential Viewing
Audiovisual Synchrony
r 2 = .29,
NS
C
DD group
Preferential Viewing
Audiovisual Synchrony
r 2 = .17,
NS
INV
UP
Increased Upright
Audiovisual Synchrony,
Increased Upright Looking
UP
Increased Inverted
Audiovisual Synchrony,
Increased Inverted
Looking
INV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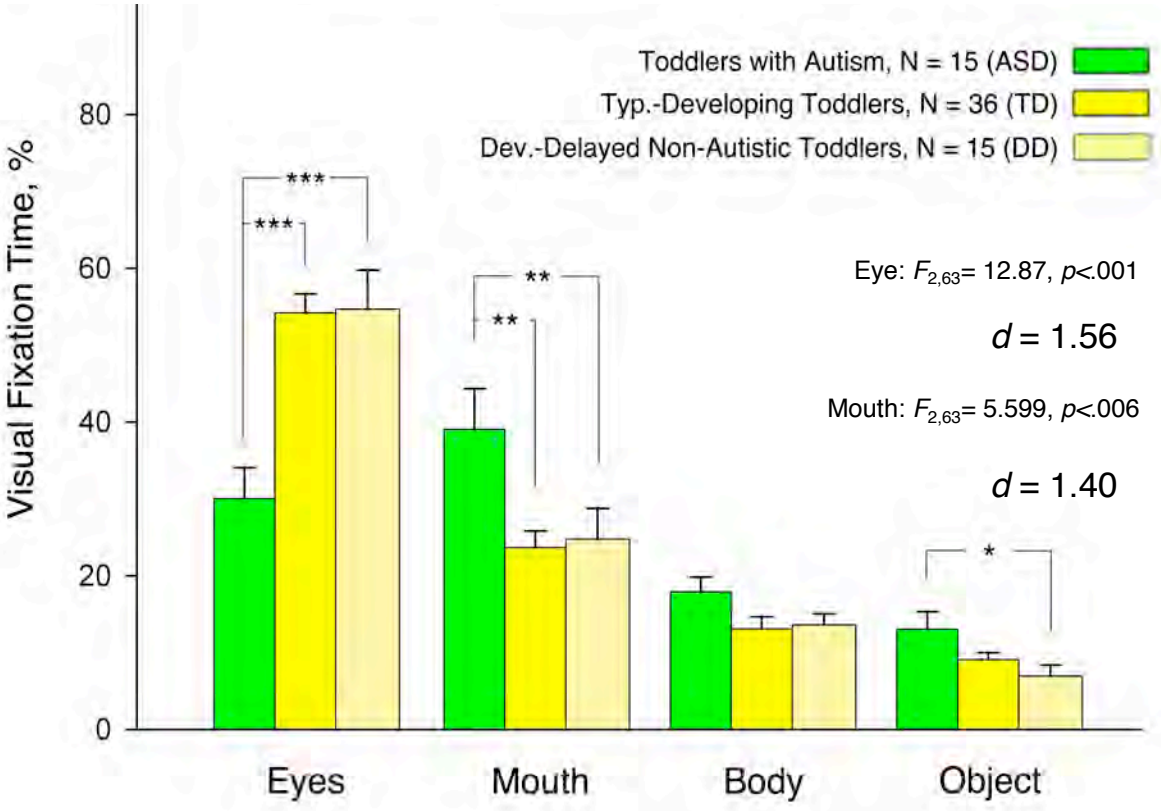
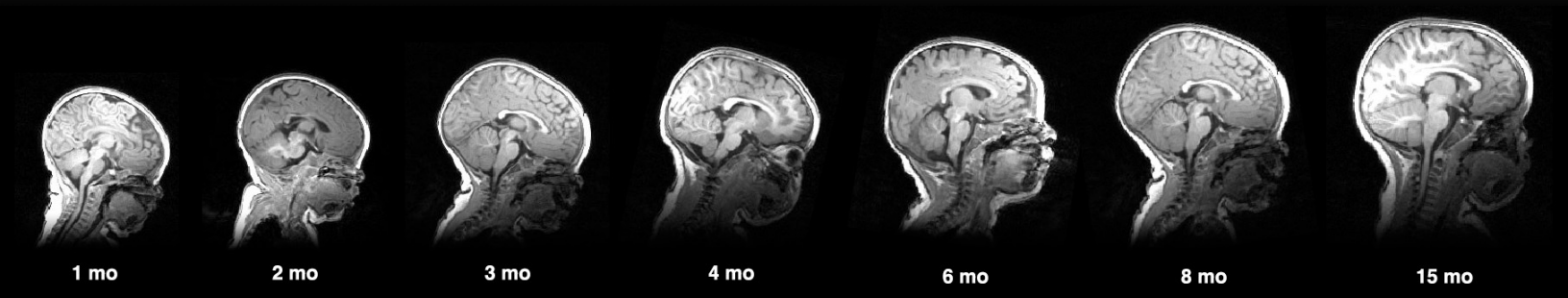
DD group
Preferential Viewing
Audiovisual Synchrony
r² = .17,
NS
D
ASD 1
ASD 2
Preferential Viewing
Audiovisual Synchrony
<.0001
.0002
.0024
.1674
P2
P1
INV
UP
Increased Upright
Audiovisual Synchrony,
Increased Upright Looking
Increased Inverted
Audiovisual Synchrony,
Increased Inverted
Looking
UP
INV

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



Jones, Carr, Klin (2008). *Arch Gen Psychiatry*. 65(8):946-54.

Social Interaction is the Platform for Brain Development



Brain size doubles in the 1st year of a baby's life, synaptic density quadruples.

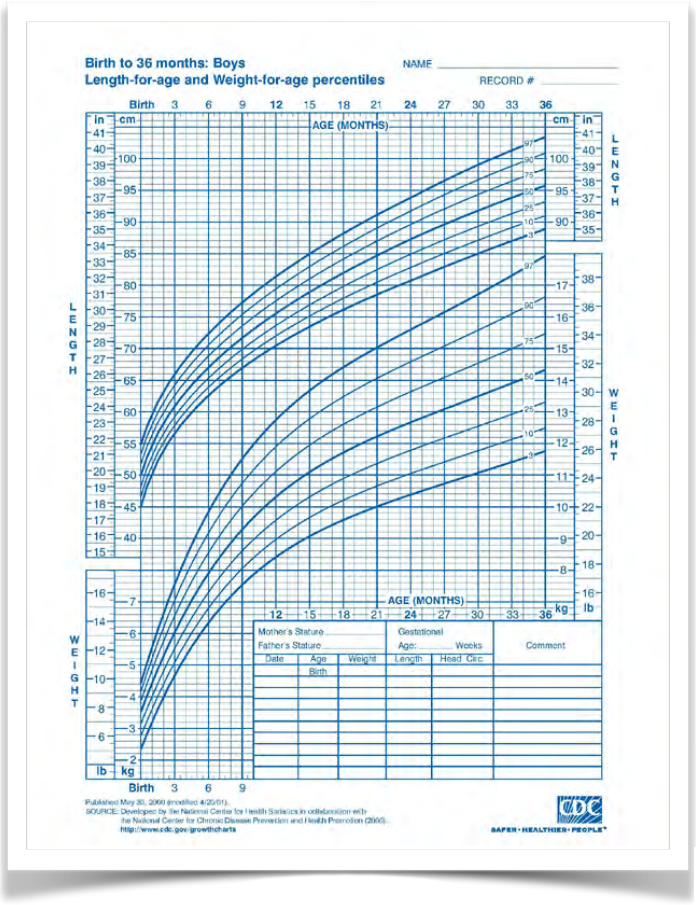
(Gilmore *et al*, 2007; Pfefferbaum *et al*, 1994; Huttenlocher, 1979; Petanjek et al, 2011)

Eye-tracking measures of Social Visual Engagement

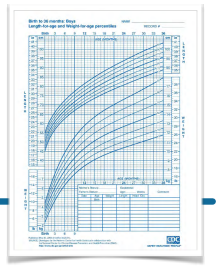
Jones & Klin (2013). *Nature*.

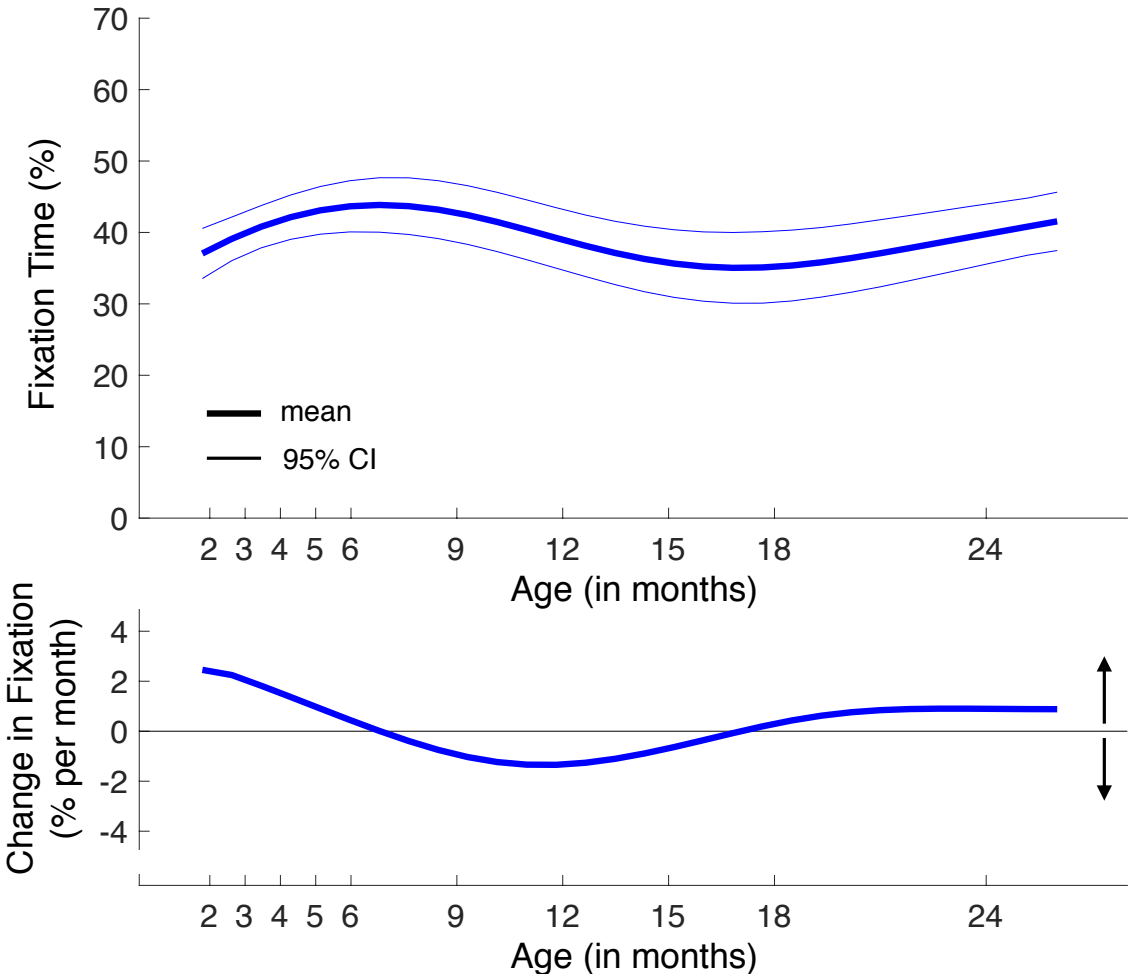
Typically-Developing 5-Month-Old

Growth Charts: of Social Visual Engagement



Normative Growth Charts of Social Visual Engagement

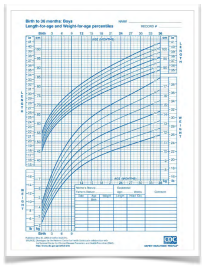


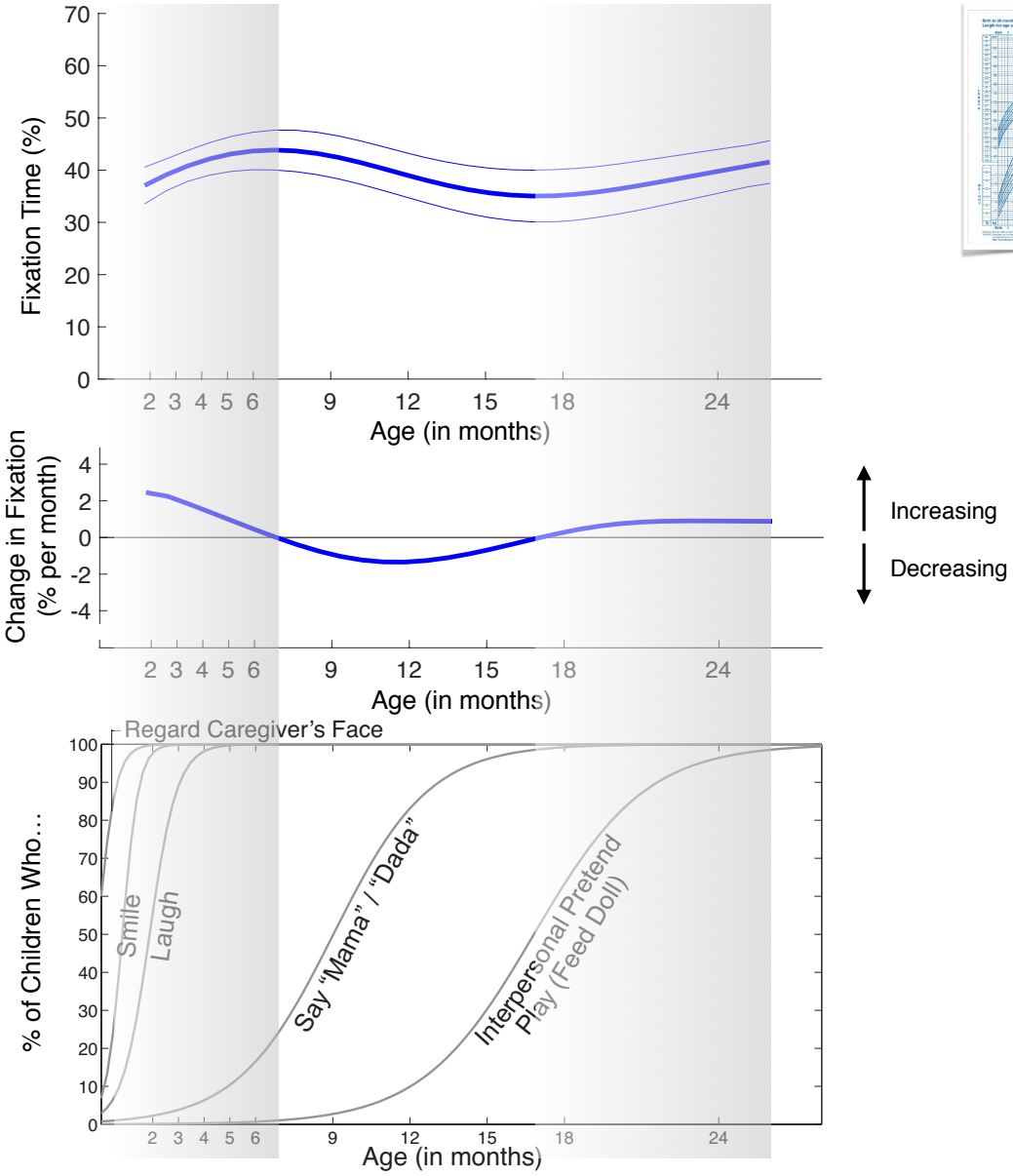


TD eyes

TD, N=63

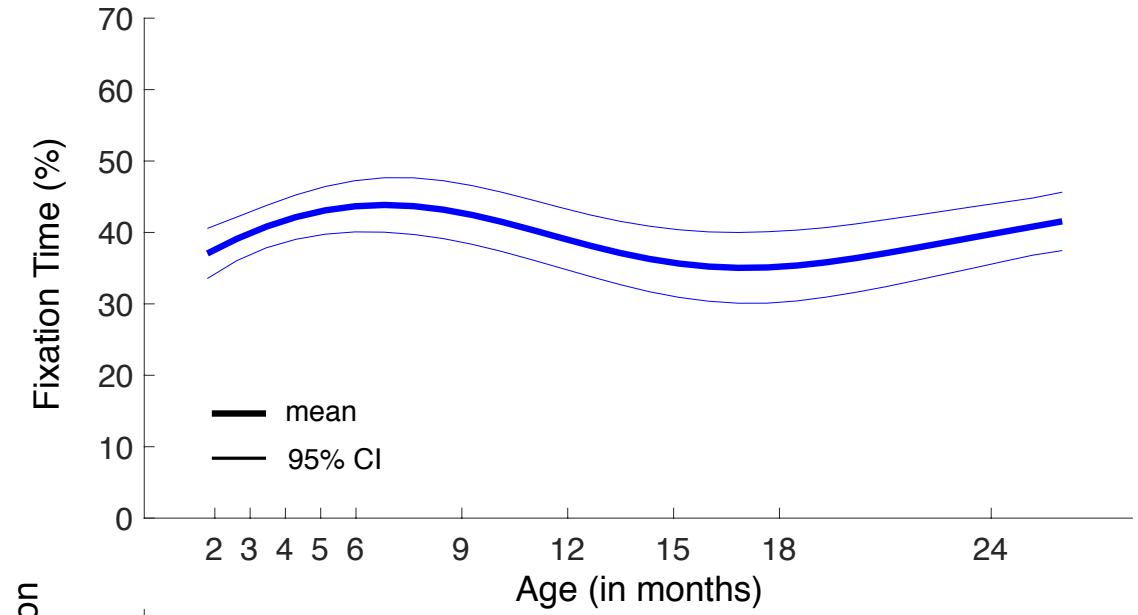
Growth Charts



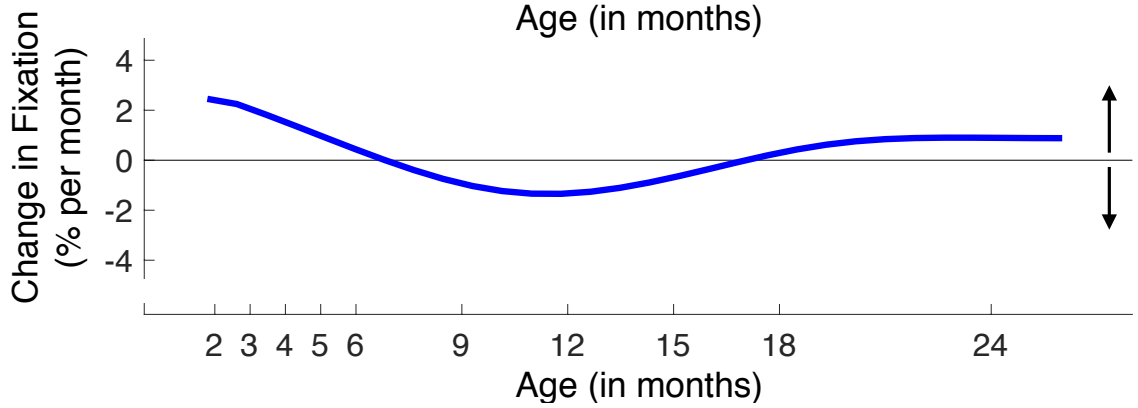


5-Month-Old with Autism

Eye-Looking in Typically-Developing Infants and Infants Later Diagnosed with ASD



TD eyes



D_t TD eyes

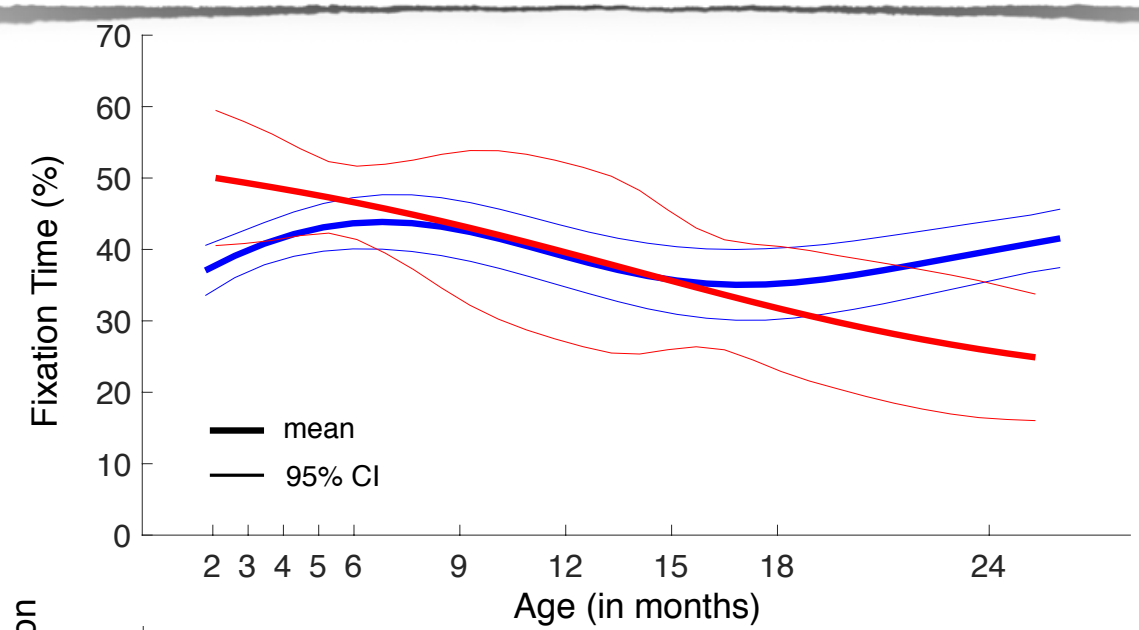
Increasing

Decreasing

TD, N=63

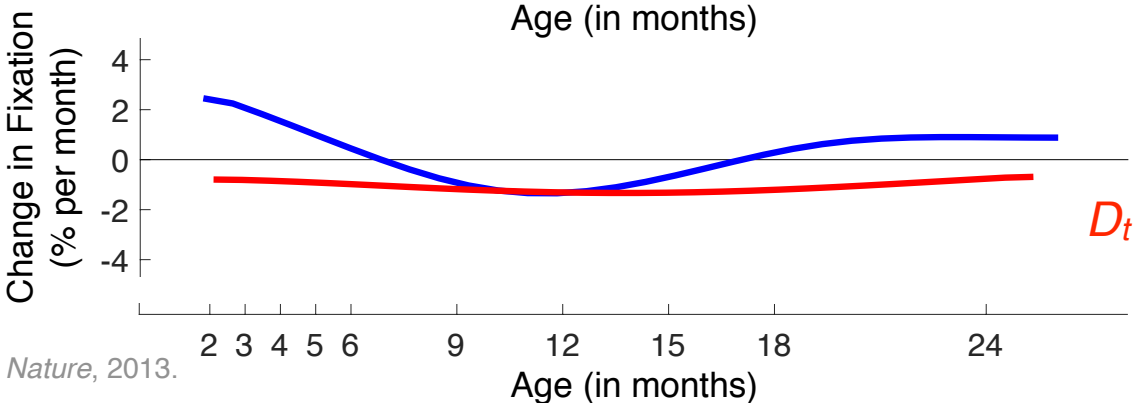
Attention to eyes is present but in decline in 2–6-month-old infants later diagnosed with autism

Warren Jones[1,2,3] & Ami Klin[1,2,3]



TD eyes

ASD1 eyes



D_t TD eyes

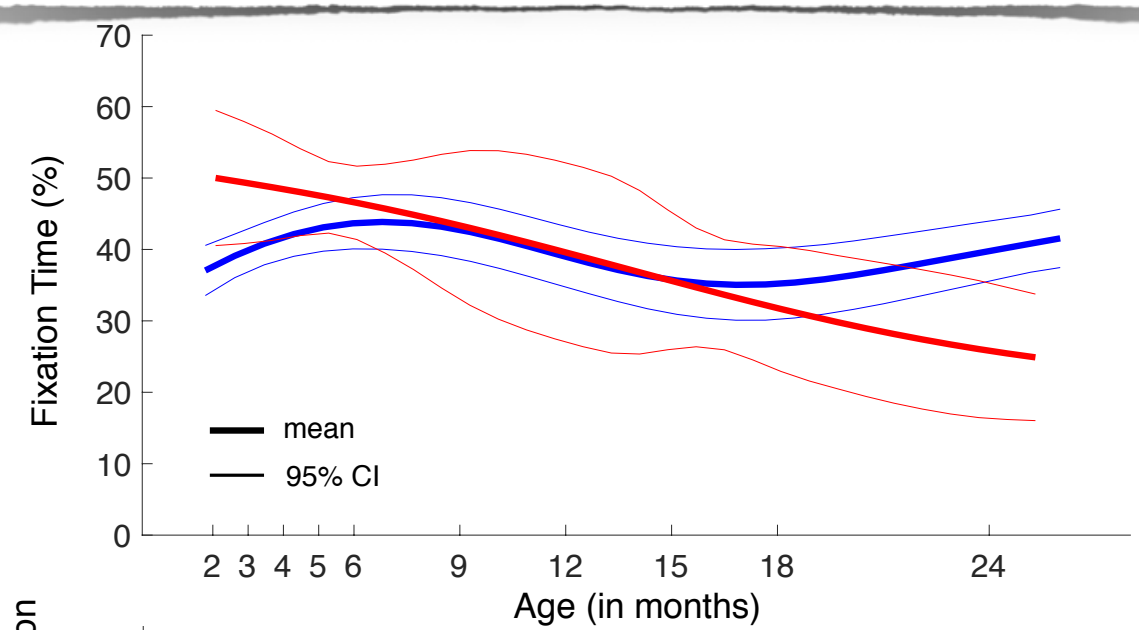
D_t ASD1 eyes

TD, N=63
ASD1, N=11

Jones & Klin, *Nature*, 2013.

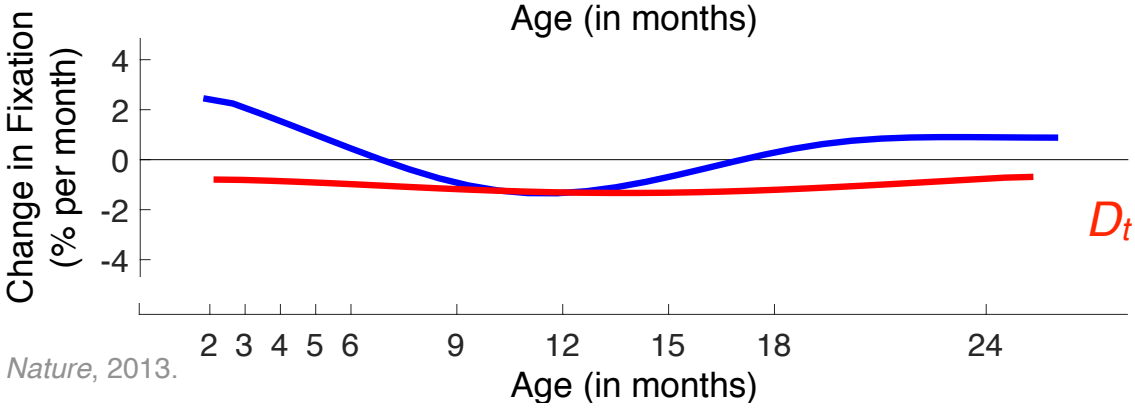
Attention to eyes is present but in decline in 2–6-month-old infants later diagnosed with autism

Warren Jones[1,2,3] & Ami Klin[1,2,3]



TD eyes

ASD1 eyes



D_t TD eyes

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TD, N=63
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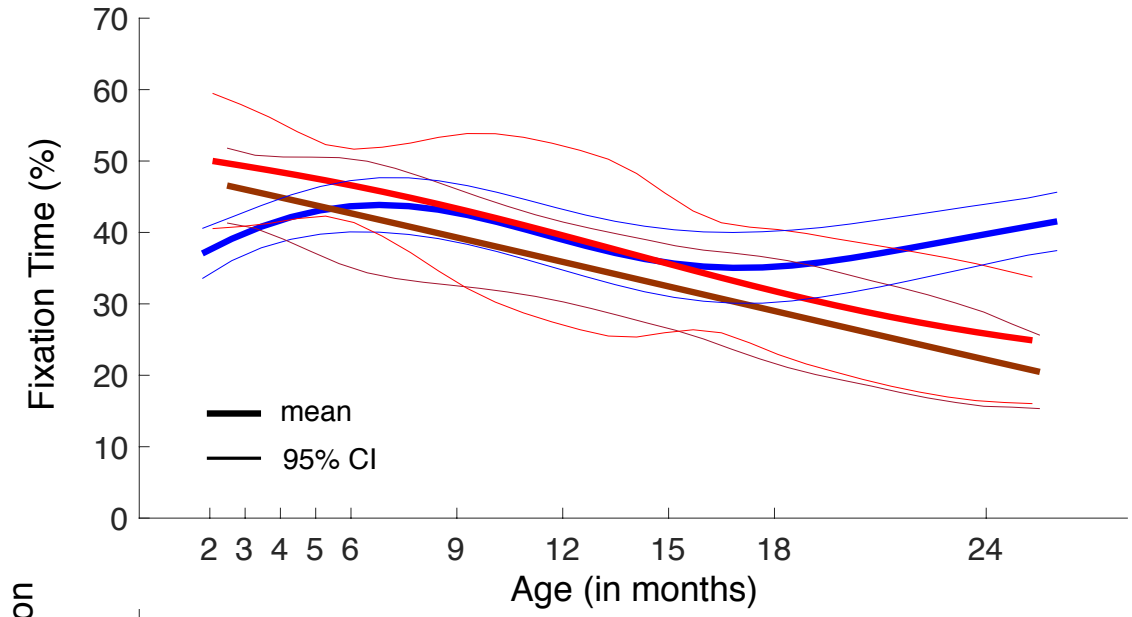
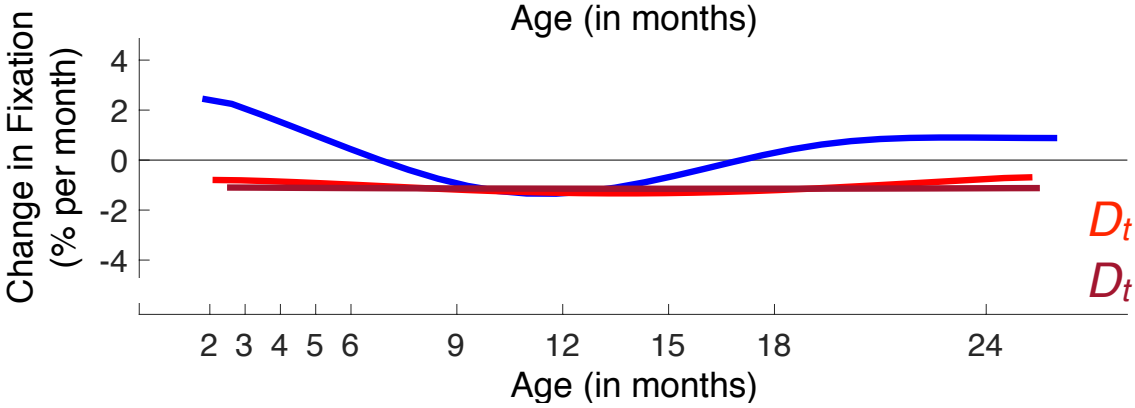
Jones & Klin, *Nature*, 2013.

First Replication Cohort





TD eyes

ASD1 eyes

ASD2 eyes

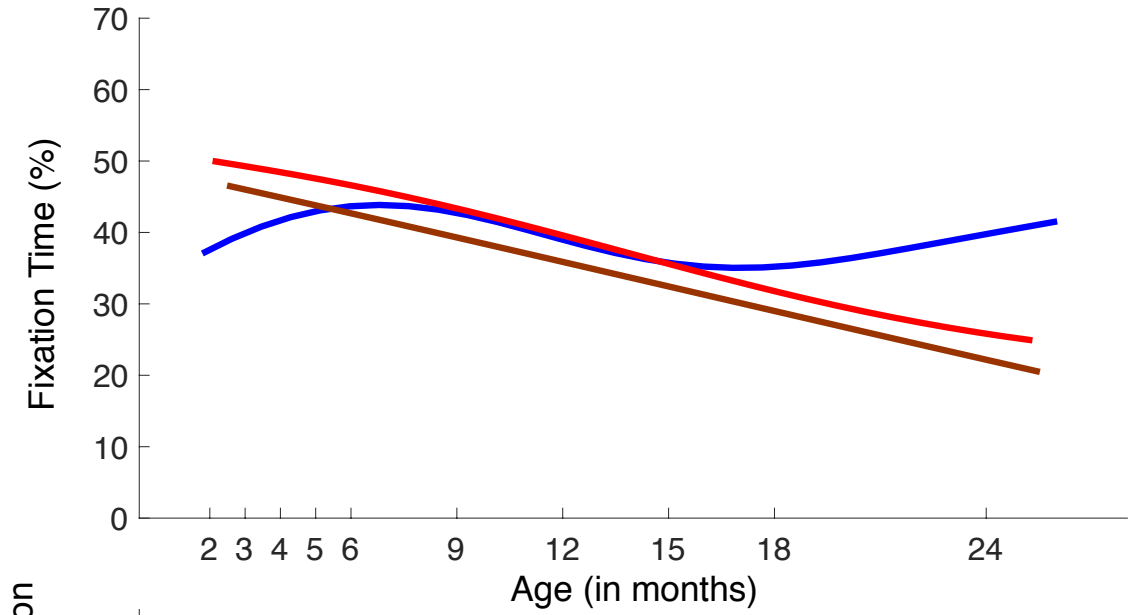
D_t TD eyes

D_t ASD1 eyes

D_t ASD2 eyes

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

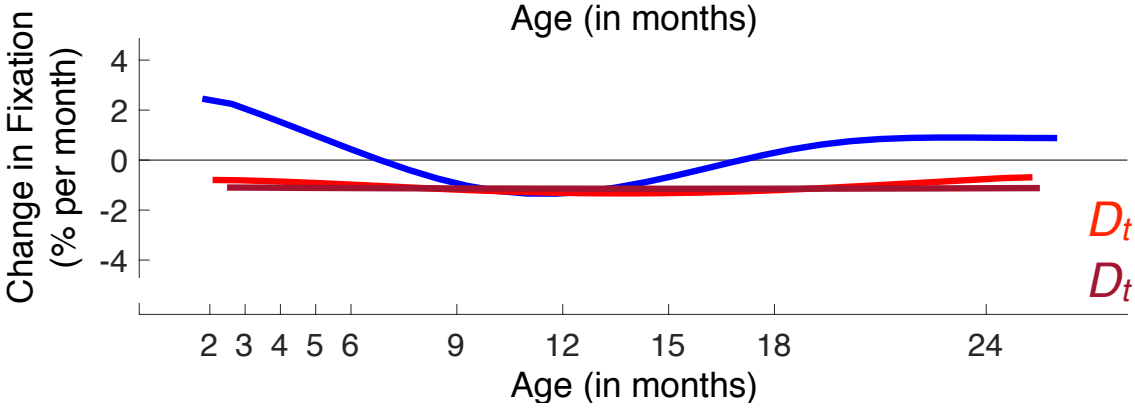
First Replication Cohort



TD eyes

ASD1 eyes

ASD2 eyes



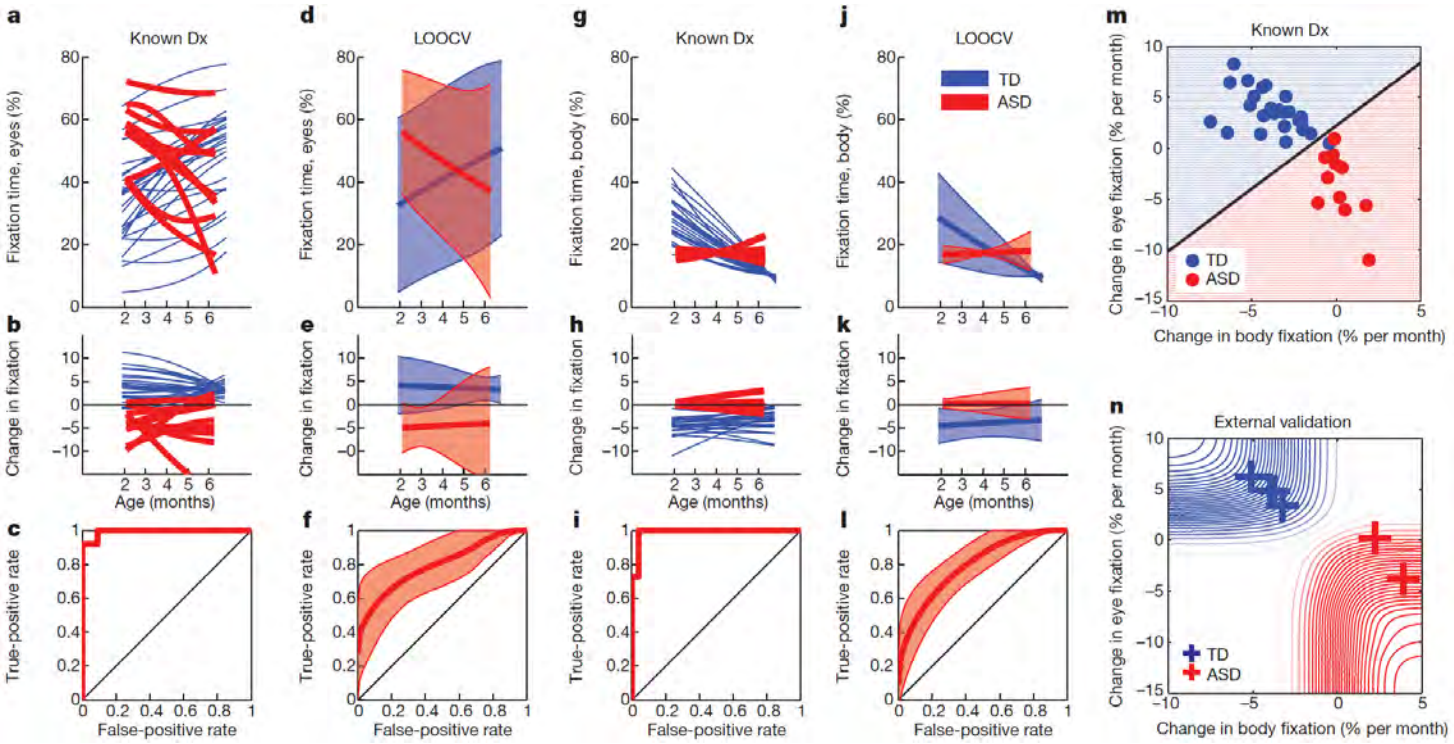
D_t TD eyes

D_t ASD1 eyes

D_t ASD2 eyes

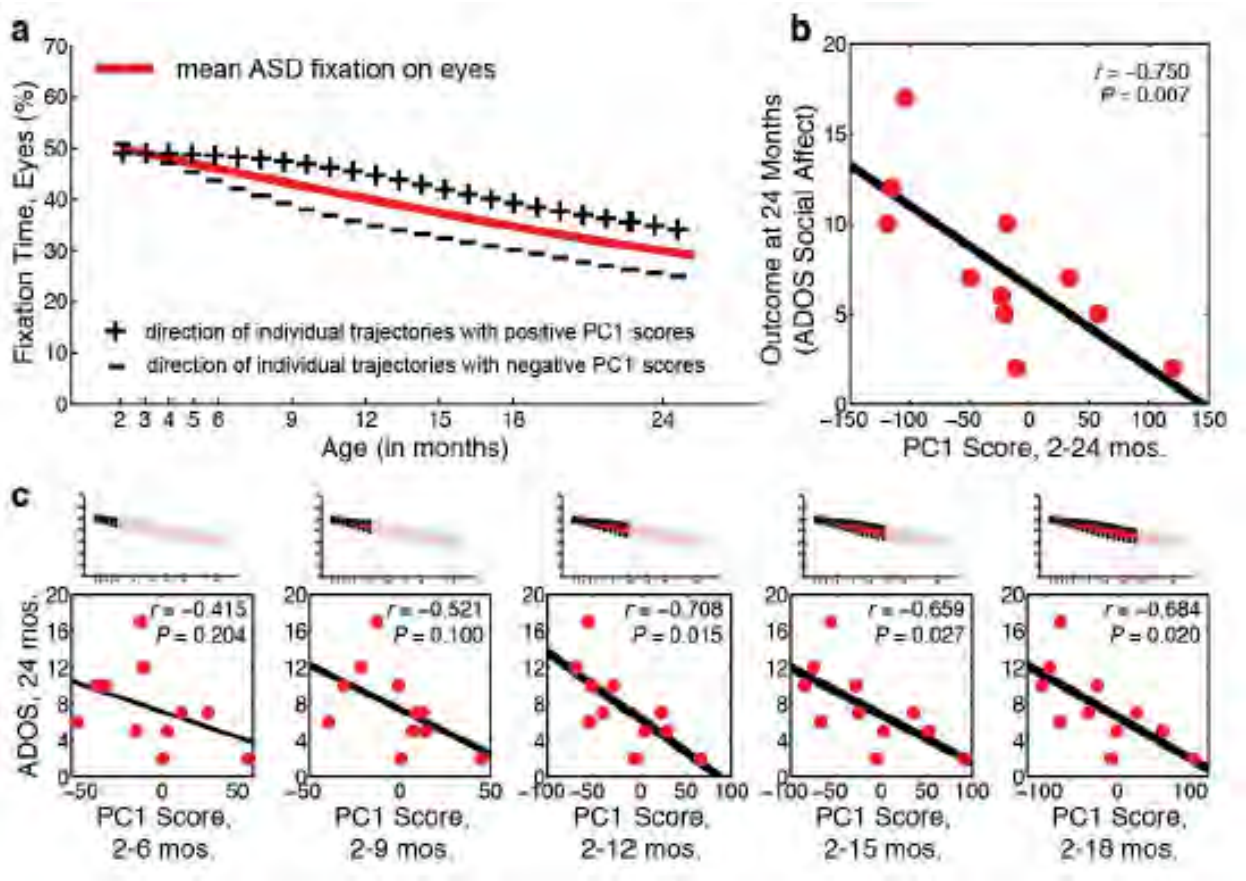
TD, N=63
ASD1, N=11
ASD2, N=13

Eye Fixation in the first 6 months of life



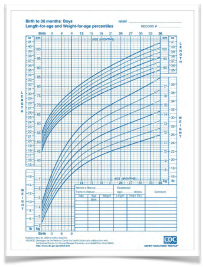
- Markers of ASD in the first 6 months of life
- Predictive of individual child's diagnostic classification at outcome (24-36 months)
- Internal and external validation of results

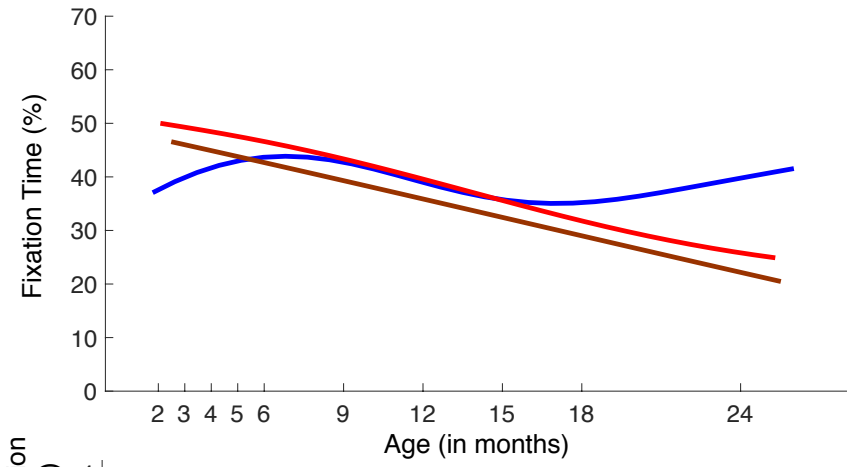
Predicts level of disability at outcome

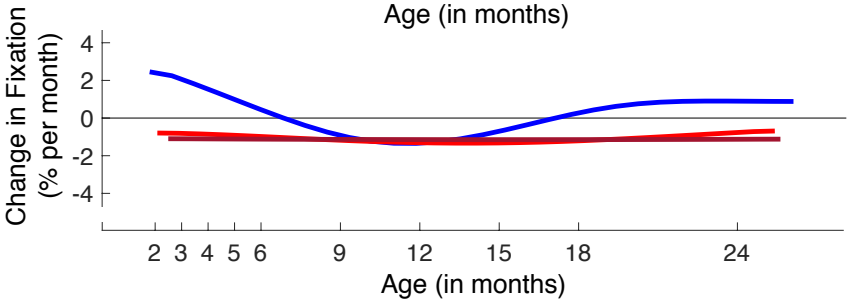


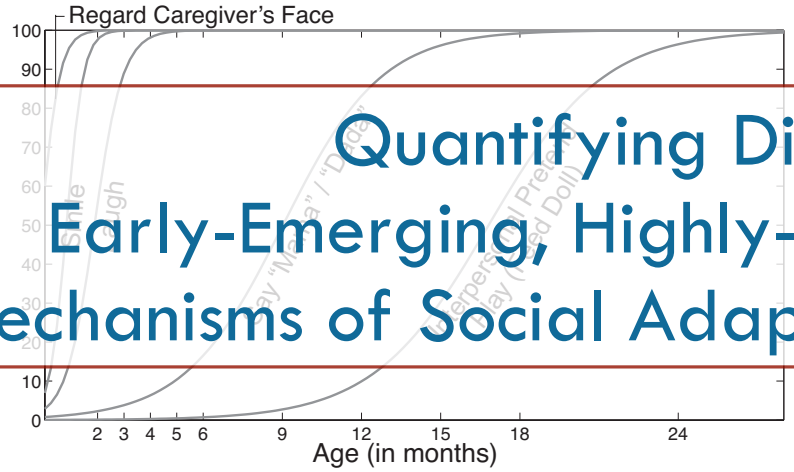
- Decline in eye fixation (2-12 through 2-24 months) predictive of outcome levels of ASD severity at 36 months

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

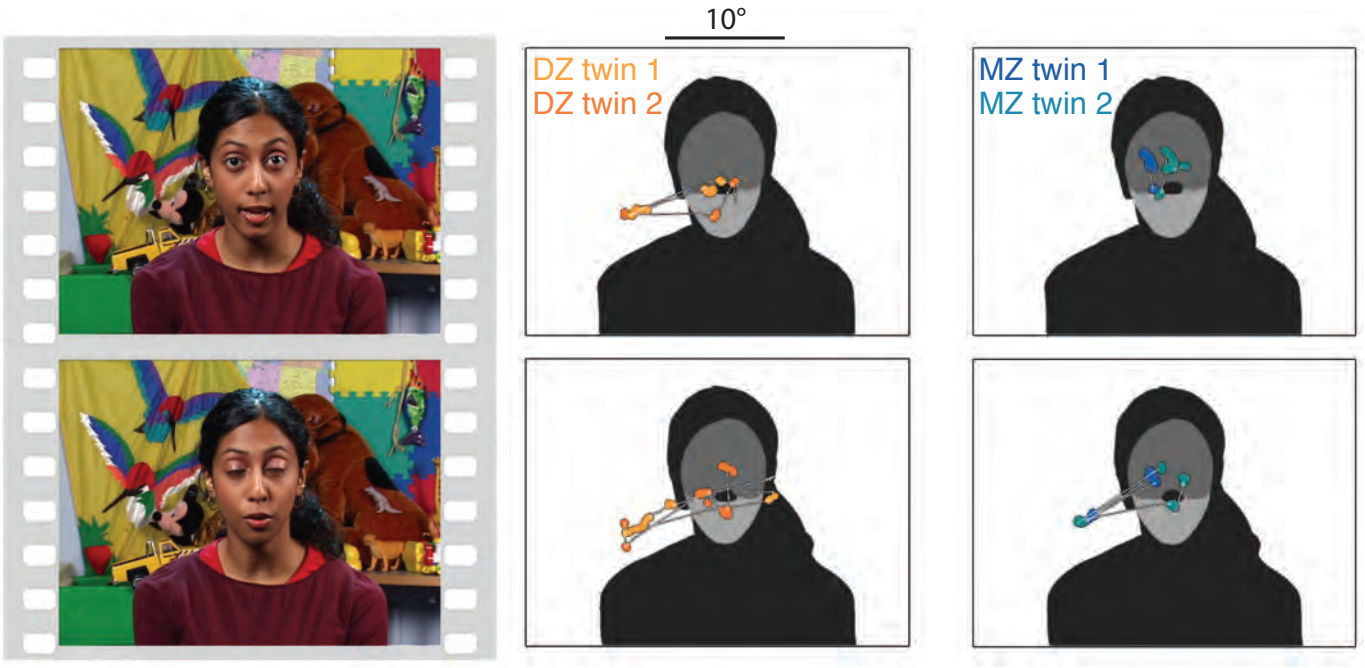
The genetic basis of Social Visual Engagement

Constantino et al.; *Nature*, 2017; 547(7663):340-344

Concordance in social visual engagement as a function of zygosity.


MZ males
Constantino & Colleagues

Social visual engagement when viewing scenes of dyadic caregiver interaction



Constantino et al.; *Nature*, 2017; 547(7663):340-344

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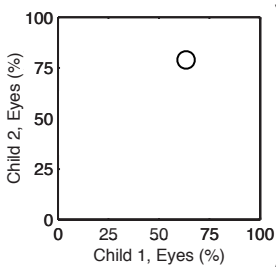
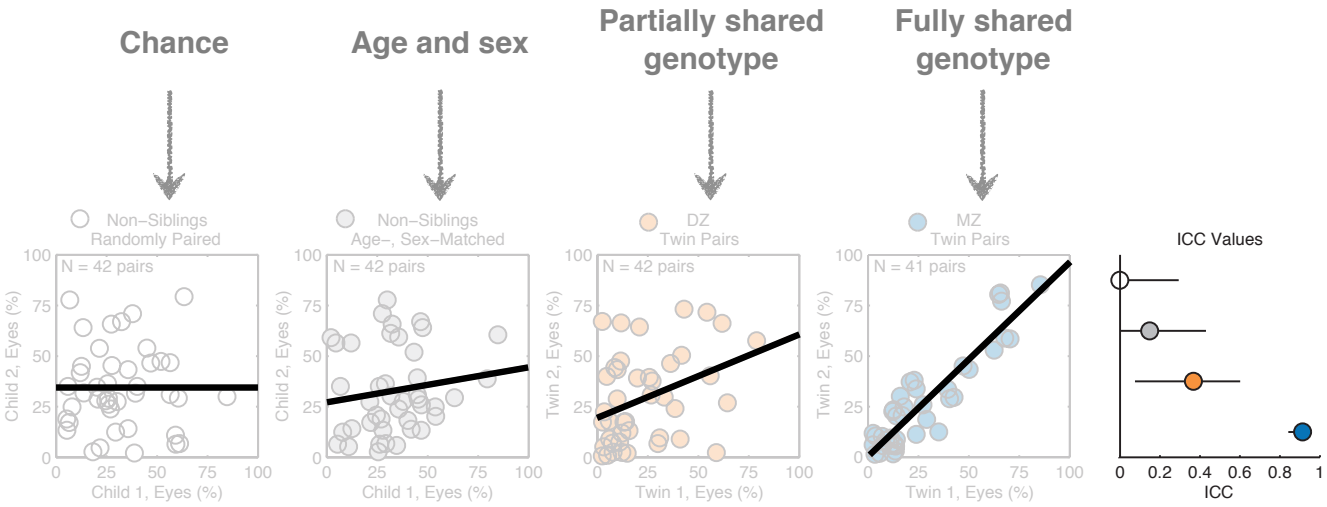


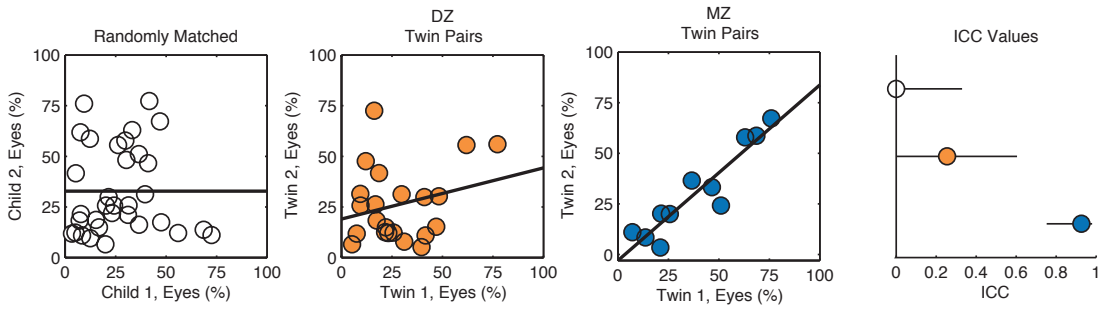
Constantino et al.; *Nature*, 2017; 547(7663):340-344

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



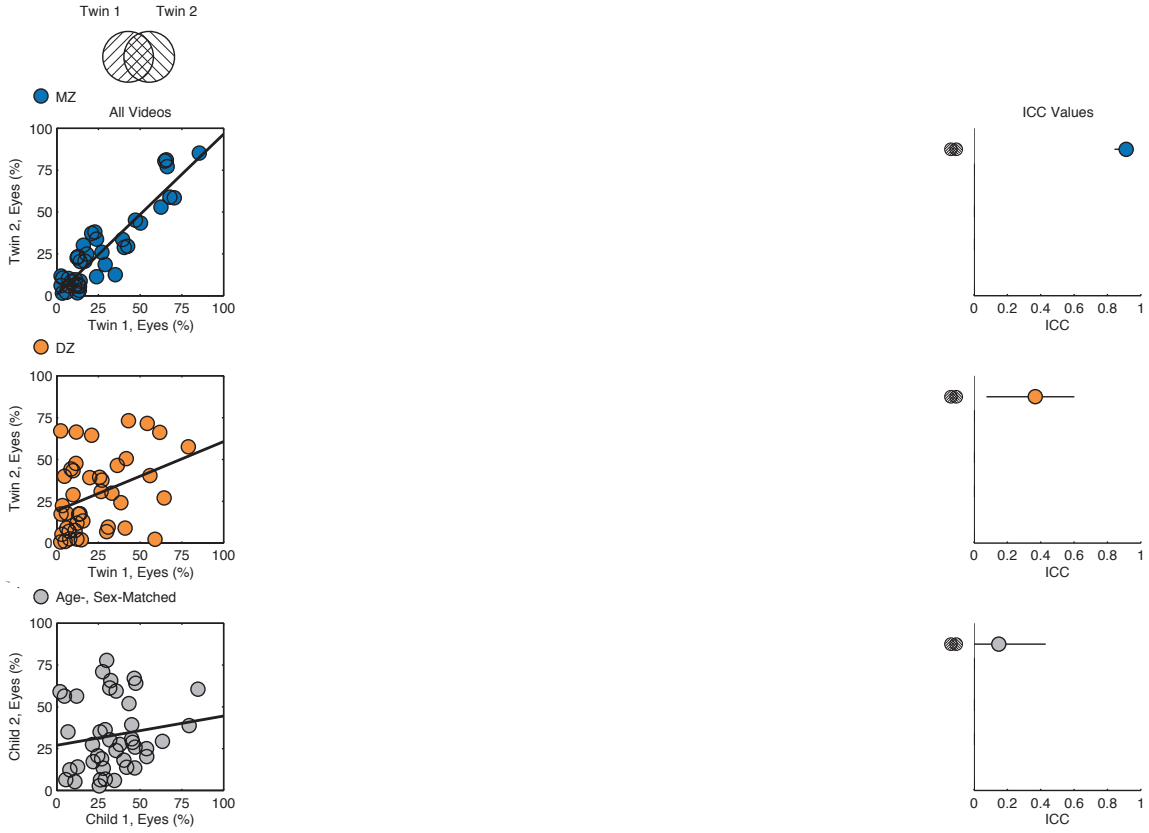
Constantino et al.; *Nature*, 2017; 547(7663):340-344

Strong genetic influence persists across development.



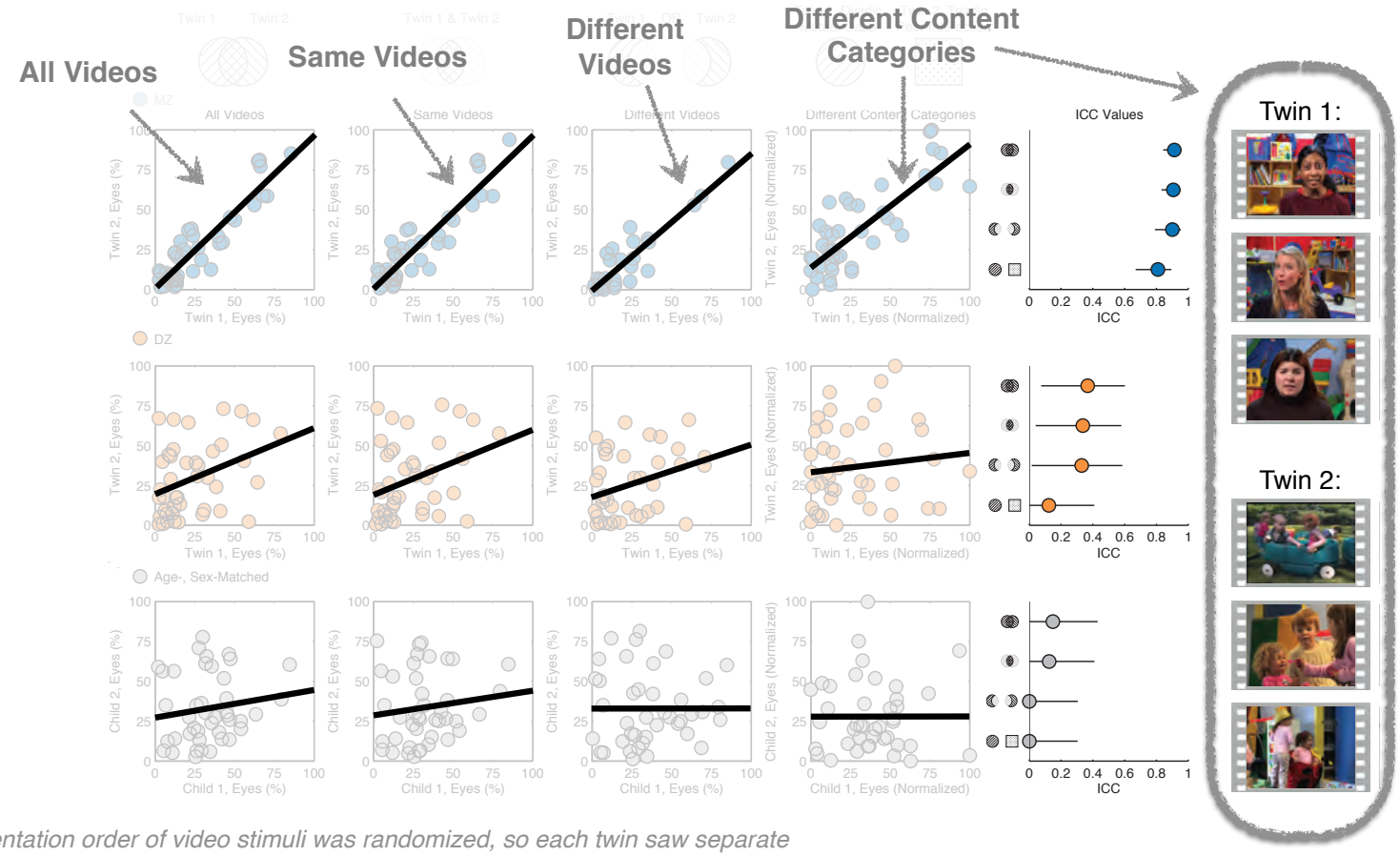
Twins tested again 15 months later, at 36 months.
(N=22 MZ, N=44DZ)

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.



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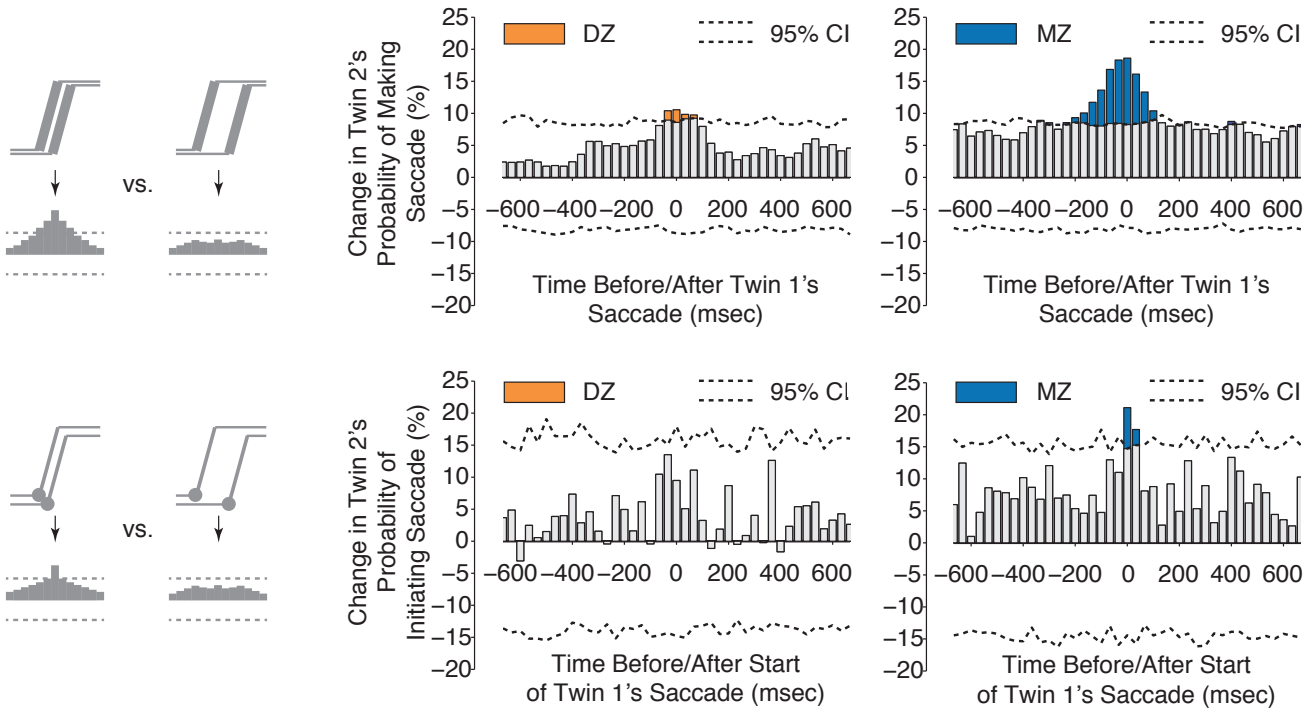
Genetic influence exerts effects on a moment-by-moment basis.

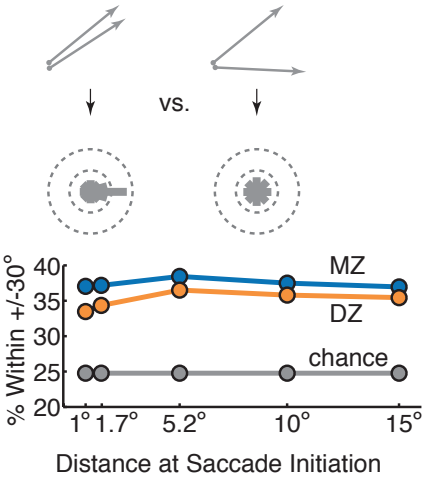

MZ males
Constantino & Colleagues

MZ twins are more likely to…

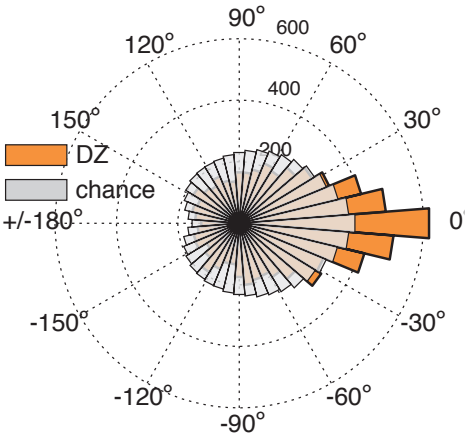


…move their eyes **at the same moments** in time.

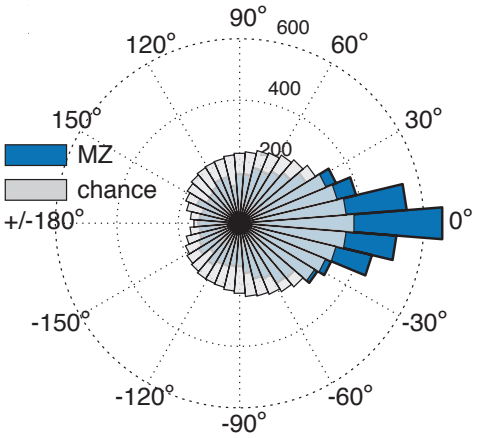
MZ twins are more likely to…



Distance at Saccade Initiation



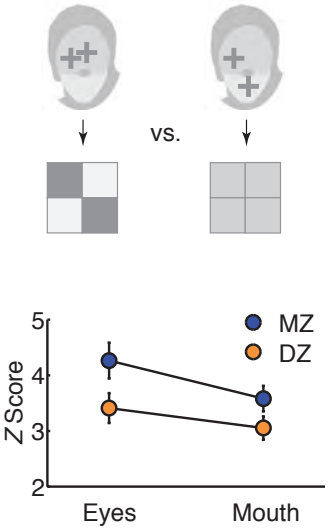
Difference in Saccade Direction

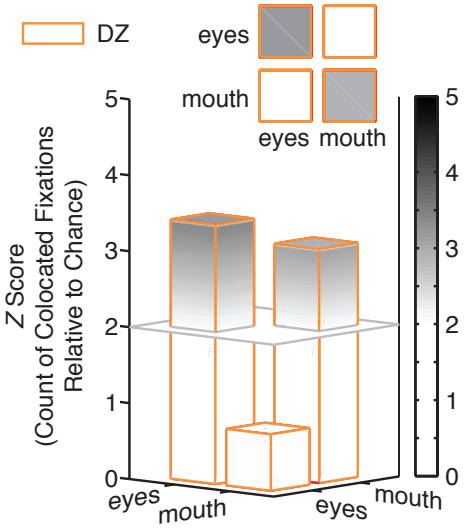


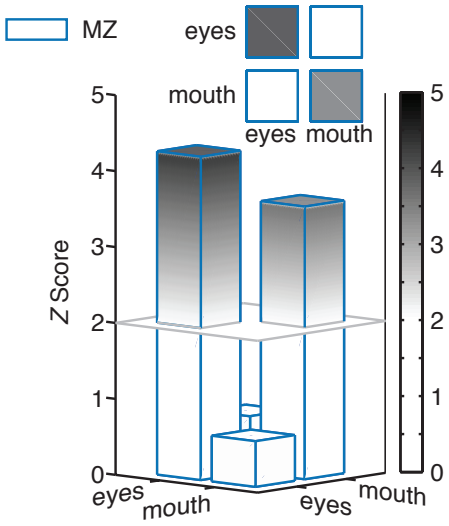
Difference in Saccade Direction

…move their eyes **in the same directions**.

MZ twins are more likely to…

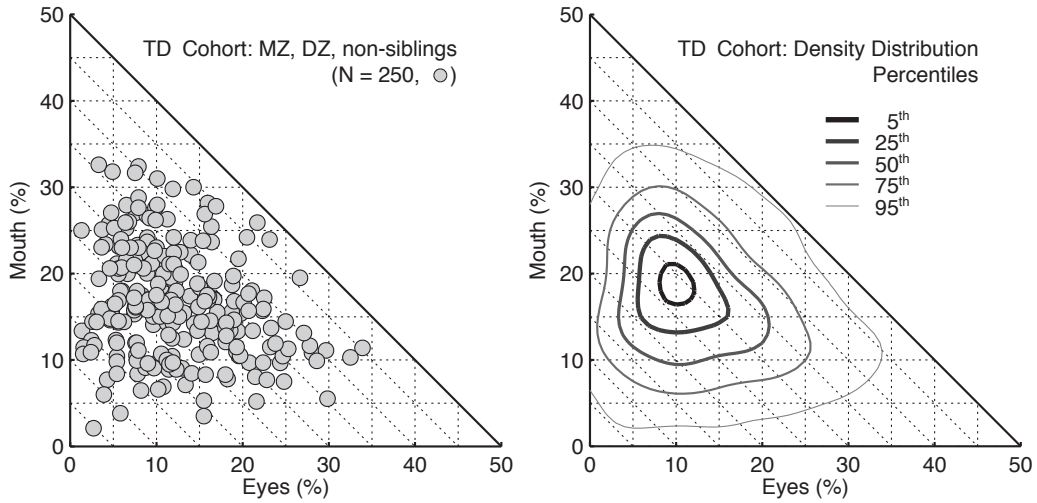






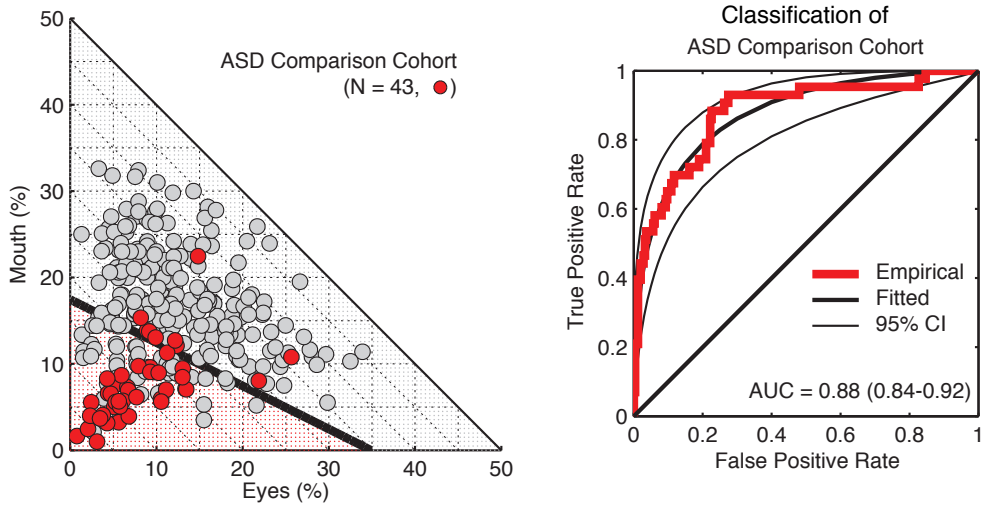
…fixate on the **same semantic content** at the **same moments in time**.

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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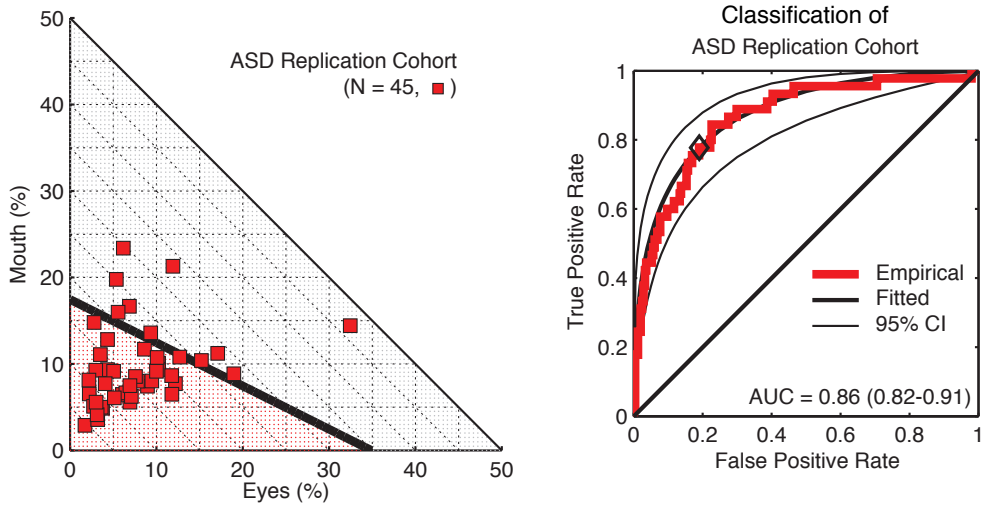


…are also those that most clearly distinguish typically-developing children from those with autism.

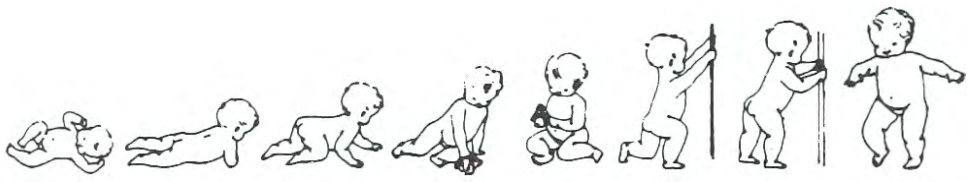
high ***Heritability*** (eye- & mouth-looking)

\+ high ***Probability*** (shifting eyes at same moments,
in same directions,
towards same content)

= profound influence on

human biological niche construction

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

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
- 6,600,00 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 Heat 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

Marcus
AUTISM CENTER
NIH Autism Center of Excellence

Our ultimate goal

To make autism an issue of diversity, not of disability