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

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EMORY UNIVERSITY SCHOOL OF MEDICINE

Children's Healthcare of Atlanta

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NIH Autism Center of Excellence

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

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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

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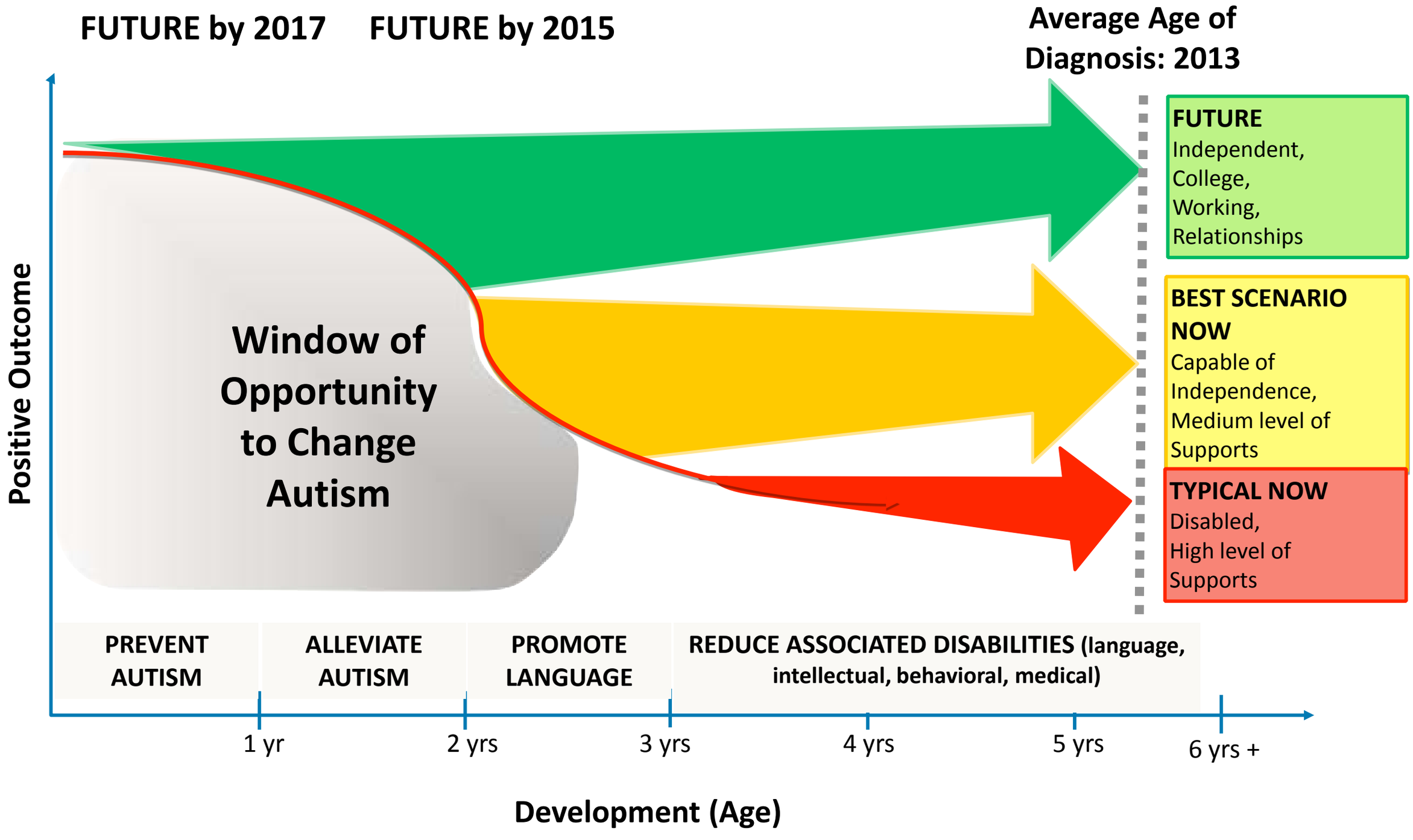
The Realities of Autism:
…Changing the nature of autism for children tomorrow



Jones et al. (2008). Arch Gen Psy, 65(8), 946-54.; Klin et al. (2009). Nature, 459, 257-61.; Jones & Klin (2009). J Am Acad Child & Adoles Psy,, 48(5), 471-3; Shultz et al. (2011). PNAS, 108(52), Jones & Klin (2013). *Nature*, in press.

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The Science of Clinical Care

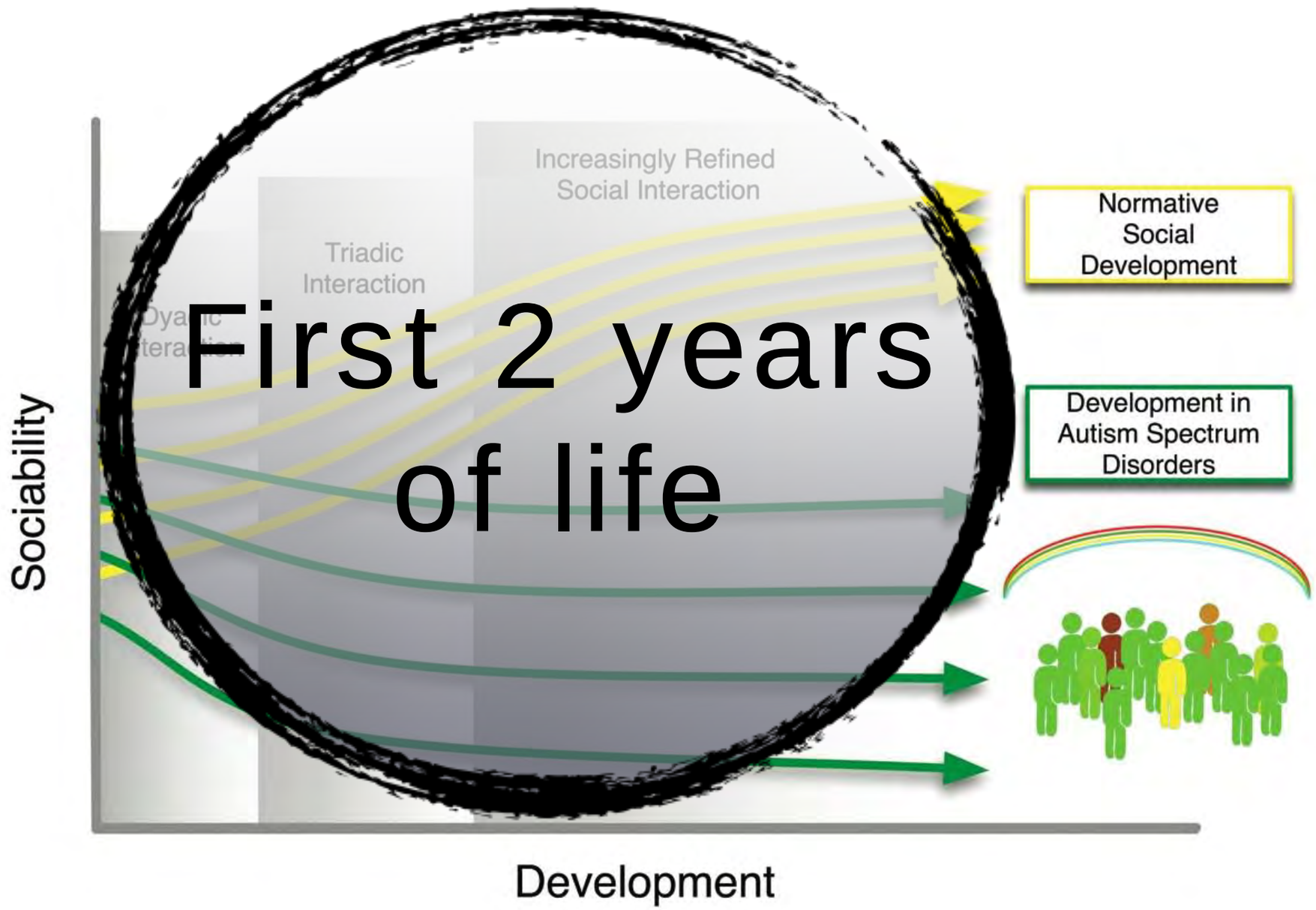
- The largest and most comprehensive center for CLINICAL CARE in the country (5,712 unique patients seen in 2013; ~ 8 fold larger than leading centers)
  - Clinical Assessment, Medical Care & Treatment Programs
  - Care Coordination and Advocacy
  - Community and Educational Outreach

- 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

GENETIC LIABILITY

MECHANISMS OF SOCIALIZATION

BEHAVIORAL SYMPTOMS



Jones & Klin (2009). ***J of the American Academy of Child and Adolescent Psychiatry, 48(5): 471-3.***

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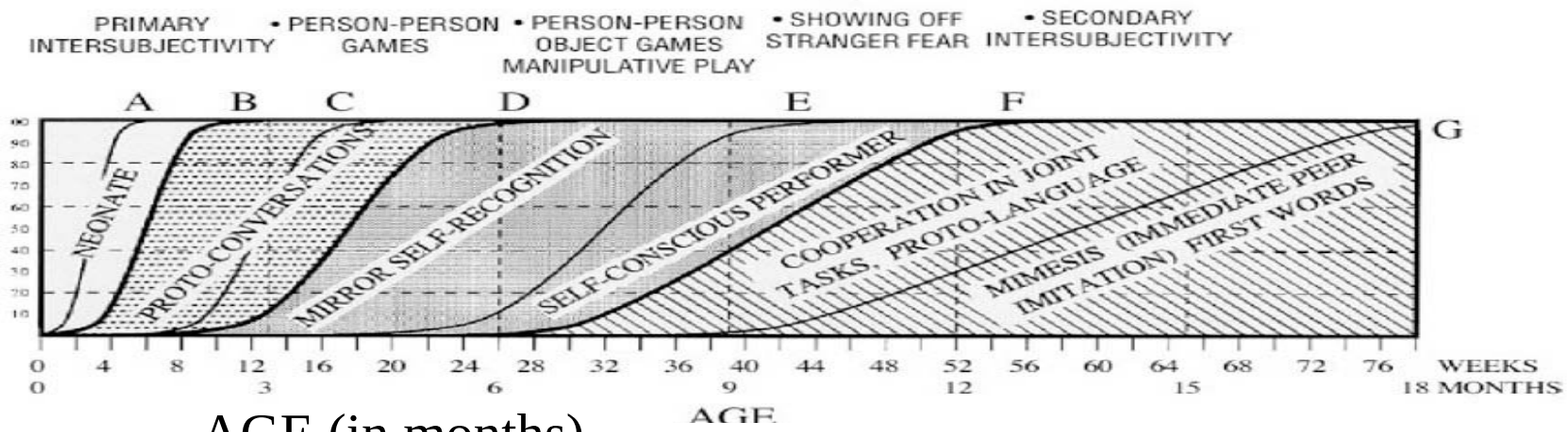
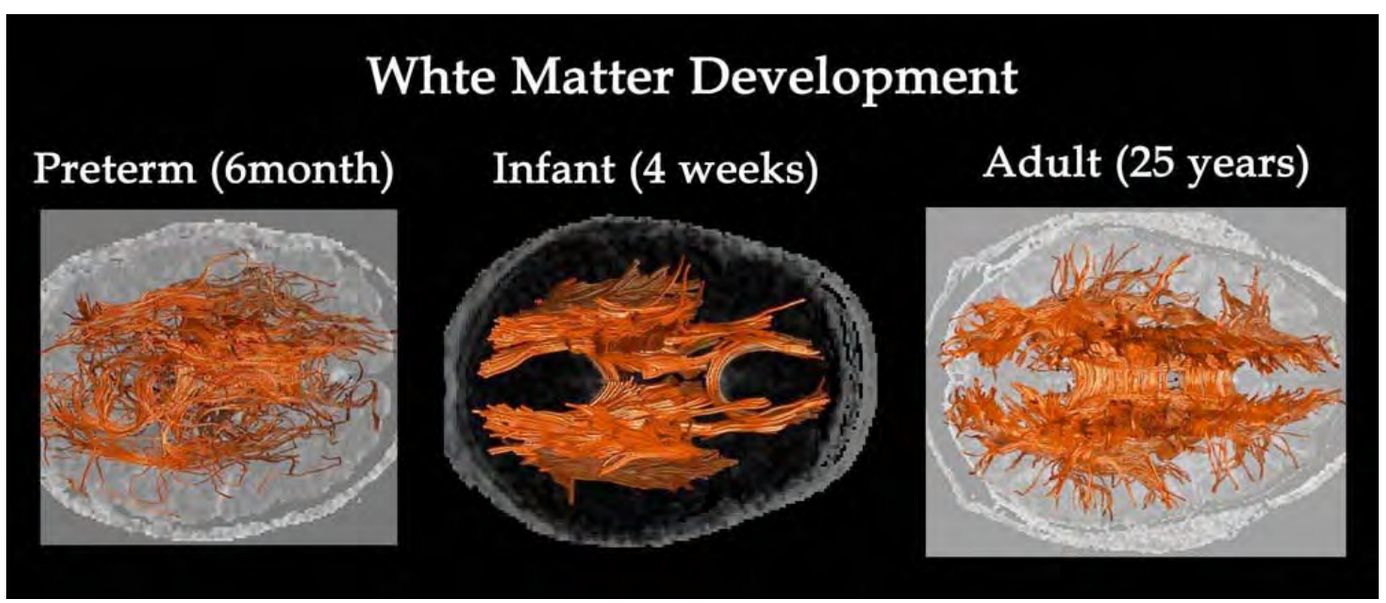
Autism Disrupts the Platform for Brain Development

MH Johnson PhD



AGE (in months)

birth — 18 months

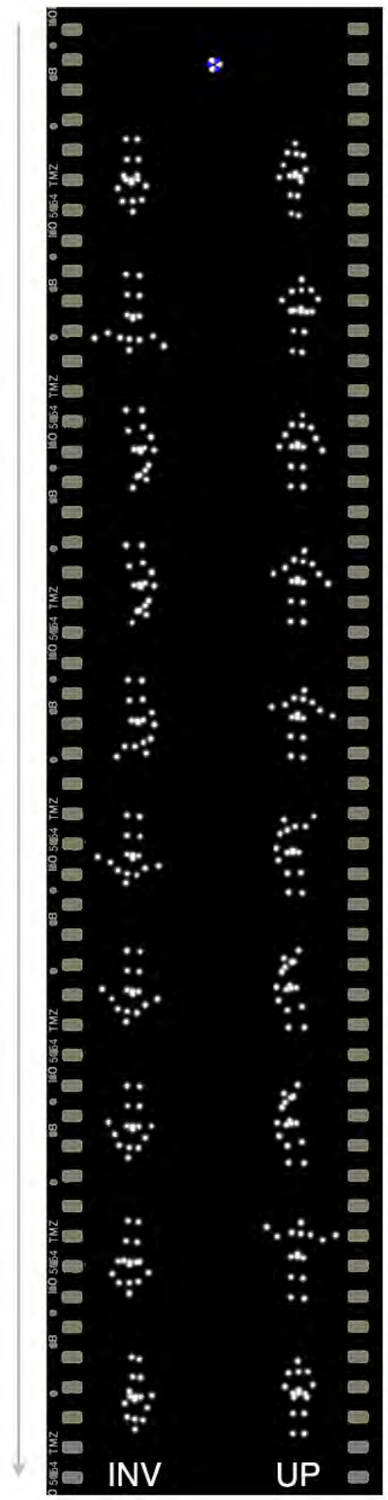


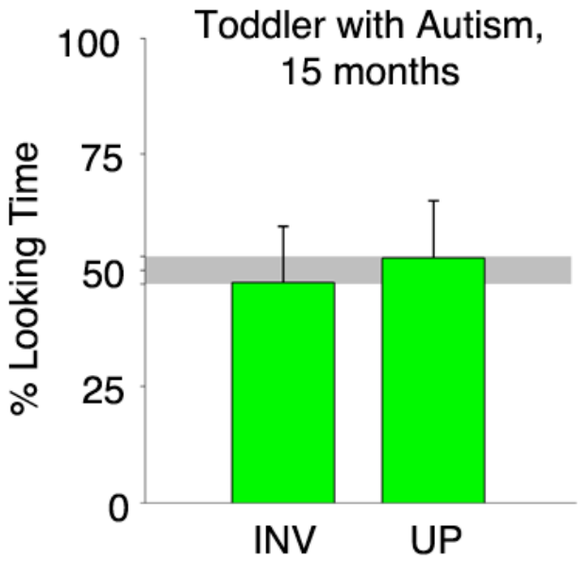
H-J Park PhD

The Brain Becomes Who We Are....

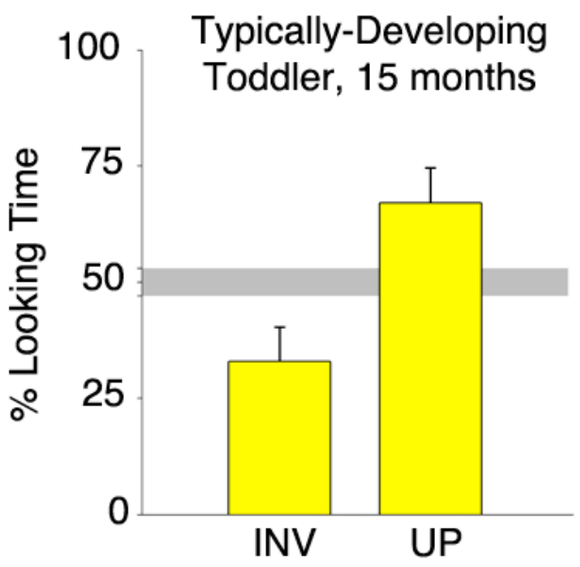
JE LeDoux PhD

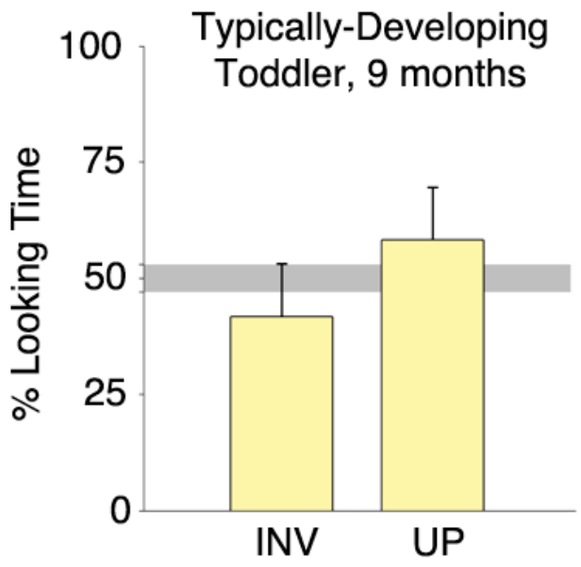
Attention to Biological Motion





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





Klin & Jones (2008). *Developmental Science* 11(1),40-6.

nature International weekly journal of science

Vol 459 | 14 May 2009 | doi:10.1038/nature07868

LETTERS

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

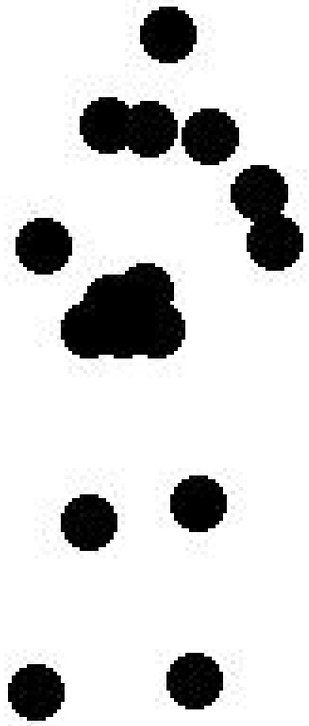
Ami Klin[1], David J. Lin[1]†, Phillip Gorrindo[1]†, Gordon Ramsay[1,2] & Warren Jones[1,3]

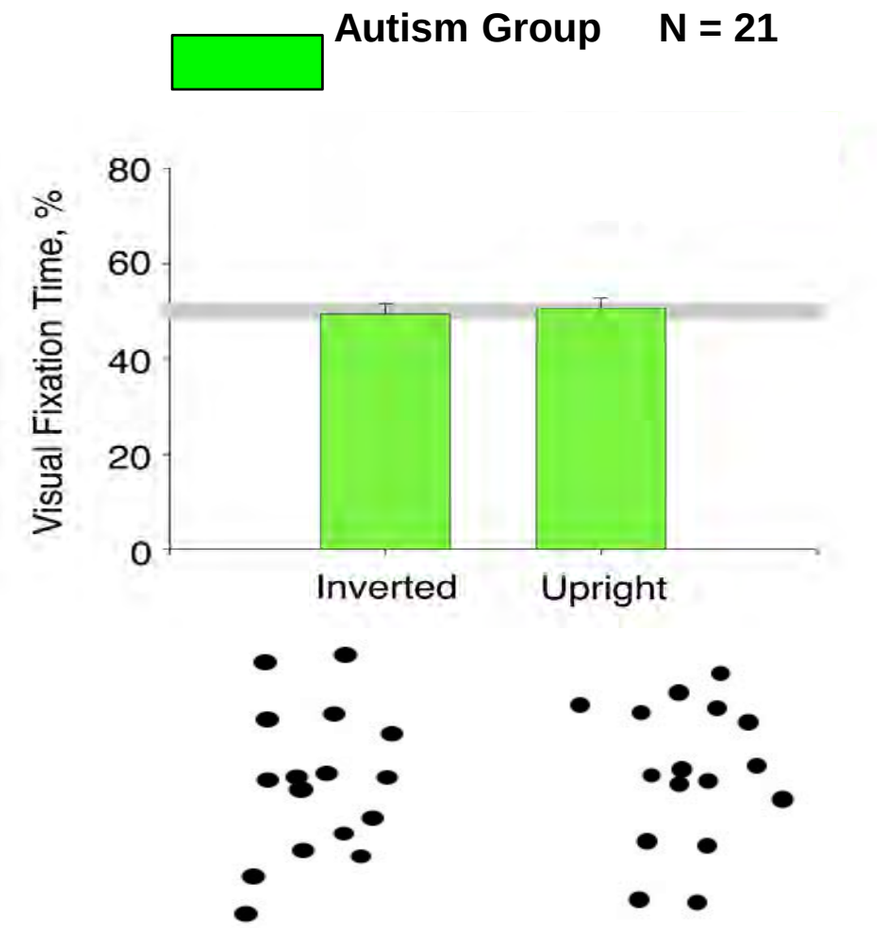
Typically developing human infants preferentially attend to biological motion within the first days of life[1]. This ability is highly conserved across species[2,3] and is believed to be critical for filial attachment and for detection of predators[4]. The neural underpinnings of biological motion perception are overlapping with brain regions involved in perception of basic social signals such as facial expression and gaze direction[5], and preferential attention to biological motion is seen as a precursor to the capacity for attributing intentions to others[6]. However, in a serendipitous observation[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

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[5]).

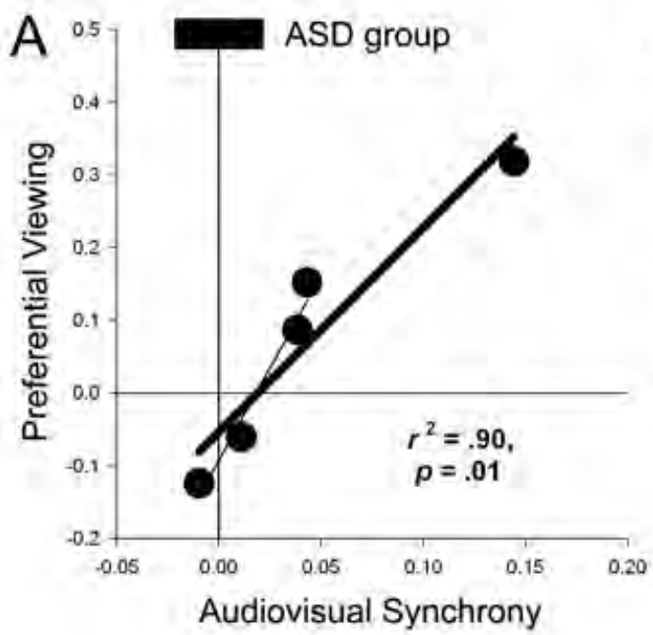
Notably, many of the same behaviours have also been shown as deficits in children with autism: deficits in social interaction, diminished eye contact and reduced looking at others, problems with imitation, deficits in recognizing facial expressions, and difficulties following another's gaze[20]. Autism is a lifelong, highly prevalent, and strongly genetic disorder defined by impairments in social and communicative functioning and by pronounced behavioural rigidities[21]. Although the preponderance of evidence points to prenatal factors instantiated in infancy, knowledge of the first two years of life in

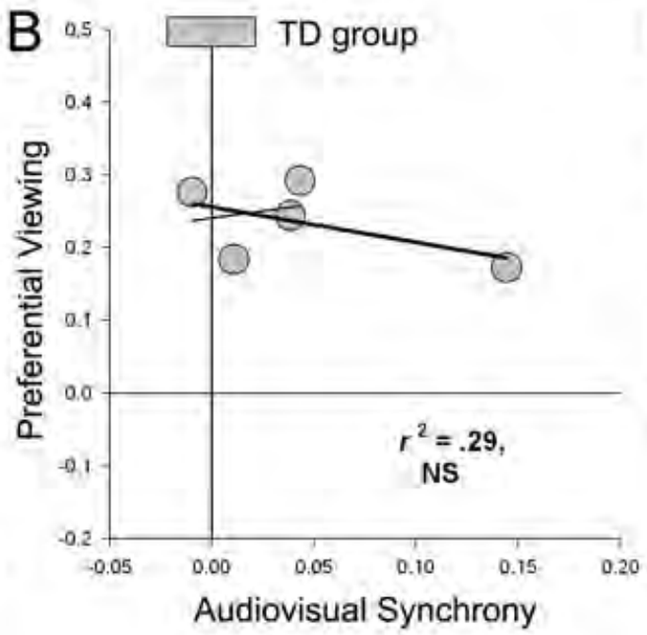
Exploring Audiovisual Synchrony

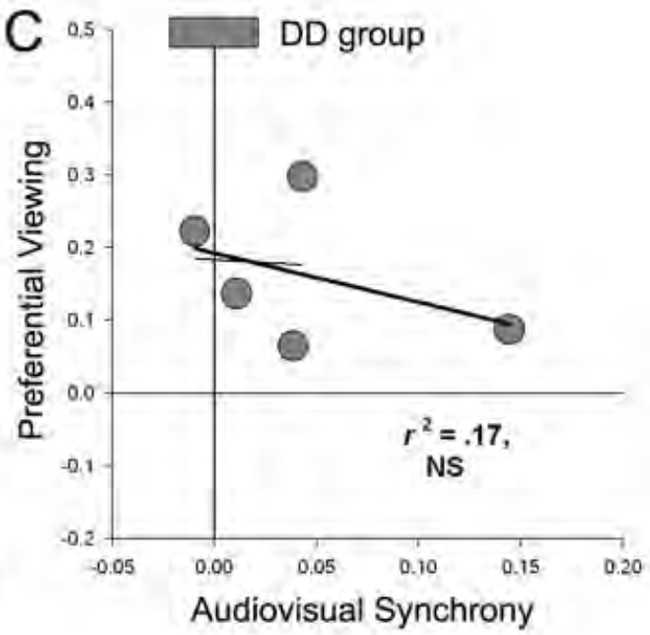


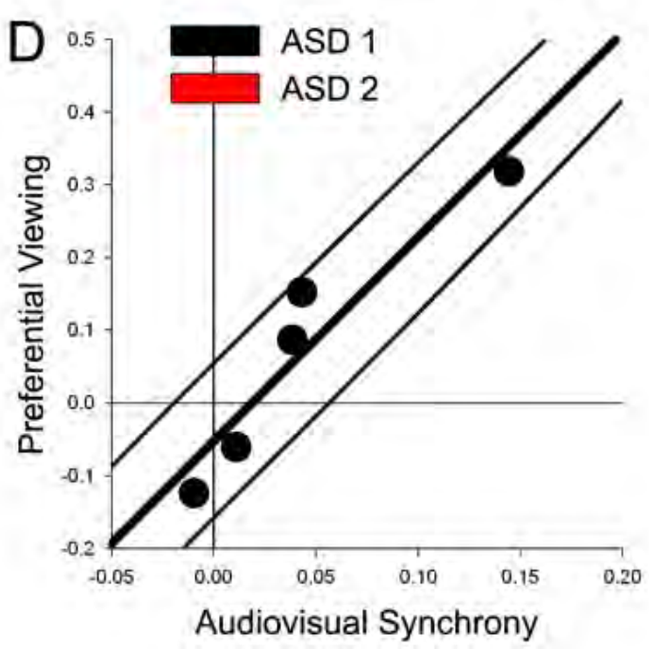


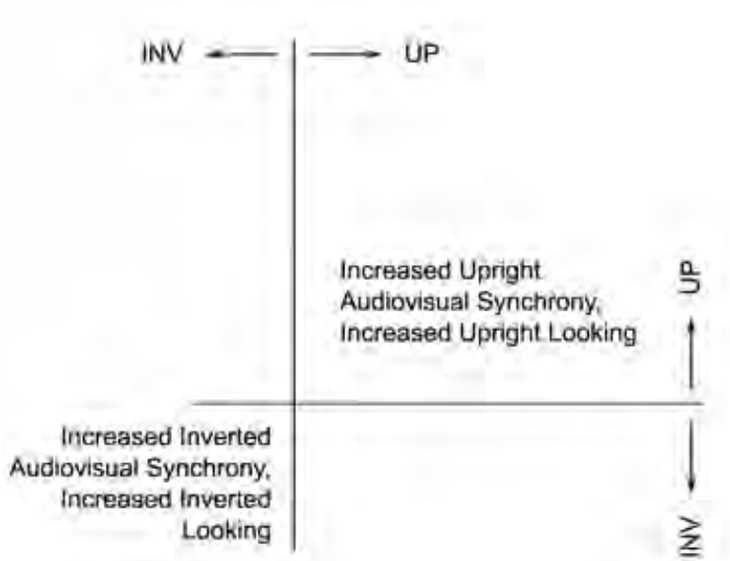
- A “pat-a-cake” finding led to the hypothesis that children’s visual behavior was being guided by physical, not social contingencies.









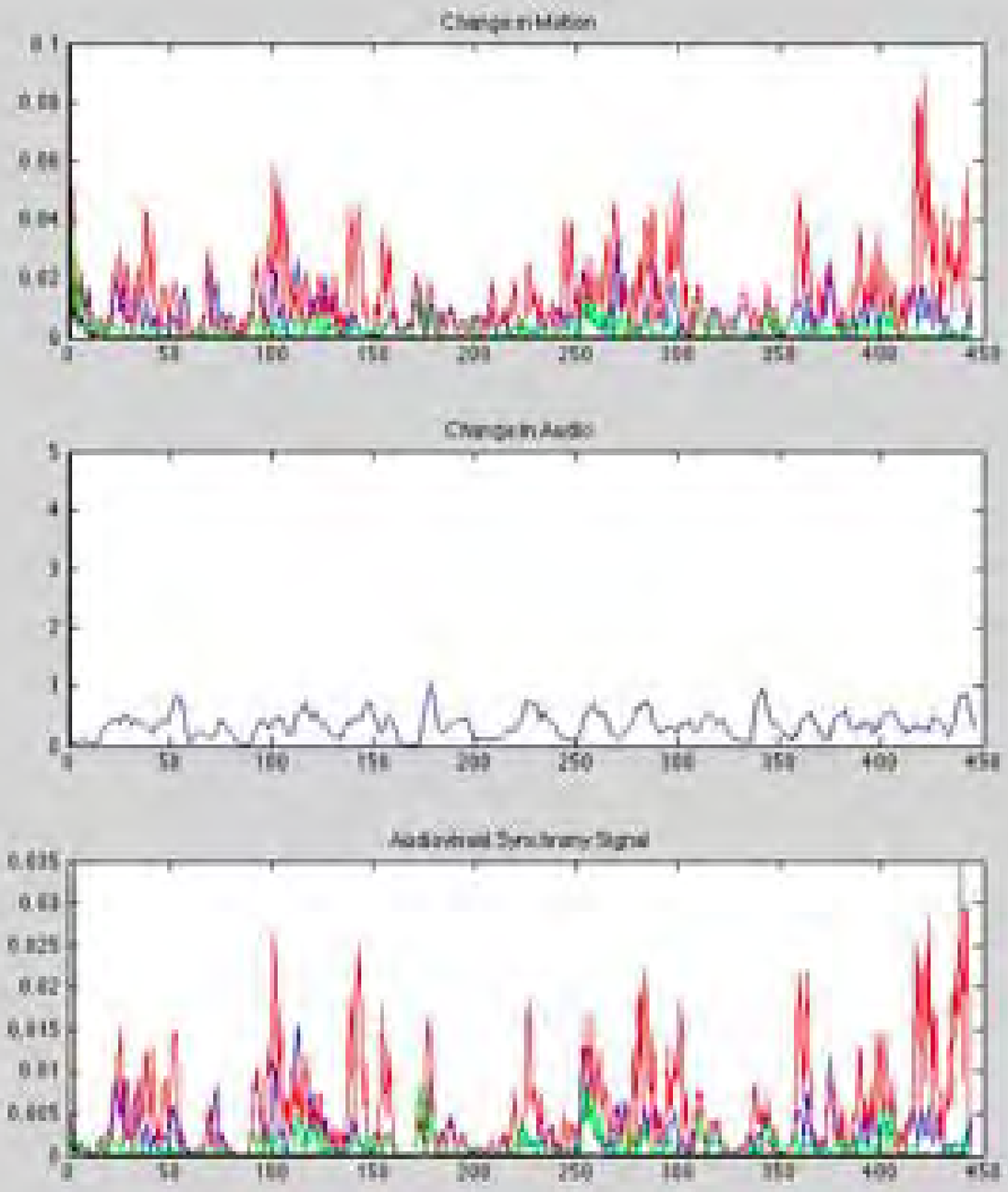


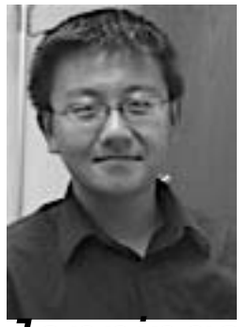
Klin, Lin, Gorrindo, Ramsay, & Jones (2009). *Nature, 459, 257-261.*

Patterns of visual fixation to approaching caregiver

Jones, Carr, Klin (2008). *Archives of General Psychiatry*. 65(8):946-54.

Watching a face … but seeing physical properties?

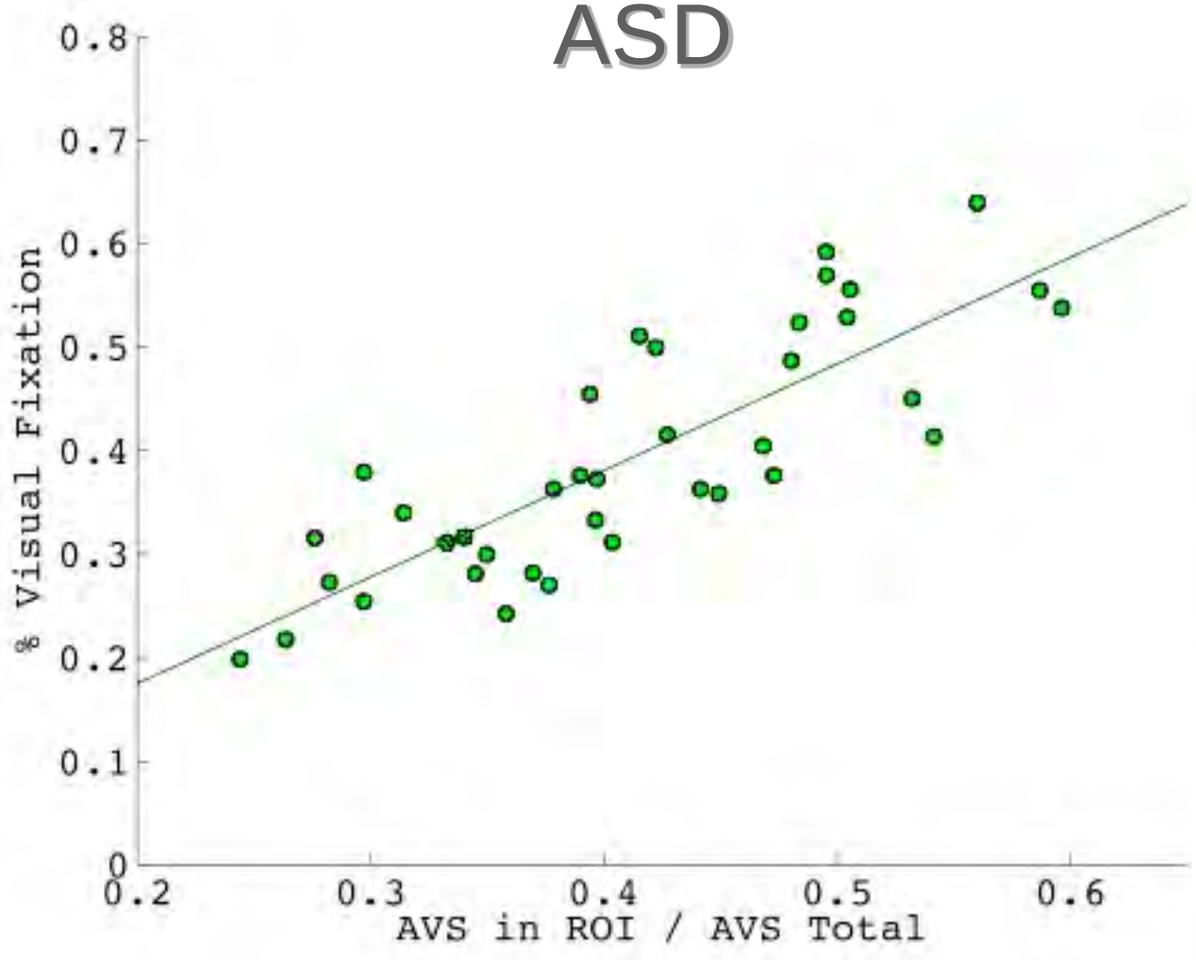




Jennings
Xu

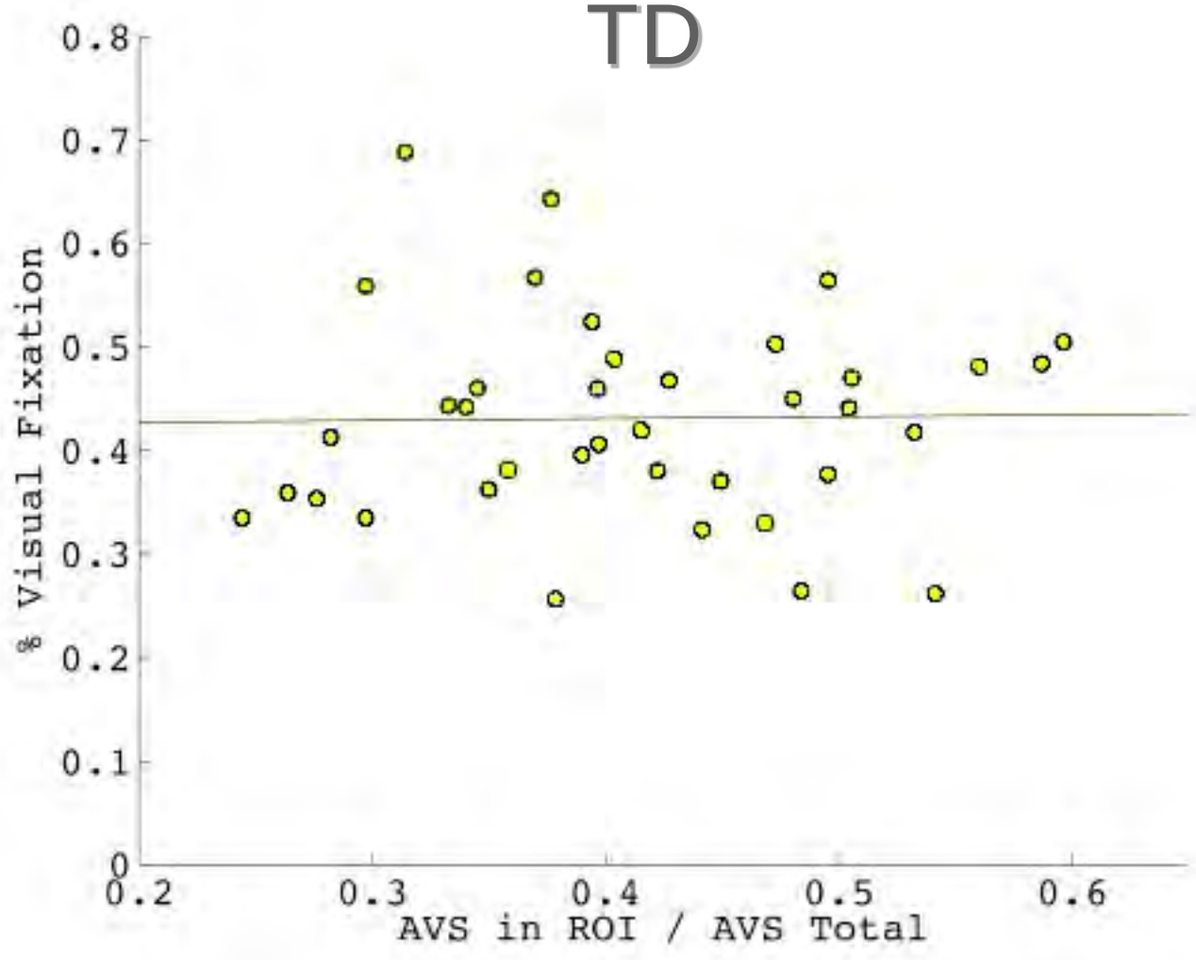
Fixation on Mouth and Eyes as a Function of Audiovisual Synchrony

ASD



	R^2	p
Eye	0.296	0.016
Mouth	0.302	0.015
Both	0.685	<1.5e-10

TD

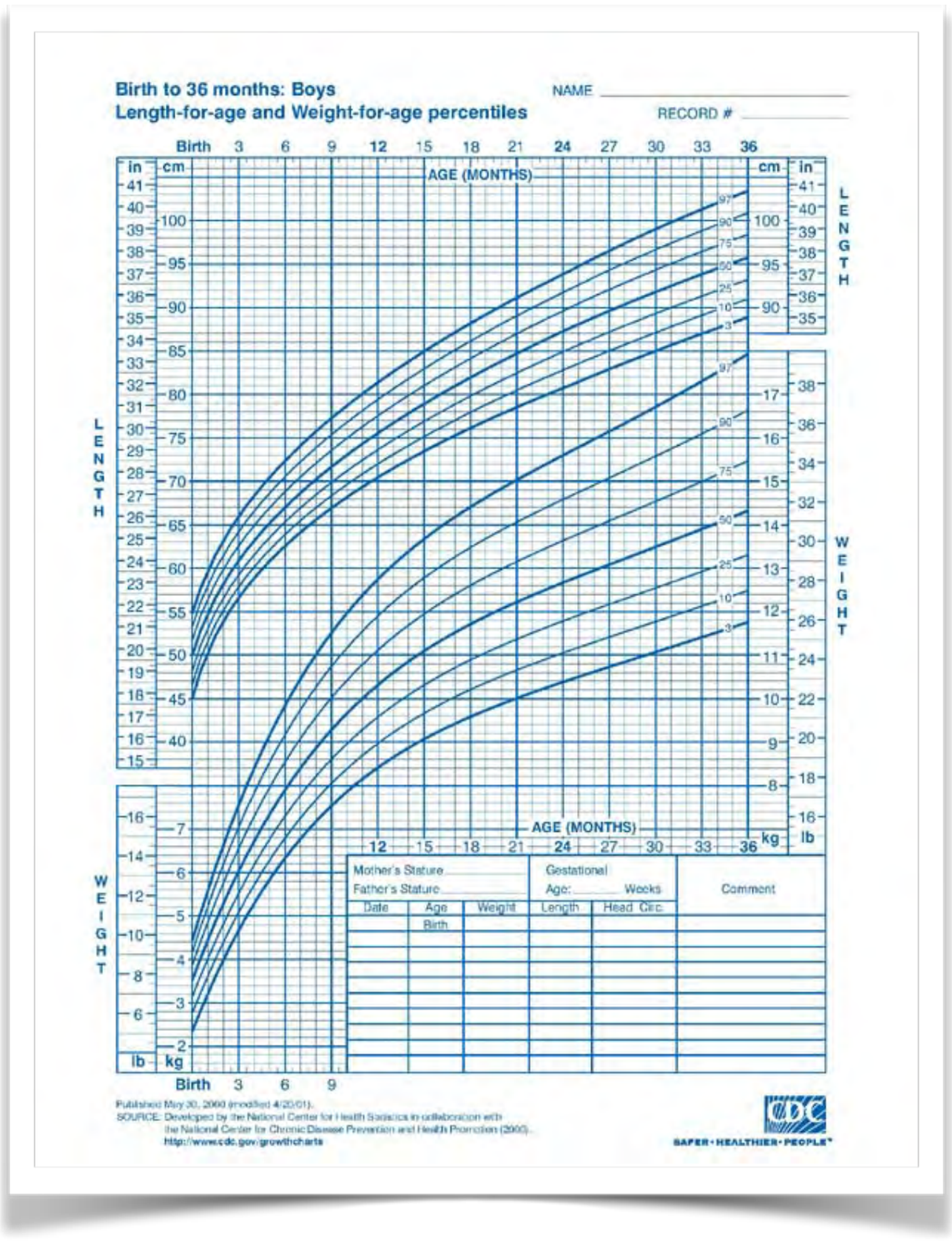


	R^2	p
Eye	0.111	0.164
Mouth	0.161	0.089
Both	0.0003	0.919

The Brain Becomes Who We Are....

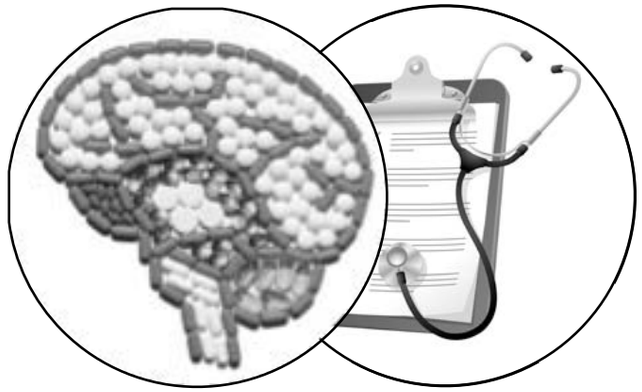
JE LeDoux PhD

Growth Charts of Social Engagement

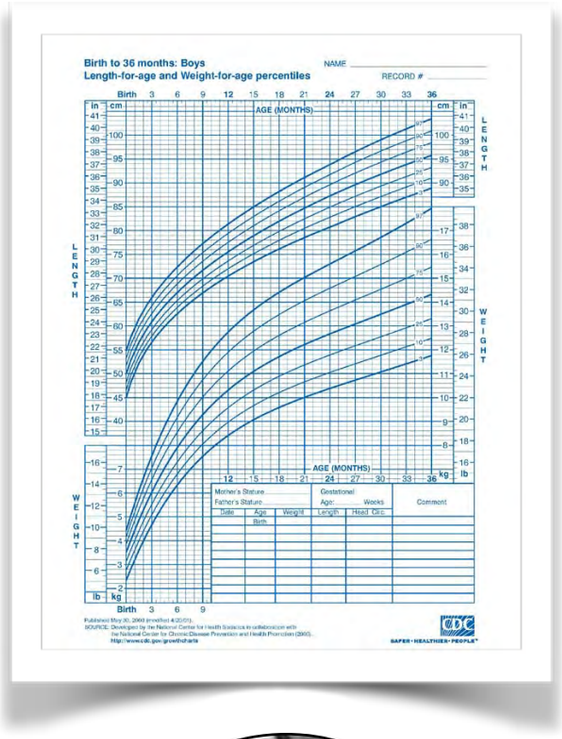


Strategic Plan

Diagnosis & Treatment



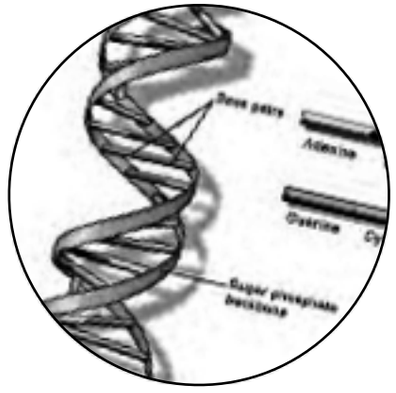
Psychopharmacology & Clinical Trials



Behavioral Neuroscience

Animal Models

Neurobiology



Genetics

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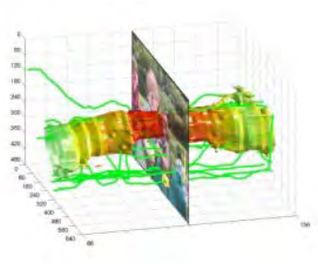
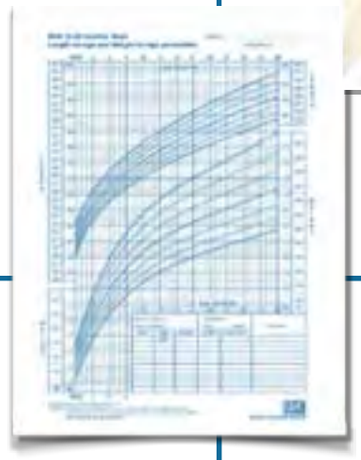
An NIH Autism Center of Excellence

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

EMORY | YERKES NATIONAL PRIMATE RESEARCH CENTER

Georgia Tech

nature International weekly journal of science

LETTER

doi:10.1038/nature12715

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]

Deficits in eye contact have been a hallmark of autism[1,2] since the condition's initial description[3]. They are cited widely as a diagnostic feature[4] and figure prominently in clinical instruments[5]; 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

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[1,2]) 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[20] (10 males, 2 females), indicating a conversion rate of 20.3%[19]. 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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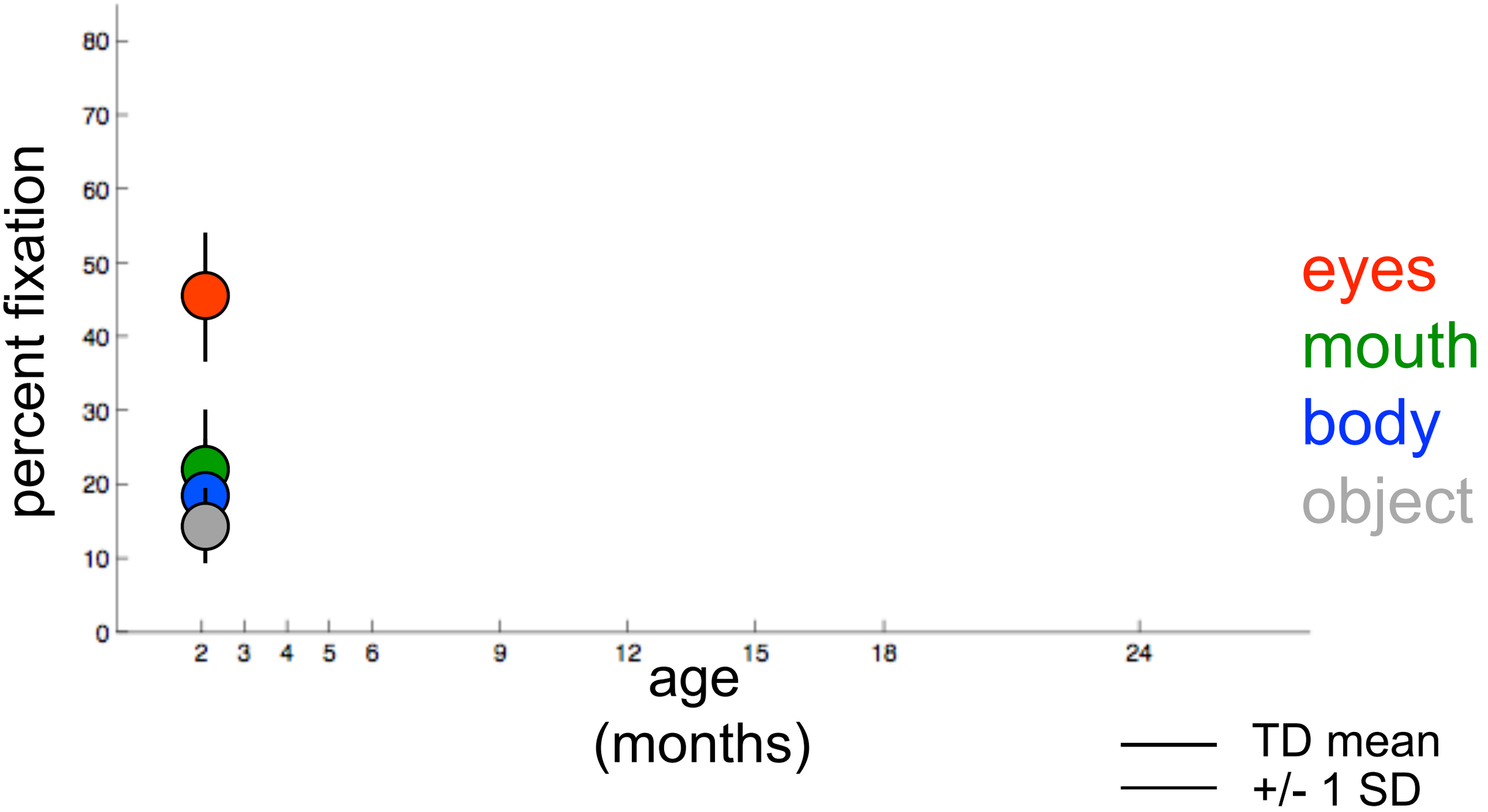
D:048 H:299 V:292
01:14:08:29

Growth Charts of Social Visual Engagement

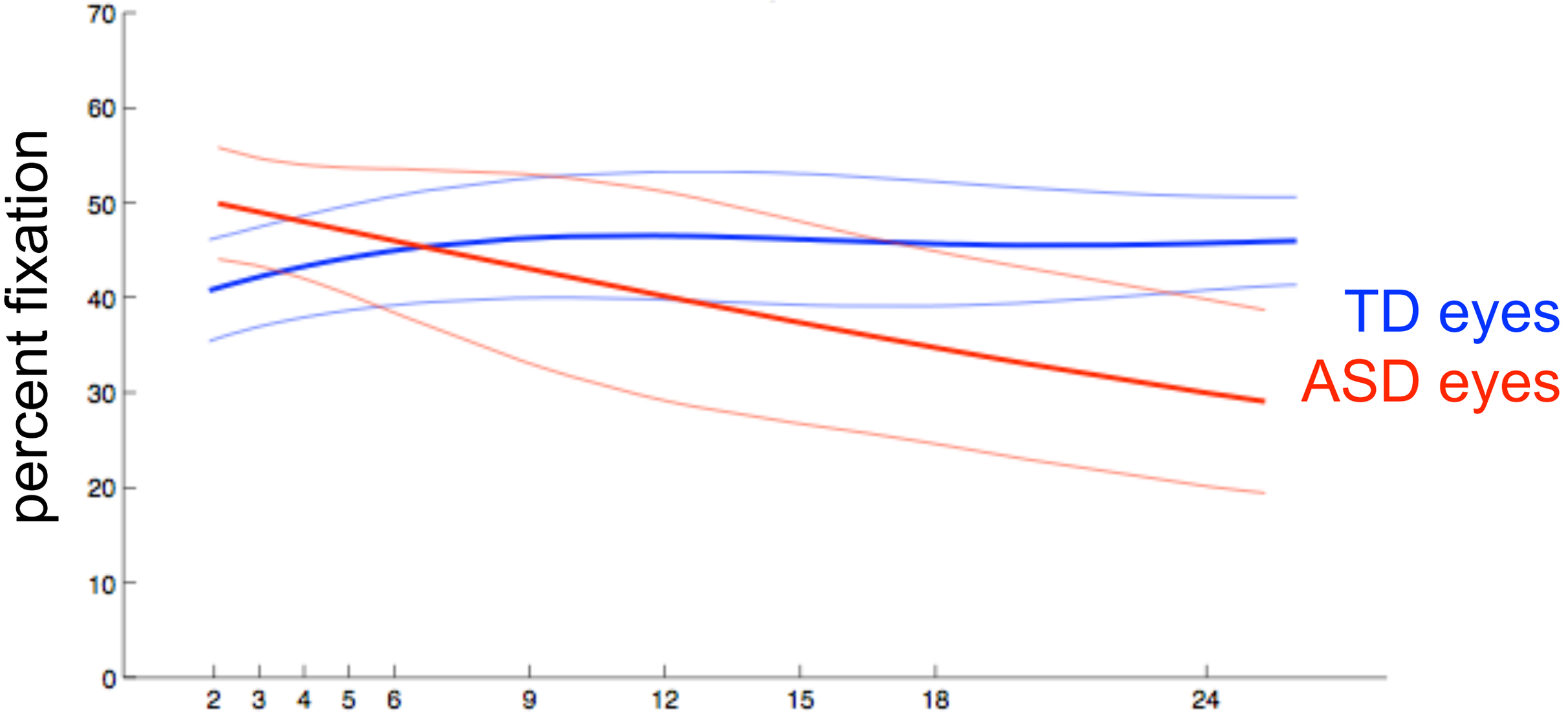
(Typically-Developing Children)



Jones & Klin (2013). ***Nature, 504, 427-431.***

Eye Fixation

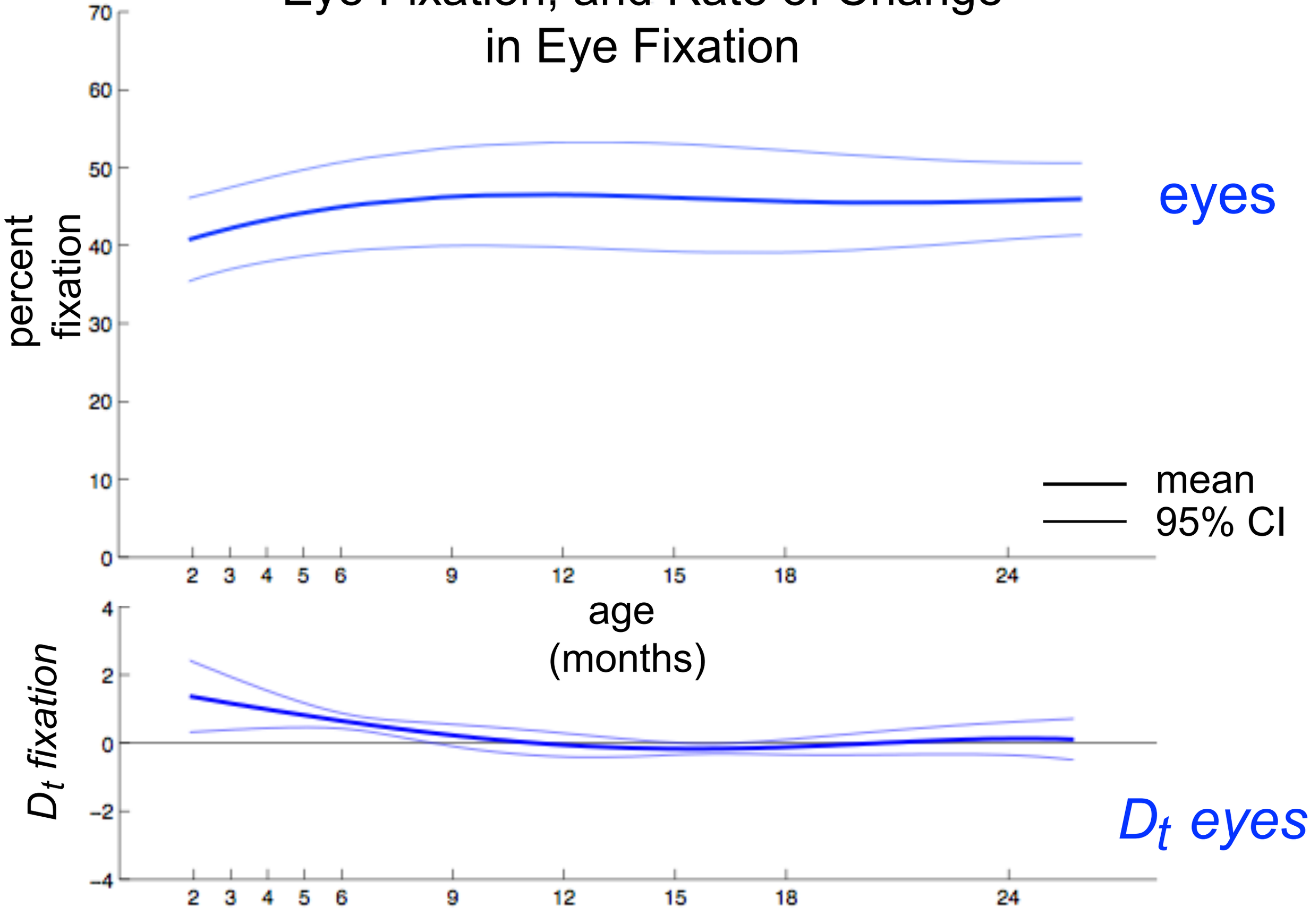
Children with ASD relative to Typically-Developing Norms



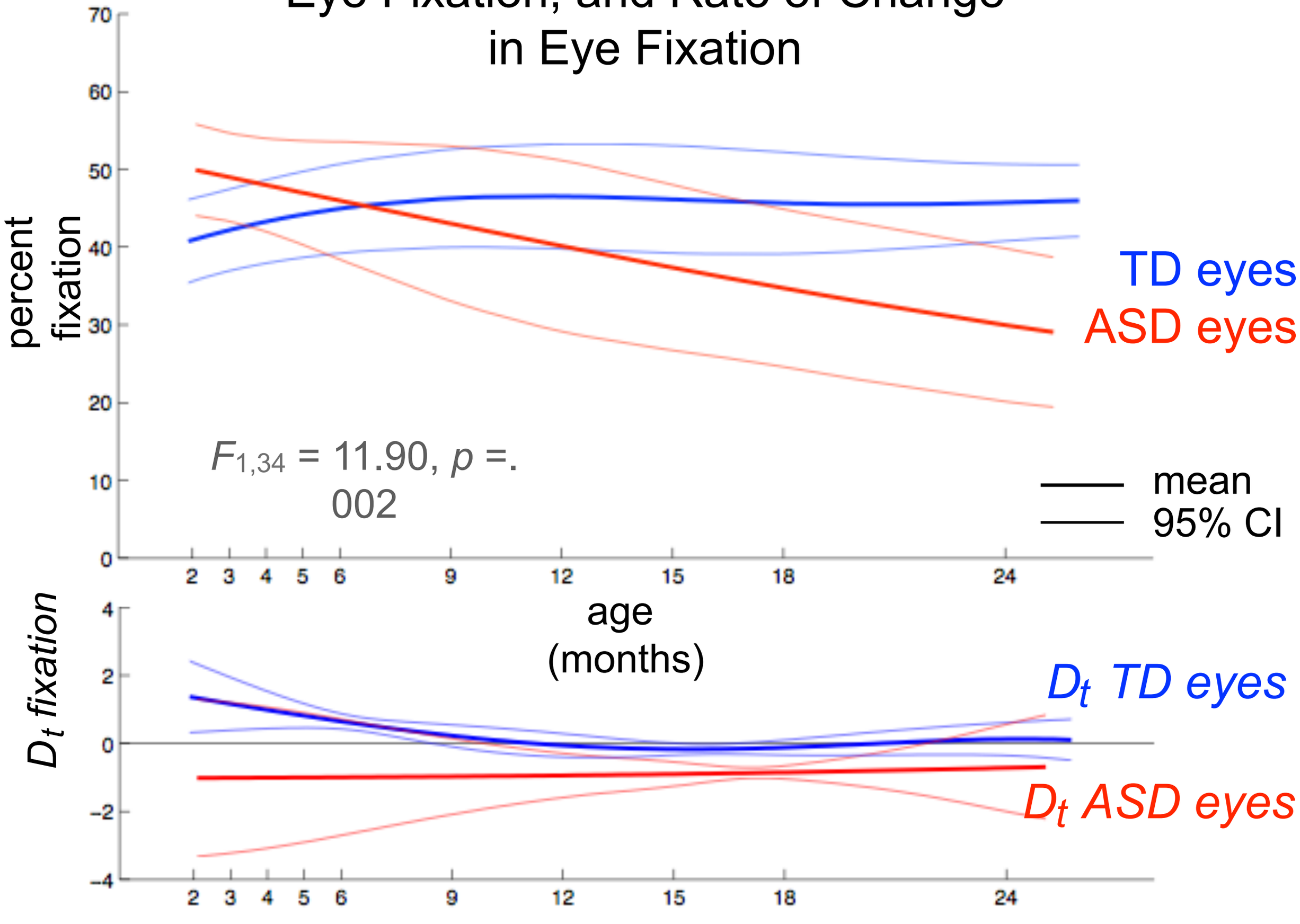
TD, N=25, male, 1637 trials

ASD, N=11, male, 747 trials

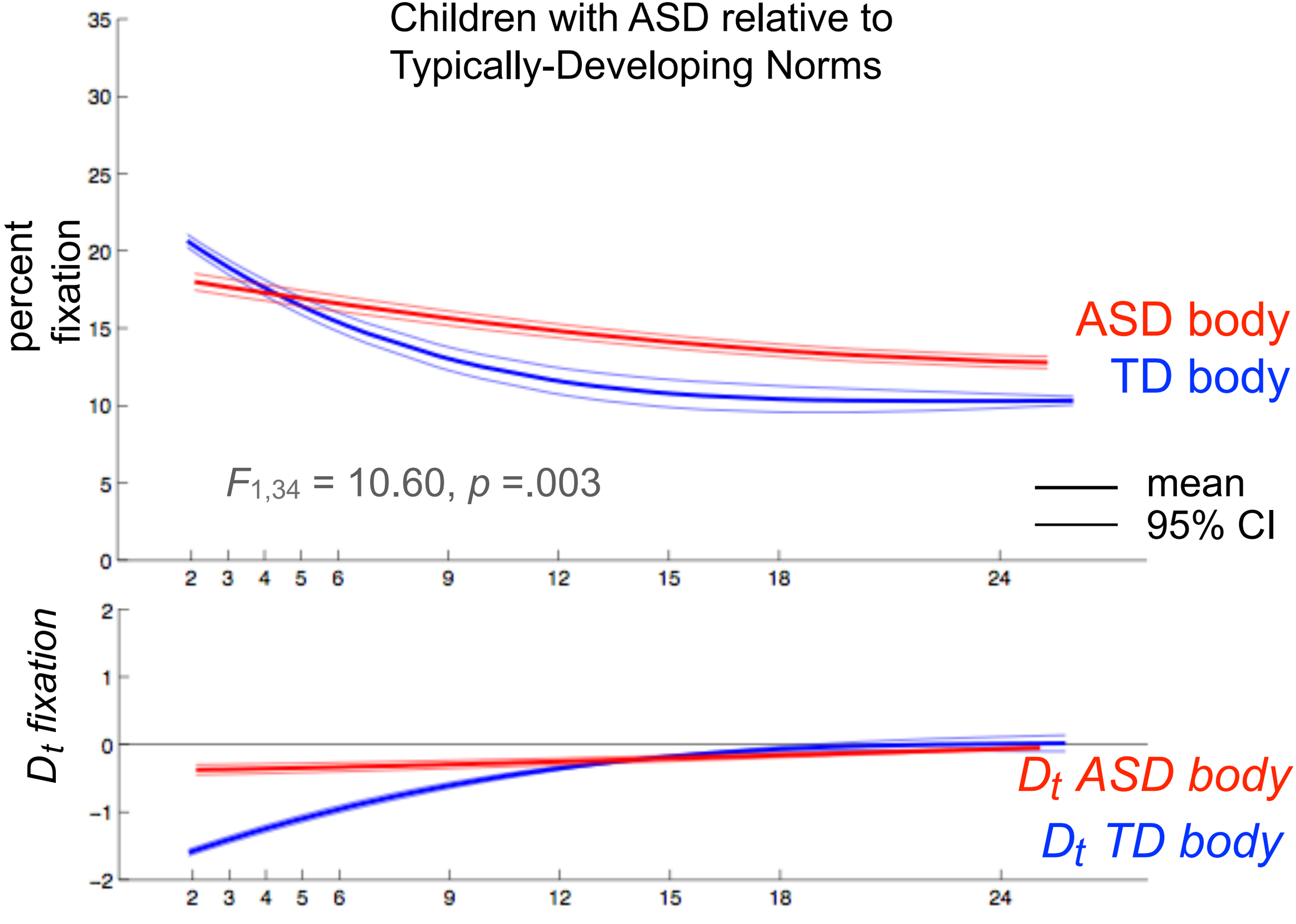
Eye Fixation, and Rate of Change in Eye Fixation



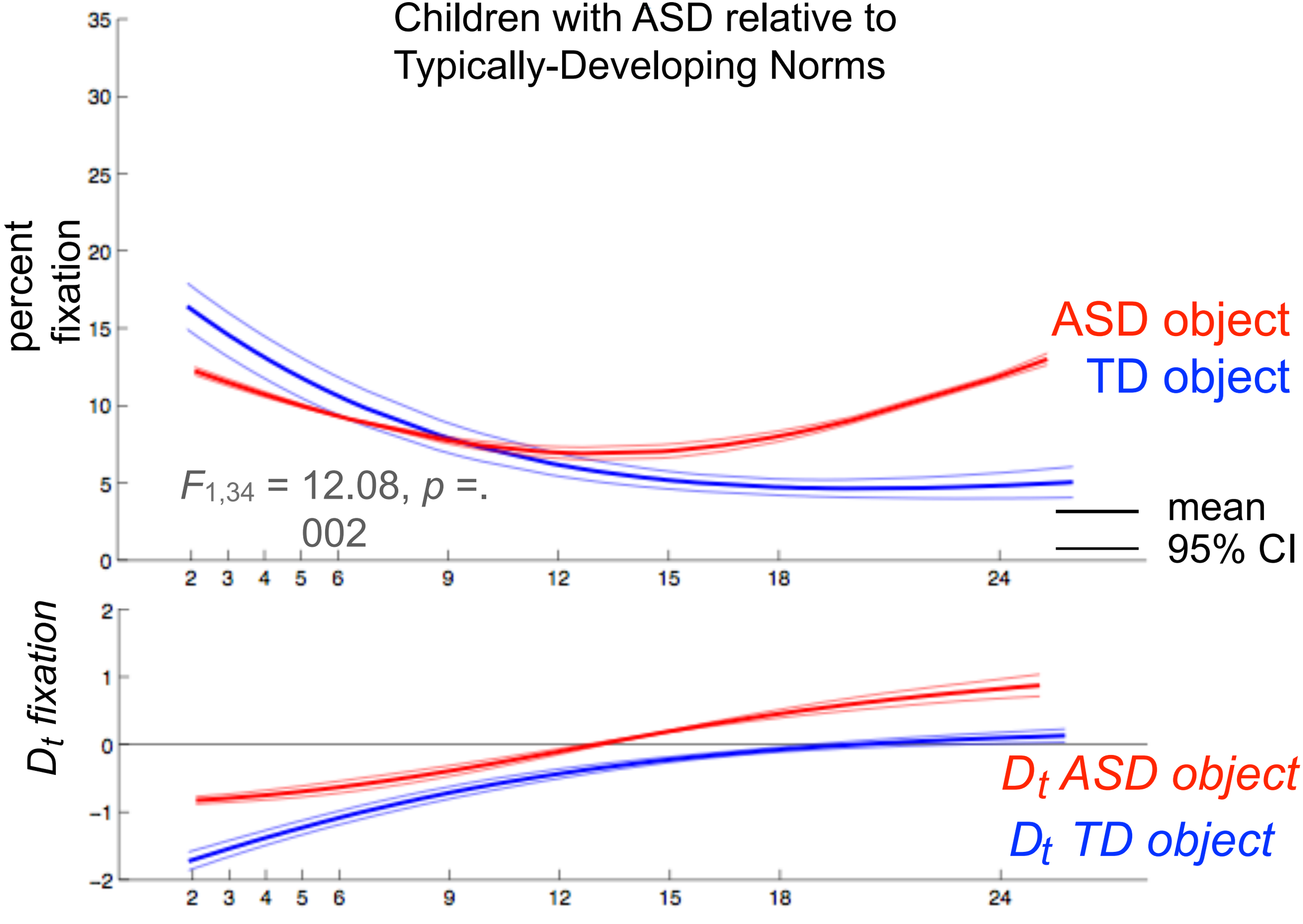
Eye Fixation, and Rate of Change in Eye Fixation



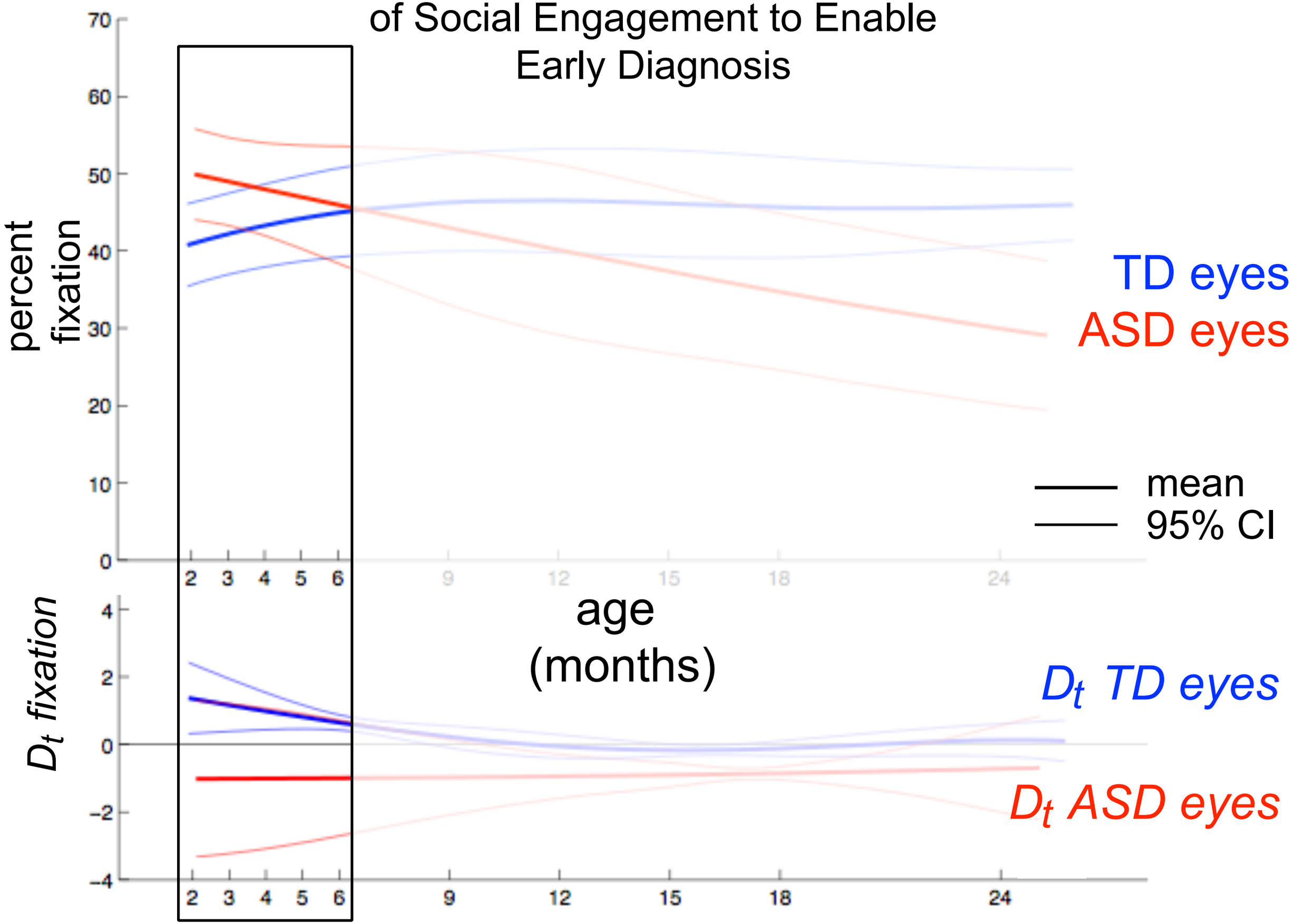
Body Fixation
Children with ASD relative to Typically-Developing Norms



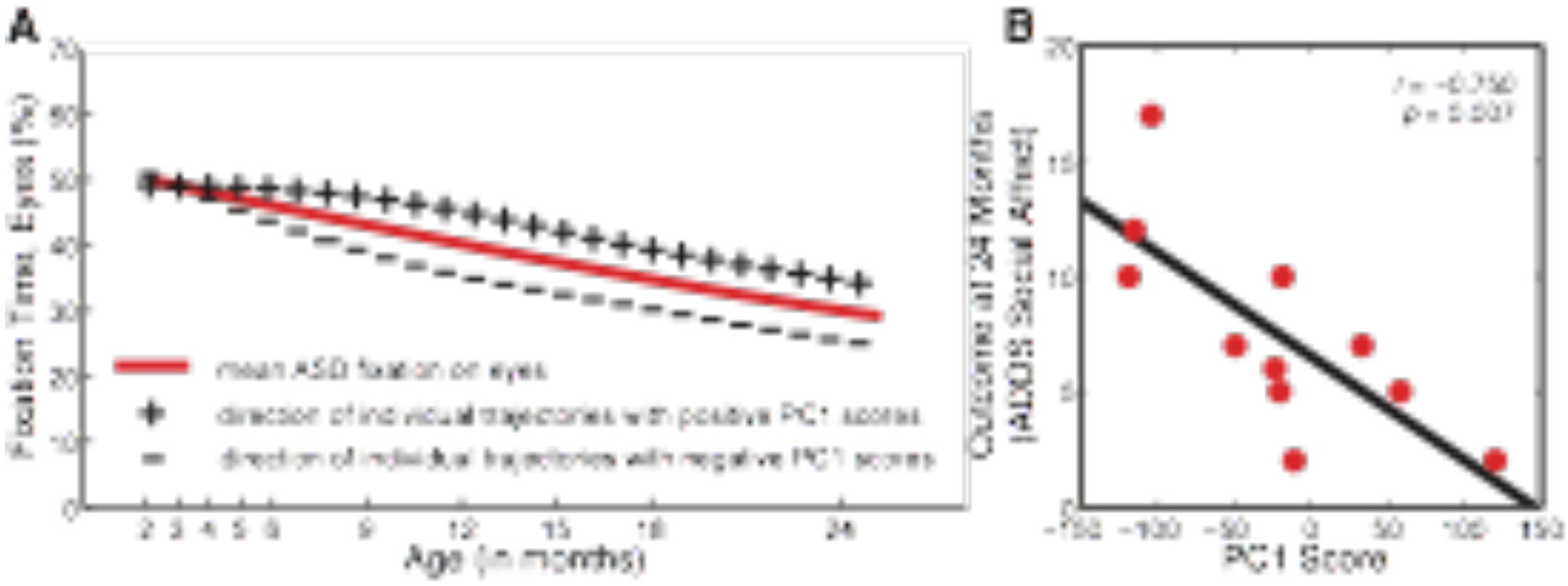
Object Fixation
Children with ASD relative to Typically-Developing Norms



Growth Charts of Social Engagement to Enable Early Diagnosis



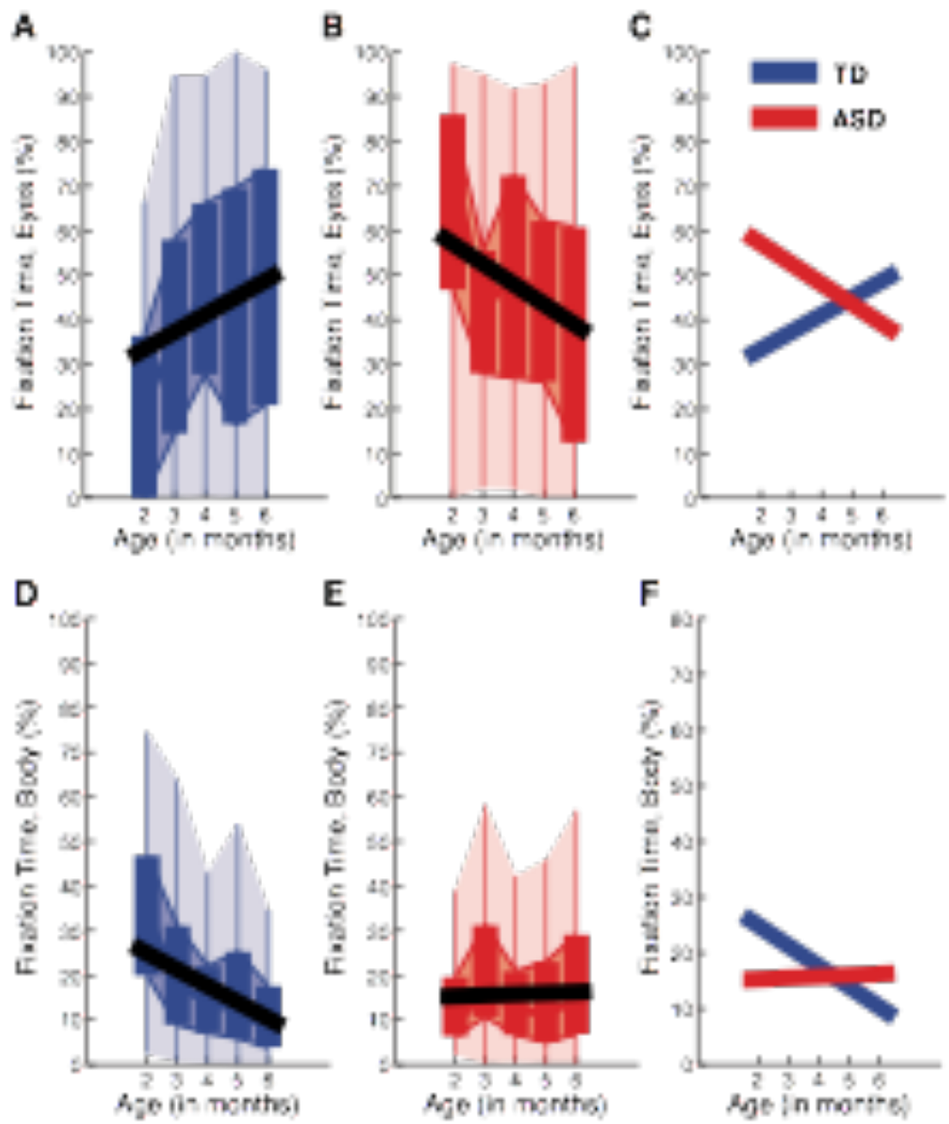
Decline in Eye Fixation Predicts Severity of Outcome



Differences Present within the First 6 Months of Life

eyes

body



Internal Validation

eyes

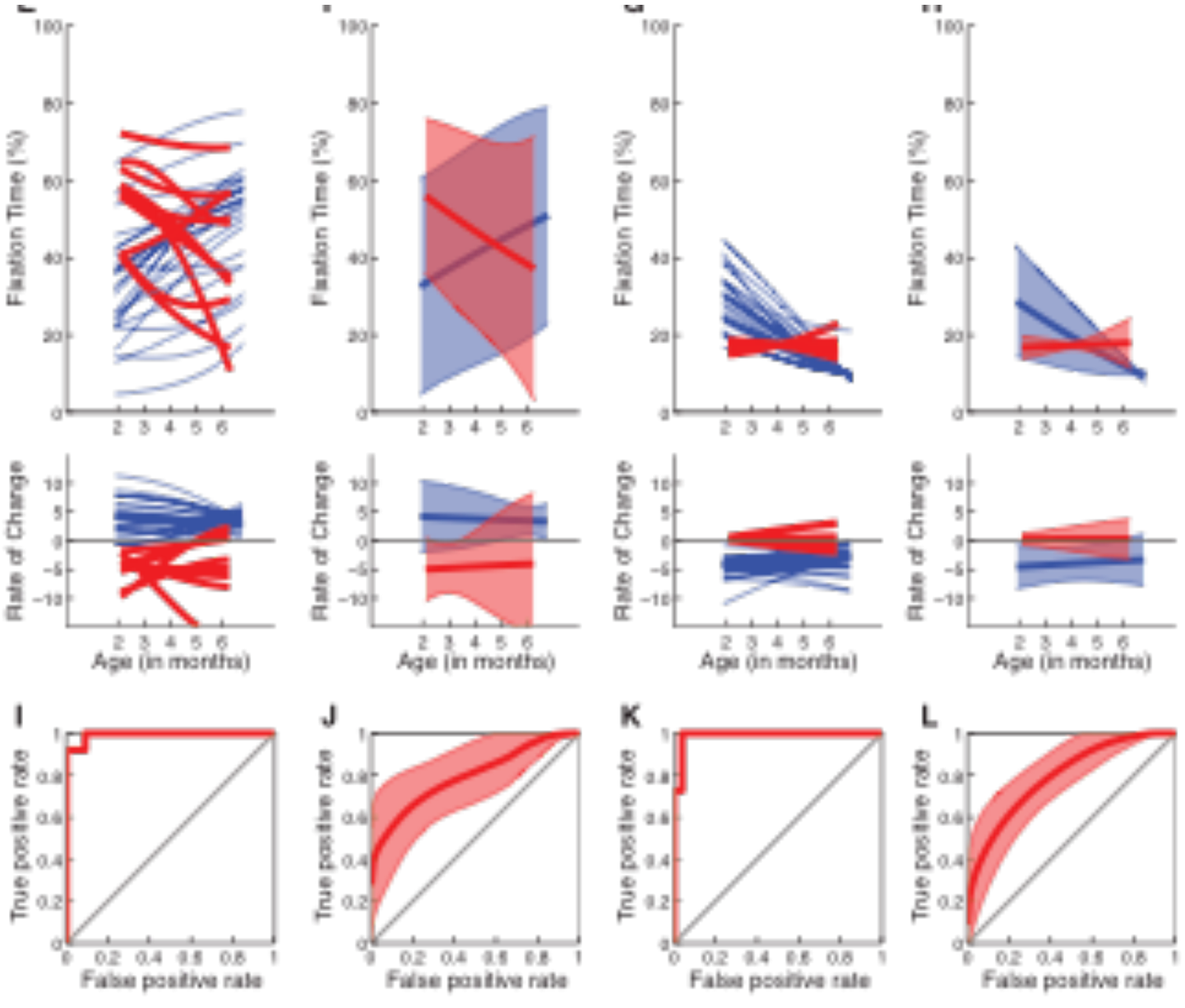
body

Known Dx

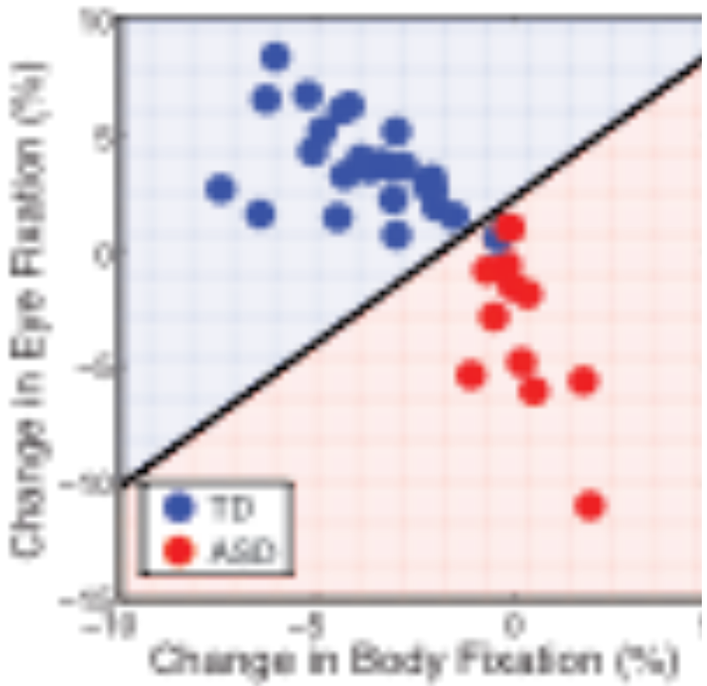
LOOCV

Known Dx

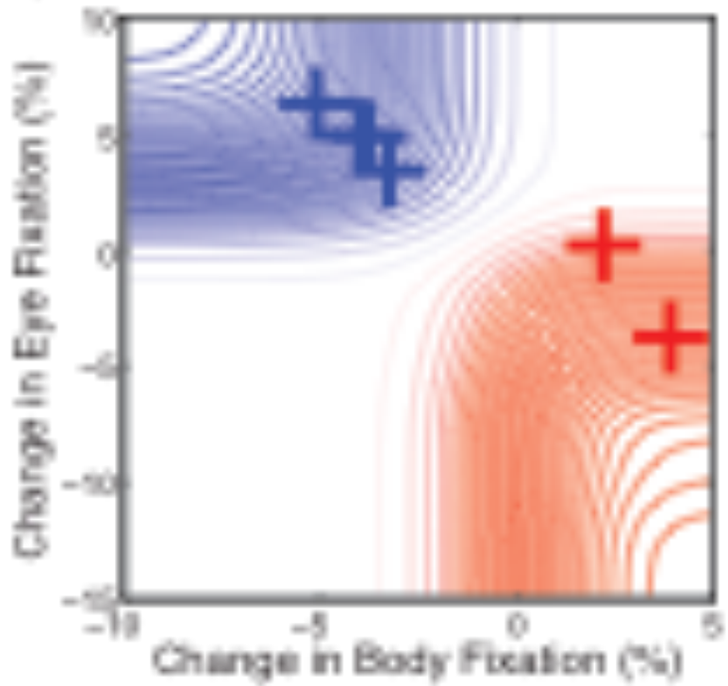
LOOCV



External Validation



6 Independent
Test Cases

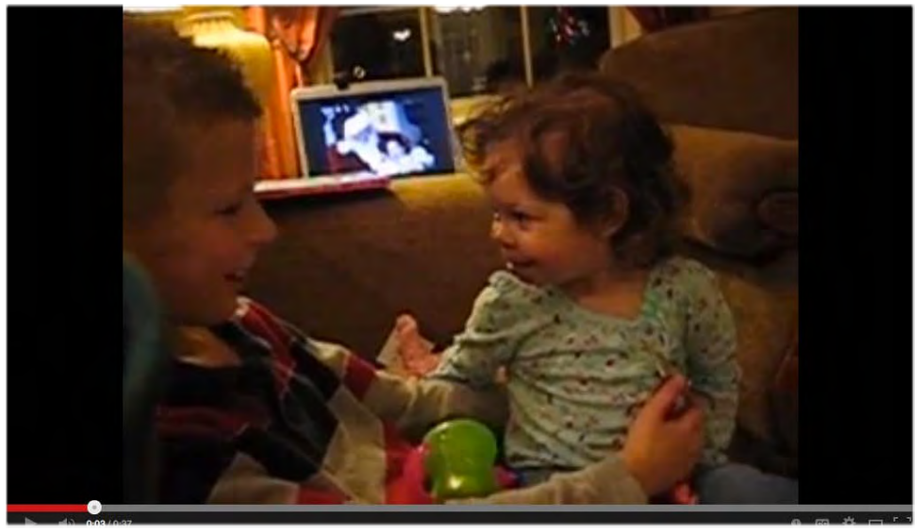


Translational Opportunities

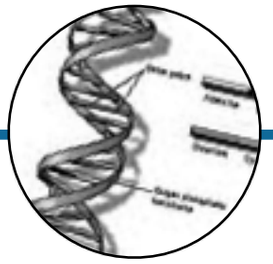
- High-throughput, low-cost, deployment of universal screening in the community
- Early detection, early intervention, optimal outcome
- Prevention or attenuation of intellectual disability in ASD

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

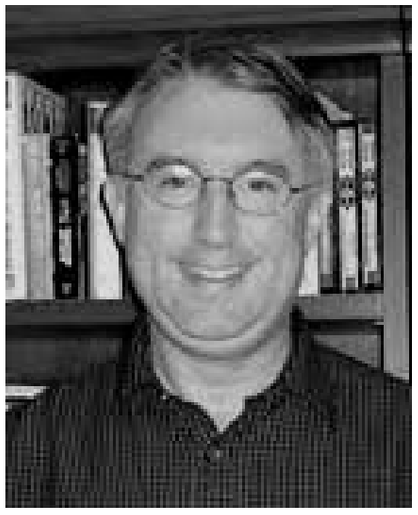


Steve Warren, PhD, FACMG

Mike Zwick, PhD

Jen Mulle, PhD

Peng Jin, PhD



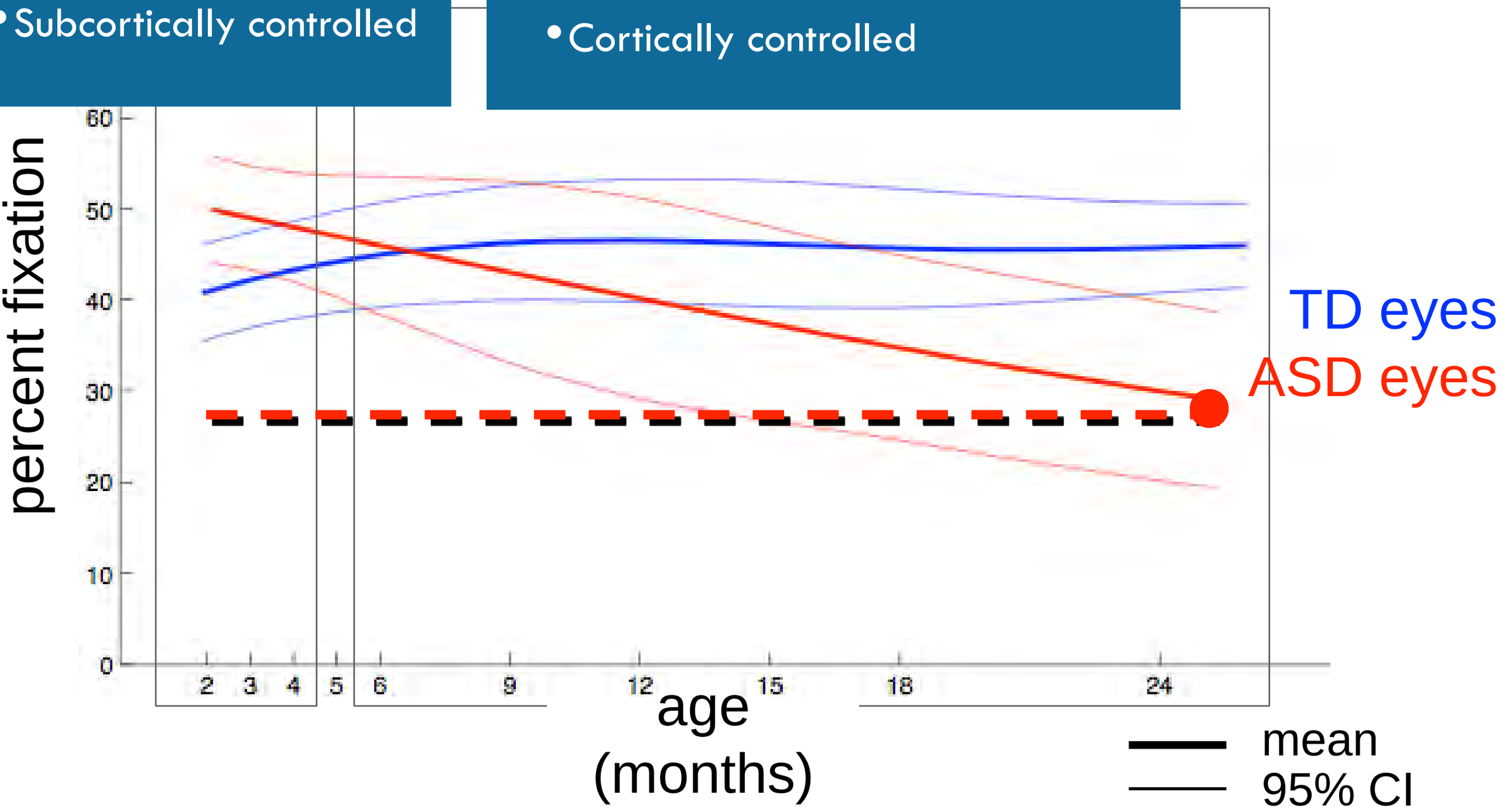
David Cutler, PhD

Eye Fixation

Are we wrong? Not one but in fact two curves?

- Reflexive
- Experience Expectant
- Subcortically controlled

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



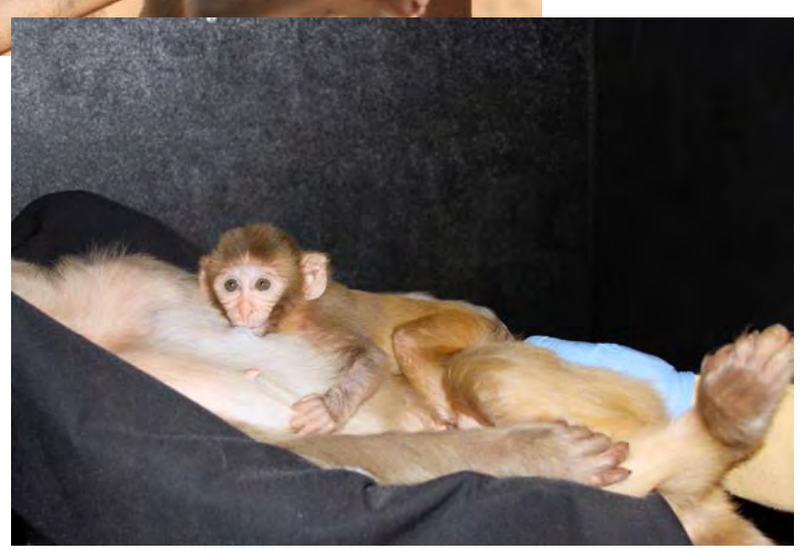
New Scientific Hypotheses

- 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

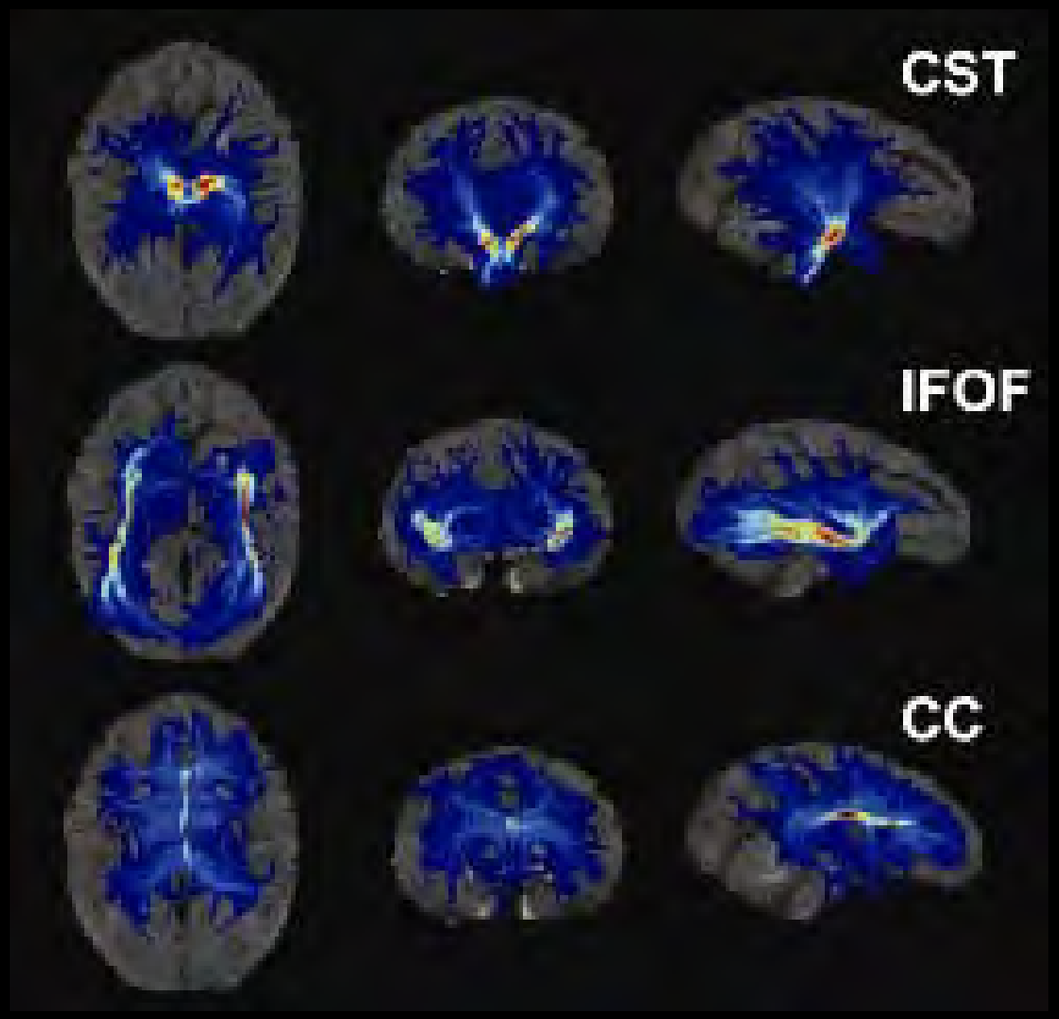


Jocelyne Bachevalier, PhD

Xiao Ping Hu, PhD

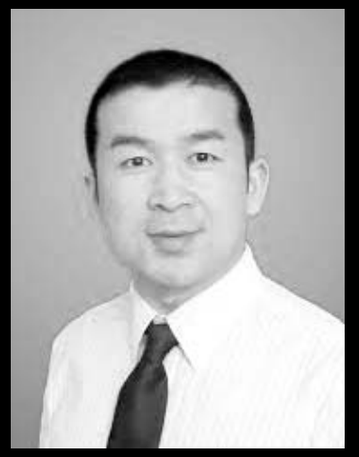
Lisa Parr, PhD

Ontogeny & Neural Basis of Social Visual Engagement in Monkeys



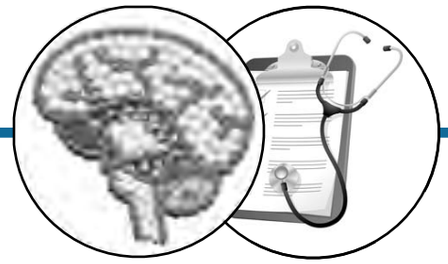
In vivo diffusion MRI data showing major white matter pathways in a 2-week-old *rhesus macaque*.

Jocelyne Bachevalier, PhD



Longchuan Li, PhD

Psychopharmacology & Clinical Trials



Larry Scahill, MSN, PhD

Karen Bearss, PhD

Nathan Call, PhD

William Sharp, PhD

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

- MAJOR CHALLENGE
- QUANTIFYING Autism

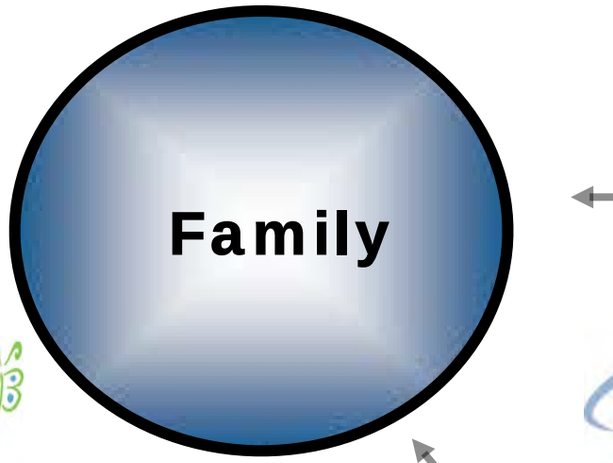
Improving Access to Early Intervention
….from 5 years to 2 years

(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

Marcus AUTISM CENTER
NIH Autism Center of Excellence



Amy Wetherby, PhD

Jennifer Stapel-Wax, PsyD

Kids Health First

Children's Healthcare of Atlanta

Early Intervention Because.. Babies Can't Wait

Bright from the Start
Georgia Department of Early Care and Learning

Autism Navigator™
Bridging the Gap Between Science and Community Practice

the Community: Families, Pediatricians, Early Intervention Providers

Autism NAVIGATOR™ for Early Intervention Providers

IDEAS | GLOSSARY | RESOURCES | HELP

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

slide **35** of 66

Resume Unit

Course Introduction

Unit 1: Improving Early Detection

Unit 2: Collaborating with Families

Unit 3: Developmental Perspective

Unit 4: Evidence-based Intervention Strategies

Unit 5: Prioritizing Intervention Outcomes

Autism NAVIGATOR™

Everyday Activities

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

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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

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Goals for Early Treatment:

Every wakeful hour in the home and in the community

Child Behaviors	Parent Behaviors
ACTIVE ENGAGEMENT	**TRANSACTIONAL SUPPORTS**
1. Emotional Regulation	1. Participation & Role
2. Productivity	2. Make Activity Predictable
3. Social Connectedness	3. Follow Child's Attention
4. Gaze to Face	4. Promote Initiations
5. Response to Verbal Bids	5. Balance of Turns
6. Directed Communication	6. Support Comprehension
7. Flexibility	7. Modeling
8. Generative Ideas	8. Expectations & Demands

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Our ultimate goal

To make autism
an issue of diversity,
not of disability