Redefining Autism:
A new framing for more effective early childhood interventions and policy

Alliance for Early Success: Every Child, Every State
Virtual, May 19, 2021

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Thanks & Disclosure

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- This presentation includes research related to investigational device development.
  - Dr. Klin is an inventor and patent holder of investigational device technologies licensed in 2020 to EarliTec Diagnostics.
  - EarliTec Diagnostics is a company that develops medical technologies for early diagnosis of autism and gives revenue to support treatment of children with autism. Dr. Klin is an equity holder in EarliTec Diagnostics.
  - Dr. Klin's external activity with EarliTec Diagnostics has been reviewed and approved by Emory University's Conflict of Interest Review Office and by Emory University School of Medicine's Dean's Office.

Public Health Challenge

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Autism is a Public Health Challenge

- Prevalence: 1:54 autism; more than any other complex neurodevelopmental condition
- 73,000 children born every year in the US will have autism
- Autism Societal Cost/Year in the US: $ 126 billion
- Autism Lifetime Cost of Care Per Child: $ 1.5 - 2.4 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
- Not enough expert clinicians, major healthcare disparities
- 5-6 hours of evaluation, costly, not accessible, not available (gold standard used in < 6% of the population of children with ASD)

CDC, 2016, 2018, 2020; 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; Hyman et al., 2020

Healthcare Disparities in ASD at a Glance

- The burden of intellectual disabilities (ID) in 8-year-olds with ASD
  - **Ascertainment:** Rates per 1000 for White (W), Black (B) and Hispanic (H)
  - **ID:** IQ <70, percentages for White (W), Black (B) and Hispanic (H)

- CDC ADDM 2012, 2014, and 2016 cohorts (Christensen et al., 2016, Baio et al, 2018, and Maenner et al., 2020)

- Ascertainment:
  - (W): 15.5/1000; (B): 13.2/1000; (H): 10.1/1000
  - (W): 17.2/1000; (B): 16.0/1000; (H): 14.0/1000
  - (W): 18.5/1000; (B): 18.3/1000; (H): 15.4/1000
- Burden of ID:
  - (W): 21.3%; (B): 43.9%; (H): 24.7%
  - (W): 22.0%; (B): 44.0%; (H): 35.0%
  - (W): 27.0%; (B): 47.0%; (H): 36.0%

Intellectual Disability Burden Among AA children is almost double that in W children

In regards to AA children with ASD

- AA children (and Latino children) with ASD, on average, are diagnosed later, are more likely to have carried non-ASD diagnoses, have poorer access to healthcare services, and are less likely to have a medical home.

- Constantino, Abbacchi, et al. "Timing of Autism in African American Children", *Pediatrics* (2020); accompanied by Pediatrics editorial on structural racism and healthcare access to developmental services
- Largest-available repository of diagnosis and phenotypic information on AA children with ASD (N=584) - Event History Calendar Interviews
  - Average age of ASD diagnosis was 64.9 months (+/- 49.6), on average 42.3 months (+/- 45.1) following parents' first concerns about their children's development
    - Age Parental First Concerns: 23.0 (17.9)
    - Age Parent First Shared Concerns with a Professional: 29.1 (23.1)

A "Diagnostic Odyssey", and that's only the beginning of the journey

Public Health Opportunity

Redefining Autism

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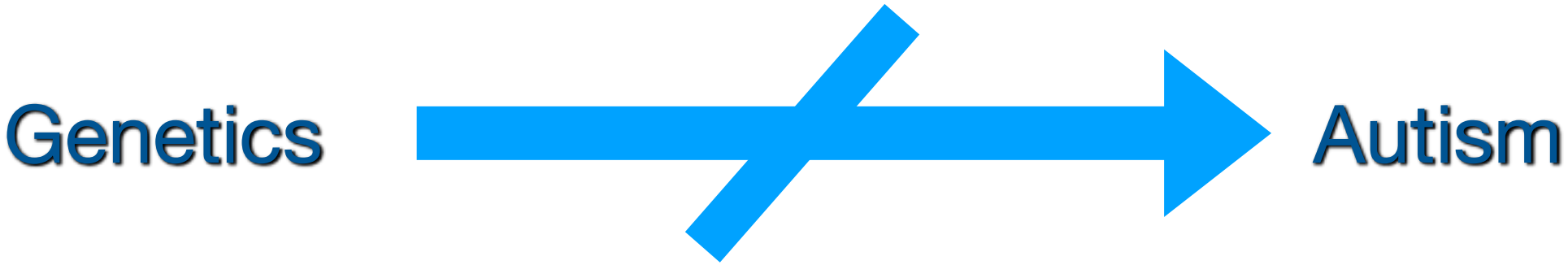
Autism symptoms RESULT from deviations from normative socialization



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.* Klin et al. (2020) *D&P.*

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Autism symptoms RESULT from deviations from normative socialization

Genetics → Autism

Normative Behavior & Brain Development

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.*

The beginning

Shultz, Klin & Jones (2018). *Trends in Cognitive Sciences, 22(5):452-469.*

Neonates preferentially orient towards stimuli that…

More Preferred

mother, engaging

stranger,
eyes open

Less Preferred

stranger,
eyes averted

stranger,
eyes closed

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.

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

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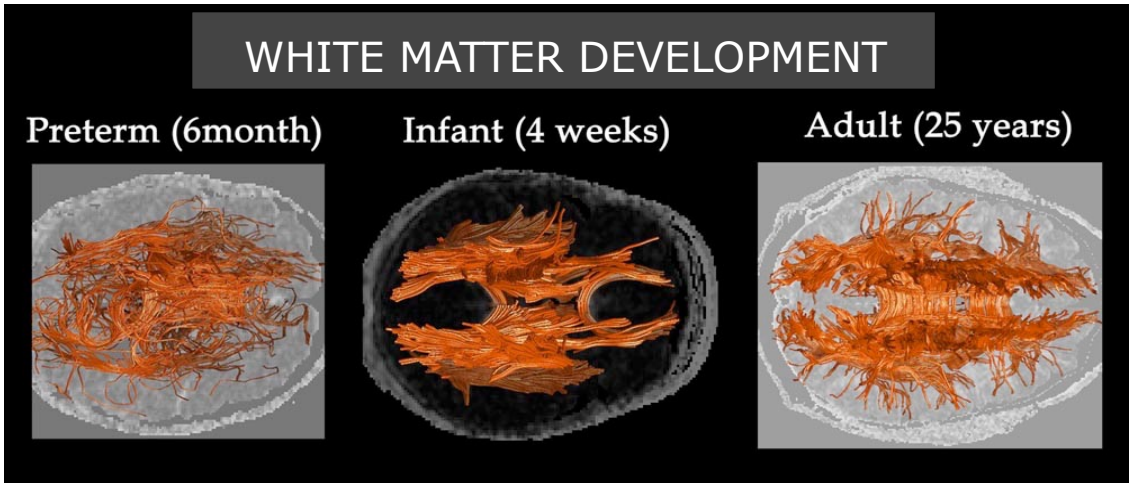
Universal Principle: the Platform for Development of Social Brain

Born to Socially Orient

MH Johnson PhD

Reciprocal Social Interaction

Neuroplasticity



H-J Park PhD

Autism at 15 months

Klin et al. (2004). *American Journal of Psychiatry, 161(11), 1981-1988*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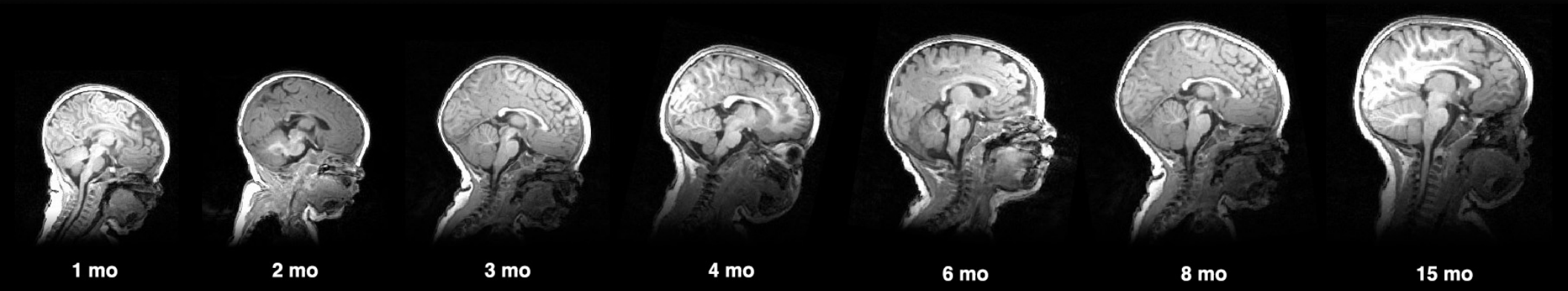
Social Interaction is the Platform for Brain Development

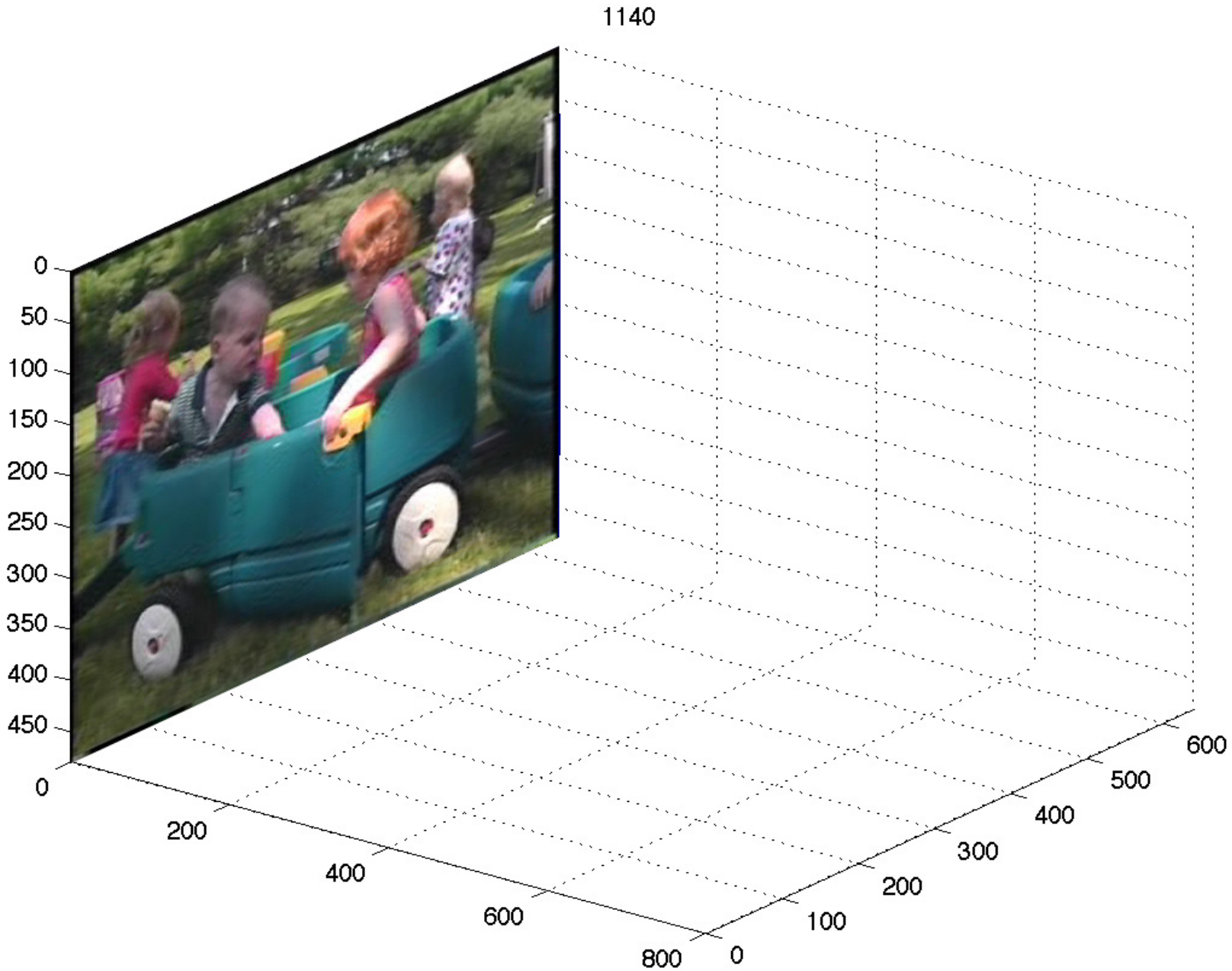


"Our brains become who we are." (J LeDoux)

Brain structure and function are physical instantiations of lived experience.


What kind of world is she creating?
OCT 7.02 AM 9:34:37

Quantifying social visual engagement, moment-by-moment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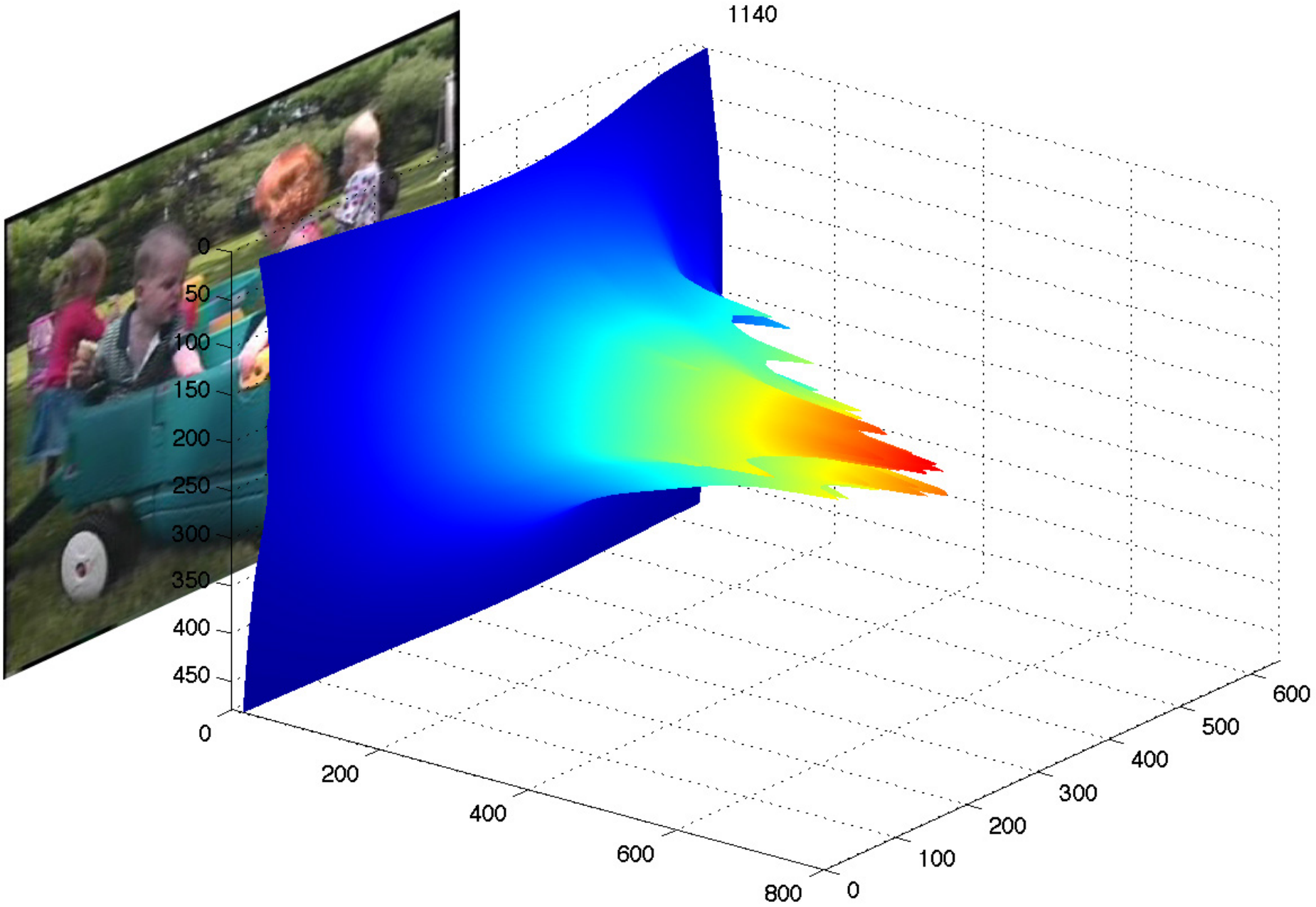
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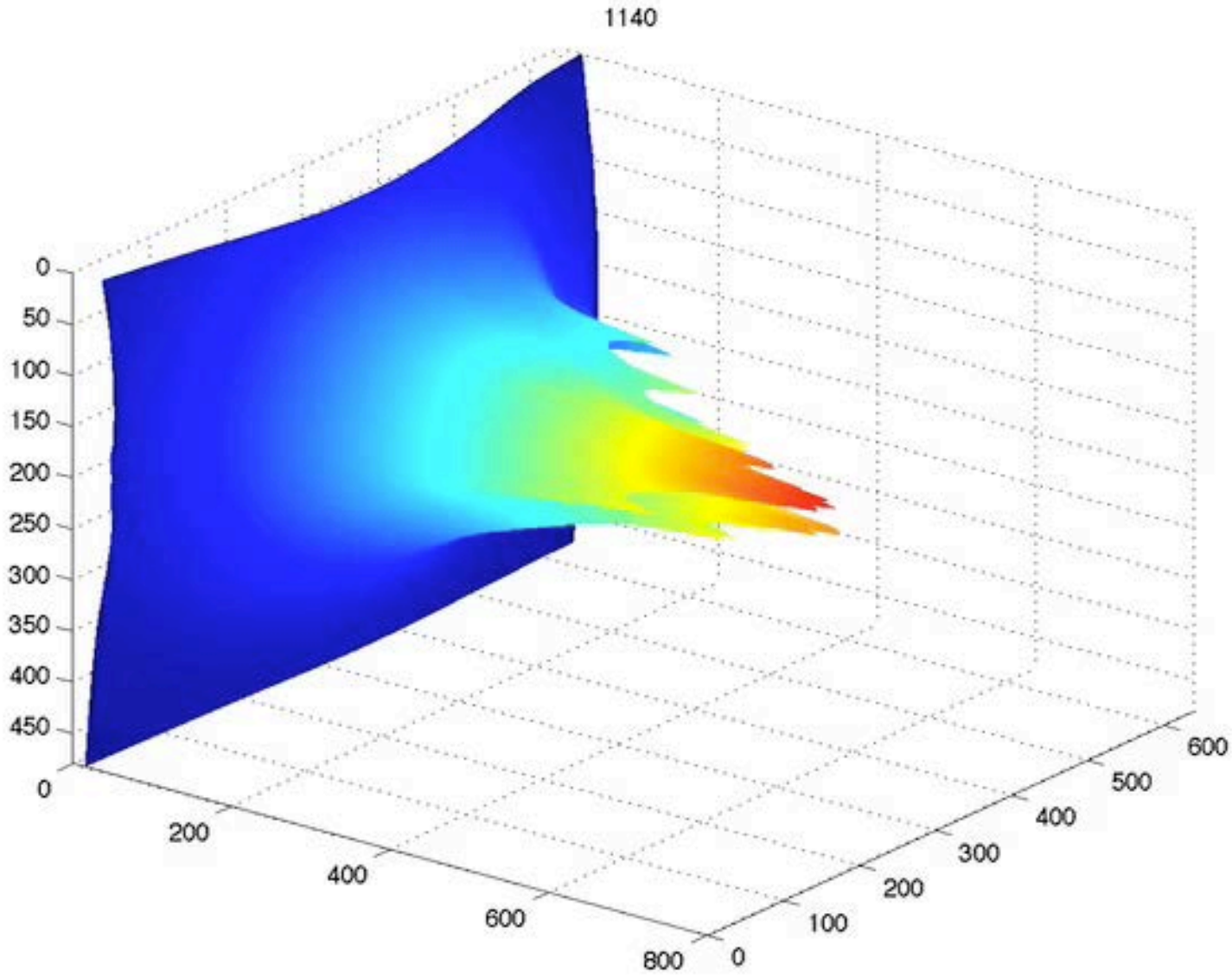
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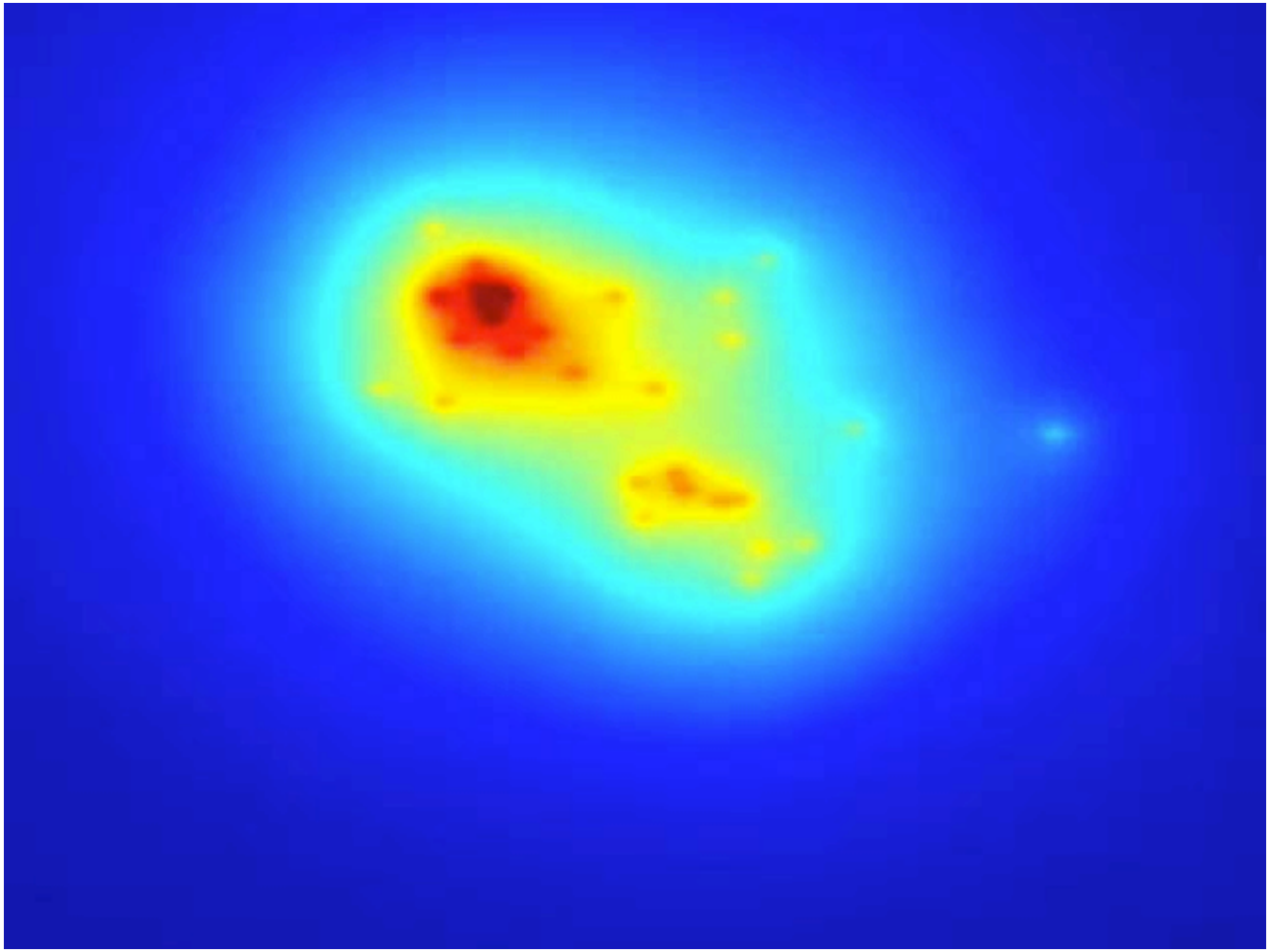

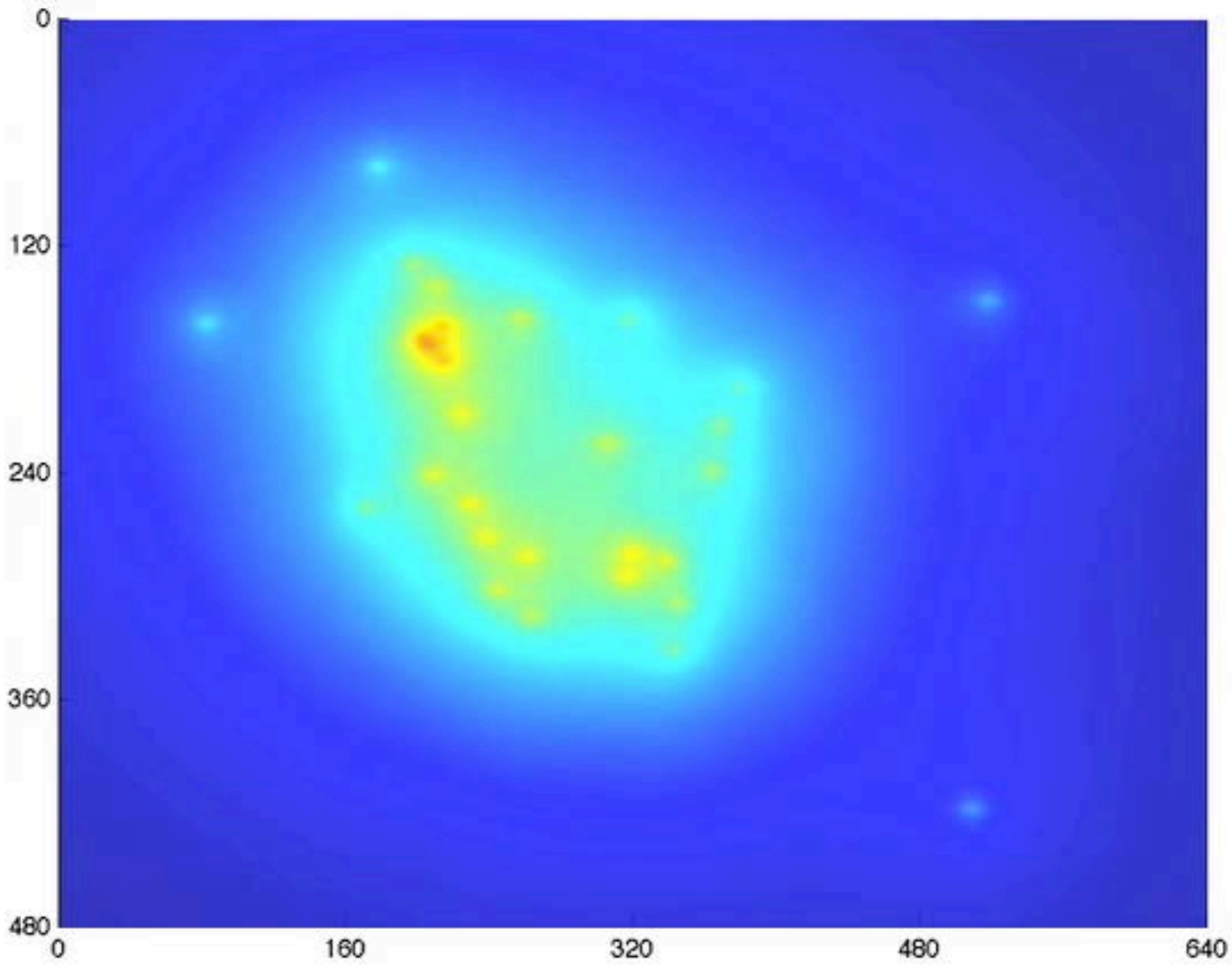
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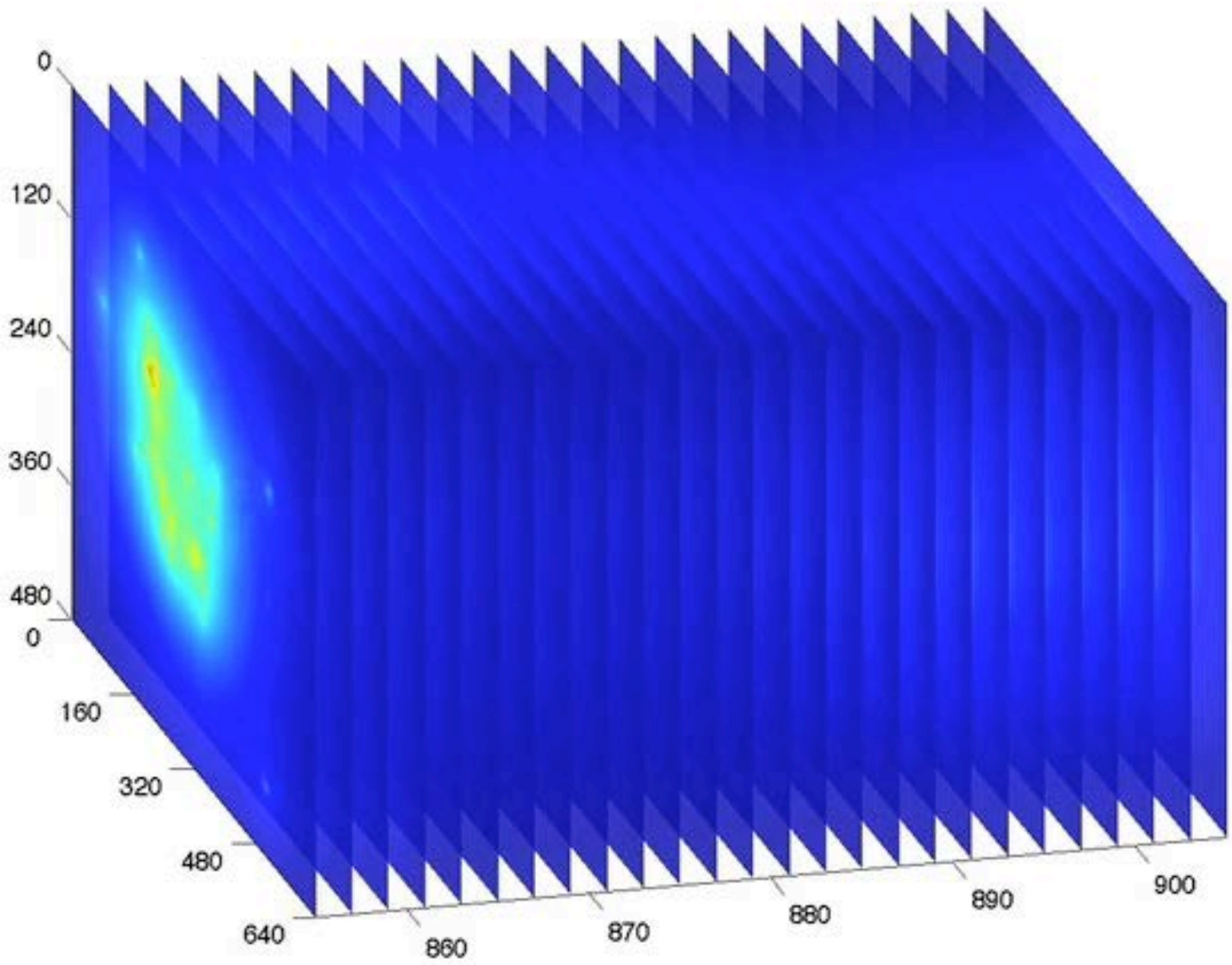
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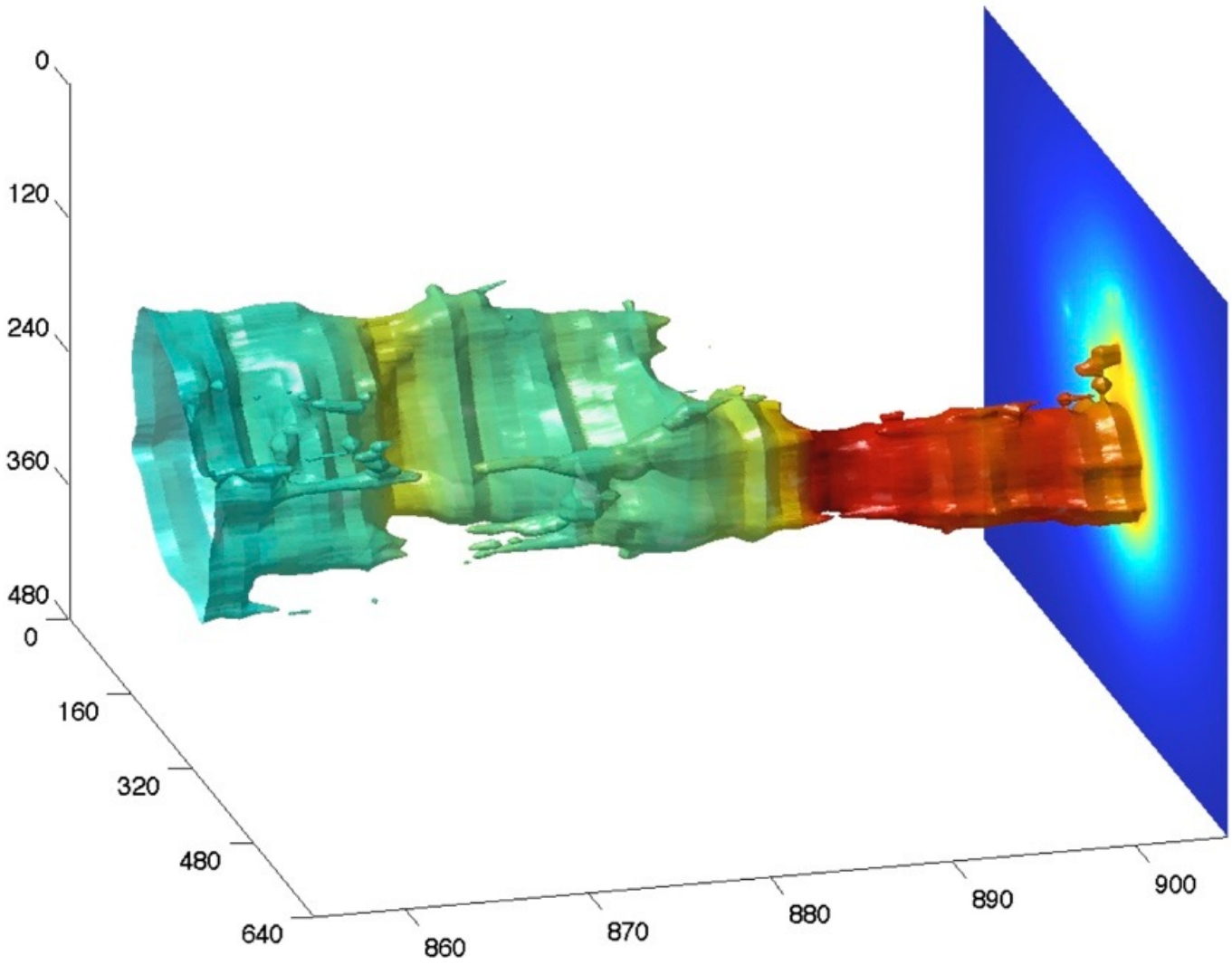
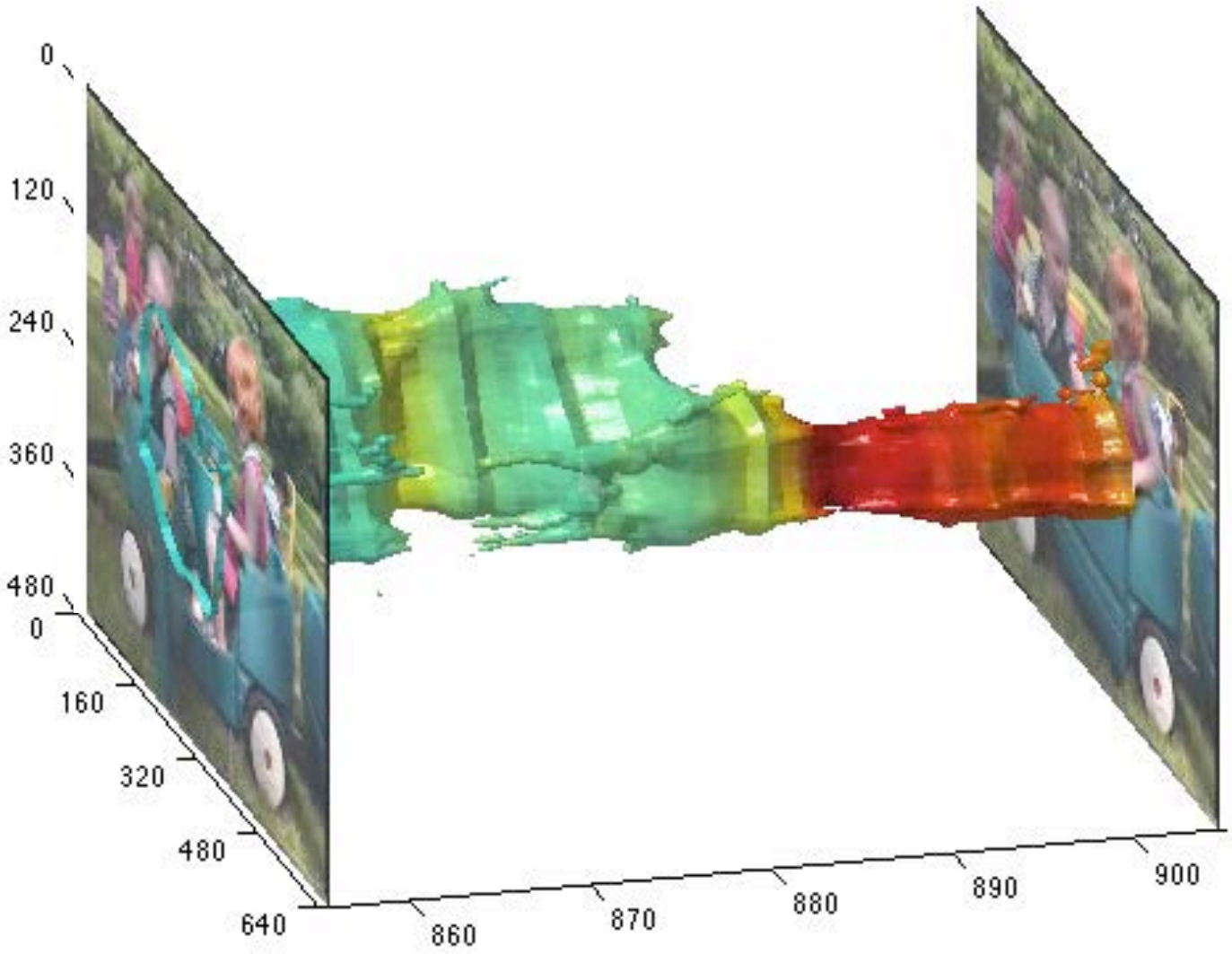
Derivation of Attentional Funnel

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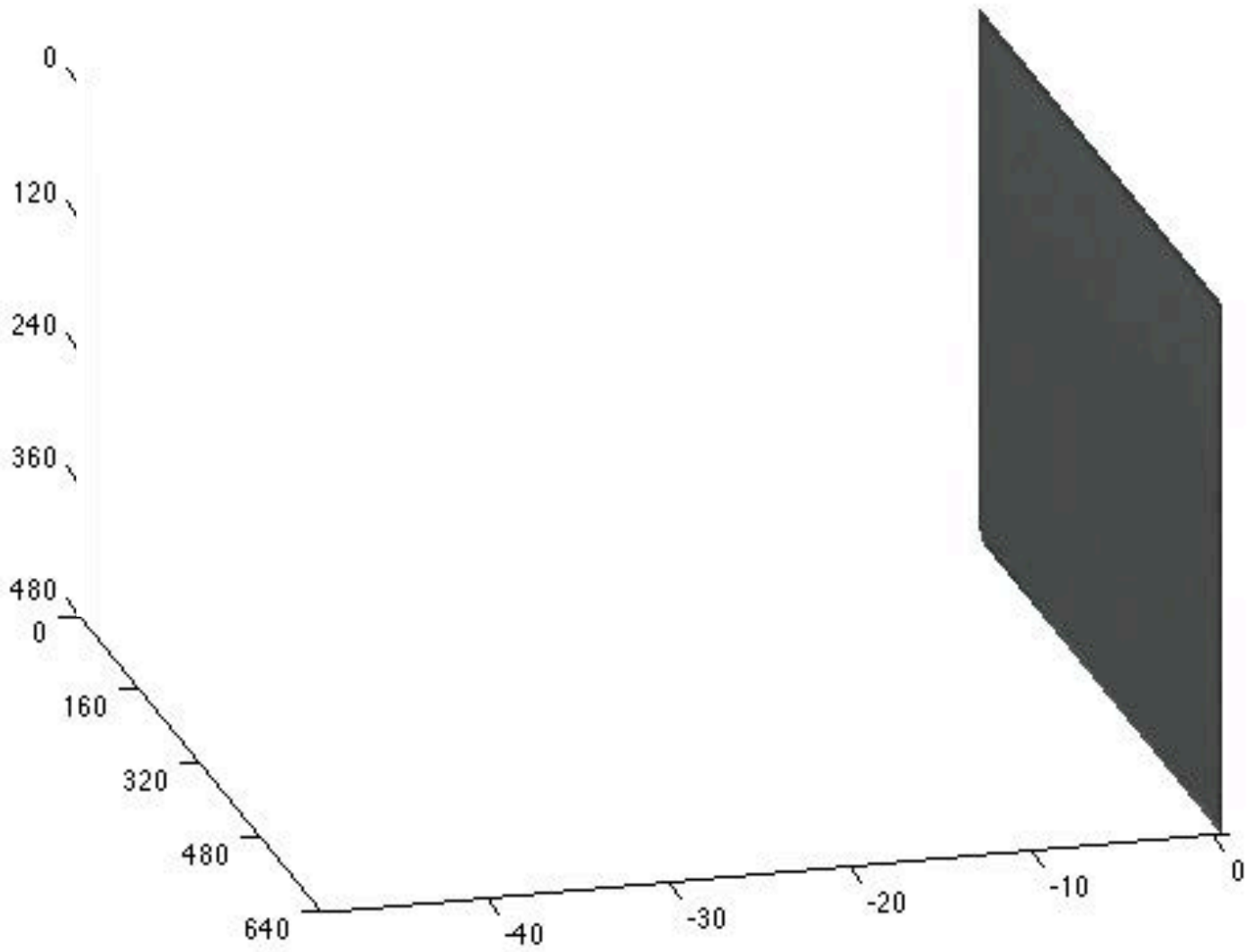
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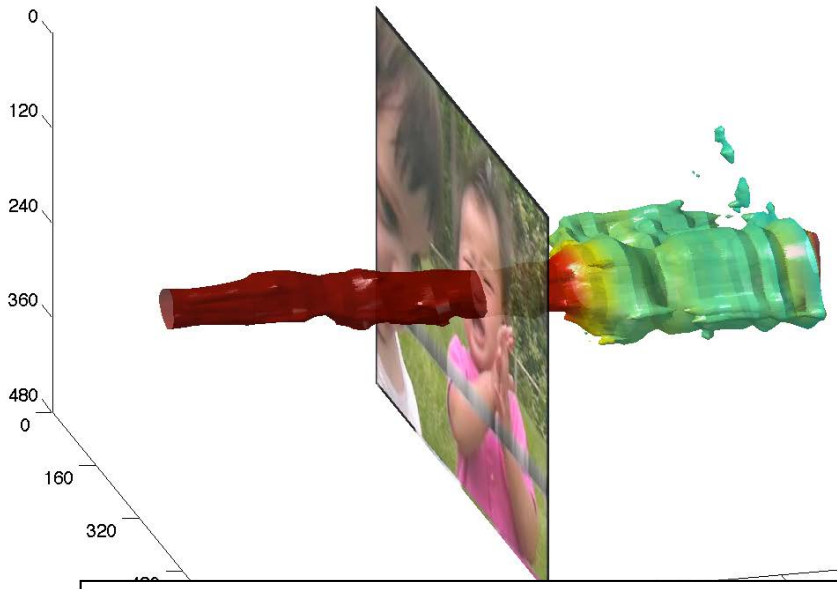
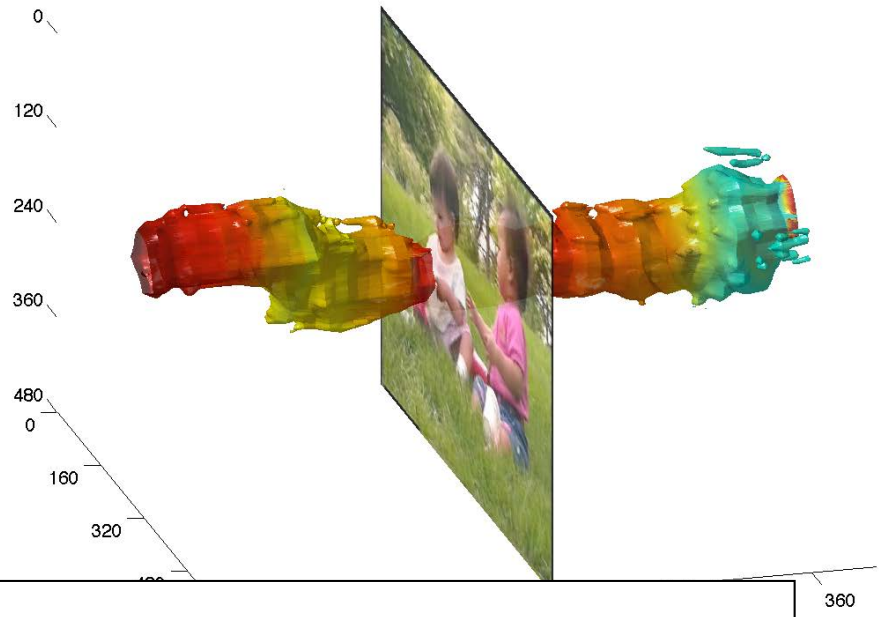
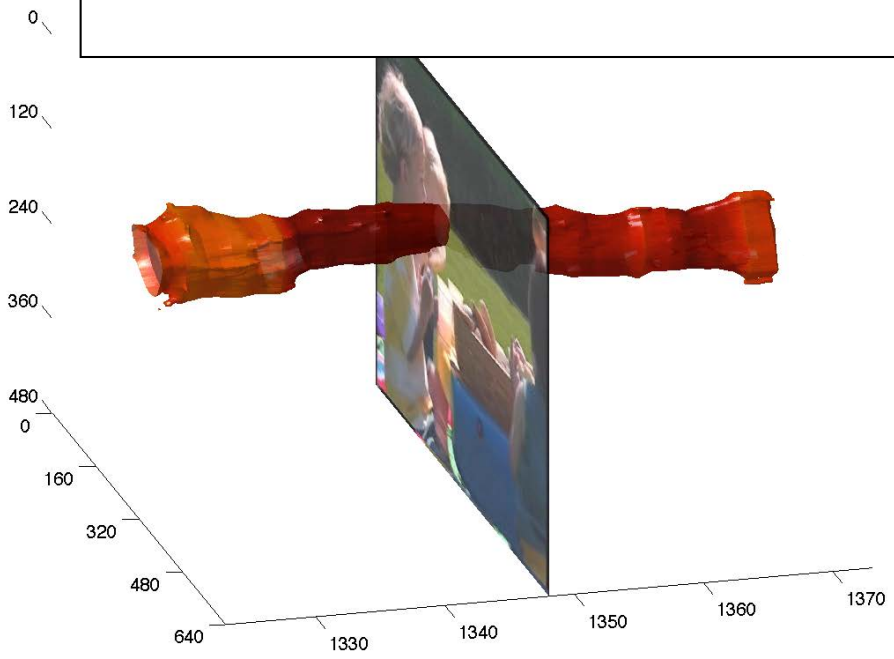
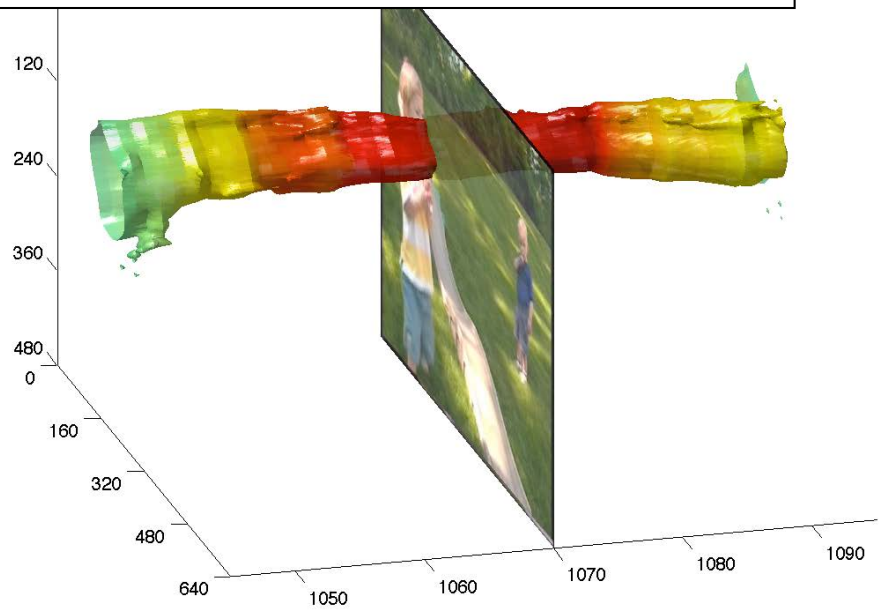


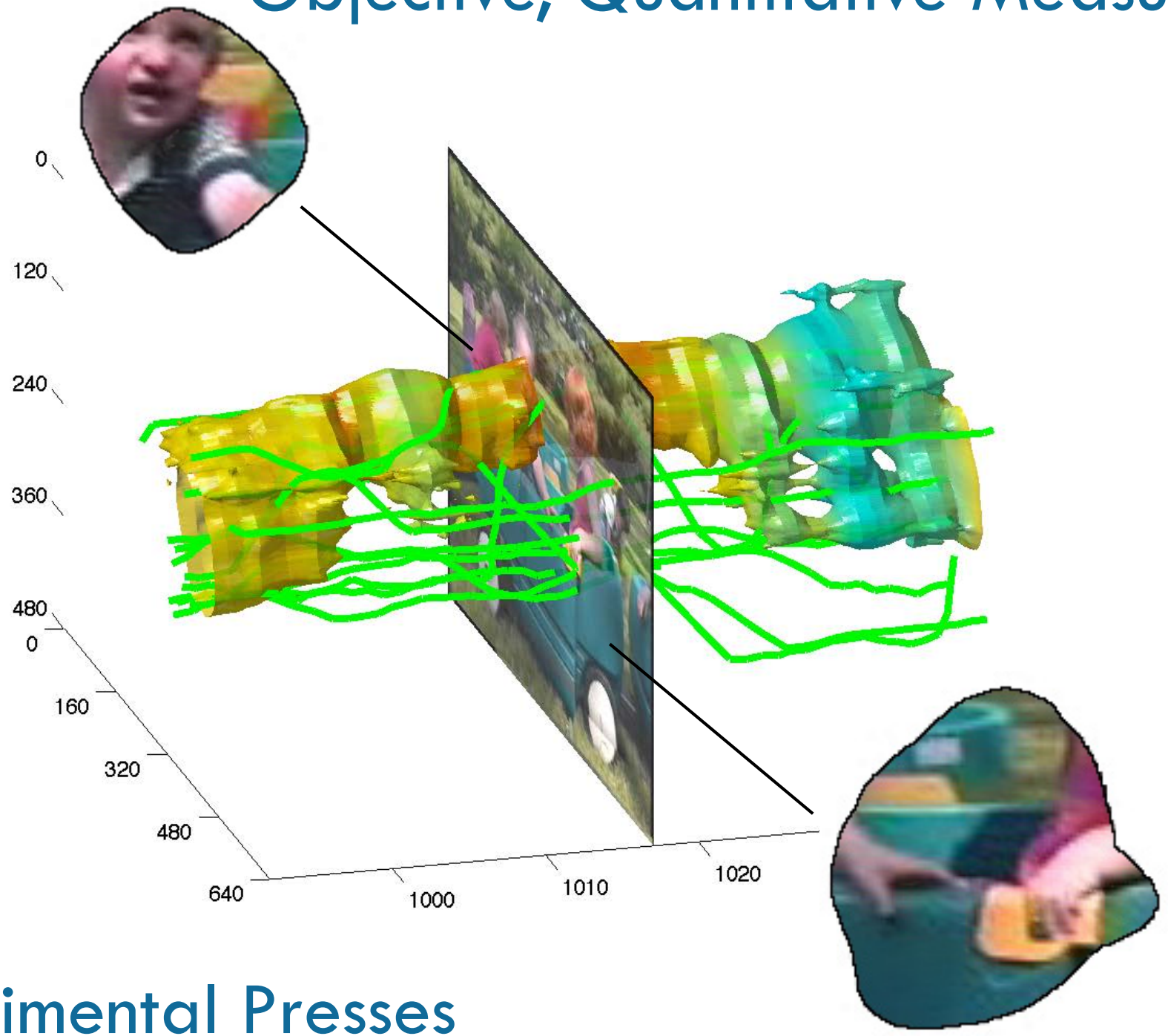


The majority of typically-developing 2-year-olds fixate on the same locations, at the same moments, during 80% of viewing time.

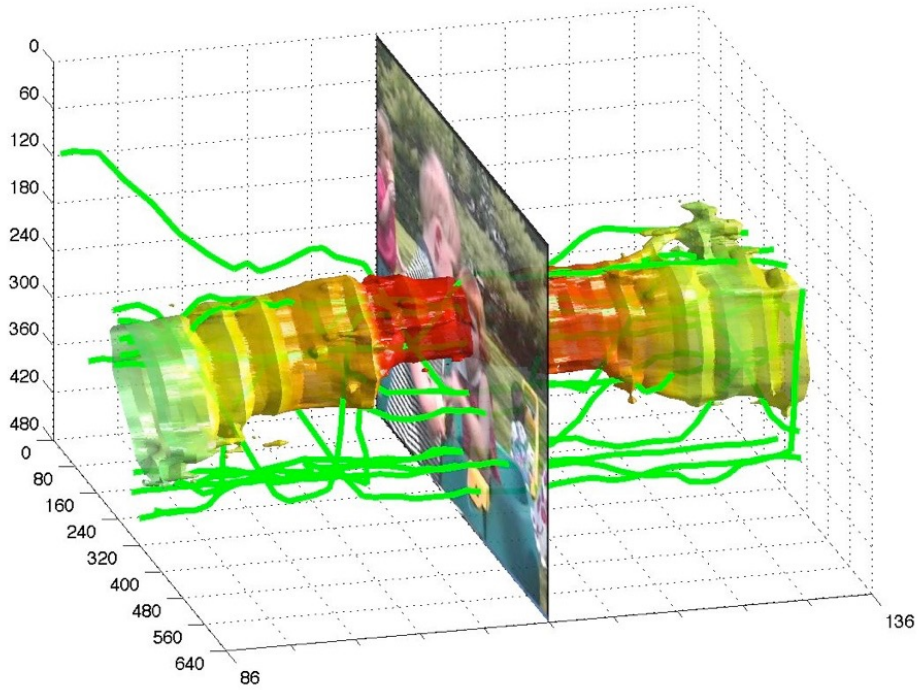




Objective, Quantitative Measures



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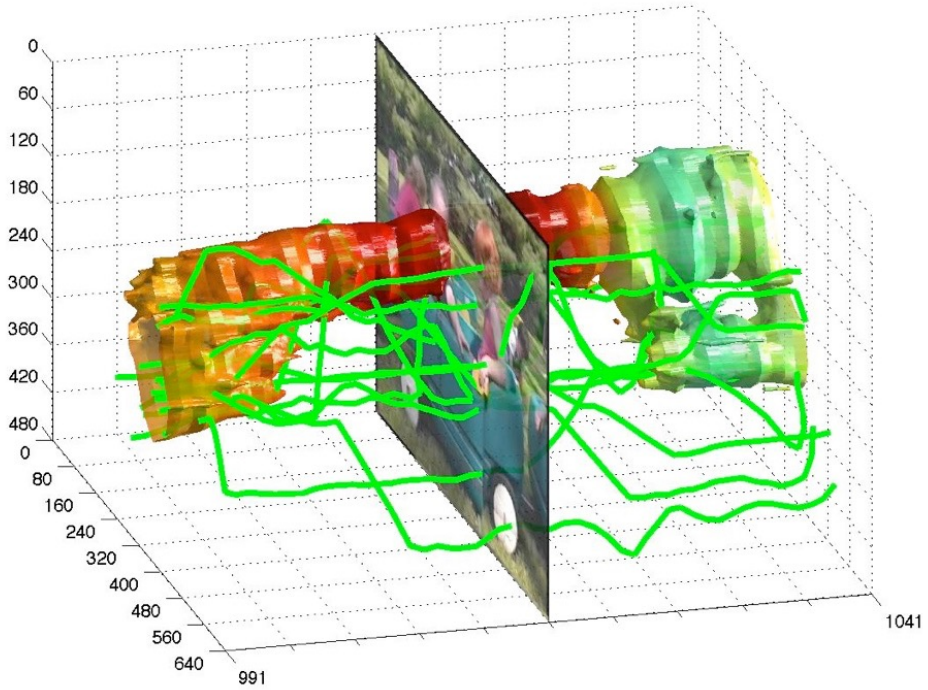
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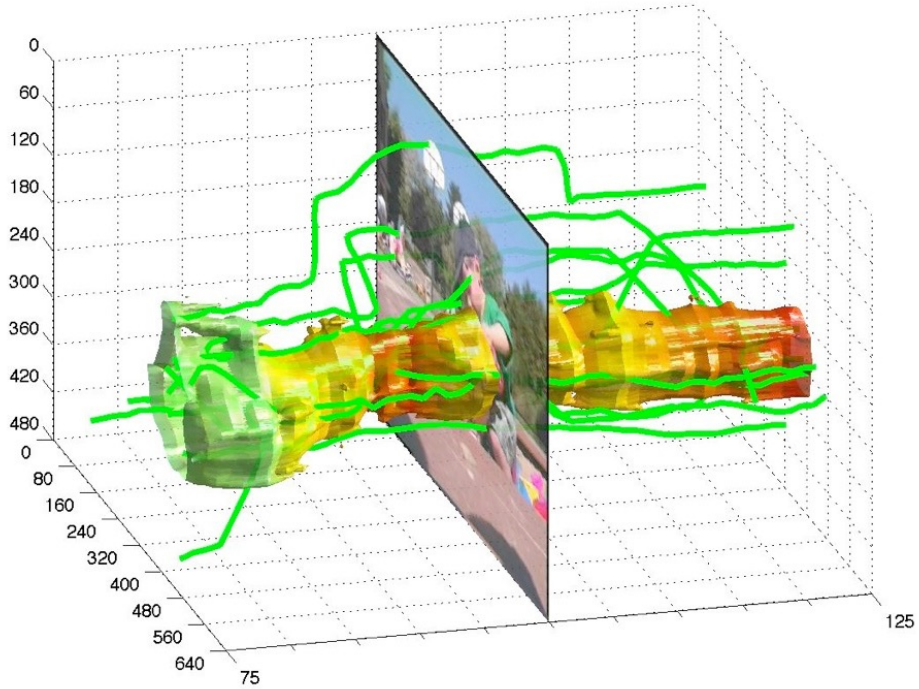
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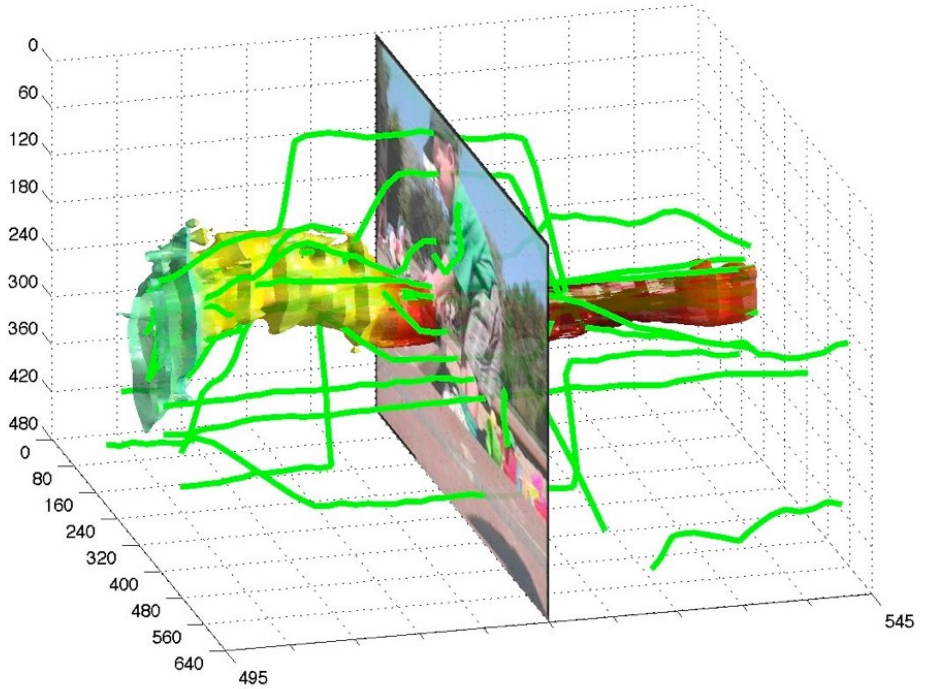
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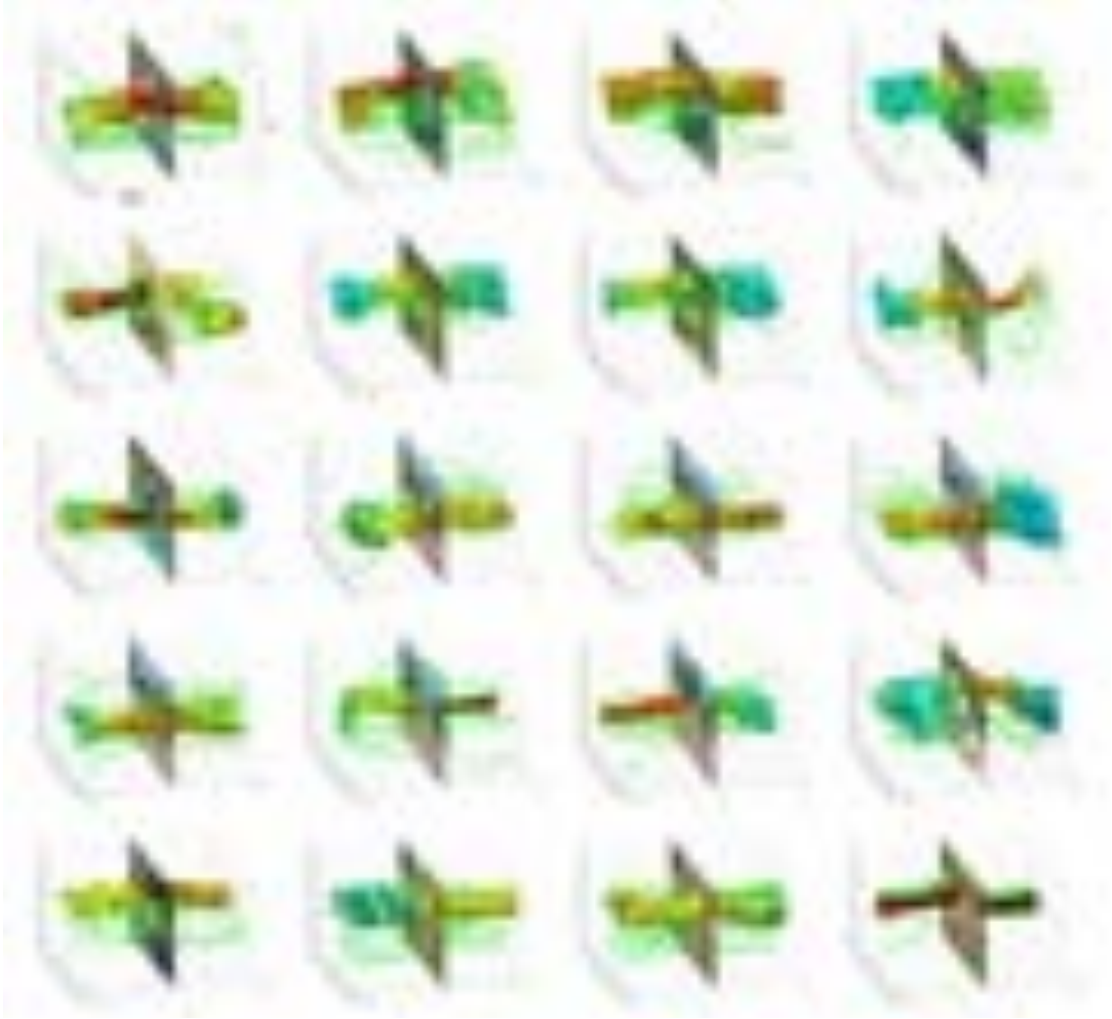
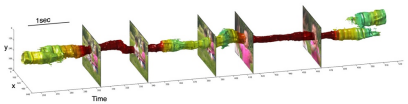
Hundreds of natural experiments within a 5-minute free viewing video experiment



- 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

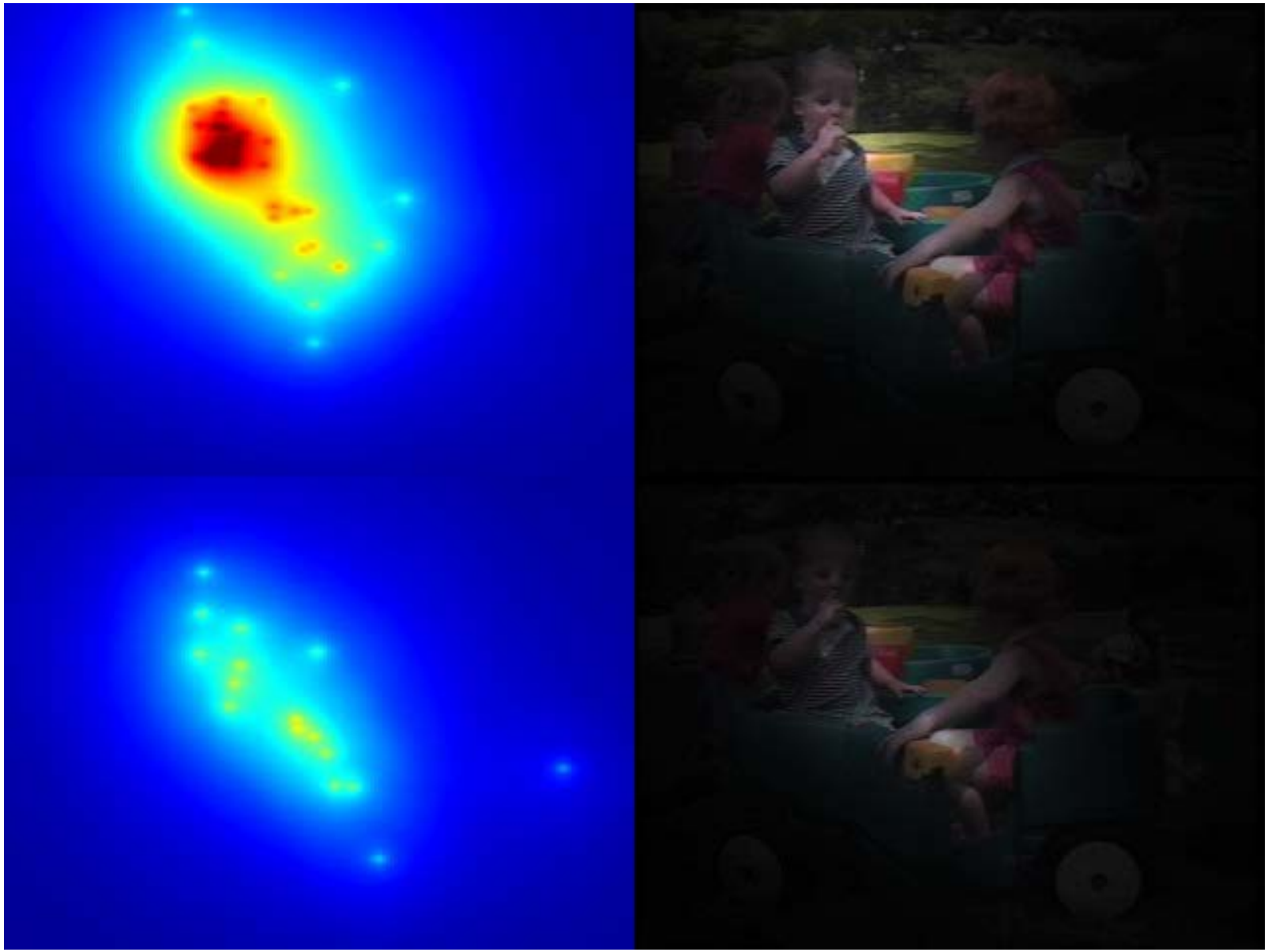
TD normative funnels = 

ASD comparison scanpaths = 

Scenes of Social Action

Typically-Developing

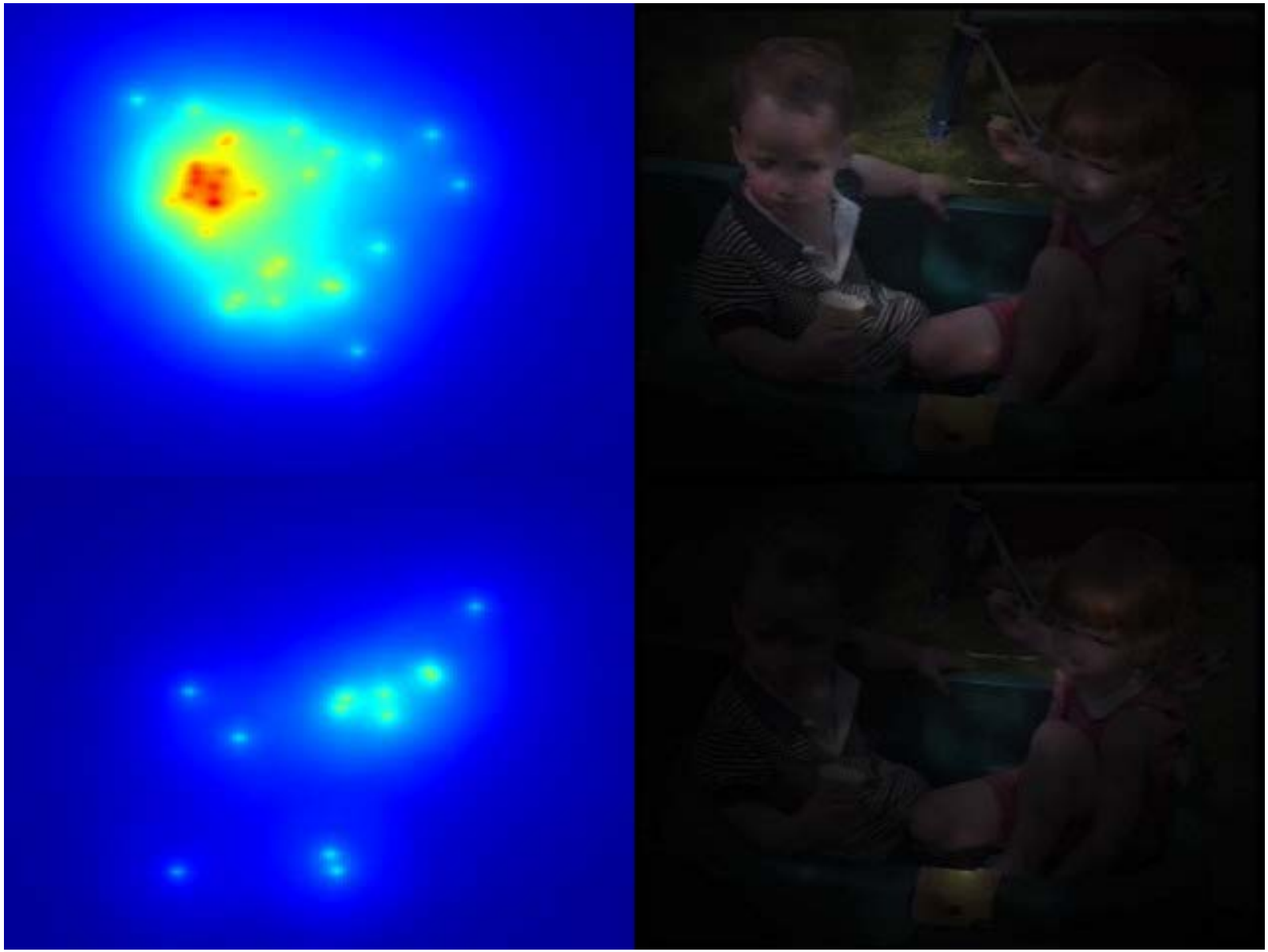
Toddlers with Autism



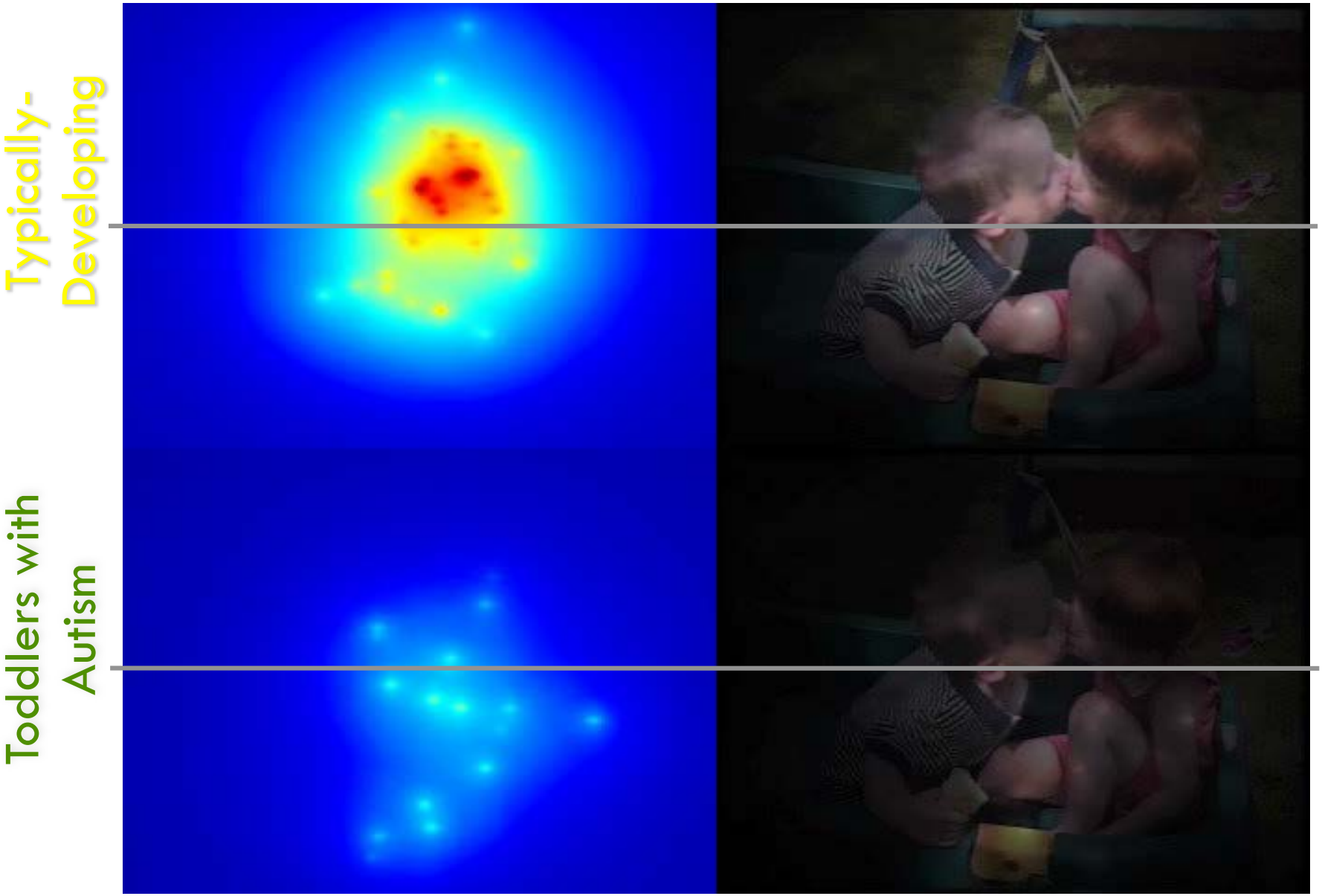
Scenes of Social Interaction

Typically-Developing

Toddlers with Autism



Scenes of Social Interaction



Greater Access to Early Diagnostic Services

Marcus Autism Center

Translational Opportunities

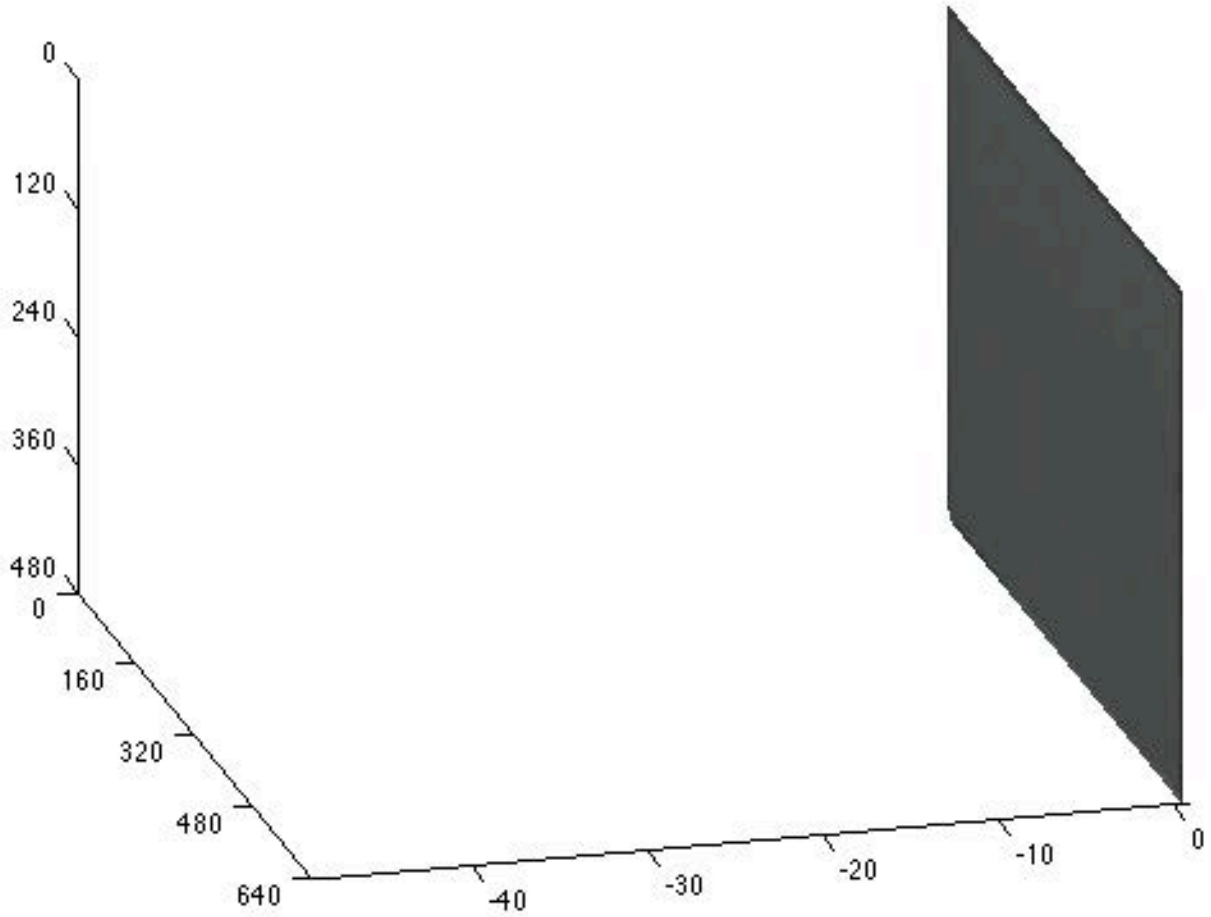
- Objective, quantitative, & rapid measures of social adaptive & maladaptive behavior
- Leverage automated measurement technology to enable early detection
- Support a public health system that does not have enough expert clinicians

Investigational Device:
Neurodevelopmental Assessment via Eye-Tracking

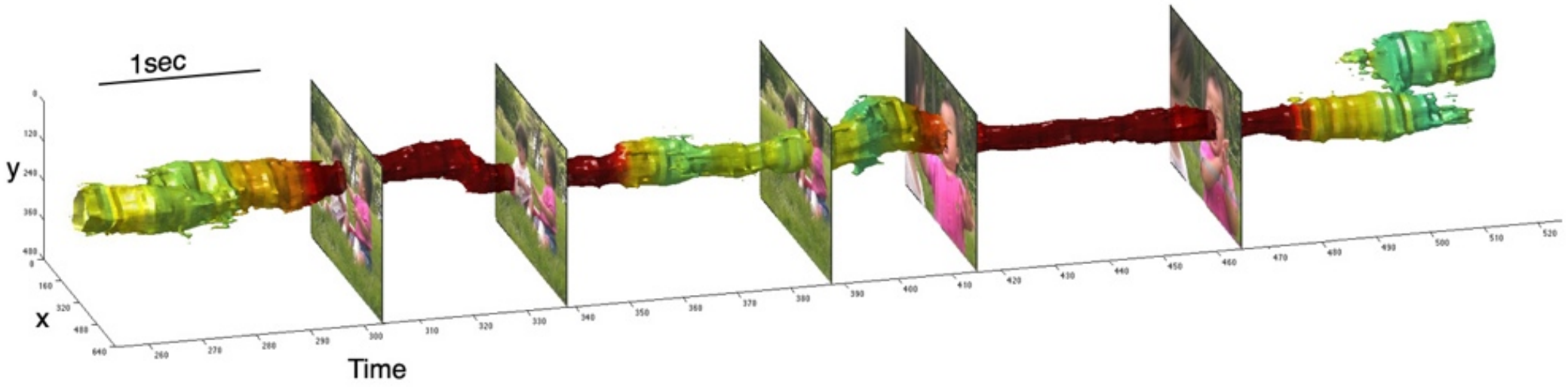
Utility of our eye-tracking assays to diagnostic and developmental characterization

Moment-by-moment entrainment to socialization "hot spots"

16 to 30 months

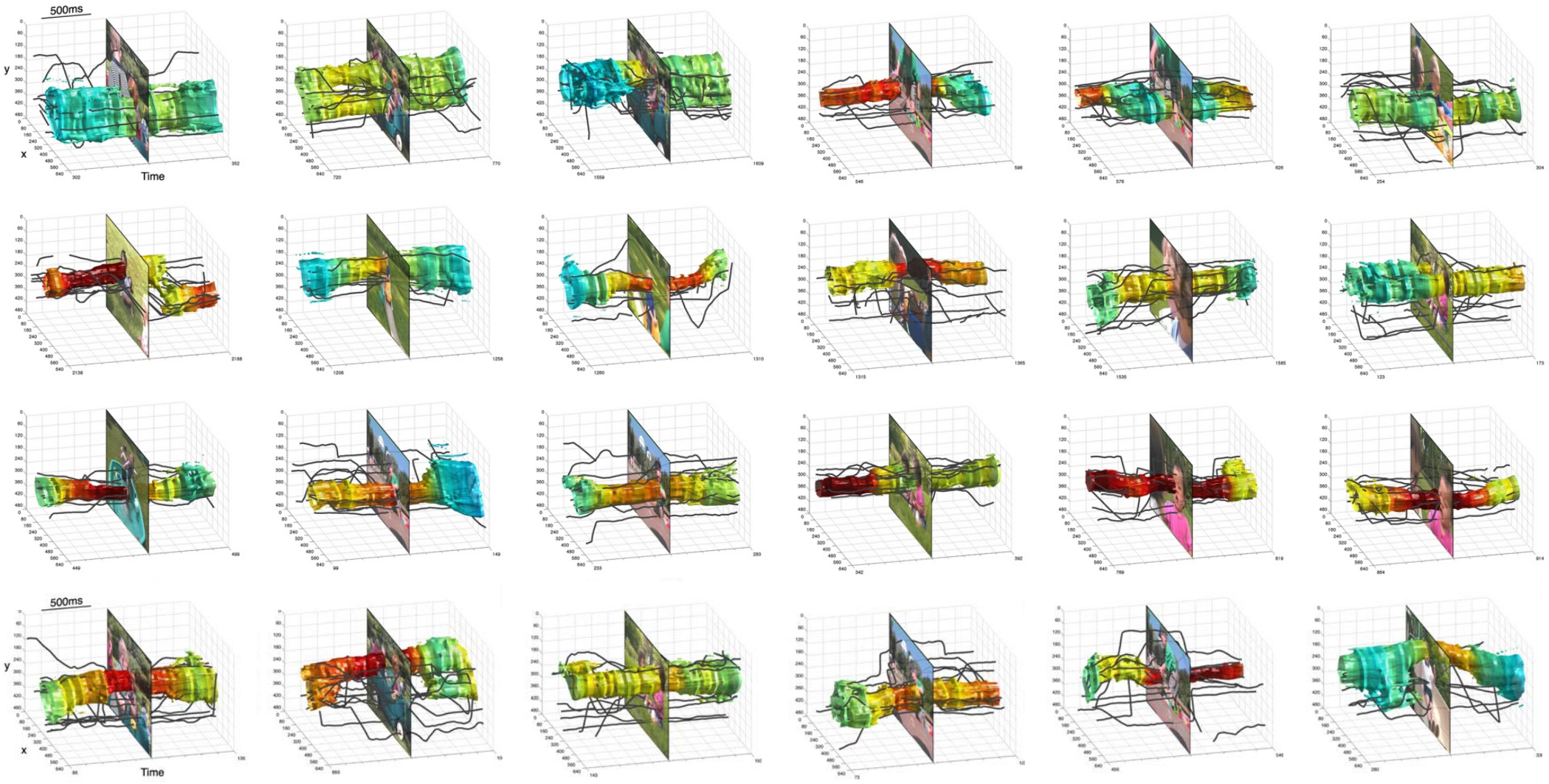


Discovery Cohort
Normative Data Model

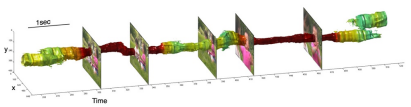


Non-ASD data from the discovery cohort defined benchmark normative data against which all other comparisons were made.

Quantitative Indices for Assessing Presence of ASD



TD normative funnels =



ASD comparison scanpaths =

Data Harmonization: Participants N=1,059, by Reference Standard Outcome Diagnosis

Discovery Cohort (lab-based eye-tracking research setting)

measure	ASD	non-ASD
N	300	389
age, months	22.5(3.6)	21.6(3.5)
ADOS Total score, mean(SD)	17.4(4.9)	4.5(2.5)
Mullen Verbal age equivalence	11.9(5.8)	23.1(5.7)
Mullen Nonverbal age equivalence	18.3(5.0)	22.2(4.9)

Replication Cohort (standalone investigational device in community clinic)

measure	ASD	non-ASD
N	187	183
age, months	28.3(5.8)	26.0(5.9)
ADOS Total score, mean(SD)	19.4(5.0)	5.5(3.2)
Mullen Verbal age equivalence	14.8(7.7)	23.1(8.0)
Mullen Nonverbal age equivalence	20.7(6.8)	27.3(9.8)

Index Test Eye-Tracking Measures

Discovery cohort data collection

- Lab-based university research setting

Replication cohort data collection

- Standalone investigational eye-tracking device located in a community clinic

Naturalistic videos of peer social interaction

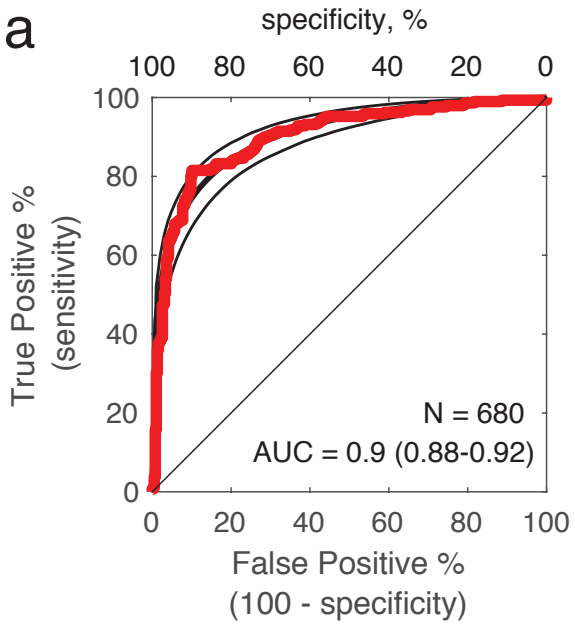
- 14 videos, each ~53 seconds in duration
- 12 min 26 sec of videos in total

Presence of ASD: Diagnostic Accuracy (ASD vs non-ASD)

Discovery Cohort

N=680

a



Replication Cohort

N=361

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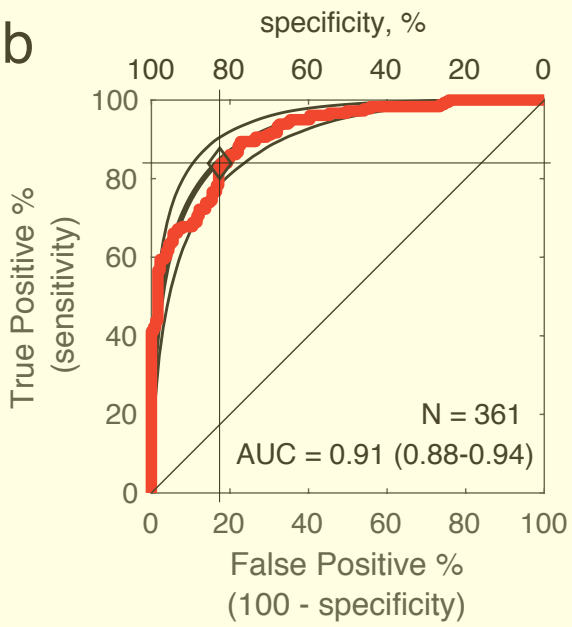

Replication *se*, *sp* at Discovery Threshold

c

	%	95% CI
Sensitivity	83.9	(77.8-88.6)
Specificity	82.3	(76.1-87.2)
PPV	82.5	(76.3-87.4)
NPV	83.7	(77.5-88.5)
Accuracy	83.1	(78.9-86.6)

9 children in each cohort with insufficient data for meaningful analyses.

se ~83%, *sp* ~82%

Presence of ASD:
False Positives from Eye-Tracking Assays

'Patient has family history of ASD. Caregivers wanted to find out if child has autism.'
'Patient presented for an evaluation following referral from SLP at Fayette who reported that
'Patient presenting with language delays and social skills difficulties. Parents report his
'Patient presenting with language delays, sleep concerns and behavioral issues. Family
'Patient presenting with some language delays. Family history is significant for anxiety and
'Child presenting with language delays. She displays good social overtures, but her eye
‘Typical - no concerns'
'Clear language delays - concerns about social communication - generally not
'Speech delay. Mom had many more concerns that were not consistent with her
'Clear language delay- also had some repetitive behaviors. Language repetitive (frequent
'No ASD concerns. Did show hand-flapping and some posturing but social reciprocity
'Did not provide a diagnosis - follow up evaluation in 1 year. Was on the fence - social
'Patient presenting with language delays. Patient's parents also reported visual-motor
'Patient presenting with language delays and social skill difficulties. Family history is
'Patient presenting with variable eye contact, though displayed adequate social overtures
'Patient was previously seen at MAC in the PNC/CAD where he received a multidisciplinary
'Patient presents with some language delays. Family history is significant for ASD and
'Patient's mother reports concerns with regard to her response to name and social skills.

Presence of ASD:
False Positives from Eye-Tracking Assays

'Patient h ... has autism.'
'Patient p ... tte who reporte
'Patient p ... rents report his
'Patient p ... al issues. Fami
'Patient p ... cant for anxiety
'Child pre ... res, but her ey
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'No ASD c ... ial reciprocity
'Did not pu ... fence - social
'Patient pr ... visual-motor
'Patient pr ... ily history is
'Patient pr ... social

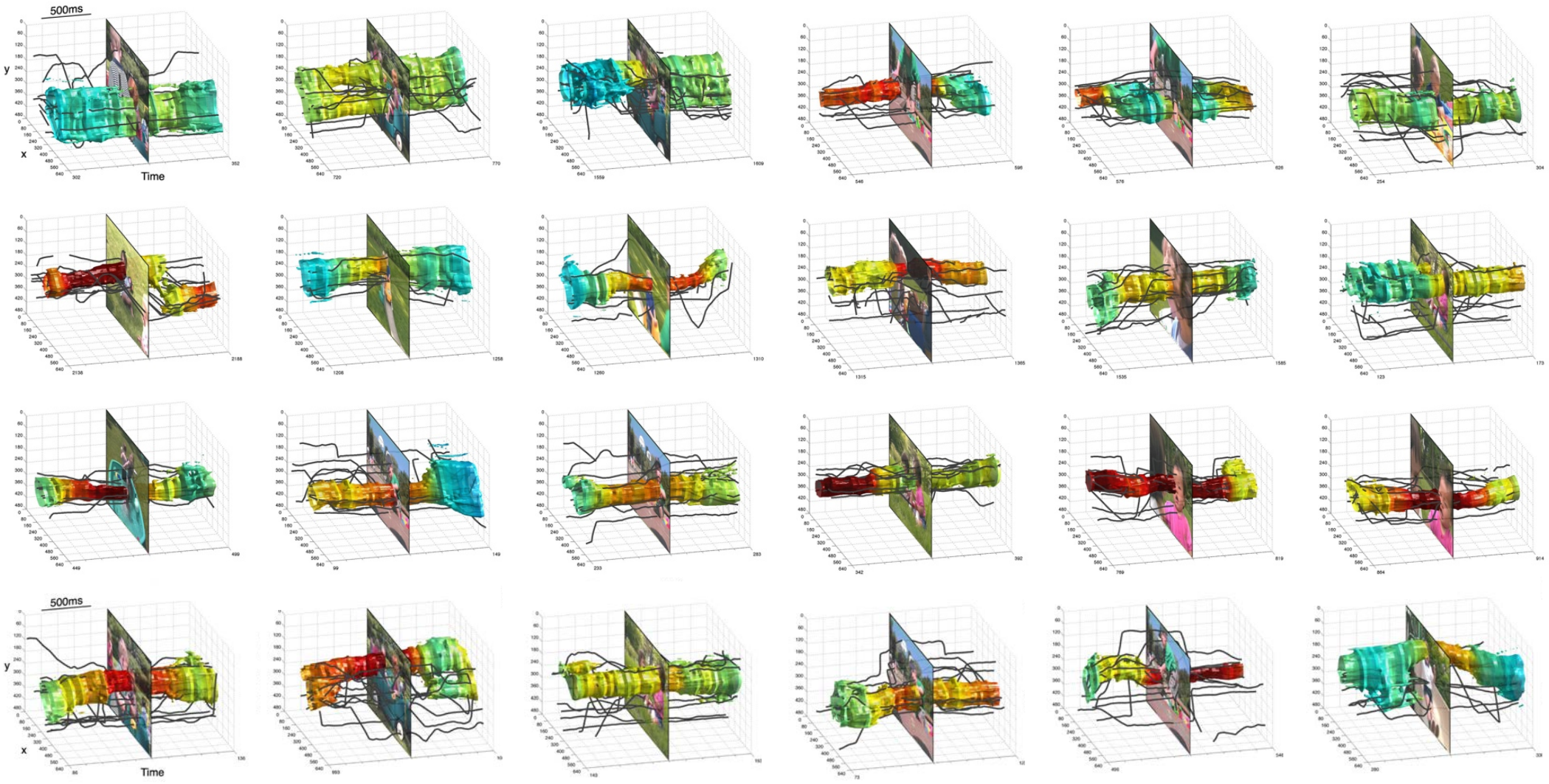
Identification of Actionable Vulnerabilities

80% of "false positives" via eye-tracking assays were given a different clinical diagnosis:

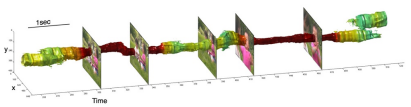
- "language delay" or "global developmental delay" (25%),
- provisional diagnosis of "sub-threshold symptoms of ASD" (35%) or "sub-threshold communication disorder" (15%) (both with requests to return for re-evaluation within a year),
- or suspected genetic disorder (5%) (referred for genetic testing).

Half of the children given a provisional sub-threshold diagnosis were later given an ASD diagnosis.

Quantitative Indices for Assessing Severity of ASD Symptoms



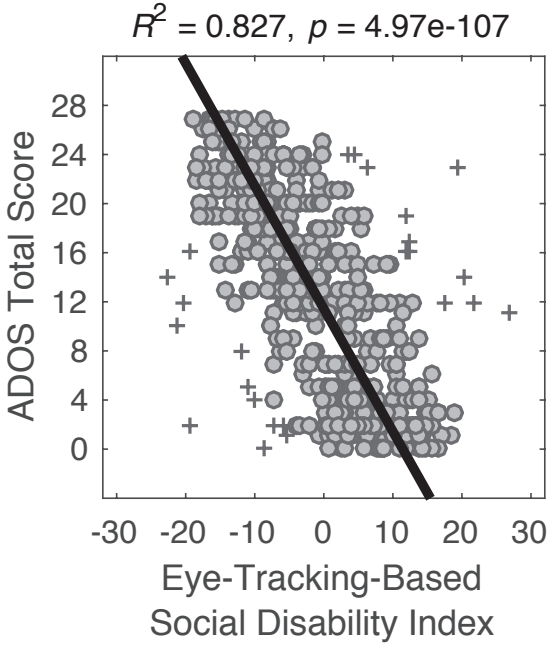
TD normative funnels =



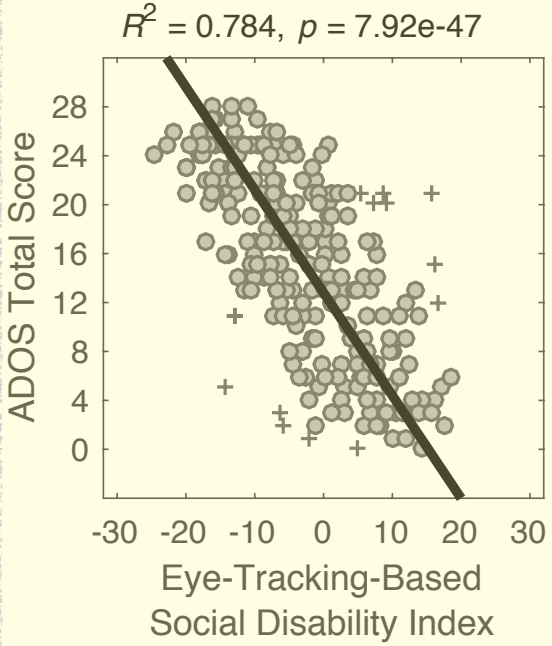
ASD comparison scanpaths =

Quantitative Indices for Assessing Severity: Social Disability

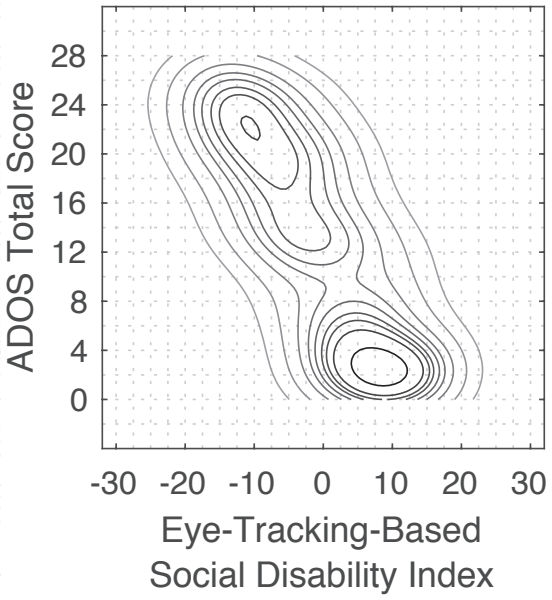
Discovery Cohort



Replication Cohort



Pooled Population Prediction



○ Individual data

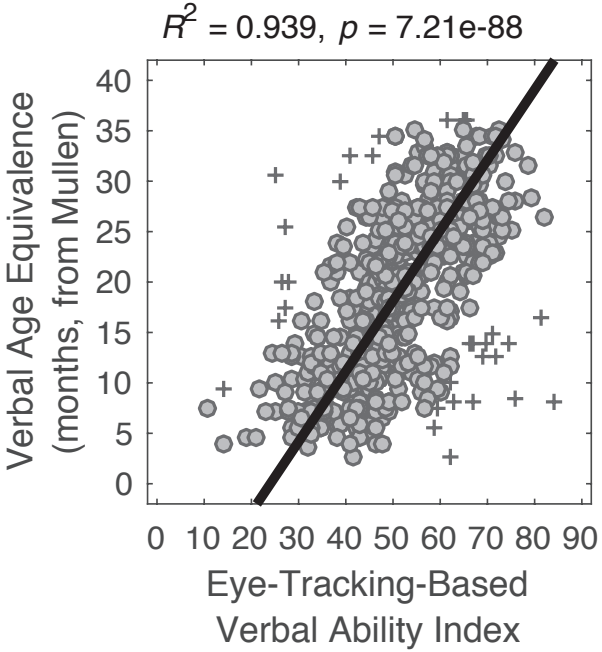
\+ Points with Cook's D > 3x mean

— 5th… 95th percentiles

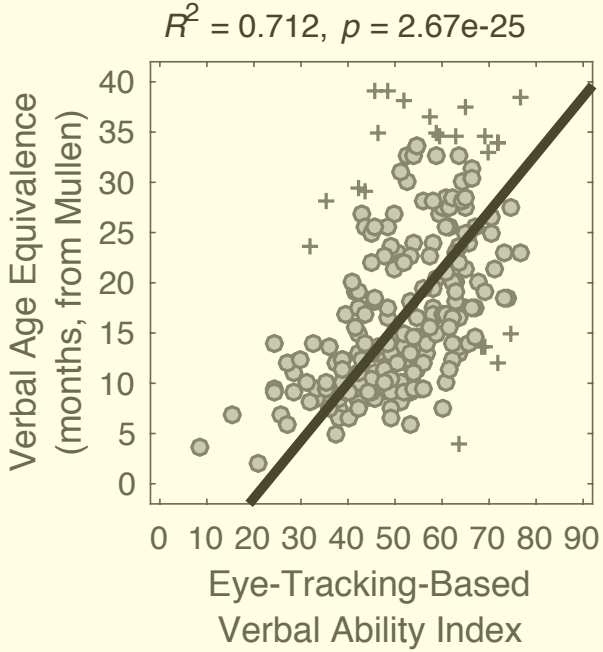
~78% of variance in ADOS total scores

Quantitative Indices for Assessing Severity: Verbal Ability

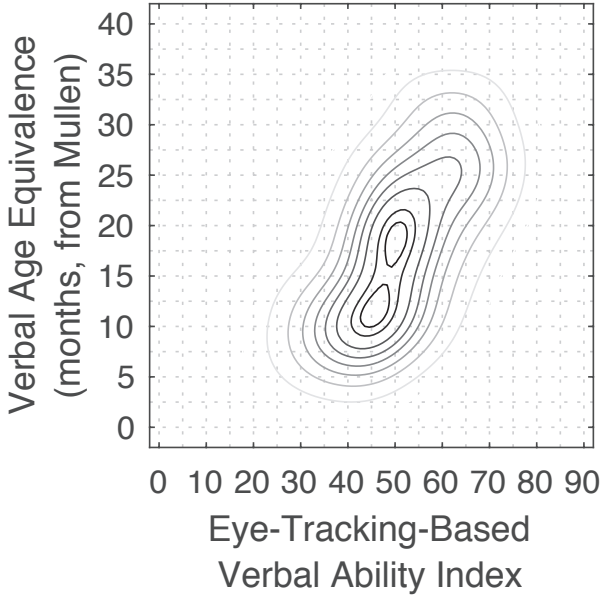
Discovery Cohort



Replication Cohort



Pooled Population Prediction



○ Individual data

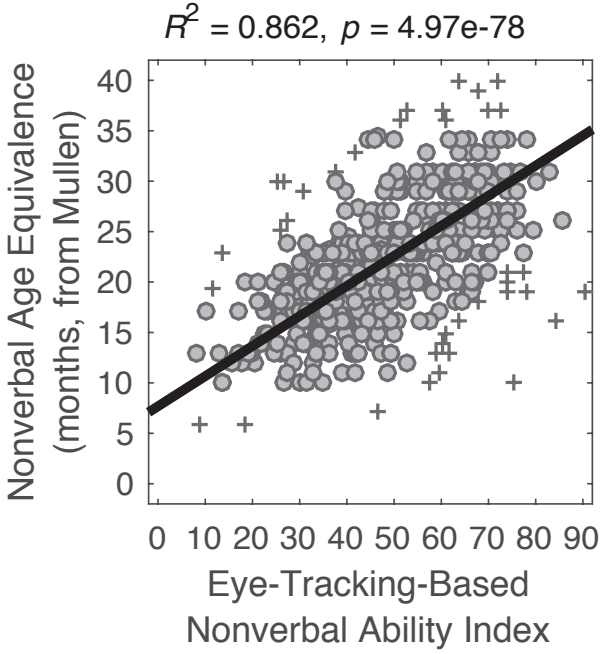
\+ Points with Cook's D > 3x mean

— 5th… 95th percentiles

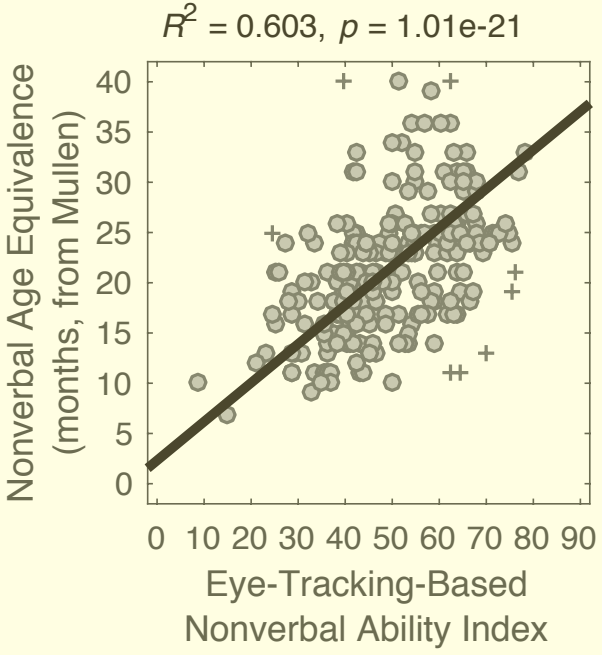
~71% of variance in Mullen verbal age equivalents

Quantitative Indices for Assessing Severity: Nonverbal Ability

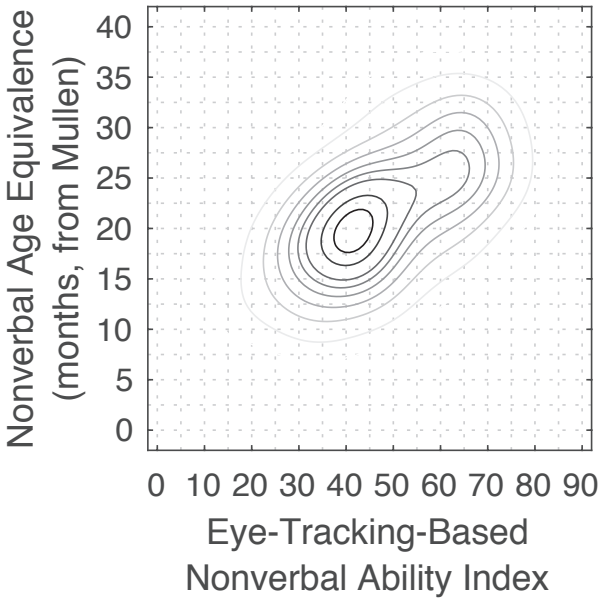
Discovery Cohort



Replication Cohort



Pooled Population Prediction



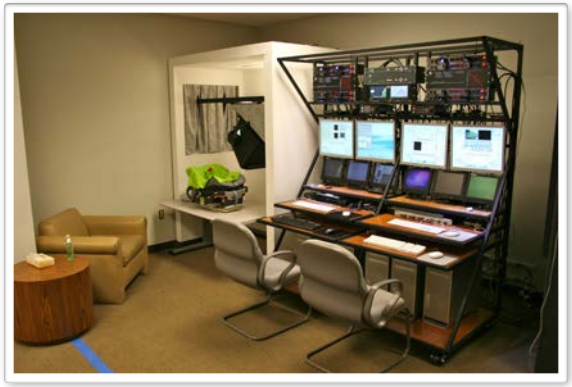
○ Individual data

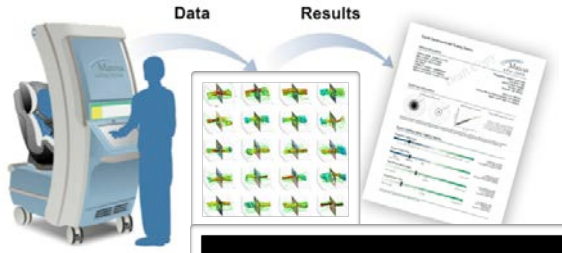
\+ Points with Cook's D > 3x mean

— 5th… 95th percentiles

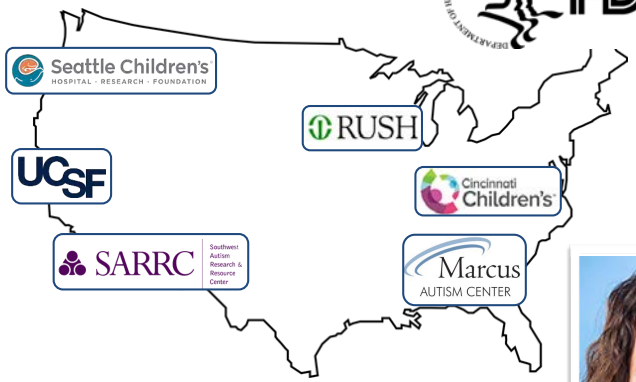
~60% of variance in Mullen nonverbal age equivalents

Translating this science into a tool for increasing access to diagnostic services





Warren Jones



Cheryl Klaiman

Enrollment

- Complete: 503
- Target: 472

MINNETRONIX® MEDICAL
Accelerating Breakthroughs

TIETRONIX

Validated Cloud

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

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

Greater Access to Early Treatment

Marcus AUTISM CENTER
NIH Autism Center of Excellence

Caregivers' most important role in promoting early brain development in their children

Amy Wetherby, PhD

Providing the social experiences children are missing

Augmenting access to early intervention services: parent-mediated treatment

- www.autismnavigator.com
- www.babynavigator.com

the Community: Families, Pediatricians, Early Intervention Providers

Parent-Delivered Early Social Interaction

Wetherby et al., 2014

Marcus AUTISM CENTER
NIH Autism Center of Excellence

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 social reciprocity

- Natural reinforcers
- Waiting for initiation and balance of turns
- Clear message to ensure comprehension

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 waking 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

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

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!

5 Steps for Brain-Building Serve and Return

Dr. Jack Shonkoff

Center on the Developing Child
HARVARD UNIVERSITY

Dr. David Willis

An Early Brain and Child Development Focus

U.S. Department of Health and Human Services
HRSA
Health Resources and Services Administration

LANGUAGE NUTRITION

TALK WITH ME BABY

Dr. Brenda Fitzgerald

DPH
Georgia Department of Public Health

CDC
Centers for Disease Control and Prevention

Brain Trust 4 Babies

Marcus
AUTISM CENTER
NIH Autism Center of Excellence

Our ultimate goal

To make autism
an issue of diversity,
not of disability