Disclosure Statement

Intellectual property related to eye tracking tests described in this presentation are governed through the University of California, San Diego. The eye tracking tests are licensed through the University of California, San Diego, with partial royalties to KP.
38% have an Intellectual Disability - IQ < 70
61% of individuals have IQs < 85
~Average age of 1st diagnosis/tx ~ 4 years

AUTISM BEGINS in the WOMB

Post Mortem: Disrupted Cortical Layering

Post Mortem: Increased Neuron Number

Courchesne et al., JAMA, 2011

Stoner et al., NEJM, 2014

The Prenatal Hormone Milieu in Autism Spectrum Disorder

Human Frontal Cortex Neural Development & Circuit Formation (Conel J.I., 1939)

Average Diagnosis and Service Age

*Based on Data from CDC's ADAMS Network

Human Frontal Cortex Neural Development & Circuit Formation (Conel J.I., 1939)

Average Diagnosis and Service Age

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Autism+Prenatal = 3.082 Results

Optimal Age for Services ~3-4 yr

Average Diagnosis and Service Age

*Based on Data from CDC's ADAMS Network
Early Treatment by 18 Months Results in Significant Gains for Children

1. Cochlear Implants/Hearing Loss
   > 18 months
   < 18 months

2. Institutionalized Infants (Romania)

3. Autism

- Post Tx RL
- RL
- Baseline
- 18 mo
- 27 mo

Receptive Language Project

<table>
<thead>
<tr>
<th>Age at Placement</th>
<th>DD</th>
<th>Baseline</th>
<th>18 mo</th>
<th>27 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-18</td>
<td>14</td>
<td>84.9</td>
<td>19.38</td>
<td>31.36</td>
</tr>
<tr>
<td>18-24</td>
<td>16</td>
<td>89</td>
<td>+19</td>
<td>+3</td>
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<tr>
<td>24-30</td>
<td>22</td>
<td>80</td>
<td></td>
<td></td>
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<tr>
<td>30+</td>
<td>9</td>
<td>79.7</td>
<td>28.08</td>
<td>34.26</td>
</tr>
</tbody>
</table>

Cota et al., (2003) JAMA Otolaryngol
Nelson et al., Science (2001)

SAN DIEGO PEDIATRICIAN NETWORK
N=243

To Date > 150,000 babies screened in San Diego! + 40,000 more in Phoenix!

Early ASD Identification: The Get S.E.T. Early Model

Early treatment
Average amount of Total Early treatment
*20 hours per week

Mean Age at Screen: 17.16 mo
Modal Age at Screen: 12 months

1. SCREEN

N=57,603

2. Evaluate/Diagnose

3. Treat and Support

First screen age band

Get S.E.T. Early Impact

San Diego Pediatrician Network, 2023
How often are children that have the disorder detected by the screen?
How often are children that don’t have the disorder does the screen say are negative?

Out of all of the positive findings, how many are true positives?
Out of all of the negative screens, how many are true negatives?

SENSITIVITY
SPECIFICITY

POSITIVE PREDICTIVE VALUE
NEGATIVE PREDICTIVE VALUE

FUNDAMENTALS OF SCREENING/Biomarker Tests

The Power of Eye Tracking

1. Reduce age of 1st Dx
2. Reveal Distinct Biological Subgroups
3. Prognostic Indicator
4. Guide Tx Planning
5. Marker of Tx Response

Objective
Quantitative
Doesn’t rely on clinical judgement

EYE TRACKING IS UBIQUITOUS

CONSUMER Behavior
What part of the ad are people looking at, and for how long?

Concussion
Signs of brain injury
Are pupil sizes uneven?
Able to track objects smoothly?

Safety
Is the truck driver closing eyes/falling asleep?

Reading Issues
Does the child skip words or spend too long on a single word?

Yarbus’s Eye Tracking Machine – 1960

Ha!
How Do Modern Eye-Trackers Work?

1. Near-infrared light beams illuminate the pupil and creates reflection patterns on the cornea.
2. Cameras record relative position of the center of the pupil and the corneal reflection.
3. Gaze point is calculated based on the vector between the pupil center and the corneal reflections as the eye moves.

Eye Tracking Metrics

- Gaze Point/Fixation
- Time to First Fixation
- Fixation Sequence
- % Fixation Within Area of Interest (AOI)
- # of Saccades per second
- Blink Rate (Hz)

Related to different cognitive processing states (less blinking more interested): Shultz et al., (2011)

Infants are Born Socially Interested

9 MINUTE old infants prefer faces over non-face patterns.

Goren 1975, replicated by Johnson 1991
The Geometric Preference Test for Autism

Visual only
No sound

% Fixation within the 'social' AOI

Enhanced Visuospatial Abilities/Local Processing
Interest in repetition
Superior Math

% Fixation within the Geometric (non-social) AOI

GEOMETRIC PREFERENCE TEST FOR AUTISM:
ASD 15 MONTHS

Typical 14 MONTHS

RESULTS from Eye Tracking Test 1: Geo Pref Test
N=1,863 toddlers

Classification Accuracy by AGE

Classification Accuracy by RACE & ETHNICITY

Wen et al., 2022, Scientific Reports
**Genetic Underpinnings of Social Attention in ASD**

- (Image of scatter plots showing genetic associations with social attention in ASD)

**Are Saccade Profiles Different in ASD Subgroups?**

- (Image of graphs comparing saccade profiles across different ASD subgroups)

**Relationship Between Subgroups and Clinical Phenotype**

- (Bar chart showing association between ASD subgroups and various clinical phenotypes)

**Sleep fMRI**

- (Image of a child sleeping with fMRI equipment)
Impact on Brain’s Functional Organization

Major Resting State Networks (Raichle)

Visual Network - Default Mode Connectivity

ASD Generalized
Pref ASD Social
Pref LDI TD ASD TD

N=195

6 Eye Tracking Tests and the Autism Score

Frontal 
Social 
Brain

Cerebellar 
Language/ 
Temporal & STS

Autism 
Score

TD

N=195
**Reduced Attention To Speech**

1. **REDUCED PREFERENCE FOR BABY TALK (aka MOTHERESE) SPEECH**
   - Miller et al., (2017)
   - 156 infant siblings (20 with final diagnosis of ASD)

2. **REDUCED ORIENTING TO NAME**
   - Miller et al., (2017)
   - 156 infant siblings (20 with final diagnosis of ASD)

3. **REDUCED BRAIN RESPONSE TO LANGUAGE in SOME, But not Others**
   - N = 103 (total)

**BABY TALK (aka. “Motherese”)**

- **Characteristics**
  - Higher Pitch
  - Slower Tempo
  - Heightened Positive Affect
  - Exaggerated Speech Contours
  - High Rate of Questions

- **Function**
  - Stimulates: attention, joint attention, learning
  - Improves: language acquisition, affective engagement, reactivity

**Gaze Contingent Training**

1. Child must fixate on the central smiley face to start the training trial
2. Minimum 2 gaze shifts to “pass” training

**TD: 24 months**
**Toddler : 18 months**

![Image of a toddler holding a toy]

**Baby-Talk/Motherese Speech vs Highway Traffic Sounds**

- **N = 588**
- **AUC = .70**
- **p = .0001**
- **CI = .64-.77**
- **Sens = 18%**
- **Spec = 98%**
- **PPV = 94%**
- **NPV = 40%**

**Pierce et al., 2023, JAMA Network Open**

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**Sleep fMRI**

- It's time little sheep...

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**Overall fMRI Activation Maps (N=71 Toddlers)**

- **NON-ASD** (Typical+Delay)
- **ASD toddlers**

- N=31
- N=40

**MILD Social Affective Speech**

**MODERATE Social Affective Speech**

**HIGH Social Affective (Motherese) Speech**

**Han et al. Nature Human Behaviour, 2022**
**SIMILARITY NETWORK FUSION - Data Combining and Subtyping Tool**

6. Data Domains
   - CLINICAL
   - EYE TRACKING
   - FMRI

B. Subject Distance Matrices

C. Subject Similarity Networks

D. Fused Networks

E. Subject Clusters Extracted

**Cluster Results**

- IMRI-Clinical Subtypes
  - Cluster 1
  - Cluster 2
  - Cluster 3
  - ASD
  - Typical

- Socialisation Scores

- Social Attention Eye Tracking

**6 Eye Tracking Tests and the Autism Score**

Eye Tracking as a Tool to Index JOINT ATTENTION

**Joint attention** – the shared focus of two individuals on an object achieved when one individual alerts another to an object by means of eye-gazing, pointing, or other verbal or non-verbal signals.
Eye Tracking as a Tool to Index JOINT ATTENTION

N=728 (543 ASD, 91 Non-ASD Delay, 94 TD)

Mean age 25 months

Does Eye Tracking Index Joint Attention?

External Validation with Standardized Tests

Independent Replication?

Sayed et al., In Preparation

Faster and more objective alternative to manual coding joint attention!
How to use this information to move towards precision medicine and Tx optimization?
1. **Eye Tracking in Social Stimuli**

   "Eye-tracking results showed that administration of Vasopressin was associated with a large and statistically significant increase in biological motion orienting preference (ES=0.8, \( p=0.047 \))." (Umbricht et al., 2017)

2. **Overactivity in Gene Pathways**

   "Decline in mouth looking as indexed by eye tracking between Time 1 and Time 2 was associated with greater language gains."  
   (Gazestani et al., 2019, Nature Neuroscience)

3. **Too Many Brain Cells**

   "Excess brain cells cause challenges with postnatal sculpting."  
   (Courchesne et al., 2001)

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**ET Useful Marker of Tx Response?**

21. The Use of Eye Tracking as a Biomarker of Treatment Outcome in a Pilot Randomized Clinical Trial for Young Children with Autism

   Jessica Bradshaw, Frederick Sisk, Joshua N. Holden, Erin H. Horvitz, Amy C. Bennett, Tamotsu Geuma, and Ty W. Verme

   "Decline in mouth looking as indexed by eye tracking between Time 1 and Time 2 was associated with greater language gains."

22. A Single Dose, Randomized, Controlled Proof-Of-Mechanism Study of a Novel Vasopressin 1a Receptor Antagonist (RG7713) in High-Functioning Adults with Autism Spectrum Disorder

   Gene Expression
   Increased prenatal network activity PI3K-AKT, RAS-ERK and WNT

23. Overactivity in gene pathways related to cell cycle and proliferation

24. Too Many Brain Cells

   Brain Cortical Organoids

   Asymmetrical brain growth patterns in early life in patients with autistic disorder in 152 cases.

   Courchesne et al., 2001

   "3D model Marchetti et al., 2017"
EXCESS BRAIN CELLS CAUSE CHALLENGES WITH SCULPTING: A DTI Study

ENLARGED TRACTS IN ASD INFANTS & TODDLERS

Inferior Longitudinal Fasciculus

Forcips Minor vs. Uncinate
White ± Tracts not different in ASD

Solso et al., (2016) Biological Psychiatry

VISIBLE BRAIN PHENOTYPE RELATIONSHIPS

From Courchesne et al., 2016

YES, may help reduce age at 1st diagnosis to be between 12-18 months as standard of care
Unusual visual and auditory preferences may impact brain development and result in observable neural subtypes
Unusual eye gaze patterns are associated with more challenges with language and increased symptom severity.
Experience dependent mechanisms may interplay with unusual fixation patterns in non-socially responding ASD toddlers to contribute to a poorer prognosis than other ASD toddlers.
Eye tracking derived ASD subtypes may require treatments tailored to each child’s unique profile – steps towards precision medicine!

Thank you!! to the hundreds of children and families who participate in our studies!

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Lab Co-Director: Eric Courchesne
Eye Tracking:
• Autism Research
• Teresa Wen
• Paul Singh
• Javad Zahiri
• Yakta Sayed

Visit us at: autism-center.ucsd.edu