# Applying Neuroscience to Improve Clinical Understanding of Autism

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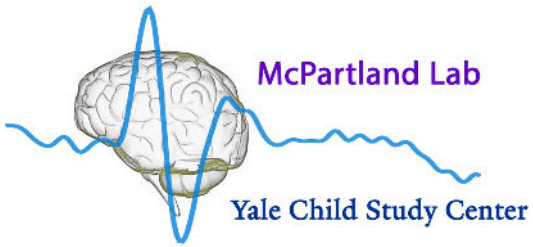
McPartland Lab

Yale Developmental Disabilities Clinic

Yale Center for Brain and Mind Health

Autism Biomarkers Consortium for Clinical Trials





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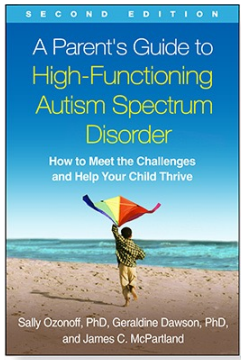
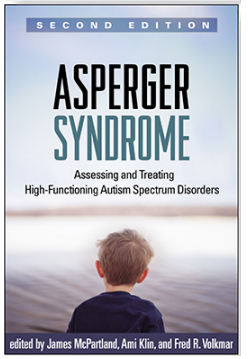
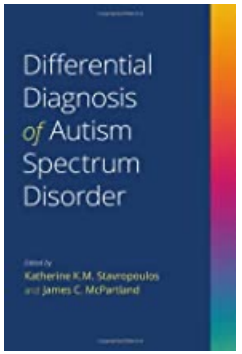
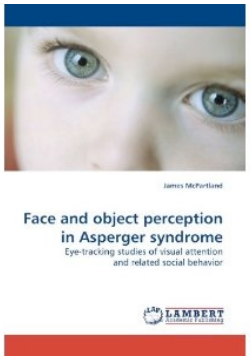
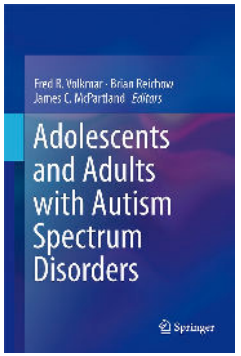


# Overview

- Autism and neuroscientific challenges
- Biomarkers
  - Operationalizing biomarkers
  - Scientific and practical considerations in ASD
  - Example of lab-based progress
    - N170 event-related potential
  - Limitations of lab-based work
- Paths forward
  - Rigorous large-scale studies
    - Autism Biomarkers Consortium for Clinical Trials
  - Increasing inclusivity
  - Therapeutic translation

# Autism Spectrum Disorder

- Developmental condition impacting
  - Social-communicative function
  - Interests and behavioral flexibility
  - Sensory perception and response

***Behaviorally defined***

***Multiple causes and mechanisms***

***No biological assays of clinical utility***

***Critical need for biomarkers***

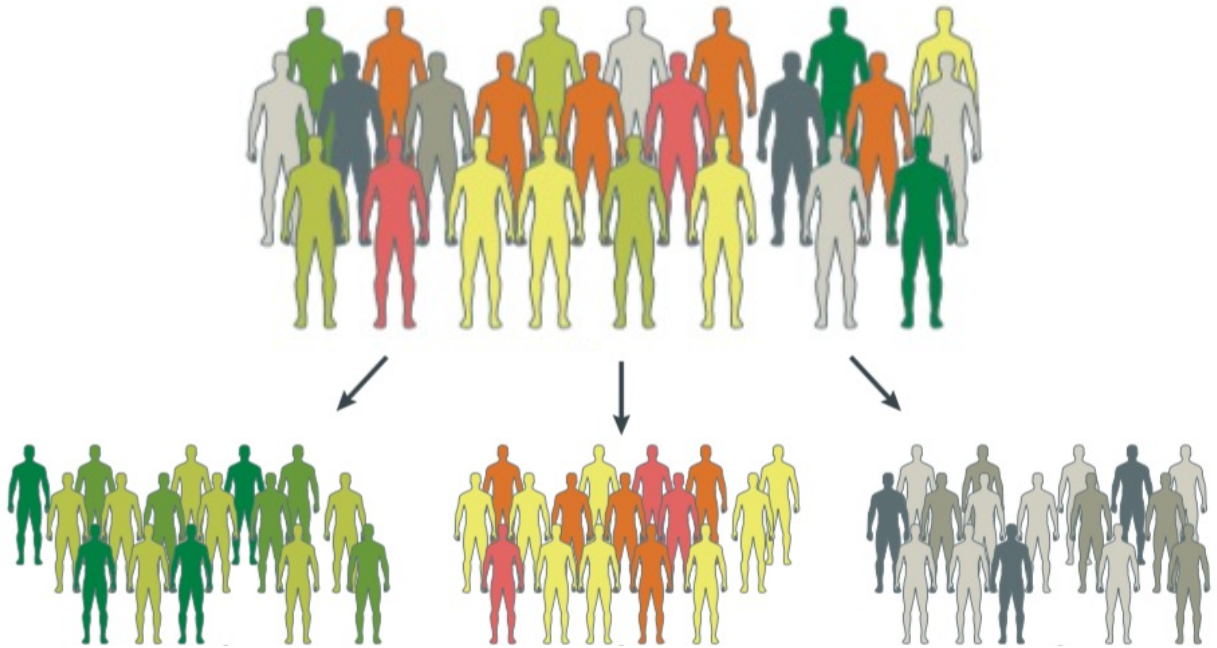
# FDA Biomarker Definition

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

*FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and other Tools) Resource, 2020*

# FDA Biomarker Categories

- Diagnostic
- Susceptibility/risk
- Pharmacodynamic/response
- Prognostic
- Predictive
- Stratification



*Loth et al., 2015*

# Evaluating Biomarker Performance

- Sensitive to diagnostic status
- Associated with function
  - Specificity
- Applicable across development
- Robust to variation in behavior
- Sensitive to change in clinical status

***Not all attributes needed for utility***

***Different attributes for different contexts of use***

*Walsh, Elsabbagh, Bolton, Singh, 2011; Loth et al., 2015; McPartland, 2016*

# Evaluating Biomarker Performance

- **Sensitive to diagnostic status**
- Associated with function
  - Specificity
- Applicable across development
- Robust to variation in behavior
- ~~**Sensitive to change in clinical status**~~

**Diagnostic**

***Not all attributes needed for utility***

***Different attributes for different contexts of use***

*Walsh, Elsabbagh, Bolton, Singh, 2011; Loth et al., 2015; McPartland, 2016*

# Evaluating Biomarker Performance

- Sensitive to diagnostic status
- Associated with symptoms
  - Functionally specific
- Applicable across development
- Robust to variation in behavior
- **Sensitive to change in clinical status**

**Response**

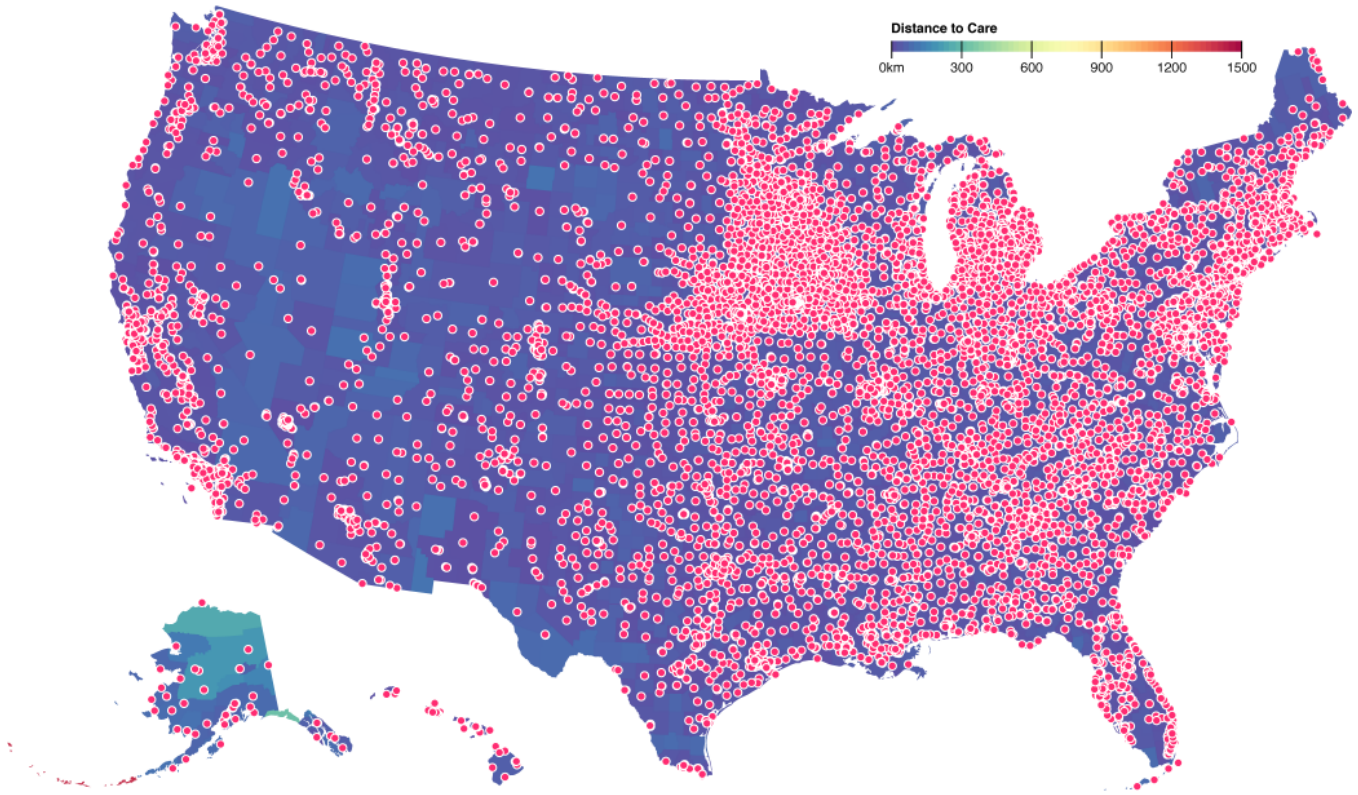
***Not all attributes needed for utility***

***Different attributes for different contexts of use***

*Walsh, Elsabbagh, Bolton, Singh, 2011; Loth et al., 2015; McPartland, 2016*

# Practical Considerations

- Viable in populations with special needs
- Cost effective
- Accessible

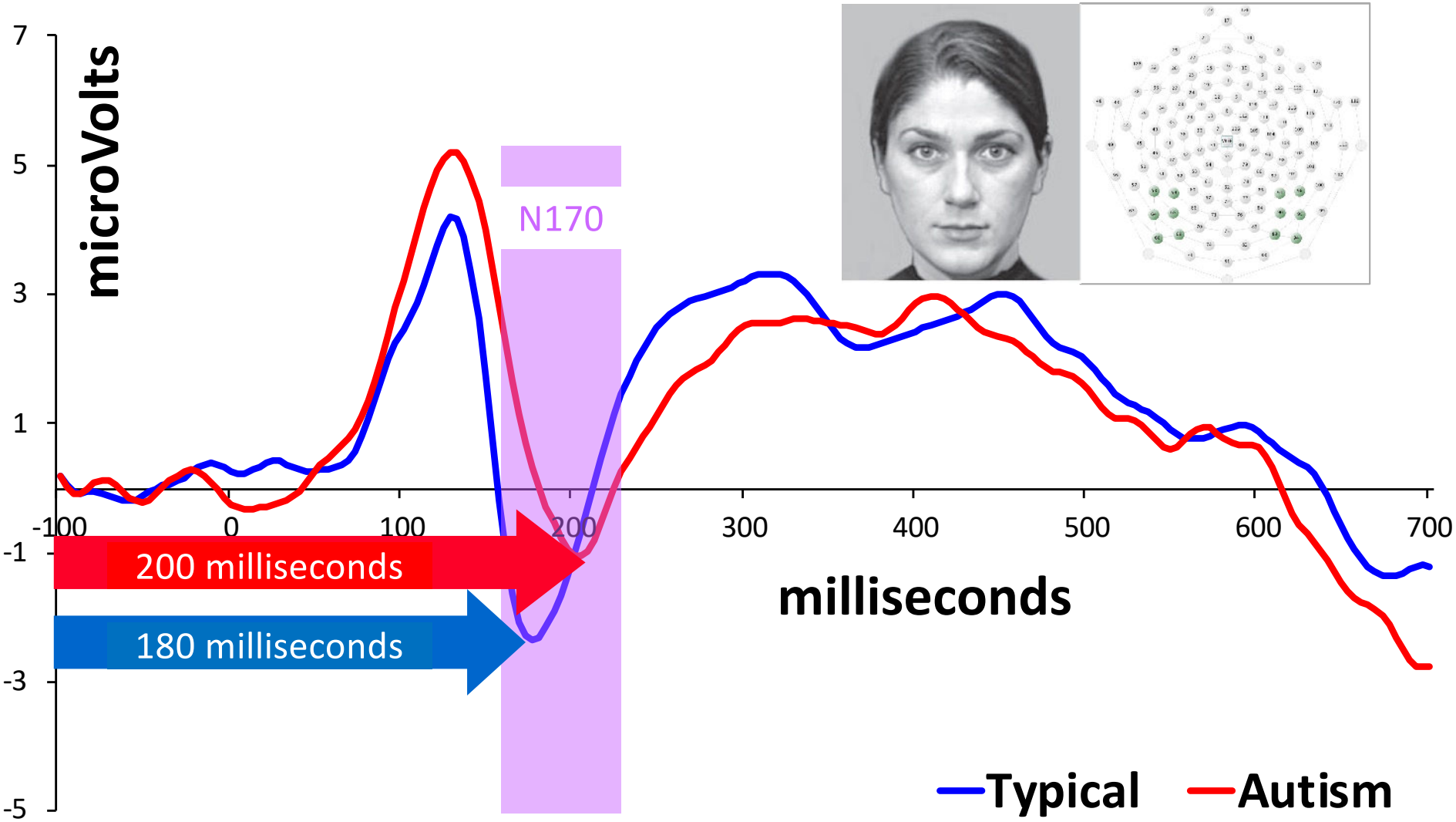



*Walsh, Elsabbagh, Bolton, Singh, 2011; Loth et al., 2015; McPartland, 2016*

# EEG Biomarkers

- Electrical brain activity recorded from scalp
  - At rest
  - In response to perceptual events
- Viable across range of cognitive and developmental levels
  - Non-invasive
  - Movement tolerant
- Practical
  - Cost effective
  - Accessible
- Well studied in neurotypical social-communicative development

# N170: Sensitive to Diagnostic Status



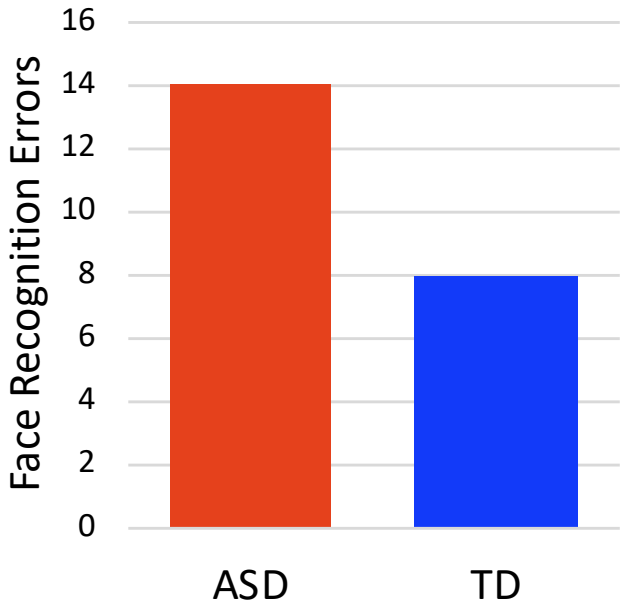

**N170 latency slower in ASD relative to TD**

*McPartland, Dawson, Webb, Panagiotides & Carver, 2004*

# N170: Associated with Function

- Administration of standardized tests of facial recognition in ASD
  - Increased errors among adolescents and adults with autism
  - Performance correlated with N170 latency

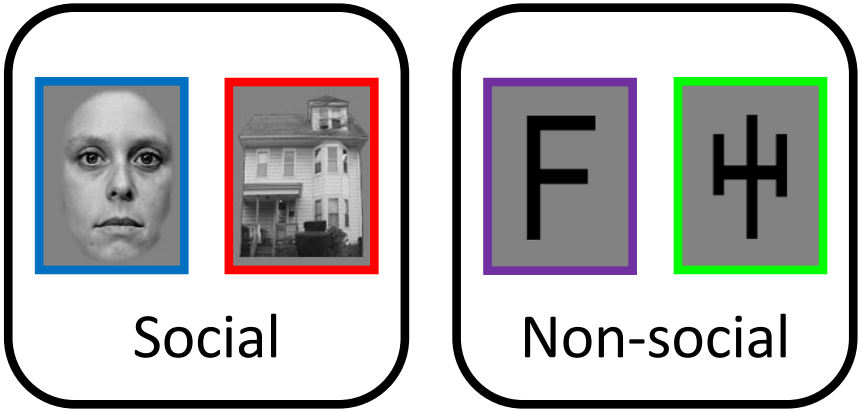
**N170 latency correlates with function**




*McPartland, Dawson, Webb, Panagiotides & Carver, 2004*

# N170: Functional Specificity

- Are N170 differences particular to social information?
  - Might they reflect general perceptual slowing?

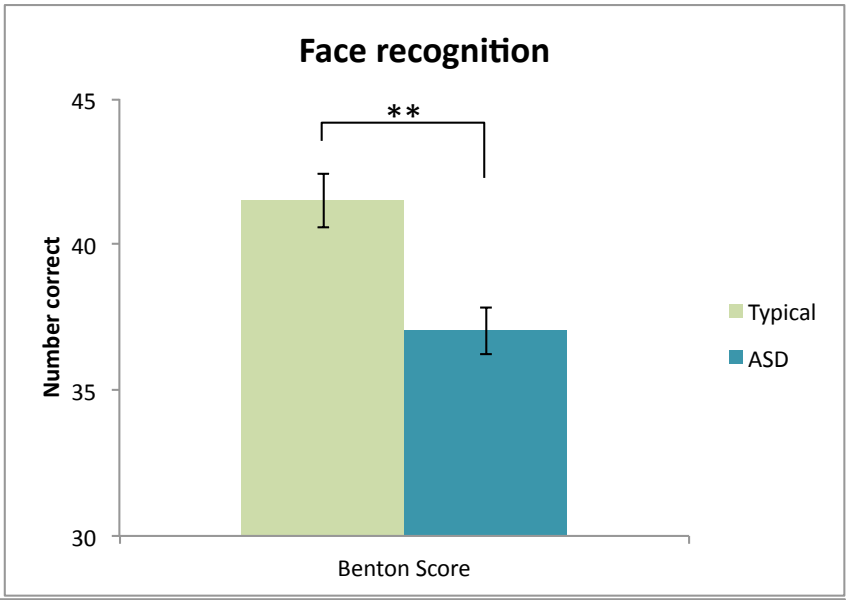


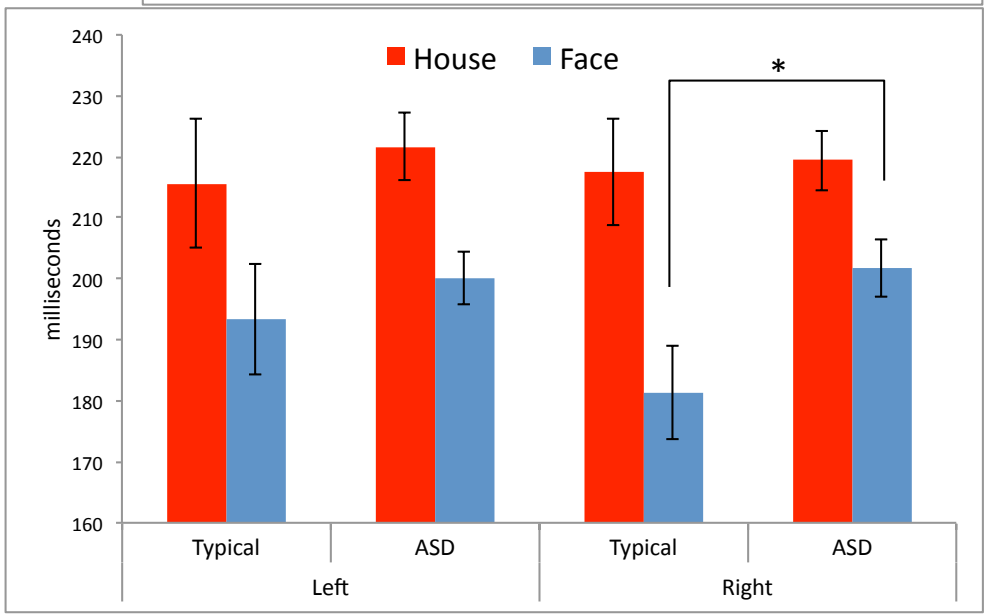

- Opportunity to replicate in a younger cohort

# N170: Applicable Across Development


- Lower face recognition scores in ASD
- Slowed face processing (N170) in ASD in right hemisphere

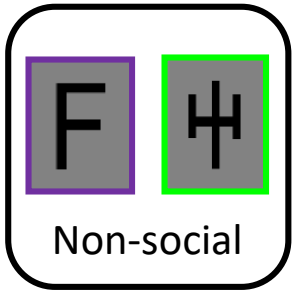
**N170 latency delay consistent in children, adolescents, and adults**



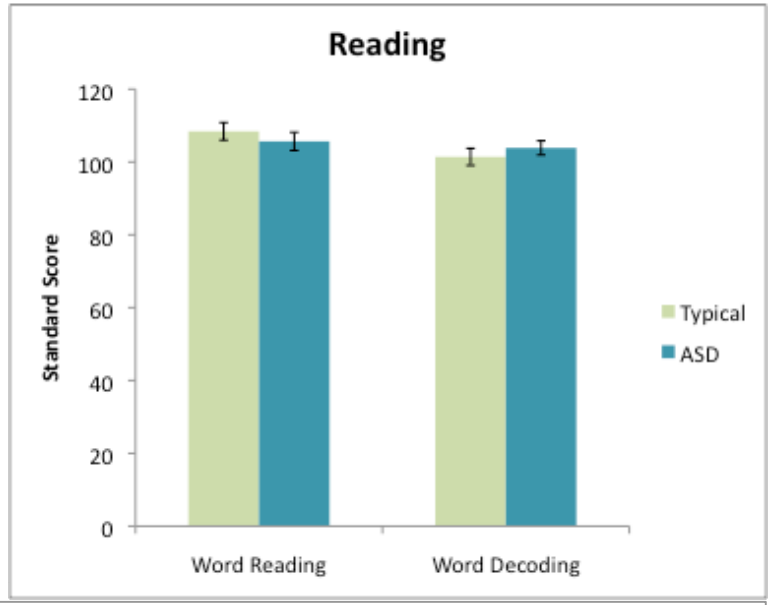

*McPartland, Wu, Bailey, Mayes, Schultz & Klin, 2011*

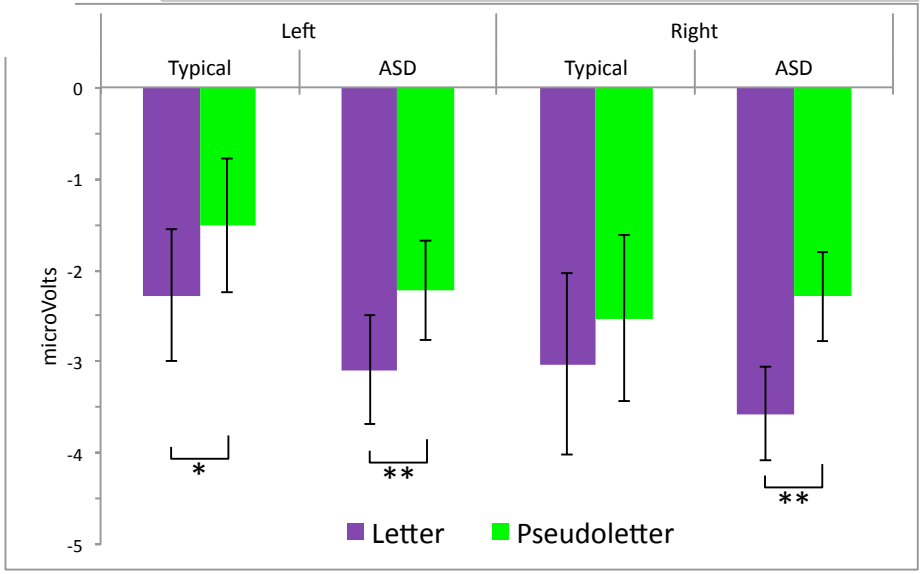
# N170: Functionally Specific




- Normative reading scores
- Normative specialization for letters
  - Enhanced amplitude
  - Comparable latency

**N170 delays specific to social domain**

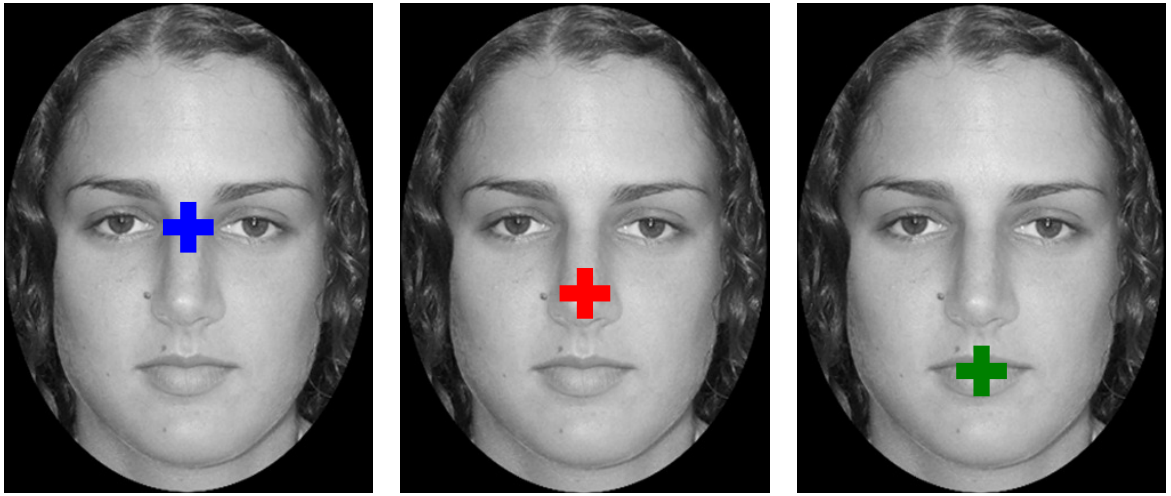



*McPartland, Wu, Bailey, Mayes, Schultz & Klin, 2011*

# N170: Robust to Variation in Behavior

- N170 latency modulated by gaze
  - Faster to eyes
- Reduced attention to eyes in ASD
- Variation in gaze could explain N170 delays

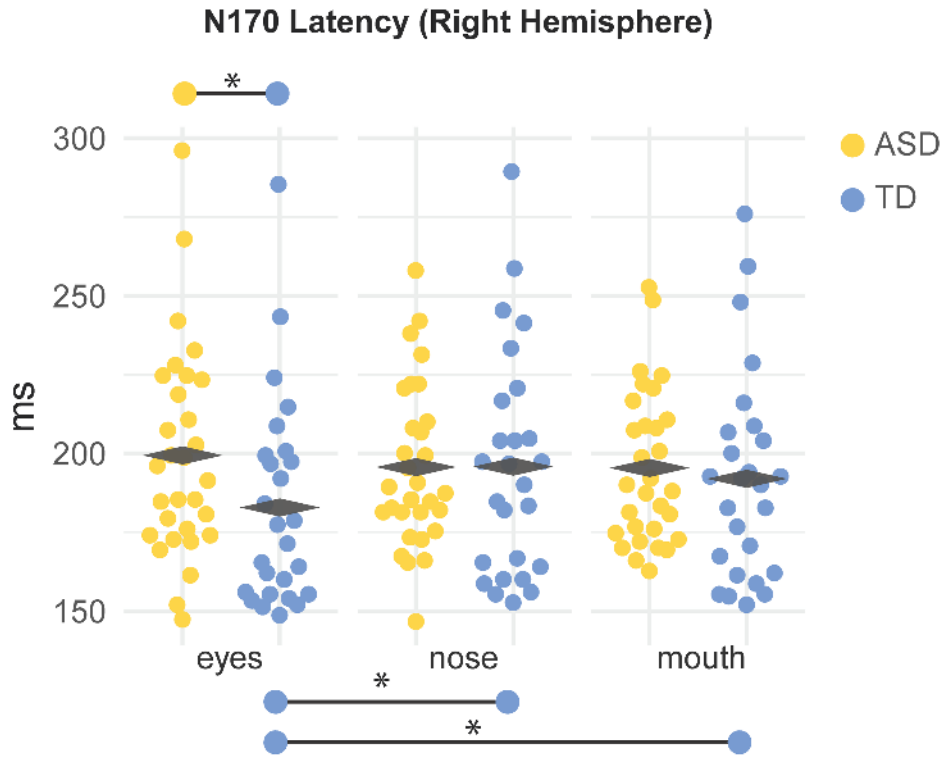


Eyes Nose Mouth

*Parker et al., 2021*

# N170: Robust to Variation in Behavior

- Shorter latency to eyes in TD only
- Longer latency in ASD

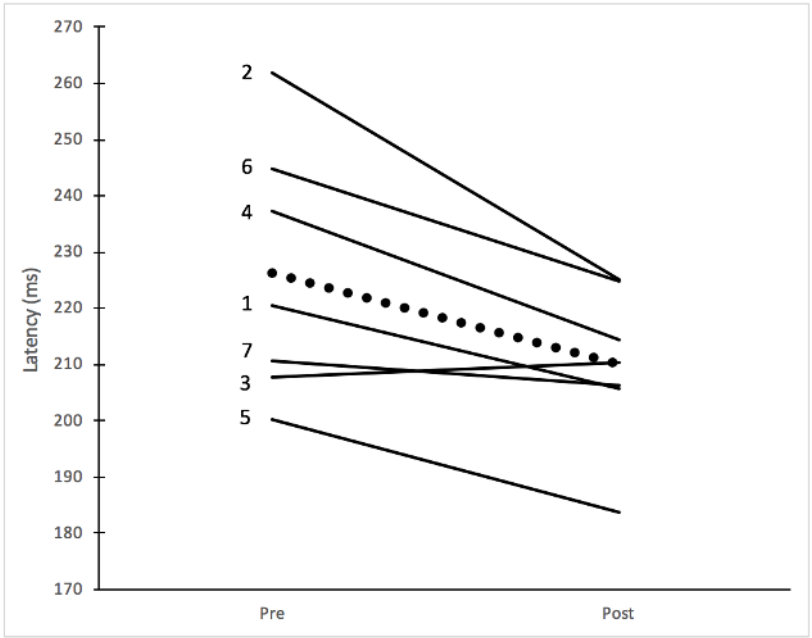



**N170 delays not artifact of gaze behavior**

*Parker et al., 2021*

# N170: Sensitive to Change in Clinical Status


- Pivotal Response Treatment
  - Empirically-supported, naturalistic intervention
  - Preschool-aged children received 14-week course of treatment
- Increased neural efficiency for faces




**N170 latency changes with clinical status**

*Kala et al., 2021; Dawson et al., 2012; Ventola et al., 2013*

# N170: Viable ASD biomarker?

- ✓ Sensitive to diagnostic status
- ✓ Associated with function
- ✓ Functionally specific
- ✓ Applicable across development
- ✓ Robust to variation in behavior
- ✓ Sensitive to change in clinical status
- ✓ Viable in populations with special needs
- ✓ Cost effective
- ✓ Accessible

# Remaining Challenges

- Promising evidence for many biomarkers
- Limited reproducibility
  - Individual differences in face processing
  - Small, underpowered studies
  - Methodological inconsistencies/rigor
- Reliability/practice effects not known
- Absence of normative reference in large TD samples
- Need for rigorous, large scale biomarker research

# ABC-CT: Study Design

- Multi-site, naturalistic study designed to address limitations of existing biomarker research
  - Replication of well-evidenced biomarkers
  - Deeply phenotyped cohorts
  - Large samples (including TD)
  - Longitudinal design (Baseline, 6 weeks, 24 weeks)
  - Practical assays (ET, EEG)
  - Blood draw for ASD participants and parents
- Phase 1 (2015-2020)
  - 280 children with ASD and 119 with TD
  - Ages 6-11
  - IQ 60-150

*McPartland et al., 2020*

# ABC-CT: Study Design

- Combined effort of government, academia, and industry





- Unprecedented rigor
  - Regulatory (Good Clinical Practice)
  - Methodological
  - Statistical
- Harmonized with European AIMS-2-Trials network

# ABC-CT: Clinical Measures

- **Clinician administered**
  - Autism Diagnostic Observation Schedule
  - Autism Diagnostic Interview – Revised
  - Vineland Adaptive Behavior Scales
  - Differential Ability Scales
  - Clinical Global Impression Scale
- **Caregiver report**
  - Aberrant Behavior Checklist
  - Autism Impact Measure
  - Pervasive Developmental Disorder Behavior Inventory
  - Social Responsiveness Scale – Second Edition
  - Child and Adolescent Symptom Inventory
  - ACE Family/Medical History
  - Intervention History
  - Demographics/Screening

# ABC-CT: Biomarker Assays

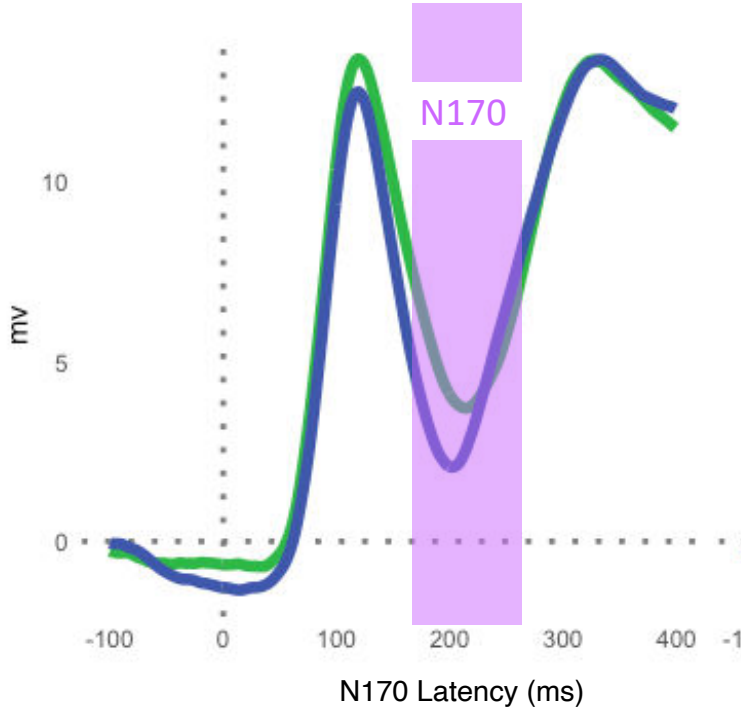
- **EEG**
  - Resting EEG*
  - Visual evoked potentials
  - Biological motion
  - **ERPs to faces***
- **Eye-tracking**
  - Activity monitoring
  - Interactive social task
  - Static social scenes*
  - Biological motion*
  - Pupillary light reflex*

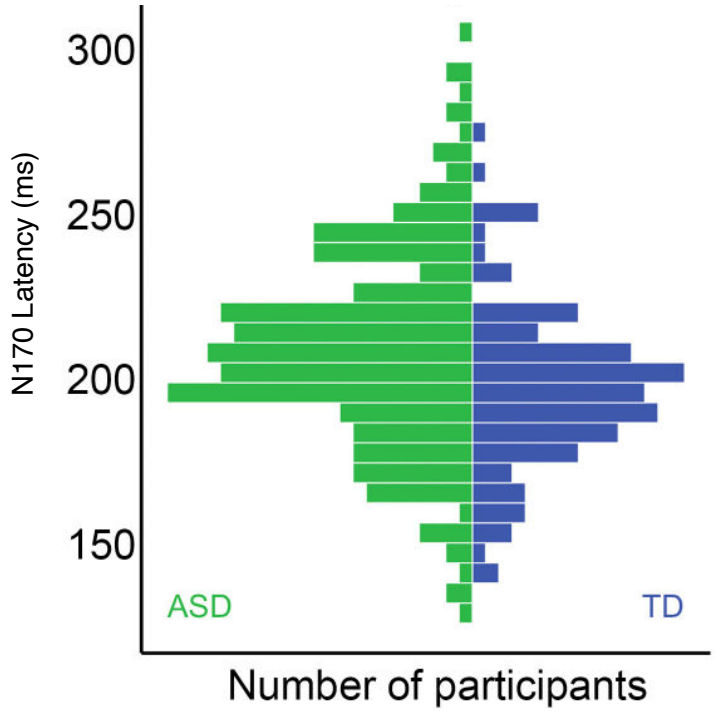
** AIMS-2-Trials harmonized paradigm*

# ABC-CT: N170 latency

| | TD | ASD | *p* | *p (adj.)* |
|---|---|---|---|---|
| Valid signal | 97% | 76% | | |
| Group discrimination | 196.86 (25.7) | 209.63 (32.4) | <.001 | .001 |
| Six-week stability (ICC) | .75 | .66 | >.05 | |
| Twenty-four-week stability (ICC) | .75 | .56 | <.05 | |

- N170 correlated with face memory (NEPSY): $r$ = -.21
- Baseline N170 predictive of 24-week face memory

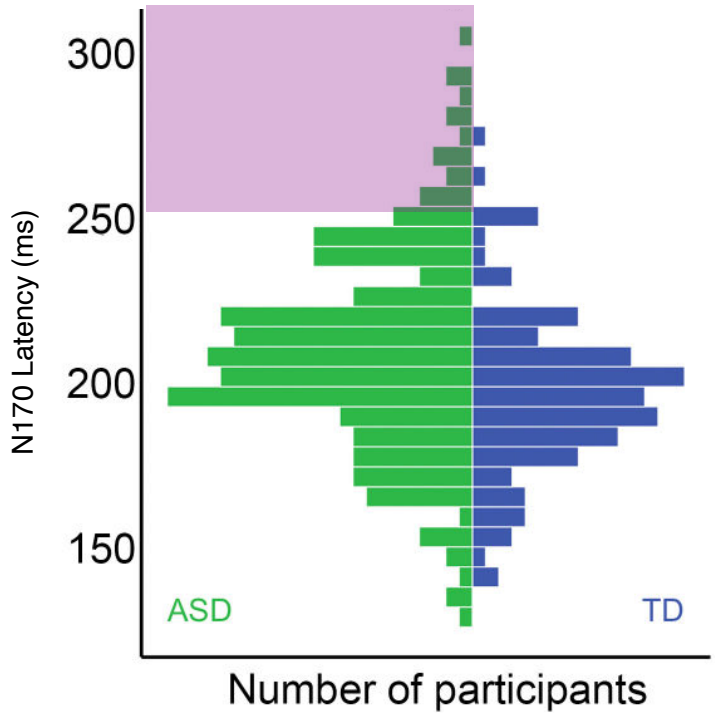



*Webb et al., 2022*

# ABC-CT: Biomarker Qualification

- LOIs accepted into the FDA Biomarker Qualification Program
  - N170 Latency to Upright Human Faces (5/6/19)
  - Oculomotor Index of Gaze to Human Faces (3/17/20)
- Proposed COU: Diagnostic biomarker
  - Biologically homogeneous subgroup
  - Enrich clinical trials by reducing heterogeneity
- FDA U01 awards to develop BQ Plans
- Ongoing discussion with FDA
  - Quantifying reliability
  - Thresholding continuous distribution
  - Validating subgroups
  - Need for clinical trial
  - Methodological generalizability

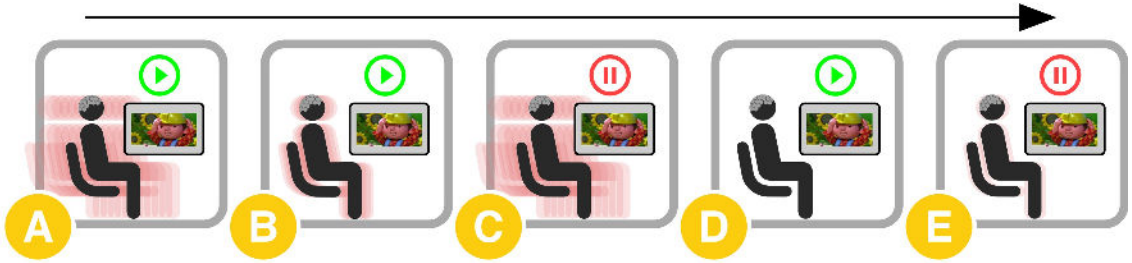


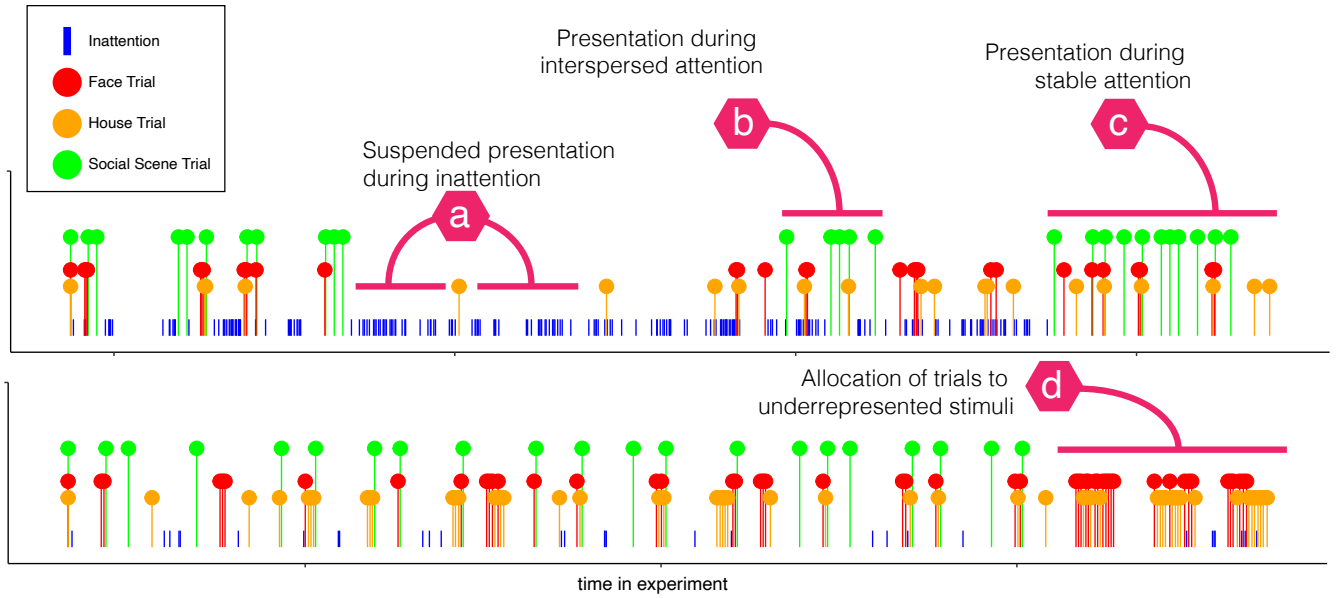
# ABC-CT: Phase 2

- Renewed in July 2020
- Follow-up study
  - Re-evaluate original cohort 2.5-4 years post-enrollment
    - Long term stability
    - Sensitivity to change
    - Longitudinal predictive value
  - Data collection (May 2021 – August 2022)
    - 261 (65%) of original 399 participated in study
- Confirmation study (April 2022 – March 2025)
  - 200 ASD, 200 TD 6 to 11-year-old children
    - 499 currently enrolled
  - Baseline, 6-week, 24-week assessments
  - Same ET and EEG batteries, eliminating biological motion
- Feasibility study (August 2024 through June 2025)
  - 25 ASD, 25 TD 3 to 5-year-old children
  - Viability of modified battery at single time point

# Increasing Inclusivity

- Individuals with ASD+ID excluded from neuroscience research
- Innovative biomarker acquisition approach
  - Hardware setup
  - Experimental administration



# Translating Biomarkers to Care

- Treatments for ASD
  - Target social function
  - Reflected in altered STS activity
- Apply TMS to directly stimulate STS
  - Improved social behavior
  - Reduced restricted, repetitive behaviors

*Voos et al., 2012; Ni et al., 2017, 2021*

*Thank you to the individuals and families that partner with us in research!*

## Yale Developmental Disabilities Clinic

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# ABC-CT
Autism Biomarkers Consortium *for* Clinical Trials

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www.asdbiomarkers.org

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Foundation for the National Institutes of Health

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Autism Innovative Medicine Studies-2-Trials

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