Developing Biological Markers to Improve Clinical Care in Autism

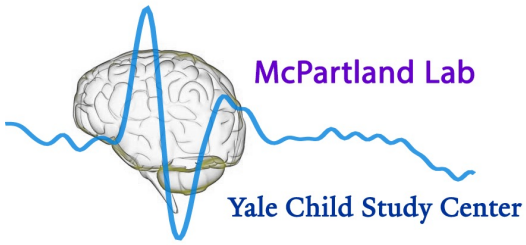
James McPartland, Ph.D.

McPartland Lab

Yale Developmental Disabilities Clinic

Yale Center for Brain and Mind Health

Autism Biomarkers Consortium for Clinical Trials



Overview

- What is autism, and why do we need biological markers?
- Biomarkers
  - What is a biomarker?
  - In what ways could biomarkers improve care?
  - What makes a good biomarker? What makes a good autism biomarker?
  - What does progress look like?
  - What's the goal?
- Innovations
  - Using biomarkers to develop new treatments
  - Including the full spectrum in biomarker science

Autism

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

Multiple causes and mechanisms

Centrality of social-communication

Reliance on behavior

Need to harness biology

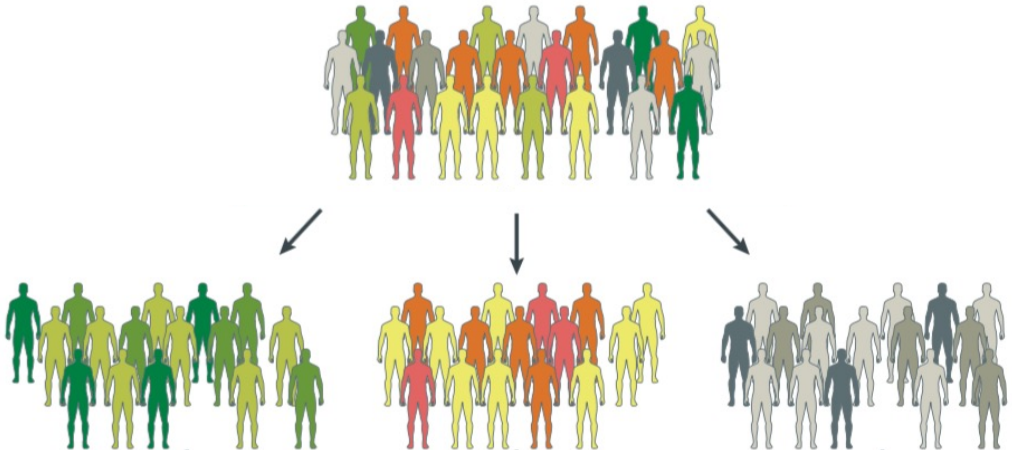
FDA Biomarker Definition

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

Uses for Biomarkers in Autism

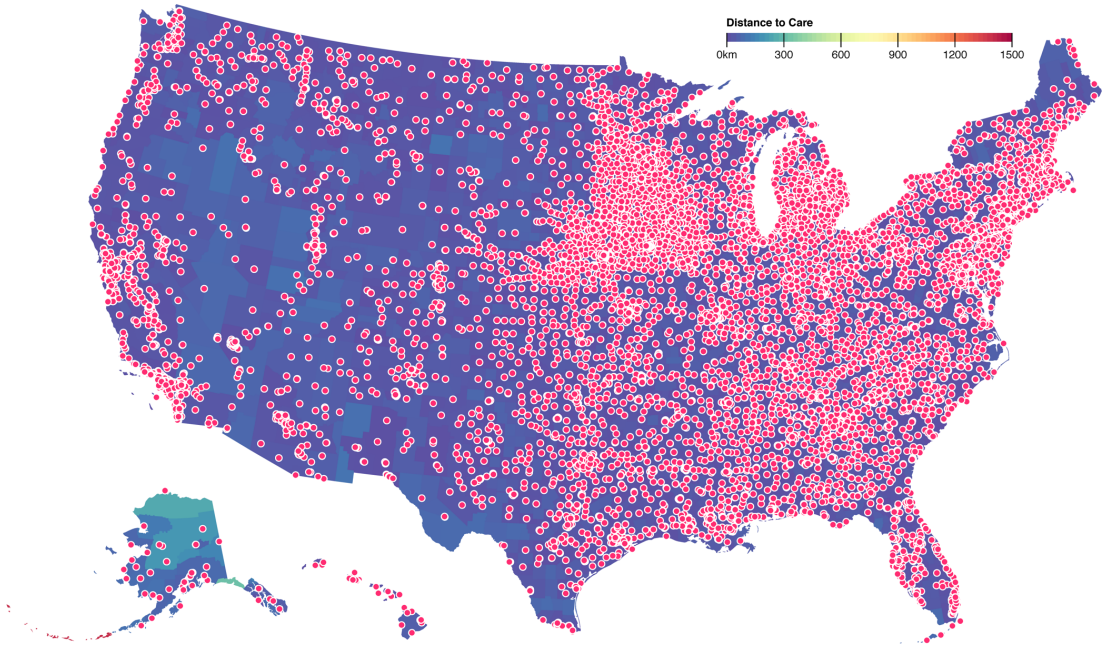
- Presence of autism (diagnostic)
- Likelihood of developing (screening)
- Developmental course (prognosis)
- Treatment selection (prediction)
- Measuring outcome (treatment response)
- Subgroups (stratification)



Loth et al., 2015

General Considerations for Biomarkers

- Replicable
- Reliable
- Tolerable for autistic people and children
- Cost effective
- Accessible



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

Autism-specific Considerations for Biomarkers

- Different in autistic and non-autistic people
- Associated with social-communication
  - Specifically associated
- Relevant in children and adults
- Sensitive to clinical improvement

Not all attributes needed to be useful

Different attributes important for different purposes

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

Autism-specific Considerations for Biomarkers

- **Different in autistic and non-autistic people**
- Associated with social-communication
  - Specifically associated
- Relevant in children and adults
- **Sensitive to improvements**

Not all attributes needed to be useful

Different attributes important for different purposes

Diagnosis

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

Autism-specific Considerations for Biomarkers

- **Different in autistic and non-autistic people**
- Associated with social-communication
  - Specifically associated
- Relevant in children and adults
- **Sensitive to clinical improvement**

Not all attributes needed to be useful

Different attributes important for different purposes

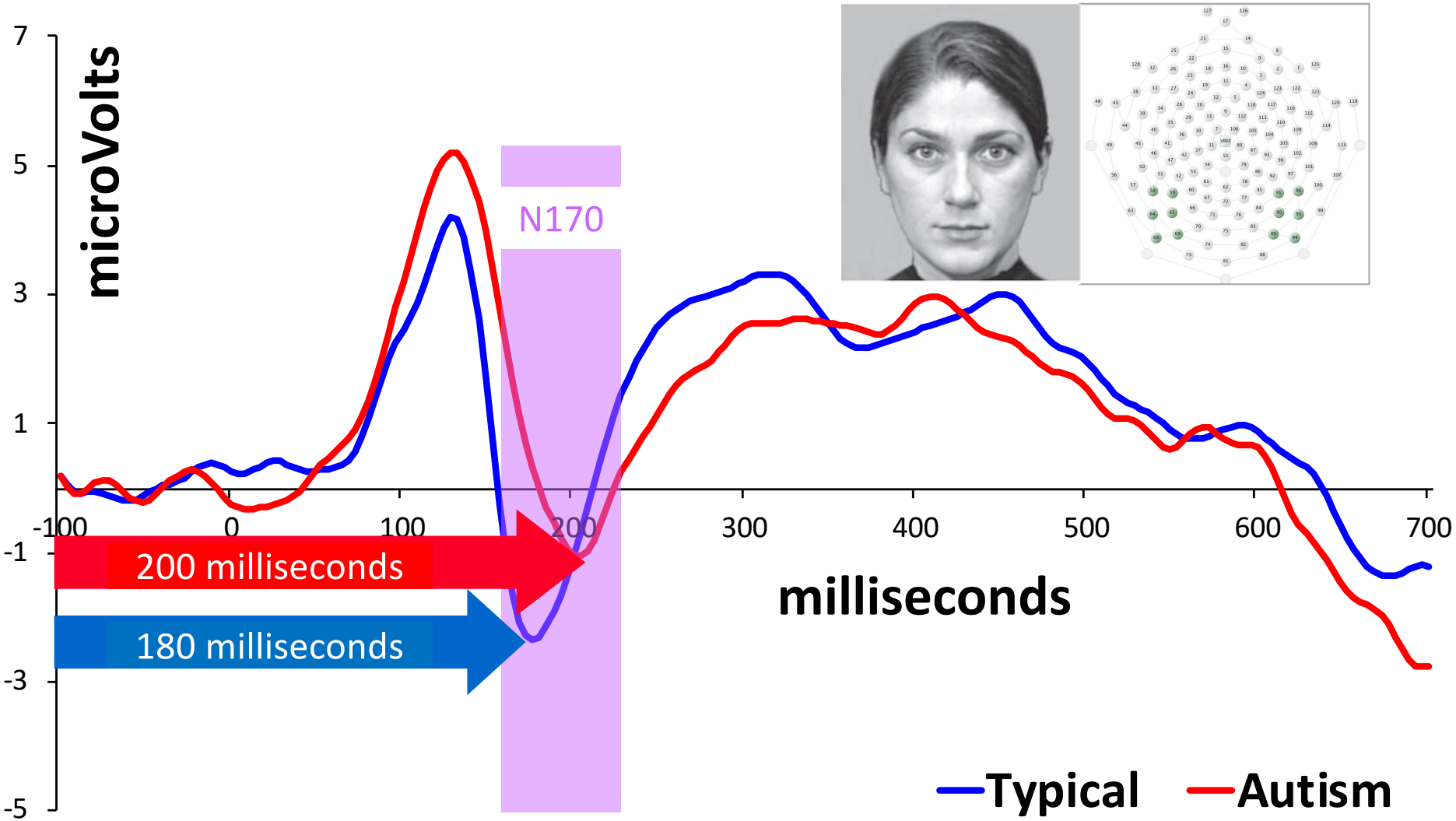
Treatment Response

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

Electroencephalography (EEG)

- Electrical brain activity recorded directly from scalp
- Viable across ages and levels of function
  - Non-invasive
  - Movement tolerant
- Practical
  - Cost effective
  - Accessible
- Informative about social-communication

N170 is Slower in Autism



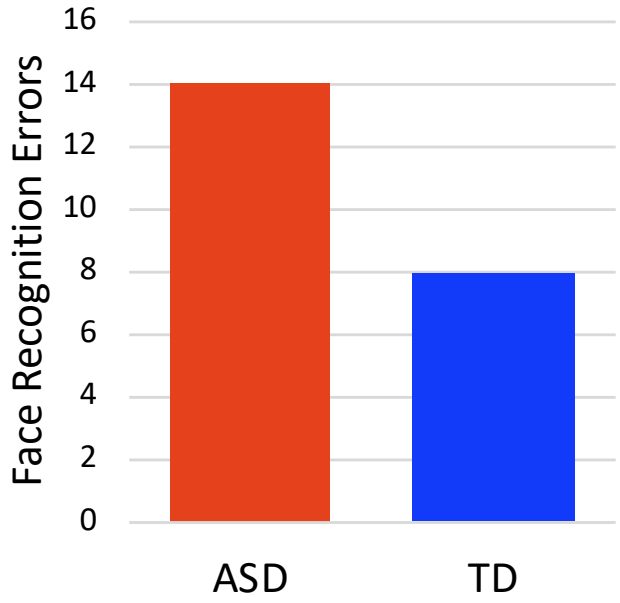
N170 is different in autistic and non-autistic adolescents and adults

McPartland, Dawson, Webb, Panagiotides & Carver, 2004

N170 is Associated with Social Function

- Standardized tests of face recognition
  - Increased errors among adolescents and adults with autism
  - Errors correlated with N170

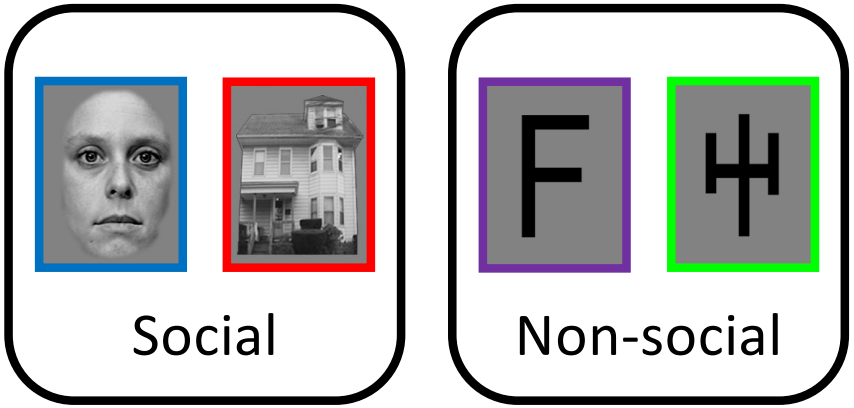
N170 is related to social-communication



McPartland, Dawson, Webb, Panagiotides & Carver, 2004

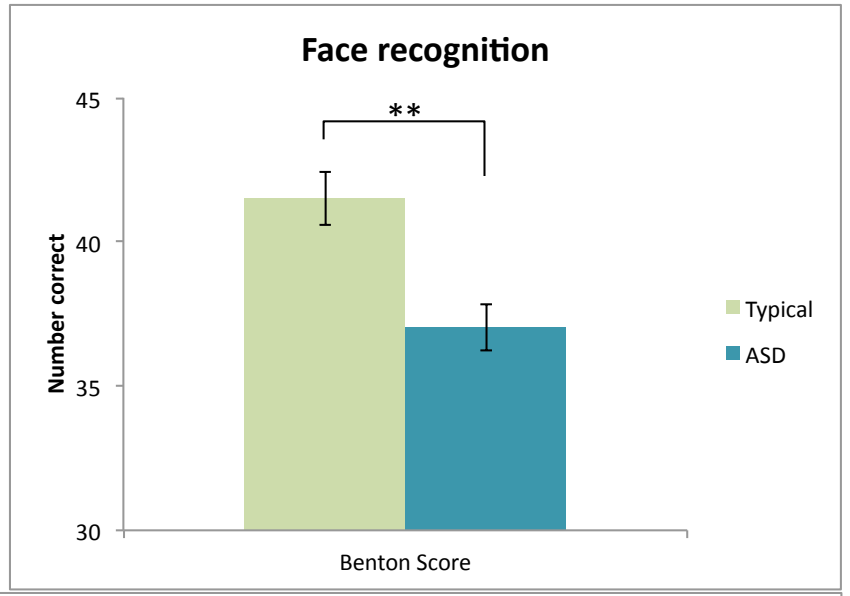
N170 Specificity

- Are N170 differences particular to social information?
  - Are differences observed in children?

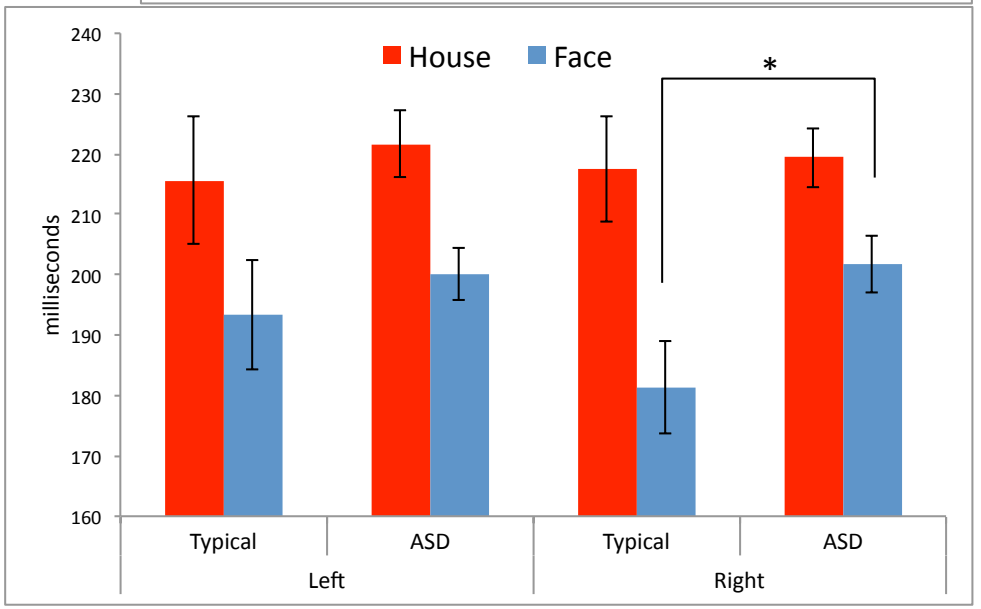


N170 Differences Observed in Younger Children

- Lower face recognition scores in autism
- Slower face processing (N170) in autism

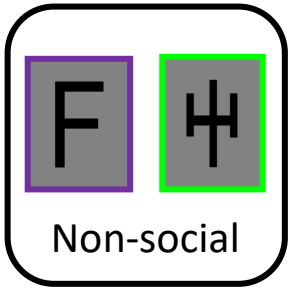


N170 differences consistent across children, adolescents, and adults



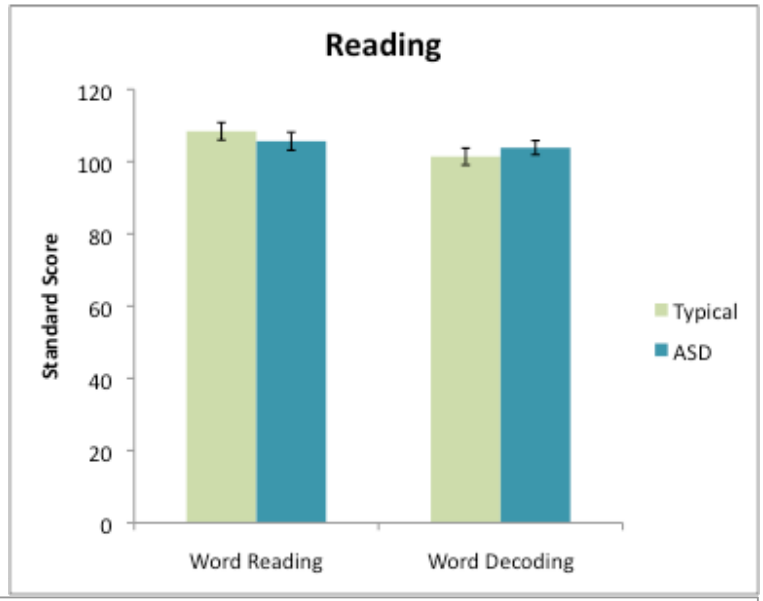
McPartland, Wu, Bailey, Mayes, Schultz & Klin, 2011

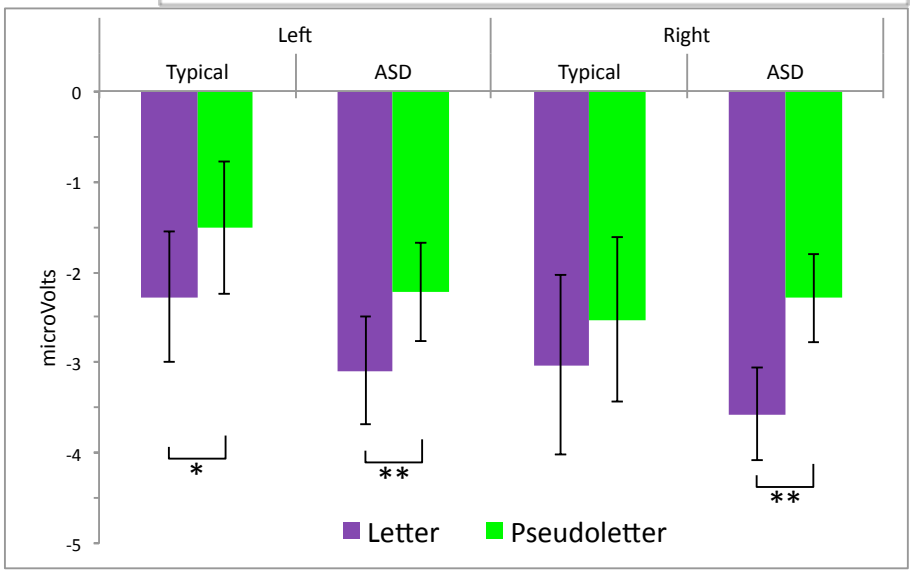
N170 Differences are Specific to Social Information



- Average reading scores
- Brain response to letters comparable to non-autistic children
  - Enhanced amplitude
  - Comparable speed

N170 differences specific to social-communication

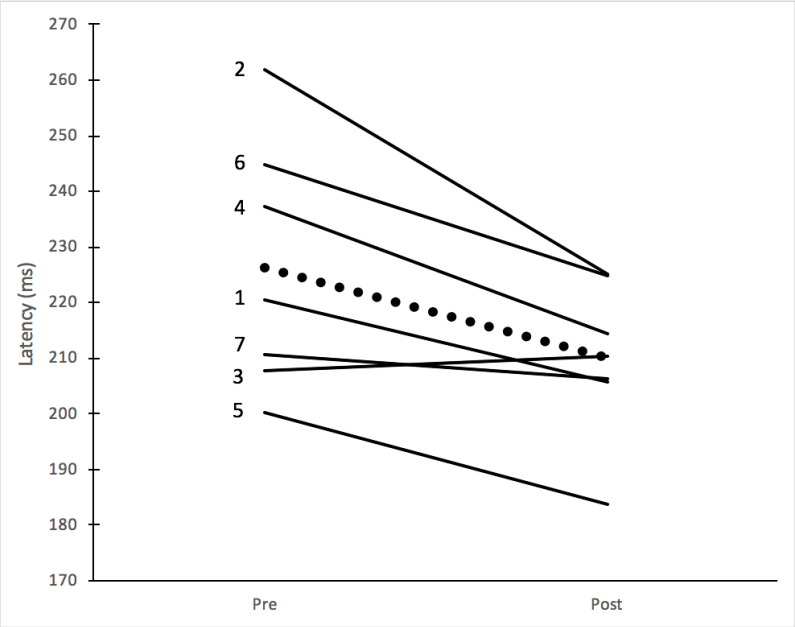




McPartland, Wu, Bailey, Mayes, Schultz & Klin, 2011

N170 is Sensitive to Clinical Improvement

- Pivotal Response Treatment
  - Naturalistic behavioral intervention
  - Preschool-aged children received 14-week course of treatment
  - Measured N170 before and after treatment
- Increased N170 speed after treatment



Changes in N170 speed parallel changes in social-communication

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

Autism-specific Considerations for Biomarkers: Evidence for the N170

- Different in autistic and non-autistic people
- Associated with social-communication
  - Specifically associated
- Relevant in children and adults
- Sensitive to clinical improvement

The Next Step: Qualifying Biomarkers

- Evaluate most promising biomarkers
- Large groups of children
- Confirm consistency across laboratories
- Multiple time points to understand stability
- Stringent scientific standards
- Cost-effective, accessible methods

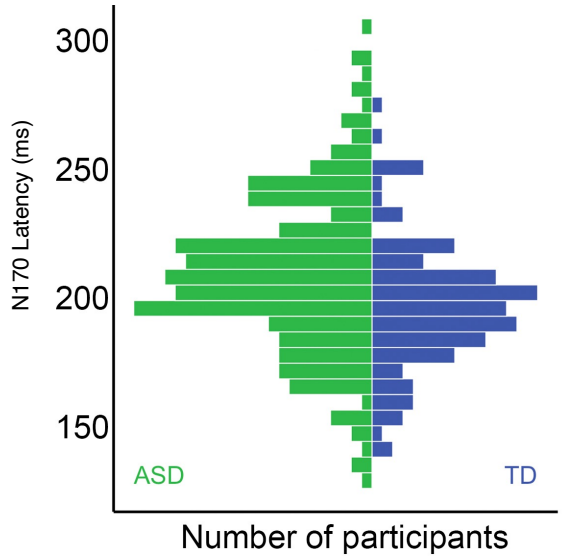
ABC-CT Study Design

- Phase 1 (2015-2020)
  - 280 school-aged children with ASD and 119 with TD
  - Baseline, 6 weeks, 24 weeks
- Phase 2 (2020-2025)
  - Long term follow-up with Phase 1 cohort (~3-4 years)
  - Replication sample of 200 ASD and 200 TD children
  - Evaluate feasibility in preschool-aged children
- Measures
  - Comprehensive clinician and caregiver reports
  - Four EEG and five eye-tracking biomarkers
    - Including N170 latency

McPartland et al., 2020

ABC-CT Progress: N170

- Replication of N170 delay in autistic children
  - Across all four time points (6 weeks to approximately 4 years)

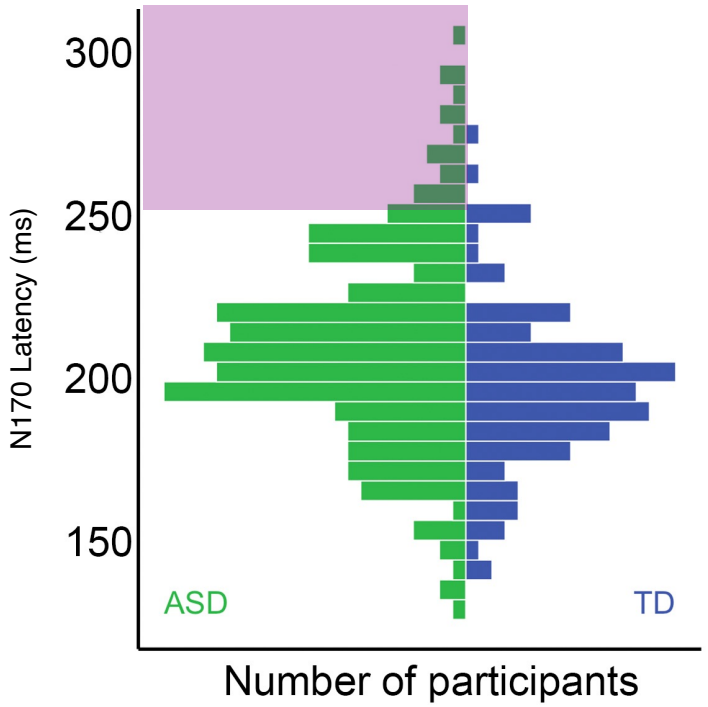


- Replication of relationship with social function (face memory, *r* = -.21)
- Stable in children over:
  - 6 weeks (ICCs = .66-.75)
  - 24 weeks (ICCs = .56-.75)

Webb et al., 2022

ABC-CT: Biomarker Qualification

- Letter of Intent submitted to the FDA Biomarker Qualification Program
  - Accepted in May 2019
  - First biomarker for a psychiatric condition
- Proposed purpose: Subgrouping (stratification)
  - Biologically defined subgroup
  - Improve clinical trials by reducing variability
- Ongoing development of qualification plan with FDA
- Challenges
  - How to define the subgroup?
  - How to validate subgroup?
  - How to measure what it means for treatment?
  - How easily can this approach be applied in other settings?

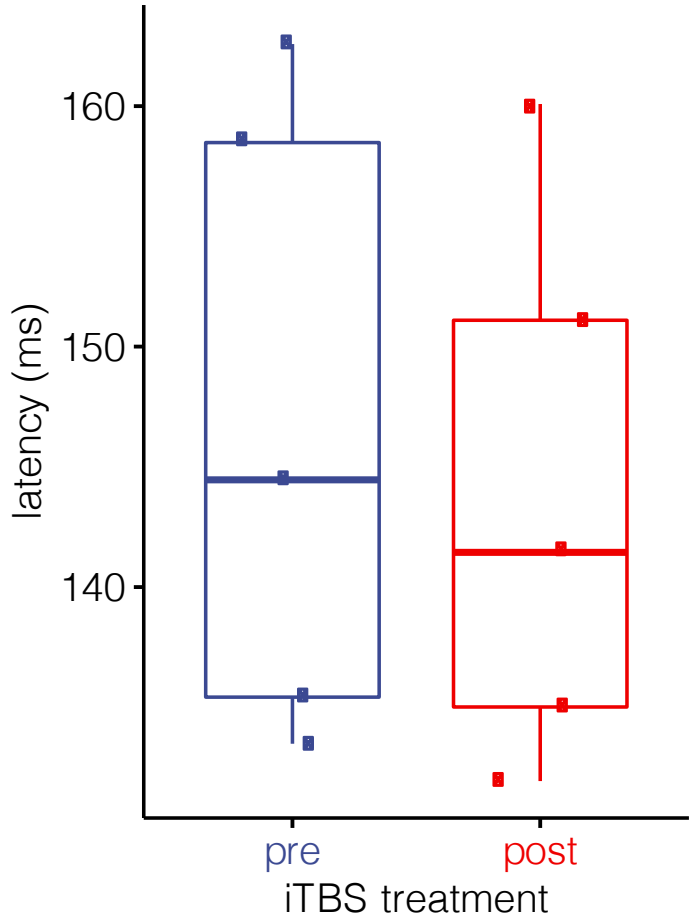


Translating Biomarkers to Care

- N170 linked to function of specific brain region (STS)
  - Involved in social perception and thinking
  - Observed to change during behavioral treatments
- Could we use the N170 as a guide to boost function in this area?
  - Would it enhance social-communication?

Translating Biomarkers to Care

- Proof of concept in neurotypical adults
  - Faster N170 latency after stimulation

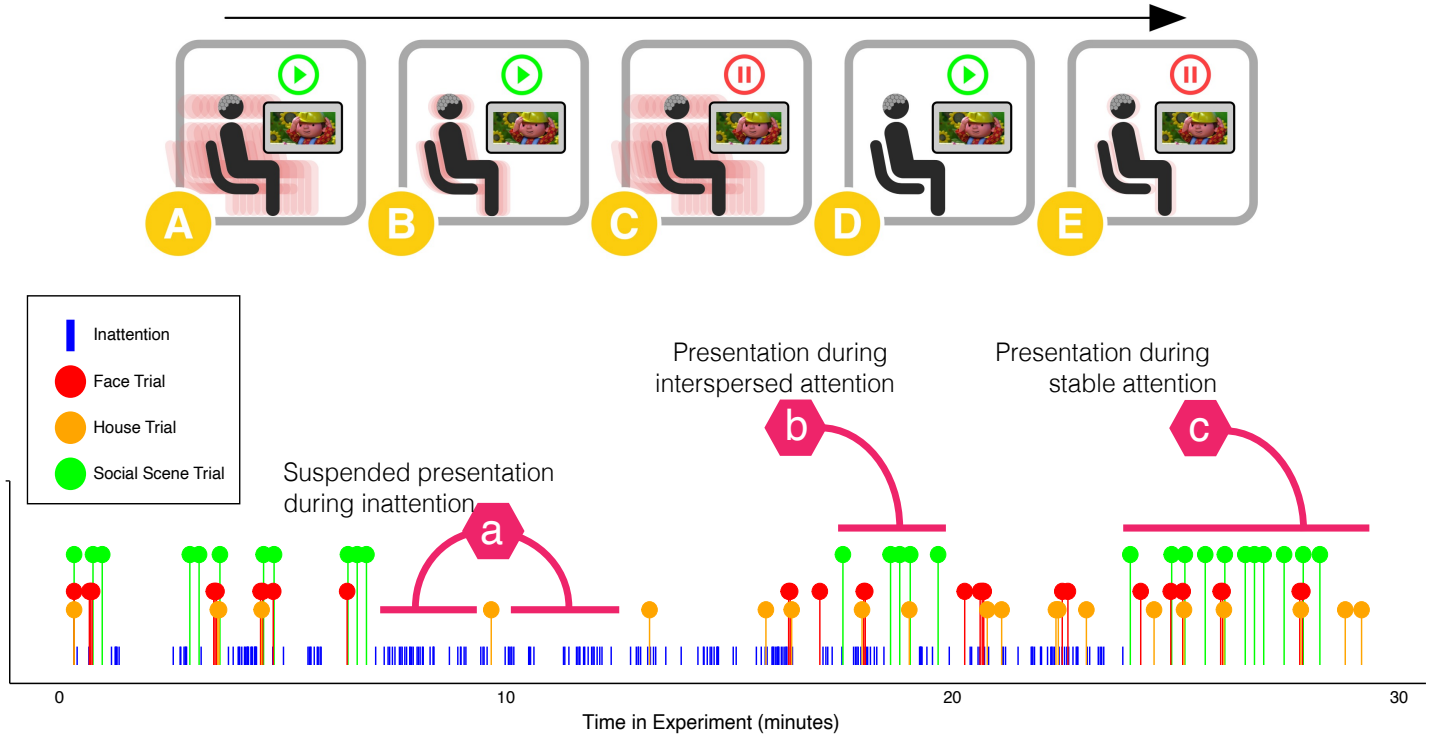


Increasing Inclusivity of Biomarker Research

- Individuals with ASD and intellectual disability excluded from most neuroscience research
  - 38% of those with autism
  - 1% of neuroscience studies
- Failure to meet the needs of those in most significant need of support

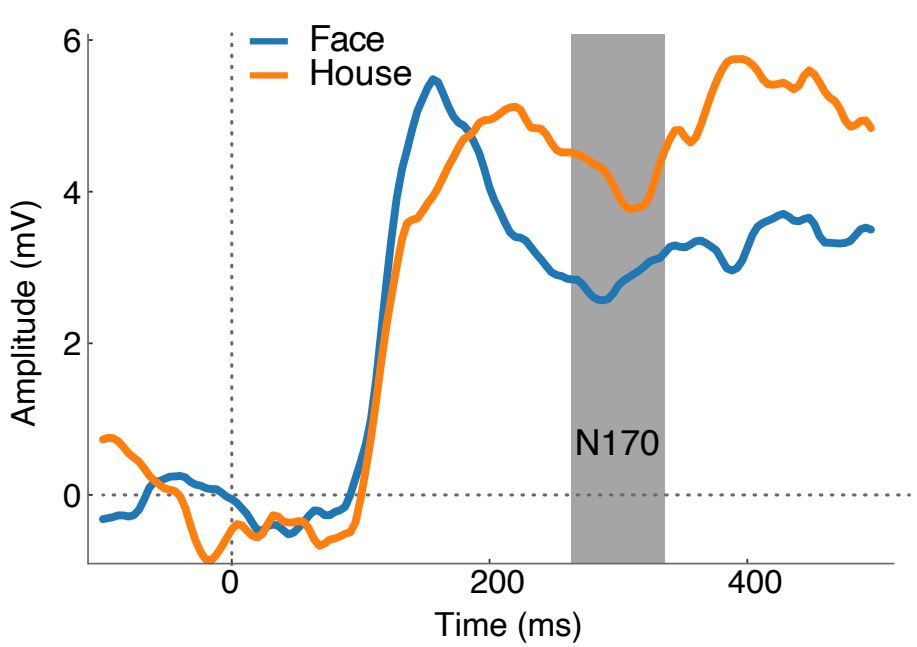
Increasing Inclusivity of Biomarker Research

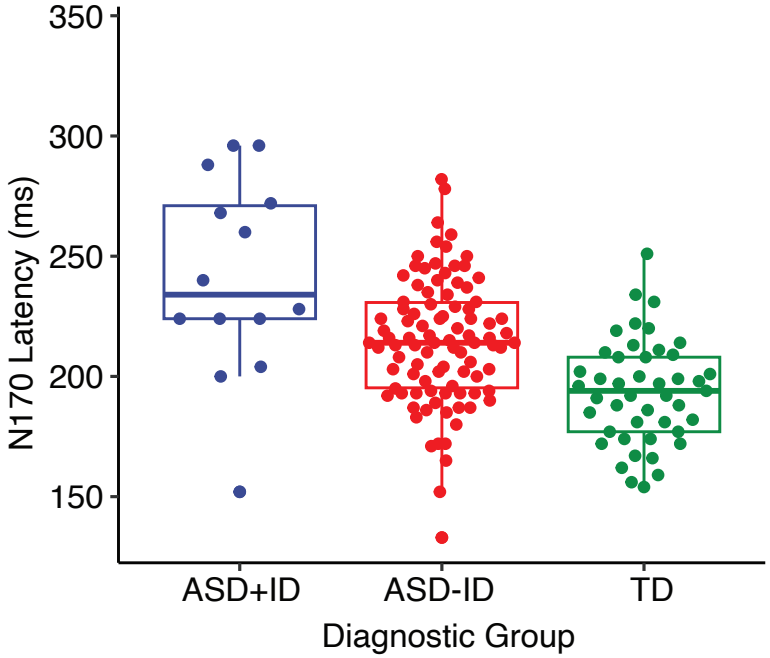
- Innovative strategy
  - Laboratory setup
  - Behavioral protocol
  - Experimental approach



Increasing Inclusivity of Biomarker Research

- High success rate in ASD+ID (IQ ~31)
- Valid response patterns
- Replication of N170 findings





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

Yale Developmental Disabilities Clinic

Michele Goyette-Ewing
Pamela Ventola
Julie Wolf
Kelly Powell
Leah Booth
Shannon Brooke
Christine Cukar-Capizzi
Leah Wang
Kathy Koenig
Lynn LaValley
David Grodberg
Cara Keifer
Kartik Pattabiraman
Teal Raffaele
Paola Ayora

ABC-CT
Autism Biomarkers Consortium *for* Clinical Trials

PI: James McPartland

www.asdbiomarkers.org

National Institutes of Health

FNIH
Foundation for the National Institutes of Health

THE biomarkers CONSORTIUM

SFARI
SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

Admin Core

Julie Holub

Taylor Hoffman

DCC

Jim Dziura

Cynthia Brandt

Lisa Nanamaker

Nancy Shelton

Laura Simone

Sites

Susan Faja

Marika Coffman

Kasia Chawarska

Geraldine Dawson

Charlotte DiStefano

Shafali Jeste

Natalia Kleinhans

Julie Wolf

DAAC

Sara Webb

Fred Shic

Catherine Sugar

Gerhard Hellemann

April Levin

Adam Naples

Maura Sabatos-Devito

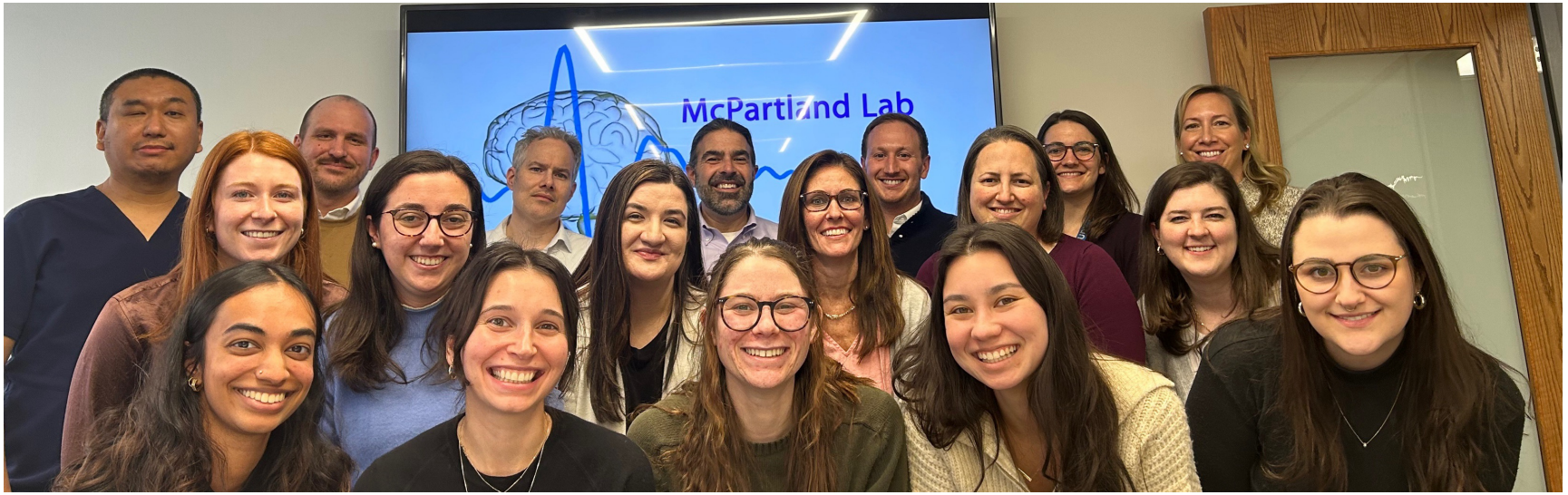
Damla Senturk

Collaborators

Janssen Research & Development

Roche

Autism Innovative Medicine Studies-2-Trials



www.mcp-lab.org; mcp.lab@yale.edu

Adam Naples
Julie Wolf
Nicole Wright
Jason Griffin
Sara Silber
AZA Allsop
Teal Raffaele
Leah Wang

Bela Ponjevic
Christine Cukar-Capizzi
Bridget Walicki
Shreya Kannan
Lindsey Rosenthal
Sherab Tsheringla
Sophie Benjamin-Cramer
Daniela Miro-Rivera

Max Rolison
Shara Reimer
Monique Staggers
Cara Keifer
Shash Kala
Alan Gerber
Nicole Herman
Lauren Robinson

You can help!!!

Research Participation

- Aged 3 – Adult
- With or without ASD or ID
- Clinical report
- Up to $300

Bela Ponjevic
autism@yale.edu
(203) 787-3439
www.mcp-lab.org