Developing Biomarkers to Improve Clinical Research in Autism

ABC·CT
Autism Biomarkers Consortium *for* Clinical Trials

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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, 2017

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Biomarker Types and Objectives

- Prognostic
- Pharmacodynamic/Response
- Diagnostic
  - Condition
  - Subgroup
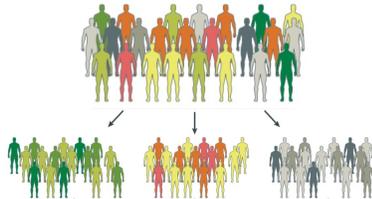
BEST Resource, 2017; Walsh, Elsabbagh, Bolton, Singh, 2011; Loth et al., 2015; McPartland, 2016

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ASD Biomarkers: Scientific Goals

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

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

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ASD Biomarkers: Practical Goals

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

Distance to Care
0hrs 300 600 900 1200 1500
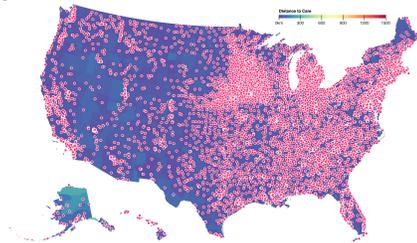
Walsh, Elsabbagh, Bolton, Singh, 2011; Loth et al., 2015; McPartland, 2016

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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 normative social-communicative development

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N170: Sensitive to Diagnostic Status

microVolts

N170

200 milliseconds
180 milliseconds

milliseconds

—Typical —Autism
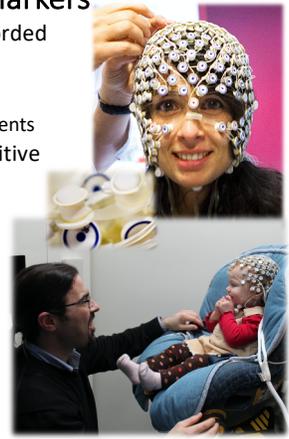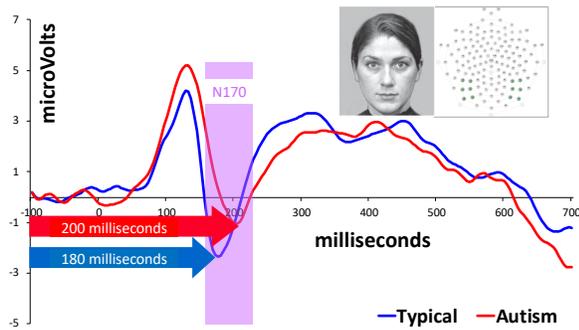
N170 latency slower in ASD relative to TD

McPartland, Dawson, Webb, Panagiotides & Carver, 2004

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N170: Associated with Symptoms

- 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 symptomatology

Face Recognition Errors
16 14 12 10 8 6 4 2 0
ASD TD
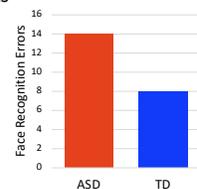
McPartland, Dawson, Webb, Panagiotides & Carver, 2004

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N170: Functional Specificity

- Atypical specialization for social information
- Non-specific perceptual delays; inability to specialize

Social   Non-social
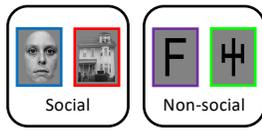
- Opportunity to replicate in a younger cohort

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N170: Applicable Across Development

Social

- Lower face recognition scores in ASD
- Slowed face processing (N170) in ASD in right hemisphere
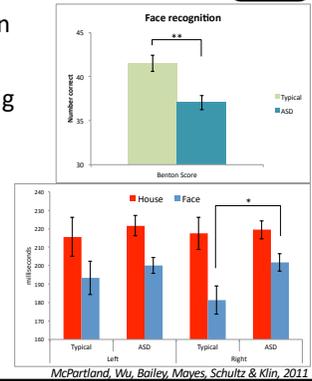
N170 latency delay consistent in children, adolescents, and adults

Face recognition

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

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N170: Functionally Specific

Non-social

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

N170 anomalies specific to social domain

Reading

McPartland, Wu, Bailey, Mayes, Schultz & Klin, 2011
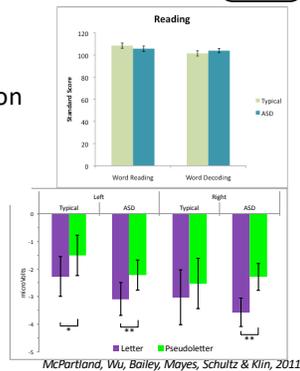
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N170: Robust to Variation in Behavior

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

Eyes   Nose   Mouth
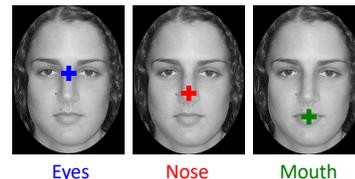
Parker et al., 2021

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N170: Robust to Variation in Behavior

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

N170 Latency (Right Hemisphere)
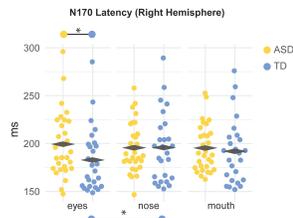
N170 delays not artefact of gaze behavior

Parker et al., 2021

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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
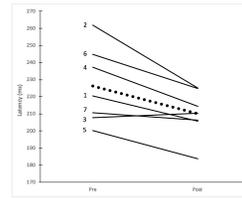
N170 latency changes with clinical status

*Kala et al., in revision; Dawson et al., 2012; Ventola et al., 2013*

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N170: Viable ASD biomarker?

- ✓ Sensitive to diagnostic status
- ✓ Associated with symptoms
- ✓ 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

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Remaining Challenges

- Promising evidence for many biomarkers
- Limited reproducibility
  - Individual differences in face processing
  - Underpowered studies
  - Methodological inconsistencies
- Reliability/practice effects not known
- Absence of normative reference
- Need for more rigorous biomarker research
- FDA Qualification

McPartland et al., 2004, 2011; Grice et al., 2005; O'Connor et al., 2005, 2007; Dawson et al., 2005; Senju et al., 2005; Valdizan, 2005; Kemner et al., 2006; Webb et al., 2006, 2009, 2012; Boeschoten et al., 2007; Gunji et al. , 2009; Magnee et al., 2008; Wong et al., 2008; McCleery et al., 2009; Akechi et al., 2010; Churches et al., 2010, 2012; Hileman et al., 2011; Batty et al., 2011; Apicella et al., 2013; Khorammi et al., 2013; Wagner et al., 2013; Tye et al., 2013, 2014; Cygan et al., 2014; Key et al., 2014; Faja et al., 2016; Graman et al., 2016; Neuhaus et al., 2016; Shen et al., 2016; Tavares et al., 2016; Groom et al., 2017; Luckhardt et al., 2017; Monteiro et al., 2017; Kang et al., 2018; Lin et al., 2018; Sysoeva et a., 2018; Naumann et al., 2018; Luyster et al., 2019; Malaia et al., 2019; Magnuson et al., 2019; De Pascalis et al., 2020; Key et al., 2020; Magnuson et al., 2020

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Next Generation Biomarker Studies

- Test well-evidenced biomarkers
- Well-characterized cohorts
- Large samples (including TD)
- Longitudinal design
- Methodological rigor
- Practical assays

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ABC-CT: Study Design

- Multi-site, naturalistic study
  - Administrative Core: Yale Center for Clinical Investigation
  - Sites: Duke, UCLA, UW, Boston Children's Hospital, Yale
  - Data Coordinating Core: YCCI/YC Analytical Sciences
  - Data Acquisition and Analysis Core: SCRI, SiStat, Duke, Yale, BCH, UAB
- First phase: 280 children with ASD and 119 with TD
  - Ages 6-11
  - IQ 60-150
- Practical assays (EEG, Eye-tracking)
- Longitudinal design (Baseline, 6 weeks, 24 weeks)
- Blood draw

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ABC-CT: Study Design

- Combined effort of government, academia, and industry
- Unprecedented rigor
  - Regulatory (Good Clinical Practice)
  - Methodological
  - Statistical
- Harmonized with European network (EU-AIMS)

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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

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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*

* EU-AIMS harmonized paradigm

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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
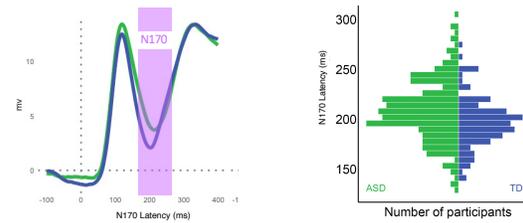
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ABC-CT: Biomarker qualification

- 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
- Discussion with FDA
  - Determining cut points
  - Functional differentiation of subgroup
  - Methodological generalizability
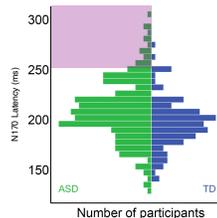
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ABC-CT: Phase 2

- Renewed in July 2020
- Confirmation study
  - 200 ASD, 200 TD 6 to 11-year-old children
  - Baseline, 6-week, 24-week assessments
  - Same ET and EEG batteries, eliminating biological motion
- Follow-up study
  - Re-evaluate original cohort 2.5-4 years post-enrollment
    - Long term stability
    - Sensitivity to change
    - Longitudinal predictive value
- Feasibility study
  - 25 ASD, 25 TD 3 to 5-year-old children
  - Viability of modified battery at single time point

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Translating Biomarkers to Care

- Behavioral treatments
  - Target social function
  - Reflected in altered STS activity

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Translating Biomarkers to Care

- Behavioral treatments
  - 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

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Translating Biomarkers to Care

- Biomarkers for early efficacy
  - Faster N170 latency • Increased fixation to eyes
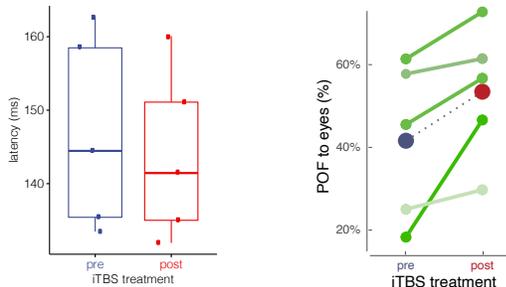
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Thank you to the individuals and families that partner with us in research!

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Shannon Brooke	Amy Vatner
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ABC·CT — Autism Biomarkers Consortium *for* Clinical Trials

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Please partner with us!

Research Participation
- Aged 3 – Adult
- With or without ASD, ID
- Clinical report
- Up to $550

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