Developing Biomarkers for Autism Spectrum Disorder

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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.

Biomarker Objectives

• Diagnosis/screening
• Treatment response
• Stratification
  • Treatment selection
  • Enrichment

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

ASD Biomarkers: Practical Goals

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

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
**N170: Sensitive to Diagnostic Status**

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

N170 biomarker correlates with symptomatology

**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: Functionally Specific**

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

**Pattern of biomarker results consistent in children and adults**

**N170: Functionally Specific**

- Normative reading scores
- Normative specialization for letters
  - Enhanced amplitude
  - Comparable latency
  - Functionally specific association with social communication

**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
N170: Robust to Variation in Behavior
• Shorter latency to eyes in TD only
• Longer latency in ASD overall

N170 anomalies evident irrespective of gaze behavior

McPartland et al., in prep

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
    • Emotional expressions

N170 latency changes with clinical status

Rolison et al., in prep; Dawson et al., 2012; Ventola et al., 2013

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

Remaining Challenges
• Promising evidence for many biomarkers
• Limited reproducibility
  • Heterogeneity and understanding of individual differences
  • Underpowered studies
  • Methodological inconsistencies
• Reliability/practice effects not known
• Absence of normative reference
• Critical need for more rigorous approaches to develop practicable biomarkers

McPartland et al., 2004, 2011; Gries et al., 2009; O’Connor et al., 2006, 2007; Dawson et al., 2009; Senju et al., 2009; Valdizan, 2005; Kemner et al., 2006; Hileman et al., 2006, 2009, 2011; Webber et al., 2007; Senju et al., 2009; Wagner et al., 2008, 2009; Nunez et al., 2005; Apicella et al., 2010; Churches et al., 2010, 2012; Boeschoten et al., 2007; Gunji et al., 2009; Magnee et al., 2008; Wong et al., 2008, 2009, 2010; Senju et al., 2009; Akechi et al., 2010; Apicella et al., 2013; Tye et al., 2013, 2014; Khorammi et al., 2013; Tavares et al., 2016; Faja et al., 2016; Graman et al., 2016; Neuhaus et al., 2016; Shen et al., 2016; Luckhardt et al., 2017; Monteiro et al., 2017; Luyster et al., 2017; Malaia et al., 2017; Kang et al., 2017; Sysoeva et al., 2018

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

Next Generation Biomarker Studies

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, Prometheus
  • Data Acquisition and Analysis Core: SCRI, SiStat, Duke, Yale, BCH, Penn
• 200 children with ASD and 75 with TD
  • Ages 6-11
  • IQ 60-150
• Practical assays (EEG, Eye-tracking)
• Longitudinal design (Baseline, 6 weeks, 24 weeks)
Combined effort of government, academia, and industry

Unprecedented rigor

• Regulatory (Good Clinical Practice)
• Methodological
• Statistical

Harmonized with European network (EU-AIMS)

ABC-CT: Study Design

• EEG
  • Resting EEG*
  • Visual evoked potentials
  • ERPs to faces*
  • Blood draw
  • Proband
  • Both biological parents

• Eye-tracking
  • Biological motion*
  • Activity monitoring
  • Interactive social task
  • Pupillary light reflex*
  • Static social scenes*

* EU-AIMS harmonized paradigm

ABC-CT: Biomarker Assays

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: Clinical Measures

ABC-CT: Progress

ABC-CT: Interim Analysis

• Acquisition and psychometrics
  • Successful acquisition (across demographic/clinical factors)
  • EEG: 96% valid data
  • Eye-tracking: 100% valid data
  • Consistent results across sites
  • Appropriate distributional properties
  • Construct validity
  • Viability as social-communication biomarker
  • Discrimination between ASD and TD
  • Test-retest reliability (T1-T2)

ABC-CT: Interim Analysis

N170 latency to upright faces

• Replication of discriminant validity
• Evidence of test-retest reliability
• First Autism Submission to FDA Biomarker Qualification Program
Next Generation Biomarkers: Social Simulations

- Increasing realism of social-communicative assays via interactive social simulations
- Eye-tracking for gaze-contingent EEG

Naples, Wu, Mayes & McPartland, 2017

Next Generation Biomarkers: Social Simulations

- Neural marker of shared gaze
  - Elicited by reciprocal eye contact
  - Predictive of social function

Naples, Wu, Mayes & McPartland, 2017

Next Generation Biomarkers

- Expand behaviors measured
  - Posture
  - Facial expression
  - Speech
- Applying to minimally verbal individuals with ASD
  - Control for attention
  - Motion tracking
    - Video
    - Chair
    - Behavioral shaping

Next Generation Biomarkers: Imaging Interaction

- Measuring brain activity during face-to-face interactions with Hirsch Brain Function Laboratory

Next Generation Biomarkers: Molecular Markers

- Collaboration with David Matuskey, Yale PET Center
- In vivo measurement of
  - Glutamate receptor density
  - Overall synaptic density
- Adapt technique for pediatric populations

Translating Biomarkers to Care

- Behavioral treatments target social brain systems
- Using transcranial magnetic stimulation to “turn on” these circuits directly
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