



Autism Biomarkers Consortium for Clinical Trials

Project Overview

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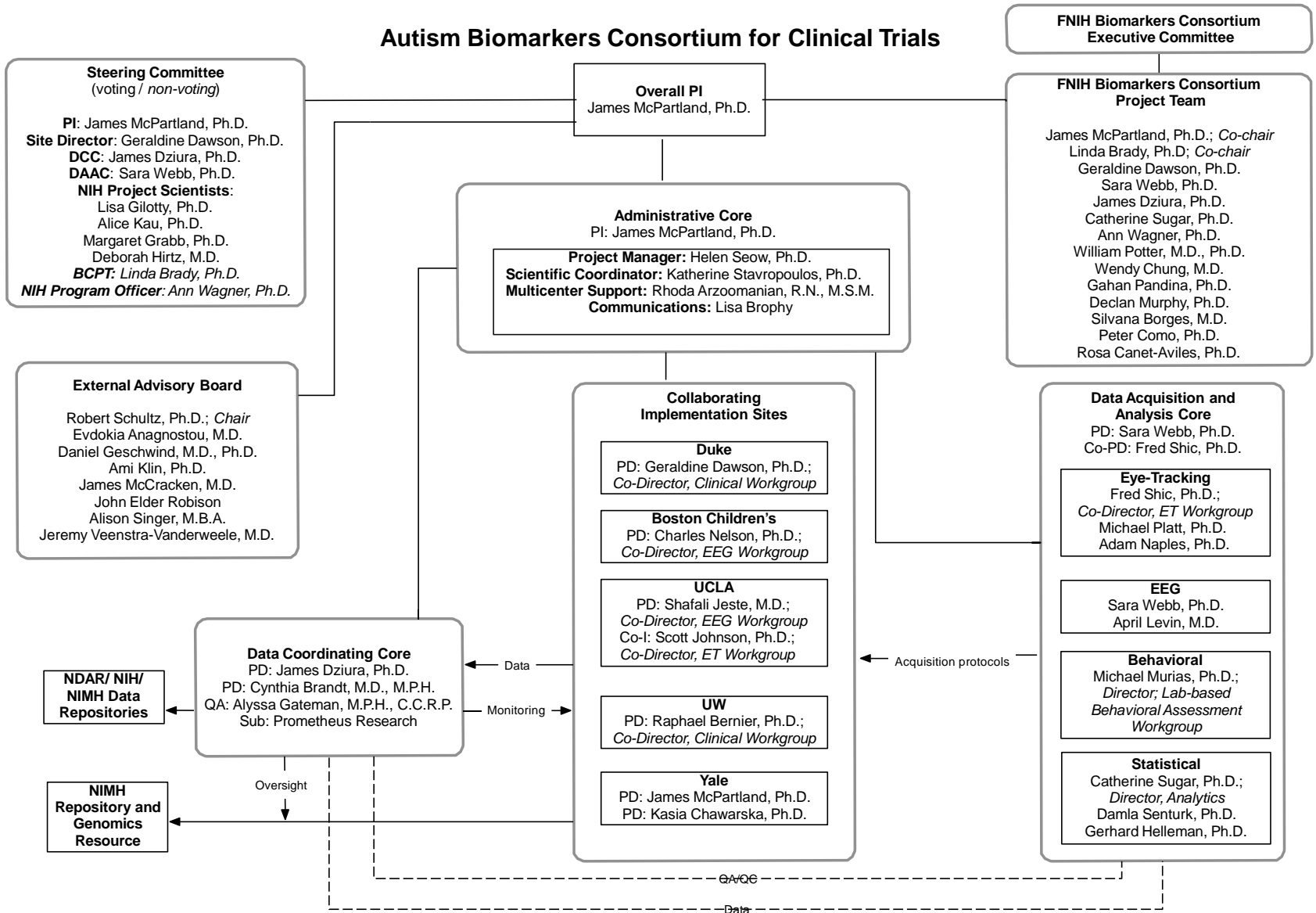
Scientific context for ABC-CT

- ASD is a complex neurodevelopmental disorder of unknown etiology, characterized by:
 - Difficulties with social-communication
 - Restricted, repetitive behaviors and interests and/or atypical sensory responsivity
- Heterogeneous clinical presentation
 - Symptom profile
 - Language
 - Cognitive ability
- Early stage evidence of social-communicative biomarkers
- The ABC-CT will provide methodologically rigorous multi-site evaluation of potential biomarkers in a large sample
 - Infrastructure designed to support future clinical trials

ABC-CT study design

- Multi-site, naturalistic study
 - *Administrative Core*: Yale
 - *Sites*: Duke, UCLA, UW, Boston Children's Hospital, Yale
 - *Data Coordinating Core*: YCCI, Prometheus
 - *Data Acquisition and Analysis Core*: SCRI, Duke, Yale, BCH, SiStat
- 4 to 11 year-old-children with ASD (N = 200) and typical development (TD; N = 75) with IQ 50-150
 - Feasibility study (25 ASD, 25 TD)
 - Three time points (Baseline, 6 weeks, 24 weeks)
- Potential biomarkers of social-communicative function
 - Eye tracking (~EU-AIMS)
 - EEG (~EU-AIMS)
 - Lab-based measures
- Commonly used clinician and caregiver assessments
- Blood draw for participant and parents

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Sample characteristics:

Inclusion/exclusion criteria

- ASD inclusion
 - ADOS, ADI, DSM-5
 - IQ 50-150
 - Medication stable 8 weeks
- ASD exclusion
 - Genetic/neurological
 - Epilepsy
 - Sensory/motor impairment
 - Metabolic/mitochondrial
 - Pre/perinatal
 - Environmental
 - Misc. invalidating factors
- TD inclusion
 - IQ 50-150
 - Medication stable 8 weeks
- TD exclusion
 - ASD/sibling with ASD
 - Genetic/neurological
 - Epilepsy
 - Sensory/motor impairment
 - Metabolic/mitochondria
 - Misc. invalidating factors
 - Clinical score on CASI

ASD Biomarkers Project – Objectives

1. Compare sensitivity of objective indicators of social communicative function to conventional clinician and caregiver assessments with respect to clinical status
 - Correlations with clinical status at each time point and across time points
2. Evaluate potential utility of these measures, individually or in combination, as biomarkers for use in clinical trials
 - Feasibility of implementation; Construct validity; Test-retest reliability, consistency, and stability; Discriminant validity; Convergent validity; Sensitivity to change; Adequate variability within and between groups
3. Collect DNA samples for future genomic analyses and other potential analyses from all subjects, including parents of ASD subjects, to create a **community resource** of raw, processed, and analyzed data across modalities

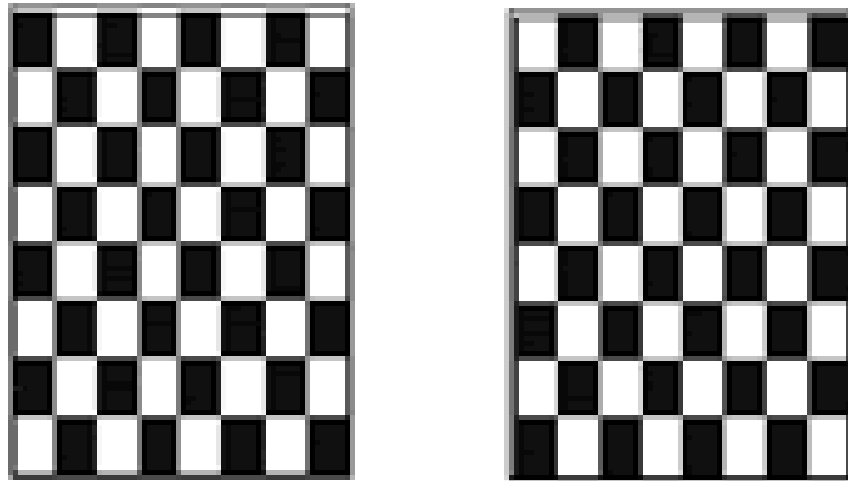
EEG Paradigms

EEG: Resting state

- Videos of non-social, abstract moving images
- Resting spectral power
 - Connectivity and coherence
 - Hemispheric asymmetry
 - Multiscale entropy
- Baseline for event-related EEG measures
- Discriminates ASD vs. TD in infants, children, adults
- Association with language ability

EEG: Visual evoked potentials

- Checkerboards reversing phase
- Low level visual processing
 - Functional integrity of visual pathway
 - Baseline for more complex (social) visual perceptual tasks

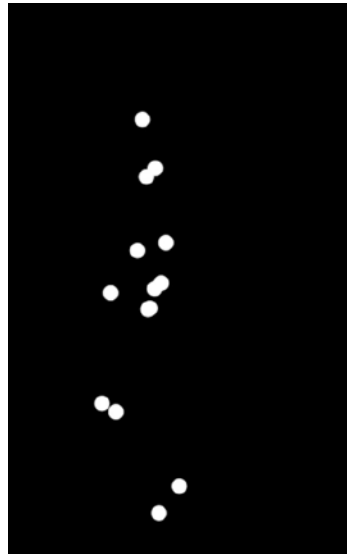


- Discriminates ASD vs. TD in infants

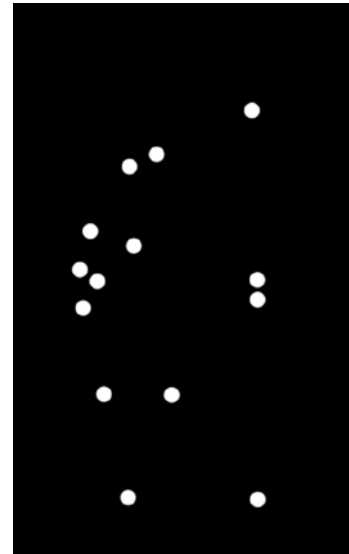
EEG: Biological motion

- Neural response to point light displays of human motion

Bio. motion



Scrambled



- Discriminates ASD vs. TD in school-aged children
 - Data collected across four study sites

EEG: Face processing

- EU-AIMS task
- Neural response to faces (vs. houses), inversion effect



- Discriminates ASD vs. TD in HR infants, children, and adults
- Association with social and communicative function
- Sensitive to change in response to treatment

EEG: Emotional faces

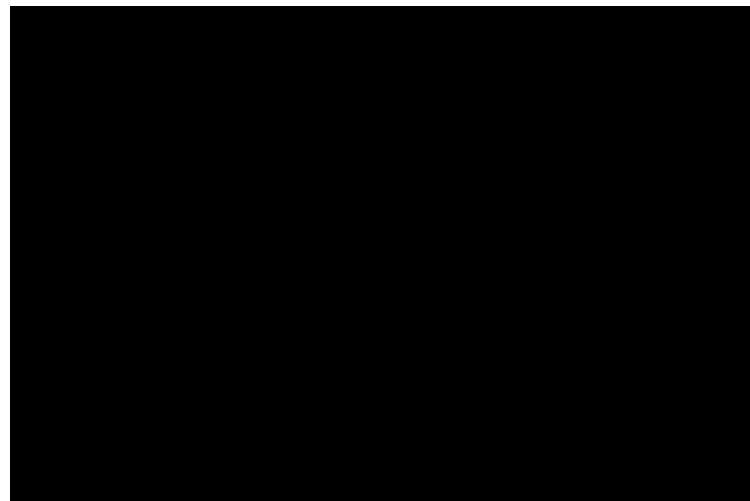
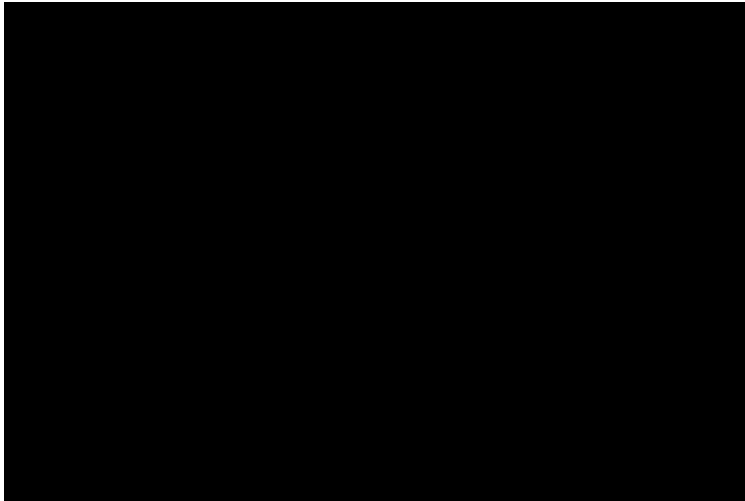
- Neural response to neutral versus fearful expressions



- Discriminates ASD vs. TD in children and adults
- Association with social function

EEG: Social scenes

- EU-AIMS task
- Neural response to social and non-social dynamic scenes

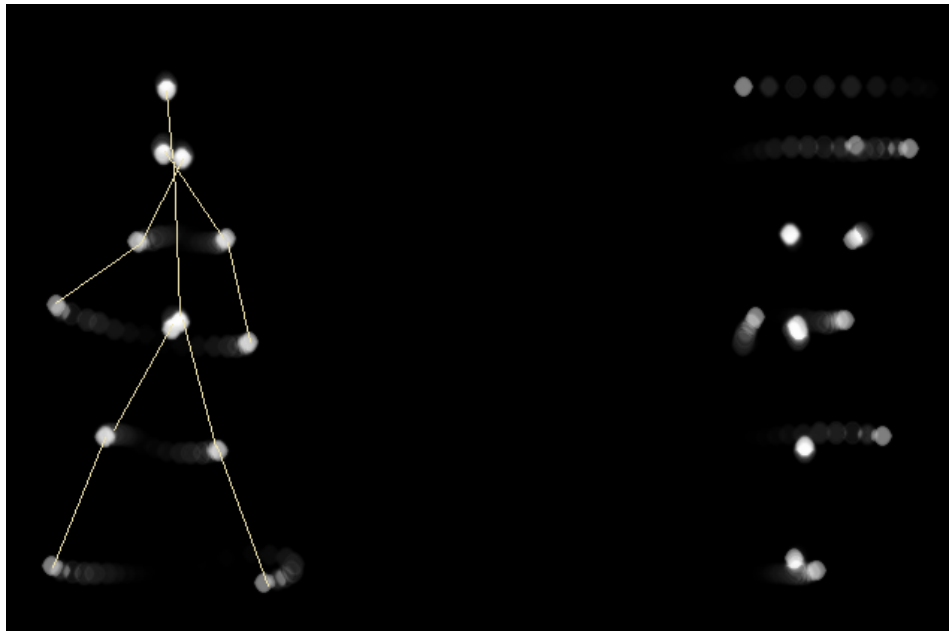


- Discriminates ASD vs. TD in infants

Eye-tracking Paradigms

ET: Biological motion

- Overlap with EU-AIMS task
- Preferential attention to human motion



- Discriminates ASD vs. TD in toddlers through adults
- Collected across two study sites

ET: Spontaneous social orienting

- Response to bids for dyadic engagement, joint attention



- Discriminates ASD vs. TD in infants through preschool
- Stratification by developmental trajectory
- Associates with social function

ET: Activity monitoring

- Attention to shared social activity versus background distracters



- Discriminates ASD vs. TD in toddlers through adults
- Associates with social function
- Collected across two study sites

ET: Interactive social task

- Attention to naturalistic social activities between child partners



- Discriminates ASD vs. TD in school-aged children

ET: Dynamic naturalistic scenes

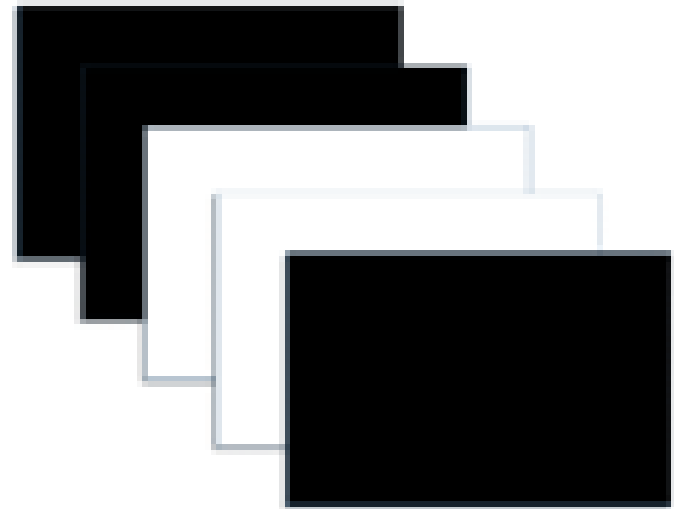
- Scanning patterns towards complex, dynamic social scenes



- Discriminates ASD vs. TD in school-aged children
- Scan patterns stratify children by social impairment
- Collected across two study sites

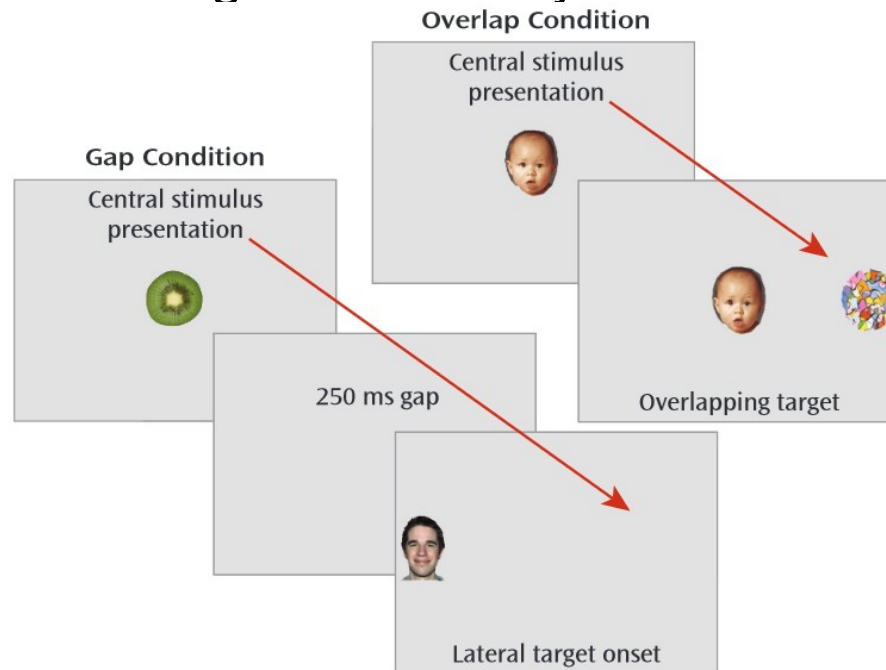
ET: Pupillary light reflex

- EU-AIMS task
- Central fixation on black background flashes white for 75ms
 - Interspersed video clips induce saccades
- Discriminates
 - ASD vs. TD in infants, Children, and adults



ET: Gap overlap task

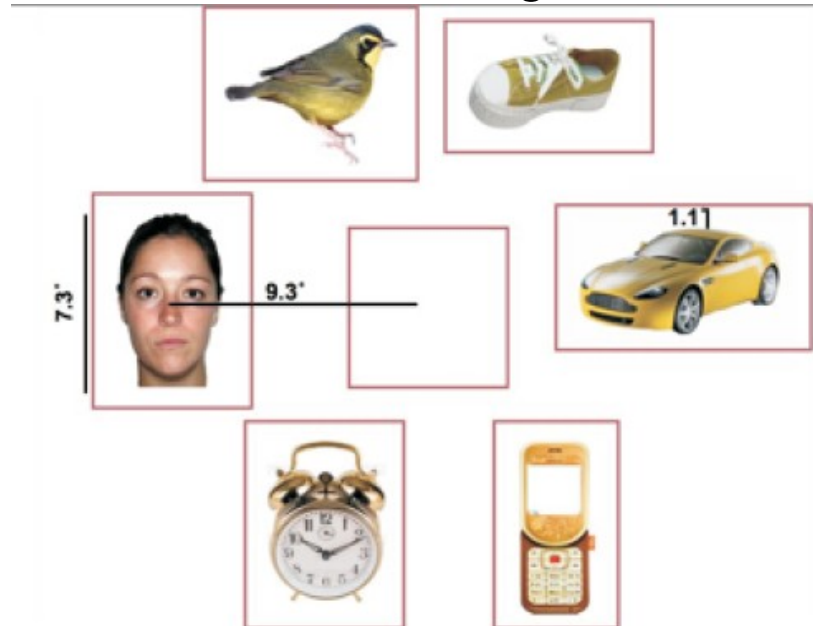
- EU-AIMS task
- Attention shifting and flexibility



- Discriminates ASD vs. TD in infants, children, adults

ET: Visual search/Static images

- EU-AIMS task
- Salience of social stimuli among distracters

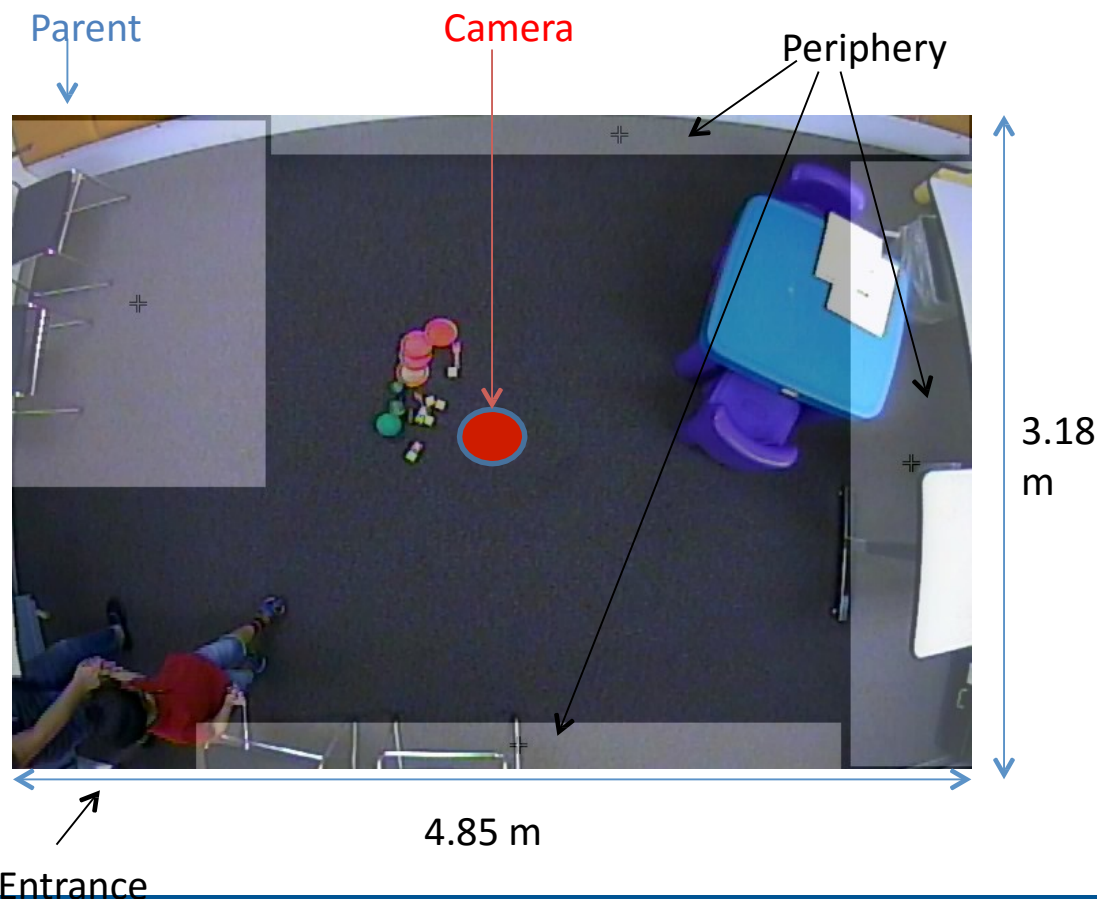


- Discriminates ASD vs. TD in children

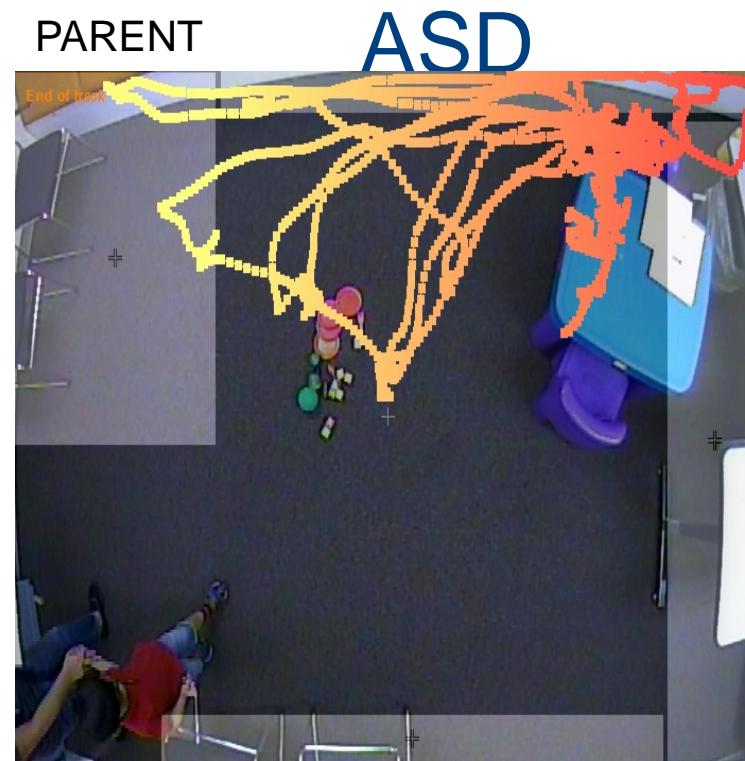
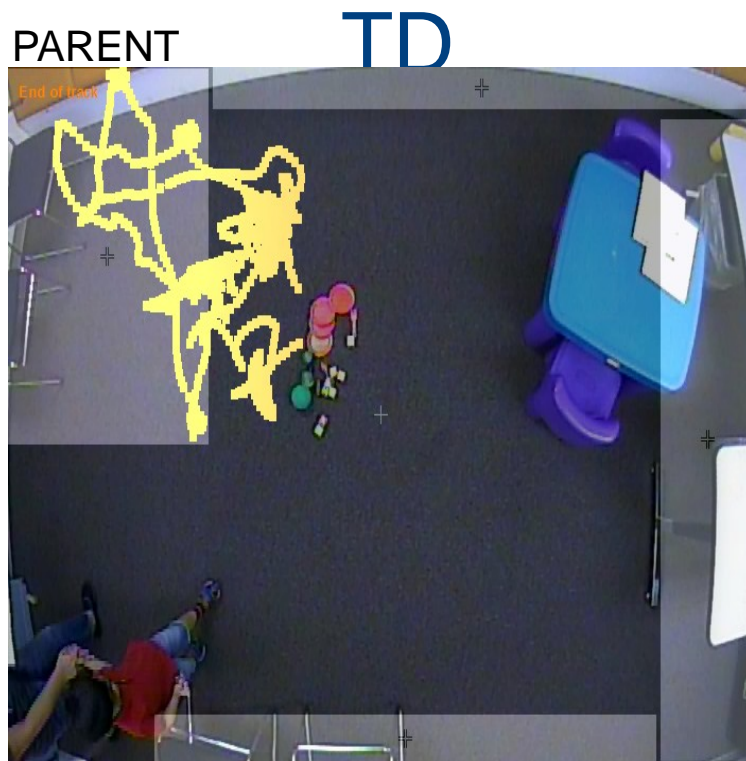
Lab-based Measures

Lab-based measures: Video Tracking

■ Proximity seeking during free play



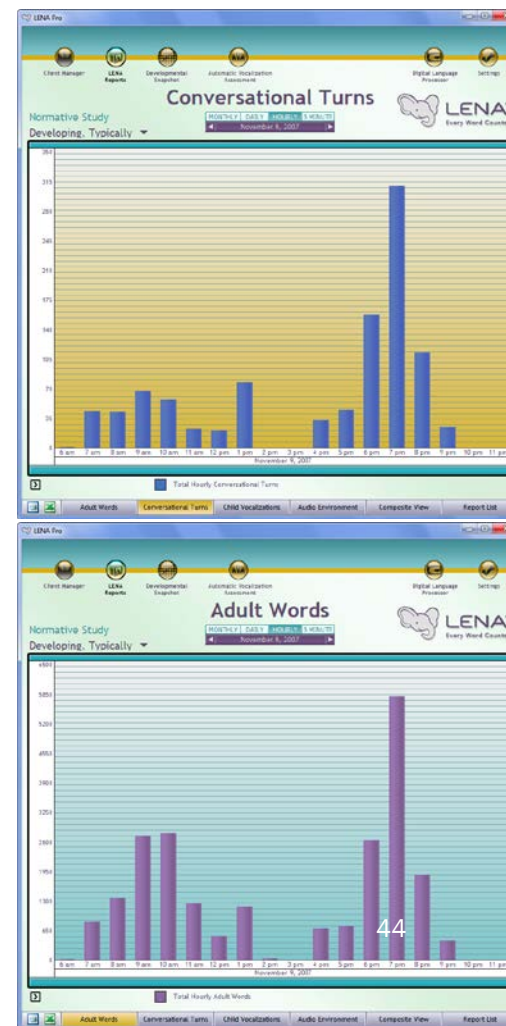
Lab-based measures: Video Tracking



- Social avoidance correlates with social-communicative impairment

Lab-based measures: LENA

- Language ENvironment Analysis
 - Conversational turns
 - Vocalizations
- Data collected in lab and at home
- Associated with social communicative function in Duke clinical trial



Lab-based measures: Face and affect recognition

- Affect recognition
 - NEPSY-II
 - Administer to all
 - Normed 3-11
- Face recognition
 - Kaufman Assessment Battery for Children
 - Administer to age 4
 - Normed 3-6
 - NEPSY-II
 - Administer to all
 - Normed 5-11

Clinician/caregiver assessments

■ 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
- Behavior Assessment System for Children – Second Edition
- Pervasive Developmental Disorder Behavior Inventory
- Social Opportunities Questionnaire
- Social Skills Improvement System
- Social Responsiveness Scale – Second Edition
- Child and Adolescent Symptom Inventory
- Pediatric Quality of Life
- Caregiver Strain Questionnaire
- ACE Family/Medical History
- Intervention History
- Demographics/Screening

Biospecimens

- Blood draw
 - Proband and available biological parent(s)
 - Simons Foundation SPARK
 - 1 EDTA for DNA extraction and sequencing
 - NIMH Repository
 - 1 LCL/ACD tube for generation of cell lines
 - 1 EDTA
- Genetic feedback to families via SPARK

Planned Interim and Final Data Analyses

- Assess technical and biological viability of the measures as potential biomarkers:
 - Identify EEG and eye tracking biomarkers and lab-based measurement variables with good performance metrics
 - Examine the relationship and sensitivity among EEG and eye tracking biomarkers, lab-based measures, clinician/caregiver assessments, and independent measures of clinical status
 - Evaluate longitudinal change in eye tracking, EEG, and lab-based measures to identify if they will be sensitive tools for intervention trials
- Use multivariate methods to find meaningful groups of individuals or variables
 - Cluster analysis to identify homogenous subgroups based on these variables and check for their correspondence with known/observed patterns of heterogeneity in ASD symptoms and behaviors
 - Multidimensional scaling to identify composites by capturing heterogeneity in the sample across measures

Expected Outcomes

- The ABC-CT is an early stage biomarker validation effort
 - Determine if biomarkers are robust enough to be used for subject selection of school-aged ASD subjects for clinical trials
 - Assess technical and biological variability of the measures in pre-
 - school and school-aged children
 - Assess the utility of investigator-administered assessments of domains of social impairment as predictors of clinical outcomes
- A public data resource
 - An integrated data set of EEG, eye tracking, lab-based, and clinical
 - measures from pre-school and school-age ASD subjects, as well as
 - blood samples from ASD subjects and their parents for future genomic analyses
 - All data and analyses made publicly available through the National
 - Database for Autism Research

Status and timeline

- Current status
 - Complete
 - Protocol review by External Advisory Board
 - In-person protocol finalization meeting with SC and BCPT
 - Experimental paradigms and clinical protocols
 - Hardware configuration and standardization
 - Study-wide and site-specific trainings
 - Electronic case report forms and data management infrastructure
 - Site visits by DCC and DAAC
 - Feasibility study enrollment commenced December 8
 - Feasibility analyses ongoing
 - Three month goal for feasibility study completion
 - Presentation to Biomarkers Consortium Executive Committee
- Timeline
 - Three year data collection period
 - Finalization of analyses and publication in Year 4