

# Increasing Sensitivity & Specificity of Outcome Measures in Trials for Neurodevelopmental Disorders Using Both Clinical Outcome Assessments & Neuroimaging Approaches

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## Parent/Caregiver- Report Outcomes

Wide range of parent/caregiver-  
report outcome scales

Behavior/symptom inventories

# Assessments for Young Children

1

Bayley Scales of Infant and Toddler Development (Bayley-III/-4)

2

Mullen Scales of Early Learning (Mullen)





# Adaptive Behavior

## Vineland Adaptive Behavior Scales- Third Edition (Vineland-III)



Communication, Daily Living Skills, Socialization, Motor, Maladaptive Behaviors



Two versions:

1. Interview
2. Questionnaire (Rating Scale)

# Cognitive Assessments: Wechsler Scales

## Versions are age-based, continuous from 2:6 through age 90

- Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV)
- Wechsler Intelligence Scale for Children (WISC-V)
- Wechsler Adult Intelligence Scale (WAIS-IV)
- Wechsler Abbreviated Scale of Intelligence (WASI-II)

## Assessments of cognition

- WPPSI-IV and WISC-V are comprehensive; WASI-II is abbreviated
- Measures verbal and nonverbal abilities; WPPSI-IV and WISC-V also measure working memory and processing speed

# Scores Yielded

Raw Scores

Standard Scores/Scaled  
Scores/T-Scores

Age Equivalent Scores

Growth Score Value (GSV)



# Rare Disease Guidance:

## Development of Indication- Specific Outcome Measures



**Rare Diseases:** Common Issues in Drug Development Guidance for Industry. FDA DRAFT GUIDANCE, January 2019

### **Increase specificity**

- Disease/symptom specific

### **Increase sensitivity**

- More granular approach

### **Involvement of Key Stakeholders**

# Rare Disease Guidance:

## Development of Indication- Specific Outcome Measures



### Growing need for these specifically adapted measures in Neurodevelopmental Disorders Trials

- No consensus outcome measures
- Patients are heterogeneous
- Rely on report from clinicians/caregivers
- Need outcomes that are sensitive: detect granular changes in cognition or behavior
- Need outcomes that are proximal to target mechanism: specific to domain drug/therapy is thought to change

### Adapt well-accepted measurement tools to Neurodevelopmental Disorders Trials

- Clinical Global Impressions Scale (CGI)
- Visual Analog Scale (VAS)
- Caregiver Impressions of Change Scale



# Examples of Indication-Specific Outcome Measures

Rett Syndrome Behaviour  
Questionnaire  
(Mount, Charman et al., 2002)

Unified Batten Disease Rating  
Scale (UBDRS) (Marshall, de  
Blieck, Mink et al (2005)

Sanfilippo Syndrome Rating  
Scale (Shapiro et al., 2015)

# Development of Indication-Specific Outcome Measures

Improve **sensitivity** and **specificity** of the scale.

Improve **reliability** between clinicians and over time.

## Key Considerations

### Sources of information

- Caregiver-report; patient-report; observation of the patient; other team members; psychometric scores

### Granularity of ratings

- Likert scale or visual analog scale

### Content of ratings

- Specific symptoms/behaviors that should be considered
- Domain-level ratings and/or overall severity/change ratings

# Development of Indication-Specific Outcome Measures

Improve **sensitivity and specificity** of the scale.

Improve **reliability** between clinicians and over time.

## Key Considerations

### Anchors

- Developmental or symptom severity anchors
- General guidelines for rating conventions

### Comparison group

- Typical development; other individuals with the disorder; within-subject comparison (compared to the best/worst ever for the patient)

### Timeframe for rating

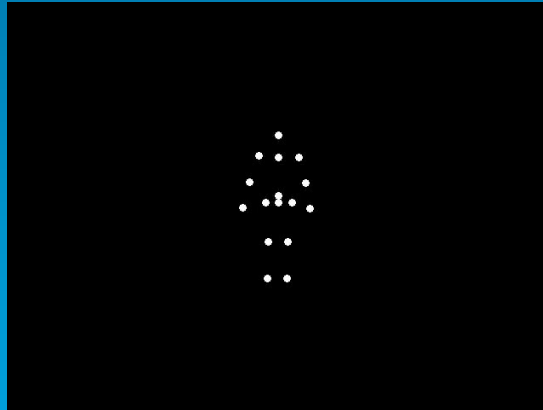
- Past week; past month; since baseline

# Development of Biological Markers:

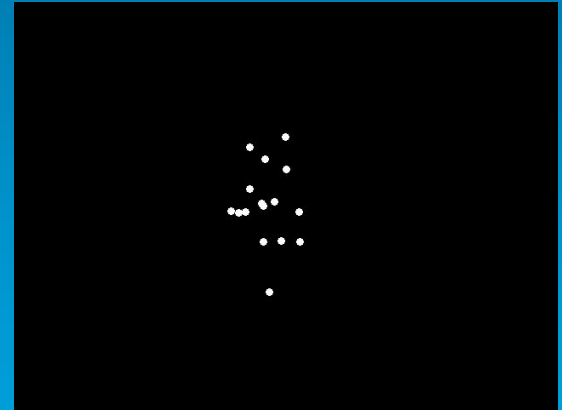
Probing brain function to  
understand mechanism of  
action



Coherent  
Biological  
(BIO)

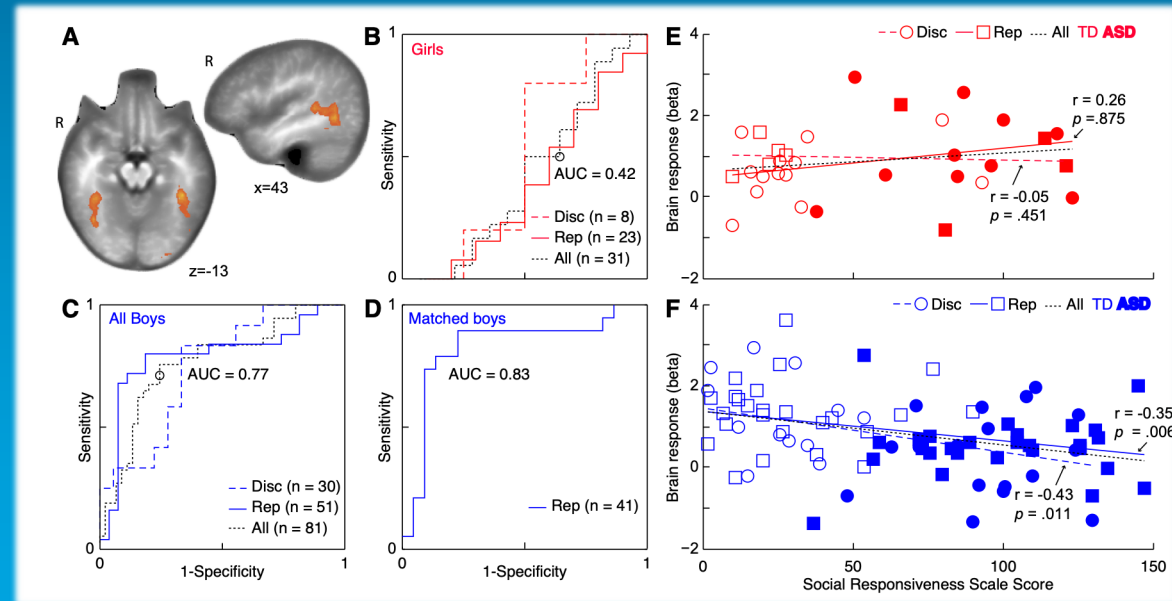
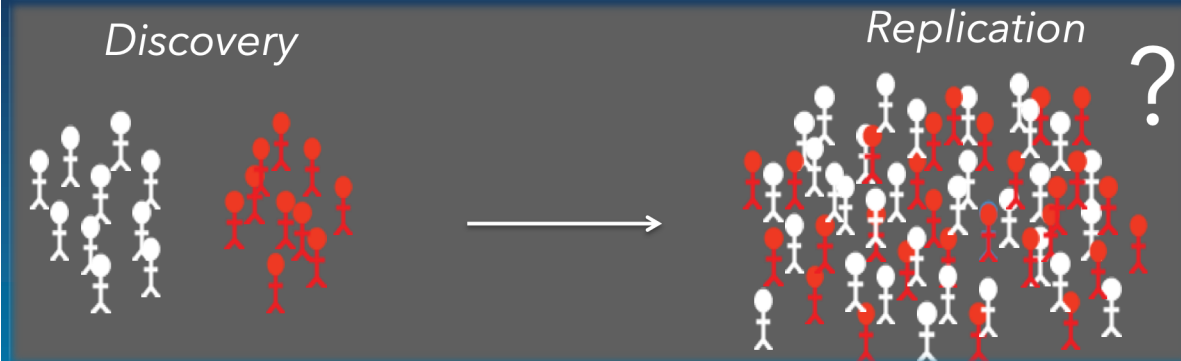


Scrambled  
Biological  
(SCRAM)



# Development of Biological Markers:

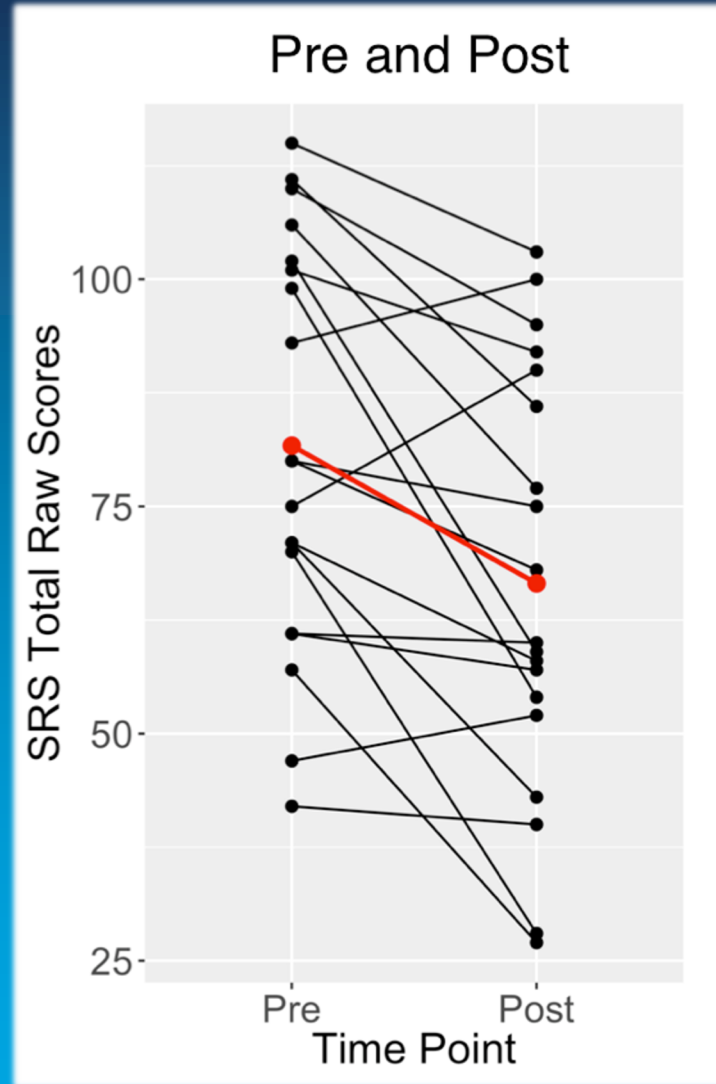
Sensitivity at the level of the individual person



# Development of Biological Markers:

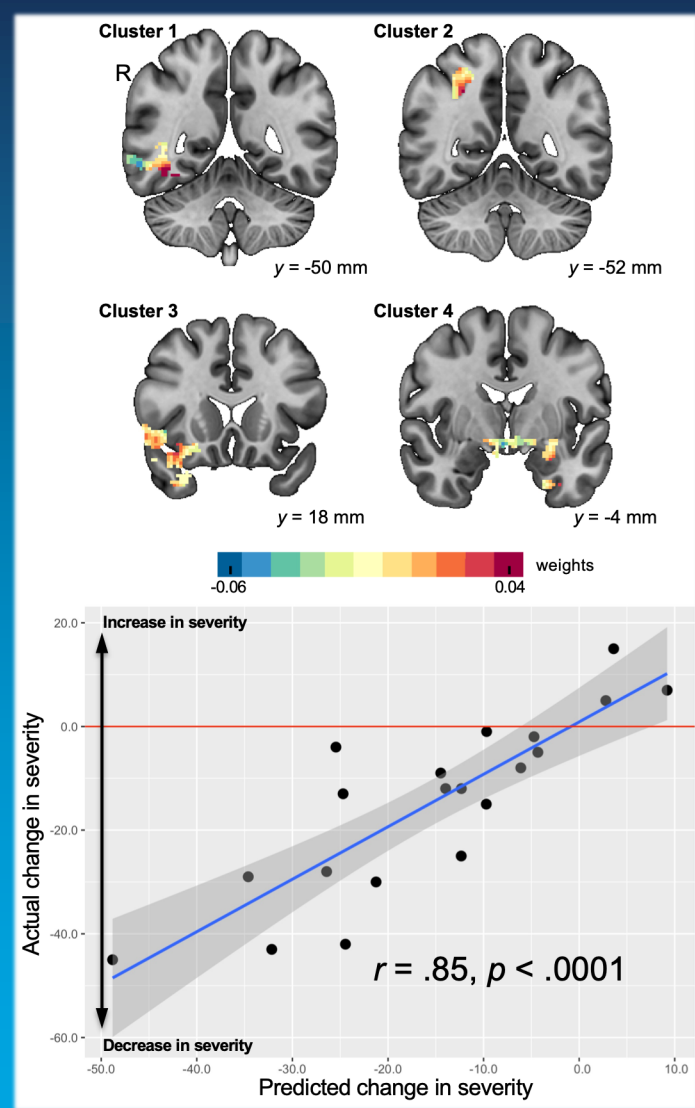
## Predicting individual responses to Pivotal Response Training among autistic children

Predicting individual responses to Pivotal Response Training among autistic children



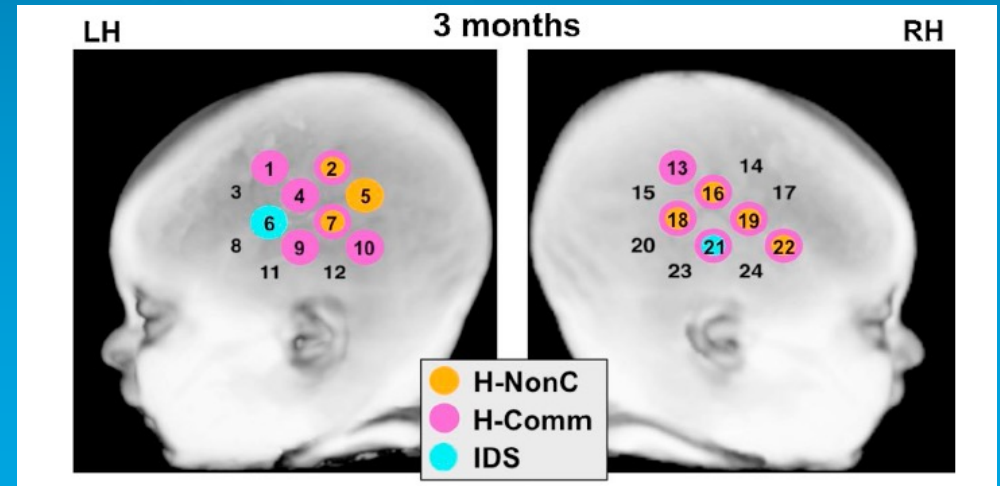
# Development of Biological Markers:

Predicting individual responses to Pivotal Response Training among autistic children



# Development of Biological Markers:

Practicability and scalability of biological markers





# Acknowledgments and Contact

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