Pushing the boundaries of early diagnosis of autism spectrum disorder



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No conflicts to disclose

Objectives

After attending today's presentation, participants will be able to:

- Recognize behavioral features of ASD detectable in infants at risk.
- List child and family factors associated with timing of ASD diagnosis
- Consider strategies to improve diagnostic capacity in their own communities

Why does age of diagnosis matter?

- Parents often recognize differences by 12-18 months, but diagnosis generally does not occur until much later.
- Potential long-term benefits of early interventions.

Anagnostou et al., 2014; Zwaigenbaum et al., 2009; 2015ab

Advances in early diagnosis!

- Advances in knowledge regarding early behavioral and biomarkers of ASD, pushing boundaries of earliest detection

Zwaigenbaum et al., 2015a; Hazlett et al., 2017

Challenges in ASD diagnosis

- Infant studies of behavioral and biomarkers of ASD mainly limited to high-risk cohorts followed at major university centres.
- Pre-symptomatic detection ≠ early diagnosis

Advances in early diagnosis!

- Robust evidence base for stability of ASD diagnoses as young as 18 months of age

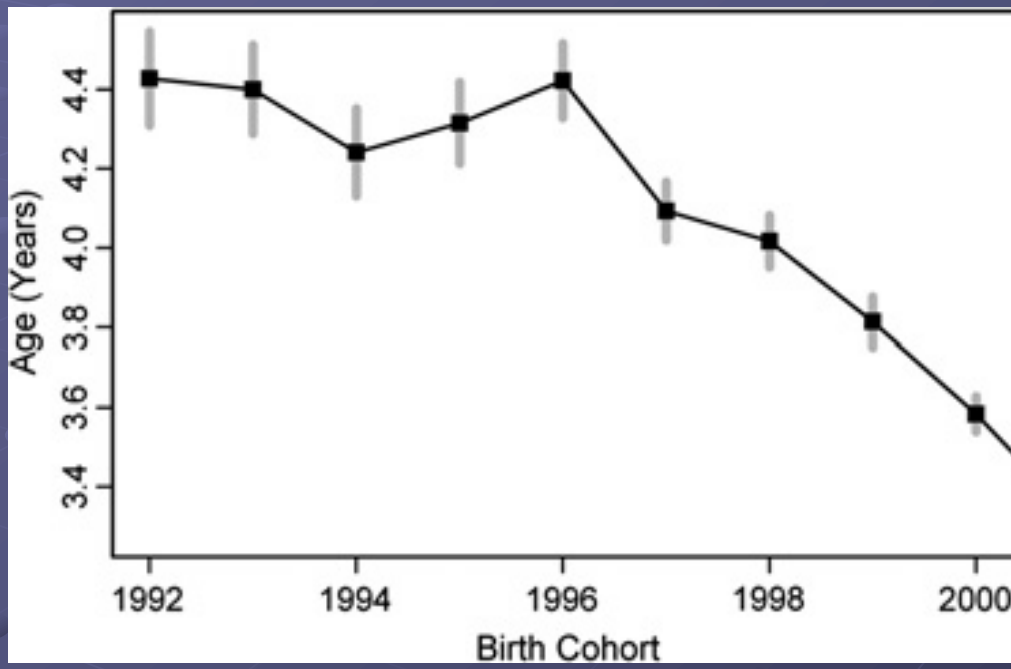
Ozonoff et al., 2015; Zwaigenbaum et al. 2016

Challenges…

- Early diagnosis is more challenging in children with milder symptoms and/or more advanced intellectual and language development

Advances…

- Modest reductions in age of ASD diagnosis
  - (17 of 21 studies reviewed by Daniels & Mandel, 2014)



Fountain et al., 2011

Challenges…

- Recent studies in US and UK suggest no change in age of dx
- Persistent disparities related to SES, ethnicity and clinical severity.

Brett et al., 2016; Sheldrick, Maye & Carter, 2017; Daniels & Mandel, 2014

‘Baby Sibling’ Studies

BSRC
AUTISM BABY SIBLINGS RESEARCH CONSORTIUM

- ‘High-risk’ design
  - Well suited to ASD research
    - Early onset (can study younger siblings in infancy)
    - Early diagnosis

Canadian 'Infant Sibling Study'

(Zwaigenbaum, Bryson, Brian, Roberts, Smith, Szatmari, Roncadin, Garon)

- **Participants**
  - 476 siblings of children with ASD
  - 182 comparison infants (no family history of ASD)
- **Assessed every 6 mo. to age 24 mo.; measures:**
  - **Early behavioral signs: AOSI (6-18m), ADOS (18-24m)**
  - **Language and cognition: Mullen, MacArthur CDI**
- **Independent diagnostic assessment (ADI, ADOS, clinical judgement) blind to prior study data at 3 years**
  - **473 HR (126 with ASD) and 179 LR (2 with ASD)**

Autism Observation Scale for Infants

(Bryson et al., 2008)

- Visual tracking
- Disengagement of attention
- Response to name
- Social babbling
- Eye contact
- Social smiling
- Social anticipation (peek-a-boo)
- Social interest and affect
- Response to change in facial emotion
- Imitation
- Coordination of eye gaze and action
- Reactivity
- Transitions between activities
- Motor behavior
- Atypical motor behaviours
- Atypical sensory behaviours
- Engagement of attention
- Insistence on having or playing with particular objects
- Social referencing

AOSI 12-month findings

- **ASD-risk marker (HR-ASD > HR-N, LR)**
  - **Orients to name**
  - **Social (solitary) babbling**
  - **Eye contact (gradient across 3 groups)**
  - **Social interest and affect (gradient across 3 groups)**
  - **Social referencing**

Zwaigenbaum et al., in preparation

AOSI 12-month findings

- **ASD-risk marker (HR-ASD > HR-N, LR)**
  - Orients to name
  - Social (solitary) babbling
  - Eye contact (gradient across 3 groups)
  - Social interest and affect (gradient across 3 groups)
  - Social referencing

  - **Transitions (gradient across 3 groups)**
  - **Insistence on particular object (gradient across 3 groups)**
  - **Atypical sensory behavior**
  - **Engagement of attention**

Can Parents' Concerns Predict ASD?

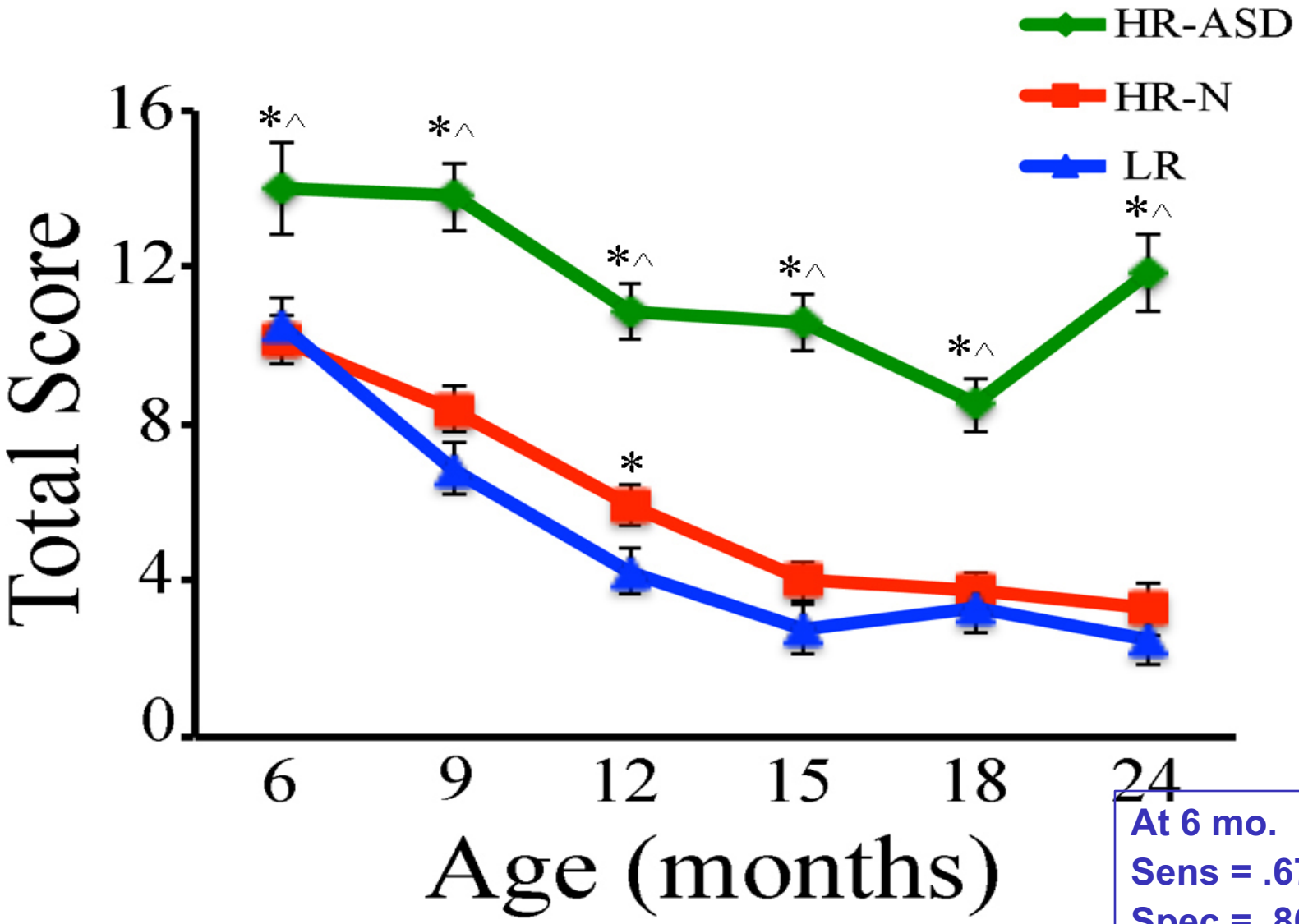
Sacrey et al., *JAACAP*, 2015

1. Concerns regarding 'core' features of ASD begin to differentiate ASD at around 1 year
   - 12-15 months for social and communication
   - 18 months for repetitive behaviours and restricted interests
2. Concerns regarding 'prodromal characteristics' of ASD begin to differentiate ASD as early as 6 months
   - 6 months for sensory regulation and motor behaviours
   - 9 months for play (sensory-oriented – visual/tactile)

Autism Parent Screen for Infants (APSI)

(Sacrey et al., 2016)

* = different from LR; ^ different from HR-N



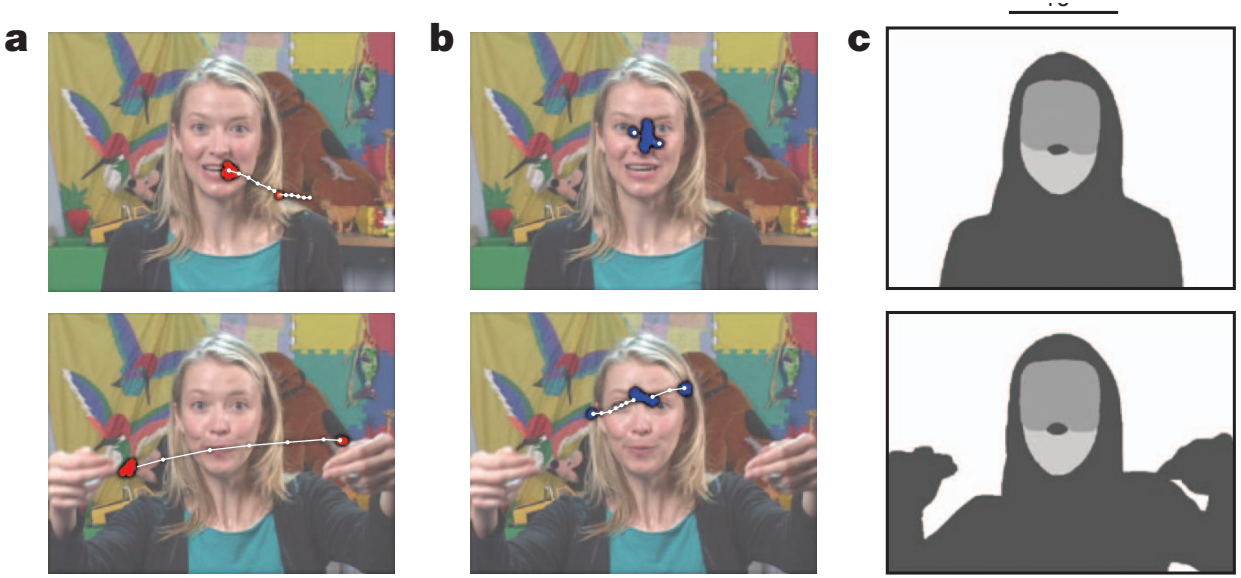
At 6 mo.
Sens = .67
Spec = .86

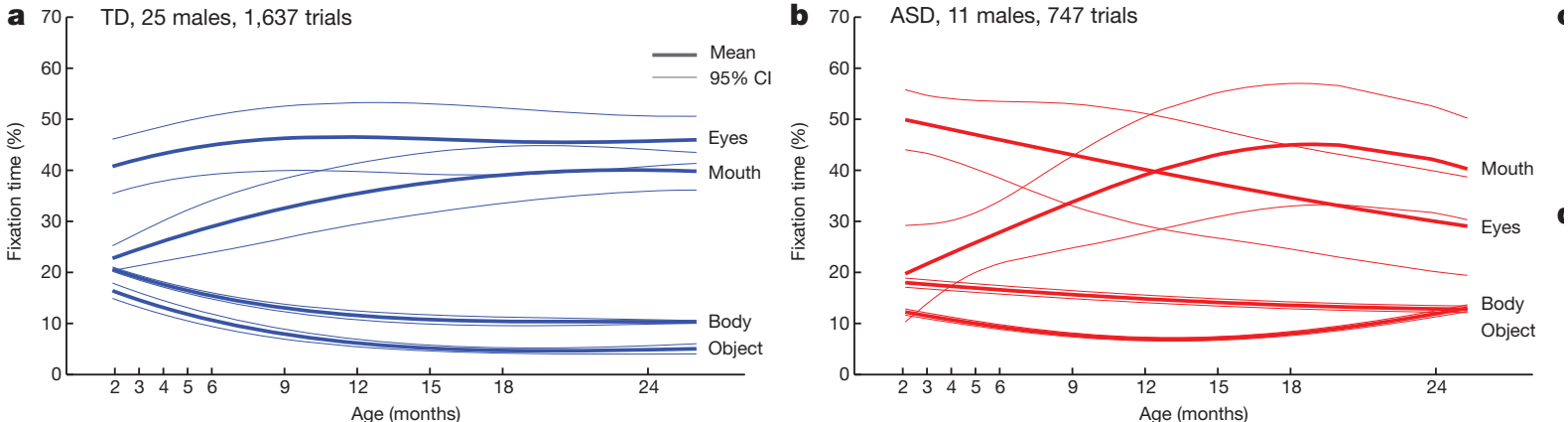
New directions:
Technology-based risk markers?

- Eye-tracking
- EEG/ERP
- Neuroimaging
  - Brain volume
  - Brain connectivity
- Genetic/epigenetic

Jones & Klin, Nature, 2013

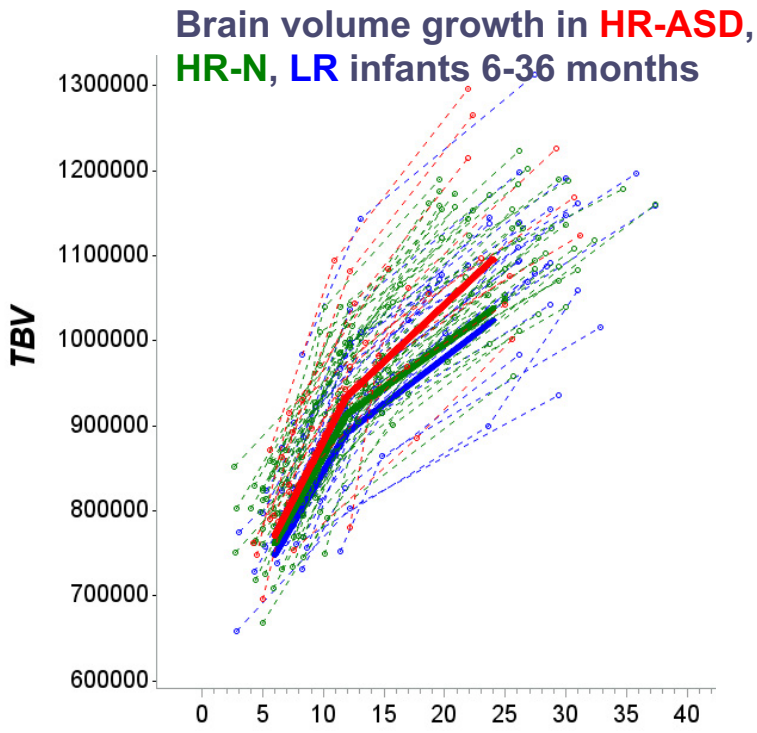
- 59 HR infants (12 later dx with ASD) and 51 LR infants 2 to 36 mo.
- Compared on % time eye gaze to eyes vs mouth, body, object during dynamic social scenes using eye tracking; 'growth chart' approach
- Change in eye gaze to person's eyes from 2-6 mo predictive of ASD in HR gp

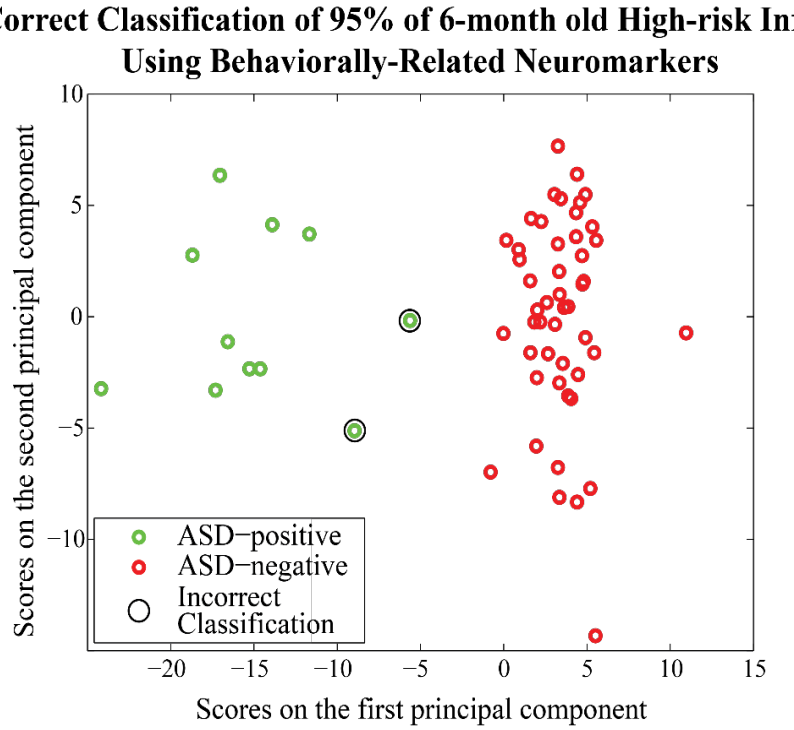




Infant Brain Imaging Study

(Piven et al, UNC NIH ACE Network)





Hazlett et al., Nature, 2017
106 HR (ASD=15) and 42 LR infants. Hyperexpansion of cortical surface area at 6-12 mo. precedes brain volume overgrowth at 12-24 mo in infants diagnosed with ASD at 24 months. A deep-learning algorithm based on 6 and 12 month MRI data predicted ASD with PPV = 81% and sensitivity = 88%.

Emerson et al, Sci Transl Med, in press
machine learning algorithm using functional connectivity indices at 6 months correctly identified which children (n=59) would receive a clinical diagnosis at 24 months with 96.6% accuracy (81.8% sens, 100% spec).

So…where are we at with early detection of ASD?

- **Behavioral markers**
  - Non-specific (?) prodromal features (e.g., motor, sensory, attention differences) by 6-12 months
  - ASD symptoms by 12 months
  - Sens and spec better for parent report?
- **Biological markers**
  - Imaging markers may be highly sensitive and specific by 6-12 months
  - Caveats+++

Early risk markers of ASD: Caveats of HR infant studies

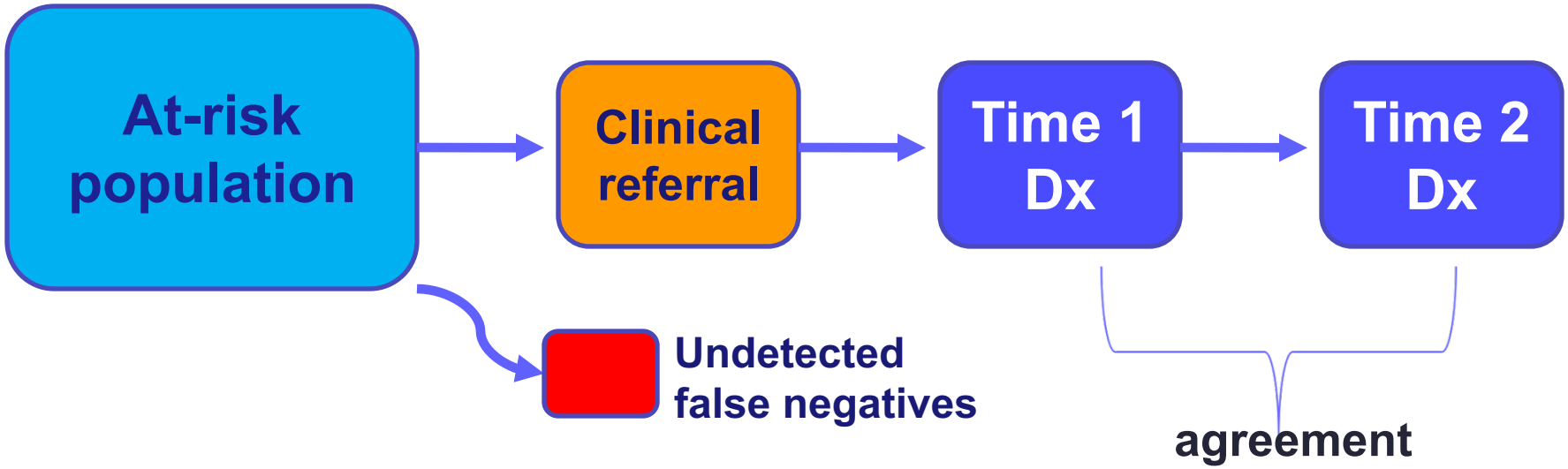
- Discriminant validity of early markers (e.g., from AOSI) must be assessed in other samples
  - Some markers may be non-specific in relation to ID (e.g., Jeste et al., 2016; Roberts et al., 2016; Yaari et al., 2006)
- Technology based measures (e.g., eye tracking, ERP, MRI) remain to be assessed outside research context; resources constraints may be prohibitive
- Clinical and ethical issues related to 'pre-symptomatic' detection.

How Early Can We Diagnose ASD?

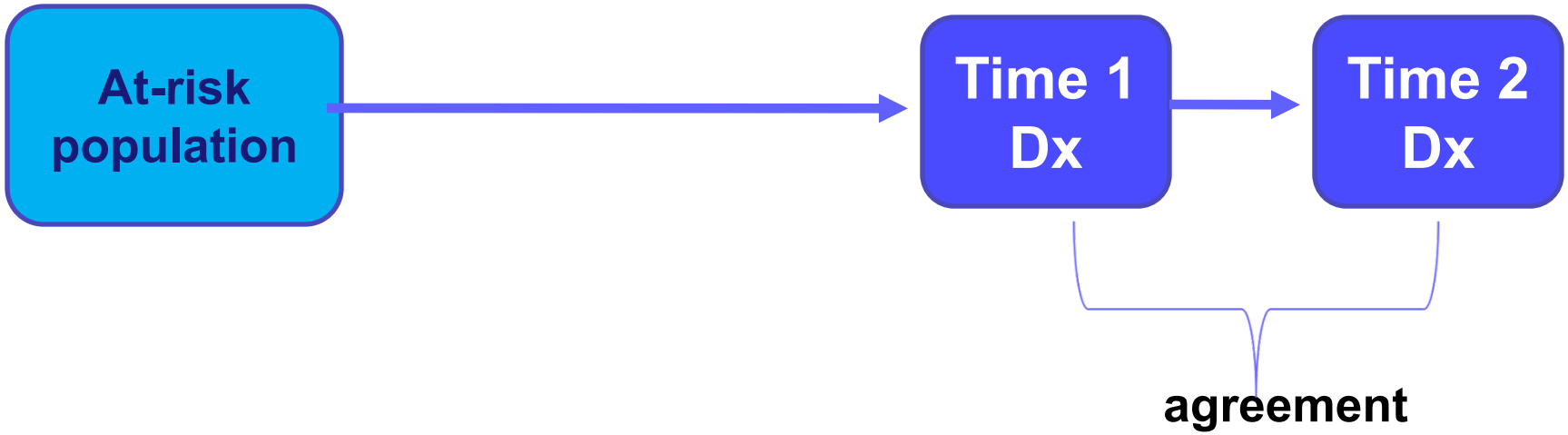
Stability of early ASD diagnoses
(reviewed in Zwaigenbaum et al., 2015b)

- **15+ published studies: children were assessed for possible ASD prior to age 3 then reassessed at least 1 year later**
- **Stability of ASD diagnoses established at 24 months or later was very high**
  - autistic disorder: 68% - 100% (median = 92%)
  - PDD NOS: 40% - 100% (median = 61%)
  - Also – high stability of ASD diagnoses prior to 24 mo (Chawarska et al., 2008)

Previous studies examining stability of early ASD diagnosis



'Infant sibling' studies



We examined stability of ASD diagnoses in high risk (HR) infants

- **Of 381 HR infants followed to 24 months**
  - 61 were diagnosed with ASD (15%)
  - 56 of 61 confirmed at age 3 (92%)
  - includes 19 of 23 (83%) diagnosed by age 18 mo
- **Factors associated with timing of diagnosis**
  - Which children are missed at age 24 months?

Zwaigenbaum et al., *Autism Research*, 2015
(also see Ozonoff et al. BSRC, *J Child Psychol Psych*, 2015)

Comparison of infant sibs with ASD by timing of clinical diagnosis (*at 24 mo*)

	Diagnosis 18 mo n =19	Diagnosis 24 mo n =37	Diagnosis 36 mo n = 47	p-value
Mullen Expr lang	34.8	40.8	48.4	**<.001**
Receptive language	32.7	31.2	48.9	**<.001**
Visual Receptive	42.9	40.9	50.4	**.04**
Fine Motor	39.9	38.8	46.9	**.01**
VABS - commun	74.4	82.5	93.5	**<.001**
VABS - social	78.3	81.5	90.3	**<.001**
VABS - ADL	76.6	79.4	88.0	**<.001**
ADOS severity	6.0	7.3	**4.1**	**<.001**

Summary

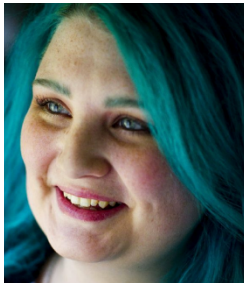
- **Clinical ASD dx stable at 24 months in HR infants**
  - 56 of 61 confirmed at age 3 (92%)
  - includes 19 of 23 (83%) diagnosed by age 18 months
- **However, 47 of 103 children (46%) diagnosed with ASD at 36 mo were *not* diagnosed at 24 mo**
  - Verbal, higher functioning
  - ASD symptoms milder but present at 12-24 months
  - May be less likely to be referred early, and if referred, diagnostic assessment (e.g., ADOS) may be inconclusive
  - Consistent with findings from '*Pathways in ASD*' study

Autism: trait or state?

Developmental Perspective on ASD Diagnosis…







Pre-symptomatic | Symptomatic | Early diagnosis | Later diagnosis

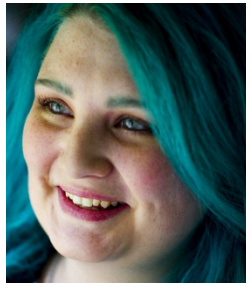
age 0……12 mo……18-36 mo (?)……

Contributing factors
- Symptom severity, IQ, language level
- Comorbid emotional-behavioral disorder ('diagnostic overshadowing)
- Socio-demographic factors

Developmental Perspective on ASD Intervention…







Pre-symptomatic | Symptomatic | Early diagnosis | Later diagnosis

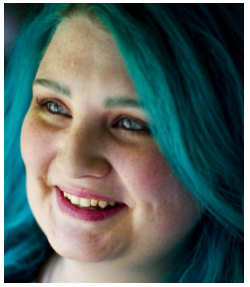
age 0……12 mo……18-36 mo (?)……

- Clear evidence for efficacy of interventions
- Shift from traditional ABA approaches to ‘NDBI’s
- i.e., more functional, more parent involvement, less resource intensive?

Developmental Perspective on ASD Intervention…







Pre-symptomatic | Symptomatic | Early diagnosis | Later diagnosis

age 0……12 mo……18-36 mo (?)……

- Newer concept in ASD field, but builds on strong EI evidence for infants/toddlers more generally
- Application of NDBIs (e.g., Ontario Pilot)
- Risks?
- Focus on targeting functional impairments, skill development, addressing parents' and clinicians' concerns

What do we know about early intervention for toddlers with ASD?

Naturalistic + Developmental + Behavioral Intervention (NDBI)

(Schreibman et al., 2015)

Approach	Strengths	Limitations
Naturalistic	Variation of stimuli; daily contexts, incidental teaching, natural rewards, child choice = improved attention/motivation. Reduced escape/avoidance behaviours	Reduced practice; loose contingencies; reduced learning opportunities
Developmental	Focus on foundational (core/pivotal) skills: imitation, social engagement, social context for learning, active engagement in leaning, developmentally appropriate, meaningful	Reduced practice; loose contingencies; reduced learning opportunities
Behavioural	Strong evidence base in preschoolers w ASD. Operant procedures, objective measurement; strong contingencies	Limited generalization/ developmental appropriateness
Combined NDBI	Reduced prompt dependence, natural-sounding language, efficiency of learning, generalization, resistance to distraction Family friendly; parents can learn strategies and find them acceptable	**Optimal approach?**

NDBI: Common elements

Common Elements
Three-part contingencies [BEHAVIOURAL] (A-B-C; natural reinforcement)
Manualized procedures
Fidelity of implementation measures
Individualized treatment goals
Ongoing measurement of child progress
Child-initiated teaching episodes
Environmental arrangement
Prompting/ prompt fading/ modeling
Balanced turns in play (shared control)
Imitation
Broadening the attentional focus
Parent coaching/ education

Schreibman L., et al. (2015). Naturalistic Developmental Behavioral Interventions: Empirically validated treatments for ASD. *Journal of Autism and Developmental Disorders.*

Parent-mediated toddler NDBI's: *Summary of RCTs [2010-2017]*

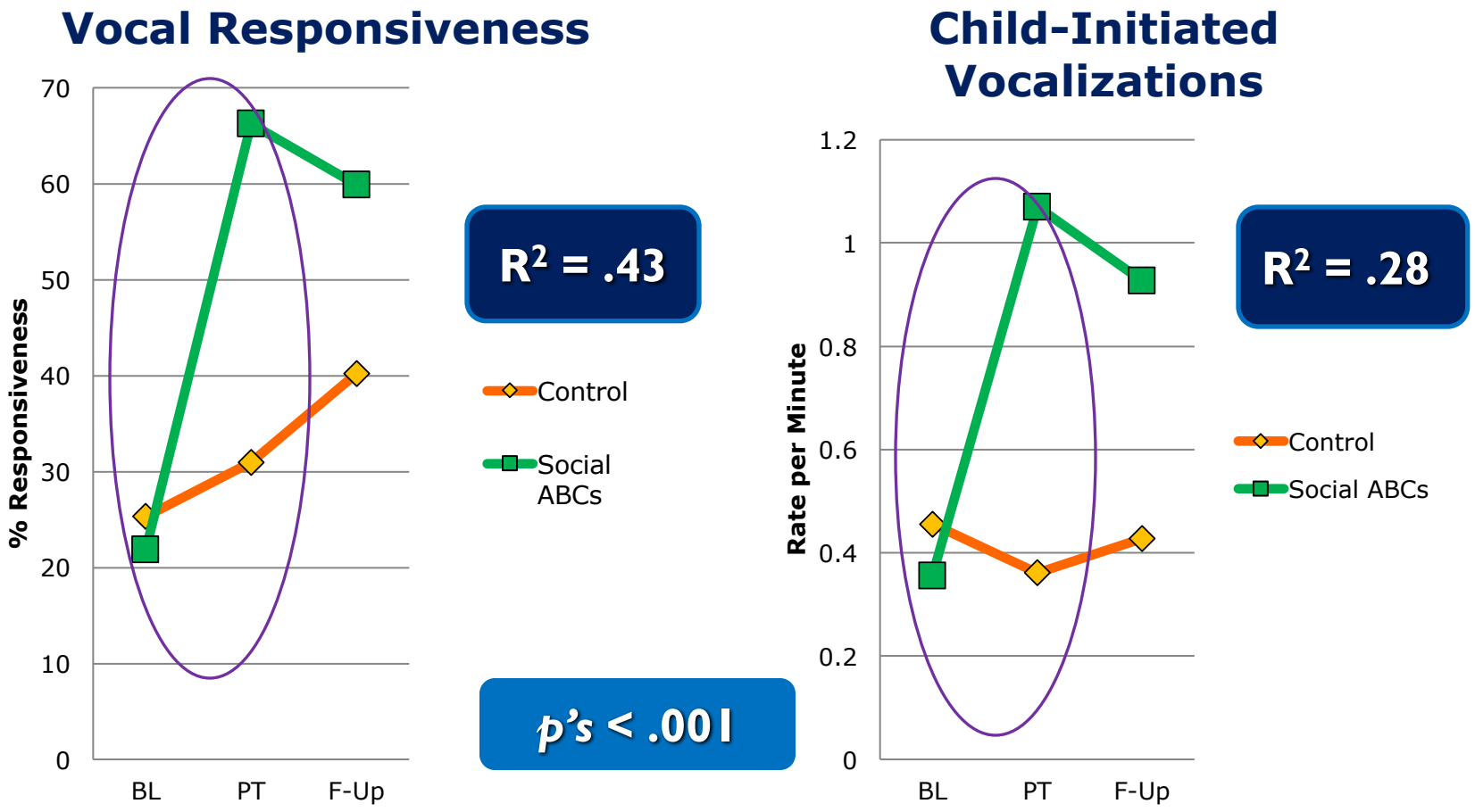
Gains in:

- **Communication**
  - *Wetherby et al (2014); Baranek et al (2015); Brian (2017)*
- **Engagement/ social attention**
  - *Kasari et al (2010); Schertz et al (2013); Green et al (2015); Brian et al (2017.)*
- **Socialization/ play**
  - *Kasari; Wetherby; Green; Baranek*
- **Parent effects**
  - *Rogers (2012); Baranek; Brian*
- **Positive affect sharing**
  - *Brian (2017)*

The *Social ABC's* *(Brian et al., 2017)*

- Manualized, caregiver-mediated program
- For toddlers (aged 12-30 mos) with confirmed or suspected ASD
- Based on parent responsiveness and naturalistic ABA (via PRT)
- 12 weeks in-home **live coaching**
- Targeted model:
  - **Functional Vocalizations**
  - **Shared Smiling**
- Data at 3 key time-points:
  - **BL → PT (wk 12) → F-up (wk 24)**

RCT findings: *Increased child vocal responsiveness and initiations*



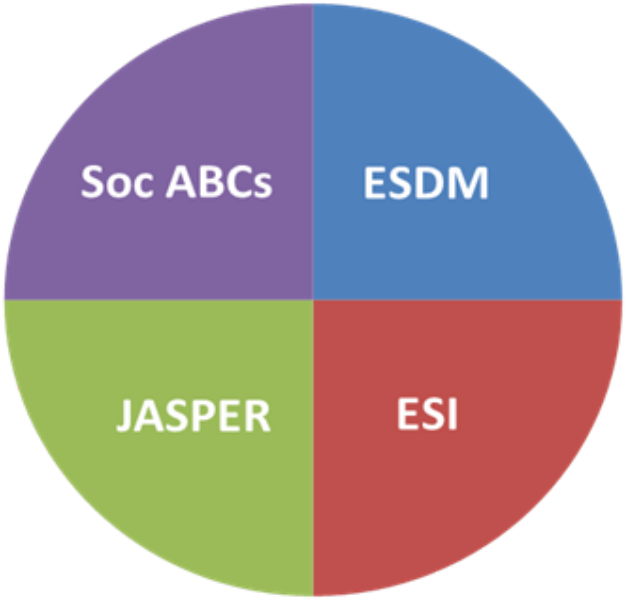
From: Brian, Smith, Zwaigenbaum & Bryson (2017). Autism Research

Community extension -MCYS

Ontario
MINISTRY OF CHILDREN AND YOUTH SERVICES

NeuroDevNet

kids brain health network

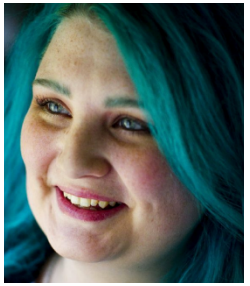


- *Underway…*
- 4 models for at-risk toddlers PRE-Dx
- 3-year community-based demonstrations
  - *Feasibility*
  - *Acceptability*
  - *Portability*
  - *Cost*
- Potential for long-term uptake

Developmental Perspective on ASD Intervention…







Pre-symptomatic | Symptomatic | Early diagnosis | Later diagnosis

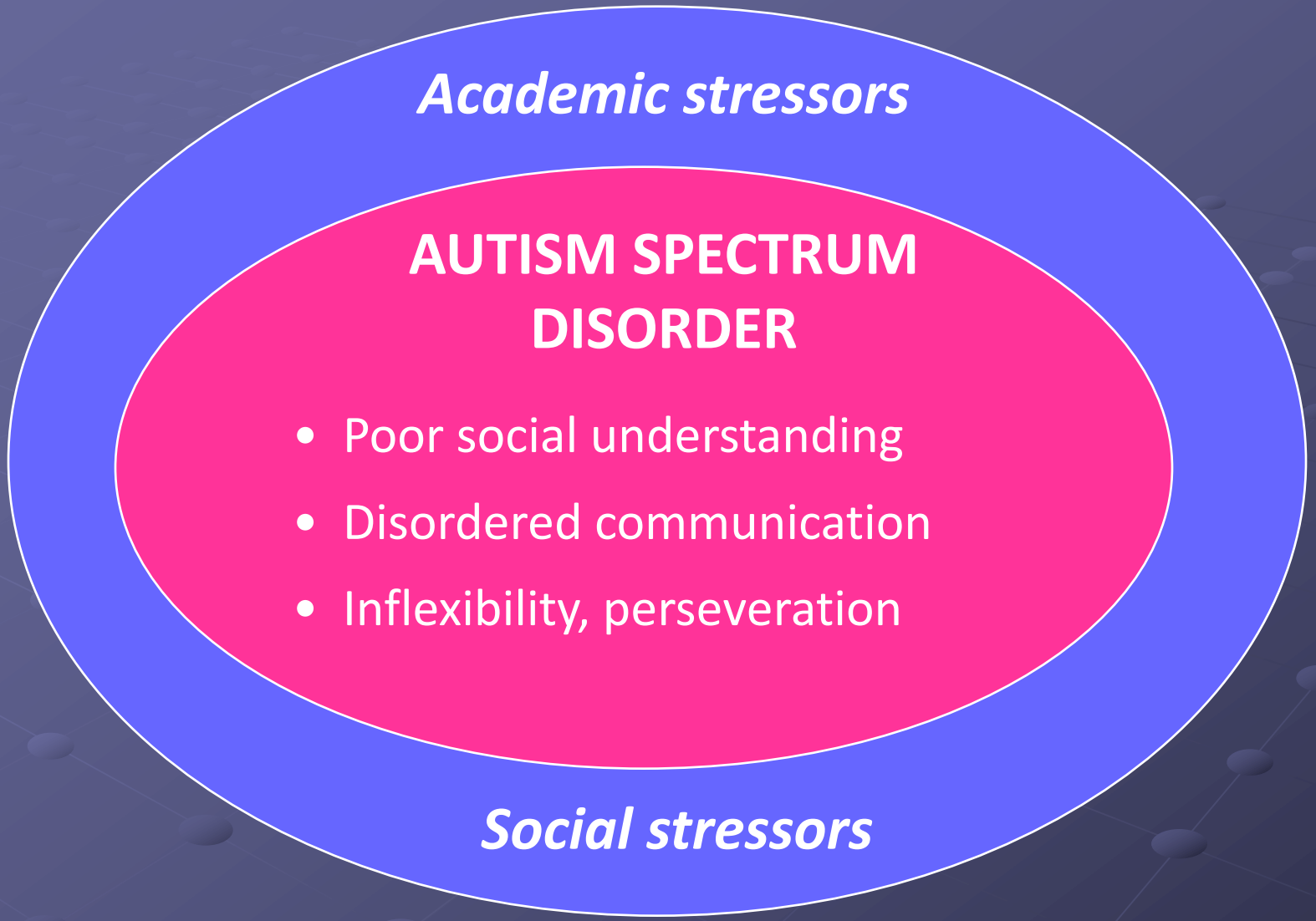
age 0……12 mo……18-36 mo (?)……

- More contentious – what are the intervention targets?
  - Biology, basic processes, early function
  - Target deficits or enrich environment?
- What do we mean by ‘symptoms’?
- But do the risks potentially outweigh the benefits? And what do parents want?

	Mean Age 1st Parental Concern	Mean Age Clinical Diagnosis
Children with autism	18 months	5.5 years
Children with 'Aspergers' (autism without cognitive and language delay)	30 months	11 years

Howlin & Asgharian, *Dev Med Child Neurol*, 1999

Presenting symptoms



DEFIANCE

TASK AVOIDANCE

Academic stressors

Autism Spectrum Disorder

- Poor social understanding
- Disordered communication
- Inflexibility, perseveration

Social stressors

ANXIETY

OUTBURSTS

ADOS in (complex) clinical setting
(Mulloy et al., *Autism*, 2011)

- 310 school-aged children with suspected ASD evaluated at tertiary dev-behav clinic in Cincinatti
- ADOS classification vs. clinical diagnosis
- Findings
  - Rate of ASD diagnosis = 47% (most common other diagnoses: ADHD, anxiety disorder, language disorder)
  - Mod 2 (phrase speech): ADOS sens=88%, spec=68%
  - Mod 3 (fluent speech): ADOS sens=87%, spec=48%

Challenges of adult diagnosis

- Poorly developed service system
- Limited pool of experienced diagnosticians
- Initial diagnosis in adulthood implies complexity
- Differential diagnosis differs from children
- Extremely important for supports/services, self-identify, finding a community

Considerations in diagnostic assessment models

Building community capacity for ASD diagnosis

Summary and final thoughts

- Prospective studies of ASD with high-risk infants have been informative for early markers predictive of ASD; potential to integrate behavioral and biological risk.
- Reliable diagnosis (at least in some) by 18-24 months.
- Where on the developmental continuum should we target interventions? Are there advantages in starting prior to diagnosis?
- Need for ‘timely diagnosis’ across the lifespan, further attention and research aimed at improving accuracy and efficiency of assessment models for youth and adults.

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