Classification and Measurement of Regression in ASD

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What is the phenomenon of regression in ASD?

- Regression: term used since Leo Kanner describes individuals with autism who lose skills during the onset of the disorder

- Regression also describes the significant decline in skills associated with (what was formerly known as) childhood disintegrative disorder, mitochondrial disorder, specific epilepsy syndromes and other neurologic problems (e.g. loss of motor skills in Rett Syndrome)

Behavioral "Outcome" of autism with regression vs. without regression

- Reports of worse ASD symptoms (e.g. Bernabei, et al., 2007; Kalb, et al., 2010; Richler, et al., 2006; Rogers & DiLalla, 1990)

- Slightly worse ASD sx, but no (or not clinically meaningful) differences in cognitive skills (Baird, et al., 2008; Meilleur & Fombonne, 2009; Hansen et al. 2008)

- No differences:

  Fombonne & Chakrabarti, 2001; Werner et al. 2005 ; Shumway et al. 2011; Nordahl et al. 2011; Ozonoff et al. 2011

*** studies differing in type (language vs. other social-communicative regression) measurement, and outcomes studied`

Regression in Onset of Autism

- Previous studies using categorical definitions often found regression occurs in ~25%
- Recent data indicate loss of skills OR decline in socialization behaviors, occurs frequently in the ontogony of autism symptoms
- Questions this raises:
    - what is pre-loss development like?
    - How frequent is pre-loss development "normal"?
    - Does all loss occur simultaneously?

Evidence for Early Delays in Children with Regression

- Werner and Dawson (2005) found developmental abnormalities of social, communication, repetitive behaviors, or regulatory behaviors in nearly **one-half** of children with autism and regression

- Ozonoff, et al. (2005) found 35% of the definite regression group also had delays in three or more different skills typically attained by 18 months of age

- Baird et al. (2008) examined language regression & found age of 1st phrases did not differ b/w those who regressed and not (but 1st words were earlier in language regression group)

- Luyster et al. (2005) first to consider pre-loss skills in defining social-communication regression (25% of the skills they had gained in an area, in at least three areas)

Taking Early Delays into Account:
Four Categories of Onset Patterns in Autism

	Loss of Skills	
	NO	YES
Early Symptoms (symptoms before 1st birthday)	Early Onset (Early delays, no loss) Hindsight of problems in first 12 months (Q4=0) and No loss of language (Q11=0) and No loss of social engagement/responsiveness (Q25=0)	Delay+Loss (Some delays before loss) Hindsight of problems in first 12 months (Q4=0) and Loss of language (Q11=1) and/or Loss of social engagement/responsiveness (Q25≥1)
No Early Symptoms (symptoms NOT present before 1st birthday)	Plateau (No early delays, no loss) Hindsight of NO problems in first 12 months (Q4≥1) and No loss of language (Q11=0) and No loss of social engagement/responsiveness (Q25=0)	Regression (No delays before clear loss) Hindsight of NO problems in first 12 months (Q4≥1) and Loss of language (Q11=1) or Loss of social engagement/responsiveness (Q25≥1)

How can the amount and type (and timing) of early delays truly be measured?

- Using Retrospective report, can consider whether *specific* skills were ever developed, when, and loss of these specific skills (and if so, when)

Study Showing Distributions of Delays & Loss

- Data collected on 244 children
  - 125 AUT, 42 PDD-NOS, 46 DD, 31TD
- Methodology:
  - Regression Validation Interview- Revised (RVI)
    - a detailed semi-structured interview that includes questions about attainment and loss of specific skills:
      - pre-speech behaviors, communicative gestures, and vocabulary.

Thurm et al. 2014

Percent of skills attained

Skill	AUT N (%)	PDD-NOS N (%)	DD N (%)	TD N (%)
First words	93 (75)	38 (93)	36 (82)	31 (100)
Response to name	83 (70)	26 (74)	28 (82)	26 (100)
Smile to mom/dad	93 (84)	31 (86)	38 (93)	28 (97)
Smile to others	82 (73)	30 (81)	36 (90)	28 (97)
React to "There's mom/dad"	52 (47)	25 (68)	34 (81)	24 (96)
Babbling	94 (84)	30 (81)	34 (85)	30 (100)
Peek-a-boo	95 (86)	30 (81)	38 (93)	24 (96)
Follow a point	55 (56)	22 (69)	34 (83)	23 (96)
Eye contact	66 (58)	18 (50)	30 (73)	26 (96)
Show object	39 (33)	19 (47)	33 (75)	30 (100)
Give object	75 (64)	30 (77)	35 (85)	29 (100)
Point to express interest	28 (24)	23 (59)	34 (81)	28 (100)
Point to request	43 (43)	26 (76)	35 (87)	28 (97)
Wave bye-bye	63 (54)	21 (58)	32 (76)	27 (100)
Extend arms up	93 (80)	29 (78)	33 (79)	29 (100)

Continuous Distributions of Delays & Loss (cont'd)

- Results:
  - In the AUT group, loss of at least one skill was reported in 63% of children
  - Loss of point to express interest, wave bye-bye, and eye contact were all reported in more than 50% of children with AUT who had attained the skills.
  - Skill loss occurred at different age for different skills

Thurm et al. 2014

Skills Attained vs. Skills Remaining After Loss, According to Dx Group
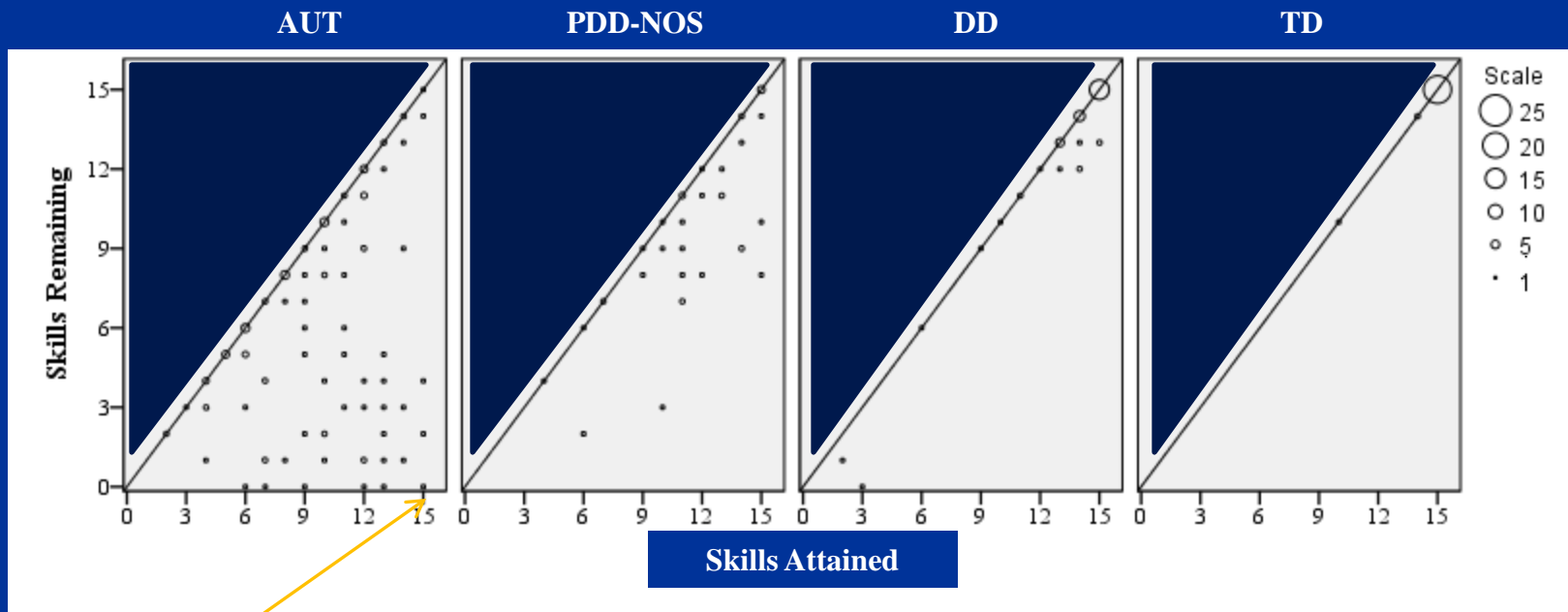
Note: those on the line did not lose any skills

Gained all
skills and
lost all

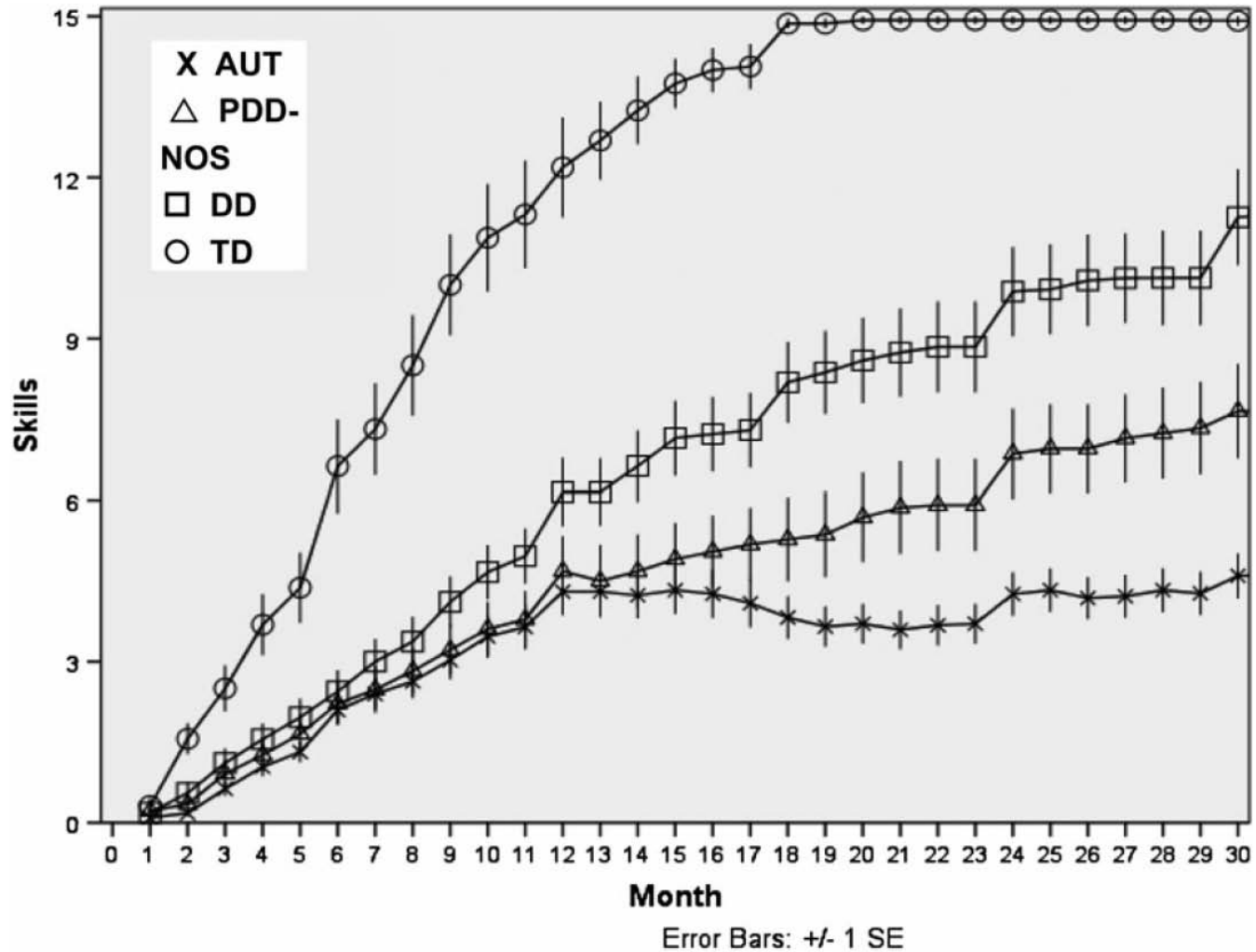Findings show distribution of skills lost, with lack of clear cutoff for "regression"

Figure 2. Patterns of skill attainment and loss over time in children. AUT, autism; PDD-NOS, pervasive developmental disorder not otherwise specified; DD, developmental delay; TD, typical development.

Beyond Onset Pattern of Social-Communication Skills

- Onset of ASD involves unfolding of deficits in social-communication skills AND development of repetitive behavior and restricted interests

- How does onset on each of these domains affect the other?

Social-communication impairments

Repetitive Behaviors & Restricted Interests
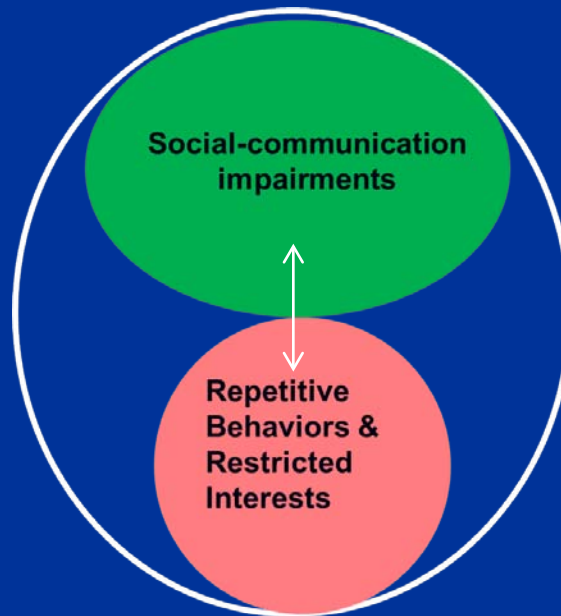
Does the onset of repetitive behavior need to be considered in measuring regression?

Timing of Repetitive vs. Loss of Skills	Percentage of Children
Repetitive Behaviors Preceded Loss of Skills	25 (61%)
Concurrent Repetitive Behaviors and Loss of Skills	2 (5%)
Repetitive Behaviors Followed Loss of Skills	14 (34%)

# Given the dimensions and factors, can regression be categorized alone?

- How to "capture" on one variable, at least two dimension (early delays & loss) that vary at least somewhat independent of each other?
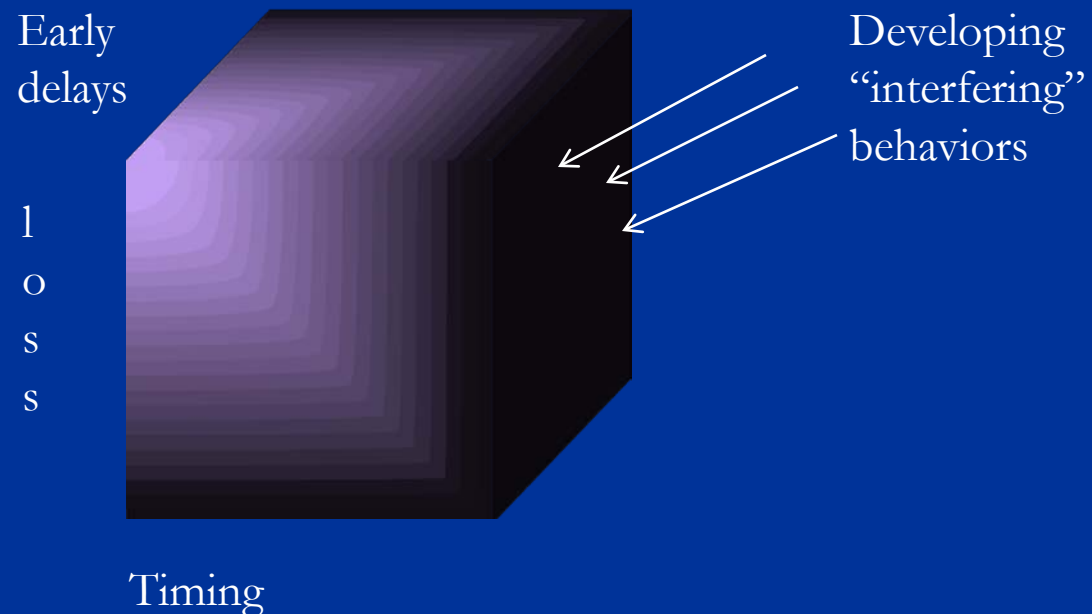
Reporting of Regression

- Parent report consistency over time
  - There are several reports of inconsistencies of up to 20% between parent reports of regression over 2 time points
- Parent retrospective report vs. Parent prospective reporting (vs. clinician observation)
  - Studies from infant siblings provide opportunity explore agreement among reports

Phase II: Prospective Examiner Ratings
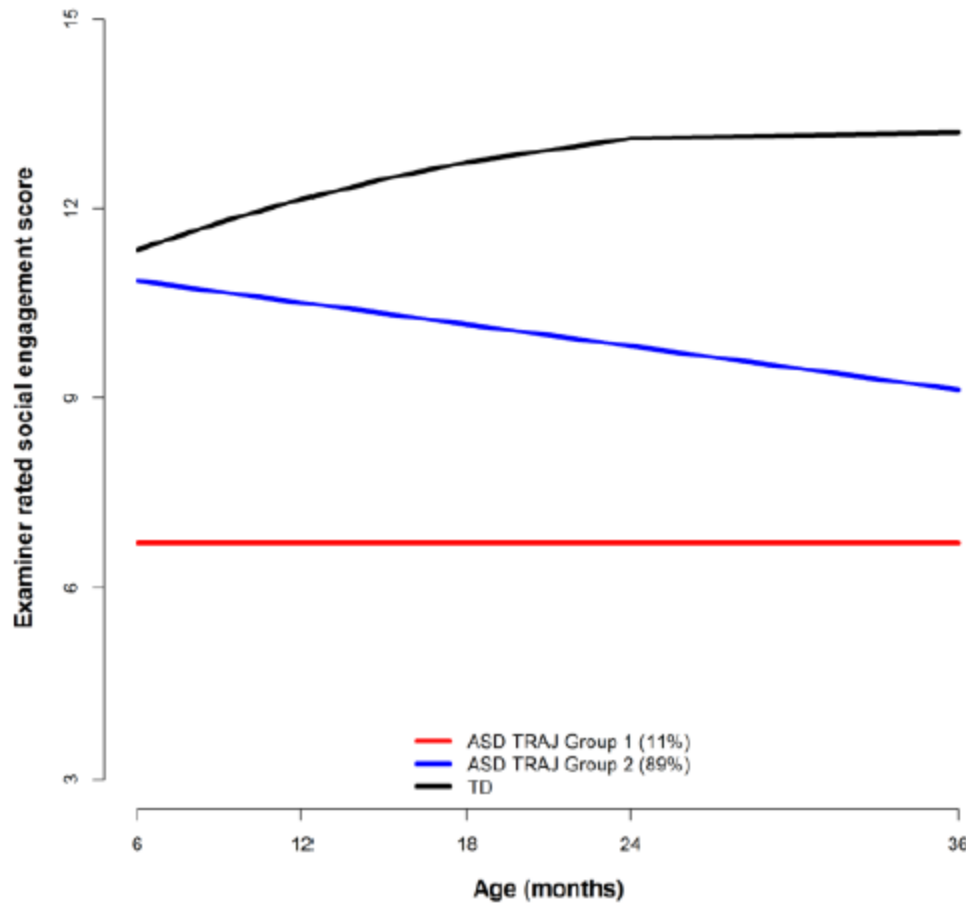
89% of ASD sample have a declining trajectory by prospective examiner report

Ozonoff et al. 2014; IMFAR

Phase II: Prospective Parent Ratings

valid reporting?

71% of ASD sample have a declining trajectory by prospective parent report

Ozonoff et al. 2014; IMFAR
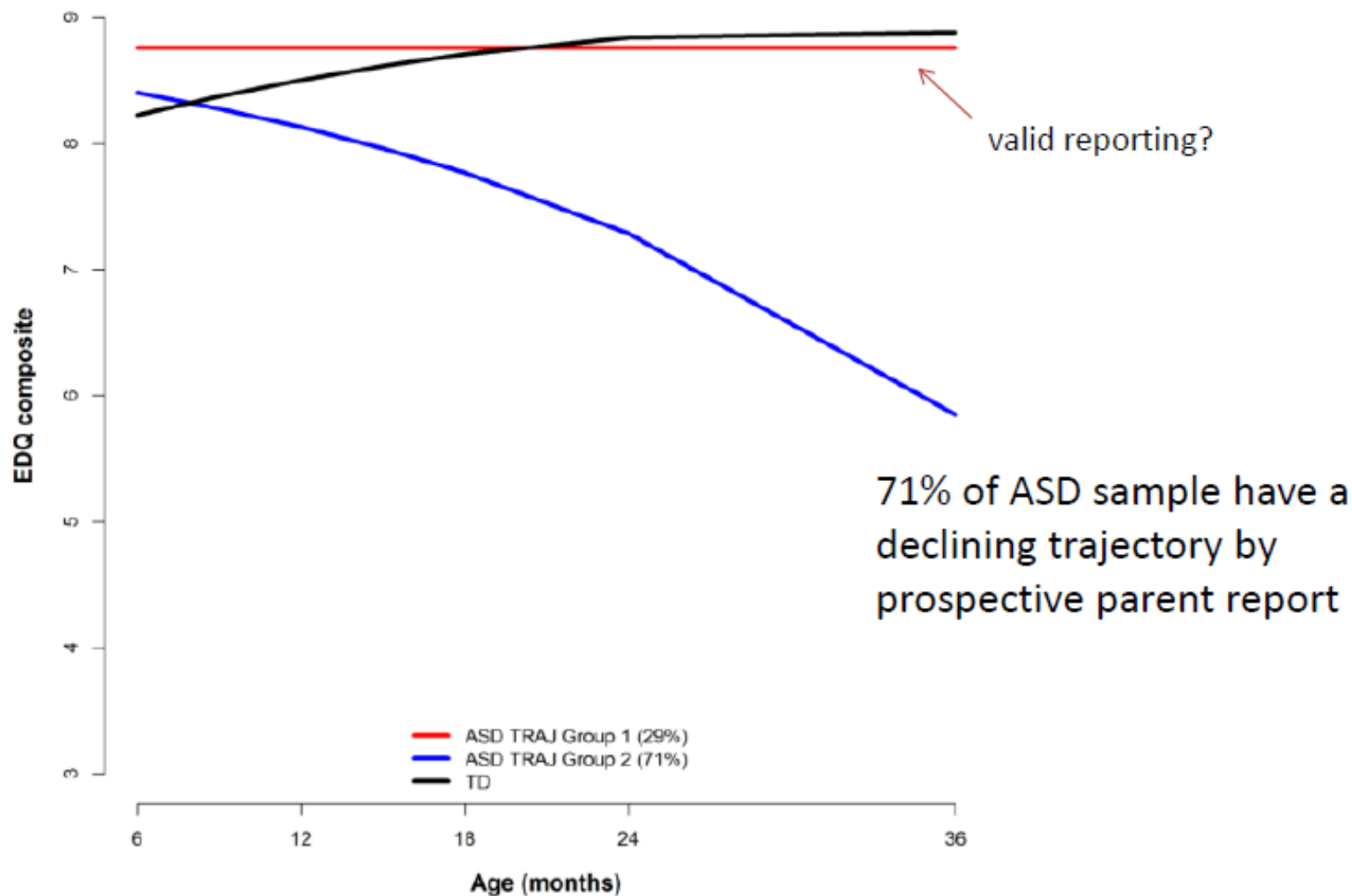
Conclusions

- Need an algorithm to capture and measure onset patterns dimensionally to correlate with other neurobiologic continuous measures

- Need large N studies with in-depth phenotyping (starting as early as possible) to determine if and how onset pattern affects later course of symptoms and comorbid/biologic presentation

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