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Early identification of autism and ADHD: A transdiagnostic perspective

Meghan Miller, Ph.D.

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Disclosures

- I have nothing to disclose.

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Outline

- Identifying prodromes in infancy: Rationale and methods
- Early mechanisms underlying atypical development in ASD and risk for ADHD
- Transdiagnostic early developmental pathways to ASD and ADHD
- Summary and future directions

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Early detection and diagnosis: Why?

- Infancy/early childhood ideal period in which to investigate phenomenology of childhood disorders: accurate/earlier detection, critical timepoints/domains, causal mechanisms
- Early identification → early treatment → improved outcomes
- Decrease service utilization, economic burden
- Challenges: false positives, unnecessary treatment



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Ultimate goal

Theoretical impact

- Improve understanding of etiological mechanisms
- Inform theoretical models of ASD, ADHD, comorbidity



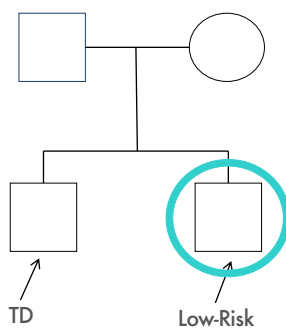
Clinical impact

- Screening/early detection
- Prognostic models
- Prevention and intervention targets

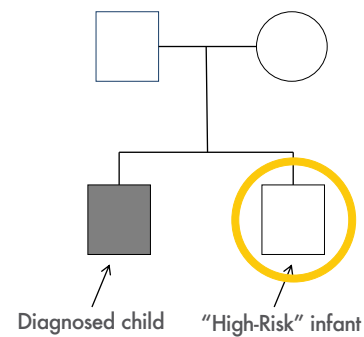
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Familial risk design

Typically Developing

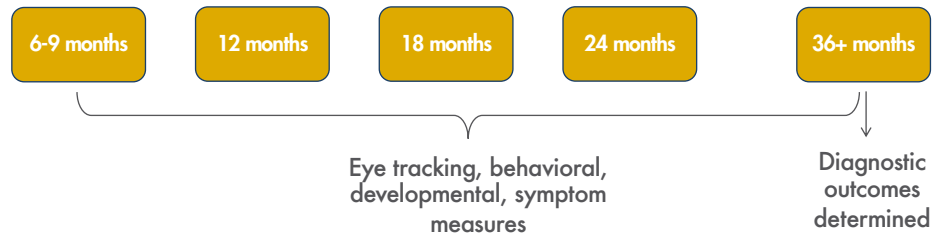


"High-Risk"



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Prospective familial risk design



Strengths of prospective familial risk designs

- Allow for examination of key developmental psychopathology principles
 - Continuities/discontinuities
 - Equifinality/multifinality
 - Mediation mechanisms
 - Exploration of reciprocal transactional processes
 - Identification of sensitive periods
 - Distinguishing correlates from risk factors; identification of protective factors

Autism spectrum disorder (ASD)

Social-communication

- Difficulties with social-emotional reciprocity
- Difficulties with nonverbal communication
- Challenges developing, maintaining, understanding relationships

Restricted interests/ repetitive behaviors

- Stereotyped/repetitive motor movements, object use, speech
 - Insistence on sameness, inflexible adherence to routines, ritualized patterns of behavior
- Restricted, fixated interests
- Hyper-/hyporeactivity to sensory input, unusual interest in sensory aspects of the environment

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Early behavioral markers of ASD

Social Communication

- Eye gaze
- Vocalizations
- Social smiles
- Response to name

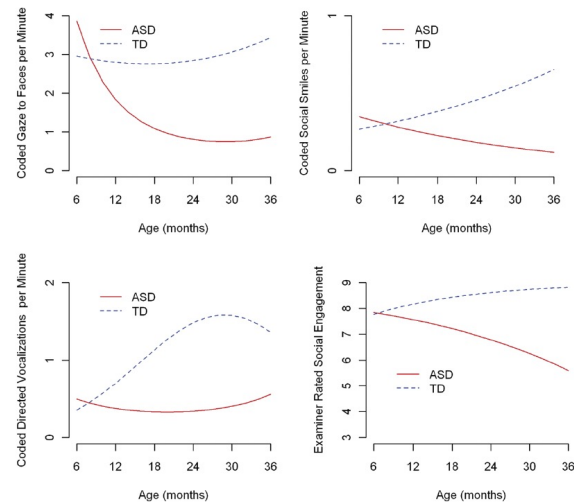
Repetitive behavior

- Repetitive object play



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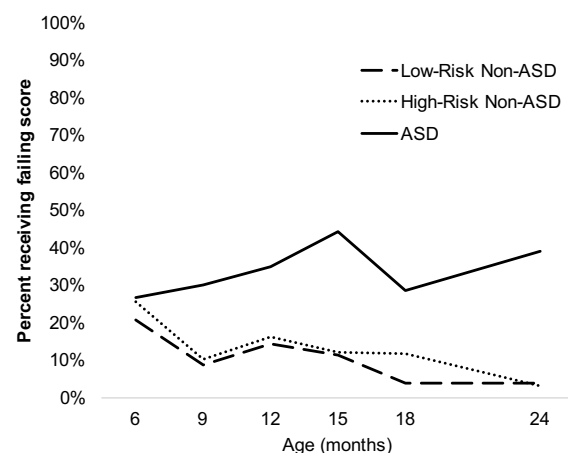
Emergence of social communication behaviors



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Response to name

- Names as social cues for orienting to salient aspects of environment
- Diminished response to name consistently identified by 12 months via retrospective or paper-pencil measures (Palomo et al. 2006; Osterling et al., 1994; Osterling et al., 2002; Werner et al., 2000)
- Little known regarding developmental progressions, direct assessment (vs. parent report)
- Response to name probe from AOSI
 - Name called up to 4x
 - Failure = no response on any trial



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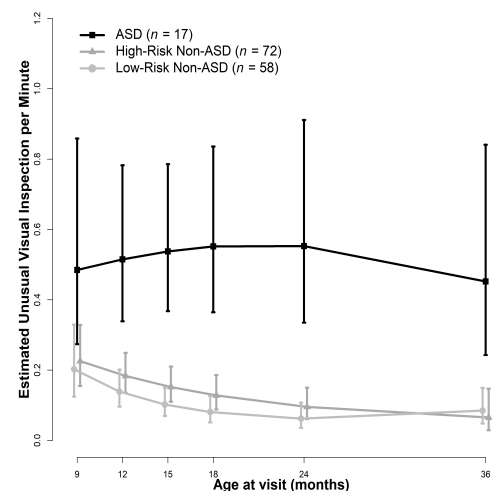
Mechanisms underlying social deficits & repetitive behaviors

- Social motivation hypothesis (Chevallier et al., 2012; Dawson et al., 2005)
- Repetitive behaviors in ASD present by 12 months in infant siblings who develop ASD (Elison et al., 2014; Ozonoff et al., 2008; Wolff et al., 2014)
- Unusual visual inspection of objects particularly striking in one prior study, but limited to single timepoint (Ozonoff et al., 2008)
- Longitudinal course early in life via direct assessment
- Predictive associations between repetitive and social behaviors

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Repetitive behaviors & mechanisms underlying social deficits

- Unusual visual inspection of objects present, stable as early as 9 months of age in infants developing ASD
- 9-mo unusual visual inspection predicts 12-mo social engagement controlling for baseline social engagement *but not vice versa*



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Red flags for ASD in the first years of life

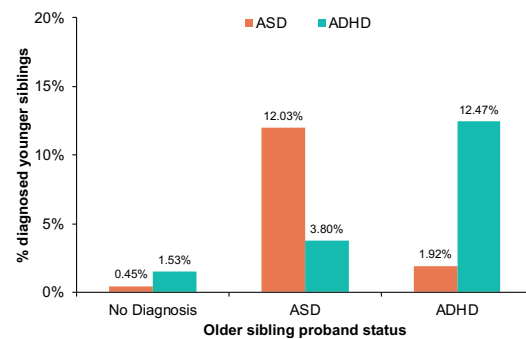
- Lack of appropriate gaze
- Lack of warm, joyful expressions with gaze
- Lack of sharing enjoyment or interests
- Lack of alternating to-and-fro vocalizations with parents
- Lack of response to name
- Delayed onset of babbling past 9 mo
- Decreased or absent use of pre-speech gestures (waving, pointing, showing)
- No single words by 16 mos
- No two-word utterances by 24 mos
- Repetitive movements or posturing of body, arms, hands, or fingers
- Loss of language or social skills at any age

UC Davis MIND HEALTH INSTITUTE | Dawson et al., 2000; Hatch, ... Miller, 2020; Landa et al., 2013; Miller et al., 2017; Osterling & Dawson, 1994; Osterling et al., 2002; Ozonoff et al., 2008; Ozonoff et al., 2011; Werner & Dawson, 2005; Werner et al., 2000; Zwaigenbaum et al., 2005)

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What about the siblings who don't develop ASD?

- Multifinality apparent
 - Greater emotional, behavioral, cognitive dysregulation and pragmatic language difficulties in preschool period (Miller et al., 2015; 2019)
 - Vulnerabilities continue through school-age (Miller et al., 2016 – IACC top research advance)
- Elevated risk for ADHD at school-age follow-up: ~25% of high-risk non-ASD vs. 9.5% of low-risk (unpublished data)
- Shared familial risk (Miller et al., 2019)
- Can these carefully phenotyped, closely tracked samples of infants at risk for ASD be leveraged to address questions related to the emergence of ADHD?



Miller et al., 2019 (JAMA Pediatrics)

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Attention-deficit/hyperactivity disorder (ADHD)

Inattention

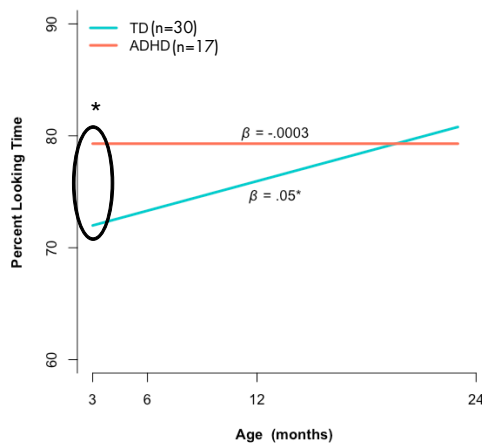
- Careless mistakes
- Difficulty sustaining attention
 - Doesn't listen
- Difficulty with follow through, completing tasks
- Organizational challenges
- Dislikes/avoids activities requiring sustained mental effort
 - Loses things
- Easily distracted
- Forgetful

Hyperactivity-Impulsivity

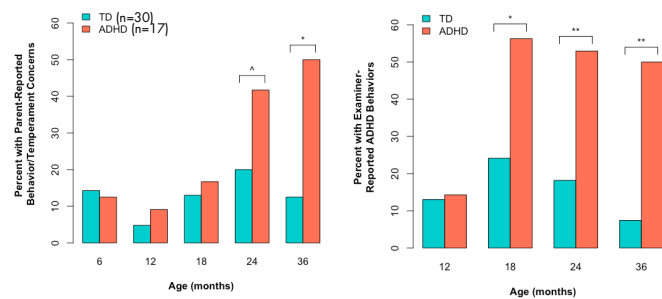
- Fidgeting/squirming
- Difficulty remaining seated
- Running/climbing excessively
- Difficulty playing/engaging in leisure activities quietly
 - "On the go", "driven by a motor"
- Talks excessively
- Blurting out answers
- Difficulty waiting turns
- Interrupts/intrudes

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Early ADHD symptoms?



School-age follow up of infants at risk for ASD with ADHD vs TD outcomes



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Early detection of ADHD

- Diagnosed around age 7
 - More severe cases – approximately age 4
- Careful, thorough preschool diagnoses persist (Lahey et al., 2005; Riddle et al., 2013)
- Prior studies highlight associations between non-specific factors and later ADHD symptoms (Arnett et al., 2013; N. Miller et al., 2019a, 2019b; Sanson et al., 1993; Willoughby et al., 2017)
- Can we identify early indicators of ADHD, like we've done in ASD?

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Examples

Videos removed for patient privacy

Normative attention, activity, impulsivity

Reduced attention, high activity/impulsivity

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Can familial risk for ADHD be detected in the first years of life?

Dimension	Examiner rating: Behavior Rating Inventory for Children (BRIC)	Second-by-second behavioral coding during MSEL FM
Attention	BRIC Attention (1-5 scale)	Inattention (frequency)
Activity level	BRIC Activity (1-5 scale)	Out-of-seat (frequency)
Impulsivity	BRIC Impulsivity (1-5 scale)	Grabbing (frequency)

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Can familial risk for ADHD be detected in the first years of life?

Videos removed for patient privacy

Low-risk

ADHD-risk

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Can familial risk for ADHD be detected in the first years of life?

Table 4. Parameter estimates (SE) for the mixed-effects regression models predicting ADHD behavior.

	Examiner ratings ^a			Behavior codes ^a			Parent concerns ^a
	Attention	Activity	Impulsivity	Inattention	Out-of-Seat	Grab	
Estimated trajectory for Low-Risk group							
Baseline (12 mos)	2.07 (0.16)**	2.40 (0.18)**	1.85 (0.17)**	0.84 (0.14)**	−0.59 (0.27)*	0.95 (0.14)**	−4.23 (0.74)**
Change from 12 to 18 mos	0.68 (0.19)**	0.54 (0.23)*	0.84 (0.23)**	0.31 (0.18) [^]	0.98 (0.32)**	0.04 (0.19)	−0.82 (0.89)
Change from 12 to 24 mos	0.36 (0.20) [^]	0.14 (0.23)	0.99 (0.24)**	−0.04 (0.20)	0.74 (0.33)*	−0.36 (0.21) [^]	1.28 (0.71) [^]
Estimated difference between ADHD-Risk and Low-Risk group							
Baseline (12 mos)	0.49 (0.23)*	0.63 (0.26)*	0.84 (0.24)**	0.05 (0.20)	0.93 (0.35)**	0.42 (0.20)*	1.89 (0.89)*
Change from 12 to 18 mos	−0.22 (0.28)	−0.25 (0.32)	−0.28 (0.33)	0.26 (0.26)	−0.33 (0.42)	0.02 (0.26)	2.29 (0.99)*
Change from 12 to 24 mos	0.29 (0.28)	0.09 (0.33)	−0.26 (0.33)	0.33 (0.29)	−0.37 (0.44)	−0.08 (0.28)	−0.10 (0.84)

Note: * $p < .05$, ** $p < .01$, *** $p < .001$, [^] $p < .10$. SE = standard error; ADHD = Attention-Deficit/Hyperactivity Disorder.

^aFrom mixed-effect linear regression (for examiner ratings), negative binomial (for coded behavior), or logistic (for parent concerns) models with fixed effects for group (ADHD-risk, low-risk), time (12 [baseline], 18, and 24 months), and their interaction and person as a random effect.

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Why ASD and ADHD?

- Co-occur at rates above chance (Rommelse et al., 2011)
- May share causal mechanisms:
 - Shared heritability, familial transmission, genetic underpinnings (Miller et al., 2019; Musser et al., 2014; Rommelse et al., 2010, 2011; Ronald et al., 2008; Stergiakouli et al., 2017; Taylor et al., 2015)
 - Overlapping symptomatology (Johnson et al., 2015; Mikami, Miller, & Lerner, 2019; Ronald et al., 2008 & 2014)
 - Some similar neuroimaging, neurocognitive findings (DiMartino et al., 2013; Geurts et al., 2004)
 - Theories highlighting disrupted attentional mechanisms, cognitive control, and reward processing in both ASD and ADHD (e.g., Barkley, 1997; Demetriou et al., 2019; Keehn et al., 2013; Sonuga-Barke, 2002; Willcutt et al., 2005)

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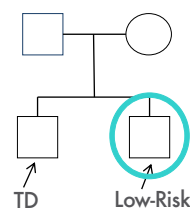
Implications of transdiagnostic approaches

- Identification of general indicators of atypical development
 - Treatments/prevention programs targeting shared impaired processes across diagnoses
- Applications during period in infancy when child's outcome still unclear
- How/when do similarities and differences first emerge in ASD and ADHD?

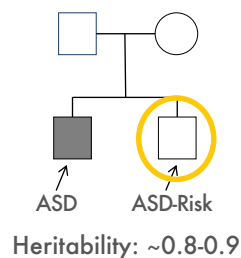
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Study design

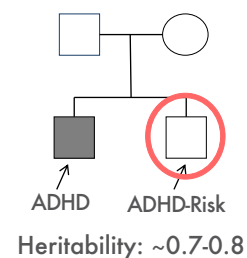
Typically Developing



ASD



ADHD



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ADHD Concerns outcome

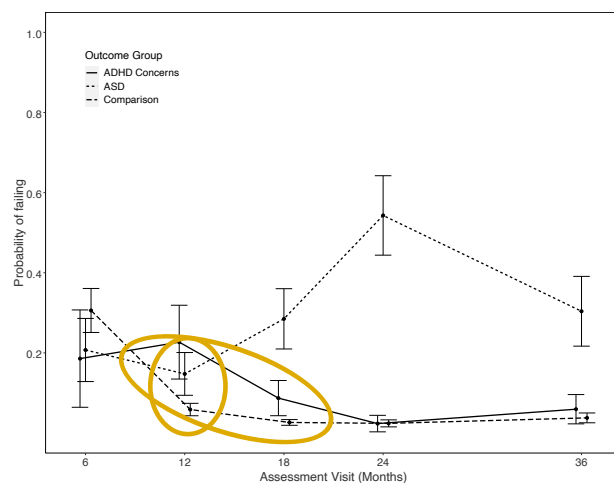
Domain	Definition		
Clinical Judgment	CBE of “ADHD Concerns” based on examiner observation during assessment		
- AND -			
Symptoms (<i>or</i> rule)	≥4 <i>DSM-5</i> ADHD symptoms <u>within</u> one symptom category (inattention <i>or</i> hyperactive-impulsive) across raters	- OR -	≥5 <i>DSM-5</i> ADHD symptoms <u>across</u> symptom categories (inattentive and hyperactive-impulsive combined) across raters
- AND -			
Settings	≥1 symptom endorsed by parent on ADHD-RS Preschool	- OR -	≥1 symptom endorsed by teacher on ADHD-RS Preschool

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Response to name



- Persistent differences between ASD and Comparison groups beginning at 12 months
- Differences between ADHD Concerns and Comparison groups between 12 and 18 months only
- May be general marker for ASD and ADHD risk in infancy but specific indicator of ASD by 24-months



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Latent classification

Classification measures	Examiner rating	Parent report
ADHD symptoms	BRIC	Preschool ADHD-RS
ASD symptoms	ADOS CSS	SCQ

Risk group	"TD" (n = 108)	"ADHD" (n = 39)	"ASD" (n = 19)	CBE outcome	"TD" (n = 108)	"ADHD" (n = 39)	"ASD" (n = 19)
Low-risk	34 (31%)	5 (13%)	0 (0%)	Non-ASD/Non-ADHD Concerns	98 (91%)	16 (41%)	1 (5%)
ADHD-risk	25 (23%)	12 (31%)	1 (5%)	ADHD Concerns	2 (2%)	15 (38%)	2 (11%)
ASD-risk	49 (45%)	22 (56%)	18 (95%)	ASD	2 (2%)	8 (21%)	16 (84%)

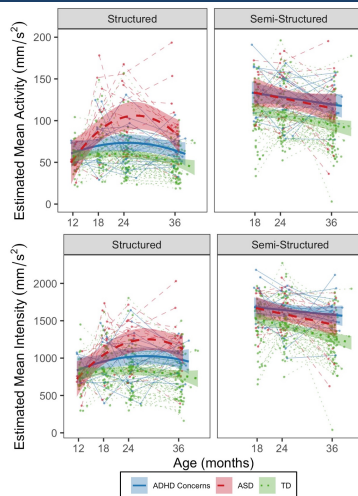
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Domains evaluated

Domain	Measure(s)
General development	MSEL Verbal & Nonverbal
ADHD-relevant behavior	Frequency of coded inattention, out-of-seat, and grabbing behavior during MSEL FM
ASD-relevant behavior	Examiner-rated social engagement (frequency of eye gaze, social smile, overall initiations/responses)

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Objectively-measured activity



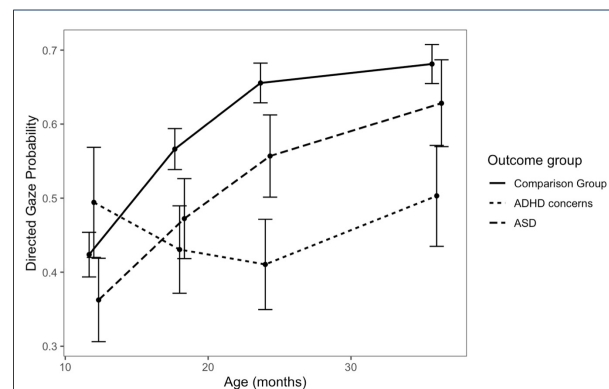
- Does increased motor activity represent a distinct versus shared early predictor of ASD and ADHD Concerns?
- ASD and ADHD Concerns groups had higher activity levels than TD group by 18 months across contexts
- ASD group exhibited higher activity than ADHD Concerns group from 24-36 months *in structured context only*

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Objective measurements of sustained attention



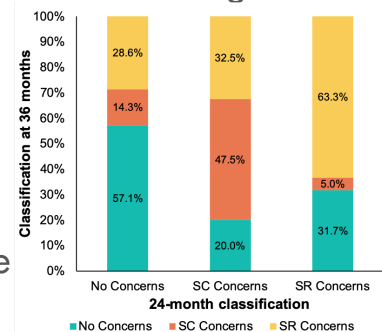
- Attention atypicalities common in both ASD and ADHD
- Eye-tracking task of sustained visual attention
- ADHD Concerns lower % looking time relative to TD by 18 months, with ASD group intermediate
- Detailed analysis of trial-level data ongoing



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“LAAMB” Study (*Learning About Autism/ADHD Markers in Babies*)

- 1 To identify shared and distinct early behavioral and physiological markers of, and mechanisms underlying, self-regulation and social communication problems among infants at risk
- 2 To evaluate continuity of self-regulation and social communication problems across early childhood, and identify infant predictors of stability and change



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Summary and future directions

- Much progress in early detection of ASD with clear implications for science and practice
- Potential for earlier detection of attention, behavior regulation problems/ADHD symptoms than previously possible
- Mixture of overlapping and distinct manifestations of ASD- and ADHD-like profiles may wax and wane, difficult to disentangle early in life
- Focus on objective measurements indexing aspects of attention, hyperactivity, affect and self-regulation may yield new insights
- Development or refinement of measures of ADHD symptoms in the context of both early childhood and ASD

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Acknowledgments

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Collaborators

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