Early Autism:
Advances in Research and Clinical Practice

Child Study Center
Yale School of Medicine

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Yale Child Study Center

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™
Hezekiah Beardsley Connecticut Chapter

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World Autism Awareness Day: April 2nd

Presidential Proclamation:

"Every person deserves the chance to reach for their highest hopes and fulfill their greatest potential.

On World Autism Awareness Day, we reaffirm our dedication to ensuring that belief is a reality for all those who live on the autism spectrum -- including 1 in 68 children.

*And we uphold our obligation to help make sure every man, woman, and child, regardless of ability or background, is **accepted for who they are and able to lead a life free from discrimination and filled with opportunity**."*

*"I encourage all Americans to learn more about autism and what they can do to support individuals on the autism spectrum and their families, and to help **shape a world in which all people, including those with autism, are accepted for who they are**."*

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Autism in young children: Core and comorbid symptoms

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Research strategy

- Identify behavioral symptoms of ASD and predictors of outcome in toddlers
- Investigate mechanisms underlying core social attention and emotional processing deficits in toddlers with ASD

Clinic-referred toddlers 12-36 months

- Identify prodromal features in infants who later develop autism in the first year of life

High-risk siblings 0-12 months

- Identify predictors of comorbid symptoms including attention and anxiety disorders

Clinic-referred and high-risk children 0 to 6 yrs

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Autism Spectrum Disorder

- Complex neurodevelopmental disorder
  - Behaviorally defined
  - Developmental disorder
  - Early onset
- Prevalence in 8 year olds: 1 in 68 cases (14.7 per 1,000)
- Male to Female ratio: 4:1
- Core domains (DSM-5):
  - Social Communication and Social Interaction (3/3)
  - Restricted Repetitive Behaviors, Interests, and Activities (2/4)
- Additional clinical specifiers:
  - Intellectual impairment or language impairment
  - Known medical (e.g., epilepsy), genetic (e.g., Rett, FXS), and environmental factors (e.g., exposure to valproic acid or extreme prematurity)
  - Associated with other neurodevelopmental, mental, and behavioral disorders (e.g., ADHD, anxiety disorder, sleep disturbance)
- DSM-5 removes restrictions on co-occurring conditions such as anxiety and ADHD in ASD

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Symptoms of ASD in toddlers

- Social reciprocity
  - Atypical eye contact
  - Limited engagement in face-to-face interactions
  - Limited drive to share experiences with others (joint attention)
  - Restricted affective range
- Communication
  - Low frequency of communication
  - Limited facial expressions, gestures, and vocalizations
  - Prevalence of instrumental over declarative goals
  - Stereotypical/idiosyncratic use of language (e.g., echolalia)
- Atypical activities
  - Interest in specific visual stimuli
  - Seeking/avoiding specific sensory inputs
  - Interest in details of objects (e.g., wheels, dials)
  - Hand and finger mannerisms

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Etiology

- Genetic factors: Risk for ASD increases with increasing relatedness to an affected child.
  - Swedish sample of over 1.3M births between 1982 – 2006: ASD heritability estimate of 50% in monozygotic and 8.5% in dizygotic twins
- Exposures:
  - Valproic acid exposure – Danish study of all children born between 1996-2006 (over 650,000): increase after correcting for maternal epilepsy (Christiensen et al., JAMA 2013)
  - SSRI exposure, especially during 2nd and 3rd trimester – Quebec Pregnancy/Children Cohort of FT singletons (146,000) (Boukhris et al., JAMA Pediatrics, 2016)
  - Traffic-related pollution - association between traffic-related air pollution during pregnancy and early childhood (small study) (Volk et al., JaMA 2013)
  - Maternal infections, especially requiring hospitalization (Jiang et al., 2016)
- Other non-genetic factors:
  - Advanced maternal and paternal age - population based study from Denmark, Israel, Norway, Sweden, and Australia: advanced maternal (40-49) and younger maternal age (<20) also associated with ASD (Sandin et al., Molecular Psychiatry 2016)

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Populations at increased risk for ASD

- Prevalence of ASD in younger siblings of children with ASD
  - risk estimates between 8.5% to 18.9%
- Prevalence of ADS in premature infants (7.1%)
  - risk decreases as GA increases: 15.0% for 23–24 weeks GA, 6.5% for 25–26 weeks, and 3.4% for 27 weeks (Joseph et al., 2016).
- Prevalence of ASD in genetic syndromes:
  - Angelman Syndrome (40%)
  - Phelan McDermid Syndrome (84%)
  - Cortical dysplasia-focal epilepsy syndrome (70%)
  - Fragile X (25% of males, 6% of females)
  - PTEN mutation
  - Tuberous sclerosis (20%)
  - Congenital Heart Disease (5%)

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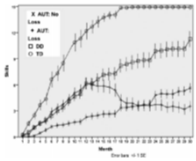
Patterns of symptom onset

- Inherent lack of engagement from birth
- Failure to progress (developmental plateau)
- Regression (skill must be functional for at least 1 to 6 months before they are considered "lost")
  - Reported onset: 12 -24 months
  - Prevalence: 15% – 50% of cases
  - Magnitude: gradual or partial loss the most common
  - Presence of delays during pre-regression period
  - Not unique to ASD: Developmental Delay, Rett Syndrome, Childhood Disintegrative Disorder, epilepsy syndromes, Phelan-McDermid syndrome, and others
- More recent work suggests that within the same child, some skills may fail to progress (e.g., social smiling or social vocalizations), whereas others may tend to regress (e.g., eye contact)



Thurm et al., 2014, *Development and Psychopathology*

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Behavioral signs of ASD in the first 18 months

- Behavioral presentation at 6 months- largely **negative** results:
  - Eye contact and affective responses to mother or examiner
  - Social reciprocity
  - Vocalizations
  - Verbal and nonverbal skills
- Positive findings with regard to social orienting of attention as well as atypical brain growth patterns at 6 months
- Behavioral presentation at 12 months- largely **positive** results:
  - Eye contact, affective responses, requesting, gestures
  - Vocalizations
  - Response to distress of others
- Behavioral presentation at 18 months- at least 40% of siblings with ASD can be **reliably diagnosed** using existing standard assessment practices (Ozonoff et al., BSRC, 2015)

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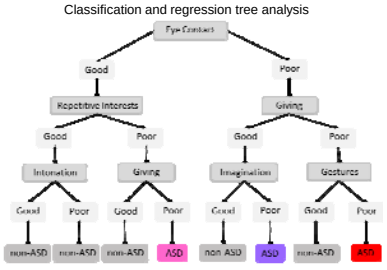
What are the behavioral signatures of autism at 18 months?

Classification and regression tree analysis



(Chawarska, Shic, Macari et al., BSRC (2014). 18-month predictors of later outcomes in younger siblings of children with ASD. Journal of American Academy of Child and Adolescent Psychiatry

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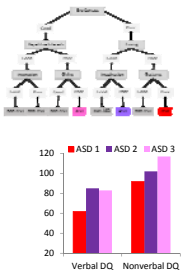
Predictive signatures of autism at 18 months

- Low functioning infants were more likely to show 'prototypical' signs of autism
- In higher functioning infants, the early signs may be less prototypical and may not include impaired eye contact, but include poor communicative behavior and emerging RRBs
- Implications for screening and diagnostic practices:
  - Different combinations of behaviors at the same age level may be diagnostic of ASD



Chawarska, Shic, Macari et al., BSRC 2014. 18-month predictors of later outcomes in younger siblings of children with ASD. Journal of American Academy of Child and Adolescent Psychiatry

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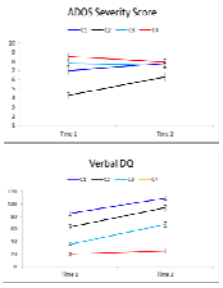
Stability of an early ASD diagnosis

- Early studies on short-term stability *(Lord et al., 2006; Chawarska et al., 2009)*
  - Very good for ASD diagnosis (80-90%) from 2 to 4 years
  - Changes expected within spectrum due to shifts in type and intensity of symptoms
- Recent studies on short-term stability *(Kim et al., 2015)*
  - Toddlers diagnosed between 12 and 24 months, received ~14hrs/week of intervention, followed at 36 months
  - Overall diagnostic stability: 93%
  - High stability in severity of autism symptoms



Kim, Maenner, Koller, & Constantino, 2015, JCPP

Clinical implications for closing the gap between symptom onset and age of diagnosis

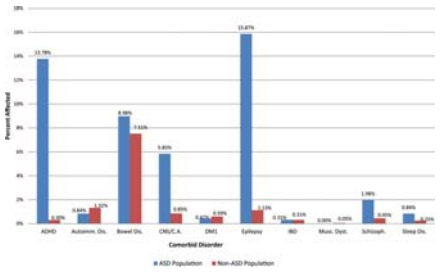
- At 18 months, 40% of toddlers can be reliably and precisely diagnosed with ASD; this proportion increases to 60% by 24 months
  - Screen early and often
  - If ASD is present, implement treatment & provide family support
  - Disseminate diagnostic practices developed in academic centers into broader community
  - Continue work on improving precision of screening and diagnostic practices for identifying ASD in early childhood
- Search continues for reliable markers of social dysfunction in the first year

Comorbid disorders in ASD

Comorbidities

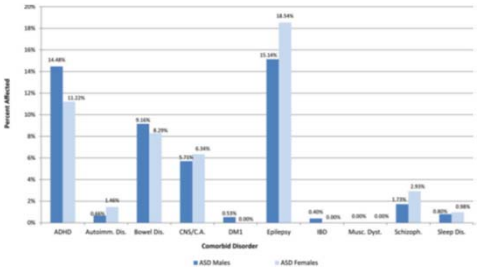
- How phenotypic overlaps between ASD and other disorders emerge:
  - Core and comorbid symptom disorders originate from the common set of causal factors – i.e., symptoms are highly related and all 'autism specific' (highly correlated severity in both disorders)
  - One disorder emerges as a consequence of the other – e.g., autism from anxiety, or attention disorder from autism (limited ability to prioritize stimuli for processing) (no evidence from prospective studies) (not only high correlation but also specific developmental sequence)
  - Initially disorders may be independent, but over time disruption in one network interacts with a disruption in another network, giving rise to complex clinical phenotypes (e.g., affective interacting with social, attention with social) (may not be correlated initially, but over time the relationship between symptoms in both domains may strengthen
- Implications for:
  - Improved precision of diagnostic differentiations
  - Implementation of preventative and therapeutic interventions

Comorbid conditions in ASD: the STRIDE cohort



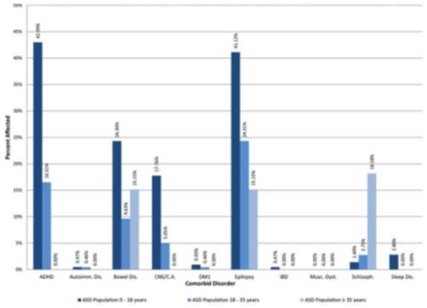
Supekar et al., Autism Research 2016

Comorbid conditions in males and females with ASD: the STRIDE cohort



Supekar et al., Autism Research 2016

Comorbid conditions in ASD – age effects: the STRIDE cohort



Supekar et al., Autism Research 2016

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ADHD in children with ASD

- Comorbidity: 28-38% (higher in clinic-referred samples – over 50% of children with ASD under the age of 7 years show moderate to severe ADHD-related symptoms
- Children with co-occurring ASD and ADHD are at greater risk for poor cognitive performance, attention, and memory as well as poor social adaptation, greater behavioral symptoms, and poorer daily living skills than children with ASD w/o ADHD symptomatology
- Sex differences: in general population, males are 2-3 times more susceptible to ADHD than females
- Co-occurrence of ADHD symptoms in ASD
  - Inattentiveness is more often endorsed than hyperactivity – a more specific link with ASD
  - Severity of inattention increases with age
  - ADHD symptoms are more prevalent/severe in children with more severe ASD and lower IQ
  - Links between ASD and hyperactivity-impulsivity is weak
- Co-occurrence of ASD symptoms in ADHD
  - Less commonly studied
  - Evidence for lower social competence and social adaptation but not for but not low social initiative – no evidence for autism-like social difficulties in ADHD

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Affective disorders in children with ASD

- Prevalence of Anxiety disorders in ASD: 41-42%
  - Specific phobias (30%)
  - Generalized anxiety disorder (15-22%)
  - Social anxiety disorder (17%)
  - Separation anxiety disorder (7-9%)
- Anxiety symptoms are already more prevalent in preschoolers with ASD than in preschoolers with other disorders in children across the range of IQ
- Presence of anxiety may limit learning opportunities and affect perception, attention, and cognition beyond difficulties related to autism
- Severity of anxiety symptoms in childhood predict adaptive functioning in young adulthood (Gotham et al. 2015; Sukhodolsky et al., 2008)

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Early signs and developmental antecedents of comorbid symptoms in young children with ASD

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Temperament

- Neurobiologically-based individual differences in reactivity and regulation in the domains of emotion, motor activity, attention
  - Surgency: expression of positive affect, reward seeking, and high activity level
  - Negative Affectivity: anger/fear/distress in response to novelty and uncertainty
  - Effortful Control: self-regulatory capacity to promote adaptive responses
- Temperamental patterns are already apparent in infancy
- Largely stable over time, though to some extend, subject to the influences of maturation and experience
- Temperamental characteristics in toddlerhood are linked with later:
  - Surgency: risk for low social competence, poor peer relationships, and school adjustment
  - Negative Affectivity: risk for anxiety & depression
  - Effortful Control: risk for externalizing behaviors, aggression, attentional difficulties, and depression

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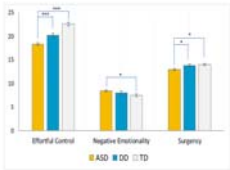
Parent-report based temperamental markers in toddlers with ASD

- Sample: 326 16- to 36-month-old toddlers with ASD, DD, and TD, 80% of sample seen at 4 years
- ASD-specific atypical EC and Surgency; shared with DD atypical NA
- Temperamental difficulties were independent of severity of autism symptoms (all r < .-12)
- Highly stable over time
  - EC: r = .56
  - NA: r = .61
  - Surgency: r = .54
- Temperamental difficulties at 2 years contributed independently to severity of autism symptoms at 4
- Already in toddlerhood, children with ASD exhibit temperamental vulnerabilities that may make them susceptible to affective, behavioral, and attentional difficulties in preschool



Macari et al. JCPP 2017

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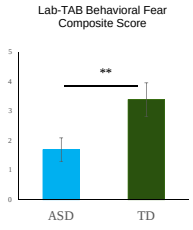
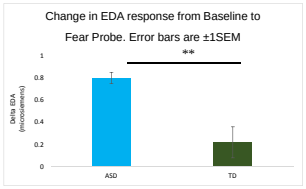
In-vivo measures of emotion processing and regulation in toddlers with ASD

- Measurement of affective expressions *and* physiological arousal in response to emotionally challenging events

- Video

Divergent behavioral and physiological responses to threat in toddlers with ASD





Clinical Implications

- Early comorbid psychopathologies mediate the severity of autism symptoms and the level of social adjustment and school performance in children with ASD independent of age, sex and full scale IQ
- Prevalence of various comorbidities changes with age, hence there is a need for continuous monitoring for emergent problems - e.g., schizophrenia becomes highly prevalent in individuals 35 yr old and above, but ADHD is most prevalent in school-age and adolescent individuals, declining later on
- Prevalence of comorbid disorders depends on sex – e.g., females are more susceptible to seizures, while males are more susceptible to ADHD and schizophrenia

Clinical Implications

- Prognostic signs of emerging comorbid conditions can be detected in early childhood in ASD
  - Existing screening instruments (Infant Behavioral Questionnaire, Early Childhood Behavioral Questionnaire, and Childhood Behavioral Questionnaire) are useful for examining temperament profiles from infancy into preschool age
    - Need to improve precision of the screening instruments for comorbid conditions in the early stages of ASD
    - Need to determine the precise role temperamental vulnerabilities play in shaping developmental trajectories in ASD – determine how they mediate or moderate outcomes
- Clinicians should avoid diagnostic overshadowing and maintain clear distinctions between ASD and other psychopathologies, screening for them and addressing each in a clinically relevant manner as children with ASD may benefit from treatment specific to these conditions
- Adequate detection and treatment is likely to improve long term outcomes in children with ASD

Thank you!

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