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Emerging cognitive profiles in high-risk infants with and without autism spectrum disorder

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ABSTRACT

This paper examined early developmental trajectories in a large, longitudinal sample at high-risk for ASD ('HR') and low-risk ('LR') controls, and the association of trajectories with 3-year diagnosis. Developmental assessments were conducted at 6, 12, 24 months, and 3 years, with blinded "clinical best-estimate" expert diagnosis at age 3. HR infants were enrolled based only on familial risk. LR infants, from community sources, had no first- or second-degree ASD relatives. All infants were born at 36–42 weeks, weighing ≥2500 g, with no identifiable neurological, genetic, or severe sensory/motor disorders. Analytic phase I: semi-parametric group-based modeling to identify distinct developmental trajectories ($n = 680$; 487 HR; 193 LR); phase II: Trajectory membership in relation to 3-year diagnosis ($n = 424$; 310 HR; 114 LR). Three distinct trajectories emerged (1) inclining; (2) stable-average; (3) declining; trajectory membership predicted diagnosis ($\chi^2 = 99.40$; $p < .001$). Most ASD cases were in stable-average (50.6%) or declining trajectories (33.8%); most non-ASD-HR infants were in inclining (51.9%) or stable-average (40.3%) trajectories. The majority of LR controls were in the inclining trajectory (78.9%). Within the declining trajectory, over half had ASD (57.8%), but 40% were non-ASD-HR infants. Declining/plateauing raw scores were associated with, but not exclusive to, ASD. Findings underscore the importance of monitoring the emergence of ASD symptoms and overall development in high-risk children. Evidence of developmental slowing or decline may be associated not only with ASD, but with other suboptimal outcomes, warranting careful clinical follow-up.

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1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social-communication deficits and repetitive/restricted behavior (APA, 2013). Recent prevalence estimates of 1/68 (CDC, 2014), with recurrence of close to 20% in younger siblings (Ozonoff et al., 2011), underscore the need for careful monitoring of this high-risk population. Considerable heterogeneity exists in ASD, with variability not only in ASD symptom presentation, but also in intellectual development. Intellectual functioning in ASD varies along a continuum from severe impairment to well above average and can significantly impact daily functioning, school placement, and prognosis (Harris & Handleman, 2000; Howlin, Goode, Hutton, & Rutter, 2000). Intellectual deficits are reported to occur in 30–50% of cases (Chakrabarti & Fombonne, 2005; CDC, 2014), but characterization of intellectual disability in ASD and cross-study comparisons are complicated by sample heterogeneity and different conceptualizations/measures of "intelligence." Moreover, despite the assumption that intelligence/IQ is stable, strong evidence of variability over time exists, even into adolescence, in typical development (Ramsden et al., 2011). The issue of IQ stability may be particularly relevant to special populations, such as those with low intellectual functioning (Whitaker & Taylor, 2008), dyslexia (Ingesson, 2006), low birth weight (Mortensen, Andressen, Krusse, & Sanders, 2003), or ASD, in which variability is a particular consideration under age three (Lord & Schopler, 1989a, 1989b). While early improvement in IQ (i.e., from 2 to 4 years) predicts better outcomes in ASD (Sutera et al., 2007; Kelley, Naigles, & Fein, 2010), questions persist as to whether differential trajectories of intellectual functioning in the first years of life in infants at high risk for ASD are associated with different outcomes, or whether declining intellectual performance mirrors other forms of regression, reported in 15–50% of the ASD population (Barger, Campbell, & McDonough, 2013; Ekinci, Arman, Melek, Bez, & Berkem, 2012; Stefanatos, 2008; Yirmiya & Charman, 2010).

Longitudinal studies of younger siblings of children with ASD ('high-risk' infants; 'HR') reveal reduced *rates* of skill acquisition on the Mullen Scales of Early Learning (MSEL; Mullen, 1995) after age 6–12 months in some infants later diagnosed with ASD (Bryson et al., 2007; Landa, Holman, & Garrett-Mayer, 2007; Zwaigenbaum et al., 2005). However, existing findings are limited by small samples, thus precluding the examination of heterogeneity. Considerable variability is anticipated in this high-risk group, given the range in intellectual functioning at the time of diagnosis even in young children, and based on our earlier case series report in which declining trajectories and severe cognitive impairment at 2–3 years were associated with an ASD diagnosis and earlier symptom onset (Bryson et al., 2007). It remains unclear whether atypical trajectories are specific to ASD, as individual differences have been obscured by group designs used to date (e.g., comparing trajectories based on outcomes, rather than examining the variation in trajectories across the high-risk group as a whole).

A recent latent class analysis of intellectual development examined domain scores on the MSEL (Mullen, 1995) in 204 HR infants aged 6–36 months. A three- and a four-class model emerged, each with strong classification quality (.92 and .89 entropy, respectively), the latter favored by the authors (Landa, Gross, Stuart, & Bauman, 2012). Infants with ASD outcomes were over-represented in a 'developmental slowing' class that was highly specific to ASD (>90% of children in this class had ASD). However, over half of those with ASD fell into one of three other classes (motor/receptive language delays, or average/accelerating to above-average language skills). A related study (Landa, Gross, Stuart, & Faherty, 2013) that included the original sample plus a small group of low-risk (LR) controls ($n = 31$) revealed skill loss in both language domains of the MSEL in 24% of the ASD participants (other domains were not examined). Four additional "non-ASD" cases had skill loss, but it is not clear whether these were from the HR or LR group because non-ASD groups were collapsed.

These studies provide initial evidence of distinct developmental trajectories in HR infants that are associated with ASD. The current paper extends these findings and is distinguished by the use of overall cognitive scores to determine trajectories, the largest sample to date in this type of investigation, and the preservation of the distinction between non-ASD HR and LR participants, supported by evidence that non-ASD HR siblings represent a unique group (Ben-Yizhak et al., 2011; Bishop, Mayberry, Wong, Maley, & Hallmayer, 2006; Georgiades et al., 2013; Messinger et al., 2013; see Drumm & Brian, 2013 for a recent review).

2. Methods

2.1. Participants

Participants were drawn from a longitudinal, prospective study of (HR) younger siblings of children with ASD (Zwaigenbaum et al., 2005), recruited through four major Canadian ASD diagnostic centers and community physicians. HR infants were enrolled at 6 or 12 months of age based only on familial risk. LR infants, recruited through community sources, had no first- or second-degree relatives with ASD. All infants were born at 36–42 weeks gestation, weighing ≥2500 g; none had identifiable neurological or genetic disorders, or severe sensory/motor impairments. All participants with relevant data from the larger study were included. Data were analyzed in two phases to maximize the use of available data; Phase I: $n = 680$; 487 HR (267 males); 193 LR (105 males); and Phase II: $n = 424$ infants (310 HR; 114 LR) followed to at least 3 years of age through our ongoing prospective study (Zwaigenbaum et al., 2005).

2.2. Procedures

Participants were assessed at 6, 12, 24 months and 3 years of age using the Mullen Scales of Early Learning (MSEL; Mullen, 1995). Data were not available at all time points for all participants (see Table 1). At age 3, an independent, "clinical