Assessment of Autism Symptoms During the Neonatal Period: Is There Early Evidence of Autism Risk?

Roberta Pineda, Kelsey Melchior, Sarah Oberle, Terrie Inder, Cynthia Rogers

MeSH TERMS
- autistic disorder
- early diagnosis
- eye movements
- infant, premature
- interpersonal relations
- nystagmus, physiologic
- social skills

OBJECTIVE. To define neonatal social characteristics related to autism risk.

METHOD. Sixty-two preterm infants underwent neonatal neurobehavioral testing. At age 2 yr, participants were assessed with the Modified Checklist for Autism in Toddlers and Bayley Scales of Infant and Toddler Development, 3rd edition.

RESULTS. Positive autism screening was associated with absence of gaze aversion, $\chi = 5.90$, $p = .01$, odds ratio = 5.05, and absence of endpoint nystagmus, $\chi = 4.78$, $p = .02$, odds ratio = 8.47. Demonstrating gaze aversion was related to better language outcomes, $t(55) = -3.07$, $p \leq .003$. Displaying endpoint nystagmus was related to better language outcomes, $t(61) = -3.06$, $p = .003$, cognitive outcomes, $t(63) = -5.04$, $p < .001$, and motor outcomes, $t(62) = -2.82$, $p = .006$.

CONCLUSION. Atypical social interactions were not observed among infants who later screened positive for autism. Instead, the presence of gaze aversion and endpoint nystagmus was related to better developmental outcomes. Understanding early behaviors associated with autism may enable early identification and lead to timely therapy activation to improve function.

Pineda, R., Melchior, K., Oberle, S., Inder, T., & Rogers, C. (2015). Assessment of autism symptoms during the neonatal period: Is there early evidence of autism risk? *American Journal of Occupational Therapy, 69,* 6904220010. http://dx.doi.org/10.5014/ajot.2015.015925

Roberta Pineda, PhD, OTR/L, is Assistant Professor, Program in Occupational Therapy, Department of Pediatrics, School of Medicine, Washington University, St. Louis, MO; pineda_r@kids.wustl.edu

Kelsey Melchior, MSOT, is Occupational Therapy Student, Program in Occupational Therapy, School of Medicine, Washington University, St. Louis, MO.

Sarah Oberle, OTD, OTR/L, is Occupational Therapist, Program in Occupational Therapy, School of Medicine, Washington University, St. Louis, MO.

Terrie Inder, MD, is Mary Ellen Avery Professor in Pediatrics in the Field of Newborn Medicine, Harvard Medical School, Boston, MA, and Professor in Pediatrics, Department of Pediatric Newborn Medicine, Brigham and Women's Hospital, Boston, MA.

Cynthia Rogers, MD, is Assistant Professor, Departments of Psychiatry and Pediatrics, School of Medicine, Washington University, St. Louis, MO.

Autism spectrum disorder (ASD) is characterized by impairments in social interaction and communication along with repetitive, restricted, and stereotyped behaviors, interests, and activities (American Psychiatric Association, 2013). The prevalence of ASD has been on the rise in recent years (Blumberg et al., 2013; Johnson et al., 2010), with the Centers for Disease Control and Prevention (2013) estimating that 1 in 68 children are diagnosed with ASD. Although the etiology of ASD can be genetic, certain groups of children, including preterm infants, have a higher risk of ASD (Arpino et al., 2010).

Preterm infants demonstrate more ASD characteristics in infancy and early childhood than do infants born full term (Movsas & Paneth, 2012). Symptoms include difficulties with social awareness, cognition, communication, and motivation (Johnson et al., 2010; Movsas & Paneth, 2012). Mothers of preterm infants notice these symptoms 2–4 mo earlier than mothers of full-term infants, and ASD symptoms are more severe among preterm infants (Movsas & Paneth, 2012). Preterm infants also have been shown to fail the Modified Checklist for Autism in Toddlers (M–CHAT; Robins, Fein, Barton, & Green, 2001) at a rate 7%–27% higher than that of their full-term peers (Kuban et al., 2009; Moore, Johnson, Hennessy, & Marlow, 2012; Yamada et al., 2011), making these infants a good population to study in order to better understand ASD.

Early identification of ASD can lead to timely initiation of targeted therapies, which can optimize function (Bryson, Rogers, & Fombonne, 2003; Eikeseth, Klintwall, Jahr, & Karlsson, 2012; Peters-Scheffer, Didden, Korzilius, & Sturmey,

2011; Reichow, 2012). Although clinicians can now diagnose ASD earlier than in previous years, many children remain undiagnosed until age 6 yr or older (Shattuck et al., 2009). Differences in screening and diagnostic practices in various settings can affect timing of ASD identification (Shattuck et al., 2009), and later diagnosis results in missed opportunities for intervention. Although early identification is important, few studies have investigated behaviors during infancy that may signal ASD.

The emerging research on early identification of ASD has focused on behavioral and motor responses present during the 1st year of life and how they relate to later diagnosis of ASD. Children who receive a later diagnosis of ASD may demonstrate early deficits in social behavior, specifically in joint attention, eye contact, orienting to name, facial expressions, social smile, attention, and tolerance of social touch (Adrien et al., 1993; Baranek, 1999; Barbaro & Dissanayake, 2013; Bhat, Landa, & Galloway, 2011; Chawarska, Macari, & Shic, 2013; Clifford et al., 2007; Clifford & Dissanayake, 2008; Cornew, Dobkins, Akshoomoff, McCleery, & Carver, 2012; Elsabbagh et al., 2012, 2014; Hutman et al., 2010; Ibanez, Messinger, Newell, Lambert, & Sheskin, 2008; Iverson & Wozniak, 2007; Karmel et al., 2010; Mitchell et al., 2006; Nadig et al., 2007; Osterling, Dawson, & Munson, 2002; Ozonoff et al., 2010; Phagava et al., 2008; Rozga et al., 2011; Wan et al., 2013; Werner, Dawson, Osterling, & Dinno, 2000; Yirmiya et al., 2006; Zwaigenbaum et al., 2005). Motor deficits, including hypotonia, poor quality of movement, and head lag, also have been reported as early signs of ASD (Ferrari, Cioni, & Prechtl, 1990; Flanagan, Landa, Bhat, & Bauman, 2012; Karmel et al., 2010; Phagava et al., 2008).

Despite the emerging evidence of ASD markers in the 1st year of life, only one study has investigated ASD markers as early as the neonatal period (Karmel et al., 2010). In that study, no differences were observed in the neonatal period between children who were and were not later diagnosed with ASD. At age 1 mo, however, arm tone deficits and asymmetric visual tracking were observed in infants later diagnosed with ASD. Most studies of markers of ASD in infancy were conducted through retrospective analysis of home videos, which decreases the ability to differentiate infants who have a heightened risk of ASD. One recent study found that, contrary to the later presentation of the disorder, infants diagnosed with ASD demonstrated a clear orienting response to faces at 7 mo old (Elsabbagh et al., 2013). Research has also shown that the typical decline in social interaction occurs between age 2 mo and 6 mo (Jones & Klin, 2013).

This recent literature suggests that the recognized core features of ASD may not be present in early infancy. However, with only one study investigating neonatal markers of ASD, this body of knowledge is not complete. Nuanced social behavior that provides clues to later risk of autism may be present during the neonatal period. Therefore, this study aimed to explore early social interaction behavior of preterm infants at term-equivalent age and associations with ASD risk at age 2 yr. We hypothesized that infants who screened positive for ASD at 2 yr of age would demonstrate alterations in early social interaction behavior at term-equivalent age, such as gaze aversion, and would demonstrate better orientation to objects than to people at term-equivalent age. Because many children with ASD have comorbid developmental problems (Levy et al., 2010), we also explored a secondary hypothesis that early social interaction would also be related to developmental outcome.

Method

This study used a sample of 62 infants from an overarching, longitudinal study aimed at understanding brain development in very preterm infants. The Human Research Protection Office approved this study, and parents signed informed consent. Participants were admitted to the St. Louis Children's Hospital neonatal intensive care unit (NICU) and enrolled by their 3rd day of life. Inclusion criteria, based on the criteria of the overarching study, were birth at ≤30 wk estimated gestational age and no known congenital anomaly. Social interaction behavior was assessed at term-equivalent age (37–40 wk postmenstrual age) in the NICU. Participants returned for developmental testing at 2 yr of age, which included assessing ASD risk.

Early Social Interaction

Early social interaction was captured from neurobehavioral testing using the NICU Network Neurobehavioral Scale (NNNS; Lester & Tronick, 2005). Neurobehavioral testing was conducted by a single, trained occupational therapist certified in the NNNS. The NNNS is a 115-item, comprehensive neurobehavioral assessment conducted over 20–25 min. Use of standardized assessment procedures and reliability of scoring each item were ensured through a certification process for the NNNS by a single, certified examiner. The NNNS has been shown to have good predictive validity (Lester & Tronick, 2005) and has been used extensively in other research investigating early infant outcomes. The NNNS requires the infant be in a specific state to enable appropriate assessment of specific domains of function. For example, visual and auditory items are not assessed in an infant who is not able to achieve an awake state.

Standardized scoring of the NNNS was used to document responses to handling, abnormal eye signs, and visual responses. Social interaction behaviors included cuddling; irritability; consolability; crying; and the presence of abnormal visual signs such as gaze aversion, visual locking, tight blinking, roving eye movements, endpoint nystagmus, sustained nystagmus, obligatory following, and hyperalertness (Table 1). Additionally, orientation items were captured and included visual tracking of a human face and auditory orienting to a human voice (including interactive prompting and calling the infant's name), visual tracking of a red ball, and auditory orienting to the noise of a rattle (see Table 1).

For the purposes of this study, standard scoring was not used for orientation items, because they do not reflect quality of performance. Instead, orientation items were recoded on an ordinal scale to reflect scores that were poor, fair, good, or excellent to better define successful performance (see Table 1 for descriptions). Whether the infant responded better to human interaction, compared with interaction with objects and toys, was also captured, according to the best response to the orientation items.

These social factors from the neurobehavioral assessments were used to define social interaction behaviors in this study. Note that for the purposes of this study, the individual items of the NNNS were used to isolate specific social behaviors. However, the tool was designed to weight each individual item with final reporting of 13 summary scores rather than for the reporting of specific behaviors as was done for the purposes of this study.

Medical Complications and Interventions

Medical information was extracted from the electronic medical record. Descriptive factors (Table 2) included gender; race (White or non-White); estimated gestational age at birth; birth weight (in grams); days on the ventilator; initial medical severity; length of stay (in days); presence of moderate to severe brain injury; mother's age; and whether the mother had a college education, was married, was on public insurance (Medicaid), or used illicit drugs during pregnancy (from toxicology reports). The Clinical Risk Index for Babies (CRIB; Tarnow-Mordi & Parry, 1993) score was used as a marker for initial medical severity. Moderate to severe brain injury

Table 1. Descriptions of Social Neurobehavioral Factors

Factor	Description
Social interaction	
Cuddling	Infant resists being held and/or failed to participate with whole body while cuddling in arms.
Irritability	Infant cries or fusses for most (>50%) of the interaction.
Consolability	Infant is able to be soothed with human interaction, such as being talked to or held, moving from an active awake or crying state to a quiet alert, drowsy, or sleep state.
Crying	Infant cries for at least 15 s during the exam.
Gaze aversion	Infant actively moves eyes or head away from visual stimulus to avoid the stimulus.
Visual locking	Infant demonstrates a stare at a stimulus that was difficult to break.
Tight blinking	Infant closes eyes tightly to avoid the stimulus when stimulus is presented
Roving eye movements	Infant demonstrates rapid eye movements that were not oriented to a stimulus when presented.
Endpoint nystagmus	Infant demonstrates rapid, repetitive horizontal eye movements when orienting to a stimulus at the end of the visual range.
Sustained nystagmus	Infant demonstrates rapid, repetitive horizontal eye movements during any attempts to visually orient.
Obligatory following	Infant responds to a visual stimulus with an exaggerated response and rapid, predictable eye and head movements toward the stimulus.
Hyperalertness	Infant responds with overly intense alertness, often seen with bulging eyes and a panicked expression.
Visual and auditory orientation	
Auditory animate orientation (human voice)	*Poor* = No auditory orientation
	Fair = Brightening with shifting of eyes
Auditory inanimate orientation (rattle)	*Good* = Head turning to side of stimulus and localizing <2 out of 4 times
	Excellent = Head turning and finding the stimulus ≥2 out of 4 times
Visual animate orientation (human face)	*Poor* = No visual tracking
	Fair = Focusing on object with brief following <30°
Visual inanimate orientation (red ball)	*Good* = Tracking ≥30° to one side
	Excellent = Full tracking to both sides with smooth eye movements
Preference for animate objects	The infant scores higher on animate visual and auditory orientation than on inanimate visual and auditory orientation.

Table 2. Sample Characteristics ($N = 62$)

Characteristic	*n* (%), *M* (*SD*), or Median (IQ Range)
Child	
Female	30 (48)
White	38 (61)
Gestational age, wk	26.7 (1.8)
Birth weight, g	961.9 (272.3)
Days on ventilator	3.0 (1.0–24.0)
CRIB score	3.5 (3.2)
Length of stay, days	91.7 (28.5)
Moderate to severe brain injury	12 (19)
Mother	
Age, yr	29.5 (7.4)
Has college education	28 (45)
Single	34 (55)
Public insurance	34 (55)
Illicit drug use during pregnancy	2 (3)
Child developmental outcomes	
Bayley–III Cognitive	86.2 (10.0)
Bayley–III Motor	83.7 (11.7)
Bayley–III Language	89.3 (11.7)
Positive ASD screen on M–CHAT	13 (21)

Note. ASD = autism spectrum disorder; Bayley–III = Bayley Scales of Infant and Toddler Assessment, 3rd ed.; CRIB = Clinical Risk Index for Babies; IQ = interquartile; *M* = mean; M–CHAT = Modified Checklist for Autism in Toddlers; *SD* = standard deviation.

was defined by routine cranial ultrasound and MRI at term-equivalent age. Moderate to severe brain injury was defined as Grade III or IV intraventricular hemorrhage, cystic periventricular leukomalacia, or cerebellar hemorrhage.

Autism Risk

ASD risk was determined at age 2 yr using the M–CHAT. The M–CHAT is a 23-item ASD screening tool for children ages 16–30 mo. The internal reliability of the M–CHAT is adequate (Cronbach's $\alpha = .85$), and a discriminant function analysis of the six critical items found that 99% of the time they correctly identified children as having ASD (Robins & Dumont-Mathieu, 2006). Sensitivity has been found to be between .70 (Snow & Lecavalier, 2008) and .97 (Robins et al., 2001), with specificity between .38 (Snow & Lecavalier, 2008) and .99 (Robins et al., 2001). A positive or negative screen for ASD on the M–CHAT was used as an outcome variable in the current study to define ASD risk. The M–CHAT is a screening tool, and a positive screen does not indicate a diagnosis of autism; it signals the need for formal diagnostic testing (Robins & Dumont-Mathieu, 2006). Although diagnostic testing is underway in the participants who screened positive in the current cohort, the results are not yet available for reporting.

Developmental Outcome

The 2-yr developmental outcome was assessed between ages 24 and 36 mo, using the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley–III; Bayley, 2006), and was conducted by a trained psychometrician who was supervised by a neuropsychologist. Composite scores for the Language, Motor, and Cognitive subscales at 2 yr corrected age were used as secondary outcome measures.

Statistical Analysis

Categorical variables related to early social interaction (cuddling, irritability, consolability, crying, gaze aversion, visual locking, tight blinking, roving eye movements, endpoint and sustained nystagmus, obligatory following, hyperalertness, and preference for human interaction rather than interaction with toys or objects) were investigated for associations with ASD risk on the M–CHAT using χ^2 analyses. Continuous variables (visual and auditory orientation) were investigated for associations with ASD risk using logistic regression. Relationships between social interaction factors and developmental outcome (Language, Cognitive, and Motor outcome on the Bayley–III) were investigated using independent samples *t* tests and linear regression models. All analyses were conducted using $\alpha = .05$. Analyses were rerun, controlling for CRIB and brain injury.

Results

All infants from the overarching study who had neurobehavioral testing at term-equivalent age and developmental follow-up testing at age 2 yr were included in this investigation ($N = 62$). Table 2 lists characteristics of the infants in the study sample, which were representative of the study site's NICU population (Pineda et al., 2014).

Table 3 lists atypical social interaction traits for the entire sample, for those who screened positive and negative for ASD, and for those with and without developmental delay at age 2 yr. The number of infants tested for each trait was less than the total sample of 62, because not all infants met the requirements for testing each trait. For example, for visual and auditory orientation traits, not all infants achieved an awake state during testing, a requirement for appropriate assessment of these traits. Of the 62 participants, 13 (21%) had a positive autism screen, and 28 (45%) had developmental delay. As a result of reports that the Bayley–III underestimates developmental delay (Anderson, De Luca, Hutchinson, Roberts, & Doyle, 2010), we chose a conservative cutoff score; *developmental delay* was defined as having any of the three composite

Table 3. Atypical Traits of Infants in the Sample

Trait	Total for Each Trait	ASD Screen, *M* ± *SD* or *n* (%)		p^b	Developmental Delay,[a] *M* ± *SD* or *n* (%)		p^b
		Positive (*n* = 13, 21%)	Negative (*n* = 49, 79%)		Yes (*n* = 28, 45%)	No (*n* = 34, 55%)	
Social interaction[c]							
Poor cuddle (*N* = 56)	28 (50)	4 (14)	24 (86)	.19	13 (46)	15 (54)	.79
Irritability (*N* = 57)	27 (47)	5 (19)	22 (81)	.66	9 (33)	18 (67)	.13
Poor consolability (*N* = 33)	9 (27)	2 (22)	7 (78)	.93	3 (33)	6 (67)	.39
Cry	56 (97)	12 (21)	44 (79)	.46	24 (43)	32 (57)	.84
Gaze aversion	41 (71)	5 (12)	36 (88)	.01	14 (34)	27 (66)	.03
Visual locking	25 (43)	4 (16)	21 (84)	.44	10 (40)	15 (60)	.68
Tight blinking	2 (3)	0 (0)	2 (100)	.46	0 (0)	2 (100)	.21
Roving eye movements	46 (79)	8 (17)	38 (83)	.23	18 (39)	28 (61)	.23
Endpoint nystagmus	21 (36)	1 (5)	20 (95)	.02	5 (24)	16 (76)	.03
Sustained nystagmus	7 (12)	1 (14)	6 (86)	.66	3 (43)	4 (57)	.99
Obligatory following	16 (28)	2 (13)	14 (87)	.34	5(31)	11 (69)	.26
Hyperalertness	12 (21)	4 (33)	8 (67)	.23	4 (33)	8 (67)	.44
Visual and auditory[c]							
Auditory animate orientation[d] (*N* = 49)	2.1 ± 1.0	2.3 ± 1.0	2.0 ± 1.0	.61	2.0 ± 1.0	2.1 ± 1.0	.67
Visual animate orientation[e] (*N* = 50)	1.9 ± 0.9	1.4 ± 0.9	2.0 ± 0.9	.14	1.6 ± 0.8	2.0 ± 1.0	.18
Auditory inanimate orientation[d] (*N* = 50)	2.0 ± 1.0	2.2 ± 1.1	2.0 ± 1.0	.55	2.1 ± 1.1	2.0 ± 1.0	.66
Visual inanimate orientation[e] (*N* = 51)	1.6 ± 0.9	1.5 ± 1.0	1.7 ± 0.9	.61	1.5 ± 0.9	1.7 ± 0.9	.53
Visual preference for object over human face (*N* = 50)	40 (80)	6 (15)	34 (85)	.27	16 (40)	24 (60)	.56
Auditory preference for sound over human voice (*N* = 48)	24 (50)	3 (13)	21 (87)	.44	8 (33)	16 (67)	.55

Note. *M* = mean; *SD* = standard deviation.
[a] *Developmental delay* is defined as a score of <85 on any of the three composite scores (Language, Cognitive, or Motor) on the Bayley Scales of Infant and Toddler Development, 3rd ed. [b] Used independent samples *t* tests for continuous variables and χ^2 analyses for categorical variables. [c] *N* = 58 unless otherwise noted; although the total sample size was 62, not all infants met the requirements for testing all traits. [d] Scaled score: 1 = *no auditory orientation,* 2 = *brightening with shifting of eyes,* 3 = *head turning to side of stimulus and localizing <2 out of 4 times,* or 4 = *head turning and finding the stimulus ≥2 out of 4 times.* [e] Scaled score: 1 = *no visual tracking,* 2 = *focusing on object with brief following <30°,* 3 = *tracking ≥30° to one side,* or 4 = *full tracking to both sides with smooth eye movements.*

scores of the Bayley–III <85. Nine (69%) of the infants who screened positive for autism also had developmental delay.

Early Social Interaction Factors and Autism Spectrum Disorder Risk

A positive screen for ASD on the M–CHAT was associated with absence of gaze aversion ($\chi^2 = 5.90$, $p = .01$, odds ratio [OR] = 5.05) and absence of endpoint nystagmus ($\chi^2 = 4.78$, $p = .02$, OR = 8.47) in the neonatal period. No other significant associations were found between any of the social interaction factors and ASD risk.

Early Social Interaction Factors and Developmental Outcome

Demonstrating gaze aversion was associated with better Language scores on the Bayley–III, $t(55) = -3.07$, $p = .003$. Displaying endpoint nystagmus during the visual orientation task was associated with better Language, $t(61) = -3.06$, $p = .003$; Cognitive, $t(63) = -5.04$, $p < .001$; and Motor, $t(62) = -2.82$, $p = .006$, scores. Better responses to human interaction, compared with toys or objects, was associated with better Language scores ($\beta = 3.79$, $p = .02$). No other significant associations between early social interaction factors and developmental outcome were observed.

Among the 58 infants with visual signs reported, gaze aversion was observed in 41 (71%), and endpoint nystagmus was observed in 21 (36%). Gaze aversion and endpoint nystagmus were related to each other ($p = .013$): 19 infants with endpoint nystagmus (91%) also demonstrated gaze aversion. Because endpoint nystagmus could be observed during visual scanning at the extremes of range (as in gaze aversion), the relationship between visual tracking greater than 30° to the side and endpoint

nystagmus was also investigated. There were no significant associations between visual tracking at end range and endpoint nystagmus ($p = .36$). All associations remained significant ($p < .05$) after controlling for CRIB score and brain injury.

Discussion

The key finding of this study was that, contrary to our hypothesis that preterm infants who demonstrated ASD risk at age 2 yr would demonstrate alterations in early social interaction behaviors, infants who went on to screen positive for ASD were less likely to demonstrate gaze aversion and endpoint nystagmus during social interaction in the neonatal period. The absence of gaze aversion and endpoint nystagmus was also related to impaired developmental outcome. The absence of gaze aversion was associated with poorer language outcome, and the absence of endpoint nystagmus was associated with poorer cognitive, motor, and language outcomes. Core features of ASD, including gaze aversion and avoidance of social interaction, were not present during the neonatal period in the infants who later screened positive for ASD in our study. Conversely, children with later ASD risk appeared to have a pattern of visual responses that was opposite to what has been reported in ASD later in life.

Gaze aversion is defined as actively moving the head or eyes away from a visual stimulus (see Table 1; Lester & Tronick, 2005). Children with gaze aversion have been reported to demonstrate greater social disability (Jones, Carr, & Klin, 2008). Subsequently, we hypothesized that infants with later risk for ASD would demonstrate more gaze aversion during the neonatal period. Our findings did not support our hypothesis, and we found less gaze aversion among infants with later ASD risk (12%) than among infants without later risk (88%). Infants demonstrating gaze aversion during the neonatal period were 5 times more likely to screen negative for ASD.

Although children with ASD may have differences in visual and social responses from infancy through childhood, it is also possible that gaze aversion is a protective social response that children with ASD do not demonstrate, contributing to their challenges with social engagement. Gaze aversion in preterm infants has been described as a response to stress, specifically stress related to imposed social interaction that the preterm infant is not neurologically mature enough to handle (De Schuymer, De Groote, Desoete, & Roeyers, 2012; Vergara & Bigsby, 2004). Therefore, gaze aversion in preterm infants may be a normal response, and reduced gaze aversion could reflect an inability to protect oneself from social stressors that are too intense when visual orientation may be reflexive (Vergara & Bigsby, 2004). Failing to demonstrate gaze aversion during the neonatal period could be evidence of alterations in social interaction, making the infant vulnerable to social stressors during overwhelming periods of engagement. Voluntary withdrawal of social interaction, rather than gaze aversion during the neonatal period, may be observed later in the developmental progression.

The association between absence of gaze aversion in the neonatal period and ASD risk is consistent with the literature on early ASD. One study found that infants at risk for ASD clearly orient to faces among distractions and tend to select and sustain attention to faces more than do their low-risk peers (Elsabbagh et al., 2013). Other recent studies identified that eye fixation in infants later diagnosed with ASD declines at approximately age 6 mo (Jones & Klin, 2013; Ozonoff et al., 2010; Rozga et al., 2011). These studies have suggested that alterations in social interaction may not be evident until later in infancy and that infants who are later diagnosed with ASD may have a heightened social engagement response early in the developmental trajectory. Better understanding of how ASD traits emerge along the developmental pathway is an important area for future research.

Endpoint nystagmus is defined as rapid, repetitive horizontal eye movements when orienting to a stimulus at the end of the visual range (see Table 1). It is considered an abnormal or immature visual response that may result from a stressed or atypically functioning nervous system (Lester & Tronick, 2005). We hypothesized that endpoint nystagmus would be related to poor outcome, including ASD risk. However, our findings did not support this hypothesis. Infants who demonstrated endpoint nystagmus in the neonatal period were 8 times more likely to screen negative for ASD. Demonstrating endpoint nystagmus was also associated with better Language, Cognitive, and Motor scores on the Bayley–III. Previous research has identified that endpoint nystagmus can be physiologically induced in healthy people during gaze or rotation (Abadi, 2002). The visual system develops rapidly in early infancy, and more research is needed to understand the significance of endpoint nystagmus in neonates.

Previous research has demonstrated diminished nystagmus responses in children with ASD, consistent with our findings. For example, Ritvo et al. (1969) demonstrated that children diagnosed with early infantile autism had a significantly shorter length of postrotatory nystagmus than their non-ASD peers when the lights were on. The authors suggested that this response may be due to

the effect of competing sensory systems on the nystagmus response. In addition, altered nystagmus responses later in childhood have been reported in children with ASD. Scharre and Creedon (1992) reported that children with ASD had atypical nystagmus responses, such as delayed onset and shorter duration, when looking at a handheld rotary drum. Conversely, one study reported that children diagnosed with high-functioning ASD showed no significant differences in postrotatory nystagmus (Goldberg, Landa, Lasker, Cooper, & Zee, 2000). These studies are different from our study because we observed nystagmus responses in neonates, not children, during an orientation task when vestibular input was not intended. However, it is possible that a similar mechanism that causes decreased postrotatory nystagmus in children with ASD may also cause decreased endpoint nystagmus in infants later at risk for ASD.

Our finding of a relationship between increased endpoint nystagmus and better developmental outcomes is a new contribution to the literature. The presence of endpoint nystagmus implies that infants were able to visually orient at the extremes of the visual field. Thus, infants who demonstrated endpoint nystagmus may have better orientation skills, making it plausible that they would have better developmental outcomes. However, secondary analyses investigating the relationship between visual orientation and endpoint nystagmus were not significant, indicating that infants without optimal visual orientation responses also demonstrated endpoint nystagmus. However, 91% of infants with gaze aversion demonstrated endpoint nystagmus, indicating that nystagmus responses can also be observed when infants avert their gaze at the extremes of the visual field. More research is needed to better understand endpoint nystagmus.

We hypothesized that infants with later ASD risk would have better interaction responses with toys and objects than with human interaction. However, no relationships between these early social interaction preferences and ASD risk were observed in the current cohort. Although other literature has reported no relationships between early social interaction factors or arousal-mediated attention and ASD diagnosis (Karmel et al., 2010), no other studies have investigated preferences for human versus nonhuman interaction this early in infancy.

Multiple studies have found that children with ASD orient less frequently than their peers without ASD to their names being called (Baranek, 1999; Nadig et al., 2007; Osterling et al., 2002; Werner et al., 2000; Zwaigenbaum et al., 2005). Although poorer orientation to name (which can be observed during animate auditory responses on the NNNS) among infants who later screened positive for ASD was not observed in this cohort, no other studies have investigated this connection as early as term-equivalent age. Although orienting to name with discrimination is not observed until later in development (Bayley, 2006), orientation to auditory stimuli, including name calling, occurs in the neonatal period (Lester & Tronick, 2005).

Although better auditory orientation to a human voice was not observed among infants who did not screen positive for ASD in this cohort, better orientation skills and a preference for human interaction over toys and objects were associated with better developmental outcome. Greater auditory attention to a human voice than to the sound of a rattle in infants who have better cognitive and language development is consistent with other research (Benasich & Tallal, 2002; Fellman et al., 2004). The foundations of learning are present in early human interaction, and infants who better attend to parents and others in the environment may be able to better reap the benefits of these early learning experiences.

Although this study was unable to demonstrate associations between ASD risk and neonatal social behaviors reflective of the core features of ASD, it is possible that a different pattern of social behaviors is present at term-equivalent age and that altered social interaction emerges later in infancy and childhood. It is also possible that premature infants, who are at a heightened risk of developmental impairment, may have a different developmental trajectory from that of full-term infants at risk of ASD. Identification of early behavioral differences that may signal ASD is a critical area of research, because doing so could lead to early, targeted interventions to optimize outcomes. In addition to early identification, understanding the expression of ASD across the lifespan will aid understanding of the disorder.

This study was limited by a small sample size. Only 13 infants (21%) in the cohort screened positive for ASD. In addition, the primary outcome was a screening measure, the M–CHAT, that has been criticized for overidentifying ASD risk in premature infants (Kuban et al., 2009; Luyster et al., 2011; Moore et al., 2012). Moreover, it is unclear whether the M–CHAT may have been sensitive in identifying developmental delay not specific to ASD. However, ASD is infrequently diagnosed as early as age 2 yr, and these findings contribute to better understanding the pathway to ASD diagnosis.

The social interaction factors assessed were collected during a neurobehavioral exam and were not naturally occurring. Although the components of social interaction were captured in a standardized fashion on the NNNS, the tool was not designed to investigate individual items. Preterm infants also may have medical factors that impede

early neurobehavioral function, making it a challenge to distinguish ASD risk from other developmental impairment. However, controlling for brain injury and initial medical severity did not alter the findings.

The hypotheses and methodology conflate three important yet distinct skills that develop at different rates in infancy and have unique manifestations within the autism phenotype. Visual orientation, social cognition, and communication each may warrant a separate, focused investigation. In addition, the definitions of visual skills and social interaction in the current study may differ from those in other reports in the ASD literature. For example, gaze aversion has been defined elsewhere as the active avoidance of looking at faces and eyes (Senju & Johnson, 2009).

Finally, this study investigated relationships with many social interaction variables, increasing the chance of a Type I error, finding an association that does not actually exist. This study, however, is exploratory and sets the foundation for replication and extension with further longitudinal follow-up. As such, caution must be exercised in interpreting the results of this study.

Implications for Occupational Therapy Practice

The results of this study have the following implications for occupational therapy practice:

- More research is needed to generate a better understanding of the relationship between early neurobehavioral function and the implications for long-term development.
- Early neurobehavioral assessment can aid early identification of adverse outcomes, enabling earlier therapy.
- Social interaction behaviors that manifest during the neonatal period appear to be related to developmental outcomes.

Conclusion

Several core features of altered social interaction during the neonatal period were not related to ASD risk in this cohort of premature infants. Instead, absence of both gaze aversion and endpoint nystagmus was observed during the neonatal period in infants who demonstrated ASD risk at age 2 yr. More research is needed to better define relationships between early social behavior and ASD risk, specifically from the neonatal period through early childhood. Understanding the expression of ASD across the lifespan can aid in discovery of the etiological mechanisms of the disorder. Additionally, early identification of ASD can enable early activation of targeted interventions to optimize outcome. ▲

Acknowledgments

This project was supported by the National Institutes of Health (Grant ROI HD057098); the Washington University Intellectual and Developmental Disabilities Research Center (National Institute of Child Health and Human Development [NICHD] Grant P30 HD062171); the National Center for Advancing Translational Sciences (Grant UL1 TR000448), subaward (KL2 TR000450); and the Comprehensive Opportunities for Rehabilitation Research K12 award (National Center for Rehabilitation Research, NICHD, National Institute of Neurological Disorder and Stroke K12 HD055931). We thank Lauren Reynolds, Tricia Coffelt, Kelsey Dewey, Katie Ross, Laura Mazelis, Joy Bender, Hayley Chrzastowski, Odo Nwabara, Jessica Conners, and Rachel Paul.

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