

## **Behavioral manifestations of autism in the first year of life**

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### **ABSTRACT**

In the interest of more systematically documenting the early signs of autism, and of testing specific hypotheses regarding their underlying neurodevelopmental substrates, we have initiated a longitudinal study of high-risk infants, all of whom have an older sibling diagnosed with an autism spectrum disorder. Our sample currently includes 150 infant siblings, including 65 who have been followed to age 24 months, who are the focus of this paper. We have also followed a comparison group of low-risk infants. Our measures include a novel observational scale (the first, to our knowledge, that is designed to assess autism-specific behavior in infants), a computerized visual orienting task, and standardized measures of temperament, cognitive and language development. Our preliminary results indicate that by 12 months of age, siblings who are later diagnosed with autism may be distinguished from other siblings and low-risk controls on the basis of: 1) several specific behavioral markers, including atypicalities in eye contact, visual tracking, disengagement of visual attention, orienting to name, imitation, social smiling, reactivity, social interest and affect, and sensory-oriented behaviors; 2) prolonged latency to disengage visual attention; 3) a characteristic pattern of early temperament, with marked passivity and decreased activity level at 6 months, followed by extreme distress reactions, a tendency to fixate on particular objects in the environment, and decreased expression of positive affect by 12 months; and 4) delayed expressive and receptive language. We discuss these findings in the context of various neural networks thought to underlie neurodevelopmental abnormalities in autism, including poor visual orienting. Over time, as we are able to prospectively study larger numbers and to examine interrelationships among both early-developing behaviors and biological indices of interest, we hope this work will advance current understanding of the neurodevelopmental origins of autism.

### **INTRODUCTION**

Autism is the prototypical form of a spectrum of related, complex neurodevelopmental disorders referred to as the autistic spectrum disorders (ASDs; also known as the pervasive developmental disorders; PDDs). The ASDs include autism, Asperger syndrome and atypical autism (or PDD Not Otherwise Specified) (American Psychiatric Association, 1994) and affect over 1 in 250 pre-school children (Bryson and Smith, 1998; Bertrand et al., 2001; Chakrabarti and Fombonne, 2001). There is strong evidence from neuropathological studies that autism/ASD (hereafter, autism) has its origins in abnormal brain development early in prenatal life (Bauman and Kemper, 2003; Rodier, 2002). Atypical neurodevelopment continues postnatally, with a unique pattern of acceleration in brain growth as measured by head circumference (Courchesne et al., 2003; Lainhart et al., 1997), which correlates with enlarged grey matter volumes observed in MRI studies by 2-3 years of age (Courchesne et al., 2001; Courchesne et al., 2003). Although autism is typically not diagnosed until late in the preschool years (Howlin and Moore, 1997), there are marked neurodevelopmental abnormalities (outlined in detail in several papers in this special issue) that are present at birth and continue to evolve from the earliest months of life.

In this context, it is not surprising that parents' recollections of their children's behavior prior to diagnosis, and analyses of home videos, indicate that abnormalities in early development are often present in the first year. When asked about their initial concerns regarding their child with autism, at least 30-50% of parents recall abnormalities dating back to the first year, including extremes of temperament and behavior ranging from alarming passivity to marked irritability (Gillberg et al., 1990; Hoshino et al., 1987), poor eye contact (Gillberg et al., 1990; Hoshino et al., 1987; Rogers and DiLalla, 1990; Volkmar et al., 1985), and lack of response to the parents' voices or attempts to play and interact (De Giacomo and Fombonne, 1998; Gillberg et al., 1990; Hoshino et al., 1987; Ohta et al., 1987; Rogers and DiLalla, 1990; Volkmar et al., 1985). Core symptoms such as speech delay and stereotyped behavior are often evident in the second year, but these clearly are not the initial manifestations of autism (Short et al., 1988; Stone et al., 1994; Sullivan et al., 1990). Similarly, several studies of early home videos have revealed behaviors indicative of autism in children later diagnosed with ASD compared to those of typically developing children (Adrien et al., 1991; Adrien et al., 1992; Baranek, 1999; Bernabei et al., 1998; Maestro et al., 1999; Mars et al., 1998; Massie, 1978; Osterling and Dawson, 1994; Rosenthal et al., 1980; Werner et al., 2000; Zakien et al., 2000). During the first year of life, children with autism are distinguished by reduced social interaction (Adrien et al., 1992), absence of social smiling (Adrien et al., 1992), lack of facial expression (Adrien et al., 1992), failure to orient to name (Bernabei et al., 1998; Osterling and Dawson, 1994; Maestro et al., 1999; Mars et al., 1998; Zakien et al., 2000), lack of pointing/showing (Osterling and Dawson, 1994; Mars et al., 1998), decreased orienting to faces (Bernabei et al., 1998; Osterling and Dawson, 1994; Maestro et al., 1999; Mars et al., 1998; Zakien et al., 2000), lack of spontaneous imitation (Mars et al., 1998) and abnormal muscle tone, posture and movement patterns (e.g., inactive or disorganized) (Adrien et al., 1992; Teitelbaum et al., 1998).

Data from these retrospective sources have yielded important insights into what constitute initial behavioral signs of autism. Indeed, these data have guided current practice guidelines in early identification (Filepek et al., 2000), forming the basis of many of the currently available autism screening tools (Robins et al., 2001; Stone et al., 2000). However, it is not clear that we have a full and accurate picture of the behavioral manifestations of autism in the first year of life. Retrospective reports are subject to recall biases and likely include significant inaccuracies with respect to the description and perceived timing of early behavioral signs. These reports also generally lack appropriate controls; that is, parents of non-autistic children (particularly those with other developmental disorders) have not been asked about similar developmental concerns. Moreover, observations from home videos vary considerably between children and depend on the particular contexts selected for taping. We also emphasize that the focus of these studies has been mainly on identifying behavioral markers to help with early identification, with minimal attention paid to their developmental sequence or their relation to underlying neurodevelopmental mechanisms. For example, early risk markers (such as extreme reactivity or reduced propensity to orient to faces) may not be simple analogues of later signs of autism, but rather behaviors that reduce the child's opportunities to learn from social experiences, thus initiating an atypical pattern of development that eventually leads to further manifestations of autism. Abnormalities may also exist in functions mediated by early developing neural systems (e.g., visual orienting), not readily recognized by parents as being directly linked to later manifestations of autism, that may in fact be fundamental to later social and communicative impairment. Such hypotheses cannot be tested based on the retrospective, largely cross-sectional data currently available.

In the interest of more systematically documenting the early signs of autism, and of testing specific hypotheses regarding their underlying neurodevelopmental substrates, we have initiated a longitudinal study of high-risk infants, all of whom have an older sibling diagnosed with an ASD (hereafter, 'infant siblings'). A detailed prospective study is only feasible in children at high risk of ASD, to allow enough cases to be identified from an attainable sample. Recurrence risk in autism is around 9% (Szatmari et al., 1998), making siblings an ideal group to follow. The prospective design offers numerous advantages. First, assessment of infants can be initiated very early, allowing an examination of the integrity of early neurodevelopmental systems such as visual attention. Retrospective reports may be limited to behaviors that parents directly link to the autistic phenotype, and tend to focus on later infancy. Second, behaviors can be studied longitudinally, which can help address questions regarding their developmental sequence and the relationship between impairments in early neurodevelopmental systems and later behavioral manifestations. Third, behavioral and neuropsychological findings can be correlated with neurobiological phenomena such as accelerated head and brain growth measured concurrently. Fourth, early behavioral signs of autism can be elicited and measured under standardized conditions, allowing greater comparability both within and between individuals over time. Although this longitudinal study is still in its early stages, the prospective design is allowing us to systematically examine a broad range of early behavioral markers, and to begin to understand the relationship between early developing neurodevelopmental systems and later impairments characteristic of autism.

## **METHODS**

### **Participants**

Our sample currently includes 150 infant siblings of children with a formal diagnosis of ASD, including 65 siblings who have been followed to age 24 months, who are the focus of this paper. Participants have been identified through families receiving clinical services at three of the largest autism diagnostic and treatment programs in Canada: the McMaster Children's Hospital in Hamilton and The Hospital for Sick Children in Toronto, which receive referrals from across Southern Ontario, and the IWK Health Centre in Halifax, which provides services to children with autism across Atlantic Canada. Diagnosis of ASD in the older sibling is confirmed by a clinical interview using DSM-IV criteria, and by administration of the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000). Infants are mainly recruited at 6 months of age or younger, to allow a focus on the earliest stages of development, and to ensure that the sample is ascertained simply on the basis of sibling status, rather than due to specific parental concerns.

Recognizing that patterns of early development of non-autistic siblings of children with autism may not parallel those characteristic of typical development (e.g., language delays and other mild developmental impairments may be more prevalent), we have also recruited and followed a comparison group of 75 low-risk infants, of whom 23 have been followed to age 2 years. Inclusion criteria for the low-risk infants are no 1st or 2nd degree relatives with ASD, term gestation and birth weight greater than 2500 g. Control infants are recruited from nurseries across the three regions, and are roughly gender-, birth-order and age-matched to high-risk infants (Szatmari et al, 2004).

We have attempted to see participants as close as possible to 6 and 12 months of age, but have allowed for these visits to occur at 6-7 months and 12-14 months, respectively. Hence, the mean age of siblings and controls for whom 6-month data are reported is 6.44 (S.D. = 0.50) months and 6.15 (S.D. = 0.43) months, respectively. The mean age of siblings and controls for

whom 12-month data are reported is 12.50 (S.D. = 0.75) months and 12.81 (S.D. = 0.77) months, respectively. Neither of these differences is statistically different.

## **Study Measures**

### Early behavioral indicators of autism

One of the unique strengths of a prospective study of infants at high risk for autism is the opportunity to directly observe early behavioral manifestations of the disorder. However, at the outset of the study, there was no standardized instrument specifically designed to measure autism-related behaviors in young infants. Observational measures exist to screen for early signs of autism in 18-month-olds (the Checklist for Autism in Toddlers; CHAT; Baron-Cohen et al., 1996) and 24-month olds (the Modified CHAT; M-CHAT; Robins et al., 2001 and the Screening Tool for Autism in Two-year olds; STAT; Stone et al., 2000), but not for infants younger than 18 months. Moreover, the CHAT and other screening measures do not cover the breadth of developmental domains implicated in autism. Therefore, to aid systematic data collection on early signs of autism, we developed the *Autism Observation Scale for Infants (AOSI*; Bryson et al., 2004b). We have operationalized 18 specific risk markers for autism hypothesized from retrospective studies, videotape analyses, case reports and our collective clinical experience, and have developed a standardized procedure for detecting each of these markers within a brief observational assessment. Infants are engaged in semi-structured play, and systematic presses are designed to assess various target behaviors, including visual tracking and attentional disengagement, coordination of eye gaze and action, imitation, affective responses, early social-communicative behaviors, behavioral reactivity, and sensory-motor development. These behaviors are rated on a scale from 0 to 3, where 0 implies normal function, and higher values represent increasing deviation. Over a period of more than two years, the scale has been revised and refined through piloting various methods of eliciting and coding the behaviors in a range of low- and high-risk infants. Reliability analyses indicate that absolute agreement between trained raters is >90% on each item, and that inter-rater agreement on the total score is excellent: intra-class correlations (ICC) at 6, 12, and 18 months are 0.71, 0.90 and 0.92, respectively, each on a sample of 26-34 infants. Test-retest reliability (at 12 months) is also good (ICC = 0.63) (Bryson et al., 2004b).

### Visual orienting task

Our previous work has identified abnormalities in an early-developing component of visual attention that appears to be specific to autism, and is detectable using a simple visual orienting task (Bryson et al., 2004a; Landry and Bryson, in press). Briefly, children are seated in a darkened room in front of a screen, on which colorful dynamic stimuli are presented side-by-side. Once the child is engaged on a central fixation stimulus, a second (comparable) stimulus is presented on either the left or right side, and latency to begin an eye movement to the peripheral stimulus is measured. The critical manipulation is whether the central stimulus remains 'on' or is turned 'off' during presentation of the peripheral stimulus. This provides independent measures of the disengage (central 'on') and shift (central 'off') operations of visual attention. The key finding is that, relative to other developmentally disabled groups, children with autism have marked difficulty disengaging from one of two competing stimuli: their latencies to disengage are abnormally long, and, on 20 % of trials, they remain stuck on the initial central stimulus for the entire 8-second trial duration (Bryson et al., 2004a; Landry and Bryson, in press). These findings parallel those reported for normal 2-month-olds, whose attention has been described as

‘obligatory’ (also referred to as ‘sticky fixation’) (Hood and Atkinson, 1993; Johnson et al., 1991). The disengage function normally develops by 3-4 months of age (Hood and Atkinson, 1993), and is operative in children with Down syndrome (Landry and Bryson, in press). In contrast, impaired disengagement in children with autism is evident even in those with average or above average IQ (Bryson et al., 2004a; Landry and Bryson, in press).

Evidence that this impairment is syndrome-specific and distinguishes children with autism from typically developing 4-month-olds suggests that it may be one of the earliest markers of autism. In fact, impairment in the disengage mechanism of visual attention may underlie the early social orienting deficits in autism, that is, the reduced tendency to orient and attend to ever-changing, novel and socially relevant stimuli. Disrupting the normal bias towards social orienting during the critical time when developing brain circuits are being guided by input from social experiences (Johnson, 2001) may set the stage for developmental pathways characteristic of autism. As a preliminary test of this hypothesis, we have assessed whether abnormalities in visual disengagement are present in infants at risk of autism, and whether evidence of impaired disengagement precedes early behavioral markers of social impairment. Attentional disengagement is assessed using the visual orienting task described above, and also through a play-based behavioral analogue of this task on the AOSI.

### Infant Temperament

Although there is some conceptual overlap between dimensions of ‘temperament’ and behaviors considered to be part of the autistic phenotype (e.g., poor adaptation to novelty or change), temperament may be a useful construct in understanding early developmental differences in infants at high risk for autism. Early abnormalities in attention, behavioral reactivity, emotion regulation and activity level may compromise both the quality and quantity of early social interaction, and thus the prerequisite experiential input for developing neural systems critical to later social-communicative competencies. There are very few studies of temperament in children with autistic spectrum disorders (Bailey et al., 2000; Kasari and Sigman, 1997), none of which includes data predating diagnosis. We have measured temperament based on parent-report using the Infant Behavior Questionnaire (IBQ; Rothbart, 1981; Goldsmith and Rothbart, 1991) at 6 and 12 months, and the Toddler Behavior Assessment Questionnaire (TBAQ; Goldsmith, 1996) at 24 months. The IBQ is a parent-report inventory consisting of 6 sub-scales that measure different dimensions of temperament: activity level, smiling and laughing, fear, distress to limitations, soothability and duration of orienting. The inventory has been validated for use with infants aged 3-12 months, and has good test-retest reliability (Goldsmith and Rothbart, 1991). The TBAQ subscales cover activity level, expression of pleasure, social fearfulness, anger proneness, and interest/persistence. The TBAQ is designed for toddlers age 16-35 months, and also has strong psychometric properties (Goldsmith, 1996).

### Other Developmental Measures

Additional measures of language and cognitive development are administered at multiple time-points, to assess early developmental trajectories, and to better understand the developmental context for the expression of early markers of autism as assessed using the previously described measures. Participants are assessed yearly on *The Mullen Scales of Early Learning – AGS Edition* (Mullen, 1995). The Mullen consists of five scales. Four of the scales (visual reception, receptive language, expressive language and fine motor) assess cognitive ability in four different domains; the fifth measures gross motor development. The Early

Learning Composite is calculated based on scores from the first four scales, and is well-standardized for children aged 0-69 months (the gross motor scale covers 0-29 months). Additional information regarding early communicative development is obtained using the *MacArthur Communicative Development Inventories-Words and Gestures (CDI-WG)* (Fenson et al., 1993; Feldman et al., 2000) The CDI-WG is a widely used parent-report measure designed for 8- to 16-month-olds. It has been validated in both a general population and in high-risk samples. The CDI-WG was selected to provide standardized information about early use of gestures, verbal imitation and words outside of the clinic setting.

### **Assessment of diagnostic outcomes**

At 36 months, all participants are seen by an experienced clinician, blind to prospective study data and the child's risk status, for a diagnostic assessment using DSM-IV criteria and including the *Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994)* and the *Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000)*. The ADI-R is an investigator directed interview that elicits the information regarding social development, verbal and non-verbal communication skills and the presence of repetitive, stereotyped interests and behaviors required to make an ICD10 or DSM-IV diagnosis of autism. The ADI-R discriminates well between autism and other forms of developmental disability, and inter-rater reliability is excellent (Lord et al., 1994). The ADOS is a structured play schedule consisting of several activities designed to elicit the behaviors diagnostic of ASD. Cut-off scores reliably distinguish children with ASD from typical and developmentally disabled non-autistic controls (Lord et al., 2000). The clinician then makes a best estimate diagnosis based on his/her clinical assessment together with findings on the ADI-R and ADOS. We have established reliability for this procedure in previous studies (Mahoney et al., 1998). Although formal independent diagnostic assessment occurs at 36 months, participants who meet DSM-IV criteria at an earlier stage are given a clinical diagnosis (confirmed by ADI-R and ADOS) for ethical reasons. Notably, all participants are assessed using the ADOS at 24 months, as a preliminary assessment of social-communication impairments indicative of autism.

## **RESULTS**

### **Classification of infant siblings at 24 months**

The preliminary results outlined in this section are based on 65 siblings and 23 control infants who have been followed to at least 24 months of age. Notably, data are incomplete for language and temperament measures, partly because some measures were introduced after the study was initiated, and partly due to incomplete return rates for parent questionnaires. Twenty-four-month ADOS scores exceed threshold for autism in 7 siblings, all of whom have subsequently received clinical diagnoses. An additional 12 siblings exceed threshold for 'autism spectrum' (equivalent to atypical autism) at 24 months. There are little data on the predictive validity of an ADOS classification of 'autism spectrum' at this early age, and our initial experience is that siblings scoring within this range are a clinically heterogeneous group; most present with language delay or behavioral inflexibility and/or inhibition but with insufficient symptoms for an ASD diagnosis. Many of these children have not yet been seen for independent diagnostic assessment at 36 months, so few conclusions can be drawn regarding this subgroup at this point. We anticipate that some of these children will ultimately meet DSM-IV criteria for the diagnosis of ASD (in fact, this is the case for 2 of 7 who have completed their 36-month assessment). Even those who do not receive a diagnosis of autism may nonetheless continue to

exhibit atypical developmental features that may eventually lead to other diagnoses such as language and/or anxiety disorders. These phenotypes have been reported in first degree relatives of individuals with autism in other studies (Bailey et al., 1998; Smalley et al., 1995).

### **Early behavioral indicators of autism**

We have investigated whether our hypothesized risk markers (as measured by the AOSI) at 6 and 12 months predict ADOS classification at 24 months. It is important to recognize that the clinical status of many siblings may continue to evolve during the third year, particularly those in the intermediate category of ‘autism spectrum’. Even so, the 24-month ADOS provides a standardized quantification of social-communication impairments related to ASD.

Six-month data are available on 44 of 65 siblings followed to age 24 months, as well as on 15 low-risk comparison infants. There are no overall differences in the number of behavioral markers observed at 6 months between siblings with an ADOS classification at 24 months, and other infants. There are individual children within the subgroup of siblings with autism at 24 months ( $n = 4$ ) who showed evidence of not orienting to name and atypical sensory-oriented behaviors (e.g., an infant who rubs his hands repeatedly over tables) at 6 months. However, the small sample size, variability among infants later diagnosed with autism and lack of overall difference in risk marker count emphasize that our current behavioral data do not support predictions of later diagnosis based on observations at 6-months.

Greater differentiation of sibling subgroups and comparison infants defined by 24-month ADOS scores is possible from observations made using the AOSI at 12 months than at 6 months. The total number of risk markers (that is, items scored ‘1’ or above) observed at 12 months predicts ADOS classification at 24 months, based on one-way ANOVA ( $F_{3,84} = 25.4$ ;  $P < 0.001$ ). The presence of 7 or more risk markers at 12 months prospectively identified 6 of 7 children diagnosed with autism at 24 months, compared to 2 of 58 non-autistic siblings, and 0 of 23 controls. Although this finding needs to be replicated in the full sample, the sensitivity and specificity of the AOSI for autism in siblings, using a cut-off point of 7 markers, is 84% and 98%, respectively. This is remarkable in comparison to currently available autism screening tools such as the CHAT (Baird et al., 2000; Baron-Cohen et al., 1996). Individual 12-month AOSI risk markers that predict autism at 24 months include atypical eye contact, visual tracking, disengagement of visual attention, orienting to name, imitation, social smiling, reactivity, social interest, and sensory-oriented behaviors (all  $P < 0.003$  to adjust for multiple comparisons).

### **Disengagement of Visual Attention**

Preliminary data on our computerized visual orienting task (Bryson et al., 2004a; Landry and Bryson, in press) indicate that delayed disengagement in this high-risk sample predicts later social-communicative impairment. As noted earlier, on each trial of this task, infants were visually engaged on a central stimulus before either a competing peripheral stimulus or a non-competing stimulus was displayed. The critical manipulation is whether the central stimulus remains ‘on’ (disengage and shift trials) or is turned ‘off’ (shift alone trials) during presentation of the peripheral stimulus. Latency (in ms) to begin an eye movement to the peripheral stimulus served as the dependent measure. The difference between the 6-month-old sibling and low-risk comparison groups in their ability to disengage and shift gaze to the peripheral stimulus did not reach statistical significance (sibling mean = 759 ms, S.D. = 456; control mean = 575, S.D. = 312 ms;  $P = 0.12$ ). However, the sibling group showed a decrement in disengage performance between 6 and 12 months of age (paired difference: mean = -753, S.D. = 1183,  $t(19) = -2.848$ ,  $P$

= 0.01). Of those assessed ( $n = 20$ ), 25 % showed longer latencies at 12 months than at 6 months of age, as measured by a difference of more than 1500 milliseconds. Each of the infants who demonstrated a decrement in disengage performance at 12 months relative to their own performance at 6 months received an autism spectrum classification on the ADOS at 24 months. None of the infants who performed similarly or better at 12 months went on to receive an autism spectrum classification on the ADOS at 24 months. As expected, the ability to disengage visual attention at 12 months of age is predictive of ADOS algorithm scores at both 24 months ( $r = 0.42$ ,  $P < 0.05$ ,  $n = 27$ ). Hence, some siblings of children with autism appear to undergo a developmental change between 6 and 12 months of age: they have more difficulty disengaging attention at 12 months, which then predicts social-communicative impairments at 24 months of age. In contrast, no comparable between group (sibling mean = 361 ms, S.D. = 167; control mean = 345 ms, S.D. = 210;  $P = 0.78$ ) or within group age differences (paired difference: mean = -49, S.D. = 355,  $t(19) = 0.08$ ,  $P = 0.78$ ) were found in latencies to shift attention, nor did the ability to shift attention predict ADOS algorithm scores at 24 months ( $r = -0.04$ ,  $P = 0.85$ ).

### **Infant Temperament**

Temperament was measured based on parent report using the Infant Behavior Questionnaire (IBQ; Rothbart, 1981) at 6 and 12 months, and the Toddler Behavior Assessment Questionnaire (TBAQ; Goldsmith, 1996) at 24 months. Siblings with an ADOS classification of autism at 24 months were rated by parents at 6 months as exhibiting lower activity level ( $F_{3,37} = 3.75$ ;  $P = 0.019$ ), and at 12 months with more frequent and intense distress reactions to a variety of stimuli ( $F_{3,56} = 4.29$ ;  $P = 0.009$ ), and longer durations of orienting to objects; that is, a tendency to fixate on particular objects in the environment at the expense of more active visual exploration ( $F_{3,56} = 3.91$ ;  $P = 0.013$ ). At 24 months, these siblings were reported to have less attention shifting ( $F_{3,58} = 6.37$ ;  $P = 0.001$ ), less inhibitory control ( $F_{3,58} = 2.86$ ;  $P = 0.045$ ) and less positive anticipation and affective responses ( $F_{3,58} = 2.86$ ;  $P = 0.045$ ), relative to other siblings and low-risk comparison infants.

### **Early Language and Communication Skills**

Not surprisingly, there is evidence of early language delays in children subsequently diagnosed with autism. Subgroups defined by ADOS classification at 24 months differ with respect to language skills at 12 months as measured by the Mullen Scales of Early Learning (Mullen, 1995). Mullen data are expressed as standard scores (SS), with population mean of 100 and a standard deviation 15. In the case of expressive language, siblings classified with autism had lower mean scores at 12 months (SS = 86.0, S.D. = 11.0) than both other siblings (SS = 101.1, S.D. = 14.3) and low-risk comparison infants (SS = 100.3, S.D. = 12.8); this difference approached statistical significance ( $F_{2,49} = 2.68$ ;  $P = 0.07$ ). For receptive language, siblings classified with autism had lower scores at 12 months (SS = 80.2, S.D. = 7.2) compared to other siblings (SS = 98.2, S.D. = 14.3), and low-risk infants (SS = 101.5, S.D. = 14.9); here, there is an overall group effect ( $F_{2,49} = 5.51$ ;  $P = 0.007$ ), as well as significant differences between subgroups on post-hoc testing using Tukey LSD. Similar findings are obtained from the MacArthur Communicative Development Inventories-Words and Gestures (Fenson et al., 1993), which was available for 23 siblings and 12 controls. At age 12 months, siblings who are later diagnosed with autism are noted to have fewer gestures (mean = 11.5, S.D. = 4.2) compared to other siblings (mean = 24.5, S.D. = 9.6) and low-risk infants (mean = 31.5, S.D. = 8.2). Siblings later diagnosed with autism also had fewer understood phrases (mean = 3.7, S.D. = 4.1) than

other siblings (mean = 13.6, S.D. = 7.2) and low-risk comparison infants (mean = 17.0, S.D. = 4.5). In each case, there is an overall group effect ( $F_{2,47} = 8.02$ ;  $P = 0.001$  and  $F_{2,47} = 6.92$ ;  $P = 0.002$ , respectively) and significant differences between subgroups on post-hoc testing using Tukey LSD. No significant differences were found for expressive vocabulary in this small sample.

## **DISCUSSION**

We have summarized our initial findings from a longitudinal study of infants at high risk for autism (siblings of children with the disorder), which indicate that behavioral manifestations of atypical neurodevelopment characteristic of autism may be observed in the first year of life. Our preliminary results indicate that by 12 months of age, siblings who are later diagnosed with autism may be distinguished from other siblings and low-risk controls on the basis of: 1) several specific behavioral markers, including atypicalities in eye contact, visual tracking, disengagement of visual attention, orienting to name, imitation, social smiling, reactivity, social interest and affect, and sensory-oriented behaviors; 2) prolonged latency to disengage visual attention; 3) a characteristic pattern of early temperament, with marked passivity and decreased activity level at 6 months, followed by extreme distress reactions, a tendency to fixate on particular objects in the environment, and decreased expression of positive affect by 12 months; and 4) delayed expressive and receptive language.

These findings may have important implications for clinical practice, and for future research aimed at understanding basic neurodevelopmental processes in autism. To our knowledge, this is the first prospective demonstration that behavioral observations as early as 6 to 12 months of age may be predictive of a later diagnosis of autism. Although parents' retrospective reports and home video analyses also point to abnormalities in social orienting, early joint attention behaviors, social interest and affect, these data are primarily based on incidental observations made at variable time points and based on sampling strategies that are not fully independent of later outcomes (i.e., parental recall, or how video clips are selected for analysis). In contrast, our observational data are collected using standardized procedures at several points over time that include a systematic set of presses to elicit behaviors, rather than simply observing what occurs incidentally. Our study design also compares siblings with autism to other high- and low-risk infants (that is, non-autistic siblings and unrelated control infants), and most importantly, the observations are made without knowledge of later diagnostic classification.

Taken together, our study findings suggest a striking clinical picture of the child with autism during the first year of life. Based on parent ratings on a temperament questionnaire, children with autism are observed at 6 months to be somewhat passive, with relatively few initiations and less responsiveness to efforts to engage their attention. Informal observations at home and in the research clinic also suggest that these 6-month-olds vocalize less than other infants. At 12 months of age, an assessment of behavioral features using the AOSI finds that eye contact is poor and that there are marked abnormalities in visual attention (including poor visual tracking), in social responses (reduced social smiling, social interest and expression of positive affect) and in use of play materials (lack of imitation and poor coordination of eye gaze and action). Sensory-oriented behaviors in 12-month-olds often involved the use of play materials in stereotyped, self-stimulatory ways (e.g., the child dangles a string of beads and waves them in front of his/her eyes). Data from the temperament questionnaire shows increasing irritability, intense responses to sensory input (often associated with distress) and excessive visual fixation

to non-social aspects of the visual environment combined with reduced responses to social approaches from others. Delays in verbal and pre-verbal expressive skills and early language comprehension are also evident on standardized measures, and are corroborated by parent reports and our initial impressions that infants later diagnosed with autism have relatively few vocalizations overall.

Siblings who later develop autism are also observed to have atypical development of visual attention in the first year of life. Specifically, we provide preliminary evidence of difficulties disengaging from two competing stimuli. Interestingly, this problem may not distinguish infant siblings from controls at 6 months, nor is performance at 6 months predictive of later diagnosis. However, initial data on the siblings suggest that their latencies to disengage attention become longer between 6 and 12 months, and that this is particularly characteristic of infants who develop autism. In contrast, typically developing infants show clear decreases in latencies to disengage with age (Hood and Atkinson, 1993), an issue that we will address more directly with larger numbers and appropriate comparison groups.

What developing neural systems are implicated by the behaviors observed at in 6- and 12-month-old infants later diagnosed with autism? Our study has identified abnormalities in several neurodevelopmental domains, both social and non-social, but does not yet answer the essential question of how these abnormalities are interrelated, and whether there are primary impairments that initiate the developmental cascade towards the broader phenotype of autism. For example, although a decrease in social orienting may be most characteristic of autism (Dawson et al., 1998), previous studies of preschoolers with autism have suggested a more general impairment in orienting to non-social stimuli as well (Dawson et al., 1998; Landry and Bryson, in press; Townsend et al., 2001). Mundy (2003) has proposed that a general disturbance in visual orienting in autism may result from impairment in a complex axis of cerebellar, parietal and frontal functions involved in the development and control of attention (Bryson et al., 1990; Carper and Courchesne, 2000; Townsend et al., 2001), and that there may be a complex interplay between the dorsal medial-frontal cortex/anterior cingulate complex, orbitofrontal and amygdala functions, and cerebellar input in the development of social and non-social attention regulation in affected individuals. Whether this model can be applied to atypical orienting patterns in early infancy is uncertain. There may be neural systems that are more operative in visual orienting during infancy than during the preschool years. For example, the observed decrease in attentional flexibility by 12 months of age in our sibling group may correlate with maturational processes of the prefrontal cortex (Johnson et al., 1991), although this remains speculative at this point. Atypical patterns of cortical activation involving the prefrontal cortex have been observed in preschool children with autism (Dawson et al., 2001; Muller et al., 2001).

We emphasize again that the findings reported in this paper are preliminary. Diagnostic assessments at this point are limited to 24-month follow-up data, and in only a portion of our total sample, as many infants have not yet reached this age. As more and more of these children are assessed independently at age 36 months, we can confirm the stability of early diagnoses and the predictive validity of early behavioral risk markers. It may also become feasible to examine heterogeneity in behavioral profiles and developmental trajectories among the group as the total sample size (including the number of siblings diagnosed with autism) increases. Further modification of our measurement protocol may also be necessary to better understand the neurodevelopmental implications of behaviors observed in the first year. The Autism Observation Scale for Infants (AOSI; Bryson et al., 2004b) is a major advance, as it is the first measure specifically developed to assess behavioral manifestations of autism in the first year of

life. However, the behavioral coding system was designed to be relatively simple, to facilitate applicability in clinical settings for the purposes of early identification. As such, we may be missing subtle qualitative and quantitative differences that may further distinguish children with autism during infancy. We plan to complete more detailed analyses of our AOSI assessments (which are all videotaped) to examine early behavior in greater depth, and to further refine our current coding system, particularly for 6-month-olds.

Another limitation of our current study design is the lack of a comparison group of infants at risk of developmental disabilities other than ASD. Although our infant sibling group will most likely include children with language delays, other developmental disorders may not be well represented among our siblings and low-risk controls. It is important both for clinical practice and for understanding neurodevelopment to examine whether early behavioral indicators are specific to autism. To address this, we have begun to evaluate the AOSI in a total population of low birth weight infants who have a high rate of non-autistic language, motor, and general developmental delays (Saigal et al., 1991). Finally, children with autism who have an affected sibling may not be representative of all children with the disorder, so behavioral findings from infant siblings may not fully generalize to other autistic samples.

We have not yet correlated behavioral findings with measures of early brain development. Notably, there are currently no MRI data in individuals with autism prior to age 2 years, which appears to be a critical period with respect to accelerated growth and premature connectivity in brain development (Courchesne et al., 2003; Volkmar et al., 2004). Very few children with autism are diagnosed prior to age 2, although our current longitudinal study could allow us to identify younger infants at very high risk based on multiple behavioral indicators in the first year. In addition, there are significant logistic and ethical constraints to imaging infants (e.g., the need for deep sedation), as well as measurement issues that would need to be addressed prior to undertaking such studies (e.g., establishing methods to reliably differentiate white and grey matter in this age group). Notably, techniques for neonatal brain MRI have been described in other populations (Khong et al., 2003; Erberich et al., 2003) that may be effectively modified for older infants. We are currently considering a feasibility study of using MRI without sedation to assess brain development serially in very high-risk infant siblings. In a related study, we are currently in the process of analyzing head circumference data in our sibling sample, in order to assess whether accelerated head growth as reported by Courchesne et al. (2003) is associated with particular behavioral features during the first year of life.

## **CONCLUSIONS**

Our longitudinal study of high-risk infants (siblings of children with autism) has identified several neurodevelopmental abnormalities observable in the first year of life in children later diagnosed with autism. These include atypical patterns of visual attention, orienting and responsiveness to both social and non-social stimuli, and early delays in imitation and language skills. The difference in the number of behavioral markers observed at 12 months of age in children later diagnosed with autism, compared to other high- and low-risk infants, raises the possibility of earlier identification in the general community. However, additional follow-up of the current sample and evaluation of other high-risk samples will be needed to better assess the sensitivity and specificity of these findings. We have outlined various neural networks thought to underlie poor visual orienting in autism, but emphasize that we cannot readily extrapolate from findings from older toddlers and preschool children with autism. Over time, as we are able to prospectively study larger numbers and to examine interrelationships

among both early-developing behaviors and biological indices of interest, it should be possible to advance current understanding of the neurodevelopmental origins of autism.

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