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What are infant siblings teaching us about autism in infancy?

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Abstract

International research to understand infant patterns of development in autism spectrum disorders has recently focused on a research paradigm involving prospective longitudinal studies of infant siblings of children with autism. Such designs use a comparison group of infant siblings without any familial risks (the low- risk group) to gather longitudinal information about developmental skills across the first three years of life, followed by clinical diagnosis of ASD at 36 months. This review focuses on five topics: presence of ASD in the infant sibling groups, patterns and characteristics of motor development, patterns and characteristics of social and emotional development, patterns and characteristics of intentional communication, both verbal and nonverbal, and patterns that mark the onset of behaviors pathognomonic for ASD. Symptoms in all these areas typically begin to be detected during the age period of 12 –24 months in infants who will develop autism. Onset of the symptoms occurs at varying ages and in varying patterns, but the pattern of frank loss of skills and marked regression reported from previous retrospective studies in 20–30% of children is seldom reported in these infant sibling prospective studies. Two surprises involve the very early onset of repetitive and unusual sensory behaviors, and the lack of predictive symptoms at age 6 months. Contrary to current views that autism is a disorder that profoundly affects social development from the earliest months of life, the data from these studies presents a picture of autism as a disorder involving symptoms across multiple domains with a gradual onset that changes both ongoing developmental rate and established behavioral patterns across the first two to three years of life.

Introduction

Two of the most provocative suggestions that Kanner (1943) made in his 1943 paper describing autism was that it was present from the earliest months of life and that it represented a biological impairment in the capacity for social relatedness. What these symptoms of autism in earliest infancy might be has stimulated theory and research ever since, because these symptoms might lead us to brain functions subserving the development of typical social relatedness, because these symptoms might be amenable to interventions, and because these symptoms might tell us more about the core nature of the behavioral phenotype in autism than symptoms in older children, whose life experiences are increasingly and drastically changed over time by the presence of autism.

Symptoms during infancy have been examined using a variety of methods, over decades of research. Parent histories and reports were the only source of evidence for many years, and parent reports have been validated in a variety of ways. However, parent reports are affected by the passage of time, by parental sophistication about typical child development, and by knowledge of the scientific literature on early symptoms of autism spectrum disorder (ASD), and methods for directly accessing and assessing infant behavior were necessary.

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In 1991, a French research team led by Adrien et al. (1991) described a new research method – the analysis of home movies made during infancy of children who would later be diagnosed with autism. The home movie/video method provided the first opportunity for controlled, objective examination of early behaviors and has led to important new findings that have now been replicated in carefully controlled studies by labs all over the world. Home video studies have made it clear that there were indeed symptoms of autism that differentiated infants long before diagnosis occurred. However, this method also had weaknesses. Parents do not collect videos on random samples of behavior. Parents film their children for particular reasons, and in particular states and settings, according to personal motivations. Gathering uniform objective data about development and characteristics of early interaction patterns, early object exploration and motor patterns, early vocalizations and sensory responses required additional methods. Prospective longitudinal studies of infants from birth into early childhood were needed, but, given a prevalence rate of autism (4 per 10,000), such studies would need to involve too many children, over too long a time, to be feasible.

However, the findings from familial studies carried out in the 1970's and 1980's suggesting that siblings of children with ASD had a 3–8% risk of developing autism themselves (Micali, Chakrabarti, and Fombonne, 2004; see review by Bailey, Palferman, Heavey, and LeCouteur, 1998) gave rise to the idea of prospectively studying infant siblings of children with autism until the "autistic infants" in the group were identified. This method, first pioneered by Sigman, Baron-Cohen, and Yirmiya in the 1990's (as reported by Yirmiya, & Ozonoff, 2007), provided a means to examine characteristics of autism before diagnosis was made and the assumed secondary affects of identification could occur. It allowed for the use of standard experimental paradigms and measures from the infancy research field, and it allowed for prospective comparative data to be gathered across time. The Holy Grail of infant autism research was now fully defined: what are the first behavioral characteristics that predict development of autism?

The purpose of this review is to synthesize the main findings thus far, particularly highlighting unexpected findings and areas of discrepancy from selected papers, in order to suggest targets for development of new hypotheses and new research. However, all papers listed in the search engines Psychinfo and Pubmed under the keywords "infant siblings" and "autism" at the time of writing are included. The review will focus on five topics: presence of ASD in the infant sibling groups, patterns and characteristics of motor development, patterns and characteristics of social and emotional development, patterns and characteristics of intentional communication, both verbal and nonverbal, and patterns that mark the onset of behaviors pathognomonic for ASD. We will end with a discussion of surprises, contradictions and discrepancies, implications, and research needs. The review is intended to present the key findings to autism researchers in disciplines outside of developmental psychology, so that they could easily examine these findings in light of their existing findings and theories. The findings are purposefully not woven into particularly theories of autism, but instead presented for others to view from their own theoretical lenses. See Elssabagh and Johnson (2007) for a review that integrates these findings into specific psychological theories about ASD).

To integrate the findings, we need a specific terminology to apply to the children in this literature. In this paper, infant siblings of children with autism will be referred to as high risk infants and comparison infants, including infant siblings of children with typical development, will be referred to as low risk infants. The older affected sibs will be referred to as the probands. If the high risk group consists only of infants later diagnosed with ASD, they will be called ASD high risk infants. If the children with ASD have been removed from the group, they will be called nonASD high risk infants. And if children with ASD have

either not been identified or if they have not been removed from the group, then the group will be referred to as high risk infants.

How many infant sibs are affected by autism?

This important question cannot be answered by the existing studies, each of which relies on clinically ascertained samples. The samples in the studies reviewed here likely differ from community samples in important ways: severity of proband, education level of families, location, etc. Furthermore, the studies have approached identification of ASD differently. Many have not reported any outcomes yet; those that do report outcome status at different ages, which will affect rates. Children with final diagnoses of Asperger syndrome (AS) or pervasive developmental disorder not otherwise specified (PDDNOS) will likely be identified at older ages than those with Autistic Disorder (AD), and so studies reporting diagnoses at 60 months may have higher rates than those reporting 24 month outcomes. Finally, the age of enrollment in the studies may affect outcome rates. Studies that enroll infants at or after 12 months of age have an increased risk of having parents enroll their child because they already are observing behaviors that have raised their concerns about autism; thus, studies enrolling toddlers may have increased rates over those enrolling young infants.

The Canadian sample, which is the largest and one of the oldest samples in this literature, reported that out of 155 high risk infant siblings and 73 low risk infant sibs, 35 high risk infant sibs were diagnosed with an autism spectrum disorder (ASD), including diagnosis of AD, PDDNOS, and AS, by a blind expert assessor using a best estimate clinical diagnosis involving gold standard tools (Brian et al., 2008). In an Israeli sample, Gamliel et al. (2007) reported 1 child with ASD out of 39 in a sample enrolled by 4 months of age, using a very similar diagnostic approach. Iverson & Wozniak (2007) report 2 out of 21 children enrolled by 5 months. Landa & Garrett-Mayer (2006) report 37 out of 60 from a sample that enrolled up until 18 months of age, and Yoder, Stone, Walden, and Malesa (2009) report 6 out of 43. Thus, ASD affectedness ranges widely across these studies, and this wide range likely reflects the initial point, that the question cannot be answered from clinically ascertained groups.

The broader autism phenotype in infancy

The term “broader autism phenotype” (BP) has been used to characterize the presence of subclinical characteristics related to social relatedness, pragmatics of communication, and special interests that seem to resemble primary characteristics of ASD and to occur at an elevated rate in first degree relatives of persons with ASD. An important question raised by the infant sib studies involves defining the BP in very early childhood. Unlike the definition of ASD, which is fairly standardized and allows for pooling of information across the studies, there is no common definition of the BP in early childhood.

Of the papers that have described outcomes, each research group has taken a different approach to characterizing a subgroup of high risk infant who do not meet diagnostic criteria for ASD (as defined in each study) but who nevertheless demonstrate other clinical abnormalities on standardized measures of development and/or language and/or behavior problems. Some cluster children into multiple categories by the type of delay (Sullivan et al., 2007), others use the timing of the delay (Gamliel et al., 2007), and some use a general subgroup of ASD versus not (Toth et al., 2007). Gamliel et al. (2007) reported that 11of 39 in their sample had a developmental impairment that was not ASD at either 14 or 24 months (thought many of these delays were no longer present at 54 months), and Sullivan et al (2007) report 8/51 were similarly affected at 36 months. Is this the BP in infancy? There is currently not enough outcome data from these studies to know whether these early delays

will be associated with the expected profiles associated with the broader autism phenotype in latency and beyond. Understanding the nature and course of the BP in early childhood will require a common definition and taxonomy as well as longer term follow up.

Developmental Characteristics

General/intellectual development

There is general consistency that developmental differences in infants at high risk for ASD as compared to low risk infants appear by 12 months, but not by 6 months, on standardized development measures, with standard scores dropping – a developmental deceleration – which continues as the gap widens from 12 months to 24 months or beyond (Brian et al., 2008, Stone, McMahon, Yoder, and Walden, 2007). This pattern has also been reported by some in high risk groups who did not develop ASD (10 point difference reported by Brian et al., 2008).

Motor Development

Delays in motor development have been a recurrent finding in studies of infants who develop autism. Using a sample of 60 high risk infants and 27 low risk infants seen at 6, 14, and 24 months, Landa and Garret-Mayer (2006) reported differences in fine and gross motor development for infants who would later develop autism and those who do not at 14 and 24 months, though not at 6 months. However, Toth et al. (2007), using the same measure, found no differences in direct measures of gross motor, fine motor, or visual perceptual differences in high risk infants without ASD compared to low risk infants at a mean age of 20 months. The difference in findings likelyreflects the differences in samples; the Toth et al. sample has no children with ASD, while the Landa and Garret-Meyer sample has a proportion of children with ASD.

Repetitive behaviors and other abnormal movement patterns

The question of repetitive behaviors highlights an important challenge in this line of research – examining classes of behavior that are developmentally appropriate at certain ages. Repetitive behaviors are expected in infancy and are thought to contribute to motor development (Thelen, 1979). The need for low risk, typically developing contrast groups is necessary in infant sibling studies in order to determine differences in behaviors due to familial or incipient autism that involve only differences in frequencies, durations, intensity, etc. of such behaviors. Although some earlier studies of early ASD suggested that repetitive behaviors and abnormal movement patterns did not differentiate ASD in the second year of life, this viewpoint is being laid to rest by current studies of movement patterns during object play of high risk infants. Ozonoff et al. (2008) reported on 35 high risk 12 month old infants and 31 low risk infants with 36 month outcome diagnoses of ASD (n=9) no delay (n=47), or other delays (n=10). The infants were provided four objects to play with for 1 minute, and their behaviors were coded from video using Noldus Observer by raters blind to group and hypotheses. Four age appropriate behaviors (mouth, shake/wave, throw/push, and bang/tap) and four atypical behaviors were identified (spin, rotate, roll, and unusual visual regard). Of the four age appropriate behaviors, diagnostic groups differed significantly on only one – throw/push, which occurred most often in the other delay group. Of the atypical behaviors, the outcome group with ASD demonstrated significantly higher rates than both other groups for spin, unusual visual regard, and rotate, with significantly higher scores on the fourth than the nondelay group. The most frequently demonstrated atypical behavior seen in the outcome group with ASD was unusual visual regard, demonstrated by 7 of the 9 infants in this group.

Iverson et al. (2007) examined motor development and repetitive behavior in a sample of 21 high risk and 18 low risk infants observed monthly in the home from 5 to 14 months, with an 18 month old follow-up. Videotapes were gathered on 45 minutes of play and analyzed for repetitive behavior following Thelen's (1979) study. Data on motor milestones and language development were collected from parents. As in the Ozonoff et al. (2008) study, there were no significant differences on age of typical motor milestones or pointing, though there were significant distributional differences, with a higher proportion of late onsets in the high risk group. Analysis of postural stability on a subgroup of 22 infants demonstrated decreased durations of postures in the high risk group. The only atypical repetitive motor pattern involved repetitive arm movements, with the **low risk** group demonstrating a significant increase in such movements.

Finally, Loh et al. (2007) examined four postures and nine repetitive movements during a 14 minute AOSI (Autism Observation Scales for Infants, Bryson et al., 2006) assessment at 12 and 18 months, also using a taxonomy from Thelen's (1979) work. Comparison of 17 high risk siblings and 15 typically low risk infants revealed that only one behavior at one age occurred significantly more in the infants who developed ASD than both other groups – arm waving, and this is after examining 13 behaviors at two different ages. Two other behaviors occurred significantly more often in the high risk group as a whole than the low risk group – arm waving at 12 months, and covering ears at 18 months.

Thus, across these three studies, repetitive movements involving arms and hands was the only elevated behavior. Why are there such differences in rates across these studies? The answer may reflect procedural differences involving group sizes, the time period for observation, and the nature of the probes. Many of the probes in the Loh et al. (2007) study occurred during that 14 minutes of target social interaction and communication rather than object exploration, perhaps limiting the opportunities for exhibition of such behaviors.

Sensory related behaviors

Zwaigenbaum et al. (2005), working from the large Canadian study, were the first to report that items concerning over or under-responsivity to sensory stimuli differentiated children who would later develop autism at age 12 months, but not at 6 months. Toth et al. (2007), however, examining parent questionnaire data, found **lower** rates of sensory and repetitive behaviors and temperamental difficulties in nonASD high risk infants than in comparison low risk group at a mean age of 20 months.

Visual attention

Zwaigenbaum et al. (2005) have been the only group to report on visual attention shifting and disengagement using lab based paradigms. Smoothness of visual tracking differentiated the high risk group who developed ASD from both the high risk group who did not develop ASD and the low risk sibling groups at 12 months of age. Interestingly, these characteristics when measured at 6 months did not identify infants who would later develop autism or differ between the high risk and low risk groups. However, infants who would later develop autism showed increasing delays in the speed with which they could disengage from an active stimulus to view another active stimulus between the ages of 6 and 12 months, and this is a period in which the social symptoms of autism are also onsetting, as discussed later in this paper. The ability to shift attention from an inactive stimulus to an active stimulus did not differentiate autism in this sample.

Social and emotional development and differences

One of the main expectations of researchers involved in these prospective studies of high risk infant siblings has been the ability to identify early social atypicalities that would signal

the presence of ASD early in infancy. However, to date, few studies have published comparative data on early social behaviors of high risk infants before 12 months of age.

Several groups have used parent questionnaires to assess infant temperament. Somewhat surprisingly, high risk infants who developed ASD were not found to be temperamentally more difficult at 6 months of age than either high risk who did not develop ASD or low risk infants (Zwaigenbaum et al., 2005). However, over time, temperamental differences became more pronounced, with more intense distress and more time spent fixating on objects later characterizing the group who developed ASD. Two main aspects of temperament extracted from the 24 month temperament measure, behavioral approach and effortful emotional regulation, differentiated among all three groups of infants at 36 months and provided unique information about ASD diagnosis not contained in IQ or ADOS scores. Behavioral approach, involving responsivity to reward cues, differentiated between high risk sibs who did and did not later develop ASD, and it was significantly related to ASD symptom severity. Emotional and behavioral regulation differentiated the group who developed ASD from the control group. Both variables together differentiated those within the high risk group who did and did not develop ASD. (Garon, Bryson, Zwaigenbaum, Smith, Brian, Roberts, and Szatmari, 2009). Furthermore, the authors suggest that the neural substrates related to these two aspects of temperament fit well with neural models previously suggested to account for motivational, emotional, and regulatory difficulties in ASD (Mundy, Block, et al, 2007). Given that temperamental measures taken at 6 months did not differentiate diagnostic groups in this study, it appears that temperamental differences may accompany, rather than predate, the changes in other aspects of behavior that mark the emergence of autism symptoms in the affected children.

Toth et al. (2007) found nonASD high risk sib atypicalities on a variety of social measures, including parent report across age points spread throughout the entire second year of life. Directly administered assessments documented social deficits in the high risk group, but no differences in object related imitation, functional, or symbolic play were found. This group also examined and found no group differences involving parental self reports concerning various stressors, mental health, and marital relationship quality. This finding is important because studies that report social differences in high risk siblings often raise questions about the effects of having an older child with autism on the parent-infant relationship. This finding from Toth et al. (2007) suggests that, at least according to parent report, significant stress and emotional functioning on the part of the parents do not differ in these families.

Several groups have used the still face procedure from the infant research literature to examine infant social sensitivity. The still face paradigm is a classic experimental approach from infant development research, and it involves a face to face interaction between parent and infant in three segments – an active play segment, followed by a maternal still segment, followed by an active play segment (Tronick et al., 1978). Infants typically demonstrate warm engagement in the first segment, increased neutrality or distress, eventual gaze avoidance, and upset in the second segment, and recovery of social engagement with some remaining distress in the third segment. Ibanez et al. (2008) examined 17 high risk and 17 low risk dyads at age 6 months using 3 minute interactive, 2 minute still, and 3 minute reunion segments. Gazes were coded as to face or away, and the three infant variables involved frequency of gaze shifts and duration of gaze to face and gaze to other for each segment. Parent behaviors involved tickle, touch, and smiles to the infant.

While Ibanez et al (2008) had previously reported group differences involving decreased smiling in a subset of this high risk group (Cassel et al., 2007), in this 2008 publication Ibanez et al.,(2008) report no significant group differences on parent or child any variable involving affect or gaze to face in any specific episode of the still face. The high risk infants

showed as much duration of gaze at parent face as did low risk infants. The only group differences involved: (1) fewer gaze shifts in the high risk infants than the low risk infants, and (2) longer duration of gaze away from face across all the episodes. The differences are interpreted as indicating ASD related difficulties with visual disengagement and/or with non-social interest in the environment. No information on diagnostic outcomes was provided, so the possibility of relationships between frequency of gaze shifts and later diagnosis of ASD could not be examined, a situation that occurs in many of the infant sib papers cited here.

Yirmiya et al. (2006) were the first to use the still face, as well as a period of social play, with high and low risk infants, examining two groups of 21 four month old infants. Mother-infant pairs were classified as synchronous or not based on the existence of significant cross-correlations of mother and infant behavior codings in the 5 minute play sample using Tronick et al.'s (1978) time series. Findings revealed no temperamental differences between the groups and no gender related differences. In terms of dyadic synchrony, the majority of dyads in both groups were synchronous (62% of the high risk dyads, 67% of the low risk dyads), with no group differences in synchrony type or time lag. However, further analysis revealed that in one of the synchrony types – those interactions in which the infant leads and the mother follows, there was a significant group difference, with the high risk dyads showing comparatively less synchrony in that condition. In the still face procedure, there were no differences in gaze patterns between the two groups. The high risk infants showed significantly more neutral affect, but no differences in percent of positive or negative affect, than the low risk infants. The still face segment had to be ended earlier for the low risk group as a whole than the high risk group due to infant upset, which is likely another marker of affect differences, and perhaps less negative or more neutral affect in the high risk group.

Did these differences identified by Yirmiya et al (2006) indicate which infants would develop autism? There was no relationship in the high risk sibs between atypical synchrony at 4 months and any measures at 14 months. There was no relationship in the high risk sib group between amount of neutral affect in the still face at 4 months and scores on an autism screening measure – the Checklist for Autism in Toddlers (Baron-Cohen et al., 1992) at 14 months, although more neutral affect predicted less initiation of joint attention using coordinated points and gaze. The authors summarize their findings in this way: " …at the age of 4 months, the [high risk] group and the [low risk] group did not differ significantly on most of the early social engagement measures, indicating that [high risk] sibs are functioning well at age 4 months and that we were unable to identify early markers for later difficulties at this age with the measures employed in the current study."(p.519).

The lack of predictiveness across time also characterized findings by Merin et al. (2007), using the still face paradigm with one minute segments with 55 six month olds, 31 high risk and 24 low risk infants. This experiment used an interactive, two way live video paradigm with the infant recorded using a Tobii eye tracker in order to examine gaze patterns of the infant. The main hypotheses tested were two: that high risk infants would demonstrate muted affect, both positive and negative, compared to low risk siblings, and (2) that high risk infants would show decreased gaze at the eye region, and increased gaze at the mouth region, compared to low risk infants, based on the previous work by Klin et al (2002) showing gaze differences in adults with ASD. There were no differences detected in infant affect in any of the three interactive segments. Cluster analysis revealed that children who spent more time looking at mother's mouth versus eyes occurred more frequently in the high risk group. However, none of the gaze or affect variables gathered at 6 months showed any relationship to autism related variables at 24 months (Young et al., 2008). Three children in the high risk group developed autism, and all three of those children attended to the mother's eyes during virtually 100% of the still face episode. One child in the low risk group

watched the mother's mouth for 100% of the still face episode. This child showed no elevations in autism related symptoms at 24 months. A final important and counter-intuitive finding from this study revealed that only one of the gaze and affect variables gathered at 6 months was related to child development at 24 months: the duration of gaze to the mother's eyes during the 6 month still face segment was **negatively** related to child expressive language development at age 24 months (p=.001), measured both by lab administered measures and by parental vocabulary reports. These analyses by Young et al. (in press) highlight the fact that findings from studies of adults cannot be assumed to apply also to infants and they emphasize the importance of using infant research and longitudinal data to unravel the meanings of "autism specific" behaviors and risk group related differences identified early in life.

Intentional communication – language development and differences

Given the centrality of language deficits in the early behavioral phenotype of autism, researchers have closely examined language development in high risk infants. Delays in both verbal and nonverbal (gestural) communication development beginning at 12 months, but not earlier, have been documented in high risk infants who develop ASD by every group who has studied them (Zwaigenbaum et al., 2005; Yirmiya et al., 2006; Landa & Garret-Mayer, 2006; Yoder et al, 2009). The findings are not as consistent for the high risk infants who do not develop ASD. Some groups have not found any differences in the second year of life (Zwaigenbaum et al., 2005). Goldberg et al. (2005) found significant group differences between 9 high risk infants and 9 low risk infants at 17 months of age on responding to social interaction and requesting behaviors, but not initiating or responding to joint attention. Toth et al. (2007) reported a significant 8 point receptive language deficit, but no expressive deficits, in a group of 42 high risk infants who did not develop ASD compared to 20 low risk infants at 20 months, and significant deficits in three of the four composite scores from the Communication and Symbolic Behavior Scales(CSBS) – social, symbolic, and total, and a trend to significance in the fourth – speech, differences mirrored in other measures as well in this study. Decreased rates of distal gesture were also found on multiple measures. However, no differences were found on specific items involving measures of affect sharing, joint attention, social interaction, or use of conventional gestures.

Yirmiya and her colleagues (Gamliel et al., 2007) provide a fascinating picture of developmental deceleration and acceleration among high risk siblings across the 4 month – 54 month period. In a sample involving only high risk infants who did not develop ASD (n=39) compared to 39 low risk infant siblings, they first subdivided the group into four subgroups, (1) high risk infants with significant (> 2 standard deviations) language or cognitive delays at 14 months n=5, (2) high risk infants with significant cognitive or language delays at 24, but not 14 months n=6, (3) high risk infants without significant delays at either age n=27, and (4) low risk infants n=39. Subgroups 1, 2, and 3 showed significant delays on language development at 14 months. At 24 months, all three subgroups continued to show significant receptive language delays, and subgroups 1 and 2 showed expressive language delays. At 36 months, subgroups 1 and 2 continued to show significant delays in both receptive and expressive language. At 54 months, there were no significant group differences on receptive language, though there were still large effect sizes regarding decreased scores of subgroups 1 and 2. On expressive language, there was a significant group difference involving subgroup 2. A similar pattern existed with cognitive measures in this study, with groups 1 and 2 showing significant developmental immaturities at 4 months, at 14 months, and 24 months. At 36 months, their delays are no longer statistically significant, but the effect sizes are still large. At 54 months, there are no significant group differences, and no large effect sizes!

The subgroups in this study are quite small so the results should be considered tentative, but the "self-righting" of the high risk group over time is impressive. It may suggest quantitative differences in developmental rates, or it may indicate more qualitative differences in developmental routes, in early childhood. The finding of developmental recovery without intervention is an important contribution of this study, and raises an important discussion point to which we will return.

Response to name—One of the most consistently used lab paradigms in the infant sibling studies involves response to name, a variable that was demonstrated to be sensitive to ASD in several home video studies of 12 month old or younger infants who would later development autism (Osterling & Dawson, 1994; Baranek, 1999). Yirmiya et al. (2006) provided the provocative finding that high risk infants at ages 4 months and 14 months responded more frequently to name call than did the low risk sibs as a group. However, responsivity to the name call procedures was only related to one out of a large number of variables gathered at 14 months: infants who were less responsive to name call at 4 months made fewer requesting bids at 14 months.

Nadig et al. (2007) reported on 98 six month olds (55 high risk) and 147 12 month olds (101 high risk) in a paradigm that involved having a familiar experimenter give the child a toy to play with, walk out of the baby's view, and then call the child's name up to three times. Examination of the data revealed a significant group difference at 12 months, but not at 6 months, involving fewer responses in the high risk group, a finding also reported by the Canadian group (Brian et al, 2008; Zwiagenbaum et al, 2005). Nadig also examined relationships of other key variables involving language development and attention shifting to uncover possible causes for the impaired response pattern. Using a series of regression analyses, the authors determined that the best predictor of response to name was neither receptive language development nor the capacity to disengage from an object and shift attention to another object. Rather, it was the child's self initiated and spontaneous attention shifts from toy to eye contact with the examiner, seen in a separate paradigm, leading to the suggestion that differences in social interest or social motivation explain the variability in response to this task.

Response to motherese—Preschoolers and older children with autism have been found to show atypical responses to infant directed speech (IDS) (Klin, 1991; Kuhl et al., 2005). Furthermore, IDS affects infant attention to speech (Cooper, & Aslin, 1990), auditory discrimination in six month olds (Liu et al., 2003), and language development in 24 month olds (Tsao et al., 2003). For these reasons, Nadig et al (2007) examined infant preference for motherese, or IDS versus adult directed speech (ADS) in 28 high risk infants and 13 low risk infants at age 6 months using a version of the Sequential Looking Paradigm (Cooper, & Aslin, 1990). Results indicated a marginal effect of group, with the low risk infants showing more preference for IDS than the high risk group. The authors also clustered the infants in terms of their IDS versus ADS preference. The only infants who preferred ADS speech were in the high risk group, and those infants who preferred ADS showing marginally significant lower standard scores than infants who preferred IDS. Whether this preference for ADS marks a risk sign for ASD has not yet been examined.

Response to joint attention (RJA)

The most thorough examination of response to joint attention thus far published (Presmanes et al., 2007) involved 81 infants, including 46 high risk infants and 35 low risk infants, at a mean age of 15 months (range 12–23 months). The task involved 10 different probes for RJA, each containing a different combination of physical and verbal cues. Both objects and object names were novel to control for language ability. There was a main effect of group,

with the high risk infants demonstrating significantly fewer responses. Variability in RJA was not found to be associated with attentional flexibility, group differences caused by a few children with extreme scores, or deficits in visual perceptual abilities. Presmanes et al (2007) suggested that the high risk sibs were experiencing difficulty interpreting the communicative cues involved in locating the target. They did not have difficulty interpreting highly redundant cues involving head turns plus verbal plus gestural prompts. The group differences occurred when there was both head turn and verbal prompt but no gesture. This group also demonstrated associations between RJA and language development in the high risk children that provide a mechanism for explaining language delays as a part of the BP. Finally, follow-up at 33 months revealed that response to joint attention at 12 months predicted the degree of social impairment, and diagnosis of ASD, at 33 months (Yoder et al, 2009).

A second report concerning RJA came from Sullivan et al. (2007), involving 51 high risk infants at 14 and 24 months, 16 of whom developed ASD, 8 of whom developed language or social delays, and 27 of whom met neither of the above two categories. These three groups did not significantly differ on child response to joint attention probes at 14 months, and even by 24 months, this skill did not differentiate the ASD from the other delayed group, though it did differentiate both of them from the nondelayed group. However, the delayed groups had significantly more problems following joint attention probes that only involved head turns than did the nondelayed group, and at 24 months, the only children to fail to respond to all RJA probes were those who had ASD. Additionally, the high risk group who developed ASD showed much less improvement in response to RJA from 14 to 24 months than did those in the other two groups. Both delayed groups also demonstrated significantly more inconsistency in their performance across multiple probes of RJA than did the non-delayed group. These findings are in line with findings by Presmanes et al. and by Cassel et al. (2007).

Imitation

Only two groups have thus far published on imitation. Zwaigenbaum and colleagues (2005) report that performance on intentional imitation tasks involving body actions, oral acts, and actions on objects discriminated the group of infants who would later develop autism from both high risk and low risk groups as 12 months of age. However, in high risk infants who did not develop ASD, imitation tasks involving actions on objects did not differ between high risk and low risk groups at a mean age of 20 months (Toth et al., 2007).

Onset patterns

The final topic for this review involves onset patterns. The case studies published by Bryson et al. (2007) illuminate the data nicely. Bryson et al. (2007) presented data across the 6 to 24 month period for the first nine children enrolled at 6 months into the Canadian study who developed ASD. Their autism related behaviors and development will be reviewed at each age period.

Six months

The synopses of the 9 infants presents a rather uniform, and perhaps surprising, picture of responsive, social engagement. All the infants were reported to show interest and pleasure in social interaction and to have sustained eye contact and social smiles. Most of the infants showed social anticipation during peekaboo, oriented to voices and to their name, and vocalized with babble. Only two infants were noted to be fussy or difficult. Atypicalities were generally in two areas: delayed motor development and unusual visual interest or reactivity to objects. Four of the nine had difficulties with reaching, grasping, holding, and

transferring objects, with one described as “floppy,” and two were not sitting. Four of the nine showed visual fixations on objects. Two of the nine lacked smooth visual tracking, and had difficulty with visual disengagement.

Twelve months

Five of the nine infants have diminished social interest and engagement, though only two are described as having “little” social interest or engagement; the other three continue to show some episodes of social engagement and interest. These five show other concerning symptoms as well: unusual visual fixations, stereotypic body movements, motor delays, irritability, and poor language development. Three show unusual responses to sensory stimuli, two with increased reactivity and one with decreased reactivity.

The other four infants are still highly social without change from their previous 6 month levels of sociability. Three are apparently relatively typical in language development and motor behavior as well, while one shows diminished facial emotion, is over-reactive to sensory experiences, flaps her hands when distressed, is slow to approach novel toys, and seems socially reticent.

Eighteen months and beyond

Seven of the 9 display the same level of social engagement as at 12 months. One of the infants (child #4) who previously showed diminished social engagement, as well as underreactivity, visual fixations, and object fixations (and thus appeared to show an incipient ASD profile), shows considerable improvement. He is now socially engaged with pleasure and initiative, babbling, good eye contact, orientation to voice, initiates joint attention with pointing and gaze, though two stereotypies are present. He shows very few symptoms and does not fit an ASD profile at 18 months, though symptoms increase at 24 months, when he is diagnosed with autism, with an IQ under 50 at 36 months.

The other four infants who showed impaired social engagement at 12 months continue to show social impairment, with some showing further social deterioration. In addition, all four show increased symptoms in other areas, including fussing and irritability, repetitive behaviors, lack of language progress and poor nonverbal communication development, and atypical play patterns. ASD appears present, with continuous but increased symptoms from 12–18 months. All four children were diagnosed with autism at 24, three with IQs under 50 at 36 months. ASD symptoms of the fourth child, a girl, lessened over time, and her IQ was 96 at 36 months.

Of the four infants with typical sociability at 12 months, one showed diminished social interest, pleasure and engagement at 18 months, with atypical sensory reactivities, stereotypies, affected play skills, and temperamental difficulties, with ASD diagnosis confirmed at 24 months and IQ under 50 at 36 months. For the other three, social pleasure, engagement and initiative continued, but other symptoms developed. Child #8 did not show a symptom profile of ASD at 18 months, but had occasional hand flapping, poor visual tracking, and difficulty with attention and imitation. He did not meet criteria for ASD until 36 months, with global delays and an IQ of 51. Child #6 had a variety of symptoms, including sensory reactivities, head banging, lack of play, stereotypies, lack of verbal and nonverbal development, and diminished eye contact, but did not meet criteria for ASD until 36 months, with an IQ of 85. Child #2 continued to have good social relating but lacked appropriate nonverbal communicative development, appropriate play, and had echolalia, unusual fears and visual fixations. At 24 months, she was considered positive for ASD (Aspergers), with an IQ of 96.

Patterns of onset

None of these children fits Kanner's (1943) early onset pattern involving a profound social-affective impairment beginning in the earliest months of life. All were socially engaged, responsive infants at 6 months. Of the five infants who had developed social impairments combined with a variety of nonsocial symptoms between 6 and 12 months, they were clearly symptomatic of ASD during the second year of life, and this picture was sustained through age 36 months. The developmental quotients for four plummet from age 12 to 24 months, ending more than 3 standard deviations below the mean. This pattern seems marked by a fairly rapid onset in the 7–12 month period, with disruption of many aspects of development.

Four infants continued to have normal social relatedness at 12 months but were diagnosed with autism at 24 or 36 months. However, none were reported to show the regressive pattern involving frank loss of language and social skills. Rather, they present a picture of slowly accumulating and intensifying symptoms from 12 months across the next two years, a slow protracted course of developmental plateau. One child was clearly symptomatic of ASD by 18 months, one diagnosed at 24 months, and the other two finally meeting ASD criteria at 36 months. For them, the developmental sequelae are not so severe. Two have essentially normal developmental rates.

One child lost language (#4), but he also showed symptoms in many domains at 12 months, showed some recovery at 18 months, and then showed increased symptoms and diagnosis by 24 months, a pattern of fluctuating, or recurring, symptoms.

Do these child profiles indicate that there are subgroups showing unique patterns of onset, or is onset more continuous, with some children on an earlier and more rapid course, and others on a somewhat later and more gradual course, but all eventually settling into the autism behavioral phenotype (see Ozonoff et al., in press, for an elaborated discussion of this point, and Landa et al., 2007, who also describe an earlier and a later onset group). And what about those rare cases of childhood disintegrative disorder (CDD)? Do they represent the latest onset points, and do those few infants who are socially quite abnormal in the first six months of life (e.g., Vismara, & Rogers, 2008) represent the earliest?

Discussion

What are the surprises in this literature? The most surprising finding thus far involves the lack of behavioral markers of ASD at 6 months thus far identified. Given the robust social nature of typical 6 month olds, and the profound social impairment seen in toddlers with autism, the mindset of most of the investigators going into these studies was not **whether** they would find behavioral differences, but rather **what** they would be. The lack of overt behavioral identifiers at 6 months is changing our ideas about the course of autism and our ideas about the continuity of social behavior across infancy. Furthermore, the earliest differences found are subtle, as in the area of repetitive behaviors, where differences involve only a very few behaviors or a small difference in means. Lack of differentiating symptoms at 6 months suggests a discontinuity to social development, with early sociability supported by different underlying mechanisms than toddler sociability (cf with Kagan, 2008). Certainly the number of studies and number of measures used thus far is small, and the use of other risk markers may reveal clearer differences. However, even if clear differences are found that predict to diagnosis, using eye tracking, ERP, microanalysis of videos, or other very detailed methods (and I for one assume that we will find these), it will not diminish the surprise of looking at these 6 month videos and observing the smiling, social, responsive infants who will later develop autism.

Does the lack of early evidence suggest environmental causation? On the contrary, the rate of autism and related difficulties in these siblings confirms for us the importance of genetic contributors to the disorder. We assume that the biology of autism is in place at 6 months, even though the behavior of autism is not. However, reliable markers of autism in early infancy may end up coming from biology rather than behavior. We may not find a litmus test for autism, even in biology. The best we may be able to do is to settle for odds ratios and severity of risk indicators.

The second surprise involves the variety of course and timing of the onset of the behavioral autism phenotype. The patterns emerging from these studies do not fit either the early onset or the regressive patterns we have come to expect – points thoroughly discussed in recent papers by Landa & Garrett-Mayer (2006) and Ozonoff et al., (in press). The patterns instead involve slower or faster mounting of symptoms, more or less deceleration of general development, earlier or later onset of social difficulties – differences that seem more continuous than dichotomous. It is fascinating in these case studies to read that not only the core symptoms like joint attention deficits, repetitive behaviors, and language delays appear at 12 months and grow more severe over time, but even what were previously considered secondary symptoms – irritability, sensory responsivity, activity level, and poor gross motor development, are on board, and in some cases appear well **before** the social problems! These findings do not support the view that autism is primarily a social-communicative disorder and instead suggest that autism disrupts multiple aspects of development rather simultaneously. Children's developmental rates are decelerating markedly in a 12 month time period, with IQs dropping from average to below 50 for some children. There is no other developmental disorder with this kind of course (the CDD group stands out for the fastest, latest onset into the same symptom set). The social-communicative symptoms and the unusual onset appear to distinguish these children from others with multiple delays, but to suggest that autism is primarily about social communication does not fit these data well. Perhaps as a colleague recently suggested (Cameron Carter, 2007, personal communication), onset in autism will be found to resemble the pattern (though not of course the timing) seen in schizophrenia, with a modal point of onset and a rather bell shaped curve extending into earlier and later periods, perhaps reflecting random variation in genetic timing rather than environmental triggers.

A third important point – not a surprise, but a reminder – is the extreme range of severity in each of the symptoms seen in affected toddlers. Even in infancy, each of the core symptoms, and developmental rate, may be severely affected or may be much more mildly affected. It is the pattern of symptoms that defines autism, with a wide range of severity, and screeners and diagnostic measures that are sensitive to autism in less impaired toddlers, who may not show deficits in joint attention, imitation, expressive language, and symbolic play, are badly needed. These data on the variability of onset timing and the range of symptoms have significant ramifications for pediatric autism screening efforts, which will need to occur repeatedly until 36 months of age, using screeners that are sensitive to both more and less severely affected toddlers, if we are to identify most children with ASD in the preschool period.

Discrepancies exist throughout these studies. Are there abnormalities in the still face response or are there not? Do high risk infants who do not develop ASD show developmental delays at 12 months or not? Are there imitation differences in these siblings or not? Do these infants demonstrate difficulties with response to joint attention, or do they not? Many of these discrepancies likely currently exist because the methods and subjects differ across studies. The field needs a common approach to categorization of high risk subgroups. One would expect that a group of high risk infants that includes infants who will develop ASD will show more deficits, and more variability, than a group of high risk infants

who do not develop ASD. Differences in coding constructs and practices will result in different findings. Rating duration of eye contact using eye tracking technology will provide different data than rating duration of gaze from video. This is a very young field, and investigators are currently developing original experiments and methods. Hopefully, the next wave of studies will provide real replications involving a duplication of methods. Additionally, as studies are published, convergences across studies using slightly different methods will provide needed replications.

What is the nature of the broader familial phenotype in infancy? While the broader, or familial phenotype, in ASD as it occurs in older children and adults has been well characterized by others (e.g. Dawson, Webb, Schellenberg, Dager, Friedman, Aylward, and Richards, 2002; Skuse, 2001), data on infants are only beginning to emerge. The necessary design, as illustrated in the Toth et al. 2007 paper, involves a comparison of high risk infants who do not develop ASD to low risk infants, and has been carried out by very few researchers thus far. From the available data, the high risk infants who do not develop ASD do not demonstrate the range of symptoms involving temperamental problems, motor problems, and repetitive behaviors that the ASD infants show. Several studies have demonstrated atypicalities in visual processing of both social and nonsocial stimuli (Elssabagh et al, in press; Merin et al, 2006; McCleery et al, 2007; Elsabbagh et al, 2009). There is also replicated evidence of significant difference in some aspects of social communication from low risk groups, though not at the impaired level of the infants who develop ASD. We have no information on whether infant siblings without ASD who show early atypicalities will show the known patterns associated with the BAP at school age or later. Differing severities of affectedness in the BP are likely to represent points on a continuum from typical to autistic development, as occurs in older groups (Constantino, & Todd, 2003). We await data from larger studies to provide a clearer picture of the onset, course, and profiles of the high risk infants who do not develop ASD. The data and cautions from Gamliel and colleagues (2007) are particularly relevant here, though the study is quite small, and thus far not replicated. If delays resolve by 54 months in some untreated high risk children who did not have ASD, what do the delays mean? If they resolve, should we be routinely recommending treatment when delays are found in infants? And, if so, what level of severity should be the deciding point for diagnosis and/or referral? Does this apparent plasticity in the nonASD high risk sibs speak to the level of plasticity in infants who develop ASD? Will treatment be more effective if begun earlier? The recovery seen in that small group of high risk infants with delays but without ASD is one of the most provocative findings thus far in the infant sibling studies (see Elssabagh and Johnson, 2007 for further discussion on this issue).

The last point concerns the importance of “unpacking” a group difference. For Presmanes et al. (2007) Nadig et al. (2007), and Young et al. (in press), among others, identifying a group difference is only a very early step in the analytic approach. Once a difference was detected, the researchers in these studies used the follow-up diagnostic data and the other measures to determine the nature of the group difference, often with surprising results. Who would have thought that infants who look more at mouths than faces would have superior language development? Who would have thought that response to name reflects social initiative, as opposed to receptive language? What does it mean if a group difference involving poorer performance in the high risk group does not differentially affect the children who will develop ASD?

These investigators have made us acknowledge that a difference between high risk and low risk infants is not necessarily a red flag for autism risk or any other risk. It highlights a second point as well, that behaviors that connote abnormality in a later developmental period (e.g. increased gaze to mouth versus eyes during social interactions) do not

necessarily connote abnormality in an earlier developmental period. We must be quite careful to examine the meaning of behaviors anew when we take paradigms and findings from one developmental period to another. There is so much theorizing in autism, so many "just so" stories, that we are grateful to researchers who see that the task involves not just defining group differences, but rather chipping away to understand them. This approach to the data is encouraged for the field as a whole.

The questions initially driving these studies have led to some answers, and to new questions, questions that are now driving the second wave of such studies. The initial question – predicting autism risk in infancy – is now being examined in many studies through more basic measures, like eye tracking and ERP. Longitudinal studies are needed to define the ongoing course of both those sibs who develop ASD and those who do not. Do those sibs with some early delays but no ASD go on to develop greater, or diminished, problems over time? Do the two early subgroups within ASD demonstrate different trajectories of development? Are the high risk sibs with delays but not ASD the same group who will demonstrate the familial autism phenotype in later childhood, adolescence, and adulthood? How many of them will eventually be diagnosed with ASD? Are the abnormal gross and fine motor skills, increasing repetitive behaviors, and increasing sensory responsivities related in these very young children? And, of course the over-riding question: what is occurring in the central nervous system of these children that accounts for the gradual onset of autism symptoms in the second year of life? And what can be done to stop the progression and reverse the downward course? These, and many other important questions, remain to be addressed in these complex and fascinating longitudinal studies of infants at risk of ASD.

In conclusion, it appears that autism is not a disorder that profoundly affects social development from the earliest months of life. Rather, it is a disorder involving symptoms across multiple domains with a gradual onset that changes both ongoing developmental rate and established behavioral patterns across the first two to three years of life, and typically results in severe social-communication impairment.

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