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ORIGINAL PAPER

Studying the Emergence of Autism Spectrum Disorders in High-risk Infants: Methodological and Practical Issues

Lonnie Zwaigenbaum · Audrey Thurm · Wendy Stone · Grace Baranek · Susan Bryson · Jana Iverson · Alice Kau · Ami Klin · Cathy Lord · Rebecca Landa · Sally Rogers · Marian Sigman

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Abstract Detecting early signs of autism is essential for timely diagnosis and initiation of effective interventions. Several research groups have initiated prospective studies of high-risk populations including infant siblings, to systematically collect data on early signs within a longitudinal design. Despite the potential advantages of prospective studies of young children at high-risk for autism, there are also significant methodological, ethical and practical challenges. This paper outlines several of these challenges, including those related to sampling (e.g., defining appropriate comparison groups), measurement and clinical implications (e.g., addressing the needs of infants suspected of having early signs). We suggest possible design and implementation strategies to address these various challenges, based on current research efforts in the field and previous studies involving high-risk populations.

Keywords Early identification · Screening · Longitudinal studies · Prospective studies · Infant · Autism · Child development · Siblings

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L. Zwaigenbaum (✉)
Department of Paediatrics, McMaster Children's Hospital at McMaster University, PO Box 2000, Hamilton, Ontario L8N 3Z5, Canada
e-mail: zwaigenb@mcmaster.ca

A. Thurm
Division of Pediatric Translational Research and Treatment Development, National Institute of Mental Health, Bethesda, MD, USA

W. Stone
Departments of Pediatrics and Psychology & Human Development, Vanderbilt University, Nashville, TN, USA

G. Baranek
Division of Occupational Science, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

S. Bryson
Departments of Pediatrics and Psychology, Dalhousie University, Halifax, NS, USA

J. Iverson
Department of Psychology, University of Pittsburgh, Pittsburgh, PA, USA

A. Kau
Center for Developmental Biology and Perinatal Medicine, National Institute of Child Health and Human Development, Bethesda, MD, USA

A. Klin
Yale Child Study Centre, Yale University, New Haven, CT, USA

C. Lord
Department of Psychology, University of Michigan, Ann Arbor, MI, USA

R. Landa
Department of Psychiatry and Behavioral Sciences, Kennedy Krieger Institute, Baltimore, MD, USA

Introduction

Overview

Several reviews over the past decade have highlighted the importance of early recognition and specialized intervention for improving outcomes for children with autism spectrum disorders (ASD) (Dawson & Osterling, 1997; Rogers, 1996; Smith, Groen, & Wynn, 2000). Although recent service registry (Croen, Grether, Hoogstrate, & Selvin, 2002) and population-based data (Yeargin-Alsopp, et al., 2003) suggest that more children are being diagnosed prior to age 4 years than in the past, a formal diagnosis may still lag years behind the time when parents initially identify concerns (Coonrod & Stone, 2004; Howlin & Moore, 1997; Siegel, Pliner, Eschler, & Elliott, 1988). As a result, interest has increased in identifying and raising awareness regarding the characteristics of ASD present at young ages (Bryson, Zwaigenbaum & Roberts, 2004; Landa, 2003). In addition to improving outcomes, earlier diagnosis allows parents the opportunity to receive counseling regarding current estimates of recurrence risk in autism, which they may take into account in future family planning. Research to date supports the conclusions that one can: (1) reliably diagnose as young as 24 months (Lord, 1995; Stone et al., 1999); and (2) observe the behavioral markers of autism well before 24 months (e.g., Dahlgren & Gillberg, 1989; Ohta, Nagai, Hara, & Sasaki, 1987; Rogers & DiLalla, 1990).

Most of the work aimed at identifying early signs of ASD has been retrospective, focusing on early behavioral evidence of the disorder in children who have already received a diagnosis. The most common methods used to gather information about earlier behaviors have been retrospective reports from parents and analysis of early home videotapes. Although research using these approaches has supported clinical efforts aimed at earlier detection, many questions regarding early signs, their timing, and their underlying developmental mechanisms remain. Prospective research into the early development of ASD in high-risk infants is an exciting new frontier, and can potentially answering these questions more systematically, while avoiding some of the biases associated with retrospective designs. In this paper, we outline the theoretical advantages and general feasibility of prospective studies of young children at high-risk for ASD, and acknowledge and discuss the significant methodological, ethical and practical challenges that accompany these studies. Issues discussed include the design of high-risk studies, selection of comparison groups, measurement of developmental delay and deviance, generalizability, and clinical interpretation of findings.

Identifying Early Signs of Autism using Retrospective Designs

Retrospective parental reports offer a unique window into early behaviors of children with ASD, as parents have the advantage of observing their children's behavior over time and across a variety of settings. Investigators report a wide range of symptoms that are more common in children with autism under the age of 24 months than similar-aged children with developmental delays or mental retardation (DD). Early symptoms associated with autism cross several developmental domains, including social behavior (Dahlgren & Gillberg, 1989; De Giacomo & Fombonne, 1998; Hoshino et al., 1982; Ohta et al., 1987; Young, Brewer, & Pattison, 2003), communication (Dahlgren & Gillberg, 1989; De Giacomo & Fombonne, 1998; Ohta et al., 1987; Young et al., 2003), affective expression (Dahlgren & Gillberg, 1989; De Giacomo & Fombonne, 1998; Hoshino et al., 1982), and sensory hypo- and hypersensitivities (Dahlgren & Gillberg, 1989; De Giacomo & Fombonne, 1998; Hoshino et al., 1982). These findings have been very important in guiding further research aimed at identifying early signs of ASD. However, a number of factors limit parents' ability to provide accurate descriptions of early behaviors. First, a parent's incidental observations regarding the subtle social and communicative differences that characterize young children with autism may be limited compared to systematic assessment by trained clinicians (Stone, Hoffman, Lewis, & Ousley, 1994). Moreover, their tendency to use compensatory strategies to elicit their child's best behaviors (with or without their awareness) may affect their behavioral descriptions (Baranek, 1999). Retrospective parental

R. Landa
Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD, USA

S. Rogers
Department of Psychiatry and Behavioral Sciences, University of California at Davis, Sacramento, CA, USA

M. Sigman
Departments of Psychology and Psychiatry, University of California, Los Angeles, CA, USA

reports may be also be prone to errors and distortions of recall, especially when one asks parents to remember behaviors that occurred many years ago. In particular, having already received a diagnosis of autism for their child, parents may bias their reports toward behaviors that are consistent with the diagnosis. A recent retrospective study overcame some of these problems by gathering information about behaviors under 24 months from parents of preschoolers *before* they had received a diagnosis (Wimpory, Hobson, Williams, & Nash, 2000). However, limitations of this methodology remain, as retrospective reports are not generally informative on the issue of whether differences in early social and communicative development are best characterized by delayed emergence, reduced frequency, or truly abnormal or deviant quality of fundamental skills such as joint attention.

A second strategy for obtaining retrospective information about characteristics of autism present before 24 months is the analysis of early videotapes of children made by their parents. This approach has significant strengths relative to retrospective parental reports: it allows the observation of behaviors as they occur in familiar and natural settings, and enables objective rating of behavior by unbiased observers. However, this methodology is not without its limitations, the foremost being that parents record these tapes to preserve family memories, rather than to document their child's behavior across a variety of settings. As a result, tapes from different families will naturally vary as a function of the quality of the recording, the activities and settings that were recorded, and the length of time the child is visible. Moreover, if children do not behave as expected (or desired), parents may re-record taped segments until they obtain the desired response. Efforts to standardize tapes across families can be extremely difficult and time intensive (Baranek, 1999). Moreover, most studies employing home videotapes have used children with typical development (TD) rather than those with DD as comparison groups, which limits the extent of our knowledge about autism-specific deficits. Behaviors found to differentiate children with ASD from children with TD under 24 months by at least two studies are: responding to name (Baranek, 1999; Osterling & Dawson, 1994; Osterling, Dawson, & Munson, 2002), looking at others (Adrien et al., 1993; Maestro et al., 2002; Osterling & Dawson, 1994; Osterling et al., 2002), smiling at others (Adrien et al., 1993; Maestro et al., 2002), and motor stereotypies (Adrien et al., 1993; Baranek, 1999). Only two studies published to date compared behaviors of children with ASD with those of children with DD younger than 24 months; these found that children with ASD were less likely to respond to their name (Baranek, 1999; Osterling et al., 2002) and to look at others (Osterling et al., 2002). Notably, analysis of home videos also highlights that there is may be a subgroup of ''late onset'' children whose early behavioral symptoms are less apparent (Osterling et al., 2002; Werner, Dawson, Osterling, & Dinno, 2000).

Potential Advantages of Prospective Studies

Retrospective parental reports and analyses of home videos can help guide the development of early identification and screening procedures (as argued by Filipek et al., 1999), but these procedures must ultimately be validated empirically in prospective studies, with sufficient follow-up of both screen positive and screen negative children to allow estimates of sensitivity and specificity. In fact, prospective studies of high-risk infants (which, until recently, have been rare in autism) may also identify novel behavioral (and biological) markers that show the way forward in developing more effective early identification and screening measures. Prospective studies are not subject to recall biases, they can be designed to examine specific constructs of interest, and they can provide comparable data collection points and methods across children. Perhaps, most importantly, these studies allow collection of data longitudinally across different ages, which can foster our understanding of developmental trajectories and the impact of early delays in one domain (e.g., social orienting) on the subsequent development of another (e.g., language).

High-risk samples have informed studies of other neurodevelopmental and neuropsychiatric conditions, including language/reading disorders (Carroll & Snowling, 2004), attention deficit hyperactivity disorder (Faraone, Biederman, Mennin, Gershon, & Tsuang, 1996), bipolar affective disorder (Chang, Steiner, & Ketter, 2000; Geller, Tillman, Craney, & Bolhofner, 2004), and schizophrenia (Schubert & McNeil, 2004). Prospective studies of siblings and offspring of affected probands have generated significant insights regarding premorbid development and predictors of illness in these high-risk groups. For example, children with schizophrenic parents have attention and verbal memory deficits, gross motor delays, and dysfunction of smooth-pursuit eye movements (Erlenmeyer-Kimling, 2000; Schubert & McNeil, 2004), and children with a parent or sibling with dyslexia have greater difficulty with phonological processing than age-matched low-risk controls, despite normal early language development (Carroll & Snowling, 2004). Notably, these

studies generally focus on group differences between high- and low-risk children rather than the association between early markers and outcome status, because of insufficient power and/or follow-up. In contrast, autism can be diagnosed in early childhood, so outcomes can be determined after a relatively short follow-up period. Hence, one can study autism prospectively much more easily (i.e., with fewer resources and with less risk of sample loss) than an adult-onset disorder such as schizophrenia.

Prospective Studies in Autism: Siblings and other High-Risk Groups

Several populations at increased risk of ASD that can be identified in early childhood: children with early signs of autism or developmental delays (DD) identified through population screening, children at increased risk of autism due to specific medical diagnoses or genetic anomalies, and the main focus of this paper, infants with an older sibling with ASD.

At least two research groups have studied early signs of autism in high-risk samples identified by population screening. Charman et al., (1997) and Swettenham et al., (1998), reported on a high-risk group of children who failed the Checklist for Autism in Toddlers (CHAT; Baron-Cohen, Allen, & Gillberg, 1992), a screening measure administered at 18 months of age. Detailed assessment of social, communication and play skills was completed at 20 months, and diagnostic outcomes were assessed at age of three and a half. Children subsequently diagnosed with autism were compared to those subsequently diagnosed with developmental delay based to their 20-month skills. At this early age, the children with autism spent less time looking at adults during free play (Swettenham et al., 1998), were less likely to look at the face of an adult feigning distress (Charman et al., 1997), showed less gaze switching between people and objects (Charman et al., 1997; Swettenham et al., 1998), and showed less imitation (Charman et al., 1997). Wetherby et al., (2004) followed a group of children who had failed communication screening using the Communication and Symbolic Behavior Scales Developmental Profile (CSBS DP, Wetherby & Prizant, 2002). They obtained videotapes of the CSBS Behavior Sample at a mean age of 18–21 months for children who received later diagnoses of autism, DD, or who were typically developing. Specific features that differentiated children with autism from the other two groups include social-communication behaviors (e.g., reduced eye gaze, coordination of gaze with other nonverbal behaviors, directing attention, responding to name, and unusual prosody) and repetitive body and object use. Notably, the content of the initial screen (i.e., children are selected based on a particular profile of early signs), may introduce sampling biases, and the fact that data are only collected from the point of first screening onward limits the age range over which autism can be studied.

There are also children at increased risk for autism due to medical risk factors, such as Fragile X syndrome (Rogers, Wehner & Hagerman et al., 2001), specific chromosome abnormalities (Xu, Zwaigenbaum, Szatmari & Scherer, 2004), tuberous sclerosis (Bolton & Griffiths, 1997), and prenatal exposure to valproic acid (Williams et al., 2001) or thalidomide (Stromland et al., 2002). However, these specific risk factors are all relatively rare and would be difficult to study in large numbers, and may be associated with unique clinical features that may not generalize to other children with autism.

There is growing interest in studying infant siblings of children with ASD, who are arguably the most clearly defined high-risk group available. Notably, Baron-Cohen et al., (2002) originally developed the CHAT screening algorithm based on items that, at 18 months, were atypical in four siblings subsequently diagnosed with autism. More recent reports by Pilowsky and colleagues (Pilowski, Yirmiya, Shalev, & Gross-Tsur, 2003; Pilowski, Yirmiya, Doppelt, Gross-Tsur, & Shalev, 2004) support the feasibility of studying early development in siblings and Zwaigenbaum et al., (2005) reported several behavioral markers which, at 12 months, predict a subsequent diagnosis of autism in a sibling sample. In addition, Landa & Garrett-Mayer (2006) report developmental levels and trajectories in that differentiate infant siblings later diagnosed with autism spectrum disorder, beginning at 6 months of age. Autism is associated with the highest relative risk in siblings, compared to general population of all the neuropsychiatric disorders (Szatmari, Jones, Zwaigenbaum & MacLean, 1998). Previous studies found rates of autism in siblings of children with autism range from 3% to 5%, which is at least 20 times higher than rates of autism in the general population (Bailey, Phillips & Rutter, 1996; Simonoff, 1998; Szatmari et al., 1998). In fact, estimates of *recurrence* risk (that is, the risk to later-born children) may be as high as 8.6% when one child in the family has autism, and 35% when two siblings have autism (Ritvo et al., 1989). Notably, these risk estimates may be somewhat conservative, as they come mainly from studies conducted over 20 years ago, using more restrictive diagnostic criteria (DSM-III).

The risk to relatives of individuals with autism also extends beyond the traditional boundaries of the

autistic spectrum (Bailey, Palferman, Heavey, & Le Couteur, 1998). Family members have higher rates of certain psychiatric and developmental disorders, compared to individuals with no family history of autism (Landa, Folstein & Isaacs, 1991; Landa et al., 1992; Pickles et al., 2000; Piven, Palmer, Jacobi, Childress, & Arndt, 1997; Smalley, McCracken, & Tanguay, 1995; Yirmiya & Shaked, 2005). As well, because of the early age of diagnosis of the proband, one can ascertain siblings in early infancy or even prenatally, making it possible to study early neurodevelopmental mechanisms, and to partially avoid (or at least to systematically measure) the impact of potentially confounding environmental factors. Infant sibling research offers unique opportunities to study the neural origins and developmental cascade that leads to autism, potentially providing new insights into its neurobiology, improved methods of early detection, and earlier opportunities for intervention.

In August 2003, the National Alliance for Autism Research (NAAR) and the National Institute of Child Health and Human Development (NICHD) co-sponsored a workshop for researchers engaged in the study of populations of young children at high-risk for autism, particularly siblings of children with autism. Despite the theoretical advantages and exciting opportunities associated with this research design, there are clearly significant methodological, ethical and practical challenges facing researchers studying young children at high-risk for autism. In the remainder of this paper we outline several of these challenges, including those related to sampling (e.g., recruitment of adequately sized samples, determining inclusion/exclusion criteria for high-risk infants and appropriate comparison groups), measurement (e.g., selection of constructs and measures) and clinical implications (e.g., clinical management of infants who appear to have early signs of ASD). We suggest possible design and implementation solutions for these various challenges, based on current research efforts in the field and previous studies involving high-risk populations. These issues have implications not only for research with infant siblings, but also for research in other aspects of early characterization and diagnosis of autism.

Issues Related to Sampling

Sample Size

High-risk studies in other fields (e.g., schizophrenia, dyslexia) have generally been designed to compare siblings with controls on a group basis, without knowing the ultimate outcomes of individual siblings (Carroll & Snowling, 2004; Erlenmeyer-Kimling, 2000). Initial infant sibling studies of ASD by Pilowski and colleagues (2003, 2004) also focus on group comparisons. However, if the main objective of a sibling study is to identify early markers that are predictive of a specific diagnosis, then individual outcomes become important, and one must power the sample size with reference to the expected number of participants who will have the diagnosis of interest (i.e., not the total number of infants enrolled).

The required sample size for these studies will depend on the specific research question posed. A few issues are considered for illustration. First, if one defines the outcome of interest more broadly (e.g., language delay), there will be a larger number of siblings with that outcome, potentially making it easier to detect differences between 'affected' and 'unaffected' siblings. However, predictors of secondary outcomes such as language delay may not generalize outside of an autism sibling sample, limiting the clinical utility of such findings. A second issue to consider is the strength of the association between the predictor variables and outcome under study (e.g., the sensitivity and specificity of early markers for the subsequent diagnosis of autism), which will influence the power to detect a relationship. However, the investigator may sometimes select predictor variables on a theoretical basis, so the actual strength of the relation between predictor and outcome variables may be difficult to estimate with confidence. A third variable to consider is the number of outcomes/variables being studied; for example, contrasting siblings by more than two outcomes (e.g., ASD versus developmental delay versus typical development), or examining the effects of stratification variables (e.g., gender) within and across groups may be of interest, but will require even larger samples sizes.

Due to limitations on numbers of infants born to older siblings with autism within specified geographic regions, studies may maximize their efforts to collect data in a timely fashion by establishing collaborations across multiple sites and utilizing a common set of core assessment measures. Such collaborations accelerate the process of identifying early predictors of outcome by increasing the collective sample size so that investigators can address more refined questions about outcomes and predictors. Although collaborations between research groups require additional effort and resources to support the necessary steps of ensuring consistency in methods and measures, as well as inter-rater reliability for observations, these procedures allow the examination of consistency of findings across sites, ensure the fidelity of assessment

measures, and facilitate future attempts to replicate findings.

Inclusion/Exclusion Criteria

Decisions regarding inclusion/exclusion criteria for siblings also depend on the goals of the study. One major consideration is whether to include probands and/or siblings with conditions associated with autism (e.g., tuberous sclerosis, Fragile X syndrome) and those with other medical risk factors that may predispose the infant to developmental problems (e.g., low birth weight, perinatal injuries). If the main goal is to study early signs and neurodevelopmental mechanisms of autism in high-risk infants, then there may be some flexibility in whether to exclude probands and siblings with known risk factors. Children with such risk factors may differ developmentally from other children with autism, an interesting and clinically relevant issue to explore. However, if a major goal is to identify phenotypes and endophenotypes that 'run true' in families for subsequent genetic linkage studies, or to estimate recurrence rates associated with 'idiopathic autism,' then studies may need to exclude cases with known risk factors.

Issues Related to Study Design

Within a high-risk (or sibling) design, several decisions need to be made, including enrollment age for siblings, selection of comparison groups, and approach to outcome assessment. Scientific and practical considerations must guide each of these decisions.

Enrollment Age of Siblings

The main strength of the high-risk design is the potential to study ASD earlier than would be possible by ascertaining children at the time of diagnosis, which rarely occurs before age 2 years. There may be advantages to starting assessment of high-risk infants either during the first or the second year of life, depending on the particular focus of the study.

Although studying autism in the first year of life is largely uncharted territory, this strategy may be an optimal way to learn about atypical patterns of infant development that underlie later manifestations of autism. The few extant findings examining children in the first and second year of life indicate increased subtlety of impairments at earlier ages and a number of measurement challenges. For instance, two studies that focused specifically on children younger than 12 months (Baranek, 1999; Werner et al., 2000) found that children with autism show reduced social orienting compared to typically developing children, but in general, find fewer differences between the two groups than analyses of videos taken at 12 months or later. As well, preliminary data from ongoing sibling studies find that behavioral risk markers more readily distinguish autism at 12 months than at 6 months (Zwaigenbaum et al., 2005). Studying children during the first year of life presents tremendous opportunities to examine early neurodevelopmental mechanisms that may determine later impairments and developmental trajectories in autism (for example, social orienting and gaze monitoring; Moore & Corkum, 1998; Phillips, Wellman & Spelke, 2002). Moreover, preliminary findings that atypical brain growth (Courchesne, Carper & Akshoomoff, 2003) may predate behavioral differences in autism emphasize that studies that target high-risk infants earlier in life may yield unique data on early markers. Another advantage of enrolling siblings at 6 months or younger is the potential to reduce the problem of biased sampling (and inflated recurrence risk estimates) resulting from over-referral of parents who have behavioral concerns.

Prospective studies of toddlers at high-risk of autism starting in the second year of life are also informative. Recruitment at this age can include high-risk children other than siblings (e.g., population screening on the basis of delays in communication skills; Wetherby et al., 2004), allowing comparison of children with ASD across different ascertainment routes, helping to ensure the generalizability of findings. As well, while it may be easier to study basic developmental mechanisms in the first year of life, a more substantial empirical basis exists for studying behavioral markers and early signs of autism in the second year. These studies may lead to the development of new screening measures (or validation of existing measures), and generate educational strategies to help improve early detection of autism in the general community, such as in the 'First Words' initiative (Wetherby et al., 2004). Recruiting siblings during the second year of life may also be less resource-intensive than recruiting younger infants.

Frequency of Assessments

The optimal age interval to detect the onset of autistic symptoms and/or regression remains an empirical question. Research on typically-developing populations, as well as research on children with developmental disorders, indicates that there are ''critical periods'' for development of skills typically delayed or absent in autism—such as between the ages of 6 and 18 months

when social-communicative behaviors such as joint attention skills, pointing, and imitation are consolidating (Corkum & Moore, 1998). Multiple assessments within such critical period could be extremely informative for the timing and developmental sequence of these impairments. However, there are potential trade-offs between the rich detail afforded by frequent assessment, and the cost, burden on parents, and potential practice effects on some standardized measures. Frequent assessments may be most feasible using naturalistic observations that do not lead to test-related learning, such as videotaped maternal-infant interaction samples to track social development (Hsu & Fogel, 2003), speech samples or vocabulary checklists to track language development (Tsao, Liu & Kuhl, 2004) or parent diaries or report forms tracking the emergence of behaviors such as gestures (Crais, Day, & Campbell, 2004). The use of parent questionnaires or diaries and video or audiotaped behavior samples from home can facilitate data collection. One can reserve standardized assessment of language, cognition and adaptive function for ''landmark'' evaluations at less frequent intervals, depending on study design and the minimal allowable testing interval on particular tests. Some studies might combine microanalysis of the development and emergence of early social-communication processes (i.e., frequent quantitative and qualitative analyses of operationally defined, spontaneously occurring behaviors) with macroanalysis of developmental trajectories in broad domains of functioning.

Comparison Groups

If one of the goals of a high-risk study is to identify early autism-specific markers, then comparison groups are essential to control for potential confounding variables and to minimize potential sources of bias. If early markers identified in high-risk samples are to be useful in the general population community samples or clinically referred samples (i.e., to guide first- and second-level screening and surveillance), it is important to know not only whether these markers can distinguish autism from typical development, but also whether they distinguish autism from language delays and/or other developmental delays. One should base the selection of comparison groups and matching variables in sibling studies on the populations to which the research findings will be applied.

In some ways, subgroups of the sibling sample itself are ''built in'' comparison groups of infants who will have outcomes other than ASD. Based on previous family studies in autism, we might anticipate that in addition to the 5–8% of siblings who develop ASD, approximately 10–20% will exhibit milder impairments, including language delay (Bailey et al., 1998; Folstein et al., 1999; Murphy et al., 2000), leaving about 70% to develop typically. Comparing siblings who develop ASD, to siblings who do not, controls for two important factors: (1) the potential impact of exposure to an older sibling with ASD (and to related psychosocial stressors on the family); and (2) the possible expectation bias of increased risk of ASD on the part of the examiner (i.e., it may be difficult to maintain blinding to sibling status) or parent rater. However, there are also important limitations to this approach, not the least of which is the possibility of misclassification error at the point of the initial outcome assessment. For example, some siblings classified as ''typically developing'' based on standardized measures may in fact have mild impairments that may become more apparent at a later age. As well, some children who are classified as delayed or as having symptoms of a ''broader autism phenotype'' may later receive a diagnosis of an ASD (particularly Asperger's syndrome) later on. Misclassification errors will tend to minimize differences between groups and reduce power. Other groups of typically developing and developmentally delayed children may also include some who would be classified differently as they get older, but this is more likely to be an issue for siblings of children with ASD because of their genetic liability. As well, siblings with developmental delays may not be representative of other children with delays. In particular, although siblings of children with autism are not known to be at higher risk of global cognitive delay unless they also have an ASD (Fombonne, Bolton, Prior, Jordan, & Rutter, 1997; Szatmari et al., 1993), they may have specific language impairments (Dawson et al., 2002; Landa & Garrett-Mayer, 2006).

Thus, in addition to siblings of children with autism who do not develop an ASD, one should consider additional comparison groups. For example, some studies may benefit from having low-risk groups that control for the effects of being a later-born child, such as infant siblings of typically developing children with no family history of ASD. Including groups to serve as controls for the developmental delays that often accompany ASD is also important to consider, although the selection and recruitment of such groups is a challenge (Szatmari, Zwaigenbaum & Bryson, 2004). With the exception of children with identified syndromes (who are unlikely to be representative), even seemingly high-risk populations, such as siblings of children with developmental delay, may include a relatively small proportion who will ultimately receive a diagnosis of developmental delay and may not cover

the full spectrum of delays that one might observe in an unselected sample (Crow & Tolmie, 1998). One may find delays of a broader range of severity among infants referred to early intervention programs due to constitutional and/or psychosocial risk factors (Allen, 1993), and among infants attending a neonatal follow-up clinic due to prematurity (e.g., Bucher, Killer, Ochsner, Vaihinger, & Fauchere, 2002). Alternatively, if the study follows children starting at a sufficiently advanced age, then one can utilize a comparison group of children ascertained directly by developmental or communication delays (for example, through population screening; Wetherby et al., 2004). However, a substantial proportion of children identified due to this type of delay in the second year of life may ultimately receive a diagnosis of ASD (Robins, Fein, Barton, & Green, 2001), so group comparisons may not be valid or robust until one follows samples to an age at which diagnostic classification is relatively stable (i.e., at least 3 years of age).

Once one select comparison groups, one should consider other potential confounds between risk status and outcome measures as potential matching variables (Jarrold & Brock, 2004; Szatmari et al., 2004). Such confounds might include age, gender (since autism and language delays are more prevalent among boys than girls), and birth order (since early infant behaviour may be influenced by exposure to older siblings). One should also consider matching on parental education and/or socioeconomic status. Although neither factor is known to affect rates of autism, each may influence rates of other relevant outcomes such as developmental delays and behavioral disorders.

Outcome Assessment

Several ongoing studies of young infants use endpoints of at least 3 years of age, although investigators may determine and communicate diagnoses to the family before this time (Zwaigenbaum et al., 2005). This approach is consistent with evidence that the stability of autism spectrum diagnoses increases significantly by this age (Lord & Risi, 2000). Ideally, the diagnostician should be blind to the child's group and previous evaluation data to reduce expectation biases. Diagnosis should also be based on expert assessment using standardized measures (e.g., the Autism Diagnostic Interview—Revised and the Autism Diagnostic Observation Schedule) and best clinical judgment based on ICD-10 or DSM-IV-TR criteria. There is currently very little published concerning the agreement between the ADI-R and ADOS (either in combination or singly) with clinical diagnosis based on DSM-IV (de Bildt et al., 2004), although it is well-established that diagnostic agreement in general correlates positively with the experience of the clinician (Stone et al., 1999; Volkmar et al., 1994). In that regard, one should also consider the additional step of having expert clinicians review all available clinical data and then reach a consensus best estimate diagnosis (as is done in some genetic studies; see MacLean et al., 1999). However, we do not yet know whether clinical experience with older preschool children will ensure stability of autism diagnoses in toddlers. At present, there is little data on the sensitivity and specificity of measures such as the ADI-R and ADOS in children under age 2–3 years, so the interpretation of these measures requires careful clinical judgment (Lord & Risi, 2000; Moore & Goodson, 2003).

Issues Regarding Measures

Constructs for Measurement

Given the hypothesis that high-risk infants have increased rates of language disorders, impaired cognitive abilities, atypical social behaviors and other features of the broader autism phenotype, assessments should measure development across multiple domains over time in order to capture the breadth of outcomes. A comprehensive developmental approach grounded in a thorough intellectual ability assessment is necessary, as one needs to consider constructs such as play, imitation, language and social interaction in the context of the young child's cognitive abilities. Developmental assessment should include measures of expressive and receptive language, adaptive behavior and overall cognitive profile (see Klin, Chawarska, Rubin & Volkmar, 2004 for a review). Although it is challenging to find cognitive tests that include sufficient nonverbal as well as verbal components, and that one can use across a reasonable developmental range without floor or ceiling effects, such assessments will allow for outcomes such as mental retardation and specific language impairment to be distinguished from autism spectrum disorders. One of the challenges at the outset is that most available measures are designed to detect quantitative delays in early development (e.g., smaller vocabularies, lower age equivalent scores in various areas of cognition) but not atypical or qualitatively abnormal or deviant patterns of skill development (e.g., splinter skills, atypical developmental sequence) that may ultimately be more specific

to autism. Data on developmental trajectories of language and cognitive skills may ultimately be more informative than profiles from any single point in time, another advantage of studying autism in high-risk samples using a longitudinal design.

Because the existing diagnostic criteria for autism (APA, 2000) are not necessarily suitable for diagnosing very young children, evaluation of young children for signs of autism (or related communication or social problems) must include assessment of underlying developmental constructs. For example, early characteristics of autism evident in children younger than 2 years may likely include subtle deficits such as variable eye gaze, inconsistent joint attention skills, reduced vocal and/or motor imitation, and repetitive or abnormal use of objects (Zwaigenbaum et al., 2005). These behaviors or skill deficits may be markers for disrupted underlying mechanisms, such as attentional control, executive functioning, preferential orientation to social stimuli, social motivation, face processing and auditory processing (Volkmar, Lord, Bailey, Schultz, & Klin, 2004). Measures of some of these analogue skills including joint attention (Mundy, Sigman & Kasari, 1990) and imitation (Rogers, 1999; Stone, Ousley & Littleford, 1997) have become quite refined. In addition, some investigators have reported measures of face processing (Dawson & Zanolli, 2003) and eye-gaze tracking (Chawarska, Klin, & Volkmar, 2003) in very young children. However, the field generally lacks well-validated measurements for most neuropsychological processes in very young children. Although this presents an initial challenge to prospective studies of autism, high-risk samples may provide the necessary developmental substrate to evaluate innovative measures focused on early impairments and underlying mechanisms in autism. Moreover, longitudinal studies that assess the persistence and developmental progression of atypical behaviors and skills deficits offer a significant advantage over previous cross-sectional research.

Measures of Delay or Deviance

Early indicators of autism may present more as the absence of expected behaviors rather than as the presence of obvious behavioral aberrations. Measures that ''press'' for social or communication behaviors that are often delayed or deviant in children with ASD would seem appropriate for assessing high-risk infants. For example, the Autism Observation Scale for Infants-AOSI; Zwaigenbaum et al., 2005), recently developed for the purpose of assessing early signs of ASD across a range of developmental domains, adopts this approach. Similarly, the Communication and Symbolic Behavior Scales-Developmental Profile includes several specific play interactions that press for early social communicative behaviors, including measures of joint attention (Wetherby & Prizant, 2002). However, a brief period of observation in a research lab may not easily capture the range of contexts and facilitating/interfering conditions that influence these behaviors in everyday situations. As a result, one should obtain information about the persistence, quality and frequency of social responses from parental report as well as observation, with special attention paid to how one elicits the responses and how much parental prompting, supports, and accommodations are required. For instance, in addition to level and type of communication, examination of the rate of communicative behaviors during ''typical'' social situations may be informative (Charman et al., 2005). One also needs data on the quality and context of observed behaviors to complement simple frequency counts. Contributions of infant development experts may be critical for identifying measures that capture the variability of typical infant development with respect to social-communicative behaviors.

Measurement of Atypical Behaviors

Measurement of atypical behaviors in young children is also challenging. The types of unusual behaviors seen in very young children with autism, such as seeking or avoiding specific types of sensory responses and input and repetitive motor behaviors, are particularly difficult to measure because they vary in presentation within and across children. Stereotypic motor behaviors may also be less frequent at very young ages, at least by parental report (Stone et al., 1994) and may be difficult to distinguish from the normal rhythmic movements observed in typically developing infants (Thelen, 1981a; b). What is predictive of autism may not simply be the type of behavior, but rather, the persistence, quality, frequency and contexts under which the behavior is observed—but determining this will require careful quantitative and qualitative analysis, and appropriate comparison groups. There are very little normative data on the development of sensory preferences in typical infants against which to compare the sensory behaviors of infants at increased risk for ASD. It is essential that measures of repetitive behaviors and sensory interests be normed in typically developing infants so one can meaningfully interpret the significance of findings in high-risk populations.

Issues Related to Generalizability

Potential Differences between Participants and Non-Participants

Given that investigators may ultimately use the findings from prospective studies of high-risk samples to assist with identification of early signs of autism in the general population, it is important to consider which factors may influence participation rates. First, specific concerns may motivate parents to enroll their younger infants. This selection factor does not necessarily imply that early development in this group will differ from that of other infants subsequently diagnosed with autism. However, if parents are more sensitive to atypical development in one domain compared to another (e.g., verbal language versus motor imitation), this factor may bias the phenotypic distribution of participating infants. This bias is most explicit in high-risk studies that use specific screening tools to identify their participants (Wetherby et al., 2004), but may also be an issue in sibling studies. Given that early concerns may influence participation rates, one must interpret estimates of recurrence risk from infant sibling studies cautiously. Second, the characteristics of the proband (e.g., level of function, severity of symptoms) may influence parents' perceptions of risk and hence, likelihood of participating. Similarly, parents with other children or relatives with autism or autism-related conditions may also perceive greater risk in their infants. Finally, other family characteristics can influence research participation rates in general, such as socioeconomic status, parental education, and family composition (e.g., single versus two-parent family, number of siblings).

Potential Differences between Siblings who Develop ASD and other Children with ASD

Children with ASD ascertained through an affected sibling may differ from other children with ASD. For example, differences in genetic factors, that is, genes that lead to higher recurrence rates, may influence the clinical expression of autism. Notably, a slightly higher rate of the BAP occurs in extended relatives when there are two affected children in a sibship (Szatmari et al., 2000). Differences in early development may also result from the very fact that there is already a child in the family with a diagnosis of autism. For the second affected child, this may lead to earlier recognition of symptoms and initiation of intervention, as well as differences in parent–child interactions, influenced both by parents' previous experience with autism and the added stress of parenting an older child with special needs. Parents often raise the question as to whether some behaviors may result from interactions with the older sibling with autism. However, most available data on early markers of autism in young children point to the *absence of typical social-communicative* behaviors—which would be less influenced by interaction with siblings—rather that the presence of atypical, potentially learned behaviors (Baranek, 1999; Dawson & Osterling, 1997; Rogers & DiLalla, 1990). Notably, cross-sectional studies have failed to identify differences in autistic symptoms or level of function between children with autism who have a sibling with autism, and children with autism who do not (Cuccaro et al., 2003). Comparing developmental trajectories unfolding into later stages of childhood of children with ASD ascertained through sibling studies with those of children referred early (e.g., under 2–3 years) for diagnostic assessment may shed further light on potential differences between the two groups.

Clinical Issues Related to following High-Risk Infants

Addressing Concerns

Assessment and identification of possible early markers of autism have important clinical implications for individual participants and their families. Discussing and responding to clinical concerns are, inevitably, major components (and major responsibilities) in the day-to-day operation of prospective studies of high-risk infants, and present challenging clinical and ethical issues. First, what are clinically sensitive, yet scientifically rigorous, approaches to eliciting parents' concerns? How do we best collect information about parental impressions across a broad range of domains or test hypotheses about specific early signs without creating concerns or raising parental anxiety? One approach is to ask open-ended questions about particular developmental domains (e.g., ''Describe your child's play interests.''). This approach may yield richer information than a checklist of atypical behaviors. Opportunities to observe the child's naturally occurring behaviors and responses to experimentally designed presses also reduce the potential burden on parents to be the sole source of information on early signs.

Second, how do researchers communicate concerns that arise from their assessments? The involvement of an experienced clinician is critical for this aspect of the project. Providing feedback to parents regarding standardized measures of language, motor, and cognitive development is relatively straightforward when the

child's performance is consistent with age expectations; however, one requires clinical expertise to interpret and communicate assessment results when delays are found. It may also be possible to share some observations made during administration of experimental measures. However, interpretation of the severity of developmental delays or of performance on specific experimental tasks in relation to future risk of autism is much more difficult. At the outset of a study, the relation between early findings and risk of autism is generally unknown, and only descriptive feedback is possible. On the other hand, as the number of children who complete the study protocol to outcome assessment increases, data accumulate regarding the predictive validity of early markers. At what point is there an ethical obligation to share this information with participants? This issue should be given careful consideration in the study development and design, and in some situations may warrant ongoing consultation with an independent ethics committee.

Third, how do researchers respond to concerns that parents communicate spontaneously? Handling parental concerns about their infants or toddlers clearly requires clinical sensitivity and acumen. One must acknowledge concerns and treat them with appropriate seriousness, even if their implications for course and/or prognosis are unknown.

Clinical Diagnosis

Ethical standards dictate that researchers follow current best practice in dealing with diagnostic issues in high-risk samples. When children meet DSM-IV criteria for ASD, the diagnosis must be communicated to parents in a timely way to ensure that they can obtain appropriate services for their child. In some cases a clinical diagnosis is appropriate before one schedules the child's formal outcome assessment. This procedure may have an impact on outcome assessment itself, to the extent that early intervention accelerates skill development and reduces symptoms. However, one can still complete an independent (and optimally blind) assessment of diagnosis (e.g., at age 3 years), thus providing an opportunity to assess stability of early diagnoses in this group. Moreover, if researchers fail to communicate diagnoses when criteria are met, parents may seek support elsewhere and elect to opt out of studies. Selective drop-out of children with diagnoses may prove to be a greater threat to longitudinal research in high-risk samples than the effects of early intervention.

Longitudinal studies of referred samples indicate that the vast majority of children receiving an expert clinical diagnosis of ASD at 24 months retain that diagnosis in an independent assessment at age 3 years (Lord, 1995; Stone et al., 1999), but there may still be some diagnostic changes up until age 7 (Charman et al., 2005). However, only a small percentage of children with ASD are referred prior to 24 months and children with the most severe symptoms may predominate, an ascertainment bias that may inflate estimates of diagnostic stability. A high-risk sample may be more likely to include children across the full range of ASD severity, including those with milder or more subtle symptoms.

There may even be instances in which a child appears to meet DSM-IV criteria for ASD even earlier than 2 years. However, there are currently few data on the stability of diagnoses made prior to 2 years, and as noted earlier, there are no guidelines on how to interpret scores on standardized measures such as the ADI-R and ADOS, or even how to interpret DSM-IV criteria for children in this age group. Boundaries between ''early markers'' (those atypical behaviors which have a statistical association with a later diagnosis of autism) and ''diagnostic markers'' (atypical behaviors which provide evidence that DSM-IV criteria are currently met) are ill-defined. Although this situation presents a clinical dilemma in current studies of high-risk infants, prospective research in this area provides a unique opportunity to develop diagnostic criteria that are more developmentally appropriate for this age group.

The current emphasis on avoiding delays in diagnosis places a strong focus on children with ASD who are missed by early identification and screening efforts (false negatives). However, particularly as we begin to test the limits of our clinical experience regarding assigning diagnosis to toddlers with strong evidence of autism, we must also consider the significance of misclassification errors in the opposite direction (i.e., false positives, children who do not retain a stable diagnosis of autism or move in an out of ASD) (Charman et al., 2005). Although children with other developmental conditions may also benefit from early referral to intervention services, clinical best practice requires careful follow-up to at least an age where diagnostic stability is better established, and sensitive but open discussion at the time of diagnosis regarding possible change in status over time.

Intervention Referrals

Given the discrepancy between accelerating knowledge concerning early behavioral markers for autism and the lack of proven interventions for children

under the age of 2 years, combined with the notion that earlier intervention is highly desirable to maximize the chances of a positive outcome (Lord & McGee, 2001), the process of referring families for intervention is complex. To fulfill ethical requirements, informed consent must address what will occur when study measures indicate that a child has a significant problem, the criteria for which should be specified a priori (Chen, Miller & Rosenstein, 2003). Clinicians are obliged to refer children for treatment when they believe it is clinically necessary for facilitating the child's development as well as providing support to the parents. Developmental services have a responsibility to offer interventions targeting children's specific needs (mandated by law in the U.S.) However, local providers of early intervention may have limited experience in delivering interventions specialized to the social-communicative needs of children younger than age 2 years, indicating a critical need for further research in this area. One should carefully document any intervention received by participants with respect to modality (targeted skills/ideology), setting (home based versus clinic/center based), and, critically, intensity (hours per week) to try to factor such interventions into outcome analyses. Notably, we currently lack efficacy data for interventions targeting early signs of autism in this age group, so it will be difficult to determine whether the interventions change developmental trajectories or whether gains related to the natural unfolding of developmental processes. Controlled clinical trials of interventions that target the specific deficits of autism yet are developmentally appropriate to young infants and toddlers are essential to resolve this issue. However, until such data are available, the absence of a clear-cut standard of care for at-risk children will leave a significant degree of ambiguity regarding appropriate and ethical referral decisions, a situation which investigators note in other samples at high-risk of psychopathology (Heinssen, Perkins, Appelbaum, & Fenton, 2001, p. 572).

Summary and Future Directions

In summary, general recommendations for the field with respect to high-risk research include the need to pay critical attention to methodological rigor as well as human subjects concerns and practicalities in engaging families in research, retaining their research participation, and ethically considering appropriate parental involvement and feedback. Specific recommendations include a careful consideration of issues related to recruitment and sampling, the need to follow infant participants closely during "critical" age periods (6–18 months), the need to consider current knowledge limitations in making decisions about clinical concerns, diagnoses, and referrals, and the need to use appropriate comparison groups.

Other recommendations include collaboration across research groups to achieve adequate samples for successful data analysis of siblings who develop autism. Given the small sample sizes of families in any one geographic area and the low recurrence risk estimates, collaboration among research groups greatly expedite studies examining the development of younger siblings with autism. To facilitate productive collaboration, research groups should attempt to use consistent diagnostic methodologies as well as at least some common core measures.

Another avenue for maximizing the efforts of studying high-risk samples is to include researchers from disciplines such as genetics, neurobiology, developmental psychology as well as ethicists. Although autism clinical researchers may lead these studies, geneticists and neuroscientists could use early phenotypic and endophenotypic data to narrow their search for gene locations and brain mechanisms. Contributions from experts in normative development may enhance infant sibling studies by providing guidance in developing measures suitable for infants as well as evaluating variability in behaviors and in specific skill development in the first year of life. Ethicists may be necessary for designing studies that maximize data collection while ensuring participants and family members engaged in such research have a favorable risk-benefit ratio (Chen et al., 2003).

The methodological and clinical concerns that are specific to research with samples at high-risk for the development of autism continue to evolve, particularly as one identifies and tests behavioral (and biological) markers at younger ages. As research with infant siblings begins to validate early manifestations of autism empirically, and consequently early diagnostic measurements improve, both research questions and design will narrow in focus and guide the development of more refined guidelines for such investigations.

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