

Research Forum

Risk Factors Associated With Language in Autism Spectrum Disorder: Clues to Underlying Mechanisms

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Purpose: Identifying risk factors associated with neurodevelopmental disorders is an important line of research, as it will lead to earlier identification of children who could benefit from interventions that support optimal developmental outcomes. The primary goal of this review was to summarize research on risk factors associated with autism spectrum disorder (ASD).

Method: The review focused on studies of infants who have older siblings with ASD, with particular emphasis on risk factors associated with language impairment that affects the majority of children with ASD. Findings from this body of work were compared to the literature on specific language impairment.

Results: A wide range of risk factors has been found for ASD, including demographic (e.g., male, family history), behavioral (e.g., gesture, motor) and neural risk markers (e.g., atypical lateralization for speech and reduced functional connectivity). Environmental factors, such as caregiver interaction, have not been found to predict language outcomes. Many of the risk markers for ASD are also found in studies of risk for specific language impairment, including demographic, behavioral, and neural factors.

Conclusions: There are significant gaps in the literature and limitations in the current research that preclude direct cross-syndrome comparisons. Future research directions are outlined that could address these limitations.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder involving deficits in communication, social functioning, and behavior that emerge during the toddler or preschool years. ASD is diagnosed on the basis of behavioral observations and assessments, but there are significant disparities between the children who are identified by clinicians in the early years and those who are not (Daniels & Mandell, 2013). These disparities have important consequences for access to interventions that can be highly effective in reducing the severity of impairment and especially for promoting language development (Kasari, 2015). To address these issues, one recent line of research has explored the infancy period using prospective longitudinal designs in an effort to identify the earliest risk factors for ASD and related neurodevelopmental disorders, even before the onset of symptoms (Zwaigenbaum et al., 2007). In this Research Forum article I review some of the work in this area focusing on demographic, behavioral,

neural, and environmental factors that have been found in studies of infants at risk for ASD, with an emphasis on factors associated with language, and then compare these factors to those found in studies of infants at risk for specific language impairment (SLI).

ASD

Diagnosis

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*; American Psychiatric Association, 2013), ASD is diagnosed on the basis of two symptom clusters: (a) deficits in social communication and (b) the presence of repetitive behaviors and restricted interests. For children to be diagnosed with ASD, they must meet all three criteria under social communication: deficits in (a) social-emotional reciprocity; (b) nonverbal communicative behaviors; and (c) developing, maintaining, and understanding relationships. This domain includes several impairments specific to communication: failure in back-and-forth conversation; deficits in nonverbal communicative behaviors; and difficulties adjusting behavior to suit various social contexts, which includes adjusting

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language to different listeners and other pragmatic aspects of language. For the second symptom cluster a child must have at least two different atypical behavioral patterns, such as stereotyped or repetitive motor movements, insistence on sameness, highly restricted interests, or atypical sensory sensitivities. Diagnosis also requires rating the severity level on the basis of the amount of support needed. ASD is almost always accompanied by one or more co-occurring conditions that may develop during different stages of the life span. These conditions include intellectual disability, language disorder, medical conditions (e.g., genetic syndromes, epilepsy, sleep or gastrointestinal problems), and other psychiatric conditions (e.g., attention-deficit/hyperactivity disorder, tic disorders, anxiety, or depression). Recent evidence suggests that this set of comorbidities may be useful for defining meaningful subgroups within the ASD population that could serve as a basis for stratifying samples for research on etiology and pathophysiology (Doshi-Velez, Ge, & Kohane, 2014).

ASD has a strong genetic basis. It is highly heritable (Colvert et al., 2015), and current research has led to the rapid ongoing discovery of a relatively large number of *de novo* and transmitted rare and common genomic events that are associated with the diagnosis (Jeste & Geschwind, 2014). The etiology of ASD is complex, involving non-genetic or environmental risk factors, gene-environment interactions, and epigenetic mechanisms, as is true for all neurodevelopmental disorders (Tordjman et al., 2014). The genetic etiology of ASD contributes to alterations in brain development that may be traced back to the prenatal period (Bae, Jayaraman, & Walsh, 2015). Many studies of children and adults with ASD have demonstrated differences in brain structure and function, using a variety of imaging technologies (Ecker & Murphy, 2014; Lainhart, 2015). Atypical patterns in neural connectivity across the brain have been highlighted in numerous studies (e.g., Doyle-Thomas et al., 2015; Liseicka et al., 2015). In other studies, associations between atypical connectivity and cortical organization in specific neural systems have been found in relation to behavioral impairments associated with ASD (Ameis & Catani, 2015). For example, several studies have found relationships among atypical structure, lateralization, and functional connectivity in language regions (e.g., Knaus et al., 2010; Verly et al., 2014; Williams et al., 2013); however, there is still no consistent pattern of findings, largely because of heterogeneity among participants and differences in methodology across studies.

Language in ASD

In the *DSM-5*, delayed or impaired language is no longer included as a core symptom, though clinicians are required to note whether a child has a comorbid language disorder (American Psychiatric Association, 2013). There is enormous variability in the language profiles of children with ASD (Tager-Flusberg, Edelson, & Luyster, 2011). Some have intact structural language skills, scoring within (or above) the normal range on standardized language

tests; some acquire spoken language after delays in onset but never reach the normal range, thus having comorbid language impairment; and some never acquire functional spoken language even when they have had access to good interventions. These children are referred to as *minimally verbal*, but little is known about the source of their profound language deficits (Tager-Flusberg & Kasari, 2013). Estimates of the proportions of children within these subgroups vary depending on ascertainment methods, but the majority of affected children acquire spoken language but remain delayed relative to their peers (Kjelgaard & Tager-Flusberg, 2001). It has been claimed that this group of children with language impairment and ASD has comorbid SLI, but this proposal is still controversial (Norbury, 2013; Williams, Botting, & Boucher, 2008).

The early developmental profiles of language in ASD are highly variable. Most children are delayed in standard milestones, especially the onset of words and phrases. On standardized measures, receptive language appears relatively more impaired than expressive language, though this may be related more to lack of overall social responsiveness than to language processing deficits (Tager-Flusberg, 2000). After early delays, some children show accelerated language development in the third or fourth year, no longer meeting criteria for language impairment (Szatmari et al., 2000). Another group of children shows a pattern of regression: At 12 to 15 months they begin to use words to communicate with others, but then later in the second year they stop speaking (Pickles et al., 2009). This loss of language (and social) skills marks the onset of ASD (Ozonoff et al., 2010). As they develop, some of these children will regain some language, but others will not.

One important influence on the development of language in children with ASD is effective early behavioral intervention. Indeed, across several studies and different types of behavioral interventions, the most significant gains observed in children are in receptive and expressive language. For example, Dawson et al. (2010) found that toddlers receiving a comprehensive behavioral program (the Early Start Denver Model) for 20 hours a week gained on average almost 20 standard score points in receptive language and 12 points in expressive language after 2 years in the program. Briefer, more targeted interventions also lead to significant gains in language, as demonstrated, for example, in studies by Kasari and colleagues, who found that training joint attention skills in toddlers and preschoolers with ASD for 30 min a day over a 5- to 6-week period led to significant gains in expressive language (Kasari, Freeman, & Paparella, 2006) that were still evident several years after the intervention was provided (Kasari, Gulsrud, Freeman, Paparella, & Hellemann, 2012). Despite the importance and efficacy of early intervention, in every study there are children who make little or no progress at all, but little is known about predictors of response to intervention. In sum, in ASD there is enormous variability in language reflected in a range of developmental trajectories, response to treatment, and longer term outcomes.

Infants at Risk

Studying Infants at Risk for ASD

How early can we identify the emergence of atypical behavioral or brain patterns associated with symptoms or degree of language impairment in ASD? This question has led to a surge of interest over the past decade in studying infants who are at risk for ASD, beginning in the first few months of life or even prenatally, long before the onset of symptoms (Zwaigenbaum et al., 2007). This line of research is important for discovering early biomarkers that may be used to parse heterogeneity in outcomes and predict response to treatment. In almost all studies that focus on this issue, risk is defined as *familial risk*—the presence of an older sibling diagnosed with ASD—thus taking advantage of the high heritability of the disorder. The standard research design compares these high-risk infant siblings to low-risk members of a control group, usually infants who have an older sibling but no family history of ASD. The infants are followed prospectively until the time when a diagnosis of ASD can be confirmed, at the age of 2 or 3 years.

The risk recurrence rate for infant siblings is close to 1 in 5, on the basis of data accrued through the Baby Sibling Research Consortium, which brings together researchers from around the world who are conducting infant-sibling studies of ASD (Ozonoff et al., 2011). These rates are higher for males than females and for infants who have more than one older sibling with ASD. In addition to these demographic risk factors (male, family history), epidemiological studies have found that parental age is another important risk factor: Older parents, especially fathers, are more likely to have a child diagnosed with ASD (Lee & McGrath, 2015).

Studies of high-risk infants provide insight into several key issues. First, they have the potential to discover early signs and risk markers for the almost 20% of infants who are later diagnosed with ASD. This is one of the primary motivations for conducting these longitudinal studies, in the expectation that identifying these markers will lead eventually to earlier diagnoses. Reviews of the findings that have been reported over the past decade conclude that few behavioral patterns specific to ASD appear before 12 months; even then, the patterns that have been found signal risk rather than individually sensitive and specific predictors of outcome (Gliga, Jones, Bedford, Charman, & Johnson, 2014; E. J. H. Jones, Gliga, Bedford, Charman, & Johnson, 2014). Although signs of social-communicative impairment have been the predominant emphasis in many studies, risk markers are evident across multiple developmental domains, including language (e.g., Paul, Fuerst, Ramsay, Chawarska, & Klin, 2011), attention (e.g., Bedford et al., 2014), motor skills (Libertus, Sheperd, Ross, & Landa, 2014; Nickel, Thatcher, Keller, Wozniak, & Iverson, 2013), and temperament (e.g., del Rosario, Gillespie-Lynch, Johnson, Sigman, & Hutman, 2014).

Second, studies of high-risk infants have found that clinical outcomes are not limited to ASD. By age 3 years or older, a significant proportion of infants who do not

have ASD may be diagnosed with language delay (Drumm & Brian, 2013), social-communication delay (Miller et al., 2015), or developmental delay or intellectual disability (Messinger et al., 2013). This range of outcomes highlights the complexity and overlap among neurodevelopmental disorders, reflecting common underlying etiology and neuropathology (Doherty & Owen, 2014).

Third, across most studies significant differences are found between high- and low-risk infants, even when the infants with ASD outcomes are excluded from the analyses (Tager-Flusberg, 2010). At the behavioral level, studies have found that a significant number of high-risk infants carry features of the broader autism phenotype: traits associated with ASD that differentiate these infants from low-risk infants in the control groups (Messinger et al., 2013; Ozonoff et al., 2014). Other differences between high- and low-risk infants are especially striking in studies of structural and functional brain development and in experimental eye-tracking studies that can target fundamental cognitive mechanisms (E. J. H. Jones et al., 2014). These neurocognitive differences are taken as evidence for early emerging *endophenotypes* associated with ASD (Gottesman & Gould, 2003), which are defined as heritable characteristics associated with a disorder that are more commonly found in relatives of individuals who have been diagnosed with the disorder but may be independent of having the disorder. Thus, endophenotypes facilitate the identification of points of neurocognitive vulnerability to the disorder itself.

As a final point, studies of high-risk infants with and without ASD outcomes have consistently found that they follow different behavioral and neural developmental trajectories over the first few years of life (E. J. H. Jones et al., 2014; W. Jones & Klin, 2013; Luyster, Powell, Tager-Flusberg, & Nelson, 2014). These differences in development suggest that no single time point will be particularly revealing about the roots of ASD; instead, it seems that the hallmark of the emergence of ASD, usually in the second or third year of life, is alterations in development (Ozonoff et al., 2010). These differences in development also extend to some unaffected siblings, suggesting that they are part of the endophenotype of the disorder.

Early Concerns and Risk Signs for Language in ASD

Several studies have found that at 12 months, high-risk infants—in particular, those who are later diagnosed with ASD—are delayed in language and gestural communication (e.g., Iverson & Wozniak, 2007; Mitchell et al., 2006), and those delays may be closely tied to delays in motor development (Bhat, Galloway, & Landa, 2012; LeBarton & Iverson, 2013; Nickel et al., 2013). Indeed, delays in language-related milestones may be among the most reliable early signs of ASD, though this signal clearly has low specificity because children who are not at risk for ASD or who have other neurodevelopmental outcomes also have delays in language (Luyster, Seery, Talbott, & Tager-Flusberg, 2011).

In our ongoing infant-sibling study, a collaboration between Boston University and Boston Children's Hospital, we found that as early as 6 months, about one fifth of parents of high-risk infants expressed significant concerns about their child's language in weekly online diaries that they kept between 6 and 18 months (Talbot, Nelson, & Tager-Flusberg, 2015a). By 12 months, over half the parents whose infants were later diagnosed with ASD expressed concerns about their child's language, far more so than concerns about core social-communication or repetitive-behavior symptoms of ASD. For the infants in our study, the high-risk infants who were later diagnosed with ASD showed significant delays in communicative gestures at 12 months (Talbot, Nelson, & Tager-Flusberg, 2015b). In a similar vein, at this age they also vocalized significantly less than the low-risk infants or high-risk unaffected siblings (Chenausky, Nelson, & Tager-Flusberg, 2015), thus confirming findings from other studies that early delays in communication and language are hallmark features of ASD. It is important to note that this is even true for infants with ASD whose later language is well within the normal range.

Brain Mechanisms Underlying Early Language Speech Perception

A great deal is known about the development of infants' perception of speech sounds in the first year of life. At birth infants show a strong preference for listening to speech (Butterfield & Siperstein, 1970; Vouloumanos & Werker, 2007) and, like adults, they perceive phonemes categorically (Eimas, Siqueland, Jusczyk, & Vigorito, 1971). By 4 months, infants can distinguish their own language from even closely related other languages to which they have not been exposed (Bosch & Sebastián-Gallés, 2001), and by 10 months they no longer discriminate consonant contrasts that are not used in their native language (Kuhl, 2004). This *perceptual narrowing* can be measured using behavioral (Werker & Tees, 1983) or neural imaging methods, including electrophysiology (Cheour et al., 1998; Rivera-Gaxiola, Silva-Pereyra, & Kuhl, 2005). Although there is some bias toward left-hemisphere processing of speech in young infants (Dubois et al., 2009), more robust left-lateralized responses to language emerge at the end of the first year of life (Minagawa-Kawai, Mori, Naoi, & Kojima, 2007).

Kuhl (2004, 2010) has argued that this process of perceptual narrowing depends on implicit learning that takes place in a social context, specifically through interactions with social partners who provide a rich and extensive exposure to the infant's native language; these interactions promote changes in the neural organization for language. Given the social impairments that define ASD, we investigated whether infants at risk for ASD, including those later diagnosed with the disorder, would be delayed in losing the capacity to discriminate native and nonnative contrasts. We hypothesized that their relative lack of interest in social events compared with nonsocial objects (cf. Tager-Flusberg, 2010) might limit their tuning into language and hence

affect the process of perceptual narrowing. We investigated this hypothesis using event-related potentials (ERPs) to capture the development of the neural basis for speech perception in infants at high or low risk for ASD (Seery, Vogel-Farley, Tager-Flusberg, & Nelson, 2013).

We used the double oddball paradigm developed by Rivera-Gaxiola et al. (2005). A standard stimulus, /da/, was presented on 80% of trials; a native contrast, /ta/, on 10% of the trials; and a nonnative contrast, /a/, on 10% of the trials. This nonnative contrast is phonemic in languages such as Bengali, but English-speaking adults cannot distinguish it from the standard /da/. ERPs were recorded while infants sat on their mother's lap watching someone blow bubbles and the speech stimuli played through speakers. The infants who were part of our larger longitudinal study were seen at 6, 9, and 12 months of age, with an average of 30 infants in each group providing usable data at each time point.

We expected that at 6 months the amplitude of the ERP component elicited about 150–300 ms after the onset of the stimulus (the so-called *P150*) would be maximally sensitive to both the native and nonnative stop-consonant contrasts compared to the standard /da/, for both groups of infants, and indeed this is what we found over the frontal brain areas. We also expected that at 12 months, the *P150* amplitude of the nonnative contrast would no longer be significantly different from the standard, as a result of perceptual narrowing and again this is what we found, for not only the low-risk but also the high-risk infants, including those who at age 3 years were diagnosed with ASD. These results suggest that, contrary to our initial hypothesis, ASD may not involve delays in perceptual narrowing, at least not for the high-risk infants in our sample, all of whom began speaking before age 2 years (Seery et al., 2013).

We followed up on these findings in the same infants by examining group differences in the amplitude of the *P150* to repeated presentations of the standard stimulus /da/ at 9 months (Seery, Tager-Flusberg, & Nelson, 2014). Our motivation was to explore whether we would find group differences in the degree of habituation to the repeated speech sounds, as were found in an earlier study of 9-month-old high-risk infants in their responses to repeated tones; unlike low-risk infants in the control group, these failed to exhibit neural habituation (Guiraud et al., 2011). Within the constraints of our study design, which limited our analyses of habituation to three repeated stimuli, we did not find that either group showed significant changes in amplitude in response to successive presentations of the standard. This may be because infants prefer speech sounds to tones (which were used by Guiraud et al., 2011) and continue to attend to them without significantly attenuating their attention.

Although there were no group differences in habituation, high-risk infants had significantly higher *P150* amplitudes across all the standards compared with the low-risk infants in the control group. Moreover, for the high-risk group only, the amplitude of the *P150* was significantly correlated with later expressive language ability as assessed on the Mullen Scales of Early Learning at 18 months of age. Thus, for infants at risk for ASD, the atypical larger *P150*

amplitudes to repetitions of speech stimuli were associated with better language outcomes. Perhaps these infants were more focused on the linguistic stimuli, paying less attention than the low-risk infants in the control group to the other sights and background sounds during the experiment. This enhanced attention then served them well as a foundation for language development. Of course, other explanations are possible, and only further investigation will help tease apart the source and impact of this atypical enhanced amplitude to speech in high-risk infants.

Lateralized Response to Speech

The early positive peak of the waveform elicited by the consonant–vowel stimuli used in our study, the P150, captures the acoustic changes related to stop consonants. Later negative segments of the waveform, between 300 and 600 ms after the onset of the stimulus, are more sensitive to subtle hemispheric differences in speech processing. We analyzed the average amplitude of this *late slow wave* at each of the three age points: 6, 9, and 12 months.

At 6 months there were no hemispheric differences in either the high- or low-risk group. By 9 months, and again at 12 months, there was a significant Group \times Hemisphere interaction: This was driven by significant differences in the responses in the left and right temporal/parietal regions at both ages in the low-risk infants in the control group. In contrast, there were no hemispheric differences at any age among the high-risk infants (Seery et al., 2013). We have now completed similar analyses of data drawn from a larger group of fifty-seven 12-month-old high-risk infants, for whom 36-month outcome data were available; we were thus able to divide them into those with and without ASD outcomes. We found that the infants who did not develop ASD showed no lateralized response to speech. In contrast, those who developed ASD exhibited a lateralized response, but in the direction opposite to what we found in the low-risk infants in the control group. Thus, the low-risk infants in the control group showed a significant left-hemisphere bias to processing speech, whereas the infants later diagnosed with ASD showed a significant right-hemisphere bias.

Because neither of the high-risk infant groups (with and without ASD outcomes) showed a typical left-lateralized response to speech in the first year of life, this suggests that we have identified an early endophenotype, but one that does not directly relate to differences in behavioral (linguistic) outcomes. It may be that right-lateralized responses at 12 months serve as an early predictive biomarker for ASD; however, these findings are still preliminary, given our relatively small sample sizes.

Functional Connectivity for Language

There is a general consensus in the literature that ASD involves disruptions in cortical connectivity at both the structural and functional levels (Geschwind & Levitt, 2007). Neuroimaging studies of functional connectivity patterns have found both under- and overconnectivity of large-scale

brain systems (Uddin, Supekar, & Menon, 2013). Although there is considerable controversy in this area because of conflicting findings, studies have found more consistent patterns of underconnectivity between frontal and posterior brain regions important in higher order cognitive domains including, for example, language processing (Just, Keller, Malave, Kana, & Varma, 2012).

One important question is how early these patterns of underconnectivity develop. We still know little about the developmental trajectory of functional brain development, not only in children with ASD but also in typically developing children, as there have been few longitudinal studies that focus on the development of neural systems, in particular those underlying language development (Uddin, 2015). We took advantage of our speech-perception experiment to begin exploring these questions in 6- and 12-month-old infants at high and low risk for ASD (Righi, Tierney, Tager-Flusberg, & Nelson, 2014). Our measure of functional connectivity was *linear coherence*: an index of synchrony in gamma-band activity in the electroencephalogram (EEG) signal elicited by the speech stimuli in frontal and posterior regions of interest. Linear coherence assesses the correlation between the phase and power information of two EEG signals: The higher the correlation, the more synchronized and integrated the signals are, giving us a proxy measure for functional neural connectivity.

We took the EEG data elicited by the standard and deviant speech stimuli in the same time window as the P150 ERP (150–300 ms after stimulus onset). We then extracted the gamma frequency band (30–50 Hz) and computed linear coherence between a small set of electrodes over the frontal and posterior (temporal/parietal) language areas of both hemispheres for our measure of functional connectivity. At 6 months there were no significant differences between the high- and low-risk groups in average linear coherence (across all stimuli and both hemispheres). At 12 months, significant group differences were found: The low-risk infants had significantly higher linear coherence between frontal and posterior language brain areas in both hemispheres compared with the high-risk group. We then separated out the five high-risk infants who were later diagnosed with ASD and reran the analyses of the 12-month data on the three groups (low risk, high risk with ASD, high risk without ASD). We again found that the low-risk infants in the control group had significantly higher linear coherence than the high-risk infants. Those who did not develop ASD had marginally higher coherence than those who did, indicating that the infants with ASD outcomes had the lowest degree of functional connectivity by 1 year old. The developmental trajectories of linear coherence differed across the groups: Whereas the low-risk infants in the control group showed an expected increase in linear coherence between 6 and 12 months, the high-risk infants—both with and without ASD outcomes—showed a decrease.

In a second study we explored the development of neural functional connectivity for language in the first year of life in high- and low-risk infants using different language stimuli and brain-imaging technology (Keehn, Wagner,

Tager-Flusberg, & Nelson, 2013). For this study we used functional near-infrared spectroscopy, a noninvasive method for measuring the concentration of oxy- and deoxyhemoglobin in the cortex using near-infrared light probes placed on the scalp. Changes in these blood oxygenation levels provide an indirect measure of neural activity, similar to functional MRI but with much coarser spatial localization (Gervain et al., 2011). We compared the two groups of infants at 3, 6, 9, and 12 months as they listened to nonsense words composed of patterned (ABB—e.g., *ba-lo-lo*) or unpatterned (ABC—e.g., *ba-lo-ti*) trisyllables. As the infants listened to the language stimuli, they watched a silent video of moving shapes or watched someone blowing bubbles while they sat on their mother's lap. Clusters of probes were placed over four regions of interest: frontal and posterior language regions on the left and right hemispheres.

Our measures of functional connectivity were correlations between the average time course of the hemodynamic response for all possible region-of-interest pairs (within and across hemispheres). At 3 months, the high-risk infants showed significantly higher connectivity between frontal and posterior regions in the left hemisphere compared with low-risk infants in the control group. No group differences were found at either 6 or 9 months, but by 12 months the high-risk infants showed significantly lower connectivity compared with the low-risk infants in the control group.

These 12-month group differences with lower connectivity in the high-risk infants mirror what we found in the EEG connectivity analysis (Righi et al., 2014). The interesting differences at 3 months reflecting higher functional connectivity in high-risk infants suggest that these altered patterns of neural connectivity are there prenatally or soon after birth. Moreover, the findings point to strikingly different developmental trajectories in the two groups of infants that are independent of ASD outcome. Together, our studies of functional connectivity of high-risk infants in the first year of life suggest that differences in the development of neural-system connectivity related to speech and language processing are an early-emerging endophenotype.

Maternal Contributions to Early Communication

Transactional Approaches to Development

In much of the literature on high-risk infants, it is assumed that differences in behavioral or brain development between these infants and low-risk infants in control groups are related to the genetic risk traveling in families that already have at least one child with ASD. But, taken from a broader transactional perspective (Sameroff, 2010), development is a process that is integrally linked to interactions between infants and their environment. For language, the critical environmental factor is engagement with caregivers. According to this view, parents' communicative interactions with infants, which begin long before infants understand intentional communication, are important for shaping language development. As infants become more capable of

participating in these interactions they in turn influence their parents' behavior. It is therefore important to ask the question whether some of differences between high- and low-risk infants in the onset and development of language could be related to differences in how their mothers (the parent most likely to be the primary caregiver) interact with them and, reciprocally, whether high-risk infants influence their parents' social communication and language.

Studies of Maternal Behavior

A few studies have investigated the quality of mothers' interactions with their infants at high risk for ASD. In one early study, Yirmiya et al. (2006) analyzed the interactions between a small group of mothers of high-risk infants and their 4-month-old infants. They found that the mothers had less emotionally synchronized interactions with their infants compared with mothers in the control group; however, there was no significant impact of these subtle differences in interaction style on later language development, assessed when the infants were 14 months old. Wan et al. (2012, 2013) have reported that caregivers of high-risk infants were rated as more directive and less sensitive during play interactions with their 6- and 12-month-old infants compared with caregivers of low-risk infants. In these studies, the influence of caregiver–infant interactions on child language were not reported, only the relationship to later diagnoses of ASD. At 6 months, none of the rated measures predicted outcomes. At 12 months, the most significant predictors of ASD were two infant behaviors: (a) attention to mother and (b) positive affect. Another significant factor was *dyadic mutuality*—a global rating of shared enjoyment and togetherness—but it is likely that this factor was heavily influenced by the infants' behavior (less attention and less positive affect) during play with their caregiver, particularly as all three measures were highly correlated with one another.

Leezenbaum, Campbell, Butler, and Iverson (2014) assessed mothers' verbal responsiveness to their 13- and 18-month-old infants' vocal and gestural communication as they played together in their homes. Mothers of high- and low-risk infants were equally responsive to their infants' communication at both ages. At 18 months, however, the high-risk infants produced fewer pointing gestures; this in turn altered their mothers' linguistic behavior. The variability in the frequency of infants' vocal and gestural communicative attempts significantly influenced the mothers' opportunities to respond in ways that are known to support early word learning. Over time, these reciprocal influences could affect language development because opportunities for learning may be limited if the children themselves make few attempts to communicate.

As part of our infant-sibling project, we too investigated the relationship between maternal and infant gesture and word usage at 12 months, along with the influences on language outcomes at 18 months (Talbot et al., 2015b). We separated the mothers of high-risk infants later diagnosed with ASD from those whose infants did not develop

ASD. At 12 months, all three groups of mothers (high risk with ASD outcome, high risk with no ASD, low risk) were comparable in the amount of language they spoke to their infants. As expected, the mothers also communicated with their infants using gestures. The mothers of high-risk infants who did not develop ASD gestured significantly more frequently than the other two groups of mothers, who were comparable to each other in their communications with their infants. We did not find significant correlations between maternal vocal or gestural communication at 12 months and later language outcomes for any of the groups. Perhaps we lacked statistical power or variability in the socioeconomic backgrounds of our participating families, most of whom were well educated. Nevertheless, the important finding is that mothers of high-risk infants do talk and gesture to their infants, as much as or more than mothers of low-risk infants. Indeed, the significantly higher levels of gesturing we found among the mothers of high-risk unaffected infants suggest that they may be extra vigilant and aware of the risks their infants face.

In sum, there is no evidence that caregivers of high-risk infants are providing a suboptimal social-affective context for language development. When differences have been found in these mothers' interactions with their infants, they seem to be driven by infant behavior, including reduced attention, positive affect, or communicative attempts. In some cases, mothers of high-risk infants provide even richer language-promoting environments than mothers of low-risk infants, which may well contribute positively to their babies' developmental trajectories.

Risk Factors for SLI and ASD

SLI

ASD is not the only complex neurodevelopmental disorder involving language deficits that emerges during the toddler years. To evaluate the specificity of the risk factors summarized so far, it is important to compare the findings with ASD to those with other disorders. SLI is one such candidate, particularly in light of the argument that children with ASD and language impairment have comorbid SLI (Tager-Flusberg & Joseph, 2003).

SLI is diagnosed on the basis of delays and slowed rate of development of language in the absence of hearing impairment, frank neurological damage, intellectual disability, or social deprivation (Leonard, 2014). There is considerable controversy still over the terminology and definition of SLI, which, despite several decades of research, has not yet been resolved (Bishop, 2014; Reilly, Bishop, & Tomblin, 2014). In the *DSM-5* the term *language disorder* is used to encompass persistent difficulties in receptive and/or expressive language. There is general agreement that SLI involves core deficits in grammar, verbal memory, and vocabulary and that it can be diagnosed on the basis of standardized language tests, though there is no agreement on what the cutoff scores should be (Reilly et al., 2014). Nevertheless, there is some consensus that there are

several clinical linguistic markers that characterize children with SLI: impairments in nonword repetition, sentence repetition, and, for English speakers, marking grammatical tense (Conti-Ramsden, Botting, & Faragher, 2001; Tager-Flusberg & Cooper, 1999).

Like ASD, SLI is heterogeneous in both the core phenotypic expression (e.g., presence or absence of receptive language deficits) and co-occurring conditions, including, for example, speech sound disorders, attention-deficit/hyperactivity disorder, dyslexia, and social impairment (Leonard, 2014). It is highly heritable, and so far several risk genes and copy-number variants have been identified (Deriziotis & Fisher, 2013; Simpson et al., 2015). Neuroimaging studies of individuals with SLI have revealed structural and functional differences in left frontal and temporal regions associated with language as well as in basal ganglia structures (Badcock, Bishop, Hardiman, Barry, & Watkins, 2012; van der Lely & Pinker, 2014). Despite how common the disorder is, there has been relatively little systematic research on the neural systems that underlie language impairment in SLI, and most published studies include small sample sizes and different methodologies.

Risk Factors for SLI

For several decades there was considerable interest in finding risk factors for SLI. This was driven in part because diagnosis before age 4 years is complicated by the finding that although many toddlers experience significant delays in early language development, in most cases the delays are resolved during the preschool years with no long-term enduring language deficits (Paul, 1996; Rescorla, Roberts, & Dahlsgaard, 1997). These so-called *late talkers* were studied extensively in an effort to identify which toddlers would be more likely to go on to receive a diagnosis of SLI (Moyle, Stokes, & Klee, 2011).

The most consistent findings across several case-control and epidemiological studies is that family history and male gender are two important risk factors that raise the probability that a late-talking toddler will experience enduring deficits in language (Bishop, Price, Dale, & Plomin, 2003; Zubrick, Taylor, Rice, & Slegers, 2007) or that school-age children without knowledge of their language history will meet criteria for SLI (Tomblin, 1989). Socioeconomic factors, including maternal education, may also raise a child's risk for later language impairment, according to several studies (Christensen, Zubrick, Lawrence, Mitrou, & Taylor, 2014; Rescorla, 2011).

At the behavioral level, several candidate risk markers have been found. Late-talking toddlers who also have poor receptive language skills or more limited gestural communication are more likely to go on to receive a diagnosis of SLI (Ellis & Thal, 2008). Another important predictor is motor development: Toddlers with poorer motor skills are also at greater risk for significant delays in language development that could later meet criteria for SLI (Zubrick et al., 2007).

Two groups of researchers have systematically investigated infants at risk for SLI, defined on the basis of family

history, with an emphasis on neural mechanisms underlying auditory and speech processing. Friederici and colleagues focused on very young infants with a family history of SLI. Using ERPs, they found that at 2 months, a group of 14 high-risk infants showed a delayed mismatch response to changes in syllable length (Friedrich, Weber, & Friederici, 2004). At 4 to 5 months, nine infants at risk for SLI showed a delayed mismatch response for discriminating the stress pattern of two-syllable words (Weber, Hahne, Friedrich, & Friederici, 2005), suggesting that deficits in processing speech duration very early in life may be a marker for later language impairment. Benasich and colleagues studied slightly older infants at familial risk for SLI. In one behavioral study, they found that eleven 7-month-old high-risk infants were less able to discriminate tones presented in rapid succession compared with 16 low-risk controls (Benasich & Tallal, 2002; Choudhury, Leppanen, Leevers, & Benasich, 2007). Their ERP data showed that the amplitude of the mismatch ERP response was smaller and delayed in onset when listening to tones with brief interstimulus intervals (Benasich et al., 2006). They also found that between 6 and 12 months, high-risk infants have atypical lateralization of response to tone pairs compared with low-risk controls. These ERP measures predicted language outcomes, but they were assessed only when the children were 2 years old, long before a clinical diagnosis of SLI can be made.

Taken together, these studies suggest that neurocognitive differences, affecting auditory as well as speech perception, are present very early in life for infants at risk for SLI. One significant limitation of these studies is the small number of infants who were included in the high-risk group: Groups ranged from nine to 14 infants. A second limitation is that the infants who participated in these studies were not followed through the preschool years, when a diagnosis of SLI could be made. Thus, these early differences in neural responses to tones and speech may be part of the endophenotype for SLI; their potential as significant predictors of risk beyond family history is not known.

Comparisons of Research on Risk Factors for SLI and ASD

There are obvious parallels in several of the risk factors that have been found for ASD and SLI. At the demographic level, the most significant predictors for both disorders are family history and male gender. Behavioral characteristics, including paucity of gestural communication, poor receptive language, and motor delays, are associated with both ASD and SLI. Also, infants at familial risk for either ASD or SLI exhibit atypical neural responses to auditory or speech stimuli, as well as atypical lateralization. To some extent these parallels reflect commonalities in risk profiles for a broad range of neurodevelopmental disorders; to some extent they reflect overlap in etiology, for example, shared risk genes for ASD and SLI (Eicher & Gruen, 2015); and to some extent they reflect core foundational precursors for language (Iverson, 2010).

There are, however, significant limitations in comparing risk factors for ASD and SLI, which makes it difficult to discern whether there are any clear risk factors that distinguish these disorders. One major problem is that studies on risk factors for these disorders have relied on somewhat different primary research designs and methods. Most of the work on SLI grew out of small-scale studies of toddlers with language delays or infants at familial risk, or population-based epidemiological studies of poor language outcomes in children. In contrast, research on risk factors associated with ASD has been driven primarily by detailed, relatively well-powered longitudinal studies of infants at familial risk. There is a significant imbalance in the number of publications that address risk factors associated with these disorders. Most of the research on SLI is older, and there is now only a trickle of studies coming out in the literature on SLI. In contrast, since 2010 about 100 papers a year have been published on ASD; most of these are based on infants at risk, a design that offers the greatest promise to expand our knowledge of how a neurodevelopmental disorder unfolds over time. One of the main drivers of this significant imbalance in the studies of infants at risk for ASD and SLI is in the funding available for different neurodevelopmental disorders. Bishop (2010) demonstrated that in the first decade of the current century, funding from the National Institutes of Health increased 65 times more for ASD research compared with SLI research. Indeed, ASD was the fastest growing neurodevelopmental disorder in terms of research funding, which goes a long way toward explaining why high-powered studies of infants at risk for ASD, many of which were begun during this period, were possible.

Even when researchers have taken similar approaches to the study of early risk factors, differences in methodology and choice of paradigms limit the ability to make cross-syndrome comparisons. One clear example is studies of neural processing of sounds and speech in the first year of life. Research on ASD has focused on habituation to tones or speech, atypical lateralization for speech on the basis of amplitude measures, and reduced functional connectivity between major cortical language regions (Guiraud et al., 2011; Keehn et al., 2013; Seery et al., 2013, 2014; Righi et al., 2014). Research on SLI has investigated delays in the timing of ERP responses to speech or differences in processing tones (Benasich et al., 2006; Friedrich et al., 2004; Weber et al., 2005). We do not know, therefore, whether the atypical patterns found in infants at risk for ASD are the same as or different from those found in infants at risk for SLI.

Some of the most exciting findings from behavioral and brain studies of infants at risk for ASD are the differences seen in the developmental trajectories over the first year of life that have been analyzed for high-risk infants with and without a clinical outcome at age 3 years. The longitudinal nature of the research designs opens up the opportunity to carry out hierarchical modeling of development during a time of greatest change. This has led to a deeper understanding of how ASD emerges primarily from differences in behavioral or brain trajectories of change

rather than in differences that can be measured at any single point in time. There are fewer comparable developmental studies of SLI and none that include infants before the age of 18 months. We therefore cannot compare the emergence of these two disorders to investigate whether, even though there are many shared risk factors, the key differences between them might be found in their development over the first 3 years of life.

Another important difference between studies of risk factors for ASD and SLI is at the level of clinical outcomes. Most research on infants at high risk for ASD focuses on the same gold-standard objective assessments and clinical best-estimate measures of diagnosis at age 2 or 3 years. The literature on SLI is less consistent. None of the studies on infants at familial risk for SLI followed their participants longitudinally to evaluate whether their findings were endophenotypes or more specific risk markers for SLI. Also, some of the epidemiological studies relied on test score outcomes rather than clinical evaluations. One key difference between ASD and SLI is that proportionately far fewer preschool-age children with SLI are identified in clinical caseloads compared with toddlers or preschoolers with ASD, a disorder for which there is now mandated pediatric screening at both 18 and 24 months of age. This difference makes it far harder to find young children at risk for SLI at early ages before a confirmed SLI diagnosis can be made.

Although a number of studies have followed late talkers over several years to evaluate their outcomes, the results are surprising in that so few late talkers in these studies ended up with SLI—significantly fewer than would be predicted simply on the basis of the prevalence of the disorder in the general population (Rescorla, 2011). Several researchers have discussed this paradox (Rescorla & Dale, 2013). Leonard (2013) argued that a number of factors may have led to the potential exclusion of children with early language delays from the older studies on late talkers, including the use of only vocabulary size as a definition of delayed language, thus leading to underestimates of children with SLI at later ages. Indeed, Rice, Taylor, and Zubrick (2008) recently found that when expanded definitions of *late talkers* are used at 24 months in a large epidemiological sample—specifically, definitions that include use of word combinations—late language emergence does predict later diagnoses of SLI.

Conclusions

Language skill is the single most important predictor of long-term educational, social, and vocational achievement for all children, including those with ASD (Tager-Flusberg et al., 2011). Understanding the full range of risk factors that predict language outcomes is therefore of great importance for clinical practice because it will allow clinicians to identify children in need of targeted language interventions at a much younger age than would be possible if we waited until a full-blown language disorder could be diagnosed. Although significant progress has been made in identifying risk factors for language in ASD, comparatively

less attention has been paid to SLI. This is ironic, given that SLI affects far more children than does ASD.

One of the main conclusions we can draw from the research conducted so far is that many risk factors are shared across these two disorders, and these factors perhaps extend to other neurodevelopmental disorders of known or unknown etiology. Another important conclusion is that risk factors for poor language outcomes can be found at the level of genes, brains, and behavior, and in some cases even the environment, broadly construed. No one factor can be singled out; instead, a complex, cumulative model of risk is the most likely direction to take in developing a comprehensive understanding of how the full range of potential risk factors interacts over the first few years of life to shape language outcomes for all children. Future research should build on the accomplishments that have already been made. Cross-syndrome comparisons will be important for highlighting shared and distinct risk factors. Our ultimate goal is to develop preventive interventions that may be individually designed around every infant's unique cluster of risk markers in order to offer them all the best opportunity to reach their full linguistic potential.

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