

IDENTIFYING EARLY-RISK MARKERS AND DEVELOPMENTAL TRAJECTORIES FOR LANGUAGE IMPAIRMENT IN NEURODEVELOPMENTAL DISORDERS

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The effective identification of neurodevelopmental disorders is essential for early diagnosis and provision of intervention services. For many of these conditions, one of the primary domains of abnormality is language development. This review addresses what is known about the earliest indicators of language impairment across a range of neurodevelopmental disorders; consideration is given to both behavioral and neural markers, as well as patterns of change over time. A summary of the current state of the field, including challenges in research, is presented. The earliest features of the language phenotype in Down syndrome, Williams syndrome, Fragile X, specific language impairment (SLI), and autism spectrum disorder (ASD) are described, along with recent findings in the early neural markers of language impairment in SLI and ASD.

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The majority of children with neurodevelopmental disorders are delayed in language milestones and many are later diagnosed with language impairments. Across both known genetic disorders, including Down syndrome (DS), fragile X syndrome (FXS), and Williams syndrome (WS), as well as complex disorders such as autism spectrum disorder (ASD) or specific language impairment (SLI), delays and deficits in language are among the hallmark behavioral characteristics. The language phenotypes found in older children with these disorders are often overlapping and include, for example, problems with nonsense word repetition or for English-speaking children, problems with grammatical marking of obligatory tense. More emphasis has been placed in the literature on the phenotypes associated with particular disorders that are considered syndrome specific, such as pragmatic impairments in ASD, or articulation deficits in DS, though it is becoming increasingly clear that there are children with other neurodevelopmental disorders who may also share these phenotypic characteristics.

In this review paper, we address early-risk signs or precursors of language impairment in infants and toddlers who

later have enduring language impairments. We focus on those disorders that have been most extensively studied in the early years: DS, WS, FXS, SLI, and ASD. We are particularly interested in exploring to what extent early behavioral or neural risk signs are syndrome-specific or common across different disorders, and how these features may influence early developmental trajectories. These are important questions to consider in light of current trends toward earlier diagnoses of neurodevelopmental disorders in the expectation that if the potential for later language impairments can be predicted during the first or second year of life, then effective early interventions may be implemented at this stage when the greatest benefits can be expected.

GENETIC INFLUENCES ON NEURODEVELOPMENTAL DISORDERS

Before exploring the evidence for language impairments across the different neurodevelopmental disorders, it is essential to highlight the distinction between, on the one hand, disorders like DS, FXS, and WS, which are attributable to known genetic causes and often identified prior to birth or shortly thereafter, and conditions like ASD and SLI which are generally not diagnosed until the preschool or early school-age years [Autism and Developmental Disabilities Monitoring Network, 2009] exclusively based on behavioral criteria as established by either DSM [APA, 2000] or ICD [WHO, 1992].

Research on the genetic contributions to complex disorders like SLI and ASD remained minimal until recent years. Our understanding of these neurobehavioral disorders has

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undergone a remarkable shift in the past decade, with a surge of research exploring the genetic basis of these traits and conditions. Momentous discoveries were first made in heritability estimates and have progressed to the identification of specific genetic linkages associated with language impairments across a number of neurodevelopmental disorders.

The initial question of interest was to what degree language impairment or ASD was due to environmental versus genetic factors. Twin studies provided our first insights into resolving this question, through the comparison of concordance rates across monozygotic (MZ) and dizygotic (DZ) twins. Several studies indicated that concordance rates for MZ twins exceeded those for DZ twins across both SLI and ASD populations; in SLI, concordance was found in 70–96% of MZ and 48–69% of DZ twins [see Bishop, 2003 for a review]. In studies of ASD, the most recent MZ concordance rates hover between 50 and 77%, while DZ twins showed around 25–36% concordance, depending on classification procedures [Hallmayer et al., 2011]. From these studies, researchers concluded that both these conditions are highly heritable, pointing to the role of genetic variation in neurodevelopmental disorders characterized by language and communication impairments.

Follow-up studies focused more specifically on identifying susceptibility loci associated with SLI and ASD using a variety of approaches. Although the discovery of *FOXP2*, a gene associated with severe speech impairment, on chromosome 7q31 [Fisher et al., 1998], sent ripples through the genetic research community, it did not seem to be associated with SLI as it is generally construed. Instead, *FOXP2* leads to a phenotype that encompasses both language and severe speech articulation impairments. Nevertheless, chromosome 7q has been identified with other candidate regions for SLI susceptibility [O'Brien et al., 2003; Rice et al., 2009; Villanueva et al., 2011], as have, for example, chromosomes 16q, 19q [SLI Consortium, 2002, 2004] and 13q, 2p, and 17q [Bartlett et al., 2002, 2004]. More than 25 ASD susceptibility loci have been identified [see Bill and Geschwind, 2009 for a review]; it is worth noting that language delay or impairment is a phenotypic feature that has been fruitful in characterizing ASD samples in linkage analyses [e.g.,

Alarcón et al., 2002]. Finally, there are emerging indications that SLI and ASD share some genetic vulnerability factors. For example, several genes that are regulated by *FOXP2* have been associated with ASD and SLI, including *CNTNAP2* [Vernes et al., 2008], which is associated with both language impairment and ASD and *MET*, associated with ASD [Mukamel et al., 2011]. In addition, a recently discovered copy number variant on chromosome 16p11 is associated with a range of phenotypes, including ASD and speech and language impairments [Hanson et al., 2010; Rosenfeld et al., 2010].

RESEARCH DESIGNS FOR INVESTIGATING EARLY-RISK SIGNS FOR LANGUAGE IMPAIRMENT

There are profound clinical implications for the differences in age of identification for known and complex neurodevelopmental disorders, but the concern for the current discussion is the manner in which the ability to identify a disorder influences the availability of certain research methods. Prospective studies enroll infants prior to the emergence of developmental delays and follow children through the process of unfolding development; this study design is possible only when a disorder can be identified at birth or in the first few months of life, as with known genetic disorders. Complex disorders depend primarily on retrospective studies after they have been diagnosed, but the methods for these studies are subject to a number of confounding factors, including reporter inaccuracy [Ozonoff et al., 2011b], the distortion and fading of memory [Hus et al., 2011], and the incompleteness or bias in data collection of paper and video records.

In recent years, a partial solution has been offered to the problem of how to collect prospective information on children with complex disorders like SLI and ASD. The relatively high heritability of these disorders led to a new line of research that targets families with an older, diagnosed child (or in some studies other first-degree relatives) and an infant at higher risk for developing the disorder. These high-risk infant research projects yield two valuable streams of prospective data [Benasich and Tallal, 2002; Benasich et al., 2006; Rogers, 2009; Elsabbagh and Johnson, 2010]. First, they provide prospective information for the minority of these infants who will go on to develop the disorder of interest: for ASD, ~20%

will go on to develop ASD [Ozonoff et al., 2011c]; for SLI, estimates range from 13 to 70%, depending on several family and measurement factors [Tallal et al., 2001; Conti-Ramsden et al., 2007]. Importantly, studies of infants who later are diagnosed with ASD found that initially some of these infants show nonspecific signs of general developmental delay. At later ages, a proportion of these infants meet criteria for a more specific diagnosis of ASD, or in some cases, SLI, while others retain global delays [e.g., Ozonoff et al., 2010].

Second, these investigations allow a detailed characterization of the “endophenotype” associated with each disorder. The term “endophenotype” refers to “measurable components unseen by the unaided eye along the pathway between disease and distal genotype” [Gottesman and Gould, 2003, p. 636]. These are features that are (1) associated with the disorder in the general population; (2) heritable; (3) present regardless of whether the individual is symptomatic of disorder or not; and (4) more common in individuals biologically related to someone with a diagnosis than in the general population [Gottesman and Gould, 2003]. As such, gaining a better understanding of the endophenotype associated with complex conditions like SLI and ASD helps identify points of neurocognitive vulnerability along the route to disorder. High-risk infant research has offered new insights into the processes underlying neurodevelopmental disorders, but careful analysis is required. Investigators and audiences must keep clear the distinction between findings indicative of early disorder and those revealing endophenotypic features.

A final issue that influences the research on precursors and early development of language impairment in neurodevelopmental disorder is the presence of comorbidities. Children with neurodevelopmental disorders often experience simultaneous global developmental delays that are identified in assessments of motor function or cognition. These comorbidities influence the timing and rate of skill acquisition and because of the close interconnections between motor, cognitive, social, and language developments they pose particular challenges for diagnosis. Thus, clinicians and researchers alike must determine whether and to what degree language impairments are the sequelae of general developmental delay, identified

primarily in areas like motor and cognitive ability, or whether language difficulties comprise a core feature of the neurodevelopmental disorder. Altogether, then, the understanding of language impairment in children with neurodevelopmental disorders must be constructed using a comprehensive model of development that accounts for the role of other, related domains of skill or difficulty [Tager-Flusberg et al., 2009].

EARLY BEHAVIORAL PRECURSORS AND DEVELOPMENTAL PATTERNS

In the following sections, we review studies that shed light on the patterns of emergence that characterize the very early development of language within each disorder, which is of theoretical and practical interest for researchers and interventionists alike. Despite the fact that known genetic disorders lend themselves more easily to prospective research studies, there are surprisingly few large-scale longitudinal studies of early language development in these disorders; the majority of reports are limited to case studies, or focus exclusively in narrowly defined domains of language. In addition, many studies are methodologically limited and syntheses across studies are not easily made. Studies differ widely on their inclusion of comparison groups and range from the use of no comparison group to comparison groups matched on chronological age (CA), mental age (MA), or expressive language ability (LA). In many cases, the research does not distinguish between language delays that are a consequence of general developmental delay from more specific linguistics deficits.

Down Syndrome

Because of the comorbid motor impairments and dysmorphology in the oral cavity, there has been extensive work conducted on the earliest phases of speech production in DS. One longitudinal study of DS infants' vocalizations during interactions with their mothers noted a decreased frequency of early vocalizations from 1 to 3 months, relative to a group of CA matched controls [Berger and Cunningham, 1983]. The onset of canonical babbling occurs in roughly the same timeframe and with the same content as observed in typically developing (TD) infants, although delays of up to 2 months have been reported [Smith and Oller, 1981; Lynch, 1995; Stoel-Gam-

mon, 2001]. Babbling emerges in infants with DS at the same time as rhythmic hand banging [Cobo-Lewis et al., 1995], but the babbling phase can be quite protracted, with delays in the onset of first words extending into the third year of life [Oliver and Buckley, 1994; Stoel-Gammon, 2001]. During this period, verbal "clashes," where vocalizations occur concurrently, rather than reciprocally, between infants and mothers have been reported, as have differences in eye gaze patterns during mother-infant interactions [Berger and Cunningham, 1983; Moore et al., 2002].

Phonological difficulties emerge during the one-word stage and may persist through adolescence and even adulthood [Stoel-Gammon, 2001]. A longitudinal study of 17 infants found that although many of the first words to enter the lexicon were similar to those observed in typical development, their onset was delayed by an average of 12 months; the onset of two-word phrases was even more delayed, and a vocabulary "explosion" was only observed in a subset of children [Oliver and Buckley, 1994], suggesting significant deviations from the typical developmental trajectory.

Chan and Iacono [2001] observed the gesture use and language development of three girls with DS over a period of 5 months. Prior to the onset of word production, all three girls used gestures across multiple contexts, serving a variety of pragmatic functions (comments, requests, greetings, etc.). During the one-word stage, gestures serve to improve overall communicative ability and are viewed as a relative strength in toddlers with DS [Caselli et al., 1998]. Zampini and D'Odorico [2011] observed the gesture use and language development of eight children with DS who had begun using words. Infants' gesture production and vocabulary development were measured yearly. Across all children, gesture use at 24 months was correlated with vocabulary size at 36 months, and there was a trend toward significant correlation with vocabulary size at 48 months. Additionally, two patterns of gesture use emerged. One group of children showed a steadily increasing pattern of gesture production and the other showed either a flat or inverted U-shaped profile; vocabulary growth was most striking for infants demonstrating this second pattern. Thus, gestures and other nonverbal early communicative behaviors may serve a

particularly important role in the early language development of infants with DS, with deficits in nonverbal communication (particularly requesting) helping to explain some of the deficits in expressive language acquisition [Mundy et al., 1995]. Although gestures may be particularly facilitative during the transition from the prelinguistic to the early linguistic stage, children experiencing delays in the emergence of two-word speech may continue to rely on gestures and gesture-word combinations for communication [Chan and Iacono, 2001; Iverson et al., 2003; Zampini and D'Odorico, 2011]. It remains unclear whether persistent and more profound deficits in vocabulary seen in some children with DS reflect the impact of the extended timing of early delays or the impact of impairments in auditory perception on using phonological information in word learning [Nazzi and Bertoncini, 2003].

In sum, DS is best characterized as delayed language acquisition that is linked to both general developmental delays and more specific deficits in articulation and phonological development. The resulting impairments in expressive language may be compensated by increased use of nonverbal communicative gestures.

Williams Syndrome

Despite the fact that language is an area of relative strength for older children with WS, with lexical knowledge at or above that expected for general cognitive ability, early language milestones are significantly delayed, including the onset of both canonical babbling and the production of first words [Capirci et al., 1996; Mervis and Bertrand, 1997; Paterson et al., 1999; Mervis and Robinson, 2000; Masataka, 2001; Mervis et al., 2003; Stojanovik and James, 2006]. Masataka [2001] followed eight infants with WS to explore the relationship between early linguistic and motor milestones. Delays were observed in each of the vocal and motor domains scored: canonical babbling, first words, reaching for objects, rolling, unsupported sitting, pulling to stand, first steps, and rhythmic hand banging. On average, the infants began babbling at 19 months and used their first words at 24 months. As in studies of DS and TD infants, significant correlations were observed between onset of canonical babbling and hand banging, onset of canonical babbling and first words, and onset of hand banging and first words. Similar findings from other

case studies have been reported [Mervis and Bertrand, 1997; Stojanovik and James, 2006].

Generally, once infants with WS begin babbling, first words emerge within a few months, following the pattern of acquisition observed in typical development but with several notable exceptions [Capirci et al., 1996; Masataka, 2001]. In particular, both longitudinal and cross-sectional studies of infants with WS have reported the use of referential language prior to the onset of gesture use [Mervis and Bertrand, 1997; Laing et al., 2002]. Indeed, gesture use and other nonverbal communicative skills seem to be an area of particular difficulty for young children with WS. Cross-sectional studies of 30-month-olds with WS, CA-matched toddlers with DS, and an MA-matched TD group have identified impairments in WS in gesture following, communicative use of eye gaze, and gesture production for both imperative and declarative purposes [Laing et al., 2002; John and Mervis, 2010]. These deficits in nonverbal communication were similar to those observed in young children with ASD at the same age and level of expressive language, although children with WS were less impaired in social smiling [Klein-Tasman et al., 2009; see also Stojanovik and James, 2006]. Laing et al. [2002] argue that these impairments in early nonverbal abilities, crucial for triadic interaction or joint attention, may disrupt the process of early language acquisition and contribute to the delays in early word production reported for infants with WS. Other longitudinal case reports have documented delays in the onset of first words; however, once children began producing some words, vocabulary grew fairly rapidly [Capirci et al., 1996; Jacobson and Smith Cairns, 2009]. In these children, phrase speech was delayed not only in timing but also in relation to the size of the children's vocabulary. Thus, for toddlers with WS, language milestones are delayed, commensurate with delays in motor and cognitive development. However, the striking difference for this population lies in their more limited use of communicative gestures.

Fragile X Syndrome

Studying the impact of FXS on language development is complicated by the high rates of comorbid ASD in this population, with estimates ranging from 18 to 47% for autism, and up to 67% when including the entire range of

ASD [Bailey et al., 1998, 2001]. Boys with comorbid FXS and autism have the most severe outcomes and are differentiated from boys with FXS and milder forms of ASD by the presence of repetitive behaviors and more severe language impairments, particularly in receptive language [Roberts et al., 2001; Kau et al., 2004; Kaufmann et al., 2004; Philofsky et al., 2004; Bailey et al., 2000].

A few papers have reported on the development of infants with FXS in the first year of life [Roberts et al., 2001, 2009; Mirrett et al., 2004]. One prospective study investigated whether infants with FXS mutations fail developmental screeners during the first 18 months of life [Mirrett et al., 2004]. A majority of the infants were scored as failing two screeners assessing language ability: between 50 and 90% of infants at 9 months, 88 and 94% of infants at 12 months, and 94% of infants at 18 months. Agreement between one of these screeners and a standardized language assessment ranged from 64% to nearly 94%. Unfortunately, descriptive data on infants' performance on the language assessment were not reported, so although the majority of infants were scored as failing this measure, the extent and specificity of their impairments remain unknown. More recent reports on a small subset of these infants identified significant delays on standardized assessment of both receptive and expressive language at 9 months [Roberts et al., 2009], and longitudinal analyses of the larger sample found a significantly slower rate of development across all domains.

In another study, using a combination of retrospective and prospective parent report measures, the mean age of first word production (28 months) was delayed, as were other motor milestones [Roberts et al., 2001]. Development in boys with FXS is characterized by rather flat rates of growth across all domains, with language and communication typically more impaired than motor and cognitive functioning [Bailey et al., 1998; Roberts et al., 2001, 2009]. A longitudinal study of language development in a relatively large group of boys with FXS found developmental rates roughly half that expected for TD infants, with expressive language somewhat slower to develop than receptive [Roberts et al., 2001]. A cross-sectional study of 55 toddlers with FXS under the age of 3 also found significant delays in the onset of word production, with the majority of infants classified as

nonverbal [Brady et al., 2006]. This group of nonverbal infants demonstrated relative strengths in the receptive (vs. expressive) domain, but this pattern was not observed in the children who were beginning to use words. Again, because specific milestones were not reported, it is unclear how many infants in the nonverbal category demonstrated canonical babbling or other nonverbal communicative strategies.

A longitudinal study of young children with FXS in the early multi-word stage found that nonverbal communication was impaired [Roberts et al., 2002]. Performance on the Communication and Symbolic Behavior Scales [Wetherby and Prizant, 1993] revealed relative strengths in verbal production, compared to gestures, social reciprocity, and symbolic play. Only verbal production was correlated with expressive LA measured 1 year later. Given the substantial literature on the importance of early gesture in early language acquisition in TD children, it is somewhat surprising that gestures were not related to later language for children with FXS. Whether this represents an atypical developmental process is unclear; it may reflect the fact that a majority of the children were already producing two-word phrases, a stage when gestures are less important for supporting language. However, the paucity of gesture use may also reflect impairments in symbolic representation, an interpretation supported by the presence of delays in symbolic action schemes, or could be due to motor planning errors similar to those observed in older boys with FXS. Thus, although there are hints in the literature that expressive language is specifically impaired in FXS beyond expectations based on their cognitive delays, little is currently known about the precursors that might explain these impairments.

Specific Language Impairment

SLI is diagnosed on the basis of delays and continued impairments in acquiring language, in the absence of other neurological or sensory deficits, or extreme deprivation. However, early diagnosis of SLI is complicated by the fact that many toddlers with significant delays in early language milestones show no enduring deficits, so-called "late talkers" [Ellis Weismer et al., 2010]. Interestingly, there is some evidence suggesting that one feature that may be helpful for differentiating late talkers from toddlers with SLI is the use

of gesture. Late talkers use more gestures than those later diagnosed with SLI, and infants with more serious delays are similar to language-matched controls on gesture and expressive language skills, suggesting comparable developmental delays in both domains. This same pattern is also found in older children with SLI and in infants at risk for SLI [Thal et al., 1991; Thal and Tobias, 1992; Spitz et al., 1997; Hill et al., 1998].

Benasich and colleagues [Spitz et al., 1997; Benasich and Tallal, 2002; Choudhury and Benasich, 2003; Choudhury et al., 2007] investigated the development of infants at high risk for SLI, defined on the basis of either an older sibling or parent with a history of the disorder. A cross-sectional study of 10 high-risk infants found that five of these children were significantly below the mean on measures of expressive or receptive language at 22 months of age [Spitz et al., 1997]. Importantly, these same infants were not impaired on measures of nonverbal ability. This group of researchers also investigated the relationship between early rapid auditory processing (RAP) and later language ability for these high-risk infants [Benasich and Tallal, 2002; Choudhury et al., 2007]. One cohort of 7-month-old infants was trained to differentiate two tone sequences differing in pitch. After learning the direction/tone mapping, the interval between the tones was systematically reduced until the infant no longer could differentiate the sequences—defined as the infant's RAP threshold. The high-risk infants had significantly higher RAP thresholds compared with low-risk controls and RAP threshold was the best predictor of language development on subsequent language measures taken at 12, 16, and 24 months. At 36 months, RAP threshold and gender explained 40% of the variance in language outcome. Additionally, as a group, the high-risk infants demonstrated impairments on behavioral language measures across the first 3 years of life, with pronounced impairments on both expressive and receptive measures. A second cohort of infants was observed at 6, 9, 12, and 16 months. Two different measures of RAP ability at the early ages combined to predict about 38% of the variance in expressive LA at 16 months and were better predictors of language outcome than risk status. Among TD infants studies have found significant correlations between speech perception skills

at 6 months and measures of language development collected across the second year of life, and toddlers with low language scores at 30 months showed atypical looking patterns to pictures paired with phonologically deviant (mispronounced) targets at 19 months [Tsao et al., 2004; Höhle et al., 2006]. Together, this body of work suggests that early auditory processing plays an important role in the acquisition of language: infants who have more difficulty with auditory processing show delayed language development, and infants at risk for SLI are more likely to demonstrate such difficulties. However, it is not clear from the current research whether RAP represents a significant predictor of later SLI or is an endophenotype that runs in high-risk families.

Data aggregated across several studies of high-risk infants found that children who scored below the 16th percentile of language assessment at 3 years of age (a “low language” group) were more likely to have a family history of SLI [Choudhury and Benasich, 2003]. Male infants with a family history were more likely to be in this low language group than males without a family history; this was also true for the formally diagnosed children in these families. Interestingly, although there were no other demographic factors associated with low language status for the infants, autoimmune disorders were more commonly reported in the SLI families than among the low-risk controls.

Taken together, research on the early development of children later diagnosed with SLI suggests that impairments in auditory processing may be the important precursor for later language deficits.

Autism Spectrum Disorder

Early studies using retrospective reports, including parent interviews and family home videos, established that delays in joint attention, orienting to name, pointing, and showing are all evident in the first year of life in infants who develop ASD [Osterling and Dawson, 1994; Baranek, 1999; Werner et al., 2000], though these behavioral deficits did not establish whether these differences predicted social or language impairments. More recently, prospective studies of high-risk infants who have an older sibling with ASD reported on delays in the onset of babbling and other early linguistic milestones. Moreover, these infants lag

behind in their acquisition of consonants and show atypical patterns of rhythmic arm movement during the period of babble onset [Iverson and Wozniak, 2007; Paul et al., 2011]. Discriminant function analyses revealed that ASD status at 24 months was related to specific features of consonant production at 6, 9, and 12 months of age [Paul et al., 2011]. The majority, though not all, of children with ASD are delayed in the production of first words and show fairly slow developmental progress [Tager-Flusberg et al., 2005; Mitchell et al., 2006; Iverson and Wozniak, 2007]. Additionally, some infants with ASD lose language skills usually during the second year of life, with reports of both frank losses in productive language use and more subtle decreases in directed vocalizations and social engagement [Lord et al., 2004; Werner and Dawson, 2005; Ozonoff et al., 2010, 2011a]. Other developmental patterns such as plateaus in language development have also been reported, but the pattern of early regression in language skills seems to be a unique marker of risk for ASD [Tager-Flusberg et al., 2005; Pickles et al., 2009; Ozonoff et al., 2011a].

Delays in gesture production for infants at risk for ASD who are later diagnosed with the disorder are consistently reported as early as 12 months of age [Osterling and Dawson, 1994; Mitchell et al., 2006; Iverson and Wozniak, 2007; Talbott & Tager-Flusberg, in press], and there is some evidence that delays in gestures may be found among nondiagnosed siblings at 18 months [Mitchell et al., 2006]. As in the TD population, early gesture production is correlated with measures of both concurrent and later language for toddlers with ASD and high-risk infant siblings, even those who are not later diagnosed with ASD [Luyster et al., 2008; Thompson and Tager-Flusberg, 2011].

Longitudinal investigations of language growth in toddlers with ASD found that nonverbal cognitive ability, motor skills, expressive language, imitation, pretend play, gesture use, joint attention (both initiating and responding), and commenting were all significant predictors of later language [Charman et al., 2003; McDuffie et al., 2005; Toth et al., 2006; Smith et al., 2007; Luyster et al., 2008; Yoder et al., 2009; Young et al., 2011], though the strongest predictors for this population were gesture use (which incorporates motor, joint attention, and imitation

skills) and nonverbal cognitive ability suggesting that social and more general developmental measures are both important predictors for language in this population. It remains unclear why some proportion of children with ASD never acquire spoken language skills; in some cases, their deficits in expressive language are clearly well beyond what might be expected given their cognitive and receptive language abilities [Tager-Flusberg et al., 2005].

NEURAL RISK MARKERS

Several studies have explored the neural mechanisms underlying developmental language impairments with the goal of identifying neural risk markers for language impairment that are linked to behavioral precursors or atypical neural patterns that are evident in advance of overt behavioral symptoms. This line of work has primarily been conducted in infants and toddlers at risk for SLI or ASD, relying primarily on neurophysiological measures; no neuroimaging studies have been conducted on very young children with known genetic disorders.

Research on older children and adults has consistently found a reduced or reversed structural and functional lateralization of neural language networks in perisylvian cortical regions in individuals with SLI [e.g., Plante et al., 1991; Gauger et al., 1997; Shafer et al., 2001; de Fosse et al., 2004] and ASD [e.g., Herbert et al., 2002, 2005; de Fosse et al., 2004; Flagg et al., 2005; Kleinhans et al., 2008]. Several studies have also found atypical language and auditory processing in older children with SLI and ASD. For example, adolescents with SLI show disrupted processing of auditory and linguistic stimuli [Weber-Fox et al., 2010]. The findings are less consistent in ASD, perhaps because of more significant heterogeneity in language phenotypes in this population [for a recent review, see Haesen et al., 2011].

Neural Risk Markers for SLI

Prospective studies of early neural processing of linguistic and auditory stimuli in SLI have relied on electrophysiology, using both ongoing electroencephalography (EEG) and stimulus-linked event-related potentials (ERP). ERP studies showed delayed mismatch response to changes in syllable length at 2 months in high-risk infants with a family history for language impairment [Friedrich et al., 2004] and dampened mismatch response

to tone pairs at 6 months of age [Benasich et al., 2006]. They also exhibited lower resting gamma power over frontal electrodes between 16 and 36 months [Benasich et al., 2008] and a developmentally less mature trajectory of response to tone pairs over the first 3 years of life when compared with low-risk control infants [Choudhury and Benasich, 2011]. Atypical lateralization of response to tone pairs was seen between 6 and 12 months [Choudhury and Benasich, 2011]. These results are complemented by findings from a group of infants from the general population who, despite having no family history of SLI, scored poorly on language tasks administered over the third year of life. Similar to infants with a genetic risk for SLI, this group of infants who were behaviorally at risk for SLI also showed atypical electrophysiological response to linguistic stimuli earlier in life. Specifically, they showed delayed mismatch response to changes in word stress at 4–5 months [Weber et al., 2005; Friedrich et al., 2009] and failed to display a negative component linked with semantic processing (N400) at 19 months [Friedrich and Friederici, 2006].

In general, evidence suggests that linguistic and auditory processing is disrupted to some degree early in the first year of life in SLI. It remains to be determined which findings are specific to children who actually experience language impairment.

Neural Risk Markers of Language Impairment in ASD

There is strong evidence from recent fMRI studies that toddlers with ASD show atypical lateralization of neural language networks. When listening to bedtime stories, sleeping toddlers with ASD show reduced activation in temporal cortices relative to TD controls [Redcay and Courchesne, 2008] and, unlike TD toddlers, they show stronger activation in the right rather than left anterior superior temporal gyrus [Eyler et al., 2012]. Toddlers with ASD also show decreased spontaneous interhemispheric synchronization in language-related areas (including the superior temporal gyrus and inferior frontal gyrus) relative to controls. Importantly, this decreased synchronization is positively correlated with language ability and negatively correlated with ASD symptom severity and, interestingly, not present in a comparison group of toddlers with SLI [Dinstein et al., 2011], suggesting that it

may be more specifically linked to deficits in social communication, rather than simply language.

Although the above studies [Dinstein et al., 2011; Eyler et al., 2012] included infants as young as 12 months, it should be noted that all the participants were already exhibiting behavioral symptoms of ASD. To date, there is very limited work examining the presence of atypical lateralization or atypical organization of language networks before the onset of ASD symptoms. One recent study examined ERP to speech sounds between 6 and 12 months, and found that infant siblings at risk for ASD failed to exhibit lateralized response over central electrode sites at 9 and 12 months, unlike low-risk control subjects [Seery et al., in press]. This finding suggested that atypical lateralization was present in the first year of life, before the majority of behavioral symptoms emerge. However, this finding was present even in high-risk infants who ultimately did not develop ASD, suggesting that atypical lateralization in early infancy may be an endophenotype linked with increased risk for the disorder rather than predictive of a clinical diagnosis. It remains to be shown whether the atypical language lateralization in toddlers with ASD is also present in their unaffected family members at older ages. Furthermore, studies have not yet teased apart whether atypical neural response in very young children is found in all participants with ASD or whether it is specific to those who also experience language impairment.

SUMMARY AND CONCLUSIONS

The most striking feature of this review of the literature of early-risk markers and developmental patterns in language acquisition is how little overlap there is in the research conducted across different neurodevelopmental disorders. Although the behavioral literature has identified multiple factors that are important precursors to language development in TD children, not all have been examined in infants at genetic risk for language impairment. In fact, there are few comprehensive studies that have specifically investigated key predictors of later language acquisition, and even fewer that have conducted systematic comparisons across different disorders.

One important behavioral domain that has received considerable attention is the use of communicative gestures as a key precursor to language. Although

gesture has been found to be significantly related to later language in DS, SLI, and ASD, its significance for WS and FXS is less clear. Does this mean that communicative gesture is not a required prerequisite for language? If so, this would be an important finding from studies of children with neurodevelopmental disorders and may suggest different syndrome-specific developmental patterns. However, given the current state of research, particularly the paucity of relevant studies on WS and FXS, this conclusion is premature.

Studies of infants at risk for SLI highlighted the importance of auditory processing mechanisms during the first year of life, providing evidence from both behavioral and electrophysiological measures. However, auditory processing has not been investigated in other populations, not even in children with ASD. This is clearly an important area for future research, because the detection of subtle deficits in processing rapidly changing auditory stimuli has the potential to be a useful measure that could predict later language impairments across children and could be implemented as a screener before the onset of language.

The key language milestones—canonical babbling, first words, and first phrases—are important across all disorders, but it seems that the timing between these milestones (e.g., between babbling and first words; words and later phrases) varies widely both between and within disorders. It is not known what accounts for these timing differences. One possibility is that domain general processes such as nonverbal cognition or general developmental delays, which are differentially affected within and across the disorders covered here, account for at least some of variation in timing of language development, but there is little research that directly addresses this hypothesis. Another possibility is that, at least in some syndromes, language-specific mechanisms may account for the delays in language milestones. Some of the behavioral and neural evidence from infants at risk for SLI or ASD suggests this may be the case, but more work is needed to more closely investigate the relations between atypical lateralization and the timing of early language development in these and other neurodevelopmental disorders.

Although it is difficult to draw strong conclusions based on the relatively limited evidence available, it is becoming increasingly clear that in the first year of

life, before children speak their first words, there are early signs in their behavior, and perhaps in their brains, that they are at risk for impairments in later language development. More studies are needed to identify which signs are the most robust predictors for children with different neurodevelopmental disorders, and whether these signs differ significantly across disorders. Research should focus on finding the earliest sensitive and specific factors that not only predict delays in milestones but might also signal altered developmental trajectories. Ideally, comprehensive research programs should be initiated using prospective longitudinal designs with parallel methods implemented across several neurodevelopmental disorders. In this way, we will be able to address the question about whether early-risk markers differ across neurodevelopmental disorders. Ultimately, such research brings the promise of implementing interventions at the earliest developmental stages, which may eventually lead to the prevention of later language disorders.

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