www.medscape.com

Neurobiology of Specific Language Impairment

Richard I. Webster, MBBS, MSc, FRACP; Michael I. Shevell, MD, CM, FRCPC

J Child Neurol. 2004;19(7)

This review summarizes what is known about the neurobiology of specific language impairment. Despite its name, specific language impairment is frequently not specific. It is common to find associated impairments in motor skills, cognitive function, attention, and reading in children who meet criteria for specific language impairment. There is evidence that limitation in phonologic working memory may be a core deficit in specific language impairment. Both genetic and environmental factors have been shown to be important etiologic factors in specific language impairment. Structural neuroimaging studies suggest that atypical patterns of asymmetry of language cortex, white-matter abnormalities, and cortical dysplasia may be associated with specific language impairment. Abnormalities in the later stages of auditory processing have been demonstrated using auditory event-related potentials. Functional neuroimaging may cast further light on the neurobiology of specific language impairment and serve as a means of developing and evaluating therapy. A better understanding of the neurobiology of specific language impairment is critical for the rational development of therapeutic strategies to treat this common disorder.

The process of acquiring language is complex and not yet fully understood. Language is a recent evolutionary phenomenon. It is likely that the linguistic computational abilities that underlie the complexity of human language have evolved over the past 6 million years.[1] In most children, the potential for language is present at birth. However, its eventual development represents a dynamic interaction between the developing brain and a child's environment.[2] Most children acquire language through environmental exposure to language without any special assistance. However, for some children with otherwise normal development, the acquisition of language proves disproportionately difficult. Despite relatively normal nonlinguistic cognitive function and normal hearing, their language development is impaired. These children are considered to have specific language impairment.

With an estimated prevalence of 7.4% in kindergarten children, specific language impairment is a common childhood developmental disorder.[3] It potentially leads to ongoing impairment in an individual's communication, academic, and social skills.[4-6] It thus represents a major public health problem. Unlike children with global developmental delay, it is very uncommon to identify a cause of language impairment among children who meet criteria for specific language impairment.[7] Despite the high prevalence of specific language impairment, its causes and biologic basis are, at present, incompletely understood.

This review aims to summarize what is known about the biologic causes of specific language impairment. Problems defining specific language impairment are discussed first. Any theoretic framework that attempts to address the causes of specific language impairment needs to account for the characteristic pattern of language deficits seen among children with specific language impairment and for impairments seen in other neurologic functions. There is evidence that children with specific language impairment have limitations in verbal working memory and difficulties processing rapidly changing sounds. There is also evidence that the neurophysiology of language processing is different in children with specific language impairment than in children with normal language. Studies reporting that children with specific language impairment have brains that are morphologically different from normally developing children are reviewed. Finally, theories of the factors limiting language processing in specific language impairment are discussed.

One of the major difficulties relating to the study of specific language impairment is how it is precisely defined.[3,8-10] There is general agreement that specific language impairment represents an impairment in language that is disproportionately greater than the impairments in other nonlinguistic domains. Most authors would also agree that children with evidence of other neurologic impairment or disease, global developmental delay, an autistic spectrum

disorder, or significant hearing impairment should not be considered to have specific language impairment.[3,9,11-13] Difficulty results from the fact that the construct of "specific" language impairment is, to some extent, artificial and that the observed impairments are frequently not entirely specific to the language domain.

Most definitions of specific language impairment rely on a discrepancy between tests of nonverbal cognitive function and language. However, delineating the boundaries of specific language impairment has proven to be difficult; in particular, there is ongoing disagreement as to how the discrepancy between cognition and language should be defined and measured.[3,4,8,10] The debate results largely in part from philosophical differences as to whether specific language impairment should be defined on the basis of a documented "statistical" abnormality[11] or functional impairment.[3,12]

The *International Classification of Diseases-10* (*ICD-10*) uses a statistical definition of specific language impairment and requires that a child's language skills fall more than 2 SD below the mean, with language skills being at least 1 SD below that measured for nonverbal skills.[11] The *Diagnostic and Statistical Manual of Mental Disorders-IV-TR* (*DSM-IV-TR*) uses similar criteria and subdivides specific language impairment into expressive language disorder and expressive-receptive language disorder.[13] The definition includes a requirement that the language impairment is associated with functional impairment and that there is a substantial discrepancy between language and nonverbal skills. However, what constitutes substantial is not operationalized precisely.

Probably the most widely accepted definition of specific language impairment in North America is that proposed by Tomblin et al[3,14] and Leonard.[12] Specific language impairment is defined as a combination of normal intelligence (performance IQ greater than 85) and language impairment (a composite language measure falling more than 1.25 SD below the mean). A -1.25 SD cutoff for language impairment (equivalent to the 10th percentile or below) was chosen by Tomblin et al[3,14] because this is the level at which speech-language pathologists consistently clinically identify a child as having a language impairment.[14,15]

The requirement that a child should have a particular discrepancy between verbal and nonverbal scores has also been questioned.[16] Bishop notes that measures of verbal- nonverbal discrepancy may have poor reliability.[16] Performance on tests of visuospatial skills (eg, Wechsler Intelligence Scale for Children (WISC) III picture completion and block design tests) is often used as a measure of nonverbal IQ. However, in children with specific language impairment, there is evidence that visuospatial skills are also impaired.[17] Specifying a particular nonverbal cutoff for specific language impairment artificially divides what in reality is probably a spectrum disorder.

Older terms for children who would now be considered to meet criteria for specific language impairment, such as "developmental aphasia" or "developmental dysphasia," have fallen out of favor because of their association with structural neurologic injury such as stroke.[12] Children with an acquired aphasia (eg, Landau-Kleffner syndrome) are usually not considered to have specific language impairment.

In specific language impairment, language development is not only delayed, but also the actual profile of language development differs from that seen in normally developing children. Children with specific language impairment utter their first words later and combine words later than their peers, and their language development reaches a plateau earlier than normal children.[12] Moreover, when compared with younger controls matched for measures of language development (eg, mean length of utterance), children with specific language impairment show an uneven profile of development of language skills, an abnormal frequency of errors, and errors that are uncommon in children with normal language.[12]

Children with specific language impairment have deficits in all areas of language; however, some areas cause greater problems than others. In English, morphology (the structure of words) and syntax (the relationship between words and other units within a sentence) are the areas that cause the most apparent difficulty. Children with specific language impairment have particular difficulties with grammatical inflections--the units of language appended to words that express

an attribute (eg, possessive*s*, as in Jane's dog). However, not all inflections cause equal difficulty. The grammatical function of a particular inflection influences the difficulty children with specific language impairment experience. Thus, the third-person singular inflection -*s* (he walks) and the possessive inflection -s (Jane's dog) cause greater difficulties than the plural inflection - *s* (three dogs). Other areas that cause problems for children with specific language impairment are argument structure (the grammatical requirement of a verb for associated language elements) and phonology (the system of sounds of a language). Although isolated deficits in phonology are not usually considered to be sufficient to make a diagnosis of specific language impairment, the majority of young children with specific language impairment have greater difficulties than control children in producing the correct sounds for words.[12,18] Vocabulary and pragmatics (the communicative use of language) tend to cause the least apparent difficulty in language skills.[10,12,19] Thus, screening based on vocabulary may fail to identify a child with significant language impairment.

Despite the above, the profile of language impairment among different children with specific language impairment shows considerable heterogeneity. One of the hopes of researchers has been that phenotypic heterogeneity might reflect underlying specific biologic heterogeneity. A number of researchers have used clinical and statistical techniques to identify similar profiles of language performance among children with specific language impairment.[18,20-24] In the largest study to date, Conti-Ramsden and Botting used cluster analysis to identify children with similar profiles of language disability among a population of 242 7- and 8-year-olds with specific language impairment.[23,24] They identified five profiles of performance on language testing with features that were broadly similar to the categories originally proposed by Rapin and Allen based on clinical observation.[22] However, when these children were retested a year after the original assessment, only 55% of children had the same profile as previously documented. This suggests that a given deficit may be associated with a temporally evolving language phenotype.

Moreover, in younger children, specific language impairment sometimes appears to resolve.[5,18,25] In a longitudinal study of children with a diagnosis of specific language impairment at 4 years of age, 44% met the criteria for normal language skills when tested at a mean age of 5 1/2 years.[18,25] However, when these children were reviewed 10 years later, subtle deficits in language were still evident. This suggests that some children find means of compensating for an underlying deficit.[26]

Children with specific language impairment often have clinical evidence of neurologic dysfunction involving systems other than language. A number of studies have found that children with specific language impairment have an increased incidence of motor abnormalities, such as synkinesia and hyperreflexia,[27] disdiadochokinesia,[28] poor praxis,[29] and slow performance of motor tasks.[30] There is an increased incidence of attention-deficit disorders among children with specific language impairment[31] and an increased incidence of language impairment among children with attention-deficit disorders.[32]

Although most definitions of specific language impairment require that a child's nonverbal IQ falls within the normal range, studies of children with specific language impairment have reported nonverbal IQs that cluster at the lower limits of the normal range.[5,33] Although it is possible that these deficits result from covert requirements for verbal processing in tests of nonverbal IQ, tests that attempt to purely assess visuospatial skills have shown impairments in children with specific language impairment.[17]

The coexistence of specific language impairment and a reading disability is common.[5,6,34] Indeed, Snowling et al found that 43% of children with specific language impairment had a specific reading disability when assessed at 15 years of age.[6] Conversely, in a study of 102 children identified as having a specific reading disability, McArthur et al found that 52 (51%) would meet criteria for specific language impairment.[35] The association between dyslexia and specific language impairment is complex. The distinction between the two disorders depends to some extent on how the terms are defined. According to the phonologic deficit hypothesis, most children with dyslexia have difficulty realizing that spoken and written words can be further segmented into simple speech sounds (phonemes).[36,37] Similar problems are also seen in children

with specific language impairment. However, Snowling et al argue that the profile of reading acquisition among children with specific language impairment differs from that of children with dyslexia.[6] In a longitudinal study of literacy outcomes in children identified in preschool with specific language impairment, Snowling et al found that basic word decoding skills developed normally; however, children experienced increasing reading difficulties with age. In contrast, children with dyslexia tend to have difficulties with early word decoding skills; however, subsequent reading skills are acquired more easily, perhaps as a result of better language skills.

In summary, factors that lead to language impairment are frequently not specific to language and also affect other neurologic processes. Language may be the function that is most sensitive to the underlying deficit or may be clinically more easily recognized than the other impairments. Specific language impairment is thus rarely specific, and for this reason, it is has been argued that there is a need for a change in terminology.[38]

In young children, there is a strong correlation between language development and tests of phonologic working memory.[39-41] Gathercole and Baddeley developed a test of nonword repetition that they consider assesses the adequacy of a child's phonologic working memory.[39] The test involves the repetition of nonsense words with increasing numbers of syllables. Gathercole and Baddeley found that children with specific language impairment performed in a manner similar to that of control children on one- and two-syllable nonwords; however, on longer nonwords, their performance fell off markedly, suggesting that working memory limitations rather than articulatory impairments limit their performance.[42] A number of other studies have confirmed that nonword repetition is impaired in specific language impairment[6,26,30,42-44]; indeed, it is uncommon for children with specific language impairment to perform well on standardized tests of nonword repetition.[43] Moreover, in children with "resolved" specific language impairment, there is evidence of persisting poor performance on tests of nonword repetition.[26] This suggests that poor phonologic working memory may be a core deficit in some children with specific language impairment. This core deficit needs to be addressed in any theoretic account of specific language impairment.

There is evidence in some children that limitations in the processing of rapidly changing sounds may cause specific language impairment. Children with specific language impairment have particular difficulty differentiating between consonant pairs, particularly stop consonant vowel combinations (eg, /ba/ and /da/). These sounds are characterized by acoustic waveforms that change within very short time intervals--roughly 50 milliseconds or less.[45] In a series of experiments, Tallal and Piercy investigated the auditory processing abilities of a small group of children with specific language impairment using synthesized verbal and nonverbal sounds.[45-47] They found that children with specific language impairment had difficulties in discriminating between sounds if the sounds had rapid transitions in frequency or if the sounds were separated by very short intervals.[45,47] If the period during which the change in frequency occurred was lengthened, then the performance of children with specific language impairment normalized. It was considered that this resulted from impaired perception of sounds with a short acoustic duration. A subsequent study found that performance on tests of rapid auditory processing in early infancy was a strong predictor of language development at 3 years of age.[48]

Support for the importance of rapid auditory processing disorders in specific language impairment has come from two studies using training in sound discrimination with acoustically modified sounds.[49,50] After training for a month, children treated with acoustically modified sound showed gains that averaged 2 years in tests of language development (at least in the short term).

Most definitions of specific language impairment exclude children with seizure disorders,[12] so children with language impairment associated with partial epilepsy[51] or Landau-Kleffner syndrome are generally not considered to have specific language impairment. The question remains as to whether subclinical epileptiform activity might lead to language impairment in some children who otherwise meet the criteria for specific language impairment. Maccario et al report the electroencephalographic (EEG) findings in a series of seven children referred for investigation of verbal-nonverbal discrepancy; five of these children had no history of seizures, and the remaining two only had seizures with fever.[52] All

children had focal epileptiform activity, and four had periods of generalized activity. The authors report that treatment with antiepilepsy medication failed to influence epileptiform activity or the course of the language disorder and concluded that language impairment and the associated EEG findings represent epiphenomena associated with an unidentified neurophysiologic abnormality. More recently, Picard et al reported the EEG findings in a series of 52 children with developmental dysphasia.[53] Twenty-six (50%) of these children were found to have paroxysmal epileptiform activity noted on overnight sleep recordings; in the majority of cases, these abnormalities were not present during wakefulness.

Several studies have investigated the electrophysiology of auditory processing in specific language impairment. These studies have reported abnormalities in children with specific language impairment[54,55] and in affected parents.[56] Ors et al studied auditory event-related potentials in a group of 10 children with specific language impairment.[54] The study used an "oddball" paradigm in which children were asked to respond to an infrequent target tone or speech stimulus. They found that children with specific language impairment performed more poorly and had longer reaction times than controls in discriminating discrepant tone and speech stimuli. In children with specific language impairment, the P3 potential (a positive potential occurring 300 to 800 milliseconds after the original stimulus) was found to have a prolonged latency to both tone and speech stimuli. Ors et al considered that these findings resulted from an underlying deficit in the neuronal network of children with specific language impairment.[54] A subsequent study of the parents of children with specific language impairment reported prolonged P3 latencies to speech stimuli among those who had a history of childhood language delay.[56]

Uwer et al used mismatch negativity--an auditory event-related potential--to study the automatic processing of deviant tone and speech stimuli in children with specific language impairment and controls.[55] They found that children with specific language impairment had reduced mismatch negativity amplitudes in response to speech stimuli but not to tones. They hypothesized that these changes reflected abnormal sensory memory for speech stimuli.[55]

Two studies have reported on neuropathology in children with specific language impairment.[57,58] Landau et al examined the brain of a 10-year-old boy with severe language impairment and normal nonverbal intelligence.[57] At postmortem, the child was found to have bilateral loss of cortical tissue and underlying white matter that extended back from the central sulcus, involving the insula and the tissue bordering the sylvian fissures. The medial geniculate nuclei also showed signs of severe degeneration. More recently, Cohen et al described the neuropathologic findings in a 7-year-old girl with developmental dysphasia who died of Epstein-Barr virus infection.[58] The girl was found to have a dysplastic gyrus in the left inferior frontal cortex with abnormal symmetry of the auditory association cortex (the planum temporale).

Interest in the neuropathologic substrate of specific language impairment was also spurred by studies of children with a specific impairment in reading abilities (developmental dyslexia). Galaburda et al described neuronal ectopia and cytoarchitectonic dysplasia of the perisylvian cortex with associated symmetry of auditory association cortex (the planum temporale) in four young adults with dyslexia.[59] Although the extrapolation of findings in dyslexia to children with specific language impairment is questionable, the finding of abnormal patterns of asymmetry and cytoarchitectonic dysplasia involving language cortex in both disorders raised the possibility that these factors might be biologic markers for language impairment. The improved anatomic resolution of magnetic resonance imaging (MRI) when compared with computed tomography allowed these questions to be pursued in children and adults with specific language impairment.

Neuroimaging research in specific language impairment has attempted to identify morphometric factors that differentiate individuals with specific language impairment from those with normal language, in particular, whether children with specific language impairment have atypical asymmetry of language cortex. A number of studies using MRI have reported evidence of atypical patterns of asymmetry of language cortex in children with specific language impairment involving perisylvian regions,[33,60] frontal regions,[61] the pars triangularis,[33] and regions of the parietal lobe.[61] The inconsistent regions identified may reflect differences in how regions of interest were defined and evaluated. However, in contrast to the preceding studies, a study by Preis et al reported normal patterns of cerebral asymmetry in children with specific language

impairment.[62] In this study, the only factor differentiating children with specific language impairment from control children was a 7% reduction in forebrain volume. More recently, in a study comparing children with specific language impairment with children with reading disability, Leonard et al reported that children with specific language impairment were more likely to have symmetry (abnormal) of the planum temporale and lower total cerebral volumes.[63] However, the authors noted that significant differences existed in both age and handedness between the specific language impairment and reading-disabled groups of children (children with specific language impairment were younger).

There is also evidence that focal central nervous system pathology is associated with specific language impairment. Trauner et al found a high incidence of white-matter lesions, white-matter volume loss, and ventricular enlargement in a series of 35 children with specific language impairment.[27] Preis et al reported twins with specific language impairment who were found to have focal gray-matter heterotopia within the right and left parietotemporal white matter.[64] Other abnormal neuroimaging findings reported in specific language impairment include abnormal morphology of the inferior frontal gyrus[65] and increased thickness of the corpus callosum.[66]

Recently, in a study using voxel-based morphometry to analyze MRI data, Watkins et al[67] identified significant reductions in gray matter within the caudate nucleus, sensorimotor cortex, and cerebellum in 10 related individuals with a familial speech/language disorder secondary to documented mutations in the *FOXP2* gene.[68] The volume of the left caudate nucleus correlated directly with performance on tests of praxis, fine motor function, and nonword repetition.

Thus, there is evidence that children with specific language impairment have brains that are structurally different from those of children with normal language. To date, the most consistent findings are reductions in cerebral volume and atypical patterns of cerebral asymmetry. However, given the different regions of asymmetry identified, there is still uncertainty as to whether methodologic differences or underlying biologic heterogeneity has contributed to the discrepant findings.

There are strong genetic factors that influence the development of specific language impairment. Stromswold reviewed 14 studies that investigated the incidence of a positive family history of language impairment (usually a first-degree relative with language impairment or a history of language impairment) in children with developmental language impairment.[69] In these studies, the median incidence of a positive family history of specific language impairment was 39% (range 24-77%). In those studies that compared probands and controls, there was a significantly higher incidence of language impairment among the families of the probands.

Most studies have found a higher incidence of specific language impairment in boys, with reported male-to-female ratios ranging from 1.3:1 to 5.9:1.[69-71] This finding suggests that either genetic or early hormonal factors may influence the development of specific language impairment. However, in the study cited previously, Tomblin et al found no significant difference between male and female prevalence of specific language impairment in a systematically screened population, [3] which raises the possibility that ascertainment bias may contribute to the higher reported incidence in boys.[69]

Although an increased familial incidence of specific language impairment could be explained by either environmental or genetic factors, twin studies have shown that genetic factors are probably more important. Bishop et al reported a concordance rate for specific language impairment of 72% for monozygotic twins compared with 49% for dizygotic twins based on an observed 20-point nonverbal-verbal discrepancy in IQ.[72] When more liberal criteria for language impairment were used, the concordance rate increased to 90% in monozygotic twins and 62% in dizygotic twins. Bishop also reported evidence of common genetic factors leading to impairment on tests of motor performance and of spoken language (nonword repetition).[30]

In one family (the KE family), a dominant mutation in the *FOXP2* gene (a putative transcription factor) was found to be associated with a severe speech and language disorder.[67,68,73,74] Recently, two genome-wide scans have been

performed on families with specific language impairment looking for evidence of linkage to specific chromosomal loci.[44,75] The SLI Consortium found a linkage between language impairment and two separate loci on chromosomes 16 and 19.[44] The locus on chromosome 16 was associated with poor performance on a nonword repetition test,[40] whereas the locus on chromosome 19 was linked to poor performance on an expressive language test. Bartlett et al reported that a locus on chromosome 13 was linked to a discrepancy between nonverbal IQ and reading ability (a possible late consequence of specific language impairment).[75]

There is epidemiologic evidence that antenatal and perinatal factors contribute to the development of specific language impairment. In a large study from Florida, Stanton-Chapman et al examined risk factors at birth that were associated with a diagnosis of specific language impairment in early elementary school.[71] The study included 5862 children with specific language impairment aged between 6 and 7 years who were drawn from a population of 244,619 school students who had data available from birth certificates. Adjusted odd ratios showed that a 5-minute Apgar score less than 3, low birthweight < 2500 g (particularly very low birthweight < 1500 g), and high birth order (third or greater) were associated with a significant increase in the risk of the subsequent development of specific language impairment. Other factors that proved independently to be associated with an increased risk of specific language impairment were a shorter duration of maternal education, maternal marital status (single), and late commencement of antenatal care. The latter set of factors largely reflects maternal socioeconomic status and may relate to genetic or environmental influences on the development of language. However, the increased risk associated with low birthweight and a low 5-minute Apgar score suggests that chronic prenatal or acute perinatal insults to the developing central nervous system may lead to later specific language impairment.

Further evidence that prenatal or perinatal insults may specifically impair language development comes from two recent studies.[76,77] Singer et al found evidence of language impairment that was independent of cognitive function in 3-year-old children with a history of bronchopulmonary dysplasia.[76] A longitudinal study of the effects of prenatal cocaine exposure found evidence of language impairment in children.[77] The effect persisted even when the effect of covariates--such as IQ and the adequacy of the language exposure at home--were controlled for.

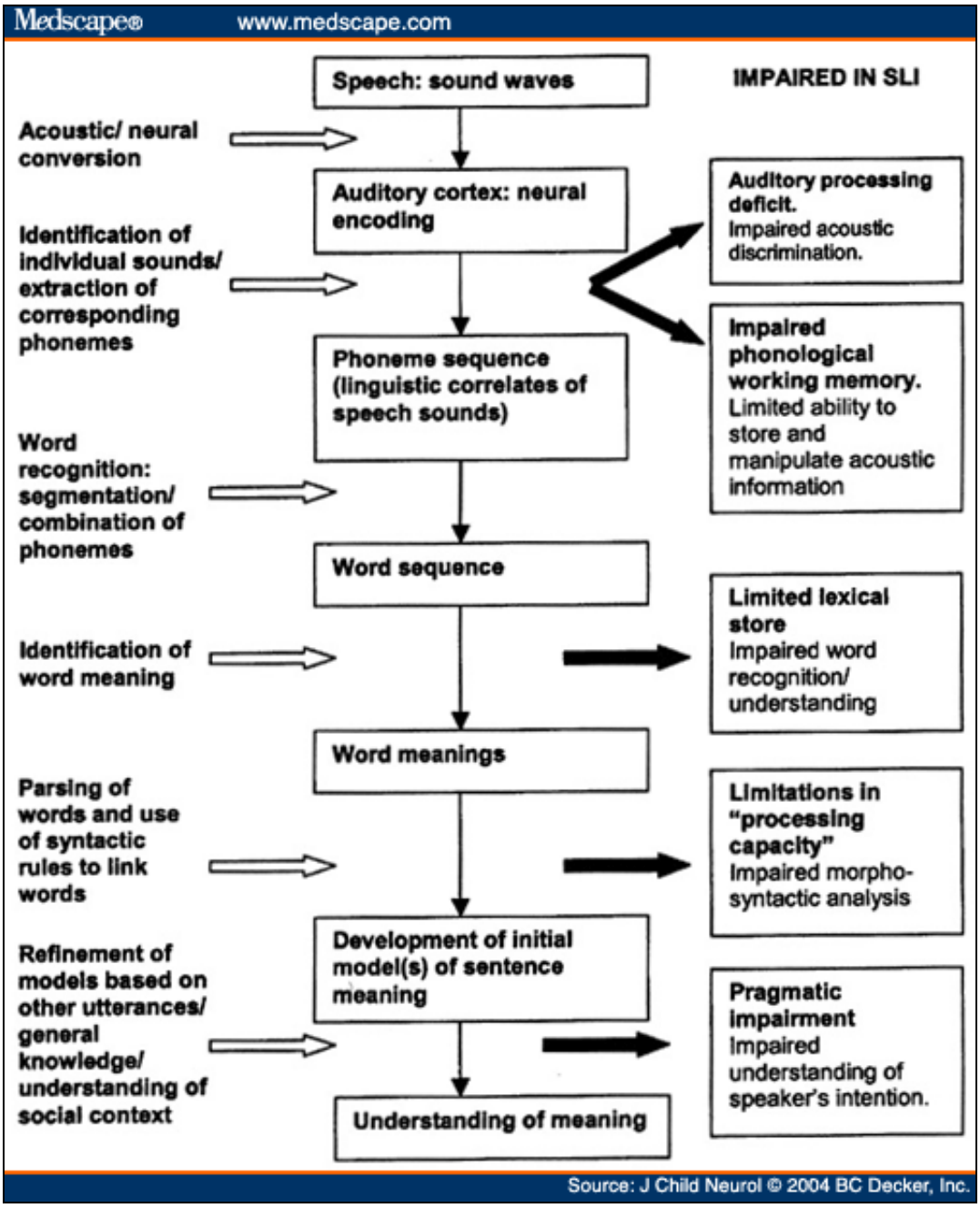
The fact that different areas of language pose particular difficulties for children with specific language impairment suggests that these areas may provide clues to core deficits in language processing that underlie specific language impairment. Several theories have been proposed to explain the deficits seen. On the basis of a study of a large family with autosomal dominant language impairment (the KE family), Gopnik and Crago hypothesized that affected individuals within the family were unable to learn the rules of grammar that allow the generation of inflections (eg, the past tense inflection *ed*, as in walk*ed*) and so learned inflected forms of words as new words.[78] They further theorized that a single gene controlled the ability to generate the inflected forms of these words. Subsequent research on members of this family found a broader phenotype among affected individuals with intellectual, linguistic, and motor impairments.[67,73,74] Moreover, affected family members were found to overregularize irregular verbs, suggesting that they did have awareness of grammatical rules but sometimes applied them inappropriately.

The surface hypothesis proposed by Leonard also addressed the particular difficulty that children with specific language impairment have with grammatical inflections, particularly third-person singular (-s), possessive (-s), and past tense (-ed).[12] These inflections are of short duration, and as noted above, children with specific language impairment have been shown to have difficulties processing rapidly changing sounds. Leonard hypothesized that as a result of processing limitations (perhaps resulting from inadequate representation in verbal working memory), these inflections were more often omitted. However, Leonard notes that the theory is unable to account for the range of linguistic problems encountered in children with specific language impairment.[12]

More recently, a number of authors have suggested that the fundamental deficit in specific language impairment is a limitation in the brain's capacity to rapidly process information.[10,12,79,80] Evidence for processing limitation is seen in

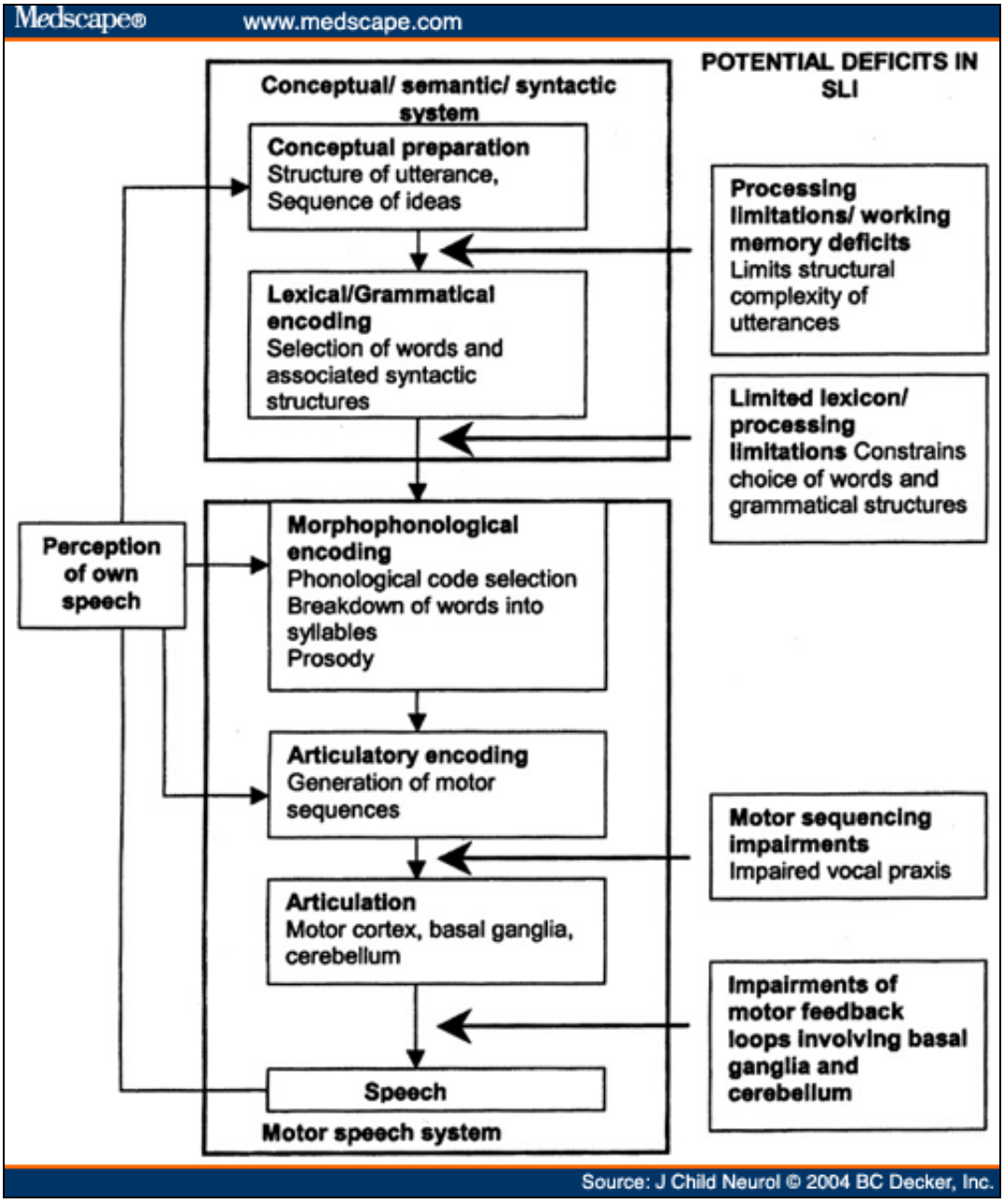
studies showing that children with specific language impairment have longer response times associated with performing linguistic and nonlinguistic tasks.[54,55,79,80] More complex grammatical structures may take longer to process than simpler structures. With increasing sentence complexity, structures that place greater demands on processing resources (such as grammatical inflections) may be omitted. Other factors that increase processing demands, such as phonologic complexity and even prosodic difficulty, can also impair comprehension and speech production in children with specific language impairment.[12] Limitations in the amount of information that can be stored in verbal working memory may further constrain language processing.[80,81]

The phases of receptive language processing and speech production influenced by hypothesized deficits in children with specific language impairment are illustrated schematically in Figures 1 and 2.



Potential limitations in receptive language processing in children with specific language impairment (SLI). The figure

illustrates stages in receptive language processing and has been adapted from Uncommon Understanding by Dorothy Bishop.[10] In the left column, the hypothesized processes involved in language processing are described, and in the middle column, incremental outcomes of processing are presented (these are based on Bishop's original figure). On the right, a column has been inserted documenting hypothesized deficits in language processing in children with specific language impairment and the effects of these deficits on language processing. Top-down feedback loops that are likely to influence language processing have been omitted from the figure.



Potential limitations in speech production in specific language impairment (SLI). A model of speech production based on that proposed by Indefrey and Levelt[84] is presented in the left and middle columns. In the right column, potential deficits in children with specific language impairment are shown. Arrows indicate the phases of speech production that these deficits might affect.

Our understanding of the neurobiology of specific language impairment has increased considerably over the past 10

years; however, a number of questions remain to be answered. Research in specific language impairment (with some notable exceptions) has largely reflected the area of interest of the investigator. Language researchers have spent considerable time attempting to classify a child's language phenotype; however, little research has been conducted into establishing a broader phenotype. For example, does the presence or absence of motor impairment change the language phenotype? How common are abnormal neurologic findings in a larger group of children with specific language impairment, and are they associated with characteristic patterns of impairment? Such information may allow the development of a more detailed phenotype, perhaps identifying biologic heterogeneity that is not obvious on tests of language.

A better understanding of the neurologic profile of specific language impairment has obvious relevance for genetic studies. It is likely that genes that affect language are also important for other neurologic functions. Detailed clinical and imaging studies have delineated a complex language, cognitive, and motor phenotype associated with the *FOXP2* mutation in members of the KE family.[67,68,73,74] Similar studies in broader groups of children with specific language impairment potentially allow the identification of genetic factors that influence not only language but also other neurologic functions.

New techniques for structural imaging have great potential to improve our understanding of specific language impairment. The question of whether children with specific language impairment have abnormal patterns of cerebral asymmetry remains unresolved. Although the majority of studies have reported atypical asymmetry patterns,[33,60,61] the fact that different regions have been identified--and that at least one study has not identified atypical asymmetry[62]--raises the question as to whether these findings are robust. Moreover, the factors that lead to atypical asymmetry (eg, white-matter volume reduction) have not been clearly delineated. New techniques that permit statistically rigorous interpretation of magnetic resonance data--such as voxel-based morphometry[82]--may resolve some of these issues.

The potential for functional neuroimaging to further our understanding of the causes of specific language impairment is considerable. Studies using functional MRI, magnetoencephalography, and event-related potentials or a combination of these measures are likely to delineate abnormalities of language processing that differentiate children with specific language impairment from children with normal language. These techniques may demonstrate both spatial (localization) and temporal abnormalities in the way that language is processed in children with specific language impairment. They may also reveal functional differences associated with the phenotypic heterogeneity seen in specific language impairment. Functional studies may also show how other networks are recruited to compensate for language processing difficulties and provide a further means of monitoring the effects of a given therapy.

A better understanding of the neurobiology of specific language impairment is not only of academic interest. Although the majority of studies show that language intervention is effective,[83] it is common for children with specific language impairment to be left with a significant language disability despite optimal therapy.[12] Therapy for children with specific language impairment tends to be empiric. Better understanding of the basis of a child's language impairment potentially allows for more specifically targeted therapy, avoidance of therapy that is ineffective, an ability to predict associated comorbidity, and a better ability to prognosticate regarding outcome. It also may allow the identification of markers indicating that a young child is at risk of developing specific language impairment, allowing the earlier commencement of therapy and a greater likelihood of an improved outcome.

Identifying a biologic cause of specific language impairment has great relevance for children with specific language impairment and their parents. A biologic understanding of the cause of a child's disability may resolve anxiety and encourage parents to pursue appropriate therapy.

Despite its title, specific language impairment is not "specific." Although language is the function that is most obviously impaired in specific language impairment, nonverbal cognition, motor skills, and attention are frequently affected. Speech requires rapid processing of information followed by the generation of complex motor plans (see Figure 2). Current

theories of specific language impairment hold that the language and cognitive impairments seen in specific language impairment result from limitations in the speed with which information can be processed.[10,12] Understanding of speech may be constrained further by limitations in verbal short-term memory[26,42,43] and in difficulties differentiating rapidly changing acoustic stimuli.[45-47] Electrophysiologic studies have provided evidence that the early phases of auditory processing are abnormal in children with specific language impairment.[54,55] Neuroimaging studies suggest that atypical patterns of asymmetry of auditory and perisylvian cortex and reduced cerebral volume are a risk factor for specific language impairment.[33,60-63] Focal damage or dysgenesis of perisylvian cortex is also associated with specific language impairment.[57,58,64]

Given the phenotypic heterogeneity seen among children with specific language impairment, it is perhaps not surprising that there is evidence of biologic heterogeneity. It is likely that both genetic[44,68,72,75] and environmental[71,76,77] risk factors contribute (and interact), leading to the development of specific language impairment. Future research into the causes of specific language impairment will hopefully identify biologic factors that limit language processing. A better understanding of the neurobiology of specific language impairment is critical for the rational development of therapeutic strategies to treat this common disorder.

References

1. Hauser MD, Chomsky N, Fitch WT: The faculty of language: What is it, who has it, and how did it evolve? *Science* 2002;298:1569-1579.
2. Bishop DVM: How does the brain learn language? Insight from the study of children with and without language impairment. *Dev Med Child Neurol* 2000;42:133-142.
3. Tomblin JB, Records NL, Buckwater P, et al: Prevalence of specific language impairment in kindergarten children. *J Speech Lang Hear Res* 1997;40:1245-1260.
4. Aram DM, Ekelman BL, Nation JE: Preschoolers with language disorders: 10 years later. *J Speech Hear Res* 1984;27:232-244.
5. Stothard SE, Snowling MJ, Bishop DV, et al: Language-impaired preschoolers: A follow-up into adolescence. *J Speech Lang Hear Res* 1998;41:407-418.
6. Snowling M, Bishop DVM, Stothard SE: Is preschool language impairment a risk factor for dyslexia in adolescence? *J Child Psychol Psychiatry* 2000;41:587-600.
7. Shevell MI, Majnemer A, Rosenbaum P, Abrahamowicz M: Etiologic yield of single domain developmental delay: A prospective study. *J Pediatr* 2000;137:633-637.
8. Lahey M: Who shall be called language disordered? Some reflections and one perspective. *J Speech Hear Disord* 1990;55:612-620.
9. Aram DM, Morris R, Hall NE: Clinical and research congruence in identifying children with specific language impairment. *J Speech Hear Res* 1993;36:580-591.
10. Bishop DVM: *Uncommon Understanding*. Hove, UK, Psychology Press Publishers, 1997.

11. World Health Organization: *The ICD-10 Classification for Mental and Behavioural Disorders: Diagnostic Criteria For Research.* Geneva, World Health Organization, 1992.

12. Leonard LB: *Children with Specific Language Impairment.* Cambridge, MA, The MIT Press, 1998.

13. American Psychiatric Association, Taskforce on DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders IV-TR.* Washington, DC, American Psychiatric Association, 2000.

14. Tomblin JB, Records NL, Zhang X: A system for the diagnosis of specific language impairment in kindergarten children. *J Speech Lang Hear Res* 1996;39:1284-1294.

15. Records NL, Tomblin JB: Clinical decision making: Describing the decision rules of practicing speech-language pathologists. *J Speech Hear Res* 1994;37:144-156.

16. Bishop DVM: Is specific language impairment a valid diagnostic category? Genetic and psycholinguistic evidence. *Philos Trans R Soc Lond B Biol Sci* 1994;346:105-111.

17. Johnston JR: Cognitive abilities of children with language impairment, in Watkins RV, Rice ML (eds): *Specific Language Impairments in Children.* Baltimore, Paul H. Brookes, 1994, 107-122.

18. Bishop DVM, Edmundson A: Language impaired 4-year olds: Distinguishing transient from persistent impairment. *J Speech Hear Disord* 1987;52:156-173.

19. Rice ML: Grammatical categories of children with specific language impairment, in Watkins RV, Rice ML (eds): *Specific Language Impairments in Children.* Baltimore, Paul H. Brookes, 1994, 69-90.

20. Korkman M, Hakkinen-Rihu P: A new classification of developmental language disorders. *Brain Lang* 1994;47:96-116.

21. Wilson BC, Risucci DA: A model for clinical-quantitative classification. Generation I: Application to language-disordered preschool children. *Brain Lang* 1986;27:281-309.

22. Rapin I, Allen D: Syndromes in developmental dysphasia and aphasia, in Plum F (ed) *Language Communication and the Brain.* New York, Raven Press, 1988, 57-75.

23. Conti-Ramsden G, Crutchley A, Botting N: The extent to which psychometric tests differentiate subgroups of children with SLI. *J Speech Lang Hear Res* 1997;40:765-777.

24. Conti-Ramsden G, Botting N: Classification of children with specific language impairment: longitudinal considerations. *J Speech Lang Hear Res* 1999;42:1195-1204.

25. Bishop DVM, Edmundson A: Specific language impairment as a maturational lag: Evidence from longitudinal data on language and motor development. *Dev Med Child Neurol* 1987 29:442-459.

26. Bishop DVM, North T, Donlan C: Nonword repetition as a behavioural marker for inherited language impairment: Evidence from a twin study. J Child Psychol Psychiatry 1996;37:391-403.

27. Trauner D, Wulfeck B, Tallal P, Hesselink J: Neurological and MRI profiles of children with developmental language impairment. *Dev Med Child Neurol* 2000;42:470-475.

28. Johnston RB, Stark RE, Mellits ED, Tallal P: Neurological status of language-impaired and normal children. *Ann Neurol* 1981;10: 159-163.

29. Hill EL: A dyspraxic defect in specific language impairment and developmental coordination disorder? Evidence from hand and arm movements. *Dev Med Child Neurol* 1998;40:388-395.

30. Bishop DVM: Motor immaturity and specific language impairment: Evidence for a common genetic basis. *Am J Med Genet* 2001;114:56-63.

31. Manor O, Shalev RS, Joseph A, Gross-Tsur V: Arithmetic skills in kindergarten children with developmental language disorders. *Eur J Pediatr Neurol* 2001;5:71-77.

32. Tannock R, Brown TE: Attention-deficit disorders with learning disorders in children and adolescents, in Brown TE (ed): *Attention Deficit Disorders and Cognitive Co-morbidities in Children, Adolescents and Adults.* Washington, DC, American Psychiatric Press, 2000.

33. Gauger LM, Lombardino LJ, Leonard CM: Brain morphology in children with specific language impairment. *J Speech Lang Hear Res* 1997;40:1272-1284.

34. Catts HW, Fey ME, Tomblin JB, Zhang X: A longitudinal investigation of reading outcomes in children with language impairments. *J Speech Lang Hear Res* 2002;45:1142-1157.

35. McArthur GM, Hogben JH, Edwards VT, et al: On the "specifics" of specific reading disability and specific language impairment. *J Child Psychol Psychiatry* 2000;40:869-874.

36. Shaywitz BA, Shaywitz SE: Dylexia. *Continuum* 2002;8(5):17-35.

37. Shaywitz SE: Dyslexia. *N Engl J Med* 1998;338:307-312.

38. Ors M: Time to drop "specific" in "specific language impairment." *Acta Paediatr* 2002;91:1025-1030.

39. Gathercole SE, Baddeley AD: Evaluation of the role of phonological STM in the development of vocabulary in children: A longitudinal study. *J Mem Lang* 1989;28:200-213.

40. Gathercole SE, Willis C, Baddeley AD, Emslie H: The Children's Test of Non-Word Repetition: A test of phonological working memory. *Memory* 1994;2:103-127.

41. Adams A, Gathercole SE: Limitations in working memory: Implications for language development. *Int J Lang Commun Disord* 2000;35:95-116.

42. Gathercole SE, Baddeley AD: Phonological memory deficits in language disordered children: Is there a causal connection? *J Mem Lang* 1990:29:336-360.

43. Botting N, Conti-Ramsden G: Non-word repetition and language development in children with specific language impairment (SLI). *Int J Lang Commun Disord* 2001;36:421-432.

44. SLI Consortium: A genome wide scan identifies two novel loci involved in specific language impairment. *Am J Hum Genet* 2002; 70:384-398.

45. Tallal P, Piercy M: Developmental aphasia: Rate of auditory processing and selective impairment of consonant

perception. *Neuropsychologia* 1974;12:83-93.

46. Tallal P, Piercy M: Developmental aphasia: Impaired rate of non-verbal processing as a function of sensory modality. *Neuropsychologia* 1973;11:389-398.

47. Tallal P, Piercy M: Developmental aphasia: The perception of brief vowels and extended stop consonants. *Neuropsychologia* 1975;13:69-74.

48. Benasich AA, Thomas JJ, Choudhury N, Leppanen PHT: The importance of rapid auditory processing abilities to early language development: Evidence from converging methodologies. *Dev Psychobiol* 2002;40:278-292.

49. Merznich MM, Jenkins WM, Johnston P, et al: Temporal processing deficits of language-learning impaired children ameliorated by training. *Science* 1996;271:77-81.

50. Tallal P, Miller SL, Bedi G, et al: Language comprehension in language-learning impaired children improved with acoustically modified speech. *Science* 1996;271:81-84.

51. Staden U, Isaacs E, Boyd SG, et al: Language dysfunction in children with rolandic epilepsy. *Neuropediatrics* 1998;129:242-248.

52. Maccario M, Hefferen SJ, Keblusek SJ, Lipinski KA: Developmental dysphasia and electroencephalographic abnormalities. *Dev Med Child Neurol* 1992;24:141-155.

53. Picard A, Cheliout Heraut F, Bouskraoui M, et al: Sleep EEG and developmental dysphasia. *Dev Med Child Neurol* 1998;40: 595-599.

54. Ors M, Lindgren M, Blennow G, et al: Auditory event-related potentials in children with specific language impairment. *Eur J Pediatr Neurol* 2002;6:47-62.

55. Uwer R, Albrecht R, von Suchodeletz W: Automatic processing of tones and speech stimuli in children with specific language impairment. *Dev Med Child Neurol* 2002;44:527-532.

56. Ors M, Lindgren M, Blennow G, Rosen I: Auditory event-related potentials in parents of children with specific language impairment. *Eur J Pediatr Neurol* 2002;6:242-249.

57. Landau WM, Goldstein R, Kleffner FR: Congenital aphasia: A clinicopathologic study. *Neurology* 1960;10:915-921.

58. Cohen M, Campbell R, Yaghmai F: Neuropathological abnormalities in developmental dysphasia. *Ann Neurol* 1989;25: 567-570.

59. Galaburda AM, Sherman GF, Rosen GD, et al: Developmental dyslexia: four consecutive patients with cortical anomalies. *Ann Neurol* 1984;18:222-233.

60. Plante E, Swisher L, Vance R, Rapcsak S: MRI findings in boys with specific language impairment. *Brain Lang* 1991;41:52-66.

61. Jernigan TL, Hesselink JR, Sowell E, Tallal PA: Cerebral structure on magnetic resonance imaging in language- and learning-impaired children. *Arch Neurol* 1991:48;539-545.

62. Preis S, Lancke L, Schittler P, et al: Normal intrasylvian anatomical asymmetry in children with developmental

language disorder. *Neuropsychologia* 1998;36:849-855.

63. Leonard CM, Lombardino LJ, Walsh K, et al: Anatomical risk factors that distinguish dyslexia from SLI predict reading skill in normal children. *J Commun Disord* 2002;35:501-531.

64. Preis S, Engelbrecht V, Huang Y, Steinmetz H: Focal grey matter heterotopias in monozygotic twins with developmental language disorder. *Eur J Pediatr* 1998;157:849-852.

65. Clark MC, Plante E: Morphology of the inferior frontal gyrus in developmentally language-disordered adults. *Brain Lang* 1998; 61:288-303.

66. Njiokiktjien C, de Sonneville L, Vaal J: Callosal size in children with learning disabilities. *Behav Brain Res* 1994;64:213-218.

67. Watkins KE, Vargha-Kadem F, Ashburner J, et al: MRI analysis of an inherited speech and language disorder: Structural brain abnormalities. *Brain* 2002;125:465-478.

68. Lai CS, Fisher SE, Hurst JA, et al: A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature* 2001; 413:519-523.

69. Stromswold K: Genetics of spoken language disorders. *Hum Biol* 1998;2:297-324.

70. Tallal P, Ross R, Curtiss S: Unexpected sex ratios in families of language/learning impaired children. *Neuropsychologia* 1989; 27:987-998.

71. Stanton-Chapman, Chapman DA, Bainbridge NL, Scott KG: Identification of early risk factors for language impairment. *Res Dev Disabil* 2002;23:390-405.

72. Bishop DVM, North T, Donlan C: Genetic basis of specific language impairment: Evidence from a twin study. *Dev Med Child Neurol* 1995;37:56-71.

73. Vargha-Khadem F, Watkins K, Alcock K, et al: Praxic and nonverbal cognitive deficits in a large family with a genetically transmitted speech and language disorder. *Proc Natl Acad Sci U S A* 1995;92: 930-933.

74. Watkins KE, Dronkers NF, Vargha-Kadem F: Behavioural analysis of an inherited speech and language disorder: Comparison with acquired aphasia. *Brain* 2002;125:452-464.

75. Bartlett CW, Flax JF, Logue MW, et al: A major susceptibility locus for specific language impairment is located on 13q21. *Am J Hum Genet* 2002;71:45-55.

76. Singer LT, Siegel CA, Lewis B, et al: Preschool language outcomes of children with history of bronchopulmonary dysplasia and very low birth weight. *J Dev Behav Pediatr* 2001;22:19-26.

77. Bandstra ES, Morrow CE, Vogel AL, et al: Longitudinal influence of prenatal cocaine exposure on child language functioning. *Neurotoxicol Teratol* 2002;24:297-308.

78. Gopnik M, Crago MB: Familial aggregation of a developmental language disorder. *Cognition* 1991;39:1-50.

79. Miller CA, Kail R, Leonard LB, et al: Speed of processing in children with specific language impairment. *J Speech Lang Hear Res* 2001;44:416-433.

80. Montgomery JW: Information processing and language comprehension in children with specific language impairment. *Top Lang Disord* 2002;22:62-84.

81. Weismer SE, Evans J, Hesketh LJ: An examination of verbal working memory capacity in children with specific language impairment. *J Speech Lang Hear Res* 1999;42:1249-1260.

82. Ashburner J, Friston KJ: Voxel-based morphometry--The methods. *Neuroimage* 2000;11:805-821.

83. Nye C, Foster S, Seaman D: Effectiveness of language intervention with the language/learning disabled. *J Speech Hear Res* 1987;52:348-357.

84. Indefrey P, Levelt WJM: The neural correlates of language production, in Gazzaniga MS (ed): *The New Cognitive Neurosciences.* Cambridge, MA, MIT Press, 2000, 845-866.

Reprint Address

Address correspondence to Dr Richard Webster, Room A-514, Montreal Children's Hospital, 2300 Tupper St, Montreal, QC H3H 1P3, Canada. Tel: 514-412-4363; fax: 514-412-4373; e-mail: richard.webster@muhc.mcgill.ca.

J Child Neurol. 2004;19(7)