Published in final edited form as:

J Speech Lang Hear Res. 2011 December ; 54(6): 1628–1643. doi:10.1044/1092-4388(2011/10-0124).

Literacy Outcomes of Children With Early Childhood Speech Sound Disorders: Impact of Endophenotypes

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Abstract

Purpose—To demonstrate that early childhood speech sound disorders (SSD) and later school-age reading, written expression, and spelling skills are influenced by shared endophenotypes that may be in part genetic.

Method—Children with SSD and their siblings were assessed at early childhood (ages 4–6 years) and followed at school age (7–12 years). The relationship of shared endophenotypes with early childhood SSD and school-age outcomes and the shared genetic influences on these outcomes were examined.

Results—Structural equation modeling demonstrated that oral motor skills, phonological awareness, phonological memory, vocabulary, and speeded naming have varying influences on reading decoding, spelling, spoken language, and written expression at school age. Genetic linkage studies demonstrated linkage for reading, spelling, and written expression measures to regions on chromosomes 1, 3, 6, and 15 that were previously linked to oral motor skills, articulation, phonological memory, and vocabulary at early childhood testing.

Conclusions—Endophenotypes predict school-age literacy outcomes over and above that predicted by clinical diagnoses of SSD or language impairment. Findings suggest that these shared endophenotypes and common genetic influences affect early childhood SSD and later school-age reading, spelling, spoken language, and written expression skills.

Keywords

genetics; speech sound disorders; reading; spelling; written expression

Speech sound disorders (SSD) present in early childhood, with an estimated 16% of children affected at 3 years of age (Campbell et al., 2003) and with 3.8% of these children continuing to present with speech delay at 6 years of age (Shriberg, Tomblin, & McSweeney, 1999). Language impairment (LI) often co-occurs with SSD, with an estimated 6%–21% comorbidity for receptive language deficits and 38%–62% for children with expressive language disorders (Shriberg & Austin, 1998). Although SSD and/or LI may resolve by early school age, more than half of these children encounter later academic difficulties in language, reading, and spelling (Aram & Hall, 1989; Bishop & Adams, 1990; Flax et al., 2003; Lewis, Freebairn, & Taylor 2000; Shriberg & Austin, 1998).

In a comprehensive review of the comorbidity of SSD, LI, and reading disorder (RD), Pennington and Bishop (2009) concluded that although there is evidence for overlap of these disorders on both the cognitive and etiological levels, the disorders are complex, with subtypes representing all combinations and varying severity of disorders. Recent studies have suggested a genetic etiological overlap and have linked candidate chromosome regions to specific cognitive processes or endophenotypes such as phonological memory, phonological awareness, vocabulary, and processing speed (Miscimarra et al., 2007; Smith, Pennington, Boada, & Shriberg, 2005; Stein et al., 2004, 2006). These endophenotypes may underlie both early SSD and LI and later RD, spelling disorders, and written expression disorders, thus accounting for the high comorbidity of these disorders.

Academic Outcomes for Individuals With Early-Childhood SSD

Studies that have followed children with early childhood SSD to school age have found later academic difficulties in 50%–75% of their samples (Aram & Hall, 1989; Bishop & Adams, 1990; King, Jones, & Laskey, 1982; Lewis, O'Donnell, Freebairn, & Taylor, 2002). Whereas comorbid LI seems to increase the risk of later RD, several studies have suggested that even isolated early SSD can impact later written expression skills. Our follow-up study of young children with these disorders revealed that 18% of participants with an isolated SSD had reading problems in mid-elementary school, compared with 75% of those with combined SSD and LI (Lewis et al., 2000). Peterson, Pennington, Shriberg, and Boada (2009) also found that children with SSD demonstrated higher rates of RD than did control children. Findings supported a multiple deficit model rather than a core phonological deficit. Rvachew (2007) reported that children with SSD and poor phonological processing skills were poorer at decoding nonwords at the end of first grade than were children with SSD and good phonological processing skills. DeThorne et al. (2006) also reported that children with isolated SSD differ significantly from controls in phonological awareness, word attack, and word identification skills at 6 years of age. Thus, deficits in phonological processing skills as well as comorbid LI may determine whether the child with SSD will experience later reading difficulties. An endophenotype such as phonological processing skills may account for both early SSD and later RD.

Endophenotypes for SSD

Endophenotypes are objectively measurable cognitive, linguistic, or neuropsychological parameters that are closely associated with a specific behavioral trait and are useful in detecting genetic influences on the behavioral phenotype (Gottesman & Gould, 2003; Inoue & Lupski, 2003). Because endophenotypes are viewed as the core determinants of a clinical phenotype, they are more directly related to the underlying genetic basis for the disorder (Gottesman & Gould, 2003). The endophenotype is hypothesized to involve fewer genes than the clinical phenotype, simplifying the genetic analysis (Gottesman & Gould, 2003). These endophenotypes are postulated to impact the core domains, such as speech production, reading, spelling, and oral language (Bishop & Snowling, 2004; Castellanos & Tannock, 2002; Fisher & DeFries, 2002; Pennington, 1997). Genes for SSD may influence multiple endophenotypes such as oral motor skills, phonological awareness, phonological memory, speed of processing, and vocabulary.

Oral motor skill is an example of a trait that may be influenced both by genes that make unique contributions to SSD and by genes that contribute to overall neurodevelopmental maturity. Several studies have demonstrated that children with speech and language disorders present with poorer motor skills than do typically developing children (Bishop, 2001, 2002; Bishop & Adams, 1990; Bishop & Edmundson, 1987; Hill, 2001). High rates of comorbidity of SSD, LI, RD, and motor incoordination suggest that slow motor performance

may be an indicator of a general underlying neurodevelopmental immaturity rather than a true motor disorder (Bishop, 2002; Hill, 2001; Visser, 2003). Twin studies have demonstrated that endophenotypes are heritable. Reported heritability for oral motor skills is .37 (Colledge et al., 2002; Kovas et al., 2005).

Phonological awareness is the ability to manipulate phonemes in spoken words and awareness of the sound structure of language. Deficits in phoneme awareness have been identified as one of the strongest earliest predictors of RD (Nathan, Stackhouse, Gouldandris, & Snowling, 2004; Raitano, Pennington, Tunick, Boada, & Shriberg, 2004). Other studies have demonstrated that children with SSD both with and without additional LI perform more poorly than do controls on phonological awareness measures (Bird, Bishop, & Freeman, 1995; Rvachew & Grawberg, 2006). A recent study by Preston and Edwards (2010) reported that children with more atypical or nondevelopmental speech sound errors (such as deletion of initial consonants) had more difficulty with phonological awareness tasks than did children with typical errors. Phonological awareness skills depend on accurate phonological representations that may be deficient in children with SSD. Thus, phonological awareness is a useful endophenotype for RD as well as SSD. Phonological awareness has been linked with several chromosome regions (Fisher et al., 2002). Our previous work has shown linkage between chromosome 3 and multisyllabic and nonsense word repetition (Stein et al., 2004). Twin studies have demonstrated heritability of phoneme awareness based on the Sound Blending, Sound Matching, and Elision subtests of the Comprehensive Test of Phonological Processing (CTOPP; Wagner & Torgesen, 1999) to be .63 (Byrne et al., 2005).

Phonological short-term memory refers to coding information phonologically for temporary storage in working or short-term memory (Colledge et al., 2002; Gathercole & Baddeley, 1990; Montgomery, Magimairaj, & Finney, 2010; Torgesen & Wagner, 1992). The ability to hold novel sound sequences in phonological memory presumably allows stable long-term phonological representations of new words to be established (Jarrold, Thorn, & Stephans, 2009). Phonological short-term memory continues to play a role in vocabulary acquisition into adulthood (Atkins & Baddley, 1998; Gupta, 2003). Deficits in phonological short-term memory impair an individual's ability to learn both spoken and written new words (Bishop et al., 2006; Raskind, Hsu, Berninger, Thomson, & Wijsman, 2000; Shaywitz, 1998). Phonological short-term memory may be under genetic influence as suggested by family aggregation and twin studies (Shaywitz, 1998). A study by Bishop, North, and Donlan (1996) reported the heritability of phonological memory based on nonword repetition to be .61 and based on a sentence imitation task to be .36.

Several investigators exploring *speed of processing* have proposed that children with LI and/or RD have a generalized slowing of information processing when compared with control children (Kail, 1994; Lahey & Edwards, 1995; Lahey, Edwards, & Munson, 2001; Miller, Kail, Leonard, & Tomblin, 2001; Snowling, 2001; Tallal, Miller, Jenkins, & Merzenich, 1997). Tallal et al. (1997) demonstrated that language-learning-impaired children, including children with RD, had particular difficulty processing rapidly presented auditory stimuli. Slower speed of processing may also impact the establishment of phonological representations for words as the phonological information held in memory may decay before the representation is established (Montgomery et al., 2010). In our previous work on SSD (Stein et al., 2004), rapid naming, a speed of processing task, demonstrated linkage to a region of chromosome 3 that was also associated with RD. Heritability for speeded naming is about .64 (Byrne et al., 2005).

Vocabulary continues to develop throughout the life span, with children learning approximately 36,000 words between 1st and 12th grades (Montgomery, 2007). Vocabulary

plays a critical role in reading acquisition. Studies of reading comprehension have demonstrated that both spoken syntax and semantic skills are the best predictors of reading comprehension for kindergarten and first-grade children (Catts, 1993; Catts, Fey, Zhang, & Tomblin, 1999; Lombardino, Riccio, Hynd, & Pinheiro, 1997). Vocabulary in particular has been related to single-word reading as children with larger vocabularies are better able to identify written words (Wise, Sevcik, Morris, Lovett, & Wolf, 2007). Poor vocabulary is a hallmark of language, literacy, and cognitive disabilities. Measures of expressive and receptive vocabulary have demonstrated linkage to chromosomes 1 (Miscimarra et al., 2007), 6p22-21 (Grigorenko, Wood, Meyer, & Pauls, 2000), and 13q21 (Bartlett et al., 2002). Heritability for vocabulary has been estimated at .52 (Colledge et al., 2002; Kovas et al., 2005).

Study Design, Aims, and Hypotheses

Data for the present study were collected as part of a longitudinal study of children with SSD recruited as preschoolers (Lewis et al., 2000, 2002; Stein et al., 2004). The goal of this study was to examine types of SSD in early childhood, follow the children to investigate later outcomes, and investigate associated cognitive–linguistic correlates and genetic antecedents of this disorder. A unique strength of this study is the collection of data on the children’s speech/language and cognitive–linguistic skills in both early childhood and at school age in children in all points of the spectrum from healthy to severely affected. The availability of measures of outcomes on the same children across these two time points provides a unique opportunity to investigate cognitive–linguistic and genetic factors associated with both the initial speech/language disorders we observed in the sample (SSD and LI) and the children’s later-emerging academic skills. To take into account correlations of predictors and outcomes within and across these two assessments, we used structural equation modeling (SEM) to examine these associations. SEM is a multivariate statistical technique that accounts for the correlation between observed variables when developing a model describing relationships between constructs or domains; these latent (unobserved) variables can be captured through observed “indicator” variables. Once a model has been developed and is considered the best fit, it illustrates relationships between variables after accounting for the correlation between them. Where standard regression analyses assess the independent association between a set of predictors and single-outcome variable, SEM accounts for the correlation among all predictor and outcome variables and then estimates statistically independent effects.

Our first objective was to develop a model to depict the relationships between endophenotypes and early childhood SSD and LI and school-age reading, spelling and written expression, and spoken language skills. The model tested was an exploratory one that examined the viability of the following associations as justified by the existing literature as summarized above:

1. Oral motor skills will be associated with early childhood SSD.
2. Poor phonological awareness skills may be related to early SSD and later reading decoding and spelling skills. Because difficulties in articulation can affect naming efficiency, speeded naming deficits will also be associated with early SSD. Speeded naming will continue to impact spoken language skills as well as literacy skills at school age.
3. Poor vocabulary skills will be associated with language skills at both early childhood and school age.
4. Because poor phonological memory skills signal difficulties in forming phonological representations, these skills will be associated with early childhood

SSD. Phonological memory will continue to impact spoken language, written expression, and reading decoding at school age.

A second goal was to examine genetic linkage of cognitive–linguistic endophenotypes measured at our initial assessment in early childhood with early SSD and LI as well as with children’s academic skills at school age. Our interest in the genetic analyses was to identify common genetic factors related to both early SSD/LI and children’s academic skills at school age. On the basis of previous findings, we hypothesized that chromosome regions that were linked to early speech and language skills would also link to later school-age skills of spoken language and written expression.

Method

Participants

The proband children ($N = 152$) were referred to the study from the clinical caseloads of speech-language pathologists at early childhood between 4 and 6 years of age. All probands were enrolled in speech-language therapy for a moderate to severe SSD. Children were recruited between ages 4 and 6, as this is the period during which children present with overt SSD. One hundred fifty-two probands enrolled in the study and completed testing. Of these, 105 were followed to school age. All of the available siblings of the probands ($N = 256$) were invited to participate in the testing. Siblings were assigned to the typically developing group or the SSD group. Siblings with SSD met the same criteria as the proband child. This project was approved by the institutional review board of the Case Medical Center and University Hospitals of Cleveland, Ohio. All consenting children in each family (proband and siblings) were assessed. Probands were required to meet the following eligibility criteria for enrollment into the study at early childhood. See Table 1 for a summary of participants’ demographics.

To be eligible for inclusion in the sample, children were required to pass a pure-tone audiometric screening at 20 dB HL bilaterally and to demonstrate normal middle ear function on an impedance test. Eligible children also demonstrated normal intelligence as defined by a prorated performance IQ of at least 80 on the Wechsler Preschool and Primary Scale of Intelligence—Revised (Wechsler, 1989) or on the Wechsler Intelligence Scale for Children—Third Edition (WISC—III; Wechsler, 1991). A normal peripheral speech mechanism was documented by a z score within one standard deviation of the reference data mean on the Total Structure subscale of the Oral and Speech Motor Control Protocol (Robbins & Klee, 1987). Children older than 5 years were screened for intact oral structures on the Oral Speech Mechanism Screening Exam—Third Edition (St. Louis & Ruscello, 2000).

We administered the Goldman Fristoe Test of Articulation (GFTA; Goldman & Fristoe, 1986) and the Khan-Lewis Phonological Analysis Test (KLPA; Khan & Lewis, 1986) to examine all consonant sounds in English and consonant blends and use of phonological processes. Eligibility was defined as a score below the 10th percentile on the GFTA, a minimum occurrence of four phonological process errors and a severity rating of 3–4 (moderate to severe) on the KLPA before enrollment in therapy. Speech sound differences due to dialect were scored as correct. Scores reported in Table 1 for the GFTA reflect the Time 2 testing when the scores improved pre-sumably due to intervention, maturation, or both.

A conversational speech sample of at least 50 utterances, obtained by standard methods (Shriberg, Austin, Lewis, McSweeney, & Wilson, 1997), was examined for speech intelligibility and phonological patterns. Speech intelligibility (the number of intelligible

words divided by the total number of words multiplied by 100) was rated by a SLP who did not collect the sample. Eligibility was defined by (a) an intelligibility rating of <90% (b) at least 4 of 10 phonological processes (error types) on the KLPA, and (c) failure to produce at least 2 of 10 distinctive speech-sound features (Shriberg & Kwiatkowski, 1982). Siblings were required to meet the above inclusion criteria for an SSD.

At early childhood, probands and siblings who met criteria for an SSD were further classified as demonstrating an isolated SSD or SSD with comorbid LI. Children with isolated SSD obtained scores higher than -1.25 standard deviations below the mean on all subtests of the Test of Language Development—Primary, Second Edition (TOLD-P:2; Newcomer & Hammill, 1988) or the Test of Language Development—Primary, Third Edition (TOLD-P:3; Newcomer & Hammill, 1997). Children with SSD plus LI met the criteria for language impairment outlined by Tomblin and Buckwalter (1998), which included a score equal to or less than 1.25 standard deviation below the mean on at least two of the composite scores of the TOLD-P:2 or TOLD-P:3.

We interviewed parents to determine family history for disorders and to identify and exclude children with developmental disorders (e.g., cognitive delay) other than speech or language or who had more than six episodes of otitis media with effusion prior to age 3. All family members (parents and children) were asked to contribute a DNA sample obtained by a blood draw or saliva sample.

Measures

Early Childhood Endophenotypes

Oral motor skills: We used diadochokinetic rates of single and multisyllables on the Fletcher Time-by-Count Test (Fletcher, 1977) to assess oral motor skills. The participants were asked to rapidly repeat nine syllabic utterances as quickly as possible. These included 20 repetitions of *pa, ta, ka, fa, and la*; 15 repetitions of *pata, paka, taka, and tata*; and 10 repetitions of *pataka*. The number of seconds for each pattern was recorded on the test form. The timed results were then compared with the age norms. Scores were standardized for analyses.

Phonological awareness: Tests of phonological awareness were the Elision and Sound Blending subtests of the CTOPP (Wagner & Torgesen, 1999). Participants younger than 5 years of age did not receive the CTOPP, and the phonological awareness measure was treated as missing data. Standard scores were used in data analysis.

Phonological short-term memory: Phonological short-term memory was assessed by the Digit Span subtest of the WISC-III, the Sentence Imitation subtest of the TOLD-P:3, and the repetition of 20 multisyllabic real words (MSW) and 15 nonsense words (NSW). Words on the MSW and NSW were scored as correct or incorrect, and the percentage of correctly produced words and non-words were age corrected and entered into data analysis. Sentence imitation has been used as a measure of short-term memory by Gathercole and Baddeley (1990) and others (Bishop et al., 2006). Nonsense words have been used to assess short-term phonological memory as the word is novel and the participant does not have it coded or stored in his or her lexicon (Estes, Evans, & ElseQuest, 2007). Raw scores were age standardized and used in data analysis.

Vocabulary: We used the Expressive One-Word Picture Vocabulary Test—Revised (EOWPVT-R; Gardner, 1990) and the Peabody Picture Vocabulary Test—Third Edition (PPVT-III; Dunn & Dunn, 1997) to assess expressive and receptive vocabulary skills, respectively. Standard scores were used in data analyses.

Speeded naming: We used Rapid Automatized Naming (RAN) of colors, objects, letters, and numbers (Denckla & Rudel, 1976) to assess speeded naming, a measure of speed of processing. Rapid naming requires efficient retrieval of phonological information. *Z* scores based on the means and standard deviations of Denckla and Rudel (1976) were used in data analysis. Children younger than 5 years of age did not receive the letters or numbers rapid naming subtests. Their scores were based on the rapid naming of colors and objects.

School-Age Outcomes

Reading decoding: We used the Word Identification and Word Attack subtests of the Woodcock Reading Mastery Tests—Revised (WRMT–R; Woodcock, 1987) to assess reading decoding of real and nonsense words. Standard scores were employed in data analysis.

Spelling: We used the Test of Written Spelling—Third Edition (TWS–3; Larsen & Hammill, 1994) to assess a child’s ability to spell both predictable and un-predictable words. The TWS–3 Predictable Words tests written spelling of words that are spelled as they sound (e.g., stop, ambiguous). The TWS–3 Unpredictable Words tests written spelling of words that cannot be predicted because they are exceptions to common spelling patterns (e.g., two, eight, feign). Standard scores were utilized in data analysis. The Contextual Spelling subtest of the Test of Written Language (TOWL; Hammill & Larsen, 1988) was also utilized as a spelling measure. Unlike the TWS–3, which taps spelling of a specific word list, the Contextual Spelling subtest relies on a spontaneous writing sample.

Written expression: The TOWL also assessed writing composition abilities. Scores from the Thematic Maturity, Contextual Vocabulary, and Syntactic Maturity subtests were used in data analyses.

Spoken language: We used the Clinical Evaluation of Language Fundamentals—Third Edition (CELF–3; Semel, Wiig, & Secord, 1995) to measure receptive, expressive, grammatical, and semantic skills. Standard scores were utilized in data analysis.

Data Analysis

Statistical analyses were conducted on the first available observation for each measure; for example, some children were tested twice at school age, so we analyzed their first assessment. Missing data were handled in a pairwise fashion. If an individual was missing data for a specific variable, then that individual’s data could not be used in the estimation of parameters associated with that variable but could be used for estimation of other parameters. We used an algorithm that is robust to violation of multivariate normality (see below for detail). The data analysis strategy followed three steps. First, prior to the analyses, each measure was stepwise adjusted for age, sex, socioeconomic status as measured by the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975), and birth order (whether the child was the first born or not). The residuals from these regression models were extracted for further analyses. We examined differences between pro-bands, siblings affected with SSD, and unaffected siblings by comparing the means of these groups. To account for familial relationships, we used a generalized estimating equation model implemented in ASSOC (S.A.G.E., 2009). Not all children whose data were utilized in the SEM model were also participants in the linkage analysis as not all participants provided a DNA sample.

Second, we conducted SEM of early childhood disorders, endophenotype measures, and school-age out-comes. SEM estimates a system of linear equations to test the fit of a hypothesized “causal” model. The first step in estimating an SEM is to draw the

hypothesized model, also referred to as a path diagram. In these diagrams, circles or ovals represent unobserved (latent) constructs, and squares or rectangles represent observed, measurable variables. Single-headed directional arrows represent hypothesized causal relationships, whereas double-headed arrows represent correlations. Latent variables that depict specific constructs (e.g., phonological awareness) are modeled using factor analysis. After a hypothesized model is fit, pathways are added and removed until the best fitting model is identified; to assess the overall model fit, we used a number of fit statistics, including the Akaike information criterion (AIC), Bayesian information criterion (BIC), and standardized root-mean-squared residual (SRMR). SEM analyses were conducted using Mplus software Version 5.1 (<http://www.statmodel.com>; Muthén & Muthén, 2008). Models were fit using a robust maximum likelihood estimator, which provides test statistics and standard errors that are robust to nonindependence of observations and non-normality (Mplus Version 5.1; TYPE = COMPLEX).

We conducted SEM of data from early childhood, endophenotype measures, and school-age assessments as shown in Figure 1. The model hypothesizes that endophenotypes (i.e., cognitive deficits underlying the phenotypic impairments: oral motor skills, phonological awareness, phonological memory, vocabulary, and speeded naming) influence early childhood clinical phenotypes of SSD and LI. These endophenotypes, along with early childhood SSD and LI, in turn predict schoolage outcomes of spelling, written expression, reading decoding, and spoken language. The model further assumes that some endophenotypes are unique to SSD (e.g., oral motor skills), whereas other endophenotypes predict both SSD and LI (phonological awareness, phonological memory, vocabulary, and speeded naming). Group mean scores for the early childhood endophenotype measures are presented in Table 2.

To model the latent construct of oral motor function, we used the single and multisyllable subscores of the Fletcher Time-by-Count Test. We used the Elision and Blending Words subtests of the CTOPP to model phonological awareness. We assessed speeded naming with the RAN (colors, numbers, letters, objects; Denckla & Rudel, 1976). Latent variables for phonological memory and vocabulary were based upon previous factor analyses done by Stein et al. (2004) and confirmed by the measurement model as specified in Figure 1 and Table 5. The composition of each factor is summarized above in the *Measures* section. See Supplemental Table 1 for the correlation matrix of measures employed in the Structural Equation Model.

To address the second study aim, we conducted analyses using model-free genetic linkage analysis. Linkage analysis evaluates how markers (pieces of DNA that can be assayed at the molecular level and followed through families) and phenotypes based on family data are jointly inherited at various locations in the genome (Lewis et al., 2006). Linkage designs use coinheritance of the trait in siblings, examining both affected and unaffected individuals to localize a gene to a general area on a specific chromosome. To conduct model-free linkage analysis, we used the Haseman-Elston regression model (Haseman & Elston 1972; see also Elston, Buxbaum, Jacobs, & Olson, 2000), which regresses a measure of phenotypic sharing on the proportion of marker alleles that the sibling pair shared identical by descent (IBD). The original Haseman-Elston model parameterizes the measure of sibling trait similarity as the trait difference squared; since then, the model has been extended to incorporate additional information about the covariance between siblings by using the mean-corrected trait cross-product. A weighted combination of the trait difference and mean-corrected trait cross-product has been shown to be most powerful (Shete, Jacobs, & Elston, 2003). We used GENIBD (S.A.G.E.) to estimate the proportion of alleles shared IBD by each sibling pair, and we used SIBPAL (S.A.G.E.) to conduct the Haseman-Elston regression analyses. For brevity, we present only multipoint analyses.

Results

Comparisons of Probands, Affected Siblings, and Unaffected Siblings

As shown in Table 3, group differences were observed on school-age measures of expressive language on the CELF, $F(2, 292) = 3.94, p = .02$; and on the TOWL subtests Contextual Vocabulary, $F(2, 297) = 4.40, p = .01$, and Syntactic Maturity, $F(2, 297) = 5.61, p = .004$.

SEM of Preschool Predictors of School-Age Outcomes

We performed an SEM analysis on a sample size of 408 individuals, including probands and siblings with and without SSD. We chose the most parsimonious model by comparing the AIC, BIC, and SRMR across a variety of models; this final model is shown in Figure 1. To make the figure clearer, we did not draw correlations, which are instead provided in Table 4; factor loadings are listed in Table 5. Latent constructs were highly inter-correlated (Table 4). The factor loadings for the subtests described above were all greater than 0.4 (Table 5). The SRMR for this model was 0.069, indicating adequate fit. The final model had a log likelihood value of -8451.558 (under the null hypothesis, log likelihood = -8887.573), with 108 free parameters.

The SEM analysis demonstrated that endopheno-types were associated with both early childhood SSD and LI as well as with school-age outcomes. Phonological awareness was associated with early SSD and later reading decoding, spelling, and written expression skills. Speeded naming was associated with both early SSD and LI and later spoken language skills. Phonological memory was associated with early SSD as well as later spoken language. Vocabulary was associated with early LI and later spoken language and written expression abilities. Oral motor skill was not significantly associated with outcomes, although weak associations were observed with SSD and writing. In addition, this model shows relationships between early childhood SSD and LI and later school-age outcomes. Early SSD was associated with later written expression skills. Early LI was associated with reading decoding. SSD and LI were also correlated ($\rho = 0.039, p < .001$).

Genetic Linkage Analyses

The genetic linkage analysis included data from 159 pedigrees comprising 447 children. Most of the children were male (61.3%). Of the 447 children, 287 were affected by SSD. The majority of those 287 participants were male (68.7%). Linkage analysis was conducted on the traits after adjustment for covariates.

The most significant linkage findings were on chromosomes 1 and 3. A region on chromosome 1 between D1S468 and D1S220 was linked to the Contextual Vocabulary subtest of the TOWL ($p = .036$), the Contextual Spelling subtest of the TOWL ($p = .0039$), the Word Identification subtest of the WRMT-R ($p = .0004$), the TWS total score ($p = .002$), and the Unpredictable Words subtest of the TWS ($p = .002$; Figure 2). A linkage was also found for the Thematic Maturity subtest of the TOWL ($p = .017$). Though the overlap of linkage peaks was not exact, the peaks were close enough (within 20 cM) to be indistinguishable using linkage analysis (Cordell, 2001).

A wide region of chromosome 3, spanning 25 cM, was linked to the Predictable Word Spelling subtest of the TWS ($p = .00002$), the total score of the TWS ($p = .0004$), the Unpredictable Word Spelling subtest of the TWS ($p = .003$), the Word Identification subtest of the WRMT-R ($p = .004$), and the Contextual Vocabulary subtest of the TOWL ($p = .0006$; Figure 3).

Linkage was also detected to regions on chromosomes 6 and 15. The Predictable Words subtest of the TWS was linked to chromosome 6p21.33 ($p = .002$). On chromosome 15, linkage was found in the 15q21-q22 region for the Word Attack subtest of the WRMT-R ($p = .036$), Word Identification subtest of the WRMT-R ($p = .001$), and the Unpredictable Words subtest of the TWS ($p = .019$).

As summarized in Table 6, spoken language endo-phenotypes demonstrated linkage to the same chromosomes as the written expression phenotypes measured at school age. Specifically, vocabulary (EOWPVT-R and PPVT-III) and phonological memory (sentence imitation) showed linkage to chromosome 1; vocabulary (EOWPVT-R and PPVT-III), phonological memory (sentence imitation and nonword repetition), and speeded naming (RAN) to chromosome 3; vocabulary (EOWPVT-R and PPVT-III) and phonological memory (MSW) to chromosome 6; and oral motor skills and phonological memory (nonword repetition) to chromosome 15. In addition, measures of the clinical phenotype of SSD showed linkages to chromosome 1 (GFTA), 3 (percentage of consonants correct [PCC]), and 15 (GFTA and PCC). As seen in Table 6, overall measures of reading, spelling, and written expression had more significant p values than did the measures of spoken language. This indicates a stronger genetic influence on written than spoken language measures. Caution must be used with this interpretation as the sample size was smaller for the written language linkage analyses than the spoken language analyses.

Discussion

This study explored associations of early childhood SSD (with or without LI) with later school-age spoken language and written language skills. Deficits in endo-phenotypes were hypothesized to influence both early childhood speech and language abilities and later school-age literacy skills. We used SEM to examine associations of endophenotypes with clinical phenotypes and outcomes and genetic linkage studies to demonstrate common genetic influences on endophenotypes and later school-age skills. Findings confirmed associations of oral motor skills, phonological awareness, phonological memory, vocabulary, and speeded naming with later school-age skills of reading decoding, spelling, written expression, and spoken language; and the linkage studies suggested shared genetic influences on these endophenotypes and school-age literacy measures.

Relationship of Early Childhood SSD to Later Literacy Skills

At school age, probands with early childhood SSD performed more poorly than did siblings who had no history of SSD or LI on all school-age reading, language, and spelling measures, although not reaching significance. Siblings with a history of SSD and/or LI differed from unaffected siblings on reading decoding of real and nonwords and spelling. These findings are consistent with results from previous longitudinal follow-up studies of children with SSD from early childhood (4–6 years) to school age (8–10 years). As reported by our research team and others (Hayiou-Thomas, Harlaar, Dale, & Plomin, 2010; Lewis et al., 2000; Nathan et al., 2004; Raitano et al., 2004), children with SSD and comorbid LI performed more poorly on measures of phoneme awareness, language, reading decoding, and spelling than did those with isolated SSD. Although children with isolated SSD did not demonstrate reading difficulties in these studies, these children had poor spelling skills relative to their reading and language abilities, suggesting a residual spelling weakness. As previously hypothesized, one explanation for these spelling difficulties is that children with histories of SSD have degraded phonological representations.

Relationship of Endophenotypes to School-Age Literacy Skills

Our SEM model supported the relationship between endophenotypes and early childhood SSD and school-age outcomes. The model also suggested a relationship between early childhood SSD and LI and later school age skills. Consistent with our predictions, oral motor skills, considered essential to articulation, were related to SSD. SSD was also associated with phonological awareness, phonological memory, and speeded naming; all skills are viewed as indicators of the strength of children's phonological representations. Consistent with previous literature (Kail, 1994; Lahey & Edwards, 1995; Miller et al., 2001; Windsor & Hwang, 1999), our results showed that LI was related to both vocabulary and speeded naming. Endophenotypes were also associated with school-age literacy outcomes. As reported in previous studies of reading acquisition, phonological awareness was related to literacy skills and phonological memory, speeded naming, and vocabulary to spoken language. A more surprising finding was the relationship of oral motor skills to written expression. Oral motor skills may have been linked to written expression due to a generalized motor deficit hypothesis. Although measures of written expression did not include a motor component such as handwriting, slow motor skills may be indicative of an overall delay. A second unexpected finding was the lack of association of early childhood LI with school-age spoken language skills. The clinical diagnosis of LI at early childhood might not be as predictive as the underlying endophenotypes. The endophenotypes that are associated with LI (speeded naming, vocabulary) are associated with spoken language in the full SEM model. Thus, when the covariance between all of these variables is taken into account, there is no independent association between LI and spoken language.

Shared Genetic Influences of Endophenotypes and School-Age Literacy Skills

SSD and LI may differ in their shared genetic influences on later literacy skills. By examining endophenotypes (i.e., specific cognitive skills), we may better understand the different predictors of later literacy. Evidence from genetic linkage analysis confirms the hypothesis of a common genetic basis for both the early childhood endophenotypes measured in this study and the spoken language and literacy skills with which they are associated. Previous studies have shown linkage between chromosome 1 and language, articulation, and phonological memory at this region (Miscimarra et al., 2007), between chromosome 3 and repetition of multisyllabic real and nonwords and vocabulary (Stein et al., 2004), and between chromosome 15 and oral motor function, articulation, and phonological memory (Stein et al., 2006). In the present study, we found that chromosome 1 was linked to reading decoding, spelling, and written expression; chromosome 3 was linked to reading decoding, spelling, and written expression skills; and chromosome 15 was linked to reading decoding of nonsense words and real words, auditory comprehension, and spelling (15q21.1). Furthermore, we found that chromosome 6 was linked to spelling and reading decoding (6p21.33). This replicates previous studies that have reported linkage of reading and spelling to this region (for review, see Rice, Smith, & Gayan, 2009; Smith, 2007).

Both SEM analyses and genetic linkage analyses (Miscimarra et al., 2007; Smith et al., 2005; Stein et al., 2004, 2006) have shown that there are shared influences of phonological awareness and phonological memory on reading, writing, and spelling outcome measures. Pennington and colleagues proposed a multiple deficit model that suggests pleiotropy, or effects of a single locus/gene on multiple language/learning disorders, including SSD, LI, and RD (Pennington & Bishop, 2009). Using behavioral data, Pennington and colleagues have investigated the relationship between SSD and literacy (Pennington & Lefly, 2001; Raitano et al., 2004; Tunick & Pennington, 2002). They have suggested that both SSD and RD are due in part to poor phonological representations, thus explaining the high comorbidity of these disorders and supporting genetic pleiotropy. Rice et al. (2009) provided

support for a multiple gene model of the comorbidity of SSD, LI, and RD. Taken together, the results of our SEM and linkage analyses may explain pleiotropic effects seen in our studies and others. For example, SSD is associated with subtests of the TOWL, and both are linked to chromosomes 1 and 3. Similarly, speeded naming indirectly influences both reading decoding and written expression, and all are linked to chromosome 3. Phonological memory has an indirect influence (through SSD) on written expression, and common linkage effects for all three of these domains are seen on chromosome 3.

The underlying genetic, neural, and environmental basis to these multiple deficits is not known. Genetic mechanisms for endophenotypes may be unique for a specific endophenotype or may have a broad influence impacting multiple endophenotypes; for example, genes that influence neural development may have broad influences on cognitive skills. Similarly, the clinical phenotypes of SSD and LI show both genetic overlap and independent effects of distinct genetic loci. Hayiou-Thomas (2008) and others (Hayiou-Thomas et al., 2010) demonstrated that genetic factors account for most of the relationship between early speech and later reading, while both genetic and environmental factors account for the relationship between early language and later reading. Thus, although there was genetic overlap between speech and language, it was not complete. Separate dimensions of language skills related to reading such as phonological skills versus semantic and syntax skills may be differentially heritable (Bishop & Snowling, 2004), accounting for the subtypes of reading disorders that we observe. For example, children with poor reading comprehension may have adequate phonological skills. In view of these findings, Vernes et al. (2008) suggested that we may move away from the study of individual genes and isolated disorders toward an understanding of molecular genetic networks. In the present analysis, we further demonstrated a relationship between genetic influences on early childhood speech and language skills and later school-age spoken language and literacy skills. We used a sample for which previous chromosomal linkages were observed at early childhood but now extend evidence for similar linkages for school-age outcomes.

Limitations of Study

One of the limitations of our study is that the SEM and genetic linkage analyses were not performed on identically overlapping data sets. To perform genetic linkage analyses, we used as the basis of our sample families that had provided DNA, whereas SEM analyses only required that data were available at both preschool and school-age assessments. Ideally, analyses would be performed on identical data sets, so future analyses are needed to replicate these findings. A second limitation is that the SEM model does not definitively establish that the influences between preschool and school-age measurements are due to genetic influences or to what degree these relationships are associated with genes. Such an analysis would require the incorporation of candidate gene data. Linkage analysis is performed at the sib-pair level, not the individual level, so linkage data is not useful in this regard. In future analyses, we plan to expand this SEM model to include candidate gene data as well as other outcomes.

The present study extends our previous findings by modeling the association of oral motor skills, phonological memory, phonological awareness, vocabulary, and speeded naming with reading decoding, spelling, and spoken language at school age. Findings from this model show that these preschool skills indeed influence later-emerging reading, spelling, and language skills.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by National Institute on Deafness and Other Communication Disorders Grant DC00528, awarded to Barbara A. Lewis, and National Center for Research Resources Grant KL2RR024990, awarded to Catherine M. Stein. Some of the results of this research were obtained using the program package S.A.G.E., which is supported by U.S. Public Health Service Resource Grant RR03655 from the National Center for Research Resources.

We wish to express our appreciation to the speech-language pathologists who assisted us in recruiting subjects and to the families who generously agreed to participate.

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Figure 1.

Structural equation modeling of endophenotypes, early childhood speech sound disorders (SSD) and language impairment (LI), and school-age language literacy outcomes was conducted with Mplus software. The most parsimonious model is shown. The arrows represent hypothesized causal pathways. Numbers above the lines indicate regression coefficients estimated from the model; bold arrows and numbers represent pathways that were statistically significant at $p < .05$, and the nonbold arrows and numbers represent pathways that, although not significant, contributed to the fit of the model. Arrows representing correlation among latent variables have been omitted to make the figure clearer; these correlations are presented in Table 3.

Figure 2.

Haseman-Elston linkage analyses for school-age measures were conducted for chromosome 1. The $-\log_{10}(p \text{ value})$ is plotted against chromosomal location for each trait, represented with different colors. Linkage results for traits when $p > .05$ are not shown. TOWLCV = Test of Written Language (TOWL) Contextual Vocabulary subtest; TOWLCS = TOWL Contextual Spelling subtest; TOWLTM = TOWL Thematic Maturity subtest; WRID = Word Identification subtest of the Woodcock Reading Mastery Tests; TWST = Test of Written Spelling—Third Edition (TWS-3) total score; TWSU = TWS-3 Unpredictable Words subtest.

Figure 3. Haseman-Elston linkage analyses for school-age measures were conducted for chromosome 3. The $-\log_{10}(p \text{ value})$ is plotted against chromosomal location for each trait. Linkage results for traits when $p > .05$ are not shown. TWSP = TWS-3 Predictable Words subtest.

Table 1

Demographics for probands and siblings with and without speech sound disorders.

Variable	Probands	Affected siblings	Unaffected siblings
<i>N</i>	152	103	153
Male:female	101:51	71:32	75:78
Age in years at Time 1 (4–6 years): <i>M</i> (<i>SD</i>)	4.9 (0.5)	5.23 (0.6)	5.0 (0.8)
Age in years at Time 2 (7–12 years): <i>M</i> (<i>SD</i>)	9.6 (1.4)	9.7 (1.5)	9.6 (1.5)
Hollingshead SES			
1	7	5	4
2	14	7	16
3	27	25	21
4	64	31	55
5	37	32	54
PIQ Time 2 standard score: <i>M</i> (<i>SD</i>)	103.4 (15.2)	102.7 (16.8)	108.9 (14.9)
GFTA Time 2 percentile score: <i>M</i> (<i>SD</i>)	38.0 (35.4)	61.0 (36.0)	87.1 (22.6)
TOLD–P:2/CELF–3 standard score: <i>M</i> (<i>SD</i>)	90.9 (18.1)	96.3 (18.6)	104.8 (15.6)

Note. Hollingshead ratings range from 1 = *low* to 5 = *high*. SES = socioeconomic status; PIQ = Performance IQ; GFTA = Goldman Frisbie Test of Articulation, Sounds in Words subtest; TOLD–P:2 = Test of Language Development—Primary, Second Edition; CELF–3 = Clinical Evaluation of Language Fundamentals—Third Edition.

Table 2

Group comparisons on measures of endophenotypes.

Domain/measure	Probands: <i>M</i> (<i>SD</i>)	Affected siblings: <i>M</i> (<i>SD</i>)	Unaffected siblings: <i>M</i> (<i>SD</i>)	<i>F</i> (df)	<i>p</i>	η^2
Oral motor skills (<i>z</i> scores)						
Single syllables (<i>n</i> = 372)	0.95 (1.2)	0.57 (1.1)	0.46 (1.1)	1.73 (2, 370)	.179	0.009
Multisyllables (<i>n</i> = 372)	-0.12 (1.3)	-0.47 (0.9)	-0.66 (0.8)	3.38 (2, 370)	.035	0.018
Phoneme awareness (scaled scores)						
Elision (<i>n</i> = 87)	9.52 (3.4)	9.61 (3.9)	10.50 (2.9)	0.42 (2, 85)	.661	0.010
Blending words (<i>n</i> = 87)	11.20 (3.0)	12.94 (2.3)	11.69 (2.4)	0.43 (2, 85)	.653	0.010
Speeded naming (<i>z</i> scores)						
RAN colors ^b (<i>n</i> = 235)	0.45 (2.1)	0.06 (1.4)	-0.31 (1.2)	5.54 (2, 233)	.004	0.046
RAN numbers ^b (<i>n</i> = 235)	1.34 (2.4)	1.00 (2.1)	0.21 (1.5)	7.03 (2, 233)	.001	0.057
RAN objects ^b (<i>n</i> = 234)	0.70 (1.5)	0.77 (2.0)	0.14 (1.3)	3.87 (2, 232)	.022	0.032
RAN letters ^b (<i>n</i> = 233)	1.61 (2.4)	1.07 (2.5)	0.24 (1.5)	9.08 (2, 231)	<.000	0.073
Phonological memory (scaled scores and % correct)						
Digit span (<i>n</i> = 305)	9.41 (3.2)	9.79 (3.3)	11.13 (3.1)	1.30 (2, 303)	.275	0.009
Multiword rep. (<i>n</i> = 392)	34.3 (27.6)	45.3 (28.2)	67.8 (23.5)	1.54 (2, 390)	.215	0.008
Nonword rep. (<i>n</i> = 393)	30.1 (24.3)	39.7 (25.4)	60.3 (22.7)	2.88 (2, 391)	.057	0.015
Recalling sentences ^{b,c} (<i>n</i> = 287)	8.49 (3.5)	9.17 (3.6)	10.64 (3.1)	11.79 (2, 285)	<.001	0.077
Vocabulary (standard scores)						
PPVT-III ^b (<i>n</i> = 334)	101.8 (17.1)	103.5 (15.1)	107.7 (15.8)	4.52 (2, 332)	.012	0.027
EOWPVT-R (<i>n</i> = 334)	113.9 (16.8)	115.1 (16.3)	121.7 (13.7)	0.51 (2, 332)	.600	0.003

Note. RAN = Rapid Automatized Naming; rep. = repetition; PPVT-III = Peabody Picture Vocabulary Test—Third Edition; EOWPVT-R = Expressive One-Word Picture Vocabulary Test—Revised.

^b Probands differ from unaffected siblings.

^c Affected siblings differ from unaffected siblings.

Table 3

Group comparisons on measures of reading, spelling and writing.

Domain/measure	Probands: <i>M</i> (<i>SD</i>)	Affected siblings: <i>M</i> (<i>SD</i>)	Unaffected siblings: <i>M</i> (<i>SD</i>)	<i>F</i> (<i>df</i>)	<i>p</i>	η^2
Reading decoding (WRMT-R) standard scores						
Word Identification (<i>n</i> = 397)	93.39 (17.1)	97.85 (17.6)	105.38 (15.6)	0.84 (2, 395)	.434	.004
Word Attack (<i>n</i> = 397)	91.50 (17.6)	93.47 (22.0)	104.17 (15.0)	0.10 (2, 395)	.903	.001
Spelling (TWS-3 and TOWL) standard scores and scaled scores						
Predictable Words (<i>n</i> = 387)	90.18 (14.2)	92.85 (14.5)	99.86 (13.8)	0.05 (2, 385)	.953	.000
Unpredictable Words (<i>n</i> = 387)	86.18 (15.0)	91.38 (17.1)	97.47 (15.1)	0.03 (2, 385)	.971	.000
Contextual Spelling (<i>n</i> = 299)	8.57 (3.9)	10.74 (13.6)	9.29 (4.0)	1.89 (2, 297)	.153	.013
Spoken language (CELF-3) standard scores						
Receptive Language (<i>n</i> = 295)	94.39 (19.4)	97.69 (20.0)	106.03 (17.2)	2.51 (2, 293)	.083	.017
Expressive Language ^a (<i>n</i> = 294)	87.13 (17.5)	94.39 (19.9)	102.40 (16.7)	3.94 (2, 292)	.021	.026
Written expression (TOWL) scaled scores						
Contextual Vocabulary ^b (<i>n</i> = 299)	8.75 (3.2)	9.87 (3.2)	9.94 (3.5)	4.40 (2, 297)	.013	.029
Thematic Maturity (<i>n</i> = 299)	7.84 (3.2)	8.19 (2.8)	8.64 (3.4)	1.78 (2, 297)	.171	.012
Syntactic Maturity ^b (<i>n</i> = 299)	7.95 (3.5)	9.34 (3.8)	10.25 (7.2)	5.61 (2, 297)	.004	.037

Note. WRMT-R = Woodcock Reading Mastery Tests—Revised; TWS-3 = Test of Written Spelling—Third Edition; TOWL = Test of Written Language.

^aProbands differ from affected siblings.

^bProbands differ from unaffected siblings.

Table 4

Correlation matrix for latent variables (all correlations significant).

Variable	1	2	3	4	5	6	7	8	9
1. Oral motor skills	—								
2. Phonological awareness	-0.54	—							
3. Phonological memory	-0.47	0.85	—						
4. Vocabulary	-0.48	0.76	0.79	—					
5. Speeded naming	0.50	-0.75	-0.53	-0.46	—				
6. Reading decoding	-0.47	0.87	0.75	0.68	-0.66	—			
7. Spelling	-0.43	0.80	0.68	0.61	-0.60	0.88	—		
8. Spoken language	-0.49	0.84	0.91	0.82	-0.59	0.77	0.72	—	
9. Written expression	-0.44	0.63	0.51	0.43	-0.50	0.52	0.64	0.63	—

Table 5

Factor loadings of measures for latent variables.

Latent variable/indicator	Factor loading	SE	p
Oral motor skills			
Single syllable	0.576	0.09	< .0001
Multisyllable	0.670	0.12	< .0001
Phoneme awareness			
Elision sound	0.762	0.08	< .0001
Blending	0.595	0.09	< .0001
Phonological memory			
Digit span	0.595	0.06	< .0001
MSW	0.869	0.16	< .0001
NSW	5.266	0.99	< .0001
Sentence imitation	0.843	0.13	< .0001
Vocabulary			
PPVT–III	0.767	0.07	< .0001
EOWPVT–R	0.811	0.07	< .0001
Speeded naming			
RAN colors	0.793	0.14	< .0001
RAN numbers	0.835	0.08	< .0001
RAN objects	0.764	0.11	< .0001
RAN letters	1.026	0.10	< .0001
Reading decoding			
Word ID	0.431	0.09	< .0001
Word attack	0.439	0.09	< .0001
Spelling			
TWSP	0.574	0.05	< .0001
TWSU	0.544	0.05	< .0001
Contextual spelling	0.359	0.04	< .0001
Spoken language			
Receptive	0.323	0.13	.011
Expressive	0.346	0.12	.004
Written expression			
Vocabulary	0.496	0.05	< .0001
Themes	0.380	0.03	< .0001
Syntax	0.521	0.04	< .0001

Note. MSW = multisyllabic real word repetition; NSW = nonsense word repetition; TWSP = TWS–3 Predictable Words subtest score; TWSU = TWS–3 Unpredictable Words subtest score.

Table 6

Summary of previously published (spoken language) and new linkage analyses (written language).

Chromosome	Spoken language		Reading, spelling, and written expression	
	Trait	p	Trait	p
Chromosome 1 ^a				
	GFTA	.069	Contextual vocabulary	.036
	EOWPVT-R	.0058	Contextual spelling	.0039
	Sentence imitation	.038	Word ID	.0004
	PPVT-III	.0068	TWST	.002
			TWSU	.002
			Thematic maturity	.017
Chromosome 3 ^b				
	EOWPVT-R	.088	TWST	.0004
	TWSU	.003	TWSP	.00002
	PPVT-III	.008	Word ID	.004
	NSW	.038	Contextual vocabulary	.0006
	PCC	.017		
	Sentence imitation	.028		
	RAN			
Chromosome 6 ^c				
	EOWPVT-R	.062	TWSP	.002
	PPVT-III	.004		
	MSW	.002		
Chromosome 15 ^d				
	MSW	.087	Word attack	.036
	NWS	.050	Word ID	.001
	PCC	.079	TWSU	.019
	Oral motor	.001		
	GFTA	.021		

Note. TWST = Test of Written Spelling-Third Edition total score; PCC = percentage of consonants correct.

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^aMiscimarra et al., 2007.

^bStein et al., 2004.

^cLewis et al., 2007; present analysis.

^dStein et al., 2006; present analysis.