Published in final edited form as:
J Speech Lang Hear Res. 2011 April ; 54(2): 487–519. doi:10.1044/1092-4388(2010/10-0068).

Prevalence and Phenotype of Childhood Apraxia of Speech In Youth with Galactosemia

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Abstract

Purpose—We address the hypothesis that the severe and persistent speech disorder reported in persons with galactosemia meets contemporary diagnostic criteria for Childhood Apraxia of Speech (CAS). A positive finding for CAS in this rare metabolic disorder has the potential to impact treatment of persons with galactosemia and inform explanatory perspectives on CAS in neurological, neurodevelopmental, and idiopathic contexts.

Method—Thirty-three youth with galactosemia and significant prior or persistent speech sound disorder were assessed in their homes in 17 states. Participants completed a protocol yielding information on their cognitive, structural, sensorimotor, language, speech, prosody, and voice status and function.

Results—Eight of the 33 participants (24%) met contemporary diagnostic criteria for CAS. Two participants, one of whom was among the 8 with CAS, met criteria for ataxic or hyperkinetic dysarthria. Group-wise findings for the remaining 24 participants are consistent with a classification category termed Motor Speech Disorder-Not Otherwise Specified (MSD-NOS; Shriberg, Fourakis, et al., in press-a).

Conclusion—We estimate the prevalence of CAS in galactosemia at 18 per hundred, 180 times the estimated risk for idiopathic CAS. Findings support the need to study risk factors for the high occurrence of motor speech disorders in galactosemia, despite early compliant dietary management.

Keywords

apraxia; dyspraxia; genetics; motor speech disorder; speech sound disorder

Consistent trends in the sparse literature on galactosemia and communicative disorders indicate high occurrence of significant and persistent speech sound disorder (SSD) in persons with galactosemia, with most reported speech findings consistent with developmental verbal dyspraxia. As recommended by the American Speech-Language-Hearing Association (ASHA, 2007), we hereafter reference apraxia of speech in children as Childhood Apraxia of Speech (CAS). The following three sections, respectively, review cognitive, language, and speech findings in galactosemia, summarize contemporary research issues in CAS, and describe rationale for the three questions about galactosemia and CAS addressed in this study.

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Galactosemia

Description

Galactosemia is an autosomal recessive metabolic disorder estimated to occur in 1 in 53,000 infants in the United States (National Newborn Screening and Genetics Resource Center; Newborn Screening and Genetic Testing Symposium, 2002). *Galactose* is one of two sugars that make up the complex milk sugar, *lactose*. Individuals with galactosemia lack or have insufficient amounts of the galactose-1-phosphate uridylyltransferase enzyme needed to break down galactose, resulting in a toxic build-up of galactose -1-phosphate in the red blood cells. The most common genotype for galactosemia, Q188R/Q188R, was found in 62% of 107 cases of galactosemia described in Elsas, Langley, Paulk, Hjelm, and Dembure (1995). Individuals homozygous for galactosemia have the Q188R allele on both of their 9th chromosomes in the 9q13 region, whereas other persons with galactosemia have different alleles, one of which may be a Q188R. The letters *Q* and *R* are symbols for the amino acids glutamine (Q) and arginine (R). *Q188R* indicates that this allele results in a replacement of arginine for glutamine at position 188 in the GALT protein. Significant cognitive, language, and speech disorders have been reported for all genotypes conferring risk for galactosemia, with homozygous Q188R associated with the largest risk for cognitive and verbal trait deficits (Elsas et al., 1995; Powell et al., 2009; Webb, Singh, Kennedy, & Elsas, 2003).

Infants in the United States and many European countries are tested for galactosemia in newborn screening programs by means of a heelstick blood sample. Because there is no requirement for the timeliness of notification, there is often a delay in providing screening results to doctors and parents. Within days of the initiation of milk feeding, infants with galactosemia develop jaundice and have liver and kidney dysfunction. The treatment for galactosemia is to immediately restrict from the diet all foods containing more than trace amounts of galactose, including human, cow, and goat milk. If infants are left untreated, the second week of life may include the development of cerebral edema, coagulopathy, muscle hypotonia, E. coli septicemia, followed by death (Ridel, Leslie, & Gilbert, 2005). Of 53 reported births of infants with galactosemia in the United States in 2000, 35 (66%) had treatment initiated in the first week of life, 10 (19%) in the second week of life, and 8 (15%) in the third week of life or later (http://genes-r-us.uthscsa.edu/resources/newborn/00/ch5_complete.pdf). Botkin (2005) estimated that prior to newborn screening, 20–30% of infants with galactosemia died. Newborn screening has reduced mortality from 33% to 15% in Ireland. Mortality statistics for galactosemia in the U.S. are not available.

Cognitive and Language Findings

Even with early initiation of a lactose-restricted diet, approximately 45% of children with galactosemia have intelligence quotients below standard scores of 85, and approximately 52% have been estimated to have language impairments (Nelson, Waggoner, Donnell, Tuerck, & Buist, 1991; Waggoner, Buist, & Donnell, 1990). In a study of the same sample of 33 children with galactosemia and speech disorder to be described in the present report, 15 of the 17 (88%) participants with borderline-low cognition had receptive and expressive language impairment and 9 of the 16 (56%) participants with typical cognition had language impairment, most often affecting only expressive language (Potter, Lazarus, Johnson, Steiner, & Shriberg, 2008). Crucially, as found in a sample of 350 persons with galactosemia reported by Waggoner et al. (1990), the presence and severity of cognitive and language disorders in the sample whose speech characteristics are described in the present paper were not associated with the duration of exposure to dietary lactose (Potter et al., 2008).

More recently, in a study using a birth order design, Hughes et al. (2009) reported cognitive-speech-language findings for the first child in the family diagnosed with galactosemia compared to outcomes for all the later-born children with this autosomal recessive disorder. Whereas a lactose-restricted diet was initiated on or before seven days after birth with the first sibling diagnosed with galactosemia, the younger siblings had essentially 0 days exposure to lactose. Hughes et al. reported that maternal lactose restriction during pregnancy did not determine severity of cognitive-speech-language outcomes. The most neurologically affected participant in the Hughes et al. study was a later-born child whose mother had restricted lactose intake throughout pregnancy. Toxic effects of lactose likely occurred during prenatal development due to the endogenous production of galactose. Waggoner and colleagues (1990) have also reported that maternal lactose restriction during pregnancy did not appear to affect outcome severity.

Speech Findings

Table 1 is a summary of findings from a literature search on the speech of persons with galactosemia. The validity and reliability of lifetime estimates of the prevalence of CAS in galactosemia is constrained by the notable lack of consensus on the speech and other features that are sensitive to and specific for CAS. As shown in Table 1, speech assessment methods ranged from parent questionnaire information to the use of measures with limited sensitivity to and specificity for pediatric motor speech disorders. This limitation is shared by all reports of CAS in idiopathic and other contexts because, as discussed later, there currently is no validated standardized protocol and validated classification criteria to identify a speaker as true positive for CAS (ASHA, 2007;McCauley & Strand, 2008).

In a sample of 243 persons with galactosemia assessed by questionnaire almost two decades ago, the lifetime prevalence of speech disorders in persons with galactosemia was estimated at approximately 60% (Waggoner et al., 1990). In a subsample of 13 of the participants in the Waggoner et al. study evaluated by an in-person speech assessment, 8 were diagnosed with apraxia of speech. An additional 5 of 11 children evaluated by telephone assessment were diagnosed with apraxia of speech (Nelson et al., 1991; Waggoner et al., 1990). The most widely cited speech finding from these and other studies is that approximately 55% (or 1 of every 2 children with galactosemia) meet clinical criteria for apraxia of speech (Nelson et al., 1991; Robertson, Singh, Guerrero, Hundley, & Elsas, 2000; Webb et al., 2003). Hughes and colleagues (2009) reported that 77% of 26 siblings with galactosemia “exhibited evidence of speech and language problems, predominantly verbal dyspraxia” (p. 723). Each of these prevalence estimates far exceeds a population prevalence estimate for idiopathic CAS of 1 per 1000 children, a preliminary estimate extrapolated from clinical referrals to one university speech clinic (Shriberg, 2010a; Shriberg, Aram, & Kwiatkowski, 1997a; Shriberg & Kwiatkowski, 1994).

Childhood Apraxia of Speech (CAS)

A Neurodevelopmental Research Framework for CAS

As noted previously, the primary methodological constraint in CAS research continues to be the lack of a standardized assessment procedure and inclusionary criteria that can be used to identify and classify a child as positive for CAS (ASHA, 2007; McCauley & Strand, 2008). Since the initial influential descriptions of apraxia of speech in children by Morley, Court, Miller, and Garside (1955), Rosenbek and Wertz (1972), and Yoss and Darley (1974), virtually every research report on CAS includes a caveat about measurement methods and inclusionary criteria in the interpretation of and generalizations from study findings. Contemporary discussions conclude that there is no consensus on the pathophysiology of CAS and therefore no consensus on the methods and classification criteria to identify

persons who are true positive for CAS (ASHA, 2007; Shriberg & Campbell, 2003). However, there is emerging consensus on the signs of acquired apraxia of speech (for rationale and extended literature reviews see Duffy [2005] and Robin, Jacks, & Ramage [2008]), with researchers in CAS holding different positions on which of these signs are also necessary and sufficient for diagnostic classification of childhood apraxia of speech (ASHA, 2007)..

A recent literature review includes a proposal to address the inclusionary criteria problems in CAS research by studying CAS as it occurs in neurological, neurodevelopmental, and idiopathic contexts in children and adults (Shriberg, 2010b). The review includes a synthesis of findings from 18 studies reporting 55 cases of severe speech disorders consistent with CAS in the context of diverse complex neurodevelopmental disorders. In addition to speech deficits consistent with CAS, most cases had deficits in cognition and language, with many also having dysmorphologies and dysarthria. Such findings, by definition, contrast with studies of idiopathic CAS, in which candidate participants are typically excluded if they have frank cognitive deficits, dysarthria, or dysmorphologies. A central premise in Shriberg (2010b) is that compared to studies of CAS in idiopathic contexts, studies of participants with CAS in similar neurological or neurodevelopmental contexts reduces heterogeneity in causal pathways.

CAS in Neurodevelopmental Contexts

The most widely-cited example of CAS in a complex neurodevelopmental context is the identification and continuing functional analyses of a point mutation in the *FOXP2* gene (chromosome 7q31) segregating with a severe and persistent SSD in approximately half the members of an extended family (Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001) and replicated, to date, in several other families (Feuk et al., 2006; MacDermot et al., 2005; Shriberg et al., 2006, 2010a, 2010b; Zeesman et al., 2006). A substantial body of evidence also demonstrates that deficits in Foxp2 (orthologs of *FOXP2* are indicated in lower case) in other vertebrate species are sufficient to disrupt both unlearned and learned vocal behaviors (see comprehensive reviews in Fisher & Marcus, 2006; Ramus & Fisher, 2009). Notably, however, for the present focus on CAS as a pediatric SSD, several unpublished studies in North America have failed to find *FOXP2* disruptions in moderately large samples of children reported to have CAS, suggesting that hereditary or de novo *FOXP2* disruptions do not account for a significant proportion of persons meeting varying diagnostic classification criteria for CAS.

Other regions of interest and candidate genes for CAS have been reported. Shriberg, Jakielski, and El-Shanti (2008) described genetic, morphologic, and speech findings for three siblings with a similar unbalanced chromosome 4q;16q translocation. The children, each of whom was monosomic for a telomeric region on chromosome 4 that contains 11 genes, have been treated for CAS for many years. Three of the annotated genes on chromosome 4 have no known function in humans, raising the question of their possible role in speech processing. Lewis (2008) described genetic, neuroimaging, and speech findings for a child with severe and persistent speech sound disorder associated with a disruption in *ROBO1*, a gene implicated in dyslexia (Lewis et al., 2006). Shriberg (2010b) includes a summary of findings from case reports of severe speech disorders consistent with CAS in an array of genetic and complex neurodevelopmental disorders.

Statement of the Problem

A literature review indicates that despite early and compliant dietary management, more than 50% of persons with galactosemia reportedly have significant SSD consistent with CAS. However, these studies have not used well-developed or consistent criteria to diagnose

CAS in GALT. Of the 13 studies reporting speech disorders in galactosemia, five used observational reports (Hughes et al., 2009; Jan & Wilson, 1973; Koch, Schmidt, Wagstaff, Ng, & Packman, 1992; Lee, 1972; Sommer et al., 1995), three used language tests (Waisbren, Norman, Schnell, & Levy, 1983; Schweitzer, Shin, Jakobs, & Brodehl, 1993; Hansen et al., 1996), two used parent questionnaires (Waggoner et al., 1990; Waggoner & Buist, 1993), two used the Apraxia Profile with a subset of participants (Robertson, Singh, Guerrero, Hundley, & Elsas, 2000; Webb et al., 2003), and one used a checklist of speech characteristics, testing some participants in person and others by telephone (Nelson et al., 1991). Detailed study of the speech of children and adolescents with this complex neurodevelopmental disorder using well-developed contemporary methods has the potential to contribute to clinical management issues in galactosemia and to inform descriptive-explanatory accounts of the origin and nature of CAS.

We pose three questions about CAS in youth with galactosemia:

Question 1: What is the estimated prevalence of CAS in children with galactosemia and prior or persistent speech sound disorder?

Question 2: What demographic, cognitive-linguistic, or dietary management variables in persons with galactosemia are significant risk factors for CAS?

Question 3: What speech, prosody, and/or voice indices best discriminate participants with galactosemia and CAS from participants with galactosemia and other speech sound disorders?

Method

Participants with Galactosemia

Recruitment—Potential participants with galactosemia and prior or persistent SSD were identified from responses to postal and email announcements sent to patients in the University of Wisconsin-Madison Biochemical Genetics Program and to regional (Galactosemia Families of Minnesota) and national (Parents of Galactosemic Children) support groups. The announcement sought to recruit participants who met the following inclusionary/exclusionary criteria: (a) a diagnosis of classic (full expression) galactosemia, (b) prior or persistent speech sound disorder, as documented by a history of treatment for speech sound disorders, (c) 4–17 years of age, (d) residence in the United States, (e) English as the only or first language, and (f) no history of significant hearing loss or craniofacial disorder affecting speech. Of 63 youth with galactosemia initially volunteered by their parents as potential participants, 30 were excluded for one or more of the following reasons: did not have a diagnosis of the classic form of galactosemia (7); did not have a history of treatment for speech sound disorders (11); were outside the target age range (6); lived outside the United States (5); first language was not English (1); repaired cleft palate (1); moderate-to-profound hearing loss (2); and unable to be scheduled due to time constraints (7). The remaining 33 individuals, whose families resided in 17 different states in the Midwestern, Northeastern, Eastern, Southern, and Western regions of the USA, were scheduled for assessment in their homes.

Assessment—Assessment of the 33 participants was completed over the course of two summers. During the first summer, 15 participants with galactosemia were assessed individually in a quiet room in their home using a preliminary version of the Madison Speech Assessment Protocol (MSAP) described in Shriberg, Fourakis, et al. (in press-a). During the second summer, two years later, an additional 18 participants were tested in their homes using the current expanded version of the MSAP. All 33 participants with galactosemia were tested by the second author, an ASHA-certified speech-language

pathologist with extensive experience in pediatric motor speech disorders. Parents/guardians of all participants signed an informed consent form granting permission for their child to participate in the study. Assent forms were signed by participants who were 11 years of age or older. Both forms were approved by institutional review boards at the University of Wisconsin-Madison and Washington State University Spokane. The examiner spent additional time with one or both parents after administering the protocol to clarify relevant case history information.

Participants with Typical Development (TD)

Recruitment—Data from two other samples of speakers were required to address the three questions posed in this study. One need was for standardization data for all MSAP tasks from children and adolescents with typical development. Scores from participants in this reference group were used to derive age- and gender-based z-scores for all speech, prosody, and voice measures so that between-group effect size comparisons could be adjusted as needed for any age and/or gender differences in subgroup composition.

A total of 70 children in east Washington State were administered the current expanded version of the MSAP for the purposes of the present and other ongoing studies of childhood speech sound disorders. This subset of an eventually larger database included 5 children of each gender within the even-numbered ages from 4 to 16 years. To be included in the database, referenced here as the Typical Development (TD) group, parents and classroom teachers of potential participants had to answer "No" to the following questions posed in a questionnaire: (1) *To your knowledge, has this student ever been referred for speech-language, hearing loss, or special education services?* and (2) *Do you have concerns about this student's progress in school?* As described later, all of the children in the TD group scored within the normal range on the Goldman-Fristoe Test of Articulation-2 (Goldman & Fristoe, 2000).

Assessment—The same examiner who tested the children with galactosemia (second author) administered the MSAP to each of the 70 TD reference database participants in a quiet room in his or her school. Consent and assent procedures were similar to those described previously for the participants with galactosemia.

Participants with Speech Delay (SD)

Description—The questions posed in this study also required comparison data from a group of children with speech delay of unknown origin. A data set of 25 children aged 3–6 years (Hauner, Shriberg, Kwiatkowski, & Allen, 2005) was selected for this purpose. This age range is the developmental period in which speech delay is most severely expressed. As reported in Hauner et al. (2005), conversational speech samples from these 25 children indicated significantly lower speech competence compared to closely matched controls with speech delay of unknown origin who had participated in research studies over several decades. Importantly for their function as a comparative group for the speakers with galactosemia, although the 25 participants in this data set had developmental psychosocial involvements, they did not have either the cognitive or motor involvements reported for children with galactosemia in the literature review.

Assessment—The 25 participants comprising the SD comparison group had each been tested by a graduate student in communicative disorders in a clinical suite at the University of Wisconsin-Madison Phonology Clinic (Hauner et al., 2005). All assessments were completed several years before development of the MSAP. Therefore, the comparison data from each of these participants with severe SD were limited to perceptual and acoustic indices (to be described) derived from conversational speech samples only.

The Madison Speech Assessment Protocol (MSAP)

As described previously, the same examiner assessed the participants with galactosemia and the participants with typical development using the Madison Speech Assessment Protocol (MSAP: Shriberg, Fourakis, et al., in press-a). For efficiency, the text, tabular, and graphic descriptions of the MSAP and summary findings for a perceptual and acoustic reliability estimate are included in Appendix A. The point-to-point reliability estimates were generally in the 80% –90% range, consistent with reliability estimates for perceptual and acoustic data reduction methods reported elsewhere (see Shriberg, Fourakis, et al., in press 2010b). The interested reader may wish to review the protocol and methods at this point, referring to it as needed for specific information.

Competence, Precision and Stability Analytics (CPSA)

Participant data from responses to the MSAP were organized using an analytic framework termed the Competence, Precision, and Stability Analytics (CPSA: Shriberg, Fourakis, et al., in press-a). Table 2 includes current CPSA entries for the three proposed subtypes of motor speech disorders in the SDCS; indices and markers for the three proposed etiologic subtypes of speech delay are in process. Technical information for the CPSA are summarized in Shriberg, Fourakis et al. and presented in detail in a laboratory manual. The CPSA provides a theory-neutral matrix to describe, quantify, and classify speech sound disorders and is used in the present report to address the three questions posed in the statement of purpose.

As shown in Table 2, the rows of the CPSA matrix divide MSAP findings into 10 domains subordinated under segmental and suprasegmental tiers. Segmental domains organize findings from the MSAP measures by vowels (monophthongs and diphthongs), consonants, and composite measures derived from tasks that yield indices from both vowels and consonants. The seven linguistic domains within the suprasegmental tier are subordinated within the constructs of prosody (phrasing, rate, stress) and voice (loudness, pitch, laryngeal quality, resonance), following the substantive, procedural, psychometric, and reference information in McSweeny and Shriberg (2001),Shriberg, Kwiatkowski, and Rasmussen (1990), and Shriberg, Kwiatkowski, Rasmussen, Lof, and Miller (1992).

As shown in the Table 2, the columns of the CPSA matrix aggregate MSAP findings within three analytic constructs termed Competence, Precision, and Stability. Competence indices, obtained using perceptual methods, quantify a speaker's mastery of the phonetic and phonological features of his or her ambient dialect of English. Precision indices, obtained using both perceptual and acoustic methods, quantify variance in speech, prosody, and voice production relative to speakers of the same age and gender. As described in Shriberg, Fourakis, et al. (in press-a), perceptual measures of precision use diacritic symbols to capture allophonic segmental detail (e.g., a backed vowel, a spirantized stop, a partially voiced stop, a lengthened vowel, a weak stop), whereas acoustic measures provide continuous data on the precision of segmental and suprasegmental parameters (frequency, amplitude, duration, laryngeal quality, resonance). Stability, also obtained using both perceptual and acoustic methods, quantifies consistency of speech production across multiple types, tokens, and contexts. Stability is computed by subtracting the coefficient of variation [standard deviation divided by the mean] from 1.

Candidate Markers for Three Subtypes of Motor Speech Disorders

As shown in Table 2, the coded entries adjacent to each precision and stability index indicate its assignment to one of the three SDCS classifications for motor speech disorders: Motor Speech Disorder-Apraxia of Speech (equivalent to CAS), Motor Speech Disorder-Dysarthria, and Motor Speech Disorder-Not Otherwise Specified. As discussed in Shriberg, Fourakis, et al. (in press-a), the addition of the latter classification to the other two subtypes

was deemed necessary to classify speech behaviors that are sensitive to motor speech disorder but are not specific for apraxia of speech or dysarthria. For example, imprecise speech sounds and slow rate are observed in both apraxia of speech and dysarthria. Assignments of each index to one of the three motor speech disorders in Table 2 (AOS: Apraxia, DYS: Dysarthria, NOS: Not Otherwise Specified) were based on literature findings in both the adult apraxia of speech and the CAS literatures (e.g., ASHA, 2007;Caruso & Strand, 1999;Duffy, 2005;Shriberg et al., 1997a;Shriberg & Campbell, 2003;Shriberg, Campbell, et al., 2003). Additional discussion of rationale for marker assignment is beyond the scope of this paper. As reported in Shriberg, Fourakis, et al. (in press-a), 83% of the current precision and stability indices are obtained using acoustic methods. Modifications of and additions to the entries in Table 2 are expected in emerging SDCS research using the MSAP and the CPSA.

For each speech, prosody, and voice marker in Table 2, the software's task is to classify a participant as positive (affected) or negative (not affected), using a set of classification rules that includes findings from multiple CPSA indices obtained from multiple MSAP sources. A liberal statistical criterion for classifying a marker as positive was used to minimize Type II errors in which a potentially informative marker is missed due to an overly conservative statistical criterion for typically low-powered effect size estimates. Specifically, participants were classified as positive for markers in which z-scores for the markers were lower or greater (directionality is indicated by the adjective in the marker) than 1 standard deviation from the relevant reference group (TD or SD) for the question posed.

Clinical Identification of Participants with Childhood Apraxia of Speech (CAS)

Rationale—A final methodological need was to determine the speech status of each of the participants with galactosemia relative to contemporary classification criteria for CAS and subtypes of dysarthria. One way to complete this task would have been to use a paneling procedure, which would yield consensus classifications from experienced judges. This approach was rejected because as observed in Shriberg, Aram, and Kwiatkowski (1997b) and other studies using paneling methods, resulting classifications of motor speech disorder are based on heterogeneous, typically non-operationalized diagnostic criteria. The present method was to obtain classifications from one clinician-researcher (third author) with extensive experience using a modified form of the most widely researched clinical classification system for acquired motor speech disorders, generally referenced as the Mayo Clinic system (Darley, Aronson, & Brown, 1975; Duffy, 2005). The modified form reflects contemporary consensus on acquired apraxia of speech and emerging consensus on CAS (e.g., Duffy, 2005; Robin, Jacks, & Ramage, 2008).

Procedures—The third author used the modified version of the Mayo system adapted for pediatric motor speech disorders and the MSAP speech tasks to classify each of the 33 participants with galactosemia. Using only the information on the video (15 participants) and audio (18 participants) recordings of MSAP administrations, the third author tallied and annotated the occurrence of speech and non-speech characteristics, including behaviors occurring during the conversational speech sample and each of the other tasks in the preliminary and expanded versions of the MSAP (Table A1). To meet criteria for CAS, a participant had to have evidence of 4 of the following 10 behaviors in three or more MSAP tasks: vowel distortions; difficulty achieving initial articulatory configurations or transitionary movement gestures; equal stress or lexical stress errors; distorted substitutions; syllable segregation; groping; intrusive schwa; voicing errors; slow rate; slow diadochokinetic rates, and increased difficulty with multisyllabic words. Participants were classified as having one or more subtypes of dysarthria if they had evidence of 3 or more of the following behaviors in three or more MSAP tasks: scanning speech; equal sentential

stress; sound distortions; irregular diadochokinetic rates (each of which is suggestive of ataxic dysarthria); slow rate; reduced range of motion; reduced strength of articulatory contacts; reduced respiratory support or respiratory incoordination; and strained or breathy phonatory quality. Other observations such as adventitious movement also contributed to this classification.

Each of the 33 participants with galactosemia and speech sound disorder was classified as having CAS and/or dysarthria based on these contemporary clinical diagnostic criteria. Because MSD-NOS had not been developed as an SDCS classification category at the time, the third author did not have the option of using MSD-NOS for MSAP responses that were not specific for MSD-AOS or MSD-DYS or for participants whose total scores did not meet criteria for either MSD-AOS or MSD-DYS. The resulting clinical diagnostic classifications for each of the youth with galactosemia were used for each of the questions posed in this study. Findings from a reliability study of these classifications are described in Appendix A. Overall interjudge agreement for a random sample of 10 participants classified by an examiner with extensive experience in motor speech disorders was 90%.

Results

Question 1: What is the estimated prevalence of CAS in children with galactosemia and prior or persistent speech sound disorder?

Prevalence of Galactosemia—Table 3 includes summary information organized to provide statistical analyses of prevalence data and risk factor data for participants with galactosemia (abbreviated to GALT) in the present study who did and did not meet the third author's criteria for CAS. As shown in the first column in Table 3 titled Group 1: GALT CAS, 8 participants with galactosemia met the contemporary clinical diagnostic criteria for CAS described previously. One of the 8 participants classified as having CAS also met the criteria described previously for dysarthria. The data from an additional participant whose speech data only met criteria for dysarthria were removed from further analyses to restrict all analyses to questions addressing CAS. Rationale for dividing the remaining 24 participants with galactosemia into two subgroups titled Group 2: GALT SD (SD = Speech Delay) and Group 3: GALT SE (SE = Speech Errors) will be presented in a following discussion of risk factor correlates.

Using the recruitment procedures, assessment tools, and diagnostic classification criteria described in Method, the prevalence of CAS in the present sample of speakers with galactosemia and prior or persistent speech sound disorder was 24% (8/33) or nearly 1 of every 4 participants sampled. This prevalence estimate is at the lower end of the range of CAS reported for youth and adults with galactosemia summarized in Table 1 (including the same participants in two studies assessed with different instruments), the mean of which is approximately 48%. The present prevalence estimate for CAS was expected to be higher than the percentages in Table 1 because those estimates were based on all participants with galactosemia whereas the present study required participants with galactosemia to also have histories of a significant speech sound disorder. An estimate of the prevalence of CAS in all individuals with galactosemia who do not have other frank risk factors can be obtained by adding to the present 33 participants used as the denominator in the calculation, the 11 candidates with galactosemia who were excluded from participation in the present study because they did not have a history of speech disorder. The resulting percentage of 4-to 16-year-old youth with galactosemia, CAS, and none of the other risk factors used to exclude participants from the present study is 18% (8/44).

Several additional factors would support the 24% conditional prevalence percentage and the 18% unconditional prevalence percentage estimates compared to exactly twice the mean

conditional estimate (48%) based on the studies in Table 1. The most likely source of difference is the more conservative contemporary clinical diagnostic criteria used to classify the 8 participants as CAS in the present study, compared to the diagnostic criteria for CAS reported in studies dating back to the early 1970s. What is significant for both theory and practice is that the 18% and 24% prevalence estimates obtained in the present sample are significantly higher than estimates of the prevalence of idiopathic apraxia of speech. Compared to the population prevalence estimate of approximately 0.1% for idiopathic CAS cited previously (Shriberg & Kwiatkowski, 1994;Shriberg et al., 1997a), the present 18% unconditional estimated prevalence rate for CAS in children and adolescents with galactosemia represents an 180-fold increased risk (i.e., 18/0.1).

Question 2: What demographic, cognitive-linguistic, or dietary management variables in persons with galactosemia are significant risk factors for CAS?

Risk Factors for CAS in Youth with Galactosemia—Table 3 also includes information on demographic and risk factors associated with CAS in youth with galactosemia. Preliminary inspection of the GFTA-2 competence data indicated the need to divide the remaining 24 participants with galactosemia (i.e., those not meeting criteria for CAS) into two subgroups based on their speech status at assessment as classified by the Speech Disorders Classification System-Typology as updated in Shriberg, Fourakis, et al. (in press-a). As shown in Table 3, the 9 participants comprising Group 2: GALT SD met criteria for active speech delay (children younger than 9 years of age) or persistent speech delay (individuals past 9 years of age with residual speech sound deletions and/or substitutions (Shriberg, Fourakis, et al., in press-a). The 15 participants in Group 3: GALT SE had a distortion-only subtype of speech sound disorder termed Speech Errors (SE) in the SDCS-Typology (i.e., they did not meet SDCS criteria for present or persistent speech delay). Thus, in addition to the TD database used to derive z-scores for all perceptual and acoustic measures and the SD comparison database, two comparison groups of speakers with galactosemia (Group 2 and Group 3) were included in the statistical analyses to be described. Between-group comparisons in Table 3 included two-tailed odds ratios (based on exact .950 confidence intervals; [StatXact, Cytel Software, 2007]); for the categorical variables in the first five rows, and two tailed effect sizes (0.950; Hedge's *g* corrected for small cell sizes) for the continuous variables (www.cemcentre.org/renderpage.asp?linkID=30325017).

Demographics: The first set of risk factor questions addressed whether there were significant differences in the gender and/or mean ages of participants within the three subgroups of participants with galactosemia. Findings from these and other comparisons were also important preliminary information for subsequent analyses of dependent variables that might be sensitive to significant between-group differences in correlates of demographic composition.

As shown by the lack of bolded effect sizes and confidence intervals in the right-most three columns in Table 3, none of the three between-group comparisons for the proportion of males was statistically significant (i.e., the confidence intervals around the mean differences includes 1.00). For the age comparison in the Table 3 statistical findings for continuous variables, for which significant effect sizes require confidence intervals around the mean difference that do not include zero, GALT SD participants were significantly younger than participants in GALT SE (ES = −1.31). For the central upcoming comparisons between GALT CAS and GALT SD groups, however, the mean ages of participants in GALT CAS (approximately 9 years) and the GALT SD group (approximately 7 years) were not significantly different. Both risk factor findings attest to the persistence of both CAS and some other type of speech disorder past 6 years of age in speakers with galactosemia. As

indicated in Table 3, there was one significant between-group difference in the parental education levels indicating that fathers of participants in the GALT CAS group averaged approximately one year less education than fathers of participants in the GALT SD group. Among all groups of participants with galactosemia, both parents averaged approximately one to two years of post-high school education.

Galactosemia: Table 3 also includes findings for three risk factors specifically associated with galactosemia. Documented genotypes were not available for all participants, limiting generalization from the non-significant trends in Table 3 for a higher percentage of GALT CAS participants to have the Q188R/Q188R genotype discussed previously. There were no significant between-group findings for the other two galactosemia variables, *Days Until Diagnosis* and *Days on Milk*. These findings, indicating that GALT CAS participants were not at greater risk for CAS than participants in either of the other two speech disorder groups, are consistent with the literature consensus reviewed previously indicating that days on milk is not a sufficient risk factor to explain the complex neurodevelopmental challenges in persons with galactosemia, including the cognitive and CAS issues considered next.

Cognition: The continuous data findings in Table 3 comparing the cognitive status of participants in the three subgroups indicated that participants in the GALT CAS group, 75% of whose composite IQs were below 85 (see Table 3), had significantly lower composite IQ's than participants with galactosemia in the GALT SD subgroup (ES = −1.04). Findings for the two nonsense word repetition tasks (NRT and SRT) were consistent with findings for the cognitive measure (KBIT-2). To adjust for the significant age difference between the GALT SD and GALT SE groups, all between-group comparisons were completed using age-adjusted z-scores derived from the TD database. As shown in Table 3, GALT CAS participants had significantly lower average z-scores than participants in the GALT SD and the GALT SE groups on the Nonword Repetition Task (ES = −1.17; ES = −1.59) and GALT SE group on the Syllable Repetition Task (ES = −1.07). Thus, whatever the speech processing constraint(s) underlying lowered performance on nonsense word repetition tasks (i.e., constraints in phonological encoding, memory, and/or transcoding [cf. Shriberg, 2010c;Shriberg et al., 2009]), the participants in this study had significantly lower scores than scores from children with typical development of similar age, with greater deficits statistically confirmed for participants with galactosemia and CAS.

Language: As shown in Table 3, there were no significant between-group differences in any of the three comparisons of scores on the OWLS receptive language scale. On the OWLS expressive language scale, however, the GALT CAS group had significantly lower scores than participants in both the GALT SD (ES = −1.12) and the GALT SE (ES = −0.93) subgroups.

Orofacial Structure and Function and Phonation Time: Finally, Table 3 includes findings for two variables scored categorically, orofacial structure and function, and one variable scored continuously, maximum phonation time. There were no significant between-group differences for orofacial structures and function as screened with the assessment procedure described in Appendix Table A1. Participants in the GALT CAS group, who were not significantly younger than participants in the GALT SD group, had significantly shorter phonation times than GALT SE participants (ES = −1.11).

Summary—The data in Table 3 are interpreted as supporting a prevalence rate for CAS in children and adolescents with galactosemia of 18–24%. This finding is consistent with prior reports indicating that CAS is highly prevalent in galactosemia, but at less than half the approximately 48% average rate in prior studies shown in Table 1. This difference in

obtained prevalence estimates is likely associated with many methodological differences between the present and prior studies, particularly in the more stringent diagnostic criteria for CAS used in the present compared to prior studies. The risk findings support prior reports of cognitive and expressive language challenges in participants with galactosemia, with participants in the present study meeting criteria for CAS being significantly more affected.

These risk factor data do not support significant differences from typical development in orofacial structure or function in any of the three groups of participants with galactosemia and speech sound disorders, but did identify significantly shorter than typical phonation times in the GALT CAS participants. A forthcoming report will focus on this latter finding and other aspects of sensorimotor speech processing in the three groups of participants with galactosemia, using data from several movement measures not included in the present report. Findings from additional examination of the present risk factor findings are reviewed in later summative discussion.

Question 3: What speech, prosody, and/or voice indices best discriminate participants with galactosemia and CAS from participants with galactosemia and other speech sound disorders?

Competence Indices Findings—Competence indices in the Competence, Precision, and Stability (CPSA) framework quantify severity of involvement. It is efficient to report detailed findings for this construct in Appendix B. Unlike findings for precision and stability, in which the statistical approach provides evidenced-based, percentage of positive marker analyses, results for competence are analyzed using conventional group-wise comparisons and effect-size statistics. Findings from these between-group analyses reported in Appendix B may be summarized as follows: (a) vowel indices: GALT CAS participants had significantly lower competence in this domain in conversational speech than both the GALT SD participants and participants with SD, (b) consonant indices: GALT CAS participants scored significantly lower than the GALT SD group on 33% of the consonant indices from continuous speech and on the GFTA-2, (c) indices that include both vowels and consonants: GALT CAS participants had significantly lower competence than GALT SD participants on the percentage of spoken words that retain the intended number of sounds and syllables in words, and (d) prosody-voice indices: GALT CAS group participants had significantly lower scores than the SD group on 57% of the suprasegmental measures, including indices of Rate, Stress, Pitch, and Resonance. Appendix B provides detailed tabular and text descriptions of all between-group statistical competence comparisons and these findings will be integrated in the Discussion.

Precision and Stability Indices Findings

Overview

Rationale for the Percentage of Positive Markers metric: The dependent variables for the between-group competence analyses in Appendix B are mean scores on each of the 30 indices of speech competence. The dependent variables for the present between-groups analyses of precision and stability indices are each subgroup's mean percentage of positive MSD markers (i.e., at least one standard deviation greater in the expected direction than the average score of TD speakers matched on age and gender). Rationale for this metric is the assumption that probabilities of disorder increase in proportion to the number of candidate signs (i.e., diagnostic markers) of the disorder on which they test positive. Such additive, scalar approaches to measurement in complex disorders are used when there is no one or more well-validated biomarker or behavioral marker pathognomonic for the disorder, and when the disorder is expressed as a syndromic-like complex of signs. As described next, whereas competence metrics in the CPSA are used to quantify severity of expression of a

disorder, the Percentage of Positive Markers metric is used to classify putative etiologic subtypes of speech sound disorder.

Statistical design: Table 4 and Figures 1 and 2 provide summaries of the analyses of candidate markers of the three SDCS motor speech disorders classifications: MSD-AOS (synonymous with CAS), MSD-DYS, and MSD-NOS. For exploratory purposes, a fourth, composite set combining markers from MSD-AOS and MSD-NOS was also derived, termed MSD-AOS/NOS. The descriptive statistics in Table 4 and graphic illustrations in Figures 1 and 2 summarize average percentages of positive markers for each participant subgroup: GALT CAS, GALT SD, GALT SE, GALT SD/SE (a composite group to be described), and SD. Horizontal brackets between subgroups in Figures 1 and 2 indicate significant (or marginally significant) differences in the average percentage of positive markers for each comparison. As just noted, for exploratory purposes, and in consideration of power limitations, marginally significant effect sizes in which the lower boundary of the confidence interval crossed zero by .003 or less are shown in parentheses without the conventional asterisk indicating statistical significance at the .05 alpha level. Figures 1 and 2 differ by the sources used for data on each set of measures. The data for all groups in Figure 1 were obtained from all available MSAP sources, whereas the data for all groups in Figure 2 were obtained from only conversational speech samples (i.e., the only data available from the SD group).

Marker Findings among Galactosemia Subgroups: The Percentage of Positive Markers comparisons shown in the four panels on the left side of Figure 1 include only one marginally significant difference. GALT CAS participants had a marginally higher percentage of positive MSD-NOS markers than GALT SE participants (ES=0.73; see Table 4 for all means and standard deviations values). Otherwise, the lack of significant between-group differences between GALT CAS and each of the other two galactosemia subgroups was viewed as support for combining the latter two subgroups to constitute one larger comparison subgroup of all 24 participants termed the GALT SD/SE subgroup. The assumption was that the increased statistical power created by pooling all galactosemia participants with speech disorder other than CAS would have greater sensitivity to true differences in the average percentages of positive markers by participants with and without CAS.

As shown in the middle-right panel in Figure 1, GALT CAS participants did not differ from the GALT SD/SE group on the average percentage of the markers considered to be positive for MSD-DYS. As shown in the other three panels on the right side of Figure 1, however, comparisons of the combined GALT SD/SE group and the GALT CAS group yielded two marginally significant and one significant between-group finding. The GALT CAS participants had marginally higher percentages of positive MSD-AOS markers than the GALT SD/SE group (ES=0.67) and marginally higher percentages of positive MSD-NOS markers (ES = 0.65). As indicated in the lower right panel, GALT CAS participants had significantly higher percentages of the combined MSD-AOS/NOS markers than galactosemia participants without CAS (ES = 0.87).

Marker Findings between Galactosemia Groups and the Speech Delay Group: The eight panels in Figure 2 are similar in format to those in Figure 1. As indicated in the bottom row of Table 4, these analyses were completed using only the information on precision and stability markers available from the conversational speech samples of participants in each of the four groups. As shown in the four left-hand panels in Figure 2, there were no significant or marginal between-group effect sizes for the 25 MSD-AOS markers and for the 12 MSD-DYS markers obtained solely from the conversational speech samples. For the MSD-NOS markers, however, participants in all three galactosemia groups had significantly higher

percentages of positive markers than participants in the SD group. Significant effect sizes for the three comparisons with the SD participants, respectively, were GALT CAS: ES = 1.32, GALT SD: ES = 0.72, and GALT SE: ES = 0.70. GALT CAS participants also had a significantly higher percentage of positive markers for motor speech disorder than participants in the SD group on the 45 combined MSD-AOS/NOS markers (ES = 1.01).

As there were no significant or marginal differences in the percentage of positive markers for motor speech disorder between the GALT SD and GALT SE groups, their marker data from conversational speech samples were combined for the analyses summarized in the four right panels in Figure 2. As shown, the larger cell size of the merged GALT SD/SE group did not increase the number of significant between-group differences compared to the marker data obtained for the non-combined SD and SE groups.

Promising Diagnostic Markers of CAS: The final analyses series inspected the individual marker data to identify competence, precision, and stability indices with the highest potential to accurately identify CAS. Findings are shown in Figure 3. As indicated by the dashed line in each panel in Figure 3, 75% was selected as the lower limit of diagnostic accuracy, but a few markers close to this arbitrary criterion for behavioral measures were included in Figure 3. The left-most bar indicates the obtained diagnostic accuracy of a potential marker, defined as the sum of the target group's true positive participants and the comparison group's true negative participants, divided by the sum of the true positives, true negatives, false positives, and false negatives multiplied by 100. The other two bars for each of the nine markers in Figure 3 indicate the marker's sensitivity to CAS (true positives) and its specificity relative to the comparison group (true negatives). Within each comparison panel, the markers are sequenced left to right by the magnitude of the percentage of diagnostic accuracy (solid filled bars) and include information on the method of data reduction (A: acoustic; P: perceptual). The data in the top panel were obtained using all eligible sources; comparisons with the SD group (middle and bottom panel) were obtained only from the conversational samples from each group.

Markers best differentiating GALT CAS from GALT SD: As indicated previously, the most informative control for the GALT CAS group is the GALT SD group because both groups have galactosemia, speech delay, and cognitive deficits. The top panel in Figure 3 includes two speech production indices with promising diagnostic ability to differentiate MSD-AOS from speech delay in the context of possible MSD-NOS: the CAS markers *Less Stable Vowel Duration* (diagnostic accuracy, 83%: sensitivity, 88%; specificity, 78%) and *Less Stable F2* (diagnostic accuracy, 77.5%: sensitivity, 88%; specificity, 67%). These two stability measures, each assigned to MSD-AOS based on the precedent literatures in AOS and idiopathic CAS, were both obtained using acoustic methods.

Markers best differentiating GALT CAS from SD: The middle panel in Figure 3 provides diagnostic accuracy findings for four measures that discriminated the participants with GALT CAS from those with SD. Although of paramount interest for research and clinical applications, constraints in the present comparison of CAS to SD limit generalizations. Again, differences in cognitive status are an important possible confound for at least some potential diagnostic markers, and the limitation of analyses to conversational speech data for this comparison constrains the sensitivity and possibly specificity of these analyses.

As shown in the middle panel in Figure 3, *Inappropriate Stress*, scored perceptually, was the most discriminating marker of GALT CAS participants compared to participants with galactosemia and Speech Delay (diagnostic accuracy, 86.9%; sensitivity, 85.7%; specificity, 88.0%). The second and third most discriminatory markers, quantified using acoustic and perceptual methods, respectively were *Slow Speaking Rate* (i.e., includes pauses, in

comparison to *Slow Articulation Rate* which does not) and *Slow Rate*. Diagnostic accuracy for *Slow Speaking Rate* was 85.8% (sensitivity, 87.5%; specificity, 84%) and diagnostic accuracy for *Slow Rate* was 85.7% (sensitivity, 71.4%; specificity, 100%). The fourth most discriminating marker was *Slow Articulation Rate* measured using acoustic methods (diagnostic accuracy, 85.5%; sensitivity, 75%; specificity, 96%). As described, the latter measure of articulation rate subtracts all pauses from speaking rates and thus is presumed more closely to index speech execution time.

Markers best differentiating GALT SD from SD: Findings for a third diagnostic accuracy analyses address the question posed previously of whether children with galactosemia and speech delay, but not CAS, have some type of motor speech disorder (i.e., MSD-NOS). As shown in the bottom panel in Figure 3, there were two measures in conversational speech that marginally met the 75% diagnostic accuracy criterion for this comparison: *Inappropriate Stress*, scored using perceptual methods (diagnostic accuracy, 77.3%; sensitivity, 66.7%; specificity, 88%), and *Slow Speech Rate*, scored using acoustic methods (diagnostic accuracy, 75.3%; sensitivity, 66.7%; specificity, 84%). Notice that these findings negate the middle panel findings in Figure 3 indicating that *Inappropriate Stress* and *Slow Speaking Rate* might be used to differentiate CAS from SD, because both the GALT CAS and GALT SD groups had higher percentages of speakers with *Inappropriate Stress* and *Slow Speech Rate* compared to the percentages for participants with SD.

Discussion

Methodological Constraints

Some methodological constraints warrant comment before discussion of findings. Clearly, the small cell sizes for the galactosemia groups constrain the reliabilities of means and variance estimates for the risk factor data in Table 3 and all descriptive statistics used in the speech competence, precision, and stability analyses. This common limitation in studies of rare disorders was addressed in the current study by combining groups when statistically warranted (e.g., Figures 2 and 3). Although the consistency of the present findings of high prevalence of CAS and other motor speech disorders in galactosemia with findings in the precedent literature suggests that the small sample was likely representative, cross-validation studies are needed.

A second methodological constraint, noted several times, is the limitation in the sensitivity of information from the participants with Speech Delay due to the lack of complete MSAP data. Analyses of MSAP data from the present and other data sets indicate that speakers may be two to three times more likely to be positive for motor speech indices in contexts other than conversational speech. For example, vowel space is routinely smaller when assessed in conversational speech than in citation speech (examples of the latter include the CVC citation forms in VT1; see Table A1), likely constraining the sensitivity of continuous speech samples to potentially significant between-group differences in vowel space. This sampling constraint was noted in Odell and Shriberg (2001), which updated findings from a prior research series in CAS (Shriberg, Aram, & Kwiatkowski, 1997a,1997b,1997c). Specifically, the later paper noted that the 1997 study series likely underestimated the numbers of true positive participants with CAS because all speech data for those analyses were based on conversational speech samples only.

A third methodological constraint in the present study was the use of a relatively liberal classification criterion for positive markers. The present criterion of a score below one standard deviation from the age- and gender-matched reference data may require more conservative adjustment to increase specificity among subtypes of pediatric motor speech disorders. Post hoc examination of findings suggests that for the goals of the present and

other studies using the SDCS, this criterion was more appropriate for sensitivity/specificity goals than use of a more stringent criterion, for example, 1.20 standard deviation units or greater. Additional study is needed on the optimum cut points in the distributions of scores in target and reference data, which will require increased numbers in both sets of reference data used in the present study—MSAP data from typically-developing speakers and from speakers with speech delay.

A final challenging methodological constraint is the circularity inherent in 'bootstrap' designs such as used in the present study. The arbitrary inclusionary and exclusionary criteria used to classify participants with CAS are as much of a design constraint in the present study as arbitrary criteria are in all other studies of CAS. Guyette and Diedrich (1981) and McNeil, Robin, and Schmidt (1997) are widely-cited discussions of this circularity problem in the childhood and adult literatures in apraxia of speech, respectively. In the present study, classification of CAS by the third author was accomplished using a set of ten putative diagnostic markers requiring an arbitrary number of positive occurrences on an arbitrary number of speech tasks. It is possible that these criteria produced some false positives for CAS, and possibly some false negatives, due to the lack of additional, diagnostically relevant information (e.g., motor speech examinations) available in the video and/or audio recordings of participants' responses to the MSAP. The premise of the present design is that the classification criteria used in the present study have sufficient validity (face, consensual, construct, concurrent) to yield study groups with an adequate number of true positives (GALT CAS) and true negatives (GALT SD, GALT SE, SD) for CAS to bootstrap to the next level of fine-grained quantitative study of promising diagnostic markers.

Prevalence of Apraxia of Speech in Galactosemia

For the first question posed in this report, findings indicated that CAS was highly prevalent (18%) in a sample of youth with galactosemia when adjusted for the present inclusionary criteria requiring active or prior speech sound disorder. This estimate is just over one-third the approximately 48% average prevalence rate reported in the most methodologically robust studies of CAS in galactosemia (Table 1) and 180 times larger than the 0.1% estimated population prevalence of idiopathic CAS (Shriberg, Aram, & Kwiatkowski, 1997a). Both of the latter prevalence estimates date back to prior decades using CAS classification methods differing considerably from those used in the present study. As suggested previously, a reasonable premise is that the present lowered prevalence estimate for CAS in youth with galactosemia (approximately 1 in 5 [20%] compared to 1 in 2 [50%]) is, at least in part, due to the more stringent inclusionary criteria used in the present report to differentiate CAS from severe speech delay.

In addition to findings supporting a high prevalence of CAS in galactosemia, the present findings support a high prevalence of some other form(s) of motor speech disorder in this rare metabolic disorder. The finding that the GALT SD and GALT SE participants had significantly higher percentages of positive motor speech markers compared to participants in the SD control group (Figure 3) is viewed as central to goals of understanding the developmental neurobiology underlying the neurocognitive and neuromotor deficits reported in youth with galactosemia despite well-managed dietary histories.

Risk Factors for and Correlates of Apraxia of Speech in Galactosemia

The second question addressed in this study was whether participants classified as positive for CAS (GALT CAS) differed significantly from participants in the other two galactosemia groups (GALT SD; GALT SE) on available risk factors for or correlates of galactosemia (Table 3). The small cell sizes, missing genotype information, and minimal clinical data for

participants limited the type and power of analytic approaches to this question. Of the 14 variables for which statistical data were available (Table 3), statistically significant effect sizes indicating that GALT CAS participants were younger and had fathers with approximately one year less education than participants in one of the other subgroups may be sampling errors and are not viewed as relevant for explanatory models of CAS. Significant effect sizes indicating that GALT CAS participants had lower maximum phonation times than participants in the other two galactosemia groups, however, might be an important clue to an eventual account of the pathophysiologies underlying CAS and/or dysarthria in galactosemia. As noted, a forthcoming paper will address speech motor control findings for the present participants with galactosemia, including phonation time and other speech findings within a larger set of motor movement measures not included in the present report.

The six significant findings indicating that GALT CAS participants averaged lower cognitive and expressive language scores than participants in one or both of the other two groups are viewed as central to both explanatory models of apraxia of speech and other motor disorders in galactosemia and for the development of effective treatment options. Explanatory models divide on whether comorbid deficits in two or more related developmental domains (e.g., speech development, language development, motor development) confer risk for each other or have common antecedents. As noted previously, cell size limitations in the present database prohibit the types of multivariate analyses that could be used to address such questions.

Statistical limitations notwithstanding, the lack of clear between-group differences among the categorical and continuous galactosemia variables summarized in Table 3 is especially notable. As discussed previously, there were too many missing data on genotypes to assess whether the homogeneous Q188R genotype was associated with higher risk for CAS. Also, there was no support for orofacial structure or function risk factors or correlates of CAS in this sample of youth with galactosemia. For the potential risk factors for CAS of *Days until Diagnosis* and *Days on Milk*, however, the descriptive and inferential statistics clearly suggest no significant differences or trends. A recent study of 59 participants with Duarte galactosemia, a less severe form of galactosemia than the classic form reviewed here, also found developmental issues in a statistically significant number of participants, despite galactose restriction until 1 year (Powell et al., 2009).

Diagnostic Markers of CAS and Other Pediatric Motor Speech Disorders

The third study question addressed what many investigators have underscored as the primary need in CAS research—what speech, prosody, and/or voice features are sensitive to and specific for this subtype of motor speech disorder? The goal of identifying one or more highly sensitive and specific biomarkers for CAS is consistent with contemporary research goals in diseases and complex neurodevelopmental disorders. We have suggested that the pursuit of that goal is aided by dividing potentially pathognomonic behavioral markers for CAS into the three clinical categories for pediatric motor speech disorders used in the present study—MSD-AOS, MSD-DYS, and MSD-NOS. Given its high co-occurrence with other subtypes of motor speech disorders (Shriberg, 2010b) and high comorbidity with language impairment, it is unlikely that any one behavioral measure will be highly specific for CAS at all levels of severity and at all ages throughout the lifespan. Some final observations address the potential utility of the SDCS for research in CAS as it occurs in neurological, neurodevelopmental, and idiopathic contexts.

First, relative to the goal above, there was no one speech, prosody, or voice marker with high diagnostic accuracy for CAS (i.e., nominally, >90%). As shown in Figure 3, the two markers with the highest diagnostic accuracy in the present study were *Less Stable Vowel*

Duration (diagnostic accuracy, 83%) and *Less Stable F 2* (diagnostic accuracy, 77.5%). The two markers share three characteristics: vowel targets, deficits in stability, and acoustic indices. The inclusionary criterion for the classification of CAS in the present study requiring vowel errors is an obvious constraint on these findings. However, inspection of the inclusionary data indicated that there were no participants who met the criteria for vowel errors who didn't also meet the other token count/task criteria for CAS. High occurrence of vowel errors has been reported in all widely-cited studies of CAS (ASHA, 2007). To our knowledge, however, the present findings provide the first quantitative support for deficits in both spatial and temporal vowel stability as promising candidates for pathognomonic speech markers of CAS in 4-to 16-year-old youth.

Second, this paper reports the first use of the MSD-NOS classification category introduced in Shriberg, Fourakis, et al. (in press-a). Findings support its productivity as a place-holder for both potential diagnostic markers of CAS and for participants who do not meet specificity criteria for the other two MSD classifications, but have speech characteristics and other risk factors not observed in participants with any form of Speech Delay of currently unknown origin. One possible clinical dividend from this working term is its potential to reduce the widely-reported overdiagnosis of CAS (ASHA, 2007). Although features such as slow rate and reduced vowel space may be sensitive to motor speech disorder, they should not be included on 'check-lists' of speech behaviors that purport to be specific for CAS. Rather, children with only such characteristics may have some type of motor immaturity, with implications for intervention and prediction of normalization that differ from those in apraxia of speech and for the several subtypes of dysarthria. As reviewed in Shriberg, Fourakis, et al., there is a significant need for systematic studies of pediatric motor speech disorders leading to a well-validated nosology.

Last, the methodological constraints reviewed previously and the limitation of the application of the present findings to those in only one complex neurodevelopmental disorder precludes generalizations about CAS as a possible idiopathic disorder. There is one puzzling finding in the present data, however, that might be interpreted as counter-support for the perspective of a core set of CAS markers across neurologic, neurodevelopmental, and idiopathic contexts. In prior studies of children with idiopathic CAS, we have reported two acoustic indices with high diagnostic accuracy for CAS: inappropriate lexical stress (Shriberg, Aram, & Kwiatkowski, 1997b, 1997c; Shriberg, Campbell, et al., 2003) and reduced variability in speech time relative to pause time durations (Shriberg, Green, et al., 2003). In the present study of youth with galactosemia and CAS, neither index had high diagnostic accuracy. Although there are some measurement differences that may be relevant, a more likely source of the failure to replicate prior findings would seem to be associated with participant characteristics in the prior studies of participants with idiopathic CAS compared to those in the present study of participants with a metabolic disorder. Research in progress is using SDCS methods described in Shriberg, Fourakis, et al. (in press-a) and in the present report to profile CAS in diverse neurological, neurodevelopmental, and idiopathic contexts. Again, we defer research and clinical generalizations from the present findings to research and clinical issues in these other contexts for CAS until empirical findings are available and cross-validated.

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 DC000496 and by a core grant to the Waisman Center from the National Institute of Child Health and Development (Grant HD03352). We thank the following colleagues and associations for their contributions to this study: Roger Brown, Marios Fourakis, Sheryl Hall, Jessica Hersh-Bollering, Heather Karlsson, Joan Kwiatkowski, Heather Lohmeier, Jane McSweeny, Lola Rickey, Rebecca Rutkowski, Alison Scheer-Cohen, Sue Siemsen, Ruth Stoeckel, Christie Tilkens, David Wilson, Parents of Galactosemic Children, Galactosemic Families of Minnesota, Graduate students from Washington State University and Eastern Washington University, and the children and parents who participated in this study.

Appendix A

Table A1

The 25 tests and tasks in the Madison Speech Assessment Protocol (MSAP).

Measure	Speech Task	Acronym	Age Group[a]				Description and Goal	Stimuli
			1	2	3	4		
Goldman-Fristoe Test of Articulation-2 (2nd ed.)[b]	X	GFTA-2	X	X	X		The Sounds-in-Words section of the GFTA-2 provides supplementary production phonology information at the single word level.	34 picture plates (53 target words)
Audiological and (optionally) Acoustic Immittance Screening Task[c]		None	X				Audiologic and acoustic immittance screening data provide status on hearing and middle ear functioning at the time of assessment and supplement case history information.	Pulsed pure tones presented at 500, 1000, 2000, and 4000 Hz at 20 dB for the audiologic screening
Conversational Speech Sample	X	CSS	X	X	X	X	The CSS is the primary data source for production phonology, including segmental and suprasegmental (PVSP) data. It can also be used to obtain language production data.	If needed, pictures or books are used to evoke spontaneous conversational speech.
Lexical Stress Task	X	LST	X	X	X	X	The LST provides perceptual and acoustic information on a participant's ability to realize lexical stress in two-syllable words produced in imitation in a carrier phrase.	24 pictured two-syllable words (e.g., "chicken"), including 8 trochees, 8 iambs, and 8 spondees; recorded stimulus for each word in the carrier phrase "Say ____"
Challenging Words Task	X	CWT	X	X	X	X	The CWT provides information on a participant's ability to correctly sequence and produce sounds in 12 challenging words containing a variety of consonants (mostly Early- and Middle-8 sounds) and vowels in imitation. Multiple repetitions provide information on the	12 pictured words (e.g., "helicopter"), each presented 3 times; recorded stimulus for each token

Measure	Speech Task	Acronym	Age Group[a]				Description and Goal	Stimuli
			1	2	3	4		
							stability of productions.	
Vowel Task 1	X	VT1	X	X	X	X	VT1 provides information on the 4 corner vowels /ɪ, æ, ʊ, ɑ/ in single words produced in imitation. Multiple repetitions provide information on the stability of productions.	4 pictured CVC words (e.g., "bat"), each presented 4 times; recorded stimulus for each token
Vowel Task 2	X	VT2	X	X	X	X	VT2 provides information on the 11 non-corner vowels and diphthongs in single words produced in imitation. Multiple repetitions provide information on the stability of productions.	11 pictured CVC words (e.g., "bite"), each presented 4 times; recorded stimulus for each token
Vowel Task 3	X	VT3		X	X	X	VT3 provides information on vowels in 5 sentences produced in imitation. Multiple repetitions provide information on the stability of productions.	5 pictured sentences (e.g., "He has a blue pen"), each presented 4 times; recorded stimulus for each token
Syllable Repetition Task		SRT	X	X	X	X	The SRT provides information on speech processing in two- (CVCV), three- (CVCVCV), and four-syllable (CVCVCVCV) nonsense words using four Early-8 consonants /b, d, m, n/ and a single low back vowel /ɑ/ to minimize articulatory challenges.	Recorded stimulus for each of the 18 nonsense words (e.g., "bamana")
Nonword Repetition Task [d]		NRT	X	X	X	X	The NRT provides information on speech processing using nonsense words.	Recorded stimulus for each of 16 nonsense words — four each of 1-syllable, 2-syllable, 3-syllable, and 4-syllable words (e.g., "teɪvak"
Emphatic Stress Task	X	EST	X	X	X	X	The EST provides information on a participant's ability to realize emphatic stress within short sentences. In each of the four trials for each of 2 sentences, a different word is stressed.	Recorded stimuli for two 4-word sentences (e.g., "May I see PETE"), repeated 4 times each

Measure	Speech Task	Acronym	Age Group[a]				Description and Goal	Stimuli
			1	2	3	4		
Rhotics and Sibilants Task	X	RST		X	X	X	The RST provides information for /r/ and /s/ productions obtained in imitated single words embedded in the carrier phrase "Say ____ again."	Recorded stimuli for 10 words (e.g., “soon,” “bird”), each repeated four times
Multiyllabic Words Task 1	X	MWT1	X	X			MWT1 provides information on single words selected to represent difficult articulatory sequences. It assists in evaluating phonological planning, sound sequencing, and transitions from one sound to another. The MWT1 includes 25 single words for children age 3;0 to 11;11.	Recorded stimulus for each of 25 words (e.g., “animal”)
Multisyllabic Words Task 2	X	MWT2			X	X	See description for MWT1. MWT2 includes 20 single words for participants age 12;0 and up.	Recorded stimulus for each of 20 words (e.g., “emphasis”)
Speech Phrases Task [e]	X	SPT	X	X	X	X	The SPT provides information on 25 two- and three-word phrases selected to represent difficult articulatory sequences. It assists in evaluating phonological planning, sound sequencing, and transitions from one sound to another.	Recorded stimulus for each of 25 phrases (e.g., “big farm house”)
Diadochokinesis Task	X	DDK	X	X	X	X	The DDK task provides information on a participant’s ability to coordinate rapid, accurate, and rhythmic alternating movements of the lips and tongue within a single place of articulation and across 2 and 3 places of articulation (bilabial, alveolar, and velar).	Two 1-consonant syllable strings (e.g., ”papapa”), three alternating 2-consonant syllable strings, one alternating 3-consonant syllable string, and the word "pattycake"
Sustained Vowel Task	X	SVT	X	X	X	X	The SVT provides information on a participant’s respiratory-laryngeal capacity and laryngeal quality.	The vowel /ɑ/
Sustained Consonant Task	X	SCT	X	X	X	X	The SCT provides information on a participant’s respiratory-laryngeal capacity.	The consonant /f/

Measure	Speech Task	Acronym	Age Group[a]				Description and Goal	Stimuli
			1	2	3	4		
Orofacial Examination Task [f]		OET	X	X			The OET provides information on the structure and function of the speech mechanism.	None
Oral and Written Language Scales [g]		OWLS	X	X	X	X	The OWLS provides information on language comprehension and production.	Two books of picture plates, one each for the comprehension and production subtests
Woodcock-Johnson III Tests of Achievement [h]		WJ-III				X	The WJ-III provides information on language skills in adults in the areas of Letter-Word Identification Test 1) and Word Attack (Test 13). [Optional tests include: Test 7 – Spelling; Test 9 - Passage Comprehension; Test 11 – Writing Samples)	Test 1: Single letters and increasingly difficult words (e.g., “provincial”) are displayed for participant’s to pronounce. Test 13: Single letters and increasingly difficult nonwords (e.g., “fronkett”) are displayed for participant’s to pronounce.
Kaufman Brief Intelligience Test (2nd ed.) [i]		KBIT-2	X	X	X	X	The KBIT provides information on cognitive functioning using scores from the KBIT2's three verbal and nonverbal subtests.	Two books of picture plates are used for all of the nonverbal and some of the verbal test items
Case History Form		CHF	X	X	X	X	The CHF provides risk factor information on a participant’s medical, social, academic, hearing, family aggregation, and speech-language history.	None
Case History Interview		CHI	X	X	X	X	The CHI supplements and clarifies the information collected on the participant’s CHF.	None
Examiner Checklist		EC	X	X	X	X	The EC provides information on the examiner’s impressions of selected aspects of the participant’s behavior and psychosocial development/affect.	None

[a] Age group1: Preschool=3;0–5;11; Age group 2: School-age=6;0–11;11; Age group 3: Adolescent=12;0–17;11; Age group 4: Adult=18;0+

[b] Goldman, R., & Fristoe, M. (2000). *Goldman–Fristoe Test of Articulation (2nd ed.)*. Circle Pines, MN: AGS.

[c] American National Standards Institute (1989). *Specification for audiometers* (ANSI S3.6-1989). New York:Author.

[d] Dollaghan, C., & Campbell, T.F. (1998). Nonword repetition and child language impairment. *Journal of Speech, Language, and Hearing Research, 41*, 1136–1146.

[e] Catts, H. (1986). Speech production/phonological deficits in reading disordered children. *Journal of Learning Disabilities, 19*, 504–508.

[f] For the present study, all 33 participants were administered a modified version of the Orofacial Examination Task (OET).

[g] Carrow-Woolfolk, E. (1995). *Oral & Written Language Scales*. Circle Pines, MN: American Guidance Service.

[h] Woodcock, R.W., McGrew, K.S., & Mather, N. (2001). *Woodcock-Johnson III*. Itasca, IL: Riverside Publishing.

[i] Kaufman, A.S., & Kaufman, N.L. (2004). *Kaufman Brief Intelligence Test-Second Edition*. Circle Pines, MN: AGS Publishing.

Appendix B

Table B1

Descriptive and inferential statistical findings for the 30 competence indices obtained from the three subgroups participants with galactosemia (Groups 1, 2 and 3) and the comparison group of participants with Speech Delay (Group 4).

Tier	Domain	No.	Speech, Prosody, and Voice Competence Indices		Group 1: GALT CAS (n=8)		Group 2: GALT SD (n=9)		Group 3: GALT SE (n=15)		Group Speech D (n=25
			Title		Mean	SD	Mean	SD	Mean	SD	Mean
Segmental	Vowels	1	Percentage of Non-rhotic Vowels/Diphthongs Correct		85.0	9.4	96.4	2.7	98.3	1.6	94.7
		2	Percentage of Rhotic Vowels/Diphthongs Correct		25.6	38.6	38.2	35.4	60.6	45.8	6.5
		3	Percentage of Phonemic Diphthongs Correct		78.0	22.8	93.5	11.1	98.9	2.2	89.0
		4	Percentage of Vowels/ Diphthongs Correct		83.1	9.6	94.3	2.3	96.1	3.8	91.6
		5	Percentage of Vowels/ Diphthongs Correct: AT		67.8	18.6	87.5	4.2	93.1	6.0	-
		6	Percentage of Non-rhotic Vowels/Diphthongs Correct Revised		85.8	9.4	96.7	2.7	98.5	1.6	95.8
		7	Percentage of Rhotic Vowels/Diphthongs Correct Revised		73.1	21.1	68.8	22.5	91.2	14.8	40.4
		8	Percentage of Phonemic Diphthongs Correct Revised		78.4	22.8	94.3	10.0	98.9	2.2	9.03
		9	Percentage of Vowels/ Diphthongs Correct Revised		85.3	9.5	95.7	2.5	98.0	2.0	94.0
		10	Percentage of Vowels/ Diphthongs Correct Revised: AT		72.7	16.9	90.6	5.1	96.6	3.3	-
		11	Percentage of Relative Non-rhotic Vowel/ Diphthong Distortions		13.0	22.4	12.7	15.1	15.0	21.2	19.5
	Consonants	12	Percentage of Consonants in Inventory		87.2	14.7	92.9	7.8	98.9	2.7	80.6
		13	Percentage of Consonants Correct		68.2	19.4	81.3	8.5	91.9	6.7	61.4
		14	Percent of Consonants Correct: AT		55.1	30.1	74.9	16.5	91.1	8.2	-

Tier	Domain	No.	Speech, Prosody, and Voice Competence Indices	Group 1: GALT CAS (n=8)		Group 2: GALT SD (n=9)		Group 3: GALT SE (n=15)		Group Speech D (n=25)
			Title	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**
		15	Percentage of Consonants Correct- Revised	73.8	17.5	85.8	8.3	96.2	3.1	68.1
		16	Percentage of Consonants Correct- Revised: AT	61.1	30.5	81.6	16.7	96.4	5.1	-
		17	Percentage of Consonants Correct in Complex Words: MWT	38.1	25.6	58.3	19.7	80.4	10.7	-
		18	Relative Omission Index	37.5	17.2	25.2	11.8	25.8	21.7	33.4
		19	Relative Substitution Index	41.3	11.9	49.6	16.9	29.0	15.5	47.2
		20	Relative Distortion Index	21.2	13.7	25.1	12.4	45.2	26.6	19.4
	Vowels & Consonants	21	Speech Disorders Classfication System (SDCS)[a]	1.75	0.71	1.44	0.53	0.33	0.49	1.68
		22	Intelligibility Index (II)	82.6	16.6	90.5	13.7	98.3	1.8	90.1
		23	Percentage of Structurally Correct Words	84.1	10.3	91.8	3.8	97.0	1.8	79.6
Supra-segmental										
Prosody	Phrasing	24	Percentage of Appropriate Phrasing	89.2	11.4	80.3	14.9	83.9	9.8	91.3
	Rate	25	Percentage of Appropriate Rate	81.0	23.8	85.6	23.3	92.2	9.2	98.6
	Stress	26	Percentage of Appropriate Stress	79.8	13.0	76.5	12.9	87.5	6.9	91.2
Voice	Loudness	27	Percentage of Appropriate Loudness	96.3	3.8	93.1	11.2	99.2	1.7	83.5
	Pitch	28	Percentage of Appropriate Pitch	99.4	1.6	98.6	2.1	99.4	1.5	100.0
	Laryngeal Quality	29	Percentage of Appropriate Laryngeal Quality	84.4	11.9	59.7	32.5	66.7	36.5	70.6
	Resonance	30	Percentage of Appropriate Resonance Quality	74.6	33.6	86.4	10.6	94.4	12.5	96.4

[a]The SDCS is a typological system for speech sound disorders (Shriberg, Austin, Lewis, McSweeny, & Wilson, 1997). For the present purposes participants with one of seven subtypes of SSD were grouped in to three classification subtypes coded using the following ordinal system: “0” = Normal or Normalized Speech Acquisition; “1” = Normal Speech Acquisition/ Speech Delay, Residual Errors 1 (distortions only), or Questionable Residual errors (for participants younger than 9 years), and ; “2” = Speech Delay, Residual Errors 2 or Residual Errors 3 (includes residual substitutions and/or deletions).

References

American Speech-Language-Hearing Association (ASHA). Childhood apraxia of speech [Technical Report]. 2007. Available from www.asha.org/policy

Botkin JR. Research for newborn screening: Developing a national framework. Pediatrics. 2005; 116:862–871. [PubMed: 16199695]

Caruso, AJ.; Strand, EA. Clinical management of motor speech disorders in children. New York: Thieme Medical Publishers; 1999.

Cytel Software Corporation. StatXact 5.0.3. Cambridge, MA: 2001.

Darley, FL.; Aronson, AE.; Brown, JR. Motor Speech Disorders. Philadelphia: W. B. Saunders, Company; 1975.

Duffy, JR. Motor speech disorders: Substrates, differential diagnosis, and management. 2nd ed.. St. Louis, MO: Mosby; 2005.

Elsas LJ, Langley S, Paulk EM, Hjelm LN, Dembure PP. A molecular approach to galactosemia. European Journal of Pediatrics. 1995; 154 Suppl. 2:S21–S27. [PubMed: 7671959]

Feuk L, Kalervo A, Lipsanen-Nyman M, Skaug J, Nakabayashi K, Finucane B, et al. Absence of a paternally inherited FOXP2 gene in developmental verbal dyspraxia. American Journal of Human Genetics. 2006; 79:965–972. [PubMed: 17033973]

Fisher SE, Marcus GF. The eloquent ape: genes, brains and the evolution of language. Nature Reviews Genetics. 2006; 7:9–20.

Goldman, R.; Fristoe, M. Goldman–Fristoe Test of Articulation (2nd ed.). Circle Pines, MN: AGS; 2000.

Guyette, T.; Diedrich, W. A critical review of developmental apraxia of speech. In: Lass, N., editor. Speech and language: Advances in basic research and practice, Vol. 5. New York: Academic Press; 1981. p. 1-49.

Hansen TW, Henrichsen B, Rasmussen RK, Carling A, Andressen AB, Skjeldal O. Neuropsychological and linguistic follow-up studies of children with galactosaemia from an unscreened population. Acta Paediatrica. 1996; 85:1197–1201. [PubMed: 8922083]

Hauner KKY, Shriberg LD, Kwiatkowski J, Allen CT. A subtype of speech delay associated with developmental psychosocial involvement. Journal of Speech, Language, and Hearing Research. 2005; 48:635–650.

Hughes J, Ryan S, Lambert D, Geoghegan O, Clark A, Rogers Y, et al. Outcomes of siblings with classical galactosemia. Journal of Pediatrics. 2009; 154:721–726. [PubMed: 19181333]

Jan JE, Wilson RA. Unusual late neurological sequelae in galactosaemia. Developmental Medicine and Child Neurology. 1973; 15:72–74. [PubMed: 4729415]

Koch TK, Schmidt KA, Wagstaff JE, Ng WG, Packman S. Neurologic complications in galactosemia. Pediatric Neurology. 1992; 8:217–220. [PubMed: 1622520]

Lai CSL, Fisher SE, Hurst JA, Vargha-Khadem F, Monaco AP. A forkhead-domain gene is mutated in a severe speech and language disorder. Nature. 2001; 413:519–523. [PubMed: 11586359]

Lee DH. Psychological aspects of galactosaemia. Journal of Mental Deficiency Research. 1972; 16:173–191. [PubMed: 4671969]

Lewis, BA. Genetics of speech sound disorders and neurological correlates. Paper presented at the Annual Convention of the American Speech-Language-Hearing Association; Chicago, IL. 2008 November.

Lewis BA, Shriberg LD, Freebairn LA, Hansen AJ, Stein CM, Taylor HG, et al. The genetic bases of speech sound disorders: evidence from spoken and written language. Journal of Speech, Language, and Hearing Research. 2006; 49:1294–1312.

Lo W, Packman S, Nash S, Schmidt K, Ireland S, Diamond I, Ng W, Donnell G. Curious neurologic sequelae in galactosemia. Pediatrics. 1984; 73:309–312. [PubMed: 6701054]

MacDermot KD, Bonora E, Sykes N, Coupe A-M, Lai CSL, Vernes SC, et al. Identification of *FOXP2* truncation as a novel cause of developmental speech and language deficits. American Journal of Human Genetics. 2005; 76:1074–1080. [PubMed: 15877281]

McCauley RJ, Strand E. Treatment of childhood apraxia of speech: Clinical decision making in the use of nonspeech oral motor exercises. Seminars in Speech and. Language. 2008; 29:284–293. [PubMed: 19058115]

McNeil, MR.; Robin, DA.; Schmidt, RA. Apraxia of speech: Definition, differentiation, and treatment. In: McNeil, MR., editor. Clinical management of sensorimotor speech disorders. New York: Thieme; 1997. p. 311-344.

McSweeny, JL.; Shriberg, LD. Segmental and suprasegmental transcription reliability. Phonology Project, Waisman Center, University of Wisconsin-Madison; 1995. (Tech. Rep. No. 2)

McSweeny JL, Shriberg LD. Clinical research with the prosody-voice screening profile. Clinical Linguistics and Phonetics. 2001; 15:505–528.

Milenkovic, P. Time-frequency analysis for 32-bit Windows [Computer software]. Madison, WI: Department of Electrical Engineering, University of Wisconsin-Madison; 2000.

Morley M, Court D, Miller H, Garside R. Delayed speech and developmental aphasia. British Medical Journal. 1955; 2:463–467. [PubMed: 13240150]

Nelson CD, Waggoner DD, Donnell GN, Tuerck JM, Buist NRM. Verbal dyspraxia in treated galactosemia. Pediatrics. 1991; 88:346–350. [PubMed: 1861938]

Odell KH, Shriberg LD. Prosody-voice characteristics of children and adults with apraxia of speech. Clinical Linguistics and Phonetics. 2001; 15:275–307.

Potter NL, Lazarus J-AC, Johnson JM, Steiner RD, Shriberg LD. Correlates of language impairment in children with galactosaemia. Journal of Inherited Metabolic Disease. 2008; 31:524–532. [PubMed: 18649009]

Powell KK, Van Naarden Braun K, Singh RH, Shapira SK, Olney RS, Yeargin-Allsopp M. Long-term speech and language developmental issues among children with Duarte galactosemia. Genetics in Medicine. 2009; 11:874–879. [PubMed: 19904210]

Ramus, F.; Fisher, SE. Genetics of language. In: Gazzaniga, MS., editor. The Cognitive Neurosciences IV. Cambridge, MA: MIT Press; 2009. p. 855-871.

Ridel KR, Leslie ND, Gilbert DL. An updated review of the long-term neurological effects of galactosemia. Pediatric Neurology. 2005; 33:153–161. [PubMed: 16087312]

Robertson A, Singh RH, Guerrero NV, Hundley M, Elsas LJ. Outcomes analysis of verbal dyspraxia in classic galactosemia. Genetics in Medicine. 2000; 2:142–148. [PubMed: 11397328]

Robin, DA.; Jacks, A.; Ramage, AE. The neural substrates of apraxia of speech as uncovered by brain imaging: A critical review. In: Ingham, RJ., editor. Neuroimaging in Communication Sciences and Disorders. San Diego, CA: Plural Publishing; 2008. p. 129-154.

Rosenbek J, Wertz R. A review of 50 cases of developmental apraxic speech. Journal of Speech and Hearing Research. 1972; 26:231–249. [PubMed: 6887810]

Schweitzer S, Shin Y, Jakobs C, Brodehl J. Long-term outcome in 134 patients with galactosaemia. European Journal of Pediatrics. 1993; 152:36–43. [PubMed: 8444204]

Shriberg LD. Four new speech and prosody-voice measures for genetics research and other studies in developmental phonological disorders. Journal of Speech and Hearing Research. 1993; 36:105–140. [PubMed: 8450654]

Shriberg, L. Childhood speech sound disorders: From post-behaviorism to the post-genomic era. In: Paul, R.; Flipsen, P., editors. Speech sound disorders in children. San Diego, CA: Plural Publishing; 2010a. p. 1-34.

Shriberg, LD. A neurodevelopmental framework for research in Childhood Apraxia of Speech. In: Maassen, B.; van Lieshout, P., editors. Speech Motor Control: New Developments in Basic and Applied Research. Oxford: Oxford University Press; 2010b.

Shriberg, LD. Speech and genetic substrates of Childhood Apraxia of Speech. Paper presented the Fifthteenth Biennial Conference on Motor Speech: Motor Speech Disorders & Speech Motor Control; Savannah, GA. 2010c.

Shriberg, LD.; Allen, CT.; McSweeny, JL.; Wilson, DL. PEPPER: Programs to examine phonetic and phonologic evaluation records [Computer software]. Madison, WI: Waisman Center Research Computing Facility, University of Wisconsin–Madison; 2001.

Shriberg LD, Aram DM, Kwiatkowski J. Developmental apraxia of speech: I. Descriptive perspectives. Journal of Speech, Language, and Hearing Research. 1997a; 40:273–285.

Shriberg LD, Aram DM, Kwiatkowski J. Developmental apraxia of speech: II. Toward a diagnostic marker. Journal of Speech, Language, and Hearing Research. 1997b; 40:286–312.

Shriberg LD, Aram DM, Kwiatkowski J. Developmental apraxia of speech: III. A subtype marked by inappropriate stress. Journal of Speech, Language, and Hearing Research. 1997c; 40:313–337.

Shriberg LD, Austin D, Lewis BA, McSweeny JL, Wilson DL. The Speech Disorders Classification System (SDCS): Extensions and lifespan reference data. Journal of Speech, Language, and Hearing Research. 1997; 40:723–740.

Shriberg LD, Ballard KJ, Tomblin BJ, Duffy JR, Odell KH, Williams CA. Speech, prosody, and voice characteristics of a mother and daughter with a 7;13 translocation affecting *FOXP2*. Journal of Speech, Language, and Hearing Research. 2006; 49:500–525.

Shriberg, LD.; Campbell, TF. Proceedings of the 2002 Childhood Apraxia of Speech Research Symposium. The Hendrix Foundation; Carlsbad, CA. 2003.

Shriberg LD, Campbell TF, Karlsson HB, Brown RL, McSweeny JL, Nadler CJ. A diagnostic marker for childhood apraxia of speech: The lexical stress ratio. Clinical Linguistics and Phonetics. 2003; 17:549–574. [PubMed: 14608799]

Shriberg LD, Fourakis M, Karlsson HK, Lohmeier HL, McSweeny J, Potter NL, et al. Extensions to the Speech Disorders Classification System (SDCS). Clinical Linguistics & Phonetics. (in press-a).

Shriberg LD, Fourakis M, Karlsson HK, Lohmeier HL, McSweeny J, Potter NL, et al. Perceptual and acoustic reliability estimates for the Speech Disorders Classification System (SDCS). Clinical Linguistics & Phonetics. (in press-b).

Shriberg LD, Green JR, Campbell TF, McSweeny JL, Scheer A. A diagnostic marker for childhood apraxia of speech: The coefficient of variation ratio. Clinical Linguistics and Phonetics. 2003; 17:575–595. [PubMed: 14608800]

Shriberg LD, Jakielski KJ, El-Shanti H. Breakpoint localization using array-CGH in three siblings with an unbalanced 4q:16q translocation and Childhood Apraxia of Speech (CAS). American Journal of Medical Genetics: Part A. 2008; 146A:2227–2233. [PubMed: 18671280]

Shriberg LD, Jakielski KJ, Raca G, Laffin JJS, Jackson CA, Rice GM. Neurodevelopmental profiles of a mother and son with a disruption in FOXP2. 2010a Manuscript in preparation.

Shriberg LD, Jakielski KJ, Raca G, Laffin JJS, Jackson CA, Rice GM. Speech, prosody, and voice characteristics of a mother and son with apraxia of speech associated with a disruption in FOXP2. 2010b Manuscript in preparation.

Shriberg, LD.; Kent, RD. Clinical phonetics. 3rd ed.. Boston: Allyn & Bacon; 2003.

Shriberg LD, Kwiatkowski J. Developmental phonological disorders I: A clinical profile. Journal of Speech and Hearing Research. 1994; 37:1100–1126. [PubMed: 7823556]

Shriberg, LD.; Kwiatkowski, J.; Rasmussen, C. The Prosody-Voice Screening Profile. Tucson, AZ: Communication Skill Builders; 1990.

Shriberg, LD.; Kwiatkowski, J.; Rasmussen, C.; Lof, GL.; Miller, JF. The Prosody-Voice Screening Profile (PVSP): Psychometric data and reference information for children. Phonology Project, Waisman Center, University of Wisconsin-Madison; 1992. (Tech. Rep. No. 1)

Shriberg LD, Lof GL. Reliability studies in broad and narrow phonetic transcription. Clinical Linguistics and Phonetics. 1991; 5:225–279.

Shriberg LD, Lohmeier HL, Campbell TF, Dollaghan CA, Green JR, Moore CA. A nonword repetition task for speakers with misarticulations: The Syllable Repetition Task (SRT). Journal of Speech, Language, and Hearing Research. 2009; 52:1189–1212.

Shriberg, LD.; Olson, D. PEPAGREE: A Program to Compute Transcription Reliability [Computer software]. Madison, WI: Waisman Center Research Computing Facility, University of Wisconsin-Madison; 1988.

Sommer M, Gathof BS, Podskarbi T, Giugliani R, Kleinlein B, Shin YS. Mutations in the galactose-1-phosphate uridyltransferase gene of two families with mild galactosaemia variants. Journal of Inherited Metabolic Disease. 1995; 18:567–576. [PubMed: 8598637]

Stein CM, Millard C, Kluge A, Miscimarra LE, Cartier KC, Freebairn LA, et al. Speech sound disorder influenced by a locus in 15q14 region. Behavioral Genetics. 2006; 36:858–868.

Waggoner DD, Buist NR. Long-term complications in treated galactosemia: 175 US cases. International Pediatrics. 1993; 8:97–100.

Waggoner DD, Buist NR, Donnell GN. Long-term prognosis in galactosaemia: results of a survey of 350 cases. Journal of Inherited Metabolic Disease. 1990; 13:802–818. [PubMed: 1706789]

Waisbren SE, Norman TR, Schnell RR, Levy HL. Speech and language deficits in early-treated children with galactosemia. The Journal of Pediatrics. 1983; 102:75–77. [PubMed: 6848731]

Webb AL, Singh RH, Kennedy MJ, Elsas LJ. Verbal dyspraxia and galactosemia. Pediatric Research. 2003; 53:396–402. [PubMed: 12595586]

Yoss KA, Darley FL. Developmental apraxia of speech in children with defective articulation. Journal of Speech and Hearing Research. 1974; 17:399–416. [PubMed: 4421901]

Zeesman S, Nowaczyk MJM, Teshima I, Roberts W, Oram Cardy J, Brian J, et al. Speech and language impairment and oromotor dyspraxia due to deletion of 7q31 that involves *FOXP2*. American Journal of Human Genetics. 2006; 140(A):509–514.

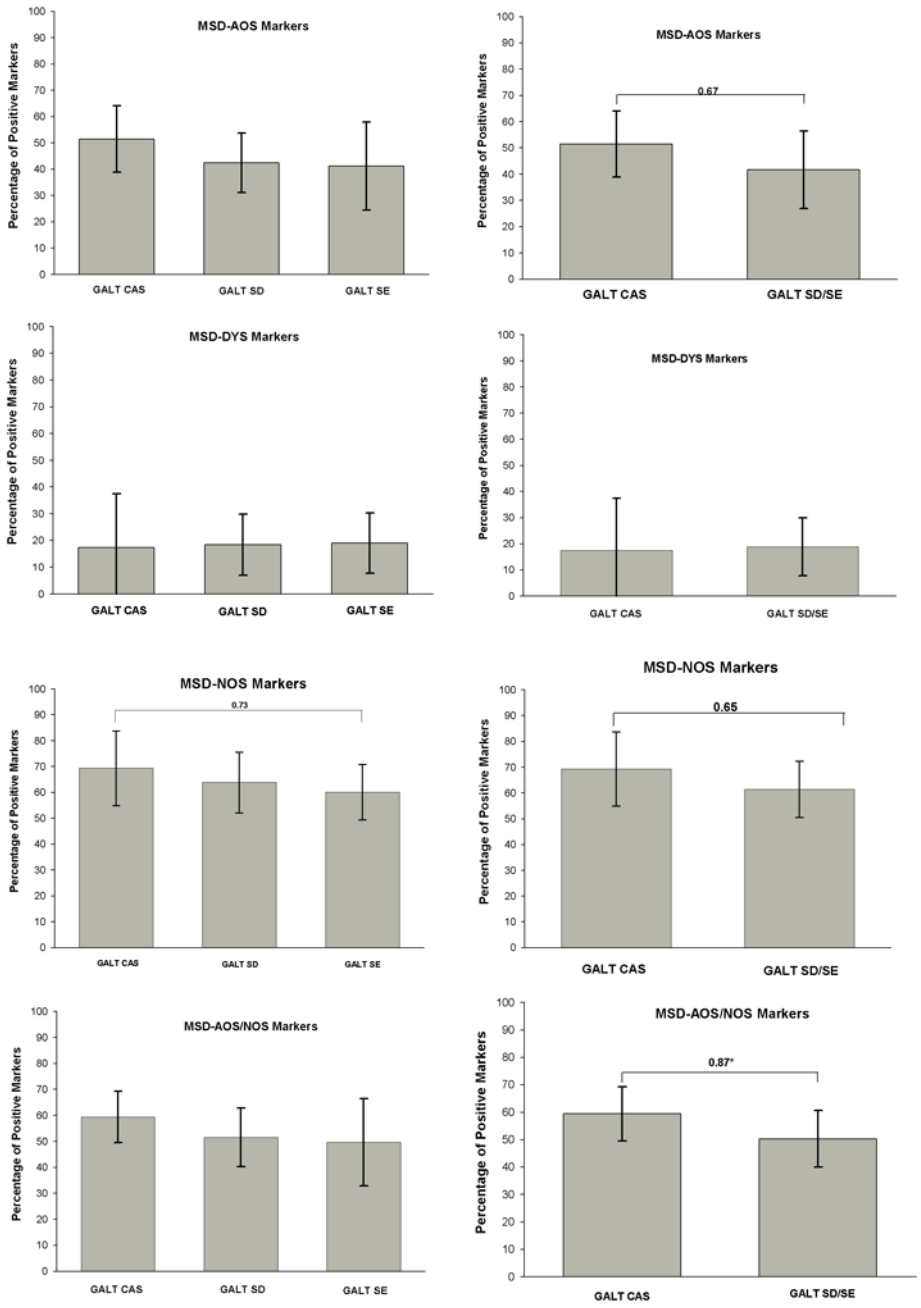

Figure 1.

Percentage of positive marker findings for participants in the three galactosemia subgroups. See text for descriptions of the motor speech markers, data sources, and rationale for combining subgroups in the four right-hand panels.

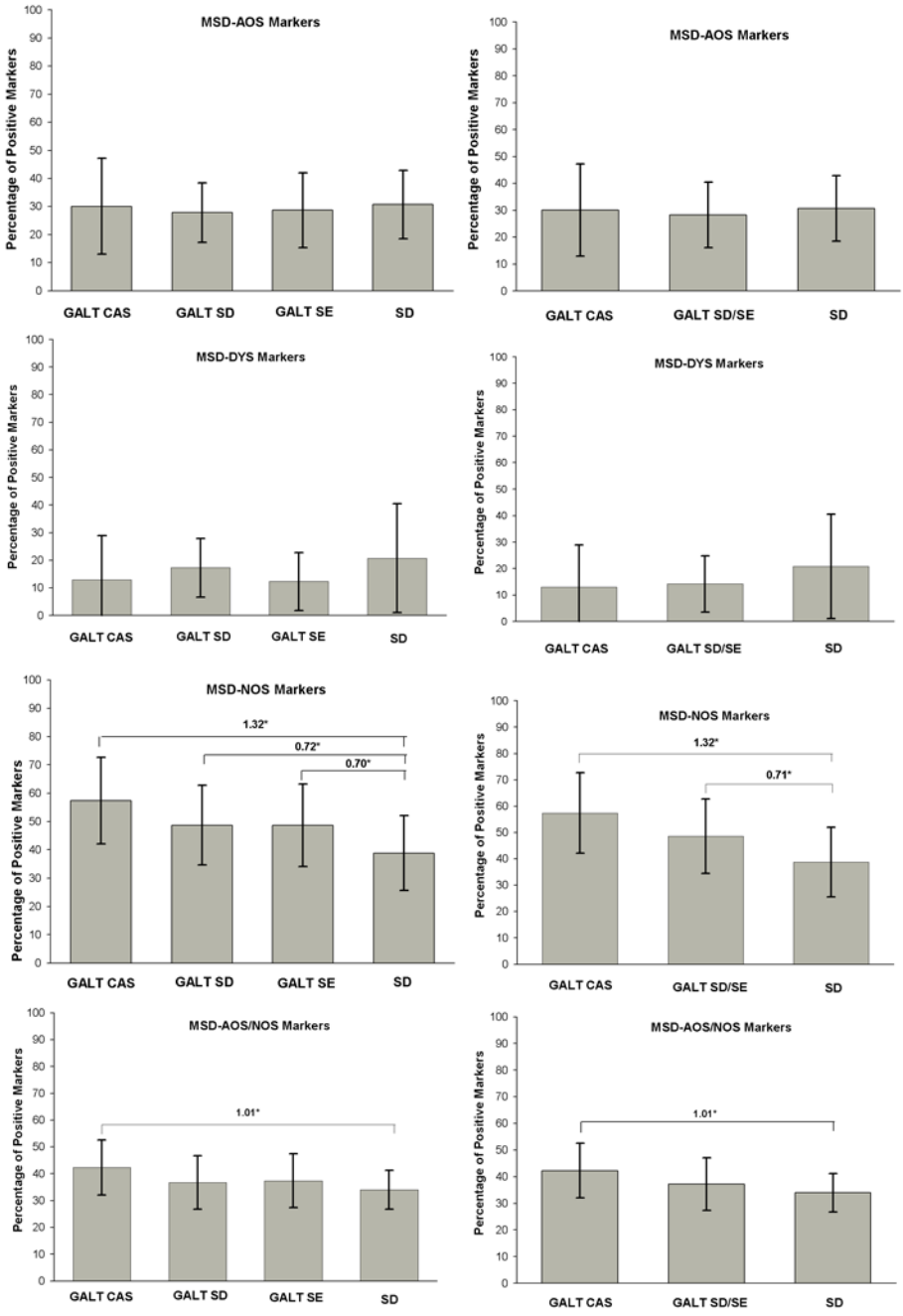

Figure 2.

Percentage of positive marker findings for participants in the three galactosemia subgroups and the speech delay participants. All findings are limited to data from the conversational speech samples; see text for descriptions of the speech markers and rationale for combining subgroups in the four right-hand panels.

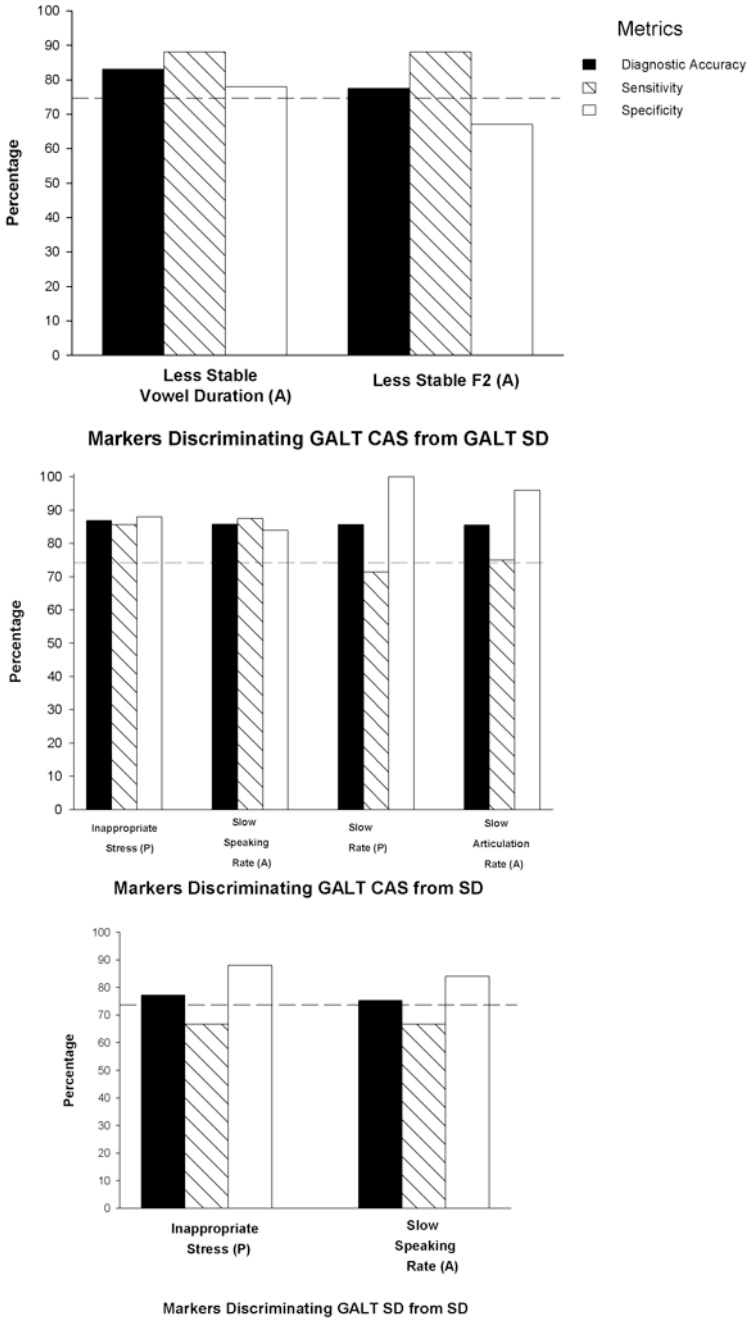

Figure 3.

Competence, Precision, and Stability indices with the highest diagnostic accuracy for Motor Speech Disorder-Apraxia of Speech. See text for criteria for diagnostic accuracy for the three subgroup comparisons.

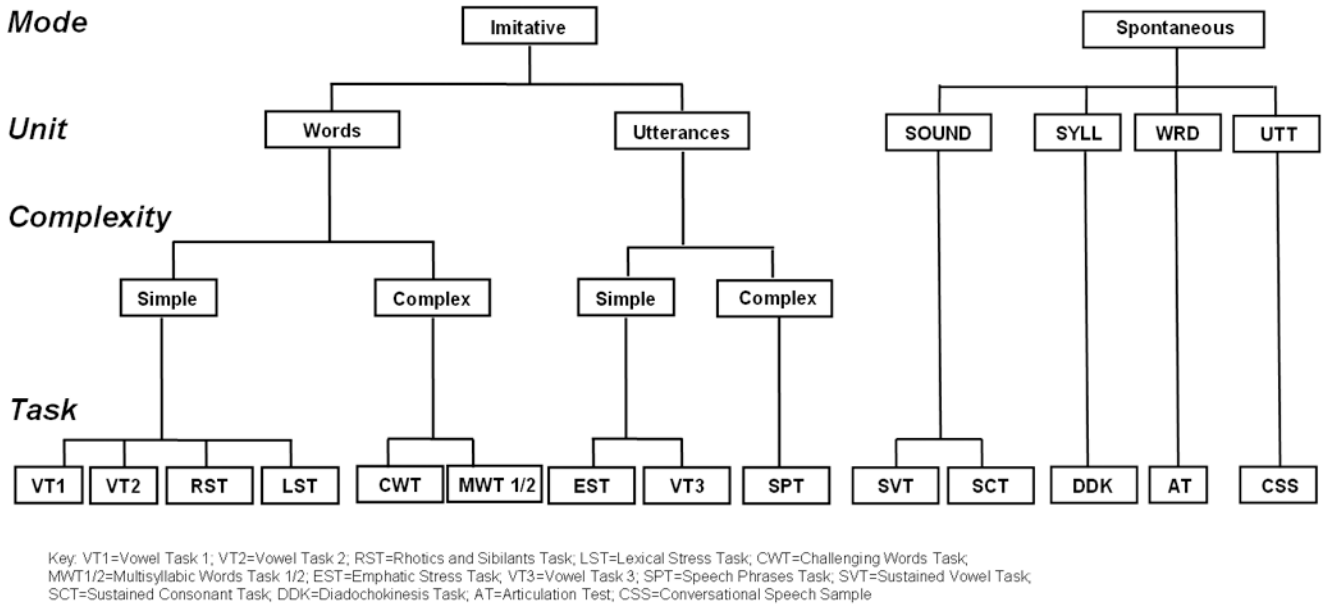

Figure A1.
The Madison Speech Assessment Protocol (MSAP) speech sampling context hierarchy.

Table 1

Speech findings in 13 studies of persons with galactosemia. Dashes in cells indicate no available information.

Study		Participants		Speech Assessment Instrument	Speech Findings (% Participants)		
Year	**Author(s)**	***n***	**Age (s) years; months**		**Apraxia of Speech**	**Dysarthria**	**Speech Disorder**
1972	Lee	60	2;2 – 17;7	-	-	-	25%
1973	Jan & Wilson	1	19	-	-	100%	-
1983	Waisbren et al.	8	4;4 – 11;7	"Variety of tests"	-	-	63%
1990	Waggoner, Buist, & Donnell[a]	243	2 weeks -37 years	Questionnaire	56%	-	-
1991	Nelson et al.[b]	24	3;1–23;7	Local protocol	54%	-	8%
1992	Koch et al.[c]	2	24, 27	-	-	100%	-
1993	Waggoner & Buist[b]	163	-	Questionnaire	59%	-	-
1993	Schweitzer et al.	66	9 mos.–33	Denver Developmental Screener	14%	-	51%
1995	Sommer et al.	5	9 mos.–27	-	-	-	20%
1996	Hansen et al.	8	0;9–19;2	ITPA[g]	50% (3/6)	-	-
2000	Robertson et al.[d]	134	3–41 years	Apraxia Profile or questionnaire[h]	38%	-	-
2003	Webb et al.[e]	24	2;6–30	Apraxia Profile[h]	63%	-	-
2009	Hughes et al.[f]	26	-	-		-	77%[f]

[a] Diagnostic classifications for 24/243 participants by D. Nelson; 11 assessed in person and 13 by telephone.

[b] The same participants also included in Waggoner et al. (1990).

[c] The same siblings described in Lo et al. (1984).

[d] 21 assessed in person and 113 by questionnaire using retrospective data: 39% of the participants with Q188R/Q188R, 38% with Q188R/Other, 36% with Other/Other genotype had apraxia.

[e] The 21 participants assessed were the same participants as reported in Robertson et al. (2000).

[f] Authors indicated that of 26 subjects tested, 77% " … exhibited evidence of speech and language problems, predominantly verbal dyspraxia."

[g] Kirk, S. A., McCarthy, J. J., & Kirk, W. D. (1968). *The Illinois Test of Psycholinguistic Abilities*. Urbana: Univ. of Illinois Press.

[h] Hickman, L. A. (1997). *The Apraxia Profile: A descriptive assessment tool for children*. San Antonio: Communication Skill Builders.

Table 2

Competence, precision, and stability indices in the Competence, Precision, and Stability Analytics (CPSA) framework. Entries in the columns indicate the interim assignment of indices to the Motor Speech Disorder (MSD) classification categories in the Speech Disorders Classification System (Shriberg, Fourakis, et al., in press-a): AOS=Motor Speech Disorder-Apraxia of Speech, DYS=Motor Speech Disorder-Dysarthria, and NOS=Motor Speech Disorder-Not Otherwise Specified. Currently, there are no classification assignments for Competence indices.

Segmental	Competence		Precision		Stability	
	Title	MSD	Title	MSD	Title	MSD
1. Vowels	Percentage of Non-rhotic vowels correct		**Reduced Vowel Space**	NOS	**Less Stable Vowel Space**	AOS
	Percentage of Rhotic Vowels Correct		**Lengthened Vowels**	NOS	**Less Stable F1**	AOS
	Percentage of Phonemic Diphthongs Correct		**Distorted Rhotics**	NOS	**Less Stable F2**	AOS
	Percentage of Vowels Correct: CSS [a]		**Reduced Pairwise Vowel Duration Variability**	NOS	**Less Stable Vowel Duration**	AOS
	Percentage of Vowels Correct: AT[b]				**Less Stable Rhotic Distortions: F3-F2**	AOS
	Percentage of Non-rhotic Vowels Correct Revised				Less Stable Vowel Errors	AOS
	Percentage of Rhotic Vowels Correct Revised					
	Percentage of Phonemic Diphthongs Correct Revised					
	Percentage of Vowels Correct Revised: CSS					
	Percentage of Vowels Correct Revised: AT					
	Percentage of Relative Non-rhotic Vowel Distortions					
2. Consonants	Percentage of Consonants in Inventory		Nasal Emissions	DYS	Less Stable Consonant Errors	AOS
	Percentage of Consonants Correct: CSS		Reduced % Glides Correct	AOS	**Less Stable Sibilant Centroids**	AOS
	Percentage of Consonants Correct: AT		**Lowered Sibilant Centroids**	NOS		
	Percentage of Consonants Correct- Revised: CSS		**Lengthened Cluster Durations**	NOS		
	Percentage of Consonants Correct- Revised: AT					
	Percentage of Consonants Correct in Complex Words: MWT					
	Relative Omission Index					
	Relative Substitution Index					

Segmental	Competence		Precision		Stability	
	Title	**MSD**	**Title**	**MSD**	**Title**	**MSD**
	Relative Distortion Index					
3.Vowels and Consonants	Speech Disorders Classification System		Increased Percentage of Phoneme Distortions	NOS	Less Stable Whole Word Errors	AOS
	Intelligibility Index		**Syllable/Word Segregation: Increased % Between/Within-Word Pauses**	NOS	Less Stable % Phonemes Correct in Complex Words	AOS
	Percentage of Structurally Correct Words					
Suprasegmental			**Precision**		**Stability**	
Prosody						
4. Phrasing	Percentage Appropriate Phrasing		Increased Repetitions and Revisions	AOS	**Reduced Speech-Pause Duration Variability Ratio**	AOS
5. Rate	Percentage Appropriate Rate		**Slower Speaking Rate**	NOS	**Less Stable Speaking Rate**	AOS
			Slower Articulation Rate	NOS	**Less Stable Articulation Rate**	AOS
6. Stress	Percentage Appropriate Stress		**Reduced Lexical Stress**	NOS	**Less Stable Lexical Stress**	AOS
			Increased Lexical Stress	NOS	**Less Stable Emphatic Stress**	AOS
			Reduced Emphatic Stress	NOS	**Less Stable Sentential Stress**	AOS
			Reduced Sentential Stress	NOS		
Voice						
7. Loudness	Percentage Appropriate Loudness		**Reduced Vowels-Consonants Intensity Ratios**	NOS	**Less Stable Vowels-Consonants Intensity Ratios**	AOS
			Increased Vowels-Consonants Intensity Ratios	NOS		
8. Pitch	Percentage Appropriate Pitch		**Lowered Fundamental Frequency Mean**	DYS	**Less Stable Mean Fundamental Frequency**	AOS
			Raised Fundamental Frequency Mean	NOS		
			Lowered Fundamental Frequency Range	DYS		
			Increased Fundamental Frequency Range	NOS		

Segmental	Competence		Precision		Stability	
	Title	MSD	Title	MSD	Title	MSD
9. Laryngeal Quality	Percentage Appropriate Laryngeal Quality		Increased Jitter	DYS	**Less Stable Jitter**	AOS
			Increased Shimmer	DYS	**Less Stable Shimmer**	AOS
			Reduced Harmonics-to-Noise Ratio	DYS	**Less Stable Harmonics-to-Noise Ratio**	AOS
			Increased % Breathy Utterances	DYS		
			Increased % Rough Utterances	DYS		
			Increased % Strained Utterances	DYS		
			Increased % Break/Shift/Tremorous Utterances	DYS		
10. Resonance Quality	Percentage Appropriate Resonance Quality		Increased % Nasal Utterances	DYS	**Less Stable: Nasal: Lowered F1: /ɑ/**	AOS
			Nasal: Lowered F1:/ɑ/	DYS	**Nasopharyngeal: Less Stable F2: High Vowels**	AOS
			Increased % Nasopharyngeal Utterances	NOS		
			Nasopharyngeal: Lowered F2:High Vowels	NOS		

Note. Bold entries indicate candidate marker analysis completed using acoustic data reduction methods.

[a] See Table A1 for key to abbreviations.

[b] AT=Articulation Test, a generic term for alternative articulation tests, including the Goldman-Fristoe Test of Articulation (2nd ed.), Sounds-in-Words section.

Table 3

Descriptive and risk factor data for 32 participants with galactosemia (one participant with ataxic dysarthria excluded) divided into three groups: Group 1: GALT CAS (n =8), Group 2: GALT SD (n=9), and Group 3: GALT SE (n=15). Bolded entries indicate statistically significant between-group effect sizes. See text for descriptions of each group.

	Group 1: GALT CAS (n=8)	**Group 2: GALT SD (n=9)**	**Group 3: GALT SE (n=15)**	**Groups 1 and 2**	**Groups 1 and 3**	**Groups 2 and 3**
Categorical Variables	***n***	***n***	***n***	**Effect Size**	**Effect Size**	**Effect Size**
Demographic						
Sex (males)	6 (75%)	7 (77.8%)	8 (53.3%)	0.65 (−1.38, 1.50)	−0.46 (−1.72, 1.03)	−0.52 (−1.74, 0.90)
Galactosemia						
Genotype (Classic)[a]	3/3 (100%)	4/6 (66.7%)	6/13 (46.2%)	−1.23 (−2.16, 1.41)	−1.65 (−2.26, 0.96)	−0.42 (−1.80, 1.18)
Cognition						
Categorical[b] (<85)	6 (75%)	3 (33.3%)	7 (46.7%)	−0.86 (−2.18, 0.63)	−0.59 (−1.84, 0.86)	0.27 (−1.15, 1.58)
Oral Facial Structure (atypical)	2 (25%)	4 (44.4%)	5 (33.3%)	0.41 (−1.13, 1.84)	0.18 (−1.29, 1.46)	−0.23 (−1.59, 1.14)
Oral Facial Function (atypical)	8 (100%)	9 (100%)	13 (86.7%)	0.00 (−1.26, 1.31)	−0.75 (−1.38, 1.03)	−0.75 (−1.39, 0.93)

	Group 1: GALT CAS (n=8)		**Group 2: GALT SD (n=9)**		**Group 3: GALT SE (n=15)**		**Groups 1 and 2**	**Groups 1 and 3**	**Groups 2 and 3**
Continuous Variable	***M***	***SD***	***M***	***SD***	***M***	***SD***	**Effect Size**	**Effect Size**	**Effect Size**
Demographic									
Age (months)	111.4	50.3	81.2	21.3	115.8	27.5	0.76 (−0.23, 1.75)	−0.12 (−0.97, 0.74)	**−1.31 (−2.22, −0.41)**
Mother's Education (years)	14.5	1.7	14.8	1.6	16.3	2.3	−0.17 (−1.13, 0.78)	−0.82 (−1.71, 0.07)	−0.70 (−1.55, 0.15)
Father's Education (years)	13.4	2.4	14.6	2.2	16.0	2.6	−0.50 (−1.46, 0.47)	**−0.99 (−1.89, −0.08)**	−0.55 (−1.39, 0.29)
Galactosemia									
Days Until Diagnosis	8.25	3.11	8.33	4.0	8.60	8.87	−0.02 (−0.97, 0.93)	−0.05 (−0.90, 0.81)	−0.03 (−0.86, 0.79)

	Group 1: GALT CAS (n=8)		Group 2: GALT SD (n=9)		Group 3: GALT SE (n=15)		Groups 1 and 2	Groups 1 and 3	Groups 2 and 3
Continuous Variable	***M***	***SD***	***M***	***SD***	***M***	***SD***	**Effect Size**	**Effect Size**	**Effect Size**
Days on Milk	7.13	3.64	6.89	5.42	7.87	8.83	0.05 (−0.90, 1.00)	−0.09 (−0.95, 0.76)	−0.12 (−0.95, 0.71)
Cognition									
Continuous[b]	74.8	19.4	93.3	14.4	88.3	12.8	**−1.04 (−2.05, −0.02)**	−0.85 (−1.74, 0.04)	0.36 (−0.47, 1.19)
Nonword Repetition Task[c]	−6.4	4.4	−2.5	1.4	−1.8	1.4	**−1.17 (−2.20, −0.14)**	**−1.59 (−2.57, −0.62)**	−0.48 (−1.32, 0.35)
Syllable Repetition Task[c]	−4.9	4.1	−1.9	2.2	−1.7	2.0	−0.88 (−1.88, 0.12)	**−1.07 (−1.98, −0.16)**	−0.09 (−0.92, 0.73)
Language									
Comprehension[d]	75.1	18.1	86.0	18.5	80.9	14.6	−0.56 (−1.54, 0.41)	−0.35 (−1.22, 0.51)	0.31 (−0.53, 1.14)
Language									
Expression[d]	68.8	17.5	86.2	11.8	83.6	14.2	**−1.12 (−2.14, −0.10)**	**−0.93 (−1.83, −0.03)**	0.19 (−0.64, 1.02)
Speech[e]	49.3	21.9	64.2	16.5	78.2	19.7	−0.74 (−1.72, 0.25)	**−1.36 (−2.31, −0.42)**	−0.73 (−1.58, 0.12)
Maximum Phonation Time (seconds)	6.6	4.1	7.8	5.2	11.7	4.6	−0.24 (−1.20, 0.71)	**−1.11 (−2.02, −0.19)**	−0.78 (−1.64, 0.08)

[a] Classic Galactosemia: Q188R/Q188R: The complete genotype for participants in each of the three groups were unknown.

[b] Kaufman, A. S. & Kaufman, N. L. (2004). *Kaufman Brief Intelligence Test, Second Edition*. Circle Pines, MN: AGS Publishing.

[c] z-scores to adjust for age differences. Dollaghan, C., & Campbell, T. F. (1998). Nonword repetition and child language impairment. *Journal of Speech, Language, and Hearing Research, 41*, 1136–1146; Shriberg, L. D., Lohmeier, H. L., Campbell, T. F., Dollaghan, C. A., Green, J. R., & Moore, C.A. (2009). A Nonword Repetition Task for Speakers with Misarticulations: The Syllable Repetition Task (SRT). *Journal of Speech, Language, and Hearing Research, 52*, 1189–1212.

[d] Carrow-Woolfolk, E. (1995) *OWLS: Listening Comprehension Scale & Oral Expression Scale*. Circle Pines, MN: AGS Publishing.

[e] Goldman, R., & Fristoe, M. (2000). *Goldman-Fristoe Test of Articulation (2nd Edition)*. Circle Pines, MN: American Guidance Service.

Table 4

Descriptive statistics for the Percentage of Positive Markers obtained for the 57 precision and stability markers in the Competence, Precision, and Stability analytic framework. See text and relevant tables for description of participant groups, motor speech subtypes, sources, and markers.

Participant Group	Source		Motor Speech Disorder Classification							
			MSD-AOS		MSD-DYS		MSD-NOS		TOTAL MSD-AOS/NOS	
	ALL	CS	Mean	SD	Mean	SD	Mean	SD	Mean	SD
GALT CAS	X		51.5	12.6	17.4	20.0	69.4	14.4	59.4	9.9
		X	30.1	17.1	13.0	15.9	57.4	15.3	42.3	10.3
GALT SD	X		42.4	11.3	18.4	11.4	63.8	11.7	51.5	11.3
		X	27.8	10.6	17.3	10.6	48.7	14.1	36.7	10.0
GALT SE	X		41.2	16.8	19.0	11.3	60.1	10.7	49.6	16.8
		X	28.7	13.3	12.3	10.5	48.6	14.6	37.4	10.0
GALT SD/SE	X		41.7	14.7	18.8	11.1	61.5	10.9	50.3	10.3
		X	28.3	12.1	14.2	10.6	48.6	14.1	37.2	9.8
SD		X	30.7	12.2	20.8	19.7	38.8	13.2	34.0	7.2