RESEARCH PLAN

Specific Aims

Speech motor impairments negatively impact communication effectiveness in as many as 80% of children with cerebral palsy (**CP**).[1] Specifically, the speech of children with CP can be slow or difficult to understand.[2] This can have deleterious effects on their participation in activities resulting in social exclusion, bullying, isolation, and loneliness.[3,4] However, speech impairments are often not diagnosed until 4 years of age in this population because of overlapping speech characteristics of speech impairment and developmental immaturity.[5–7] This critically impacts speech-language pathologists' (**SLP**) ability to accurately make a diagnosis and prognosis of speech impairment at younger ages. Recent research from the laboratory of Dr. Katherine Hustad (Primary Mentor) has worked to address this gap, showing that speech performance at 2 years is highly predictive of later communication outcomes at 5 and 8 years in children with CP.[8–10] However, there is a paucity of research examining speech or pre-speech development in children with CP under 2 years of age.

My doctoral training provided a unique opportunity to study and develop foundational knowledge in typical and atypical developmental trajectories of infant vocal production as young as 6 months of age.[11–14] In the first two years of my postdoctoral training in Dr. Hustad's laboratory, I studied the longitudinal trajectory of speech development in children with CP starting at 4 years.[15,16] I have also conducted preliminary work examining early vocal production of infants at risk for CP.[17,18] Through this work, we observed delays in the emergence of syllables with well-formed consonantal characteristics using perceptual coding measures. This may demonstrate early evidence of dysarthria and reduced speech intelligibility; however, additional research is necessary to confirm. From these experiences, I am uniquely suited to develop my independent line of research examining vocal biomarkers of speech impairment in infants at risk for CP. A third year of postdoctoral training and mentorship is critical to 1) learn recently advanced acoustic methodologies under the advisement of my expert team of mentors in acoustic and statistical methods—Dr. Hustad (Primary Mentor) and consultants Drs. Bunton and Mahr—and 2) expand the long-term translational nature of my research.

My research to-date in this area has used perceptual, human listener judgment of infant vocal categories to study features predictive of speech impairment. This method is time and cost intensive—requiring hours of student training and coding across many recordings—and involves subjective judgments of individual vocalizations.[19] With the dawn of speech detection technologies and advancements in the automatic detection of child vocalizations using dense sampling of all-day recordings,[20,21] we have identified an untapped avenue of research to study acoustic variables of infant vocalizations in infants at risk for CP. The present study will provide preliminary data necessary to launch future projects to develop diagnostic tools and automated detection technologies using acoustic information.

The proposed 1-year project meets criteria for the <u>T1 classification</u> on the translational research continuum to move fundamental discovery into health applications. This project will use an existing longitudinal dataset of 23 infants at risk for CP. Perceptual and acoustic measures of infant vocalizations will be derived from laboratory recordings at 12 months. Speech outcomes will be classified from data collected around ~36 months.

Aim 1. Compare perceptual and acoustic measures across speech outcomes in CP. Four perceptual measures and three acoustic measures will be used to conduct pairwise comparisons across two outcome groups: Speech motor impairment (**SMI**) and no speech motor impairment (**NSMI**). We predict that the SMI group will have perceptual and acoustic values representative of developmentally less complex vocalizations compared to the NSMI group. These data will quantify the extent to which individual variables have the potential to be used as standalone predictors of speech outcomes in CP.

> <u>Aim 1 Specific Objective:</u> Test the hypothesis that individual perceptual and acoustic measures can predict speech impairment in young children with CP.

Aim 2. Identify acoustic and perceptual predictors of speech outcomes in CP. Perceptual and acoustic variables will be included in a set of statistical models to determine the extent to which a combination of acoustic and perceptual variables predict speech outcome groups using principal components analysis. We predict that the quantitative acoustic measures will explain a greater percentage of the variance than subjective perceptual measures. Research from this aim seeks to identify the best combination of measures to support the early prediction of speech impairment in CP.

> <u>Aim 2 Specific Objective</u>: Challenge the existing paradigm of perceptual, human listener vocal coding methods and determine the extent to which acoustic variables can predict speech motor impairment.

Results from this project will provide preliminary data for future grants aiming to identify vocal biomarkers of speech impairment. This preliminary project is required prior to the development of clinically translatable tools to improve early detection. My programmatic line of research will directly work to develop clinical diagnostic and intervention planning to support communication outcomes in children with CP.

Significance

The uncertainty of the prognosis for speech and communication development in children with CP under 24 months can lead to a delay of speech referrals and treatment to support alternative and augmentative communication (**AAC**).[22] The "wait-and-see" approach not only creates false hope for parents, but it can negatively impact long-term communication outcomes in children if early intervention is not initiated.[23] It is critical to expand the study of early vocal and speech development in children with CP to ages under 24 months to identify vocal biomarkers of speech impairment severity given the heterogeneous nature of this diagnosis. Identifying biomarkers for speech impairment is critical to encourage early referrals to SLP to introduce AAC at younger ages for better communication outcomes in this population.

My early postdoctoral work has revealed preliminary evidence of anomalous vocal patterns in infants with CP using perceptual methods of vocal coding.[17,18] Studies using these methods are well-documented as repeatedly demonstrating vocal developmental delays in infants with later-detected communication disorders;[24,25] however, perceptual coding of individual infant vocalizations is cost and time intensive.[19] Instrumental acoustic analysis has great potential to drive automated sampling of infant vocalizations. The proposed project will provide direct training to conduct instrumental acoustic analysis to support future development of automated detection tools using acoustic parameters. Instrumental acoustic analysis has yet to be used to study vocal production in CP and can directly support a more quantitative analysis of vocal production in this and other neurological clinical populations, compared to subjective perceptual coding. This work is critical to advance automated technologies that can detect a risk or presence of speech impairment. The proposed project will provide critical data to support future grant applications aiming to develop clinically translatable tools to improve the diagnosis and prognosis of speech impairments in young children with CP.

Innovation

With the dawn of new automated technologies built to analyze speech production, the importance of incorporating acoustic measures into our assessment of vocal biomarkers of impairment is at an all-time high.[21,26,27] The completion of this project and the knowledge gained from a multi-measure approach examining a mix of perceptual and acoustic methods will directly drive translational research to improve the early detection of speech impairment in CP. Specifically, validating acoustic analysis against perceptual measures can inform the future development of automated methods to detect vocal patterns associated with later speech impairment. Additionally, comparing perceptual and acoustic measures can provide quantitative validation for clinical tools utilizing listener-judgment or parent-report measures to screen for speech impairment in CP in clinical or home settings. Dr. Hustad's (Primary Mentor) line of research has examined speech developmental trajectories in children with CP as young as two years of age. <u>My doctoral training has provided unique training to study early vocal behaviors in infancy, prior to the onset of mature speech; thus, our programmatic lines of research are fundamentally different.</u> The planned work has direct clinical implications to support diagnostic and early intervention treatment planning for improving communication outcomes in this population.

Approach

The proposed project will accomplish two objectives: 1) test the hypothesis that individual perceptual and acoustic measures can predict speech impairment in young children with CP, and 2) challenge the existing paradigm of perceptual, human listener vocal coding methods and determine the extent to which acoustic variables predict speech motor impairment. We will use laboratory-based parent-infant (**P-I**) recordings of 23 infants around 12 months of age already available for immediate analysis. Speech outcomes will be classified based on the ~36-month data of the same children. The first objective will involve pairwise comparisons of four perceptual and three acoustic measures between the two outcome groups. The second objective will involve statistical modeling of all variables to identify the best combination of predictors for later outcomes.

Recording dataset. <u>Twenty-three infants at risk for CP</u> (M=12 mo, SD=1) will be included in the proposed project; data are already available and ready for analysis. Infants were recruited from local and regional medical centers through the UW-Madison Waisman Center to participate in a longitudinal project of the emergence and acquisition of language and speech in CP (R01DC009411, PI: Hustad). My Specific Aims have

not been previously studied with these data. CP risk status was based on medical records and birth history. High quality video recordings of naturalistic P-I interactions were previously collected during laboratory visits (M=12 mins). During these sessions, parents engaged with their infant naturalistically. The perceptual and acoustic measures will be derived from infant vocalizations produced during these recordings.

Speech outcome data. Speech outcomes around ~36 months of age are available for each of the 23 infants. Outcomes will be measured using clinical judgment by a research SLP in Dr. Hustad's laboratory (**Table 1**). Clinical judgment will involve 1) observation of the verbal motor production, and 2) calculation of speech intelligibility by orthographic transcription. Previous research has indicated that children with CP with at least 25% intelligibility between 24-36 months may be more likely to develop functional speech, thus, a 25% criterion will be implemented as part of the judgment for outcome classification.[28]

Table 1. Speech motor impairment (SMI) outcomes at 36 months

Category	*Description*
NSMI	No speech motor impairment observed as indicated by mandibular/labial facial control, lingual control, and oromotor integrity. Speech intelligibility is 25% or greater.
SMI	Speech motor impairment observed as indicated by reduced mandibular/labial facial control, lingual control, or oromotor integrity. Speech intelligibility is <25%.

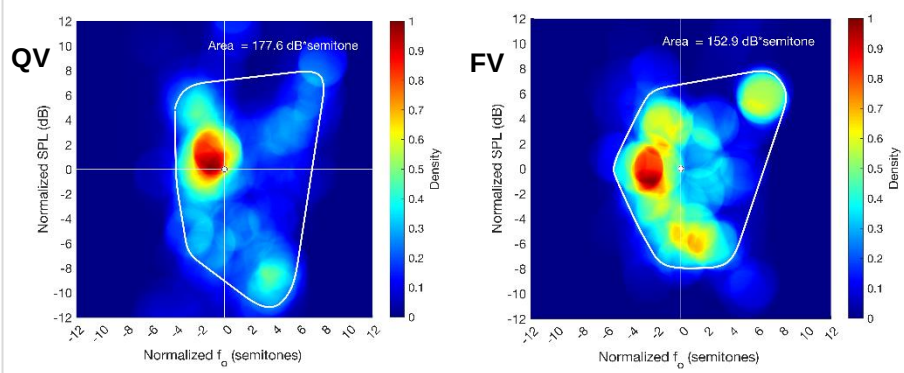
Perceptual measures. Four syllable categories will be used for subjective perceptual coding of vocalizations in each recording (**Table 2**). These categories are well-established in the literature on infant vocal development.[29] I am experienced in this method of coding and have one undergraduate student coder trained to conduct perceptual coding. We will use the Action Analysis and Coding Training (**AACT**)[30] software to categorize infant vocalizations using these categories. This program is already installed on our laboratory computers. The total count of each category will be calculated from each recording.

Table 2. Syllable categories by type and formedness

Vowel type	*CV type*
Quasivowel (QV): Vowel-like sounds with a quasi-resonant nucleus with a closed vocal tract at rest	**Marginal syllable (MB):** Consonant-like element with slow formant transition to vocalic nucleus
Full vowel (FV): Vowel sound with a fully resonant nucleus produced with an open vocal tract	**Canonical syllable (CB):** Consonantal element with adult-like formant transition to vocalic nucleus

Acoustic measures. Three well-validated, quantitative acoustic measures (described below) were selected based on recent work to provide a comprehensive profile of baseline pediatric acoustic modifications.[31] These measures will be obtained from the perceptually coded vocalizations. Vocalizations with overlapping caregiver speech will be excluded. I will write and run customized Matlab[32] scripts to perform acoustic analyses with supervised mentorship and support from Dr. Hustad and our acoustic consultant, Dr. Kate Bunton.

Fig1. Normalized vocal range profiles for QV and FV syllables of one infant



a. **Voice range density:** Voice range density will be examined as a metric for articulatory range of motion and loudness. A normalized voice range density plot (**VRDn**) will be created for each infant using the fundamental frequency (***f_o***) and sound pressure levels (**SPL**) of vocal intensity extracted from infant vocalizations. To quantify the VRD plot, we will find the area enclosed by a convex hull at a density level of 0.25 units. This area will be used as the quantitative measure of voice range density. A smaller voice range density corresponds to greater control over the production of well-formed syllables. This is evidenced by the smaller Area for FV than QV in the preliminary VRDn plots for one child (**Fig 1**). Broadly, we predict smaller Areas across all 4 perceptual categories for the NSMI group than SMI group.
b. **Periodicity:** Periodicity will be examined as a metric of voice quality using the cepstral peak prominence (**CPPS**), expressed in decibels (**dB**). A smoothed CPPS will be calculated by measuring the difference between the peak amplitude value and the smoothed spectrum at the same frequency. A high CPPS value indicates energy in the harmonic components and a clear voicing. Conversely, a low CPPS value would indicate the presence of a significant aperiodic spectral component, corresponding to a breathy or rough voice. Breathy and harsh voicing are characteristic features of dysarthria in older children and adults, thus, low CPPS values may be a potential biomarker of SMI in our sample.[33]

c. **Harmonicity:** Vocal harmonicity indicates how smooth or clear the voice signal sounds. We will measure spectral flatness of the voice signal using Weiner entropy. With Wiener entropy, we will calculate values of the power spectrum for different frequencies. Vocalizations with entropy values close to zero would correspond to less complex syllable types (QV and MB syllables), while more negative values would correspond to more complex syllable types (FV and CB syllables). Dysarthria is associated with reduced articulatory capacity to produce well-formed speech sounds; thus, we predict that the SMI group will demonstrate entropy values closer to zero (indicative of less complex types) than the NSMI group.

Aim 1: Compare perceptual and acoustic measures across speech outcomes in CP

Objective: We will test the hypothesis that individual perceptual and acoustic measures can predict speech impairment in young children with CP. We predict that the SMI group will show perceptual and acoustic values representative of developmentally less complex syllable types. Conversely, the NSMI group will demonstrate values representative of developmentally more complex syllable types across measures, potentially indicative of later positive speech outcomes.

Method & analysis plan. Reliability will be conducted for 20% of recordings for perceptual coding measures. The 23 included children will be grouped by speech outcome at 36 months: NSMI or SMI. Group-level differences will be compared within the four perceptual coding variables (QV, FV, MB, CB) and three acoustic variables (VRDn, CPPS, wiener entropy).We will conduct a series of pairwise t-tests comparing variables between each group, using familywise corrections for variables within each perceptual and acoustic category. These analyses will be used to determine whether any strongly significant differences emerge that have the potential to be used as standalone variables. These analyses will be conducted with guidance from the statistical consultant, Dr. Mahr (dedicated data scientist of Dr. Hustad's laboratory), and the mentorship team.

Potential problems & alternative strategies. Although we expect to see values representative of more developmentally complex vocalizations in the NSMI group, it is possible that we will see no significant differences between the two groups. If this occurs, we will use a multivariate approach to assess how the means and correlations among perceptual and acoustic variables differ between groups. Aims 1 and 2 are independent; however, these data can be used to support the interpretation of Aim 2 analyses.

Expected contributions of Aim 1. Highly significant variables identified in Aim 1 will be studied in longitudinal work to compare their developmental trajectories to typically developing controls across the first year of life.

Aim 2: Quantify the predictive nature of perceptual and acoustic measures on speech outcomes in CP

Objective: Challenge the existing paradigm of perceptual, human listener vocal coding methodologies and determine the extent to which acoustic variables predict speech outcomes in CP. We will model the best combination of predictors against outcome data. We predict that the quantitative acoustic measures will explain a higher percentage of variance than subjective perceptual measures.

Method & Analysis plan. We will run a set of statistical models to determine the presence of any highly significant correlations between the four perceptual and three acoustic predictor variables. We will use principal components analysis to combine the information from the correlated variables to conduct a cluster analysis of composite perceptual or acoustic predictors. After reducing these data as appropriate, we will fit a series of logistic regression models to evaluate the strongest combination of predictors among the perceptual and acoustic measures, to determine whether they jointly predict outcomes. These analyses will be conducted with guidance from Dr. Mahr and the mentorship team.

Potential problems & alternative strategies. Should any problems arise with the Aim 2 analysis plan, we will employ a stepwise regression approach to determine which variables best predict outcomes. If too many highly correlated perceptual or acoustic measures are found, alternate statistical methods will be used, such as a random forest approach[34] to study the best combination of predictors. Aims 1 and 2 are independent of one another, thus, unexpected findings in Aim 1 will not directly impact the analysis of Aim 2.

Expected contributions of Aim 2. Findings from Aim 2 will provide the necessary preliminary data to drive future research directions developing diagnostic tools using the best combination of measures identified here.

Summary and Future Directions. The data and training obtained from the proposed project will provide preliminary data to support future grant applications to advance the clinical and translational nature of my research examining vocal biomarkers of speech impairment in CP. Specifically, this research will contribute to my long-term goal of developing clinically translatable diagnostic tools to detect speech motor impairment in CP as an independent investigator at a research-intensive university. The proposed work has direct implications to support SLP treatment planning and long-term communication outcomes in children with CP.

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