DECREASED BETA DESYNCHRONIZATION IN BROCA'S AREA DURING PSEUDOWORD REPETITION IN CHILDREN WITH CHILDHOOD APRAXIA OF SPEECH.

by

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"And whatever you do, whether in word or deed, do it all for the Glory of God." ~ 1st Corinthians 10:31

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Decreased Beta Desynchronization in Broca's Area During Pseudoword Repetition in Children with Childhood Apraxia of Speech.

Childhood apraxia of speech (CAS) is a "neurological speech sound disorder in which the precision and consistency of speech movements are impaired" (ASHA, 2007). These speech errors occur in the absence of neuromuscular deficits such as abnormal reflexes or muscle tone (ASHA, 2007). Prevailing theories state that inaccurate speech production in children with CAS results from weak motor planning skills while sound representations remain intact (Bohland & Guenther, 2006; Guenther, 2006; Zuk et al., 2018).

Procedures for differentially diagnosing childhood apraxia of speech and other speech sound disorders vary by clinician and research group but often include the measurements of the inconsistency of phonemes/words/phrases (Iuzzini & Forrest, 2010; Iuzzini-Seigel, Hogan, & Green, 2017), as well as the rating of features such as vowel distortions, difficulty with coarticulatory transitions between sounds and words, syllable segregation, and disrupted prosody among others (ASHA, 2007; Iuzzini-Seigel et al., 2015; Iuzzini-Seigel & Murray, 2017; Shriberg, Potter, & Strand, 2011). It is difficult, however, to identify deficits in motor planning by behavioral assessment alone because speech production is influenced by auditory/somatosensory representations as well as by motor planning and execution. Thus, signs associated with CAS tend not to be pathognomonic and may be common to other speech sound disorders as well (ASHA, 2007). Further, diagnosing CAS can become more difficult as the disorder progresses with age and/or as the child receives intervention.

Typically, a child with CAS may be in speech therapy for nine years or more (Aram et al., 1984; Hall, Hardy, & Lavelle, 1990). There is evidence to suggest that age-related symptom variation may add to the discrepancy of prevalence rates (Velleman & Strand, 1994). Further, evidence suggests that the diagnosis of CAS may be recategorized with age, as articulation may improve with speech therapy (Lewis et al., 2004). While documentation of improved articulation exists as a result of intervention, many children exhibit ongoing CAS features, regardless of speech therapy. For example, one case study described a child with CAS who exhibited improved articulation of target phonemes over five years (from age 11 to 16) while errors persisted for novel articulatory patterns (Stackhouse & Snowling, 1992). In this regard, imaging studies of individuals with CAS may shed some light on the specific nature of their challenges. In addition to elucidating the neural substrates that are responsible for CAS, functional imaging studies offer insight into speech movement planning, the proposed core deficit of CAS.

Functional Imaging Studies of CAS

Studies of the KE family have greatly informed our knowledge about the neuroanatomy of CAS. Approximately half of the members of this family have severe CAS associated with mutation of the *FOXP2* gene (Lai et al., 2001). Two affected family members exhibited reduced blood flow in the supplementary motor area, the pre-supplementary motor area, and the cingulate cortex at the level of the face and mouth representations compared to typical speakers during word and pseudoword repetition (Vargha-Khadem et al., 1998). Affected family members also exhibited overactivation in premotor cortex and Broca's area, which the authors suggested may be compensatory. Later, Liégeois et al. (2003) examined five affected and five unaffected members of the

KE family while they performed a word-repetition task during functional magnetic resonance imaging (fMRI). In this study, the affected individuals exhibited significant hypoactivation of the left inferior frontal gyrus, a region associated with phonological and semantic verbal fluency (Costafreda et al., 2006). In addition, there was hyperactivation in the left anterior insula, which is involved in sensory and affective processing. It is unclear why the positron emission tomography and functional magnetic resonance imaging findings are contradictory, but they may reflect characteristics of the specific individuals involved in each study. It is important to note that the KE family exhibits complex presentations of CAS with comorbid deficits; beyond impaired articulation of speech sounds and orofacial dyspraxia, many affected members of the KE family also present with literacy and language impairments (Vargha-Khadem et al., 1995). The presence of these comorbidities severely limits the ability to draw clear relationships between candidate-apraxia genes and the corresponding phenotypes.

In an event-related electroencephalogram (EEG) study, Preston et al. (2014) examined eight school-aged children with CAS, comparing them to 13 typically developing control participants. Participants repeated simple (monosyllabic) or complex (two-syllable or three-syllable) words. Peak amplitude of brain activation in the 188 ms window before vocal output was lower in the children with CAS in posterior left and right hemispheres than in the typical controls. This reduced output could be the result of poor connectivity within the language network. Individuals with CAS exhibited structural differences in the arcuate fasciculus, a white-matter tract linking Wernicke's and Broca's areas, compared to typically developing controls (Liègeois et al., 2019). The arcuate fasciculus, which links auditory representations to speech articulation and transforms

phonological representations to motor programs, maintained lower fractional anisotropy (a measure of tract integrity) in the participants with CAS (Liègeois et al., 2019). Participants also performed a word-repetition task, during which the CAS group exhibited reduced activation in the left temporoparietal cortex. Compared to controls, activation was attenuated in the superior temporal gyrus, planum temporale, and supramarginal gyrus, areas responsible for phonological and articulatory processing (Liègeois et al., 2019). Taken together, the prior functional imaging studies of individuals with CAS suggest altered activation in areas of the brain responsible for translating phonological representations into articulatory programs or for initiating and inhibiting spoken responses.

Neural Measures of Motor Planning

Notably, although motor planning deficits are core to the diagnosis of CAS, prior imaging studies did not examine motor planning per se. Functional magnetic resonance imaging and positron emission tomography indirectly assess brain function by tracking blood flow while techniques such as electroencephalogram and magnetoencephalography (MEG) measure electrical and magnetic potential changes directly tied to neural activity. One electroencephalogram study found no between-group differences in motor or motor planning regions of the brain (Preston et al., 2012). However, MEG is capable of more defined spatial precision and is likely a better technique for probing the oscillations during motor planning in specific regions of interest in CAS.

Prior research suggests that oscillations in the beta frequency band (~13-35 Hz) are associated with different stages of voluntary movement (Jasper & Penfield, 1949). Power in the beta range decreases in amplitude 1-2 seconds before movement begins and

then increases, peaking after movement has been completed before returning to baseline (Little et al., 2019). The beta-power decrease before movement begins is referred to as event-related desynchronization (ERD). Event-related desynchronization in the beta-power range is typically observed during the motor planning stages of speech (Gehrig et al., 2012). In typical speakers, it occurs mainly in the left temporal cortex, specifically in the auditory, motor, sylvian parietotemporal region and the articulatory region of motor cortex. Event-related desynchronization in the motor cortex prior to speech initiation has been proposed to indicate a stage of movement preparation during which the program for moving the articulators is sent to the motor cortex and to the sensory regions responsible for auditory and somatosensory monitoring of the output (Mersov et al., 2016).

In typically developing individuals, pre-movement is often identified by specific oscillatory fluctuations and the suppression of beta power (Gehrig et al., 2012). This suppression leads to event-related desynchronization. Pre-movement suppression of beta power is influenced by a variety of factors related to motor preparation and motor planning, such as task difficulty. For example, tasks involving more complex movements or higher speeds are associated with greater suppression of beta power and thus a larger event-related desynchronization (Pfurtscheller et al., 2003). For individuals with disorders that impact speech production, event-related desynchronization may be abnormal. For example, individuals with Parkinson's disease exhibit significantly weaker event-related desynchronization compared to typically developing controls during a nonspeech movement task (Heinrichs-Graham et al., 2014). This may be due to significant difficulty in suppressing cortical beta synchronization. Some children with CAS exhibit higher levels of baseline power compared to controls, suggesting that those

with CAS may also exhibit deficits in event-related desynchronization, though likely by a different mechanism than in Parkinson's (Turner et al., 2013; van Rhijn et al., 2018; Vargha-Khadem et al., 1998). Therefore, we hypothesized that children with CAS will exhibit reduced event-related desynchronization in pre-motor planning areas compared to their typically developing peers.

The Current Study

Considering these previous studies and because of its excellent spatial and temporal resolution, MEG is optimal for investigating whether motor planning is impaired in individuals with CAS relative to typical controls. The current preliminary study was designed to evaluate the hypothesis that, compared to typical controls, children with CAS will exhibit (1) weaker beta event-related desynchronization in brain areas related to motor speech planning during a pseudoword repetition task and (2) no differences in event-related desynchronization or other aspects of evoked responses in brain areas related to auditory perception of speech during pseudoword repetition or somatosensory processing of tactile stimulation.

Methods

Participants

Participants included eight children with CAS and seven age-matched typically developing (TD) controls. Potential participants with a history of diagnosis and treatment for CAS were referred to the study by a clinician with expertise in pediatric speech sound disorders. Inclusionary testing was performed to confirm a diagnosis of CAS or typical development. All participants were administered the Goldman-Fristoe Test of Articulation, 2nd Ed. (*GFTA-2*; Goldman & Fristoe, 2000), the Clinical Evaluation of

Language Fundamentals, 4th Ed. (*CELF-4*; Semel et al., 2003), the Woodcock Reading Mastery Test, 3rd Ed. (*WRMT-3*; Woodcock, 2011), and the Reynolds Intellectual Assessment Scales, 2nd Ed. (*RIAS-2*; Reynolds & Kamphaus, 2012).

Participants in the typically developing group were required to have scores on all assessments within the normal range (i.e., standard scores of 85 or higher). Those in the CAS group were required to have a *GFTA-2* percentile score of 16 or below, in addition to a standard score of 85 or higher on the *Clinical Evaluation of Language-4th Edition* (CELF-4; Semel et al., 2003) to document language within the normal range. Two speech-language pathologists experienced in pediatric motor speech disorders blind-rated each child's speech production on the *GFTA-2*, confirming CAS diagnosis by documenting that participants with CAS exhibited at least five of the CAS features from Iuzzini-Seigel et al. (2015). A two-way mixed intraclass correlation for single measures and consistency over all signs was used to assess inter-judge coding reliability on signs of CAS for confirmation of diagnosis. The intraclass correlation value was 0.901 (excellent), $p < 0.0005$. Mean intraclass correlation for individual signs was 0.856, all $p < 0.05$. Participant characteristics are described in Table 1. Written informed consent for all participants was obtained prior to enrollment, following the guidelines of the University of Nebraska Medical Center Institutional Review Board.

Table 1. Participant characteristics. Data are reported as mean ± standard deviation. * $p < 0.05$

	TD (n = 7)	CAS (n = 8)	*F* value
Age (Years)	9.33 ± 2.88	8.62 ± 3.34	0.41
Nonverbal IQ (*RIAS*[1])	125.00 ± 15.07	112.12 ± 7.80	4.65
Word reading ***(****WRMT*[2]***)***	109.80 ± 12.21	99.71 ± 12.71	1.16
Language (*CELF*[3])	118.80 ± 11.54	102.38 ± 21.21	1.10
Articulation (*GFTA*[4])	104.00 ± 6.50	68.00 ± 16.28	**26.51***

[1]RIAS: Reynolds Intellectual Assessment, 2nd Edition.
[2]WRMT: Woodcock Reading Mastery Test, 3rd Edition.
[3]CELF: Clinical Evaluation of Language Fundamentals, 4th Edition.
[4]GFTA: Goldman-Fristoe Test of Articulation, 2nd Edition.

Experimental Paradigm and MEG Data Acquisition

All recordings were conducted in a one-layer magnetically shielded room with active shielding engaged for advanced environmental noise compensation (acquisition bandwidth: 0.1 to 330 Hz; 1 kHz sampling rate) using an Elekta Neuromag system (Helsinki, Finland) with 306 MEG sensors, including 204 planar gradiometers and 102 magnetometers. Each participant sat in the MEG chair with a dual-plane accelerometer chip attached just below the lower lip (to assist with identification of the onset of speech movement, as described below). A computer screen was positioned in front of the participant, and a fixation point (purple asterisk) was presented in the center of the screen during a 500-ms 'get-ready-to-listen' period. The participant was instructed to remain still and fixate on the asterisk while an audio recording of a pseudoword stimulus was presented. At stimulus offset, the asterisk changed to green, cueing the participant to verbally repeat the stimulus. A total of 160 trials, with a variable inter-stimulus interval of 1.8-2.0 s, was presented to each participant. Throughout both the pseudoword repetition and sensory stimulation tasks, the accelerometer chip sampled continuously.

Pseudoword Repetition Task

A set of 160 monosyllabic consonant-vowel-consonant pseudowords was created (see, Appendix A for a sample list). The pseudowords were created to adhere to the phonological constraints of English and were recorded by a male native speaker of Midwestern English in a sound-proof booth. On average, stimuli fell in the 50th percentile on common phonological metrics for similarity to other sound sequences in English such as phonological neighborhood density and phonotactic probability, based on data collected on English-speaking children and adults (Nusbaum et al., 1984; Storkel & Hoover, 2010). The distribution of phonemes in each position (initial, medial, and final) was balanced, and stimulus length was standardized at 711 ms (Munson et al., 2003).

Stimulation Tasks

Tactile stimulation was applied to the lip or tongue using a small, custom-made vibrotactile device consisting of a flexible latex pouch connected by a rubber tube to a pneumatic controller, similar to that of Briggs et al. (2004). The controller filled and deflated the pouch with air in a prespecified rhythm (125 repetitions in 6 minutes), pulsing against the lip or tongue while MEG data were being collected. For lip stimulation, the pouch was taped to each participant's lower lip margin. For tongue stimulation, participants held a small piece of foam between their top and bottom teeth, which allowed the pouch to rest on the tongue.

MEG Processing and Analysis

Brain activation measurements were collected using an Elekta Neuromag Triux system which was equipped with a whole brain sensor array comprising 102

magnetometers and 204 planar gradiometers (306 total magnetic sensors). MEG recordings were collected with a sampling rate of 1,000 Hz and were filtered within .03-330 Hz. The head position was monitored throughout the duration of recordings, using 5 indicator coils placed on the head. Raw data were then preprocessed using the Maxfilter software (Elekta Neuromag, Stockholm) to control for excess movement and to reduce noise through spatiotemporal filters (Taulu et al., 2005). We utilized default parameters (harmonic expansion origin in head frame = [0 0 40] mm; expansion limit for internal multipole base = 8; expansion limit for external multipole base = 3; bad channels automatically excluded from harmonic expansions = 7 standard deviations (s.d.) above average; temporal correlation limit = 0.98; buffer length = 10 s). Then, heartbeat and eye blink artifacts were identified and removed, using PCA within the Brainstorm software (Tadel et al., 2011). Next, every trial was baseline-corrected to remove the mean (-200ms to 0ms) from each trial. Trials with excessive movement (peak-to-peak value greater than 10,000 fT) were labeled and removed from the database.

For the pseudoword task (160 total trials), there was no significant difference between the number of usable trials for CAS (150.13 ± 7.45) and usable trials for typically developing (151.71 ± 9.76; t (13) = -.36, p = .737). For the lip stimulation task (140 total trials), there was also no significant difference between the number of usable trials for lip stimulation for CAS (126 ± 1.51) vs. typically developing (126.57 ± 1.813; t (13) = -.620, p = .547). Finally, for the tongue stimulation task (140 total trials), there was no significant difference between the number of usable trials for tongue stimulation for CAS (115.88 ± 20.28) vs. typically developing (128.29 ± 3.95; t (13) = -1.55, p = .144).

The time series were then temporally smoothed with a 60 Hz low pass filter. For each trial, the MEG data were mapped on the cortical mantle derived from Freesurfer automatic segmentation (Fischl et al., 2004). This was accomplished by first calculating a head model using an overlapping spheres model (Huang et al., 1999). To account for the smaller head size in our participants compared to the standard adult template and improve the accuracy of source localization, we co-registered each participant's MEG data to a T1 MRI scan from a child in this age range. As we did not have MRI data from any child in the current study, we utilized one collected for a prior MEG study (Centanni et al., 2018). Next, an inverse model was computed using a dynamic statistical parametric mapping approach (dSPM; Dale et al., 2000). Finally, we extracted the time-series from multiple cortical regions of interest, which were bilateral transverse temporal (A1), superior temporal gyrus (STG), primary somatosensory cortex (S1), primary motor cortex (M1), and pars triangularis (Broca's area), from the Destrieux-Killiany atlas (Desikan et al., 2006).

For data collected during pseudoword repetition, epochs were 2200 ms duration (-1.8 to .8 s), with 0 ms defined as movement onset. For the auditory analyses, epochs were 700 ms duration (-200 to 500 ms), with 0ms defined as the sound onset. A window including 50-100 ms post-stimulus onset was chosen as the processing window for the CVC stimuli in bilateral transverse temporal (Centanni et al., 2018; Travis et al., 2013). Movement onset during speech production was defined by visual inspection of the accelerometer channels by a trained technician. Within each epoch, a marker was inserted at the earliest point where movement was visible in either channel. Artifact-free epochs were transformed into the time-frequency domain using complex demodulation

(resolution: 2.0 Hz, 25 ms; Hoechstetter et al., 2004), and the resulting spectral power estimations per region of interest were averaged over trials to generate time-frequency plots of mean spectral density. For data collected during stimulation, a 40 Hz lowpass filter was applied following pre-processing to eliminate all electrical interference from the stimulation device. Epochs were 2000 ms duration (-200 to 1800 ms), with 0 ms defined as stimulation onset.

Task-related power fluctuations were characterized as event-related desynchronizations (ERD; power decreases) and synchronizations (ERS; power increases). Event-related desynchronization was calculated as the ratio of the power change in the time window of 200ms baseline activity before each trial using the equation

$$\mathrm{ERD}_j = \frac{Aj-R}{R} \text{ X } 100\%,$$

where A_j is the mean power in the time window of interest for the *j-th* trial. *R* is the baseline power in the beta (13-30 Hz) or alpha (8-12 Hz) range calculated from the 200 ms window prior to the trial onset (Pfurtscheller et al., 2003). Time windows of interest were selected as follows: -500-0 ms before movement onset (pseudoword repetition task), 0-500 ms after movement onset (pseudoword repetition task), and 100-300 ms after stimulus presentation (for auditory perception of pseudowords and somatosensory stimulation). A greater power decrease indicates a more negative voltage fluctuation; thus, a stronger event-related desynchronization will appear further away from zero on a graph (Figure 1). The terms 'stronger' and 'weaker' will be used to describe the nature of the event-related desynchronization such that a 'stronger' event-related desynchronization has a larger negative amplitude.

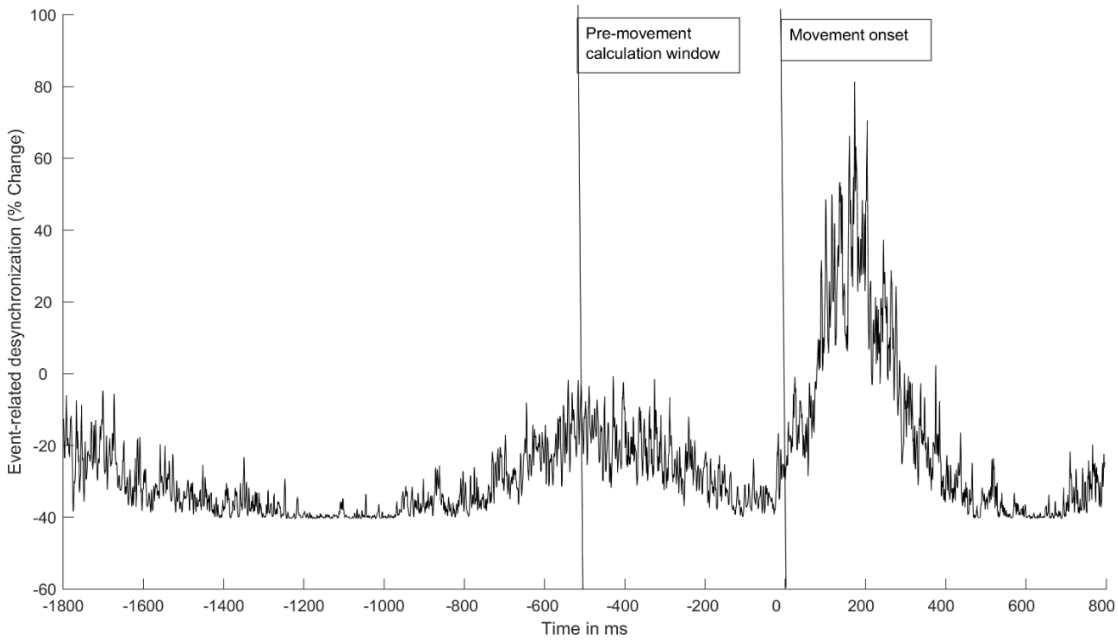

Figure 1. *Graphical illustration of event-related synchronization (ERS) and desynchronization (ERD).* When preparing for movement, beta oscillations will desynchronize (show a negative voltage fluctuation) and return to baseline following a brief period of synchronization. In the current study, a more negative event-related desynchronization fluctuation is described as 'stronger', a less negative fluctuation as 'weaker'.

Statistical Analyses

Multivariate analyses of variance (MANOVAs) were used to document appropriate between-groups differences in behavioral assessment scores which are reported as mean ± standard deviation. In primary auditory areas, a 2x2 ANOVA was used to evaluate within-subject (left vs. right hemisphere) and between-subjects (typically developing vs. CAS) differences in the evoked neural response amplitude and latency in bilateral transverse temporal and alpha event-related desynchronization in superior temporal gyrus in response to pseudoword stimuli. Mixed ANOVAs were used to evaluate within-subject (left vs. right hemisphere) and between-subjects (typically developing vs. CAS) differences in event-related desynchronization for the pseudoword repetition and stimulation tasks. Neural imaging results are reported as mean ± standard

error of the mean. Post hoc *t*-tests were used to follow up significant main effects and interactions and were two-tailed unless otherwise noted.

Due to the limited number of usable scans in children with CAS alone (N = 5), two participants with comorbid specific language impairment (SLI) (CELF-4 < 85) were included to increase our statistical power for group comparisons. In order to examine whether this variation in language ability impacted our results, specifically with reference to the pseudoword repetition task, we also utilized Pearson's r to evaluate any correlations between CELF-4 scores and significant group differences in event-related desynchronization/synchronization.

Results

Participant Characteristics and Performance on Pseudoword Repetition

A MANOVA revealed no significant between-group differences in age, nonverbal IQ, reading, or language scores, demonstrating that the CAS group was matched to the control group on these parameters (shown in Table 1). There was a trend in the difference between non-verbal IQ (*RIAS*) such that scores in the typically developing group were higher (125.00 ± 15.07) than in the CAS group (112.12 ± 7.80; F (1,11) = 4.65, p =.059, η^2_p = .34), however, it is important to note that both groups' scores were well within the average range on this measure. As expected, the CAS group's mean *GFTA-2* score (68.0 ± 6.15) was significantly lower than that of the typically developing group (104.0 ± 2.65; F (1,11) = 26.51, p =.001).

To demonstrate that all participants could complete the speech production task, we analyzed responses during the pseudoword repetition task. Unfortunately, data from two children with CAS and four typically developing children were unavailable as they

were not properly recorded and are therefore not reported. Typically developing children performed nominally better (89 ± 8%) than children with CAS (77 ± 1.19%). While this difference was not significant (t (7) = 1.55, p = 0.17*)*, this result should be interpreted with caution given the number of available participants for this analysis.

Intact Speech Sound Processing in CAS

To investigate basic auditory processing in the transverse temporal gyrus (A1), the maximum amplitude value within 50-100 ms post-stimulus onset (Centanni et al., 2018; Poeppel, 2003) was extracted from each participant's average peristimulus time histogram (PSTH). We then conducted a 2x2 ANOVA (hemisphere: left x right, group: typically developing x CAS) for both peak amplitude and latency. With regard to amplitude, there was no main effect of hemisphere (F (1,13) = .55, p = .47), or group (F (1,13) = .33, p = .578; Figure 2A). While visual inspection of the peristimulus time histograms (Figure 2A) suggests a potential left hemisphere group difference in this window, the variance across participants was quite high (standard error of the mean (SEM) values within the analysis window: typically developing = .04, CAS = .036). With regard to latency, there was a trend in the main effect of hemisphere (F *(*1,13) = 3.78, p = .074) and no main effect of group (F (1,13) = .857, p = .857; Figure 2B).

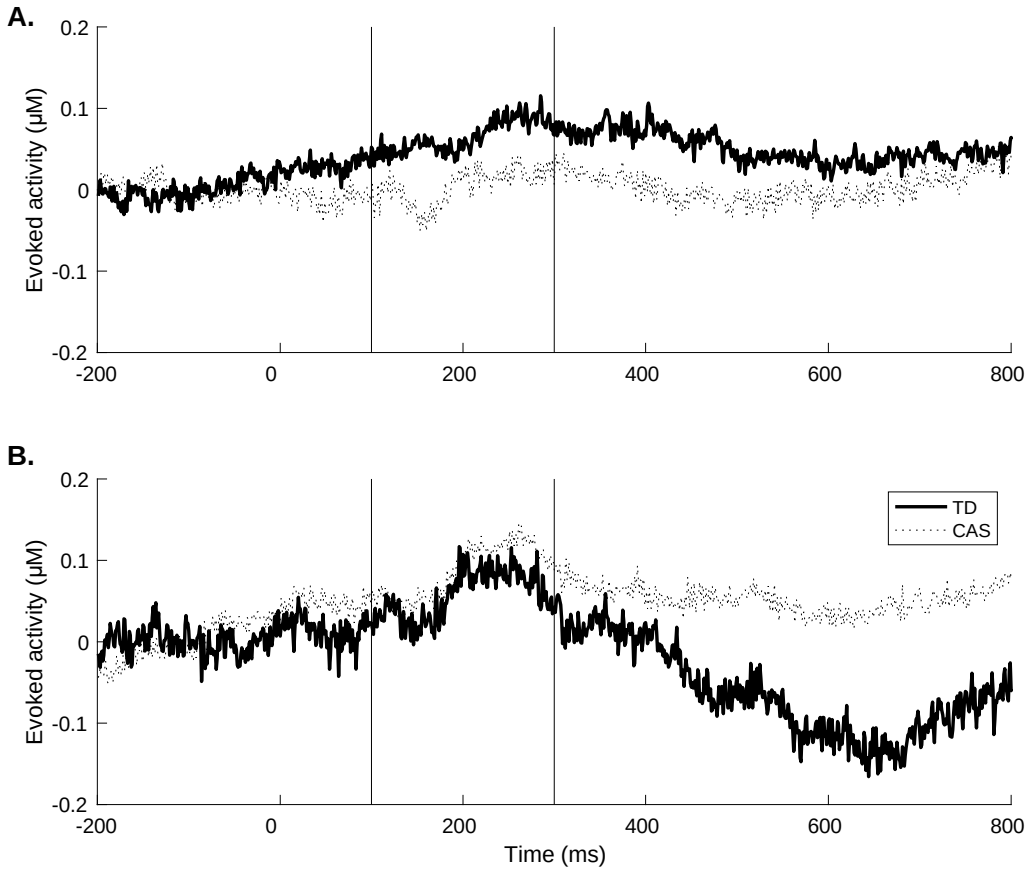

Figure 2. *Auditory Processing of pseudowords intact in children with CAS*. There was no significant group difference for peak amplitude or the latency of the peak amplitude in the initial sensory response either left (**A**) or right (**B**) primary auditory cortex. The analysis window (100-300 ms post-stimulus onset) is marked by vertical lines.

To examine auditory processing of speech sounds in particular, we also analyzed the response to speech sounds in bilateral superior temporal gyrus (STG), which is a critical region involved in phonemic processing during higher-order speech perception (Mesgarani, Chueng, Johnson, & Chang, 2014). As the alpha band is representative of auditory processing (Fujioka & Ross, 2008), we quantified alpha event-related desynchronization in this region. To account for longer delays in superior temporal gyrus compared to transverse temporal gyrus, we analyzed event-related desynchronization from 100 ms through 300 ms after stimulus onset (Centanni et al., 2018; Poeppel, 2003). We analyzed alpha event-related desynchronization during the pseudoword repetition

task using a 2x2 ANOVA (hemisphere: left x right, group: typically developing x CAS). There were no main effects of hemisphere (F (1,13) = 1.18, p = .298) or group (F (1,13) = 1.09, p = .316).

Reduced Beta Event-related Desynchronization in Left Hemisphere Broca's Area During Pseudoword Repetition

To determine whether there were group differences in beta event-related desynchronization related to premotor planning, we first analyzed the pseudoword repetition task using a 2x2 ANOVA for event-related desynchronization in the Broca's Area region of interest (hemisphere: left x right, group: typically developing x CAS). There was no main effect of hemisphere (F (1,13) = .09, p = .764) and a marginally significant main effect of group (F (1,13) = 4.67, p = .05). There was no interaction between hemisphere and group (F (1,13) = .49, p = .497). Post hoc t-tests to probe the marginally significant main effect of group revealed that the left hemisphere event-related desynchronization was significantly weaker in the CAS group (-0.81 ± 24.83) compared to the typically developing group (-50.22 ± 8.45; one-tailed, unpaired t-test: t (13) = 1.90, p = .039; Figure 3). There was no between-group difference in right hemisphere event-related desynchronization (one-tailed, unpaired t-test: t (13) = .66, p = .258).

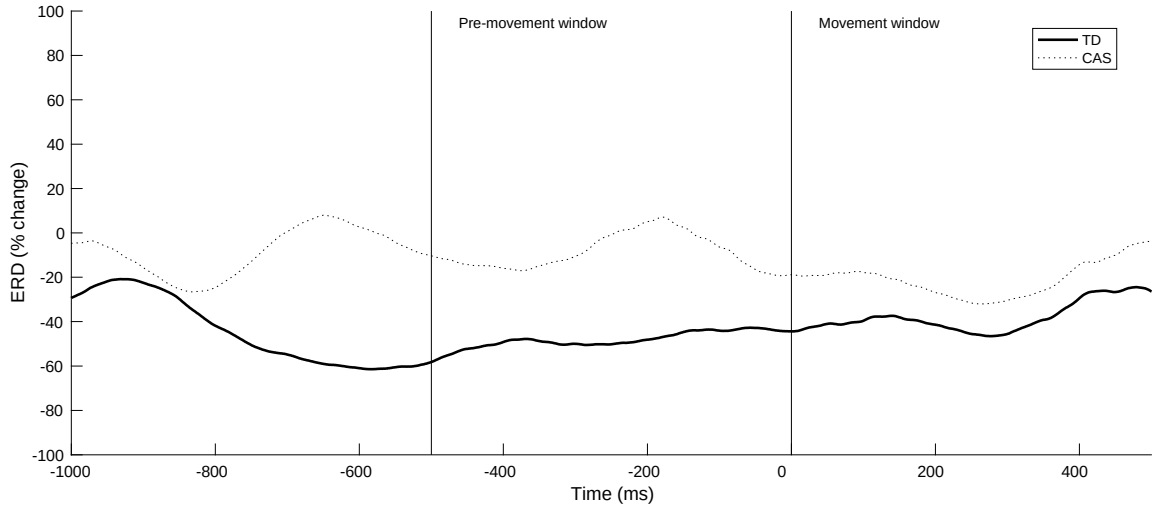

Figure 3. *Reduced beta ERD in left Broca's area in CAS during pseudoword repetition*. During pseudoword repetition, weaker ERD was observed for CAS in the left hemisphere, compared to typically developing (TD). This difference was observed in the pre-movement planning window (-500 to 0 ms, where 0 ms indicates movement onset) but not in the 500 ms window following the initiation of speech.

To determine whether the group difference in Broca's area persists through the movement itself, we also evaluated the 500 ms window following the initiation of movement. There was a significant main effect of hemisphere ($F(1, 13) = 5.06$, $p = .043$), such that the left hemisphere exhibited significantly more event-related desynchronization (-38.10 ± 8.09) than the right hemisphere (30.5 ± 28.63). However, there was no main effect of group ($F(1, 13) = 1.27$, $p = .279$) and no interaction between hemisphere and group ($F(1, 13) = .31$, $p = .587$).

Intact Event-related Desynchronization in Somatosensory and Motor Areas During Pseudoword Repetition

To determine whether the group differences during pseudoword repetition in Broca's Area extended to primary somatosensory cortex (S1), we used a 2x2 ANOVA (hemisphere: left x right, group: typically developing x CAS) to compare event-related desynchronization in the primary somatosensory cortex region of interest (Figure 4A). In

the preparatory time window, there were no main effects of hemisphere (F (1,13) = 1.52, p = .239) or group (F (1,13) = .08, p = .777). In the movement onset time window, there were also no main effects of hemisphere (F (1,13) = .92, p = .355) or group (F (1,13) = .2, p = .661).

To determine whether there were group differences in controlling the movement itself, we also analyzed beta event-related desynchronization in bilateral primary motor cortex (M1) during the preparatory phase as well as during the movement itself (Figure 4B). In the preparatory window, there were no main effects of hemisphere (F (1,13) = .16, p = .7) or group (F (1,13) = 1.11, p = .311). In the movement onset time window, there were also no main effects of hemisphere (F (1,13) = .84, p = .377) or group (F (1,13) = .35, p = .565).

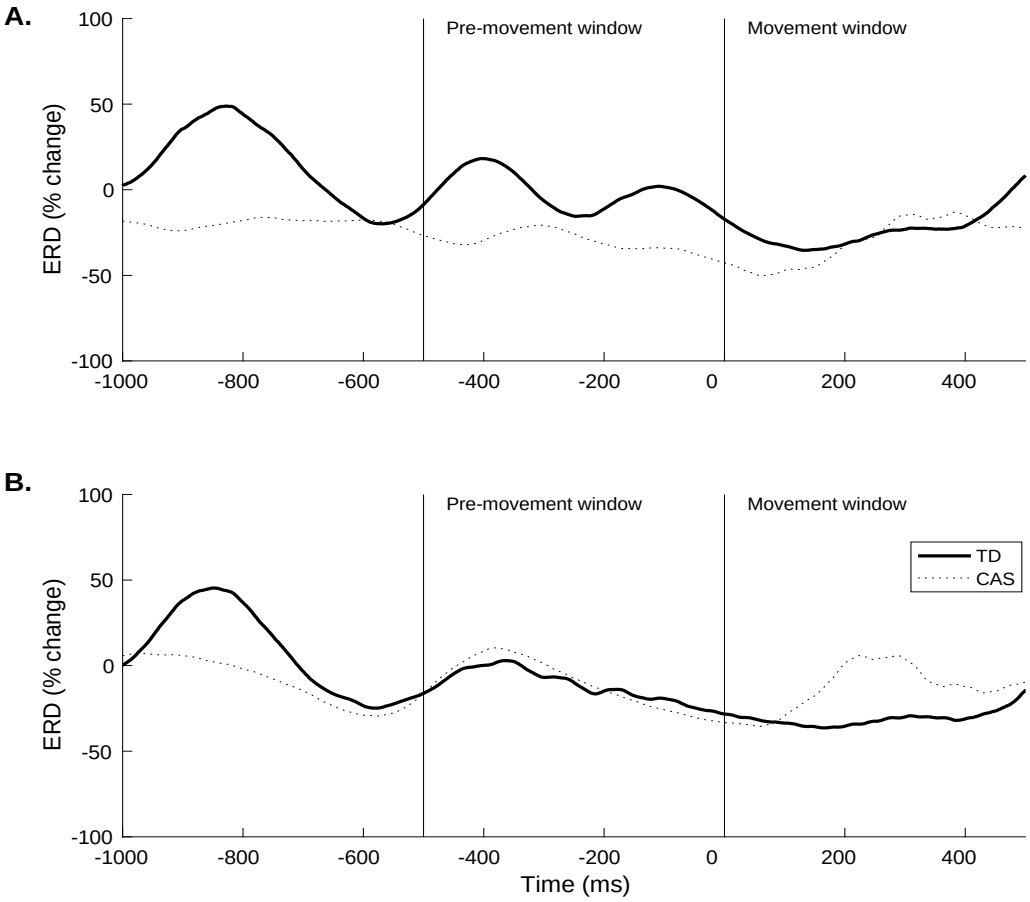

Figure 4. *Intact beta ERD in primary somatosensory and primary motor cortex in CAS.* During pseudoword repetition, children with CAS did not differ from the TD group with respect to beta ERD in (**A**) primary somatosensory (S1) cortex or (**B**) primary motor cortex (M1). This pattern was observed both in the pre-movement preparatory period as well as during the period immediately following the initiation of movement.

Impact of Language Ability on Event-related Desynchronization During Pseudoword Repetition

To improve the statistical power of our small sample study, we included two children in the CAS group who scored below average on a standardized language measure (core language score < 85 on CELF-4). To ensure that language skills did not influence the neural results, we evaluated the relationships between participants' language scores and beta event-related desynchronization during the pseudoword repetition task. We specifically investigated the significant group difference in left

Broca's area and found no significant relationship between language ability and beta event-related desynchronization across the entire sample, with a small effect size (r = .36, p = .18) but there was a trend in the CAS group alone, with a medium effect size (r = .64, p = .089) such that higher language scores were associated with less event-related desynchronization. There was no relationship in the typically developing group alone (r = .48, p = .27).

No Group Differences in Beta Response During Stimulation

Given the significant interaction between pre-motor, motor, and somatosensory cortices during movement planning and execution, it is important to examine beta oscillations in both regions of interest (Brovelli et al., 2004; Ede & Maris, 2013; Witham, Wang, & Baker, 2007). A 2x2 ANOVA of the beta response in the Broca's Area region of interest (hemisphere: left x right, group: typically developing x CAS) during lip stimulation revealed a significant main effect of hemisphere (F (1,12) = 7.16, p = .02) such that the left hemisphere in all participants exhibited a significantly higher event-related synchronization (155.34 ± 37.38), which is a correlate of idling neural structures (Pfurtscheller & Silva, 1999), than the right hemisphere homolog (32.87 ± 22.98). There was no main effect of group (F (1,12) = .47, p = .506) and no interaction between hemisphere and group (F (1, 12) = .81, p = .385). A 2x2 ANOVA (hemisphere: left x right, group: typically developing x CAS) of the beta range in Broca's Area during tongue stimulation revealed no significant main effects of hemisphere or group (ps > .124). Similarly, there were no main effects of hemisphere or group in beta event-related desynchronization/synchronization in primary somatosensory during lip

(*ps* > .855) or tongue stimulation (*ps* > .195). Descriptive statistics for these metrics can be found in Table 2.

Table 2
ERD during stimulation by location (lip or tongue) per ROI.
Data are reported as ± standard error of the mean. *p < .05

	Left Hemisphere		**Right Hemisphere**			
Broca	TD	CAS	TD	CAS	*F*-values	
Lip	189.60 ± 65.05	121.09 ± 43.25	25.85 ± 34.12	39.90 ± 36.02	Hemisphere: 7.16*	Group: .47
Tongue	63.90 ± 41.41	196.44 ± 124.38	-14.90 ± 28.82	64.43 ± 37.76	Hemisphere: 2.74	Group: 2.63
S1						
Lip	227.80 ± 186.50	199.88 ± 101.87	198.15 ± 100.81	273.28 ± 134.35	Hemisphere: .03	Group: .04
Tongue	74.85 ± 60.14	119.33 ± 67.97	155.45 ± 90.18	349.74 ± 215.02	Hemisphere: 1.88	Group: 1.02

Discussion

The aim of this study was to determine whether event-related desynchronization differences between children with CAS and typical controls exist in several regions of interest that are critical for speech production: auditory cortex (including transverse temporal gyrus and superior temporal gyrus), somatosensory cortex, Broca's area, and motor cortex. Our results suggest that children with CAS do not differ from typical controls in tasks of primary auditory or somatosensory processing. They do, however, differ in the level of event-related desynchronization exhibited in left Broca's area when preparing for speech production. To the best of our knowledge, this is the first MEG study of speech production planning in children with CAS, and thus the first to provide direct support for the hypothesis that the speech deficits in children with CAS arise from motor planning difficulties, rather than from altered auditory or somatosensory perception.

The Role of Broca's Area in Speech Perception and Production

In the current thesis, we found no evidence of primary auditory processing deficits (in either transverse temporal gyrus or superior temporal gyrus) in the CAS group. In addition, children with CAS exhibited no differences compared to controls in event-related desynchronization in primary motor cortex or primary somatosensory cortex during pseudoword repetition or in any region of interest during stimulation. These findings support the hypothesis that in our sample of children with CAS, speech production errors are likely due to deficits in premotor planning in Broca's area and not due to sensory deficits in the primary auditory or somatosensory areas or the execution of the movement itself. This conclusion is supported by prior work utilizing the current sample of children with CAS, suggesting that speech perception is not a core deficit of CAS in the absence of comorbid language impairment (Zuk et al., 2018). However, prior studies on early auditory processing in CAS have yielded mixed results. A number of studies have reported deficits in speech and auditory perception, including abnormal categorical boundaries (Groenen et al., 1996), rapid auditory processing (Tallal, 1976), and phonological encoding deficits (Thoonen, Maassen, Gabreëls, & Schreuder, 1994), while others reported no deficit (Brosseau-Laprė et al., 2020; Newmeyer et al., 2009).

It is likely that these differences are due to underlying language difficulties that were unaccounted for in participant recruitment. CAS is frequently comorbid with language impairment, and it is likely that prior studies reporting abnormal speech perception inadvertently included children with this additional impairment. For example, one report of abnormal sensory processing in CAS included a cohort of children with suspected CAS and while a language measure was administered, the scores were not used

for exclusion or as a covariate in the subsequent analyses and the authors report that 79% of their participants had a history of language processing difficulties (Newmeyer et al., 2009). A second study reported deficits in auditory perception tasks in children with CAS (at that time referred to as developmental apraxia of speech), but also reported low scores in language comprehension tests (Jaffe, 1980). In the current study, we report no deficits in early neural processing of speech sounds, but we do report a trending relationship between language scores and beta event-related desynchronization in left Broca's area during speech planning in the CAS group. Importantly, this relationship was observed during the premotor planning phase of the task, after the auditory stimulus presentation ended. It is possible that prior reports of auditory perception deficits in CAS are tied not to auditory perception itself, but to working memory processes between stimulus presentation and participant response. When speech sound input is received, this information is processed by the language network, including Broca's area, even if speech production is not intended (Tourville & Guenther, 2011). In fact, prior work has established the role of Broca's area (left inferior frontal gyrus/IFG) in speech perception (e.g. Watkins & Paus, 2004). Thus, the speech sound perception deficits previously described in children with CAS may also relate to the abnormalities in left Broca's area described in the current study. Future studies investigating the underlying neural correlates of CAS should aim to investigate this as well as control for comorbid conditions related to language and sensory processing deficits.

Potential Neural Mechanisms for Abnormal Event-related Desynchronization in CAS

Oscillatory power generated in relation to movement planning is partly modulated through the neurotransmitter GABA (Hall et al., 2011). In primary motor cortex, increased GABA corresponds with increased beta desynchronization (Hall et al., 2011; Muthukumaraswamy et al., 2013) and may serve a similar function in pre-motor planning areas. Mutations in genes associated with CAS, such as *FOXP2* (Turner et al., 2013; van Rhijn et al., 2018; Vargha-Khadem et al., 1998) and *CNTNAP2* (Centanni et al., 2015), lead to abnormalities in interneuron activity, including GABAergic neurons. For example, in mice, knockout of *Cntnap2* leads to reduced GABAergic interneurons, which likely impacts cortical synchrony (Peñaragikano et al., 2011). The release of GABA in fast-spiking pyramidal cells, the primary interneuron in the central nervous system, leads to desynchronization of the surrounding neurons (Manseau et al., 2010) and is likely the mechanism behind event-related desynchronization in premotor cortex prior to movement onset.

Children with CAS do exhibit lower integrity of the arcuate fasciculus (which connects Broca's to Wernicke's area) during speech production compared to typically developing peers (Liégeois et al., 2019). This finding suggests that critical information regarding the intended phoneme may become degraded on its way to Broca's area or that the information may not arrive in time for accurate motor planning. Future studies of motor planning in CAS should include measures of white matter integrity, to further probe the influence of the arcuate fasciculus on motor planning.

Comparison to Other Speech Disorders

The neural correlates of other persistent speech production disorders may provide some insight into the mechanisms of CAS. For example, one study comparing

developmental language disorder and speech sound disorder to typically developing controls provides evidence for abnormal gray matter within Broca's area for children with speech sound disorder, compared to controls (Kurth et al., 2018). Further, those with speech sound disorder exhibited significantly reduced gray matter volume in Broca than those with developmental language disorder (Luders et al., 2017). Interestingly, children with speech sound errors exhibit more white matter volume in the corpus callosum than those who made few errors (Preston et al., 2014). The authors noted that those findings may indicate reduced neuronal pruning in regions important for speech production. If cortical volume is abnormally high in CAS, this could lead to increased cortical noise in Broca's area. Increased neural noise is hypothesized to underlie speech sound perception errors in dyslexia (Anderson et al., 2010; Hancock, Pugh, & Hoeft, 2018) and could also contribute to errors in speech motor planning. Future work is needed to investigate whether increased cortical volume and neural noise may underlie speech production errors in CAS.

In canonical language areas, notable differences also exist between those with speech and language disorders and their typically developing peers. Children with CAS exhibit increased cortical volume in the left paracentral, supramarginal, and the right homolog of Broca's area, however no difference in callosal volume was noted (Conti et al., 2020). Increased supramarginal gyrus volume has also been reported in children with other speech and language disorders (Morgan, Bonthrone, & Liègeois, 2016); though it is currently unknown whether this region plays a functional role in speech production or is abnormal in CAS due to its connectivity with the language network more broadly. While abnormalities in these regions of interest may be common across disorders, additional

research is needed to determine the functional differences that lead to unique deficit profiles.

The Role of Abnormal Event-related Desynchronization in Speech Production Errors

To our knowledge, no other studies to date have examined event-related desynchronization related to speech motor preparation in CAS. However, the role of event-related desynchronization in speech, more broadly, is well-documented. In a variety of motor tasks, typically developing individuals exhibit significantly increased alpha and beta event-related desynchronization compared to their own baseline levels (Tremblay, Shiller, & Gracco, 2008), demonstrating these metrics are critical markers for successful movement planning. With regard to speech planning, beta desynchronization in pre-motor cortex prior to speech production reflects covert feed-forward systems from relevant sensory regions, which are necessary for assessing the starting location of the articulators (Gehrig et al., 2012).

In those with speech production errors, differences in beta desynchronization are well-documented, especially in those who stutter, including increased beta event-related desynchronization in adults who stutter (Rastatter, Stuart, & Kalinowski 1998; Mersov et al., 2016) and weaker event-related desynchronization in children who stutter (Ozge, Toros, & Comelekoglu, 2004). It is important to note that no study to date has investigated beta event-related desynchronization in children who stutter while they are preparing to speak – prior work has investigated beta event-related desynchronization only during rest (Ozge, Toros, & Comelekoglu, 2004). However, adults who stutter exhibit increased beta event-related desynchronization during speech preparation

(Mersov et al., 2016). There are a number of limitations to any comparisons between this prior work in stuttering and the results of the current study. While children who stutter exhibit reduced beta event-related desynchronization, these children were not actively preparing to speak, unlike the children in our study. In adults who stutter, increased beta event-related desynchronization during movement preparation is at odds with our finding of reduced event-related desynchronization. However, caution should be used when comparing results in children with results from an adult population for a variety of reasons, including plasticity caused by years of intervention and experience.

Regardless of the direction of the effect, some evidence suggests that patterns of atypical beta oscillations observed at the level of the cortex in those with speech production disorders may reflect compensatory activity, specifically for abnormal beta oscillations within subcortical loops (Etchell, Johnson, & Sowman, 2015; Mollaei et al., 2021). Given the importance of sensory information in speech motor planning, it is possible that white matter abnormalities between somatosensory and/or auditory cortex contribute to the abnormal beta event-related desynchronization observed in those with speech production errors. Future research is needed to evaluate the relationship between anatomical abnormalities and beta event-related desynchronization.

This abnormality in event-related desynchronization in stuttering may also reflect underlying differences in GABA release, as has been suggested in CAS. If mutations in *FOXP2* or *CNTNAP2* lead to abnormal GABA release, this may represent the main biological mechanism behind speech planning deficits in CAS. Interestingly, the direction of the effect may be different in CAS compared to stuttering and may help explain the differences in event-related desynchronization findings between prior work in stuttering

and our current results in CAS. In stuttering adults, the beta event-related desynchronization is stronger prior to movement compared to typically developing peers, suggesting an increase in GABA (Mersov et al., 2016). This may be caused by an increased motor cortex excitability, leading to increased GABA and increased event-related desynchronization. In contrast, since CAS seems to be marked by reduced beta event-related desynchronization, this suggests that GABA release is reduced in this disorder. Future research is needed to further probe this possibility and the distinction between stuttering and CAS.

Limitations

The major limitation of the current thesis is the small sample size. To determine the power of our sample, we ran a *post hoc* power analysis using the main effect of group in left Broca's area event-related desynchronization. The power analysis revealed that we were only slightly underpowered ($F = 2.57$, power = .72). In addition, our aim was to carefully select children with CAS without common comorbidities such as language delay/disorder or dyslexia, though due to our small sample size, we did include two children with comorbid language impairment. Therefore, this study should be replicated in more children with CAS and, preferably, children with more severe CAS. Finally, the current study did not include imaging of the neural anatomy, so we are unable to speak to the role of abnormal beta event-related desynchronization in Broca's area as it related to the rest of the language network.

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Appendix A: CVC Stimuli

Filename Spelling	Keyboard character	Vowel
b@v	@	æ
b^p	^	ʌ
b^v	Y	aI
bEf	W	ɑu
bIf	E	ɛ
bIv	I	ɪ
dam	c	ɔ
dap	y	j
dEv	C	tʃ
dIb	S	ʃ
dIf		
fEk		
fIf		
fop		
fYk		
g@n		
gEd		
gEn		
gIk		
gIm		
gIp		
hab		
ham		
hEg		
hEv		
hIb		
hIf		
k@v		
k^g		
kav		
kEk		
kIf		
kIg		
kof		
m@f		
m@v		
m^b		
m^p		

m^v
man
mEk
mEm
mIb
mIg
mIm
n@m
nan
nEn
nIg
nIm
p@f
p@v
pIb
pIm
pIv
tan
tEm
tEp
tId
tIg
w@n
wIb
wIf
wIv
y@n
yEd
yEn
yIl
yIn
yol
yYn
bef
boC
buf
bug
C^p
Cem
Cim
Civ

Cop
CYz
doC

Note. As the original CVC stimuli were presented through computer software, they were originally transcribed in Klattese.

VITA

Abby Sarah (Mason) Engelhart was born July 1st, 1997 to Mike and Crystal Mason as the youngest child with two older brothers, Sam, and Jordan Mason. Abby graduated with honors from Sweetwater High School in Sweetwater, TN in 2015 and then went on to graduate magna cum laude with a Bachelor of Science in Psychology from Tennessee Technological University in 2018. The month before graduation, in April 2018, Abby married her high-school sweet-heart Michael Engelhart, and the two of them graduated together.

Currently, Abby is attending Texas Christian University in Fort Worth, TX, as she is pursuing her Master of Science in experimental psychology. She plans to continue within the field of science, pursuing a career in her interests of neuroscience and psychology.

ABSTRACT

DECREASED BETA DESYNCHRONIZATION IN BROCA'S AREA DURING PSEUDOWORD REPETITION IN CHILDREN WITH CHILDHOOD APRAXIA OF SPEECH

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Department of Psychology
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Thesis Advisor: Dr. Tracy M. Centanni, Assistant Professor of Psychology

Childhood apraxia of speech (CAS) is a neurological motor speech disorder characterized by impaired motor planning in the presence of intact neuromuscular processes. We used magnetoencephalography (MEG) to examine event-related desynchronization (ERD) in the beta power band during pseudoword repetition and during stimulation of the lip and tongue in eight children with CAS compared to seven typically developing peers. Since beta ERD is a common neural marker of preparation for motor execution, abnormal ERD may be associated with deficiencies in motor planning. Overall, there were no significant differences in auditory processing, nor was ERD different in primary somatosensory or primary motor cortices. However, those with CAS exhibited significantly weaker ERD in Broca's area during motor planning compared to typically developing controls. Future work, however, should expand with a larger sample, and more complex forms of CAS.