NEURAL SYSTEMS SUPPORTING NONLINGUISTIC AUDITORY PROCESSING IN YOUNG CHILDREN WHO PERSIST AND RECOVER FROM STUTTERING

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A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

Communicative Sciences and Disorders—Master of Arts

2018

ABSTRACT

NEURAL SYSTEMS SUPPORTING NONLINGUISTIC AUDITORY PROCESSING IN YOUNG CHILDREN WHO PERSIST AND RECOVER FROM STUTTERING

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Stuttering is a speech disorder characterized by disruptions in speech fluency, typically marked by the presence of prolongations, repetitions, and blocks. There is no single known cause of stuttering. Instead, stuttering is thought to be a dynamic, multifactorial disorder resulting from interactions between genes, language, motor, and other cognitive skills, and the environment (Smith, 1999). Among preschool-age children who begin to stutter, approximately 80% will recover naturally (de Sonneville-Koedoot, Stollk, Rietveld, & Franken, 2015; Yairi & Ambrose, 2005; Yairi & Ambrose, 1999; Yairi & Seery, 2015). However, to date it is not clear why some children persist in stuttering while others recover.

One potential factor that may contribute to stuttering is auditory processing. Previous studies have found that nonlinguistic auditory processing differs between adults and children who stutter (CWS) and their fluent peers (Hampton & Weber-Fox, 2008; Kaganovich et al., 2010). The current study aimed to extend previous findings by evaluating neural indices of nonlinguistic auditory processing in young CWS who will eventually persist (CWS-ePer) and eventually recover (CWS-eRec). CWS-ePer exhibited atypical early neural markers of auditory processing compared to CWS-eRec and fluent peers. Additionally, with increased cognitive demands, or short recovery time between sounds, CWS-ePer and CWS-eRec both exhibited atypical early auditory processes. Together, these findings indicate that early auditory processing and attention skills may play a role in persistence of developmental stuttering.

ACKNOWLEDGEMENTS

This research was supported by grant R01DC00559 from NIH-NIDCD to Dr. Anne Smith and Dr. Christine Weber. I would like to thank Barb Brown for her assistance in data acquisition. I would also like to thank Dr. Amanda Hampton Wray and the members of the Brain Systems for Language Laboratory at Michigan State University for their contributions to this project. Finally, I would like to thank the participants and their families for taking part in this study.

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INTRODUCTION

Developmental Stuttering

Stuttering is a complex speech disorder comprised of a multitude of symptoms. It is characterized by overt speech characteristics, such as disruptions in the fluent production of speech—repetitions, prolongations, and blocks—as well as a number of covert characteristics. Even when the signs of stuttering cannot be directly observed through speech, there exist a number of covert characteristics that are a part of stuttering. These secondary stuttering characteristics, which are often less noticed than the disruptions in speech, include tense body movements, emotional reactions, physiological changes, and interruptions of interpersonal communication (Yairi & Seery, 2015). Together, these features make up the complex, multifaceted disorder of stuttering.

It is widely accepted that stuttering results from the interaction of multiple factors—genetic, physiological, linguistic, psychological, environmental, and emotional (Smith & Weber, 2016). Though each of these factors plays a role in stuttering, their weight varies among individuals. Several factors within these levels may influence an individual's stuttering, including social situations, self-perception, control over one's own speech motor system, and the complexity of language demands presented, each with varying impacts on the individual (Hampton & Weber-Fox, 2008; Healy, Trautman, Susca, 2004; Millard, Edwards, & Cook, 2009; Smith, 1999; Smith & Kelly, 1997; Yairi & Ambrose, 2005).

The prevalence of stuttering is higher among preschool-age children than any other age group. Between 4.5% and 11% of children are affected by developmental stuttering in their preschool years (de Sonneville-Koedoot, Stollk, Rietveld, & Franken, 2015; Millard, Edwards, & Cook, 2009; Trajkovski, Andrews, O'Brian, Onslow, & Packman, 2006; Yairi & Ambrose, 2005; Yairi & Seery, 2015). Estimates of the incidence of stuttering vary widely due to differing study designs, sample populations, and measurement of stuttering (i.e. what length of time stuttering must be reported to qualify) reported by various researchers (Yairi & Seery, 2015). However, its impact remains significant among young children.

The majority of children who stutter (CWS) will eventually recover naturally. Within the population of young children who stutter, approximately 75-80% will recover naturally, with the greatest likelihood of recovery occurring within the first 15-months post-onset (de Sonneville-Koedoot et al., 2015; Yairi & Seery, 2015; Yairi & Ambrose, 2005; Yairi & Ambrose, 1999). Among CWS who eventually recover naturally, the number of stuttering-like disfluencies may begin to decrease between 7- and 12-months post-onset (Yairi & Seery, 2015). However, severity is not a strong predictive factor in whether an individual child who stutters will persist or recover.

There is great variability among children and adults who stutter and, to date, there are few factors that predict whether an individual who stutters (IWS) will eventually persist or recover. Factors that have been identified in predicting whether a child who stutters will eventually persist or recover include genetics/heredity, sex, and age of onset of stuttering. The factor of a genetics/heredity is a strong predictor of persistence or recovery in stuttering. There is a higher incidence of stuttering in children with family members who stutter. Further, CWS with a history of family members who recovered from stuttering are more likely to follow this pattern as well. Specifically, children who have a family history of recovery from stuttering have ~65% chance of recovering as well, whereas children who have a family history of persistence have ~65% chance of persisting. Sex also plays a role in both incidence and the persistence in or recovery from stuttering. There exists a gender gap among young CWS of approximately 2:1 when comparing males to females. This gap widens as young CWS age, with ratios closer to 3:1 or 4:1 males to females among adults who stutter (AWS). This largely reflects that the natural recovery rate is higher for females than males (Yairi & Seery, 2015).

Age of stuttering onset is an additional factor surrounding both incidence and persistence or recovery in young CWS. The highest incidence of stuttering exists among children ages 2 to 4, with more than 60% of CWS begin stuttering by age 3 years and 85% of CWS having developed stuttering by age 4 years (Yairi & Ambrose, 2005; Yairi & Seery, 2015). CWS with later ages of onset tend to persist at a greater probability than their peers who begin stuttering at an earlier age (Yairi & Ambrose, 2005; Yairi & Seery, 2015). Further, males often begin to stutter at later ages than females and females often recover sooner than males. According to Yairi and Ambrose (2005), girls who stutter recover at approximately 24-months post-onset, while boys who stutter recover at approximately 29.5-months post-onset. Thus, together, sex and age play a role in potential persistence in stuttering.

While it is clear that the interaction of several factors impacts its likelihood of persistence or recovery in stuttering, these factors are relatively broad. It remains unclear whether other factors, and if so, which ones, may help predict persistence and recovery in young CWS. Research into factors such as language abilities, phonological skills, and auditory processing in young CWS could reveal further insight into the understanding of stuttering.

Relationships between Auditory Processing and Stuttering

Many factors, and the interactions among them, are thought to contribute to the development of stuttering (Smith, 1999; Smith & Weber, 2016). While differences have been identified in multiple aspects of speech processing, including phonological processing (Mohan &

Weber, 2015; Weber-Fox, Spencer, Spruill, & Smith, 2004) and language processing, such as the perception of semantic and syntactic anomalies (Bajaj, Hodson, & Schommer, 2004; Cuadrado & Weber-Fox, 2003; Kreidler et al., Hampton Wray, A., Usler, E., & Weber, C., 2017; Weber-Fox, Hampton Wray, A., & Arnold, H., 2013), these differences are often subtle and are not always consistent across studies. As speech perception involves multiple cognitive and linguistic skills, the wide discrepancy across studies suggests that the differences between individuals who stutter and normally fluent speakers (NFS) may result from differences in a more general cognitive mechanism utilized in sound perception, such as nonlinguistic auditory processing. The varied findings across studies of speech perception (Howell, 2004; Yaruss & Conture, 1996), in conjunction with empirical evidence from children and adults who stutter (Hampton & Weber-Fox, 2008; Kaganovich et al., 2010), support the hypothesis that nonlinguistic auditory processing, a generalized cognitive skill critical for speech perception, may be a key factor underlying differences between IWS and NFS.

Auditory processing is a cognitive mechanism involved in sound perception which has been hypothesized to play a significant role in stuttering (Hampton & Weber-Fox, 2008; Kaganovich et al., 2010; Yairi & Seery, 2015). Information gathered through auditory processing is integrated with somatosensory and motor information at the level of the brain to contribute to the steps necessary in producing speech. The Directions into Velocities of Articulators (DIVA) model was developed to explain the contribution of each of these components to speech production. According to the DIVA model, as infants, our brain undergoes a training process, during which babbling and word imitation create a speech sound map cell. Each of these speech sound map cells represents an auditory target for a speech sound which becomes activated both when perceiving and when producing a given sound (Guenther, 2006).

A main component of the DIVA model (Guenther, 2006) is the auditory feedback system, as it is thought to encode auditory targets for speech sounds and supply corrective motor commands for errors identified in the motor plan or perceived auditorily. The auditory feedback control mechanism is activated when a speech sound has been produced and is then perceived as outside the target speech sound region (or map cell), or as an error. The perceived error initiates corrective commands that are sent from the auditory error cells to the motor control center. This corrective feedback results in a new, compensatory articulatory response within 75-150 ms post-error-onset (Guenther, 2006).

The auditory error cells are only activated if the incoming auditory signal is outside of the target range; if the signal is within the range then these cells are inhibited (Guenther, 2006). Precise and timely auditory feedback in response to adequate auditory input is necessary for fluent speech production. Thus, it could be hypothesized that a compromised auditory processing system may result in inaccurate activation of speech production cells or auditory error cells, resulting in repetitive speech sound productions perceived as stutter-like repetitions. Further, if the corrective feedback message is delayed beyond the typical time range, the speech sound production may also result in a stutter-like block or prolongation. As precise and timely auditory feedback must be received in response to adequate auditory input, error and/or miscalculations may compromise the fluency of the auditory feedback system, potentially contributing to disfluency of speech (Guenther, 2006).

The significantly lower incidence of stuttering among people who are deaf draws attention to the relationship between auditory processing and stuttering. According to previous survey research, children with substantial hearing loss exhibit little to no stuttering. One study, which considered both oral and manual communication, found only 12 cases of CWS among 9,930 students in schools for the hearing impaired—a prevalence of .12% (Montgomery & Fitch, 1988; Yairi & Seery, 2015). Without sensory input and perception of sound, individuals do not receive feedback on their own speech. The reliance of speech development on auditory processing (Guenther, 2006) is evident in that deaf children produce speech that does not sound like typical productions, most likely due to the lack of auditory feedback (Yairi & Seery, 2015). Stuttering among individuals who are deaf is seldom reported, likely because adequate auditory input for auditory processing is absent in this population. While an error in interpreting auditory input may result in stuttering, in contrast, the absence of auditory input would not result in stuttering-like disfluencies (Guenther, 2006). Thus, based on the significantly lower prevalence of stuttering among the deaf population, it may be inferred that auditory processing plays a role in the development of stuttering.

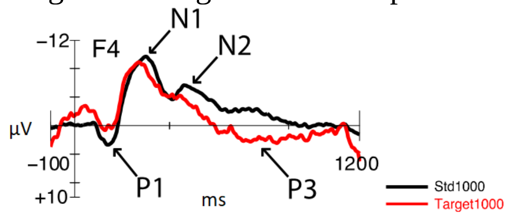
Auditory feedback plays an important role in sensory-to-motor processing between hearing and speech (Guenther 2006), thus supporting the theory that auditory processing plays a role in stuttering. For instance, IWS speak with a substantially reduced number of stuttering-like disfluencies in the presence of sufficient noise levels (Yairi & Seery, 2015). This suggests that when environmental sound bombards the auditory system and the ability to receive auditory feedback is reduced, stuttering is reduced. Further evidence supporting this link can be observed in the effects of altering auditory feedback on stuttering. One method of altering auditory feedback is delayed auditory feedback (DAF), which consists of relaying an individual's voice back to them with a timed delay. Another method is frequency altered feedback (FAF), which alters the speech signal of auditory feedback the individual receives by shifting their fundamental frequency (Yairi & Seery, 2015). Both DAF and FAF are intervention techniques which have been reported to reduce stuttering among IWS (Sparks, Grant, Millay, Walker-Batson, Hynan, 2002; Stuart, Frazier, Kalinowski, & Vos, 2008; Yairi & Seery, 2015). The impact of altered auditory feedback techniques on the presences of disfluencies in IWS supports the potentially important role of auditory processing in IWS. On the other hand, the use of methods such as DAF with normally fluent speakers causes increased disfluencies of speech (Jones & Striemer, 2007; Van Borsel, Sunaert, & Engelen, 2005; Yairi & Seery, 2015). This evidence argues for the existence of a fundamental relationship between auditory processing, auditory feedback, and the fluent production of speech. Such substantial links between auditory feedback and fluency underscore the importance of further research in this area.

Previous studies of neural processes for sounds in IWS and NFS provide evidence for a link between auditory processing and stuttering. IWS have been reported to exhibit reduced neural activity in the temporal region, which is responsible for auditory functioning (Guenther, 2006; Fox et al., 2000; Watkins, Smith, Davis, & Howell, 2008). Watkins and colleagues (2008) evaluated brain structure and function in motor and language areas in adolescents who stutter using functional magnetic resonance imaging (fMRI). Results showed that IWS demonstrated overactivation in the right anterior insula and the midbrain, which is located near the basal ganglia, and underactivation in the sensorimotor cortex and left Heschl's gyrus compared to fluent peers. These atypical functional activations occurred in cortical and subcortical brain areas related to speech production and selection and initiation of motor sequences. Furthermore, white matter abnormalities were observed in the ventral premotor cortex, which is a critical region for integration of sensory and motor information (Watkins et al., 2008). These results are indicative of differences between IWS and NFS in both structure and function of sensory and motor regions affecting speech and auditory processing. Deficits in auditory regions of the brain with stuttering have also been observed using a different neuroimaging methodology. A magnetoencephalography (MEG) study using functional neuroimaging, by Biermann-Ruben and colleagues (2005), found that AWS exhibited activations in the inferior frontal cortex and in the right rolandic area—a motor area of the cerebral cortex— in response to the participants being exposed to an auditory perception task, response patterns that were not observed in NFS. These findings provide evidence of different neural activation patterns during auditory processing between NFS and IWS, suggesting that atypical auditory processing may play a role in stuttering.

Neurophysiological indices of auditory processing in stuttering

Several previous studies have evaluated neural activity supporting auditory processing using electroencephalography (EEG). Event-related potentials (ERPs) are EEG that is time-locked to a specific stimulus. ERPs are measurements of the electrical activity from a population of neurons firing in synchrony. By time-locking neural responses to the onset of a stimulus, such as the standard and target tones used in this study, one can evaluate the ways in which the brain responds to a given stimulus within milliseconds (Luck, 2005; Mahajan & McArthur, 2012). ERPs elicited by the same type of stimuli are typically averaged together to reduce the signal-to-noise ratio, resulting in an ERP consisting of many trials. The visual representation of an ERP can be seen in *Figure 1*. The measurement of the amplitude and latency of an ERP can provide information about the neural activities associated with specific stimuli, and allow for comparisons between stimuli and between groups of participants.

Figure 1: Image of ERP components



The P1, N1, N2, and P3 event-related potential (ERP) components at the right frontal electrode site F4. Note that, to remain consistent with the ERP literature, negative is plotted upward.

ERP components associated with auditory processing include the P1, N1, N2, and P3. Earlier components, the P1 and N1, reflect the physical parameters of a stimulus, influenced by external factors. The P1 and N1, specifically, are sensitive to acoustic and physical properties of sound—frequency, duration, inter-stimulus interval, stimulus complexity, and intensity. The elicitation of these components is not task-dependent, as their elicitation does not rely on behavioral or performance demands (Kaganovich et al., 2011; Sharma, Kraus, McGee, & Nicol, 1997). In adults, auditory ERP components are elicited in a P1-N1-P2 complex, with P1 typically exhibiting a peak latency at 50 ms, and N1 typically at 100 ms (Čeponiené, Rinne, & Näätänen, 2002; Mahajan & McArthur, 2012; Sharma et al., 1997; Tomé, Barbosa, Nowak, & Marques-Teixeira, 2015). Both the P1 and N1 present with a largely frontocentral distribution (Luck, 2005). With development, the neural representation of these components changes. The maturation of these components is perhaps due to factors such as increased neuronal density, synchrony, and specialization (Ponton, Eggermont, Kwong, & Don, 2000; Sharma et al., 1997; Wunderlich, Cone-Wesson, & Shepherd, 2006).

As children age, latency of the P1 component decreases (Sharma et al., 1997). Further, it has been found that the P1 is influenced by attention when elicited in response to linguistic probes; however, P1 amplitudes in response to nonlinguistic tones—such as those used in the current study—did not demonstrate an attention effect (Giuliano, Karns, Neville, & Hillyard, 2014). The N1 also exhibits changes in its elicitation with maturation. In young children, there is evidence of an immature N1 with an increased latency, which generally presents as a broad frontocentral distribution of electrical activity (Sharma et al., 1997). With age, the latency of the N1 component also decreases and its focalization and laterality increase, presenting with larger amplitudes over medial and frontocentral electrode sites (Coch et al., 2006; Luck, 2005; Luck & Kappenman, 2012). Additionally, while the N1 is not task-dependent, its amplitude can also be influenced by attention, with larger responses typically associated with greater allocation of attention (Coch, Sanders, & Neville, 2006; Hansen & Hillyard, 1980; Herrmann & Knight, 2001; Hillyard, Hink, Schwent, & Picton, 1973), and decreased amplitude associated with stimuli repetition (Čeponiené et al., 2002).

Two later occurring components, the N2 and P3, reflect cognitive processes that are internally generated. The N2 and P3, specifically, are sensitive to the cognitive analyses of perceived sound, related to probability, quality, and duration. Presence of the N2 and P3 is often reduced in repetitive tasks, due to the increased probability of occurrence of the stimuli (Hampton & Weber-Fox, 2008; Luck, 2005; Polich, 2007; Sharma et al., 2007). Furthermore, both the N2 and P3 are elicited in response to unexpected, or rare, stimuli (Kaganovich et al., 2011; Luck, 2005). Such is the case in the oddball paradigm, which pseudorandomly alternates between common tones at a set frequency and target tones at a different set frequency; while standard stimuli will typically elicit P1 and N1, the target tones will also elicit a N2 and a P3. It is believed that these components reflect the allocation of attentional resources to a listening task and updating of working memory in response to an auditory change. Unlike the P1 and N1, the P3 component is not elicited based on the perception of any and all sound, as it is task-dependent. For example, ignored stimuli do not elicit a P3, as little or no attention is allocated to their perception. There is some variability among the P3 in young children, though, generally, the P3 has increased latency and decreased amplitude in comparison to adults. As children develop, the P3 amplitude will increase and latency will decrease (Martin, Barajas, Fernandez, & Torres, 1987; Polich 2007). A shorter P3 latency has also been associated with superior cognitive performance (Polich, 2007), suggesting that as cognitive performance increases, P3 latency decreases.

Previously, differences have been found between AWS and their typically fluent peers in auditory processing (Biermann-Ruben et al., 2005; Smith, Blood, & Blood, 1990; Watkins, 2008). Hampton & Weber-Fox (2008) explored the relationship between behavioral accuracy, reaction times, and neural processes for auditory stimuli between AWS and NFS. By exploring the relationships between these behavioral components and neural activity, they were able to evaluate the role of nonlinguistic auditory processing in stuttering using an auditory pure-tone oddball paradigm. In the paradigm, participants listened to a series of tonal stimuli at two different frequencies, the standard, more frequent (80%) tone at 1000 Hz and the rare (20%), higher-frequency target tone at 2000 Hz. Instead of typical verbal responses, which require excess language processing and place cognitive demand on the participant, they were able to measure behavioral accuracy and reaction times using responses recorded on a button keypad. Results indicated that AWS presented with slower and less accurate responses to target stimuli which trended towards significantly different than their normally fluent peers. Additionally, AWS exhibited reduced neural responses to nonlinguistic auditory stimuli compared to fluent peers. Specifically, P3 mean amplitudes exhibited by AWS were reduced compared to NFS, suggesting weaker updates in working memory. Though there were no significant differences in earlier components between groups, correlational analyses found that AWS with reduced N1 and P2 amplitudes had slower reaction times and reduced target tone detection accuracy. The authors hypothesized that these relationships indicated weaker neural representations of the auditory signal. These findings further suggest the presence of deficits in nonlinguistic auditory processing related to reduced cortical representation for auditory stimuli in at least a subset of AWS (Hampton & Weber-Fox, 2008).

Difficulty comes with studying AWS, as it is unknown whether differences observed in AWS result from brain changes in response to stuttering or are part of the cause of stuttering. In order to determine if differences in auditory processing result from physiological characteristics of brain function in IWS rather than from coping with the disorder, it is important to evaluate children close to the onset of stuttering. This reduces potential differences resulting from adaptation over time in AWS (Hampton & Weber-Fox, 2008; Kaganovich et al., 2010). Based on the previous study of atypical auditory processing in AWS (Hampton & Weber-Fox, 2008), Kaganovich and colleagues (2010) aimed to extend these findings and explore whether nonlinguistic auditory processing differed between preschool-age CWS and their normally fluent peers. Utilizing a similar pure-tone oddball paradigm, they acquired ERPs that reflected early auditory processing as well as later auditory processes that reflected attentional allocation and updating working memory. Results indicated that CWS did not differ from children who did not stutter (CWNS) in early auditory encoding. However, they found that young CWS failed to produce a P3 in response to the target tones, a response present in CWNS. The lack of a P3 in young CWS compared to CWNS is consistent with findings in adults and suggests less efficient attention allocation and working memory updating in response to nonlinguistic auditory stimuli in IWS (Kaganovich et al., 2010). Importantly, these findings extended previous findings in AWS and suggest that differences in auditory processing may be associated with the development of stuttering.

While the existing research indicated neurophysiological differences between both CWS and AWS compared to their fluent peers, to date, the ways in which nonlinguistic auditory processing may play a role in the persistence in or recovery from stuttering is unknown. The current study aims to fill this gap in the literature by evaluating whether neural systems for auditory processing differ between CWS who will eventually persist versus those who will eventually recover from stuttering. Given the evidence supporting differences in neural indices of auditory processing between IWS and NFS, it is pertinent to evaluate whether these mechanisms of auditory processing may play a role in the persistence or recovery of stuttering. By evaluating young CWS based on eventual persistence or recovery, we will be able to better understand more generalized cognitive processes in CWS who will persist or recover from stuttering, and shed light onto additional factors that may play a role in persistence in stuttering.

The current study evaluated neural processing in preschool-age CWS who will eventually persist or recover from stuttering through the use of an auditory oddball paradigm. ERPs were elicited using a pure-tone oddball paradigm, which allowed us to evaluate neural indices—P1, N1, N2, and P3—associated with auditory processing. Based on existing findings (Hampton & Weber-Fox, 2008; Kaganovich et al., 2010), we did not predict differences in early auditory encoding between CWS who eventually persist and CWS who eventually recover; however, we hypothesized that CWS who eventually persist would exhibit a significantly reduced P3, in response to target tones, as compared to CWS who eventually recover and fluent peers. If upheld, this result would provide additional support for differences in endogenous auditory processing in CWS who eventually persist, reflecting a reduced ability to allocate attentional resources and update working memory in response to an auditory change. Increased understanding of the role of auditory processing in persistence versus recovery from stuttering will enhance our knowledge of developmental stuttering and support the development of a clinically-applicable battery of tests to better predict persistence or recovery from stuttering in young CWS.

METHOD

The method described below has been previously described in detail in the study by Kaganovich and colleagues (Kaganovich, Hampton Wray, & Weber-Fox, 2010).

Participants

The participants included in this study were part of a longitudinal study conducted at Purdue University, the Purdue Stuttering Project. Data were collected at two separate sites, Purdue University and the University of Iowa (data for 32 of the CWS and 21 of the CWNS were collected at Purdue University). Researchers made their best efforts to ensure the experimental setup and execution were identical at both sites (Kaganovich et al., 2010). Prior to participation, each child's parent(s) completed a consent form in addition to the child providing verbal assent to participate. All procedures were approved by the Institutional Review Board (IRB) at Purdue University.

The current study included 78 children, mean age 4.78 years (*.065*), 42 (13 girls) children who stutter (CWS) and 36 (11 girls) children who do not stutter (CWNS). Per parent report, all participants had normal, or corrected-to-normal vision. Each participant passed a hearing screening at the level of 20 dB HL at 1000, 2000, and 4000 Hz. In addition, all participants were monolingual speakers of English. None of the participants presented with neurological injury or impairments, including ADHD, nor did they use medications that affect neurological function (i.e. seizure medication) at the time of data collection. All participants were also cleared of any symptoms presenting as impaired reciprocal social interaction and restriction of activities as measured by the Childhood Autism Rating Scale (Schopler, Reichler, & Renner, 1988). Handedness was determined by a collaboration of parent report and an abbreviated handedness inventory (5 tasks adapted from Oldfield, 1971); 5 CWS and 5 CWNS were determined to be left-handed, 2 CWS and 2 CWNS were determined to be ambidextrous, and handedness was not obtained for 4 CWS.

The majority of data collected for this project were collected in Year 1 of the longitudinal study, with data for two of the included CWNS having been collected in Year 2. Each child continued to participate in the longitudinal study for 2 to 5 years and stuttering diagnosis (described below) was determined annually. Based on the nature of the study, it is possible that children who were determined to eventually persist or recover during the course of the study may have an ultimate diagnosis different from that within the project. However, per the subjects' participation, it was determined which of the children would eventually persist and which children would eventually recover from stuttering. The current study extended previous findings from the longitudinal study conducted by Kaganovich and colleagues (2010) and was a retrospective analysis of previously acquired data, during which time all CWS were stuttering, based on eventual diagnosis of persistence in or recovery from stuttering. Thus, the CWS were divided into groups based on eventual stuttering diagnosis. Of the CWS, 26 (9 girls) were CWS who would eventually recover (CWS-eRec) and 16 (4 girls) were CWS who eventually persisted (CWS-ePer). Demographic information for each group, including age and sex, is included in Table 1.

The Hollingshead Four Factor Index of Socioeconomic Status (SES; Hollingshead, 1975) was used to determine SES. The highest level of maternal and paternal education and parental employment were included in the measure. Education was rated on level of school completed, represented on a seven-point scale, ranging from 1 (less than seventh grade) to 7 (graduate degree). Occupation was rated based on census data and was calculated on a nine-point scale, ranging from 1 (farm laborers and unskilled service workers) to 9 (higher executives, major professionals, and large business proprietors). Educational and occupational data were collected for both parents and used in calculating the SES, which was calculated by multiplying education and occupation by a weighted factor. In the case that both parents are employed, their scores were averaged together in determining SES (Hollingshead, 1975, unpublished).

Table 1:
Participants' Demographic Information

Participant Group	Sex	Age Mean (*SE*)	Age Range (years)	SES Mean (*SE*)	Maternal Education Mean (*SE*)
CWS-ePer (n=16)	4 F 12 M	4.81 (*.143*)	4.15-5.69	33.50 (*4.30*)	5.50 (*.258*)
CWS-eRec (n=26)	9 F 17 M	4.57 (*.106*)	3.69-5.74	45.86 (*2.14*)	6.08 (*.199*)
CWNS (n=36)	11 F 25 M	4.92 (*.095*)	3.62-5.92	46.74 (*2.50*)	6.17 (*.176*)

Demographic information for children who stutter who eventually persisted (CWS-ePer), children who stutter who eventually recovered (CWS-eRec), and children who do not stutter (CWNS), including areas of sex, age, socioeconomic status (SES), and maternal education level.

Stuttering Evaluation and Criteria

Participants were classified as children who stutter based on the criteria established by Yairi and Ambrose (1999). Specifically: 1) They had to be identified as a child who stutters by at least one clinician involved in the data collection of this study; 2) Children had to receive a stuttering severity rating of 2 or higher on an eight-point severity scale determined by the child's parent and/or a speech language pathologist; 3) The children had to exhibit at least three stuttering-like disfluencies (SLDs) per 100 syllables produced using a weighted stuttering index (SI) in a spontaneous speech sample (Yairi & Ambrose, 1999; as described in Kaganovich, Hampton Wray, & Weber-Fox, 2010). Stuttering information for both groups of CWS, including age of stuttering onset and weighted SI measures, is included in Table 2.

Table 2:
Participants' Stuttering Information

Participant Group	Age Onset (months) Mean (*SE*)	Weighted SI Mean (*SE*)	SLD Mean (*SE*)	Parent Rating Mean (*SE*)	Clinician Rating Mean (*SE*)	Age Recovered Mean (*SE*)
CWS-ePer (n=16)	37.56 (*2.41*)	12.23 (*1.82*)	8.01 (*1.22*)	4.40 (*2.94*)	4.22 (*.278*)	
CWS-eRec (n=26)	34.19 (*1.56*)	7.58 (*1.51*)	4.75 (*.754*)	3.48 (*.196*)	3.33 (*.196*)	6.79 (*.221*)

Stuttering information on children who stutter who eventually persisted (CWS-ePer) and children who stutter who eventually recovered (CWS-eRec), including age of stuttering onset, measurements of weighted stuttering index (Weighted SI) and stuttering-like disfluencies (SLD), parent and clinician severity ratings, and age of natural recovery from stuttering.

Behavioral Testing

As part of the study, each participant was administered a series of cognitive and language assessments. All participants included in this study demonstrated non-verbal intelligence within normal limits, as measured by the Columbia Mental Maturity Scale (Burgemeister, Blum, & Lorge, 1972). To test their language comprehension, the children completed the Test for Auditory Comprehension of Language–3 (TACL–3, Carrow-Woolfolk, 1999). As a measure of spoken language, the children completed the Structured Photographic Expressive Language Test–3 (SPELT–3, Dawson, Stout, & Eyer, 2003). The children's phonological abilities were tested using the Bankson-Bernthal Test of Phonology (BBTOP, Bankson & Bernthal, 1990). Further, the participants were administered two measures of working memory, one verbal and one nonverbal. The verbal test of working memory administered was the Test of Auditory-Perceptual Skills (TAPS), which measures working memory through digit- and word-span subtests (Gardner, 1985). The nonverbal test of working memory consisted of a block sequencing task where the children were scored on the use of both correct ordering and colors of the blocks (Goffman, 2002, unpublished) (as described in Kaganovich, Hampton Wray, &

Weber-Fox, 2010). Participants' scores on the previously described behavioral tests are included, below, in Table 3.

Table 3:
Participants' Behavioral Testing Scores

Participant Group	CMMS Mean (*SE*)	SPELT Mean (*SE*)	TACL (years)
CWS-ePer	109.94	96.50	112.50
(n=16)	(*1.88*)	(*3.24*)	(*4.03*)
CWS-eRec	109.81	99.62	113.69
(n=26)	(*1.74*)	(*2.83*)	(*2.42*)
CWNS	113.06	110.31	119.44
(n=36)	(*1.48*)	(*1.76*)	(*2.36*)

Mean (SE) scores on a battery of behavioral tests—Columbia Mental Maturity Scale (CMMS), Structured Photographic Expressive Language Test–3rd edition (SPELT), and Test for Auditory Comprehension of Language–3rd edition (TACL)—for children who stutter who eventually persisted (CWS-ePer), children who stutter who eventually recovered (CWS-eRec), and children who do not stutter (CWNS).

Electrophysiological Assessment of Auditory Processing

Stimuli

Stimuli for the ERP oddball paradigm were presented either bilaterally or unilaterally (as described below) through headphones (RadioShack). The pure tones presented consisted of one tone at 1000 Hz (standard tone) and another at 2000 Hz (oddball tone). The tones were presented to each participant pseudorandomly at a 4:1 ratio of standard to oddball tones to prevent participants from predicting the presentation of a standard versus oddball stimulus. The tones were also presented pseudorandomly at two different interstimulus intervals (ISIs)—200 ms and 1000 ms. ISIs of 200 ms and 1000 ms were chosen due to their abilities to elicit robust and distinct neural responses. The shorter ISI in particular has the ability to expose differences between the participant groups in regards to their auditory processing due to the greater challenge it poses for the auditory system on account of the reduced recovery time for neurons. This typically results in a smaller ERP amplitude elicited by the subsequent tone (Hampton &

Weber-Fox, 2008; Polich, 2007). All oddball, or target, tones were followed by 1000 ms prior to the next stimulus, while the standard tones were followed by either short or long ISI at a 1:1 ratio before the next stimulus.

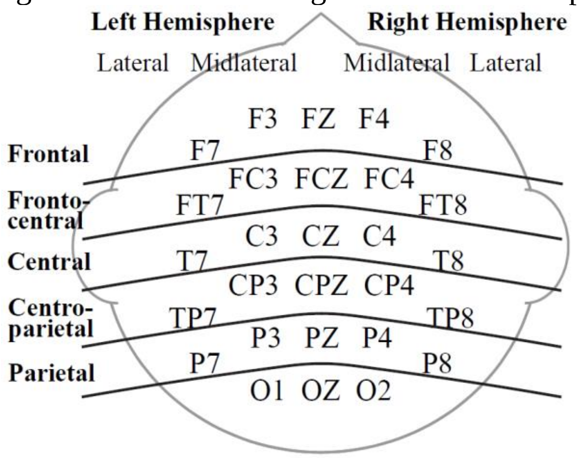
Altogether, 608 tones were presented to each participant (~122 deviants). The tones were presented randomly to the left, right, or both ears equally. The tones presented unilaterally were done so at 72 dB SPL, while those presented bilaterally were done so at 69 dB SPL, to equate the perceived loudness across each presentation.

Procedure

In a visit prior to the EEG session, the children received their hearing, stuttering, and cognitive and language evaluations. At the beginning of the EEG session, the child was fitted with an electrode cap (Quik-cap) (see Figure 2) while either watching a cartoon or playing a video game of their choice. Then, the child was seated in a single-wall sound attenuating booth (Industrial Acoustics Company Inc., NY) 140 cm from a 48 cm monitor. To help ensure that children remained relatively still throughout the paradigm and followed the task, a research assistant sat next to the child in the booth throughout the experiment. The children were instructed to listen for the higher (target) tones throughout the experiment.

In an effort to make the paradigm child friendly, and to maintain the child's attention throughout the study, the paradigm was presented as a game. The game ensured that the child would remain faced towards the screen, fixating on a point of the monitor, and that they would be attending to the audio stimuli presented through the headphones. For the game, either a child-friendly picture would be presented on the monitor, at a fixed point on the screen, or an audible spoken word would be presented every 45-105 seconds (an average of 82 tonal stimuli). Each time a picture or word stimulus was presented, the child was allowed to "fish" for a magnetic puzzle piece or build a block tower. Breaks were taken as needed to help ensure the child remained engaged in the task. If the child became distracted, the research assistant in the booth would redirect the child's attention. On average, the ERP recording session lasted 15-20 minutes, including the play breaks. At the end of the session, the child was given the opportunity to select a prize from one of five toys.

Figure 2: Electrode configuration for EEG cap



Electrode configuration for the 32 electrode cap used in recording electroencephalography (EEG) data for the participants of this study.

EEG recording and analysis

The EEG data were acquired using a 32 Ag-Cl electrode cap (Quik-cap; Figure 2), which records electrical activity at the level of the scalp (Neuroscan 4.0). The electrode sites were positioned symmetrically over the right and left hemispheres according to the International 10-20 system (American Electroencephalographic Society, 1994). The sites used are as follows: eye sites VEOG and HEOG; midline sites FZ, FCZ, CZ, CPZ, PZ, OZ; medial-lateral sites F3/F4, FC3/FC4, C3/C4, CP3/CP4, P3/P4, O1/O2; lateral sites F7/F8, FT7/FT8, T7/T8, TP7/TP8, and P7/P8. Additionally, electrodes were placed on the right and left mastoid and data were collected relative to the linked mastoids. Vertical and horizontal eye movement were tracked via electrodes over the right and left outer canthi and the left inferior and superior orbital ridge, respectively. The impedance level at each electrode at the level of the scalp was kept at 5 kOhms, while the impedance level was kept at 10 kOhms for those electrodes located on the face. During recordings, the EEG signals were amplified through a bandpass filter of 0.1 and 100 Hz and digitized online (Neuroscan 4.2) at the rate of 500 Hz.

EEG data were analyzed using EEGLAB (Delmore & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014) within MATLAB (MathWorks). ERPs for standard and target tones for the short and long ISI conditions were averaged separately. For each condition, data were epoched—a process in which the continuous EEG signal is segmented into specific time-windows. For the present study, each epoch was time-locked around a tonal stimulus, from 100 ms prior to and 1200 ms after onset of each stimulus presentation. The 100 ms preceding the onset of the stimulus served as the baseline; this time period was baseline corrected to zero in order to provide a relative zero-point for computing peak amplitudes. The data were precleaned, directly removing excessive drift, high frequency signals, and blocking from the EEG signal. Then, independent component analyses (ICA) were performed. ICA is a pattern recognition process which scans data for consistent patterns and groups identified patterns as components. Individual components reflecting blink or other eye movement were removed from the data. The data were then subjected to an automatic cleaning based on criteria that removed any remaining eye or movement artifact that exceeded a certain threshold (criteria). The automatic artifact rejection evaluated the data using a 200 ms window at 50 ms increments, excluding any epochs in which eye channels exceed a 100 µV or more change and/or a 200 µV or more change in all other channels. Finally, manual artifact rejection was performed to manually remove any epochs that contain remaining eye movement, blink, and/or muscle tension artifact.

Mean amplitudes for all ERP components of interest were evaluated. The mean amplitudes were computed relative to the baseline. Final time windows were based on visual inspection of the data, as well as previously used time windows from EEG studies of children (Kaganovich et al., 2010; Martin et al., 1988; Sharma et al., 1997; Wunderlich et al., 2006). The mean amplitudes for the ERP components of interest were assessed within the following time windows: P1 was evaluated between 90-190 ms post-onset, N1 between 170-360 ms post-onset, N2 between 350-550 ms post-onset, and P3 between 600-1000 ms post-onset.

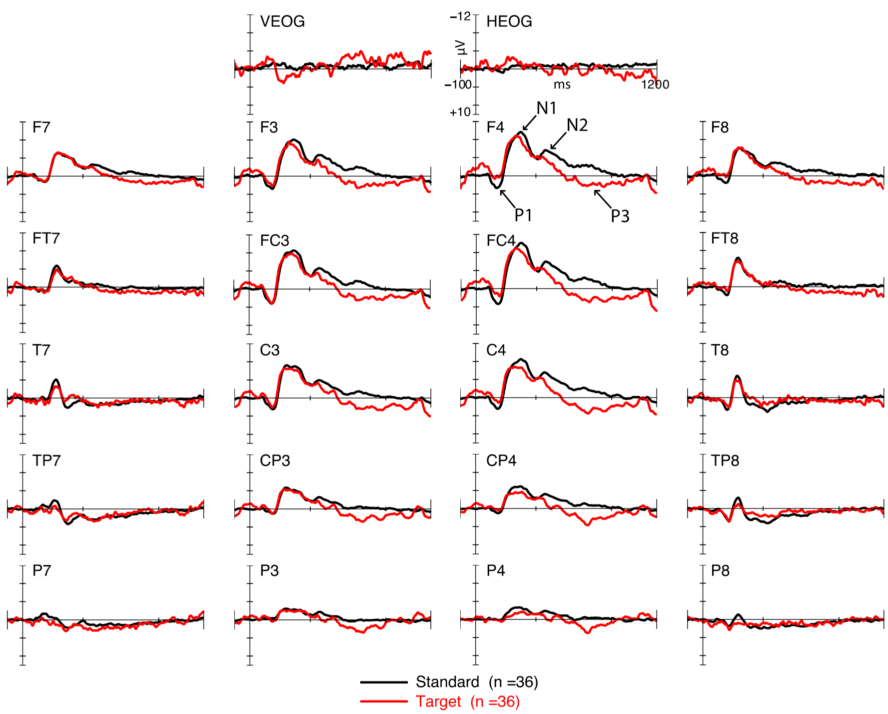
ERP analyses were conducted using SPSS (IBM). Separate repeated-measures ANOVAs were employed to assess group differences for each component of interest for the standard and target tones, for the short and long ISIs. Each repeated-measures ANOVA included a between-subjects factor (Group: CWNS, CWS-eRec, CWS-ePer) and four within-subject factors of tone condition (Cond: Standard, Target), hemisphere (Hemi: left, right), anterior-posterior scalp distribution (AP: frontal, frontocentral, central, centroparietal, occipital), and laterality (Lat: lateral, midlateral). Results which involved a significant group effect or interaction with group and condition were followed up with step-down ANOVAs with planned pairwise group comparisons, using the same ANOVA structure to evaluate differences between two groups (e.g., CWNS and CWS-eRec, CWNS and CWS-ePer, CWS-eRec and CWS-ePer). For repeated-measures with greater than one degree of freedom, the Huynh-Feldt (H-F) corrected *p*-value is reported. Results were considered significant if the *p*-value is less than .05 and trending towards significance if the *p*-value is less than 0.1. Partial eta squared (η_p^2), a measure of effect size, is reported for all significant interactions.

RESULTS

ERP Results

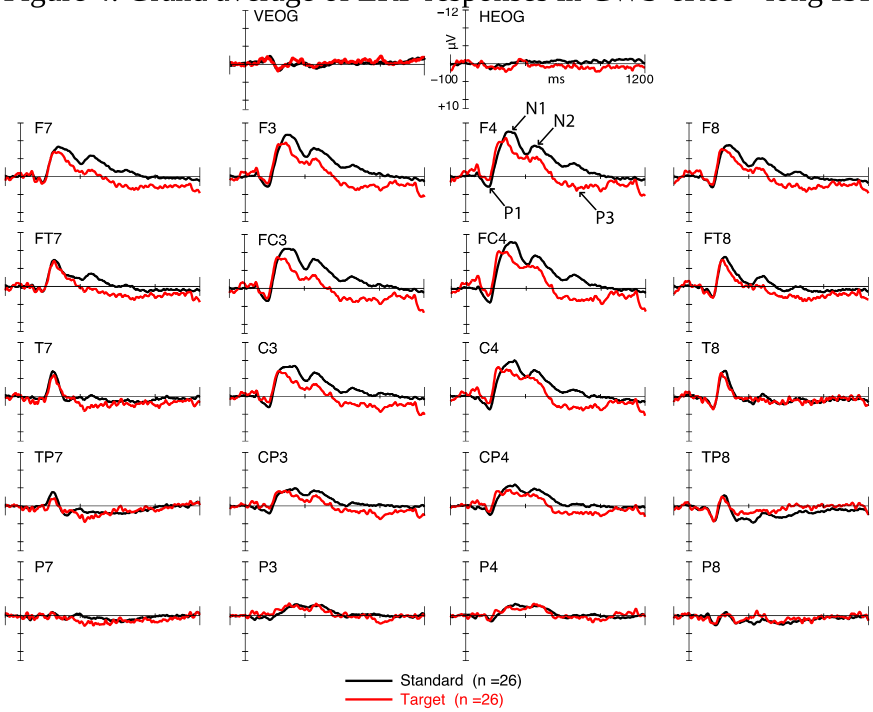
Grand averages of the neural responses to both the standard and target tones for the three groups—CWNS, CWS-eRec, and CWS-ePer—can be found in Figures 3-5 for tones presented with the long ISI and Figures 6-8 for tones presented with the short ISI. As can be seen in Figures 3, 4, and 5, long ISI tones elicited P1, N1, N2, and P3 components in all three groups. The short ISI tones also elicited P1, N1, N2, and P3 components in all three groups (Figures 6-8). Differences between groups are discussed below.

Figure 3: Grand average of ERP responses in CWNS – long ISI



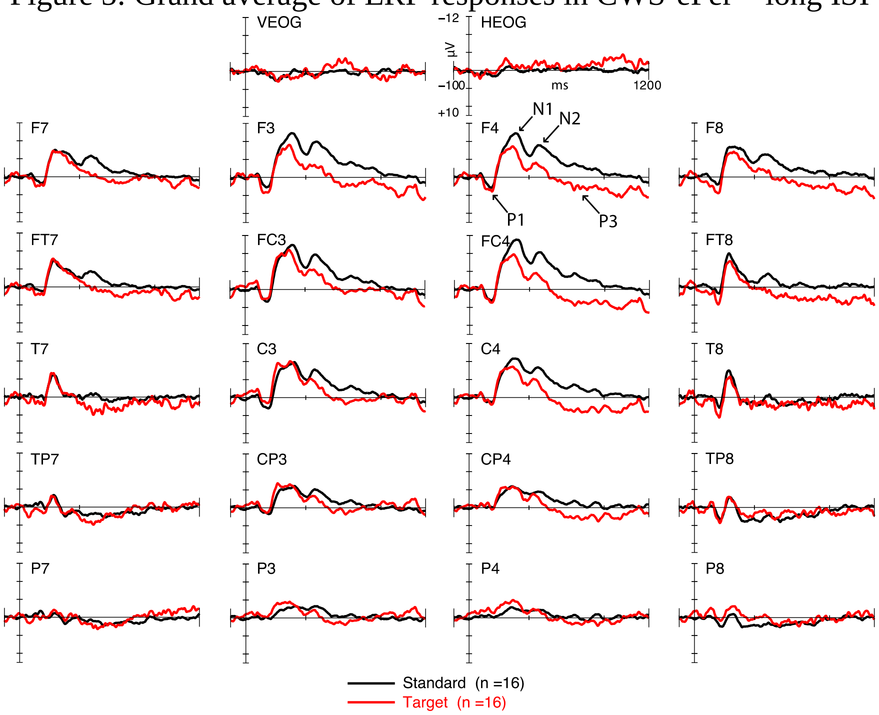
A grand average of the event-related potential (ERP) responses across electrode sites for all children who do not stutter (CWNS). ERP components were time-locked to the standard and target stimuli preceded by 1000 ms—the long interstimulus interval (ISI). For this and all subsequent ERP grand averages, negative is plotted upward.

Figure 4: Grand average of ERP responses in CWS-eRec – long ISI



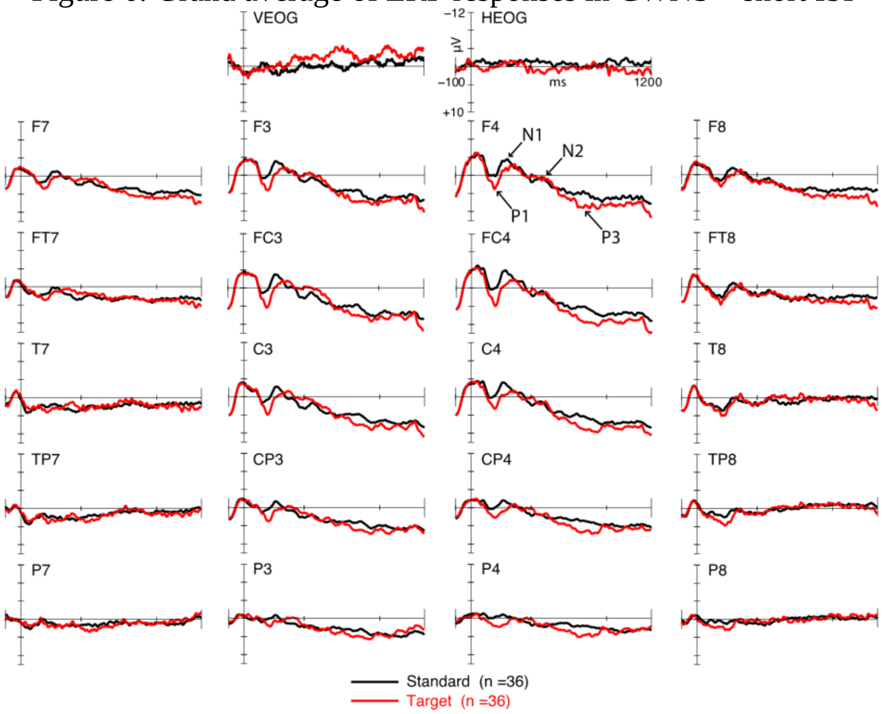
A grand average of the event-related potential (ERP) responses across electrode sites for all children who stutter who eventually recovered (CWS-eRec). ERP components were time-locked to the standard and target stimuli preceded by 1000 ms—the long interstimulus interval (ISI).

Figure 5: Grand average of ERP responses in CWS-ePer – long ISI



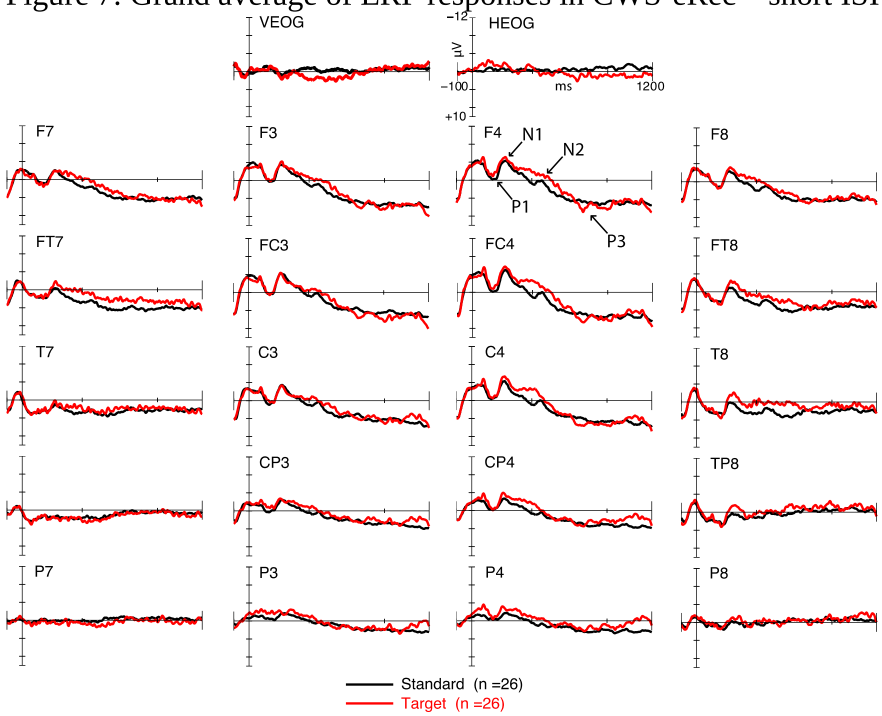
A grand average of the event-related potential (ERP) responses across electrode sites for all children who stutter who eventually persisted (CWS-ePer). ERP components were time-locked to the standard and target stimuli preceded by 1000 ms—the long interstimulus interval (ISI).

Figure 6: Grand average of ERP responses in CWNS – short ISI



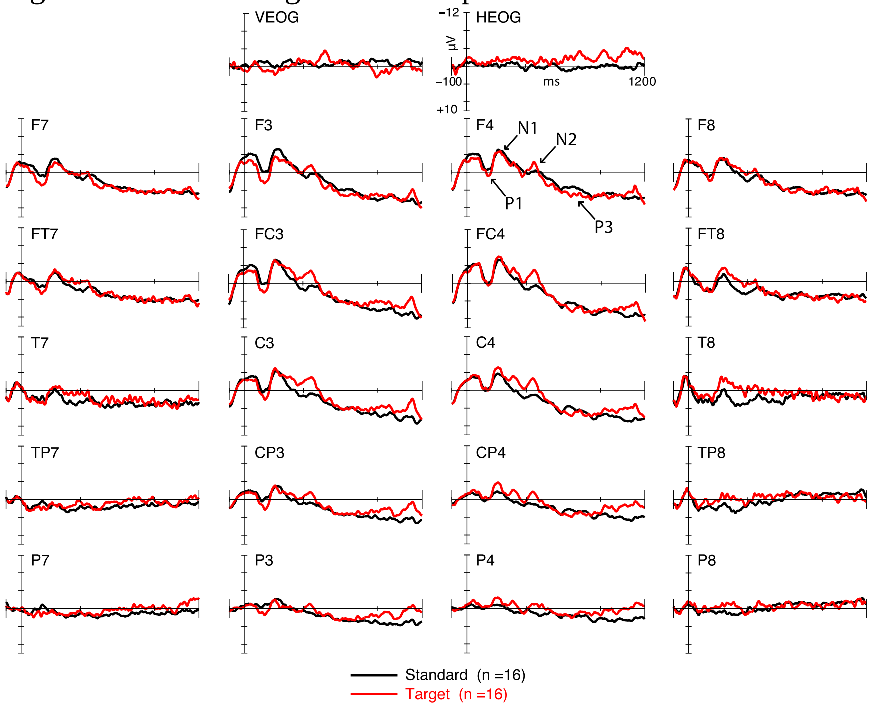
A grand average of the event-related potential (ERP) responses across electrode sites for all children who do not stutter (CWNS). ERP components were time-locked to the standard and target stimuli preceded by 200 ms—the short interstimulus interval (ISI).

Figure 7: Grand average of ERP responses in CWS-eRec – short ISI



A grand average of the event-related potential (ERP) responses across electrode sites for all children who stutter who eventually recovered (CWS-eRec). ERP components were time-locked to the standard and target stimuli preceded by 200 ms—the short interstimulus interval (ISI).

Figure 8: Grand average of ERP responses in CWS-ePer – short ISI



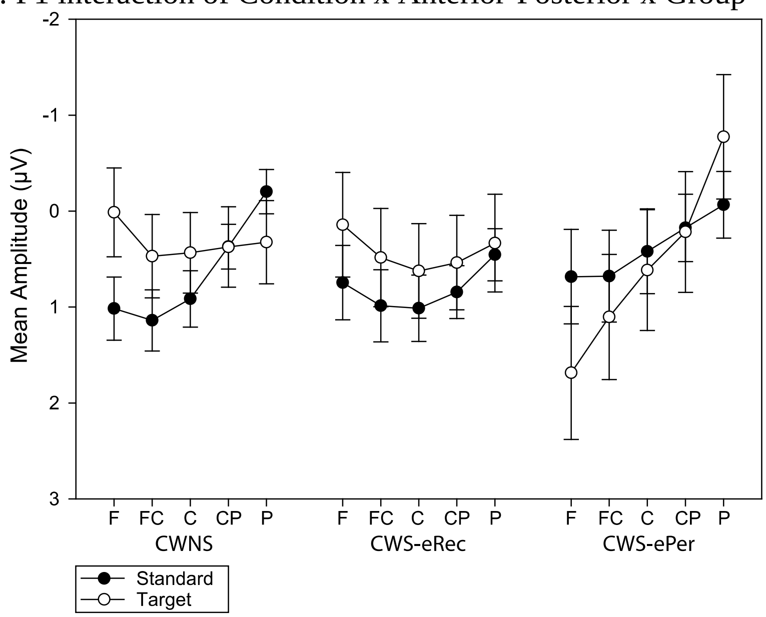
A grand average of the event-related potential (ERP) responses across electrode sites for all children who stutter who eventually persisted (CWS-ePer). ERP components were time-locked to the standard and target stimuli preceded by 200 ms—the short interstimulus interval (ISI).

Early Auditory Processing Component – P1 – Long ISI

Across the three groups, analyses of the P1 mean amplitude for the long ISI revealed significant interactions of condition and anterior-posterior scalp distribution (CondxAPxGroup: $F(2,75) = 3.078$, $p = .025$, $\eta_p^2 = .076$), as well as distribution across hemispheres (CondxAPxHemixGroup: $F(2,75) = 3.007$, $p = .010$, $\eta_p^2 = .074$). CWNS and CWS-eRec generally exhibited larger P1 amplitudes for standard compared to target tone while CWS-ePer exhibited slightly larger P1 amplitudes to target compared to standard tones, especially over frontal electrode sites.

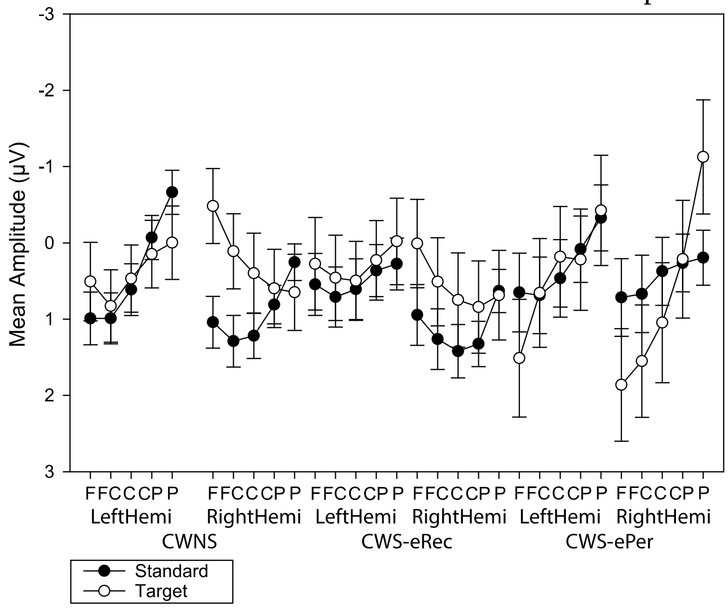
Step-down ANOVAs revealed differences in P1 amplitudes between each of the groups (Figures 9 & 10). P1 amplitudes in CWNS were largest for standard tones over frontal sites, with slightly smaller P1s for standard compared to target tones over parietal sites. A similar, but less pronounced difference between conditions was observed in CWS-eRec (CWNSxCWS-eRec: CondxAPxGroup: $F(1,60) = 1.092$, $p = .333$, $\eta_p^2 = .018$; CondxAPxHemixGroup: $F(1,60) < 1$, $p = .837$). These interactions are illustrated in Figures 9 and 10, respectively. An almost reverse P1 pattern was observed in CWS-ePer, with larger P1 amplitudes elicited by target tones, especially over frontal sites, with smaller P1 amplitudes for target compared to standard tones over parietal sites. This pattern differed between CWNS and CWS-ePer (CondxAPxGroup: $F(1,50) = 5.544$, $p = .009$, $\eta_p^2 = .100$; CondxAPxHemixGroup: $F(1,50) = 5.540$, $p = .002$, $\eta_p^2 = .100$; Figures 9 & 10) and between CWS-eRec and CWS-ePer, with the most pronounced differences observed over the right hemisphere electrode sites (CondxAPxHemixGroup: $F(1,40) = 4.201$, $p = .009$, $\eta_p^2 = .095$; Figure 10).

Figure 9: P1 interaction of Condition x Anterior-Posterior x Group – long ISI



Plots of the mean (SE) P1 amplitudes elicited by long interstimulus interval (ISI) standard and target tones for all three groups—children who do not stutter (CWNS), children who stutter who eventually recovered (CWS-eRec), and children who stutter who eventually persisted (CWS-ePer)—across anterior to posterior sites—frontal (F), frontocentral (FC), central (C), centroparietal (CP), and parietal (P). For this and all subsequent plots, negative is plotted upward to align with the ERP grand average plots.

Figure 10: P1 interaction of Condition x Anterior-Posterior x Hemisphere x Group – long ISI



Plots of the mean (SE) P1 amplitudes elicited by long interstimulus interval (ISI) standard and target tones for all three groups— children who do not stutter (CWNS), children who stutter who eventually recovered (CWS-eRec), and children who stutter who eventually persisted (CWS-ePer)—across anterior to posterior sites—frontal (F), frontocentral (FC), central (C), centroparietal (CP), and parietal (P)—over the right and left hemispheres (Hemi).

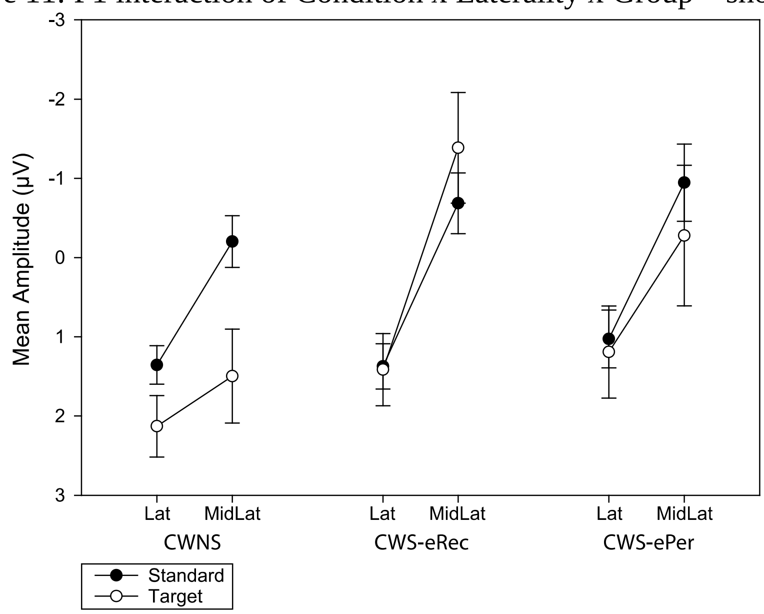
Early Auditory Processing Component – P1 – Short ISI

As with the long ISI, differences in P1 amplitudes elicited by short ISI standard and target tones were observed between groups (CondxGroup: $F(2,75) = 2.690$, $p = .074$, $\eta_p^2 = .067$; CondxLatxGroup: $F(2,75) = 3.284$, $p = .043$, $\eta_p^2 = .081$; CondxHemixGroup: $F(2,75) = 2.616$, $p = .080$, $\eta_p^2 = .065$). CWNS exhibited a robust P1 elicited by target tones over both hemispheres (Figure 12), with the largest response over mid-lateral sites (Figure 11). In contrast, CWS-eRec exhibited similar P1 amplitudes to both standard and target tones (Figures 11 & 12). CWS-ePer exhibited a larger P1 to the target tones over the left, but not right, hemisphere (Figure 12).

Step-down ANOVAs further illustrate the differences between groups. CWNS exhibited larger P1s to target tones compared to CWS-eRec (CondxGroup: $F(1,60) = 5.605$, $p = .021$, $\eta_p^2 = .085$), marked by differences in P1 amplitudes between lateral and mid-lateral electrode sites

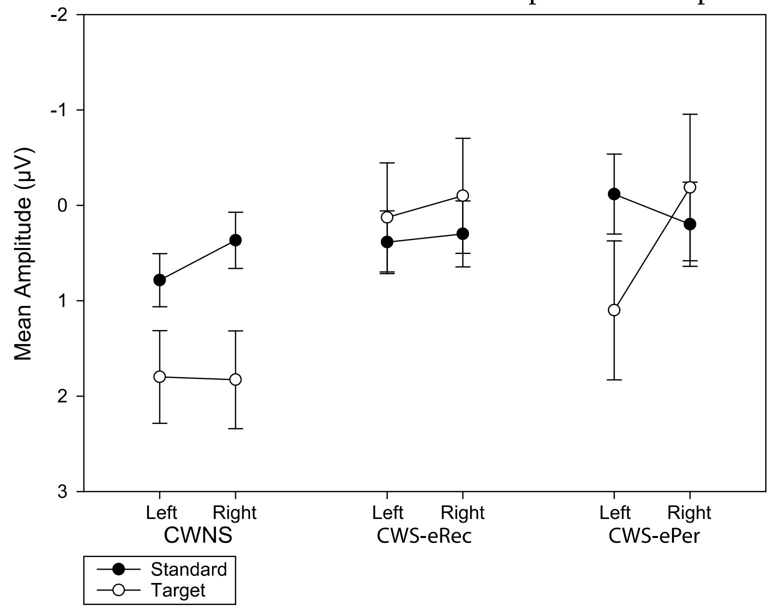
(CondxLatxGroup: $F(1,60) = 7.009$, $p = .010$, $\eta_p^2 = .105$; Figure 11). Differences between CWNS and CWS-ePer were most pronounced in P1 amplitudes over the right hemisphere, where CWNS exhibited larger P1s elicited by target tones and CWS-ePer exhibited larger P1s elicited by standard tones (CondxHemixGroup: $F(1,50) = 5.338$, $p = .025$, $\eta_p^2 = .096$; Figure 12). No significant interactions were observed between conditions or with laterality (CondxGroup: $F(1,50) < 1$, $p = .37$; CondxLatxGroup: $F(1,50) = .276$, $p = .601$, $\eta_p^2 = .005$). P1 amplitudes between standard and target tones tended to be different between CWS-eRec and CWS-ePer over the left and right hemispheres (CondxHemixGroup: $F(1,40) = 2.864$, $p = .098$, $\eta_p^2 = .067$; Figure 12), though no significant interactions were observed between conditions or with laterality (CondxGroup: $F(1,40) = 1.160$, $p = .288$, $\eta_p^2 = .028$; CondxLatxGroup: $F(1,40) = 2.326$, $p = .135$, $\eta_p^2 = .055$; Figure 11).

Figure 11: P1 interaction of Condition x Laterality x Group – short ISI



Plots of the mean (SE) P1 amplitudes elicited by short interstimulus interval (ISI) standard and target tones for all three groups—children who do not stutter (CWNS), children who stutter who eventually recovered (CWS-eRec), and children who stutter who eventually persisted (CWS-ePer)—across lateral (Lat) to mid-lateral (MidLat) sites.

Figure 12: P1 interaction of Condition x Hemisphere x Group – short ISI



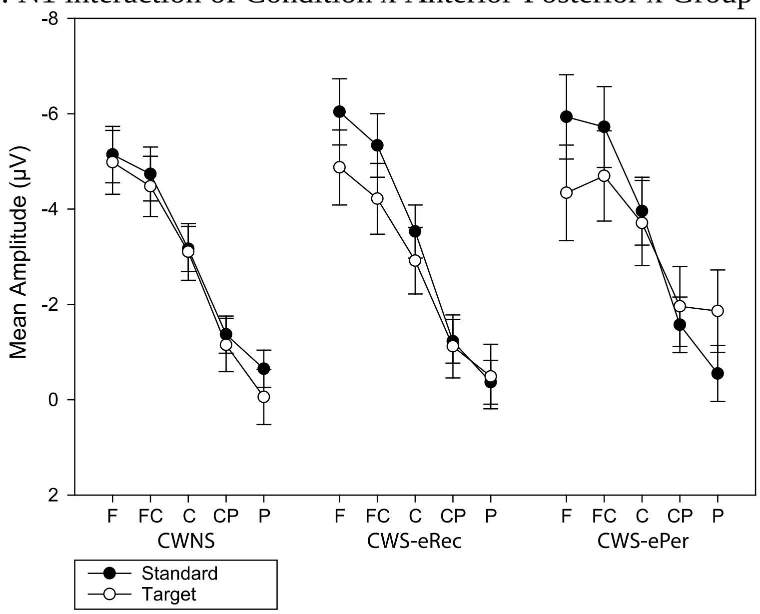
Plots of the mean (SE) P1 amplitudes elicited by short interstimulus interval (ISI) standard and target tones for all three groups—children who do not stutter (CWNS), children who stutter who eventually recovered (CWS-eRec), and children who stutter who eventually persisted (CWS-ePer)—across left and right hemispheres.

Early Auditory Processing Component – N1 – Long ISI

Between the three groups—CWNS, CWS-eRec, and CWS-ePer—there are significant differences in the elicitation of the N1 response to tones presented with the long ISI (Figures 13 & 14). CWNS and CWS-eRec exhibited similar N1 amplitudes elicited by both the standard and target tones. CWS-ePer, on the other hand, exhibited a larger N1 to the standard tones over the frontal-frontocentral sites with a larger response to the target tones over posterior sites (CondxAPxGroup: $F(2,75) = 2.800$, $p = .041$, $\eta_p^2 = .069$; Figure 13). There was a trend toward significant differences in N1 amplitudes between the three groups across hemispheres (CondxAPxHemixGroup: $F(2,75) = 2.001$, $p = .075$, $\eta_p^2 = .051$; Figure 14).

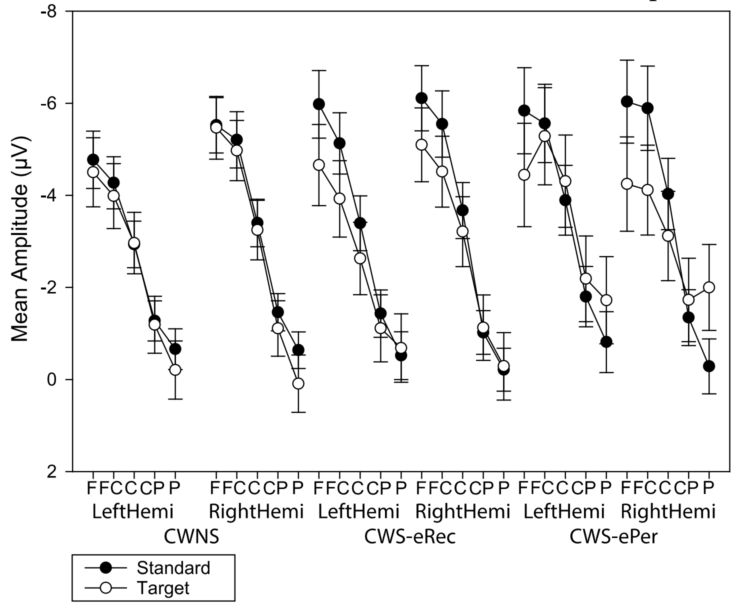
Step-down ANOVAs comparing CWNS and CWS-eRec revealed similar N1 amplitudes for standard and target tones between groups, with no significant interactions between group, condition, and anterior-posterior sites (CondxAPxGroup: $F(1,60) = 2.210$, $p = .126$, $\eta_p^2 = .036$; CondxAPxHemixGroup: $F(1,60) < 1$, $p = .824$). Differences were observed between CWNS and CWS-ePer, with CWS-ePer exhibiting reduced N1 amplitudes to target tones over frontal sites, with larger amplitudes to target tones over parietal sites compared to CWNS (CondxAPxGroup: $F(1,50) = 4.718$, $p = .020$, $\eta_p^2 = .086$; Figure 13). These differences were largest over the right hemisphere (CondxAPxHemixGroup: $F(1,50) = 4.154$, $p = .012$, $\eta_p^2 = .077$; Figure 14). A trend towards significance between CWS-eRec and CWS-ePer also revealed reduced N1 amplitudes elicited by target tones in CWS-ePer compared to CWS-eRec over the right hemisphere (CondxAPxHemixGroup: $F(1,40) = 2.453$, $p = .068$, $\eta_p^2 = .058$; Figure 14), though no difference in anterior-posterior scalp distribution alone (CondxAPxGroup: $F(1,40) = 1.002$, $p = .357$, $\eta_p^2 = .024$; Figure 13).

Figure 13: N1 interaction of Condition x Anterior-Posterior x Group – long ISI



Plots of the mean (SE) N1 amplitudes elicited by long interstimulus interval (ISI) standard and target tones for all three groups— children who do not stutter (CWNS), children who stutter who eventually recovered (CWS-eRec), and children who stutter who eventually persisted (CWS-ePer)—across anterior to posterior sites.

Figure 14: N1 interaction of Condition x Anterior-Posterior x Hemisphere x Group – long ISI

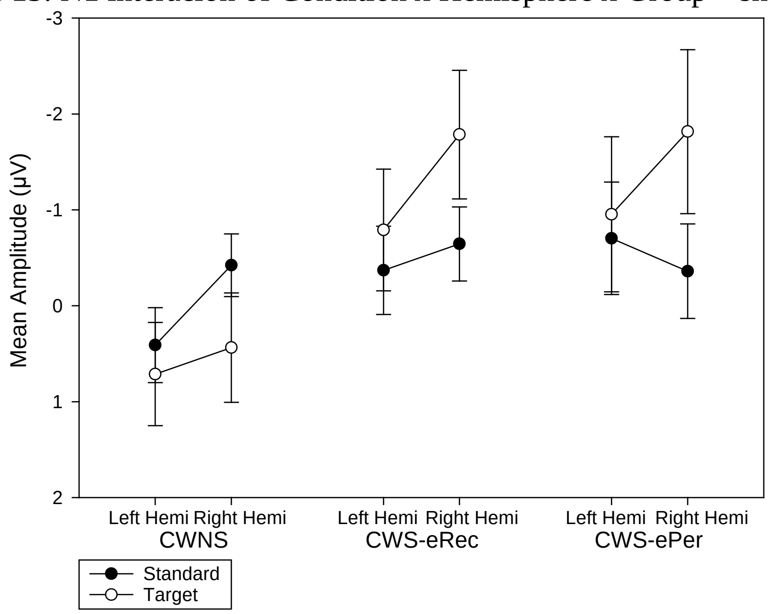


Plots of the mean (SE) N1 amplitudes elicited by long ISI standard and target tones for all three groups—CWNS, CWS-eRec, and CWS-ePer—across anterior to posterior sites—frontal (F), frontocentral (FC), central (C), centroparietal (CP), and parietal (P)— over left and right hemispheres (Hemi).

Early Auditory Processing Component – N1 – Short ISI

N1 mean amplitudes elicited by short ISI standard and target tones were different between all three groups (Figure 15). CWNS exhibited larger N1s elicited by standard tones, whereas CWS-eRec and CWS-ePer exhibited larger N1s elicited by target tones, with the largest N1 amplitude differences over the right hemisphere (CondxHemixGroup: $F(2,75) = 3.280$, $p = .043$, $\eta_p^2 = .080$; Figure 15). Step-down ANOVAs revealed that these differences for short ISI tones trended toward significant between CWNS and CWS-eRec (CondxHemixGroup: $F(1,60) = 3.331$, $p = .073$, $\eta_p^2 = .053$), while these differences were statistically significant between CWNS and CWS-ePer (CondxHemixGroup: $F(1,50) = 4.797$, $p = .033$, $\eta_p^2 = .088$; Figure 15). However, between CWS-eRec and CWS-ePer, there were no significant interactions between condition and hemisphere (CondxHemixGroup: $F(1,40) < 1$, $p = .497$; Figure 15).

Figure 15: N1 interacion of Condition x Hemisphere x Group – short ISI

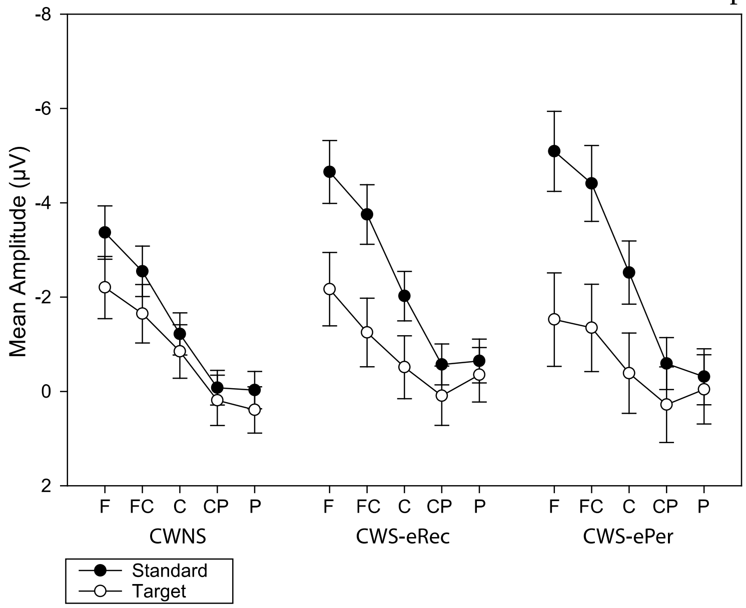


Plots of the mean (SE) N1 amplitudes elicited by short interstimulus interval (ISI) standard and target tones for all three groups—children who do not stutter (CWNS), children who stutter who eventually recovered (CWS-eRec), and children who stutter who eventually persisted (CWS-ePer)—across left and right hemispheres (Hemi).

Late Auditory Processing Component – N2 – Long ISI

In response to tones preceded by the long ISI, the N2 elicited by standard tones was smaller in CWNS across frontal and central sites than in CWS-eRec and CWS-ePer (Figure 16). The N2 amplitudes in response to standard and target tones were comparable in CWNS, while CWS-Rec and CWS-ePer exhibited larger N2 amplitudes elicited by standard compared to target tones (CondxAPxGroup: $F(2,75) = 2.049$, $p = .098$, $\eta_p^2 = .052$). Step-down ANOVAs revealed that the N2 amplitude differences trended towards significance between CWNS and CWS-ePer (CondxAPxGroup: $F(1,50) = 3.183$, $p = .054$, $\eta_p^2 = .060$; Figure 16) but not between CWNS and CWS-eRec (CondxAPxGroup: $F(1,60) = 2.127$, $p = .128$, $\eta_p^2 = .034$) or CWS-eRec and CWS-ePer (CondxAPxGroup: $F(1,40) < 1$, $p = .621$; Figure 16).

Figure 16: N2 interaction of Condition x Anterior-Posterior x Group – long ISI



Plots of the mean (SE) N2 amplitudes elicited by long ISI standard and target tones for all three groups—children who do not stutter (CWNS), children who stutter who eventually recovered (CWS-eRec), and children who stutter who eventually persisted (CWS-ePer)—across anterior to posterior sites—frontal (F), frontocentral (FC), central (C), centroparietal (CP), and parietal (P).

Late Auditory Processing Component – N2 – Short ISI

CWNS, CWS-eRec, and CWS-ePer exhibited similar N2 amplitudes elicited by short ISI tones, with comparable responses elicited by standard and target tones. No significant interactions involving group and condition were observed between the three groups (CondxGroup: $F(2,75) < 1$, $p = .619$).

Late Auditory Processing Component – P3

All three groups exhibited P3 responses elicited by target tones (Figures 3-8). Although it appears that CWNS exhibited a more robust P3 to target tones compared to the other two groups, no significant interactions involving the group and condition were observed for the P3 elicited by long or short ISI target tones (CondxGroup – long ISI: $F(2,75) < 1$, $p = .964$; CondxGroup – short ISI: $F(2,75) < 1$, $p = .389$).

DISCUSSION

The purpose of the current study was to examine whether auditory processing abilities are related to persistence or recovery in developmental stuttering. Children were followed longitudinally and eventual stuttering outcomes were determined. A group of young CWS were divided into two groups based on whether they were found to eventually persist in or recover from stuttering. We then compared the neural responses elicited by nonlinguistic auditory stimuli using an auditory oddball paradigm between these two groups of CWS—CWS-eRec and CWS-ePer—and their typically fluent peers. We found significant differences between CWS-eRec and CWS-ePer in the early indices of auditory processing, P1 and N1. Despite previous findings of differences between IWS and NFS in later indices of auditory processing, the presence of or amplitude of P3 (Hampton & Weber-Fox, 2008; Kaganovich et al., 2010), we did not find significant differences between groups in later components, N2 or P3. These findings suggest differences in earlier, but not later auditory processes may play a role in stuttering persistence in young CWS. Such findings are important for informing our current understanding of developmental stuttering. Furthermore, the current findings could inform future studies designed to develop a battery of tasks to evaluate early auditory processing skills in young CWS in order to help better predict which children will eventually persist in stuttering and which children will eventually recover from stuttering.

Early Nonlinguistic Auditory Processing (P1 and N1) in CWS

Earlier auditory processing components, P1 and N1, reflect exogenous processing of stimuli, such as external factors of a sound, including loudness and frequency. They are also influenced by underlying cognitive processes. Both the P1 and N1 have been found to be affected by attention, with greater amplitudes elicited in response to attended stimuli (Coch et al., 2006; Giuliano, Karns, Neville, & Hillyard, 2014; Hansen & Hillyard, 1980; Herrmann & Knight, 2001; Hillyard et al., 1973; Karns, Isbell, Giuliano, & Neville, 2015; Luck & Kappenman, 2012).

Long ISI Tones

In previous studies using the current oddball paradigm, significant differences in P1 amplitudes between conditions have not been identified (Kaganovich et al., 2010). However, P1 amplitudes have been found to decrease with age (Čeponiené et al., 2002; Karns et al., 2015; Luck & Kappenman, 2012; Mahajan & McArthur, 2012; Sharma et al., 1997; Wetzel, Widmann, Berti, & Schröger, 2006; Wunderlich et al., 2006). In contrast, N1 amplitudes elicited by target tones are often larger than N1s elicited by standard tones in children, with reduced differences in N1 amplitude between conditions with age (Tomé et al., 2015).

Both CWNS and CWS-eRec elicited larger P1 amplitudes elicited by standard compared to target tones. In contrast, CWS-ePer exhibited similar P1 amplitudes to standard and target tones, with slightly larger P1 amplitudes elicited by target tones, a different ERP pattern than CWNS and CWS-eRec. This finding suggests an atypical P1 response pattern elicited by long ISI tones in children who will eventually persist in stuttering and may reflect atypical or different early auditory encoding processes in CWS-ePer compared to CWS-eRec and CWNS.

For the N1, CWNS and CWS-eRec exhibited similar N1 amplitudes elicited by standard and target tones while CWS-ePer exhibited more differences between conditions, marked by larger N1 amplitudes elicited by standard tones over frontal sites and larger N1s to target tones over posterior sites. The N1 is thought to reflect both automatic neural responses to stimuli as well as attention toward stimuli. These findings suggest that CWS-ePer may demonstrate atypical early auditory encoding and attention, with potentially increased attention to the standard tones, which would be different than attention patterns in adults, which are typically larger for target, or rare, tones (Kaganovich et al., 2010). Importantly, these patterns differ from both CWS who eventually recover and children who never stuttered.

Unlike previous studies of early auditory processing components based on an auditory oddball paradigm (Hampton & Weber-Fox, 2008; Kaganovich et al., 2010), the current findings indicate that early auditory processes are distinct between children who stutter and children who do not stutter. Further, the current findings indicate that these processes, both P1 and N1, are distinct between children who persist in and those who recover from stuttering. These findings indicate that CWS-ePer exhibited atypical early auditory processing skills compared to CWNS and CWS-eRec, while early auditory processing abilities in CWS-eRec more closely resemble those of CWNS. The similarities in early auditory processing between CWS-eRec and CWNS may also account for why Kaganovich and colleagues (2010) did not find differences in early ERP components between CWNS and CWS, as their CWS group contained children who would eventually recover, which may have washed out potential differences between groups.

It appears that CWS-ePer may have atypical early auditory attention skills compared to CWS-eRec and CWNS, which may impact their encoding of auditory information. This difference in attention may also impact early auditory processes for linguistic stimuli in CWS-ePer, as reported in studies of auditory language processing (Kreidler, K. et al., 2017; Mohan & Weber, 2015; Usler & Weber-Fox, 2015). Based on the theoretical model by Guenther (2006), auditory processing and the auditory feedback system play a substantial role in the sensory-to-motor processing between hearing and speech. As explained by the DIVA model, the auditory processing system must conduct itself in a precise and efficient manner in order to produce fluent speech. Variance in early auditory processing skills of CWS-ePer may contribute to disruptions in the auditory processing system, thus playing a role in differences observed in auditory language processing, and potentially contributing to the presence of stuttering-like disfluencies.

Short ISI Tones

Presenting stimuli with a shorter ISI can poses greater demands on the auditory system because there is less time for neurons to recover and respond again to stimuli (Polich, 2007). The reduced recovery time, or neural refractory period, has been found to expose group differences between adults who stutter and fluent peers, as the shorter ISI is more challenging for the auditory system (Hampton & Weber-Fox, 2008).

A previous study in young CWS did not observe distinct ERP components for the short ISI due to the decreased neuronal recovery time (Kaganovich et al., 2010). The current study, with more participants in each group and employing a slightly different data analysis technique, observed distinct P1, N1, N2, and P3 responses elicited by the standard and target tones in all groups. Although the same ERP components were elicited by tones preceded by long and short ISIs, the patterns of ERP responses differed. Unlike early auditory ERPs elicited by the long ISI condition, where CWNS and CWS-eRec exhibited similar patterns, for the short ISI, differences were observed between these groups. In the current study, CWNS exhibited larger P1 amplitudes elicited by target than standard tones. In contrast, CWS-eRec exhibited similar P1 amplitudes for both standard and target tones while CWS-ePer exhibited larger P1s to target tones over the left hemisphere, with similar P1 amplitudes to standard and target tones over the right hemisphere. P1 amplitudes tended to differ between CWS-eRec and CWS-ePer, specifically over the left hemisphere, while P1s in CWNS differed from both CWS-eRec and

CWS-ePer. These findings suggest atypical early auditory processing in both CWS-eRec and CWS-ePer when stimuli are presented rapidly and neural recovery time is short.

CWNS exhibited N1 amplitudes that were comparable between standard and target tones, similar to their N1 responses for long ISI tones. In contrast, both CWS-eRec and CWS-ePer exhibited larger N1 amplitudes elicited by target tones. These patterns tended to differ between CWNS and CWS-eRec and reached significance between CWNS and CWS-ePer, while no differences were observed between CWS-eRec and CWS-ePer. These findings differ from findings across groups when processing stimuli preceded by the long ISI. While CWNS exhibited similar N1 responses for both long and short ISIs, CWS-eRec exhibited differences between short ISI standard and target tones that were not present when tones were preceded by long ISIs. These findings suggest that, similar to CWS-ePer, CWS-eRec may have atypical auditory processing and attention abilities; however, these difficulties are not apparent until the processing demands on the auditory processing system are increased. Increased cognitive load, as experienced with short ISIs, reveals less pronounced auditory processing difficulties in CWS-eRec, such that CWS-eRec exhibit early ERP patterns more similar to early auditory processing abilities in CWS-ePer. On the other hand, when cognitive demands are decreased, as with longer ISIs, differences between CWS-eRec and CWS-ePer can then be observed. Based on these findings, both CWS-eRec and CWS-ePer may have difficulty or deficits in their auditory processing pathway and attentional allocation; however, such differences in CWS-eRec may only be evident when these systems are subjected to increased demands. It is possible that this difference in early auditory processing between CWS-eRec and CWS-ePer, may play a role in recovery from or persistence in stuttering in young children.

Additionally, differences between N1 amplitudes elicited by the short ISI standard and target tones were predominantly over the right hemisphere. This pattern is consistent with other studies reporting differences over the right hemisphere in brain activity in both children and adults who stutter (Hampton & Weber-Fox, 2008; Kreidler et al., 2017; Mohan & Weber, 2015; Watkins et al., 2008; Weber-Fox et al., 2013; Loucks, T., Kraft, S. J., Choo, A. L., Sharma, H., & Ambrose, N. G., 2011). Together, these findings reveal that both CWS-eRec and CWS-ePer may have atypical early auditory processing abilities when demands on their auditory processing and cognitive systems are increased. Furthermore, these atypical skills may be associated with atypical language processing reported in other studies (Kreidler et al., 2017; Mohan & Weber, 2015; Usler & Weber-Fox, 2015; Weber-Fox et al., 2013).

Summation of Findings for Early Auditory Processing

CWS-ePer exhibited atypical auditory processing for nonlinguistic auditory stimuli for both long and short ISI tones. The finding of a compromised auditory processing system in CWS-ePer suggests that atypical auditory processing and attentional abilities may contribute to atypical flow of information in their auditory processing system and feedback loops. Such differences may then contribute to the presence of disfluencies in speech. CWS-eRec have auditory processing and attentional allocation abilities more comparable to CWNS until cognitive demands are increased. Analyses of neural responses to stimuli preceded by shorter ISIs help to show that CWS-eRec exhibit discrepancies in their auditory processing abilities, signifying some degree of atypical auditory processing across all CWS, regardless of eventual stuttering outcome. However, the differences are limited to situations with higher cognitive demand in CWS-eRec; this may play a role in, or contribute to their eventual recovery from stuttering. On the other hand, the more widespread differences in auditory processing in CWS-ePer compared to CWNS and CWS-eRec may be more difficult to overcome with maturation, thus contributing to persistence in stuttering. These findings are consistent with a previous study in AWS (Hampton & Weber-Fox, 2008), which found differences in correlations between early indices of auditory processing and behavioral measures of reaction time and accuracy. In studies of AWS, it is difficult know whether differences may be part of the cause of stuttering or result from years of accommodation and compensatory strategies for stuttering. However, the differences in early auditory processing in CWS-ePer in the current study may suggest that such differences among this population in adulthood may indeed be present from an early point in development.

Later Nonlinguistic Auditory Processing (N2 and P3) in CWS

Previous studies have found that IWS differ significantly in their later auditory processing abilities, interpreted as differences in attentional allocation and working memory abilities between IWS and fluent peers (Hampton & Weber-Fox, 2008; Kaganovich et al., 2010). Contrary to these findings, no significant differences in the P3 response were observed between groups in the current study. However, differences in the N2 component, another measure of later auditory processing, were observed, a pattern which was not reported in previous studies. Similar to the P3, the N2 is impacted by cognitive processes, such as working memory and attentional allocation, and is thought to reflect conflict monitoring (Luck & Kappenman, 2012). Both the N2 and P3 are found to be elicited by oddball, or target, stimuli (Luck, 2005; Polich, 2007). In the current study, all three groups—CWNS, CWS-eRec, and CWS-ePer—exhibited a typical P3 component, with a more robust response to short and long ISI target tones. All three groups also exhibited similar N2s when tones were preceded by short ISIs, with an equal response to both the standard and target tones.

Differences arose, however, in the N2 component elicited by long ISI tones. CWNS exhibited comparable N2 amplitudes to both standard and target tones, while CWS-eRec and CWS-ePer exhibited a larger N2 amplitudes to standard tones. The pattern observed in CWS is atypical, as standard tones should not require updating working memory, nor should they register as a conflict. These differences trended towards significant between CWNS and CWS-ePer only. Though CWS-eRec exhibited similar N2 patterns to CWS-ePer, the comparison between CWS-eRec and CWNS did not reach significant. Since N2 amplitudes between CWNS and CWS-eRec and between CWS-eRec and CWS-ePer were not significantly different, the trend towards a significant difference between the three groups indicates that CWS-eRec presented with N2 responses that were between CWS-ePer and CWNS. Thus, while CWS-ePer present with later auditory processing abilities that differ from CWNS, the N2 response is not a distinguishable marker of eventual persistence of or recovery from stuttering in the current study.

Implications of Current Findings

The current findings differ from previous studies of auditory processing in individuals who stutter and do not support our hypotheses. We hypothesized that CWS-ePer would exhibit a significantly reduced P3 as compared to CWS-eRec; however, no differences in P3 amplitude or elicitation were found across groups. Further, we hypothesized that there would not be differences in indices of early auditory processing between CWS-ePer and CWS-eRec, which was not supported as there were significant differences for both components of early auditory processing—P1 and N1—between CWS-ePer and CWS-eRec. These hypotheses were based on findings from previous studies of auditory processing in IWS. Previous studies of children and adults who stutter found atypical later auditory processing abilities and reduced attentional allocation and working memory abilities in CWS and CWS (Hampton & Weber-Fox, 2008; Kaganovich et al., 2010). Despite the similarities between the current and previous studies, both of the previous studies had fewer participants (n = 22, Hampton & Weber-Fox, 2008; n = 36, Kaganovich et al., 2010) compared to the current project (n = 78). The current findings may suggest that the smaller number of participants may represent a subset of IWS who have difficulty with attention allocation and/or updating of working memory. Additionally, a larger number of participants may be necessary to identify differences in early auditory processing in young children who stutter.

Another potential reason for differences between the current findings and a previous study in CWS is that the previous study only compared ERPs between CWNS and CWS (Kaganovich et al., 2010), thus averaging across children who would eventually persist and those who would recover. The current study was able to analyze ERP components between CWS once their eventual outcome in stuttering was known. Analyzing these participants as separate groups resulted in different findings. While the previous findings among CWS did not see differences in early auditory processing, the current findings indicated greater differences in CWS in early auditory processing components. Together, these studies support the hypothesis that early cognitive processes differ between CWS and CWNS.

Early auditory processes are impacted by attentional allocation (Coch et al., 2006; Giuliano, Karns, Neville, & Hillyard, 2014; Hansen & Hillyard, 1980; Herrmann & Knight, 2001; Hillyard et al., 1973; Karns, Isbell, Giuliano, Neville, 2015; Luck & Kappenman, 2012). Our findings indicate that early auditory processes and attentional allocation differ among CWS, and may be a distinguishing factor between CWS-eRec and CWS-ePer. The current findings align with a previous MRI study which indicated that CWS have abnormal connectivity differences involving the default mode network (DMN) and its connectivity with the somatomotor network, the attention network, and the executive control network. Further, this study also found differences between CWS-eRec and CWS-ePer, which indicated that atypical connection patterns between the DMN and attention and executive control networks may predict persistence in stuttering (Chang, Angstadt, Chow, Etchell, Garnett, Choo, Kessler, Welsch, & Sripada, 2018). These differences in neural connection pathways, along with the findings of the current study, provide converging evidence of differences in neurophysiological aspects of attention in CWS, and marked differences in CWS who will eventually persist in stuttering.

Limitations and Future Directions

One limitation of the current study is that of the 16 CWS-ePer, three of the children were only followed for one year after their initial participation, while the other CWS-ePer were followed for two or more years after initial participation. Though there is a great likelihood of natural recovery within 15 months post-onset (de Sonneville-Koedoot et al., 2015; Yairi & Ambrose, 1999), on average, children recover around 2 years post-onset (Yairi & Seery, 2015; Yairi & Ambrose, 2005). Even within our set of CWS-eRec, on average, children recovered during year 3 of the study. Thus, children who were followed for less than two years following initial participation may have recovered at a later time. As the purpose of this study is to determine differences between individuals who will eventually persist and those who will recover, it is pertinent that we can adequately distinguish persistence versus recovery. Otherwise, misidentified children may reduce precision in the findings and prevent us from accurately reporting differences between these populations. Future studies would benefit from following a larger population of children who stutter for additional years after initial participation in order to even more reliably determine eventual outcomes of persistence in or recovery from stuttering. This would provide additional information about differences in auditory processing skills in CWS and their relationship to persistence or recovery in developmental stuttering.

In our daily, natural environments, our auditory processing systems are taxed with more complex tasks than the pure tone task employed in the current study. Thus, it could prove beneficial to also include simple and complex nonlinguistic and linguistic auditory processing tasks in addition to a pure-tone nonlinguistic auditory paradigm in order to obtain a well-rounded picture of auditory processing abilities in CWS.

Furthermore, unlike the study conducted by Hampton & Weber-Fox (2008), which collected behavioral responses to the detection of stimuli, the current study did not require any behavioral responses from the participants. The absence of a required behavioral response is due to the young age of the participants. However, without such a task it is difficult to be certain that the children were engaged throughout the paradigm. This is an important consideration, seeing as the results indicate potential differences in cognitive processes, such as attention, in CWS. This proves problematic if, for example, when looking at group differences, the results may be skewed by decreased attention during the task itself. If certain participants are less engaged and more easily distracted during the task, then their lack of engagement during the task may account for the differences seen in the ERPs.

CONCLUSION

Given previous results indicating atypical attentional allocation and updating of working memory in young children who stutter compared to fluent peers (Kaganovich et al., 2010), the current study evaluated whether early differences in auditory processing may predict persistence or recovery from stuttering. These findings provide critical information regarding auditory processing in young CWS. Based on our results, it appears that early auditory processing may play a role in persistence or recovery in stuttering. Our findings suggest that, while CWS-eRec may have less efficient auditory processing abilities compared to CWNS, these differences are most pronounced when cognitive demands are high, such as in short ISI conditions. When cognitive demands are lower, such as in longer ISI conditions, auditory processing skills between CWNS and CWS-eRec are similar. In contrast, CWS-ePer exhibit more impacted auditory processing, evidenced by atypical auditory processing for both short and long ISI conditions. Although auditory processing skills in CWS-eRec lag behind CWNS, the current findings suggest that early auditory processes may support recovery from stuttering in at least some CWS-eRec. Similarly, atypical auditory processing in CWS-ePer may play a role in the persistence of stuttering. These findings could have implications for theoretical models of developmental stuttering. Future studies might benefit from the development of tasks that evaluate early auditory processing skills in young CWS, which may help discriminate children who will eventually persist from those who will recover from stuttering.

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