Speech-induced suppression of evoked auditory fields in children who stutter

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Abstract

Auditory responses to speech sounds that are self-initiated are suppressed compared to responses to the same speech sounds during passive listening. This phenomenon is referred to as speech-induced suppression, a potentially important feedback-mediated speech-motor control process. In an earlier study, we found that both adults who do and do not stutter demonstrated reduced amplitude of the auditory M50 and M100 responses to speech during active production relative to passive listening. It is unknown if auditory responses to self-initiated speech-motor acts are suppressed in children or if the phenomenon differs between children who do and do not stutter. As stuttering is a developmental speech disorder, examining speech-induced suppression in children may identify possible neural differences underlying stuttering close to its time of onset. We used magnetoencephalography to determine the presence of speech-induced suppression in children and to characterize the properties of speech-induced suppression in children who stutter. We examined the auditory M50 as this was the earliest robust response reproducible across our child participants and the most likely to reflect a motor-to-auditory relation. Both children who do and do not stutter demonstrated speech-induced suppression of the auditory M50. However, children who stutter had a delayed auditory M50 peak latency to vowel sounds compared to children who do not stutter indicating a possible deficiency in their ability to efficiently integrate auditory speech information for the purpose of establishing neural representations of speech sounds.

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Keywords

stuttering; child development; speech-motor control; auditory processing; M50; magnetic source imaging

Introduction

Stuttering is a developmental disorder defined by frequent and involuntary repetitions and/or prolongations of sounds as well as silent blocks that disrupt speech fluency and is prevalent in approximately 5% of preschool children (Yairi and Ambrose 1999). The onset of the disorder typically occurs between 2 and 5 years of age (Bloodstein and Ratner 2008). There is evidence for a genetic aetiology of developmental stuttering (Ambrose, Cox, Yairi 1997; Howie 1981; Kang et al., 2010; Kidd, Heimbuch, Records 1981; Lan et al., 2009; Riaz et al., 2005; Suresh et al., 2006; Wittke-Thompson et al., 2007). There are also various neuroanatomical (Beal et al., 2007; Foundas et al., 2001; Foundas et al., 2004; Jäncke, Hänggi, Steinmetz 2004; Kell et al., 2009; Sommer et al., 2002; Song et al., 2007; Watkins et al., 2008) and neurophysiological (Blomgren et al., 2003; Braun et al., 1997; Chang et al., 2009; De Nil et al., 2000; De Nil, Kroll, Houle 2001; De Nil et al., 2008; Fox et al., 1996; Fox et al., 2000; Giraud et al., 2008; Kell et al., 2009; Lu et al., 2009; Neumann et al., 2003; Neumann et al., 2005; Preibisch et al., 2003; Watkins et al., 2008) differences that have been observed in adults who stutter relative to fluent speakers. To our knowledge, only two studies have examined the neural correlates of stuttering in children (Chang et al., 2008; Weber-Fox et al., 2008). Given that stuttering typically has its onset in the preschool years there is a great deal to be gained from increasing our understanding of the neural signatures of this disorder early in its presentation and development.

Chang et al. (2008) investigated neuroanatomical differences in children who stutter relative to non-stuttering and recovered-from-stuttering peers. Similar to adults who stutter, children who stutter were found to have deficient white matter connectivity, as measured by fractional anisotropy, underlying areas near the left ventral premotor and motor cortices. However, children who stutter also differed from their age-matched fluently speaking peers in a unique way relative to previous reports of differences between adults who stutter and their fluently speaking peers. Chang et al. (2008) reported that children who stutter had reduced grey matter volume compared to children who do not stutter in the left inferior frontal gyrus and bilateral middle temporal regions. Conversely, adults who stutter have been found to have increased grey matter in the left inferior frontal gyrus and bilateral superior temporal regions, including primary auditory cortex (Beal et al., 2007; Song et al., 2007). However, Kell et al. (2009) found reduced grey matter in the left inferior frontal gyrus in adults who stutter as well as in former stutterers who had recovered from stuttering.

Weber-Fox, Spruill, Spencer, & Smith (2008) measured event-related potentials (ERPs) of children who stutter and fluent children in a visual rhyming task. Children who stutter demonstrated lower accuracy on rhyming judgments relative to fluent children. However, the children who stutter did not differ from fluent children in the ERP component associated with the rhyming effect in this task. Instead, children who stutter demonstrated differences from fluent children in the contingent negative variation and N400. These components reflect anticipation and semantic incongruity. Weber-Fox et al. (2008) concluded that the neural profile of children who stutter suggested inefficient phonological rehearsal and target anticipation for rhyming judgment, and that children who stutter may have difficulty forming the phonological neural representations needed for accurate and efficient rhyming judgments. Further exploration is required to understand if differences in neural functioning

between children who stutter and fluent children impact the early auditory processing for integrating feedback into upcoming speech-motor commands.

A central finding of previous functional neuroimaging studies of speech production in adults who stutter is a reduction in auditory cortex activation, in the presence of increased speech-motor cortex activation, relative to that of fluently speaking adults (De Nil et al., 2008; Fox et al., 1996; Fox et al., 2000; Watkins et al., 2008) but see Kell et al. (2009). Consequently, several researchers have posited that the interaction between motor and auditory cortices may be abnormal in adults who stutter (Brown et al., 2005; Ludlow and Loucks 2003; Max et al., 2004; Neilson and Neilson 1987). Specifically, some studies have proposed that stuttering may arise from difficulties controlling speech acts due to faulty neural representations of speech processes in the brain (Corbera et al., 2005; Max et al., 2004; Neilson and Neilson 1987). A crucial aspect of normal speech acquisition is the gradual transition of control of speech-motor movement from a feedback-biased to feedforward-biased mechanism during development (Bailly 1997; Guenther and Bohland 2002; Guenther 2006). Difficulty developing the neural processes for speech in childhood may interfere with the transition of speech-motor control from a predominant feedback to a more feedforward mode and contribute to the onset of stuttering (Civier, Tasko, Guenther 2010; Max et al., 2004; Neilson and Neilson 1987).

Further insight into the relation between motor and auditory cortical regions may be gained from the study of speech-induced auditory suppression, a mechanism related to this interaction. Speech-induced auditory suppression is a normal neurophysiological process thought to be related to the monitoring, and subsequent modification of, the auditory targets associated with speech-motor acts (Beal et al., 2010; Heinks-Maldonado, Nagarajan, Houde 2006; Houde et al., 2002; Numminen, Salmelin, Hari 1999; Tourville, Reilly, Guenther 2008). Various models of speech-motor control posit that projections from motor-related areas to auditory cortex relay information concerning the auditory target region for the speech sound under production (Guenther 2006; Houde et al., 2002; Kröger, Kannampuzha, Neuschaefer-Rube 2009; Ventura, Nagarajan, Houde 2009). The auditory target is compared to the actual auditory feedback and if there is correspondence then the incoming auditory signal is suppressed. If the auditory feedback is outside the range of the predicted auditory target then an error is detected and corrective motor commands are issued to the motor cortex (Heinks-Maldonado, Nagarajan, Houde 2006; Tourville, Reilly, Guenther 2008).

Speech production, from conceptual formulation to articulation, is completed in approximately 600 milliseconds (Levelt 2004; Sahin et al., 2009). On average, adults are able to produce 5 syllables per second when asked to speak at a fast rate (Tsao and Weismer 1997). Auditory feedback can be used to modify speech production within a time period ranging from 81 to 186 milliseconds (Tourville, Reilly, Guenther 2008). Millisecond level information about the sequence of cortical events comprising speech production is crucial for understanding the interaction between motor execution and auditory feedback of self-generated speech. The aforementioned investigations of speech production in adults who stutter used either positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) which are limited in their ability to resolve temporal events occurring over periods shorter than several seconds. However, magnetoencephalography (MEG) is able to measure neural events with millisecond temporal resolution combined with good spatial resolution. MEG has been used to demonstrate that speech-induced related suppression of auditory activation can be detected as early as within 50 to 100ms of vocalization in adults (Beal et al., 2010; Curio et al., 2000; Houde et al., 2002; Numminen, Salmelin, Hari 1999).

We have reported that adults who stutter had shorter auditory M50 and M100 latencies in response to the self-generated vowel /i/ and vowel-initial words in the right hemisphere

relative to the left hemisphere whereas adults who do not stutter showed similar latencies across hemispheres (Beal et al., 2010). These timing differences were observed in adults who stutter despite similar levels of auditory M50 and M100 peak amplitude reduction during active generation relative to controls. In other words, speech-induced auditory suppression resulted in peak latency differences in the adults who stutter relative to fluently speaking adults rather than peak amplitude differences. The neural timing differences may reflect inefficient access to the neural representations of speech processes, or compensation for such a deficit, in adults who stutter.

In adults, the M100 (N1 in EEG/ERP studies) is the most robust and reproducible auditory component across participants (Bruneau and Gomot 1998). Therefore, the main emphasis of MEG studies of auditory evoked responses has been the M100 (Mäkelä 2007). However, in children the morphology of the waveforms are often different such that the M50 is at a prolonged latency and more robust and reproducible across child participants relative to adults (Oram Cardy et al., 2004). From early childhood through to adulthood the evoked response morphology in MEG and EEG gradually changes, such that the M50 becomes less robust and reproducible and the M100 becomes more so (Bruneau and Gomot 1998; Gage, Siegel, Roberts 2003; Kotecha et al., 2009; Oram Cardy et al., 2004; Paetau et al., 1995; Picton and Taylor 2007; Rojas et al., 1998). Furthermore, the M50 and M100 have been shown to have a common source in primary auditory cortex (Hari, Pelizzone, Mäkelä 1987; Hari, Pelizzone, Mäkelä 1987; Kanno et al., 2000; Mäkelä and Hari 1987; Mäkelä and Hari 1987). Functionally, both the M50 and M100 are known to change in amplitude and/or latency in response to manipulations of auditory stimuli characteristics such as amplitude, pitch or interstimulus interval (Roberts et al., 2000). Given that speech is a rapid and dynamic motor process, it follows that the underlying neural system supporting it must respond in a timely, precise and sequential manner to ensure its correct production (Guenther 2006; Ludlow and Loucks 2003; Tourville, Reilly, Guenther 2008; Tsao and Weismer 1997). Therefore, it is reasonable to predict that the neural correlates of auditory feedback processing of self-generated speech will be reflected in the first measureable and reproducible auditory response component across children. The main goal of the current study was to understand the differential effects of speech-induced auditory suppression in children who stutter and in age-matched fluently speaking peers. The first observable and reproducible auditory component, namely the M50, is the focus of investigation as it is most likely to reflect early motor-auditory interaction in children ages 6 to 12 years old.

Despite auditory feedback of self-generated speech signals being crucial to the normal development of speech-motor control (Callan et al., 2000; Perkell et al., 2000), no published studies have reported on the effects of speech-induced suppression on auditory feedback in children who do and do not stutter. The current study investigated if speech-induced suppression differed in children who stutter relative to a group of age-matched fluently speaking peers. We also explored the nature of speech-induced suppression in children who stutter relative to that reported in our previous study of adults who stutter (Beal et al., 2010). Based on our data in adults, we anticipated that children who stutter would present with similar speech-induced suppression amplitude change as fluently speaking children, but show differences in the latency of the auditory response during speech, as did the adults who stutter.

Materials and Methods

Participants

Eleven children who stutter and 11 fluently speaking children participated in this study. The children who stutter were recruited from the treatment waiting lists at the Speech and Stuttering Institute as well as the Department of Speech-Language Pathology at the Hospital

for Sick Children, both in Toronto, Canada. The fluently speaking children were recruited from the university and hospital communities in Toronto, Canada. The participants were boys who ranged in age from 6 to 12 years old and who spoke English as their primary language.[1] All participants met the inclusion criterion that no speech or language deficits be revealed upon standardized testing with the Goldman Fristoe Test of Articulation – Second Edition (Goldman and Fristoe 2000) and the Peabody Picture Vocabulary Test – Third Edition (Dunn and Dunn 1997). A total of 25 children were screened to determine their appropriateness for participation in the current study. Three children (2 control participants, 1 child who stutters) who scored more than 1 standard deviation below the mean of these standardized measures were excluded from participation. Participants were all right-handed as tested with the Edinburgh handedness inventory (Oldfield 1971) and had a negative history of developmental or neural impairment via parent report. The children who stutter ranged in severity from very mild (7) to severe (34) on the Stuttering Severity Instrument – Third Edition (Riley 1994). Stuttering severity measurements were found to have high inter-rater reliability (ICC = .964, p = .01). The two groups did not differ in age, articulation or language ability (p>.05) (Table 1) as tested via multiple independent t-tests. The children gave informed assent and their parents gave informed written consent. The testing involved a pre-neuroimaging 1.5-hour session for articulation, language and hearing screening as well as training and stimuli recording (see Stimuli and Procedures below). The initial session was followed by a 1.5-hour scanning session at the MEG and MRI facilities at the Hospital for Sick Children in Toronto. The protocol was approved by the Hospital for Sick Children's Research Ethics Board.

Stimuli and Procedures

The stimuli and procedures used in the current study were similar to those used in an earlier study of adults who stutter (Beal et al., 2010) but modified to accommodate the testing of children. Prior to the neuroimaging session participants completed a training and stimulus collection session. Participants were trained to consistently produce the vowel /a/[2] at a constant volume of 70 dB SPL. Participants were seated in front of a computer monitor inside a sound insulated room while wearing a headset microphone (Shure 512; Shure Incorporated, Niles, Illinois) that maintained a constant 5 cm mouth to microphone distance. Participants were required to speak aloud the vowel /a/ in response to four white asterisks presented on a black background for 500 ms interspersed with the same white cross used in the listening tasks.

Muscle activity from articulator movement may interfere with the magnetic fields of interest (Beal et al., 2010). Therefore, to facilitate production of the vowel with minimal magnetic inference from speech muscle activity participants produced the open back unrounded vowel /a/ in blocks of five visual prompts with each prompt spaced 2.5 to 3 seconds apart. Each block of five vowel /a/ prompts was followed by a seven second rest period and a three second prompt that signalled the beginning of the next block. In this way, participants maintained an open jaw posture to facilitate the production of the vowel /a/ with minimal speech muscle movement during the active period and then closed their jaw during the rest period to facilitate swallowing and mouth moistening for comfort. After successful training, verbal productions of the vowel /a/ stimuli were collected from each of the participants for

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[1]This age group was selected relative to the usual length of recovery that ranges 2 to 3 years (Yairi & Ambrose, 1999) and the age of onset 2 to 5 years old (Bloodstein, 2006) with the rationale that children identified as stuttering at age 7 are likely to show predictive signs of recovering or persisting in the future. It is more difficult to predict recovery in children who are of preschool age as at least 70% as these children are likely to recover. Only children who did not show signs of recovery were included in the study.
[2]The open back unrounded vowel /a/ was used because it requires relatively minimal muscular movement to articulate. Minimization of such movement was important as muscular activity introduces unwanted magnetic noise to the brain signals of interest for recording via MEG.

playback of their self-produced stimuli during the MEG passive listening task *listen vowel*. The children's productions were recorded using a Tascam US-122L (TEAC Corporation, Tokyo, Japan) external sound card and Audacity software (version 1.2.6) on a laptop computer. Stimuli were then sound normalized to 70 dB SPL based on normalization of the intensity root mean square using PRAAT sound editing software (version 5.1).

Participants performed three independent tasks during the MEG recording session: *listen tone*, *listen vowel* and *speak vowel*. The two listen tasks, namely *listen tone* and *listen vowel*, required the participants to listen to acoustic stimuli while fixating on a static white cross on a black background. The stimuli for the *listen tone* and *listen vowel* tasks were presented binaurally via ear-insert phones at 70 decibels sound pressure level (dB SPL). In the *listen tone* task, participants listened to trials of a 1 kHz tone pip that was 50 ms in duration. In the *listen vowel* participants listened passively to trials of their recorded self-produced vowel /a/, previously prepared during the training and stimulus collection session described above. The third task, *speak vowel*, required the participants to speak aloud the vowel /a/ in response to a visual stimulus as they had been previously trained to do during the training session. Prior to the start of the *speak vowel* task, participants practiced producing the vowel /a/ with a constant volume of 70 dB SPL as they had been previously trained to do.

The order in which the tasks were completed during the MEG scanning session was counterbalanced across participants. All tasks contained 80 trials with an interstimulus interval ranging from 2.5 to 3 seconds. All stimuli were presented on a rear-projection screen in front of the participant using the presentation software SuperLab Pro version 2.0.4 (http://www.superlab.com).

Data acquisition

A photographic storybook was used to introduce parents and children to the MRI and MEG scanning environments prior to the data acquisition appointment. Auditory evoked magnetic fields were recorded continuously (2500Hz sample rate, DC-200 Hz band pass, third-order spatial gradient noise cancellation) for all tasks using a CTF Omega 151 channel whole head first order gradiometer MEG system in a magnetically shielded room at the Hospital for Sick Children in Toronto. The auditory stimuli presented to the participants during the *listen tone* and *listen vowel* tasks and the participants' self-generated speech produced during the *speak vowel* task were recorded simultaneously with the MEG via an accessory channel on the MEG system. Concurrent acquisition of the auditory and speech signals together with the magnetic field activity facilitated accurate stimulus onset marker placement for data analysis. Fiducial coils were placed at the nasion and each auricular point. Head movement was monitored online via fiducial movement and video surveillance. Fiducial locations were also used to facilitate coregistration of the MEG data to an anatomical MRI obtained for each participant in order to specify the neural sources of the magnetic fields. A 1.5-T Signa Excite III HD 12.0 MRI system (GE Medical Systems, Milwaukee, WI) and an eight channel head coil was used to obtain neuroanatomical images. A T1-weighted 3D fast spoiled gradient echo (FSPGR) sequence (flip angle = 15°, TE= 4.2ms, TR = 9ms) was used to generate 110 1.5-mm-thick axial slices (256×192 matrix, 24 cm field of view).

Data analyses

The primary investigator evaluated audio-visual recordings of spontaneous speech and reading samples of the children who stutter using the SSI-3 (Riley 1994). A trained speech-language pathology student evaluated a random sample of 4 of the 11 (36%) children who stutter and a 2-way random-effects intra-class correlation coefficient was calculated to determine inter-rater reliability.

The primary investigator monitored participant performance online to ensure that the tasks were performed correctly and that no vowel repetitions or prolongations were included in the data collection. The onsets of the auditory stimuli presented during the passive listening tasks, and the vocalizations generated by the participants during the active generation tasks, were identified offline via an automated routine implemented in Matlab 7.1 (Mathworks Inc) and manually checked for accuracy. Preparation of the acoustic signal for the onset identification routine consisted of normalization, application of a participant-specific band pass filter, re-normalization and envelope extraction. An onset was identified when the acoustic signal exceeded the specified thresholds for noise, amplification and acceleration. These methods of onset identification have previously been demonstrated to reduce the influence of sound specific biases and yield accurate time marking results (Kessler, Treiman, Mullennix 2002; Tyler, Tyler, Burnham 2005).

The identified onsets were used to epoch the MEG data from 500 ms prior to the auditory stimuli onset to 1000 ms post onset. Source analysis was performed on the averaged individual trials using an event-related vector beamformer (Quraan and Cheyne 2010; Sekihara et al., 2001) to create volumetric images (2.5 mm resolution) of source activity throughout the brain at selected time intervals (Cheyne, Bakhtazad, Gaetz 2006; Herdman et al., 2003). We used the beamformer analysis because it has been shown to be able to suppress anticipated large subject-generated noise artefacts in the MEG recordings of auditory responses during the overt speaking task (Beal et al., 2010; Cheyne et al., 2007). Binaurally elicited auditory evoked fields produce highly correlated sources that can result in suppression of beamformer output and concomitant errors in localization and amplitude (Dalal, Sekihara, Nagarajan 2006; Quraan and Cheyne 2010). In order to circumvent these effects, we used an event-related vector beamformer with coherent source suppression capability as described by Dalal, et al. (2006) to image correlated sources in bilateral auditory areas. We generated source activity waveforms associated with the voxels of peak activity identified in the volumetric images using the single dominant current direction from the vector output of the beamformer, at ± 10 ms of the M50. Further details of this approach can be found in Quraan & Cheyne (2010).

Source plots were created for each participant via the co-registered anatomical MRI. To combine source localization results across subjects, pseudo-t source images co-registered to each subject's MRI were spatially normalized to the MNI (T1) template brain using SPM2 (Wellcome Institute of Cognitive Neurology, London, UK). Linear and non-linear warping parameters were obtained from each individual's T1-weighted structural image and used to warp source images to standardized stereotactic (MNI) space prior to averaging across subjects. Several studies have verified that MRIs of children from 6 years of age and older can be successfully warped to an adult template (Burgund et al., 2002; Kang et al., 2003; Muzik et al., 2000). Significant peaks of activity in the group images were identified after thresholding the images using a non-parametric permutation test (Nichols and Holmes 2002) adapted for beamformer source imaging (Singh, Barnes, Hillebrand 2003). Peak locations were reported in MNI coordinates. To obtain the group average time course for each peak activation we averaged the source waveforms computed at the peak response location in each subject's original source image. This was achieved by first unwarping the group mean peak-voxel location (in MNI coordinates) back to MEG coordinate space for each individual participant and searching for a peak within a 10 mm radius of that location. A search radius of 10mm ensured that we found the true peak location for each participant that corresponded to the group response. Within each participant's source waveform, the M50 peak was identified as the largest positive peak occurring within a time window of 50 to 110ms following stimulus onset.3 Across participants for each task and group, the peak amplitudes and latencies of the moment signal of this time course were measured and extracted for averaging.

Statistical analyses of the amplitude and latency data were completed separately for each condition. Analyses of the tone amplitude and latency data were completed using a 2-way mixed analysis of variance to test for differences in either peak amplitude or latency of the M50 response for the within-group variable of hemisphere (left vs. right), between groups (controls vs. children who stutter) and interaction. Analyses of the vowel data were completed using a 3-way mixed analysis of variance to test for differences in the within group variables of hemisphere (left, right) and task (listen, speak), between groups (children who do and do not stutter) and any interactions. We also calculated the speaking induced suppression percent difference of the group mean amplitude values [$100*(1-\text{amplitude}_{speak} / \text{amplitude}_{listen})$] (Ventura, Nagarajan, Houde 2009). Lastly, exploratory bivariate correlation analyses were conducted between the behavioural measurements (participants' age, Peabody Picture Vocabulary Test scores - 3A, Goldman Fristoe Test of Articulation – 2 scores or Stuttering Severity Index scores) and the neurophysiological data (source amplitude and latency).

Results

Listen Tone task

The source of the M50 localized to the auditory cortex in both hemispheres in children who do and do not stutter. These sources are shown in Figure 1 as well as the group averaged source magnitude variation across time for the evoked auditory fields to the tone. The corresponding MNI coordinates are provided in Table 2. No amplitude or latency differences were found (Figure 2). Consistent with previous studies of development of magnetic auditory responses to tones, the M50 occurred at a prolonged latency for both fluently speaking children (84.95 ± 7.86 ms) and children who stutter (84.29 ± 8.92 ms) relative to the latency expected for adults in the literature (62.0 ± 1.9 ms; Oram-Cardy et al., 2004). No correlations between age, receptive vocabulary, articulation ability or stuttering severity and either amplitude or latency were found.

Listen Vowel and Speak Vowel tasks

The source of the M50 localized to the auditory cortex in both hemispheres for the vowel tasks in children who stutter as well as fluently speaking children (Figures 3 and 4; see Table 2 for the MNI coordinates). The group averaged source power variation across time for the evoked auditory fields during the *listen vowel* and *speak vowel* tasks are shown in Figures 3 and 4. As shown in Figure 5, consistent with our hypothesis both children who stutter and fluently speaking children demonstrated a reduction in M50 amplitude for the *speak vowel* condition (16.30 ± 8.42 nAm) relative to the *listen vowel* condition (25.94 ± 10.07 nAm) (F ($1, 20$) = 16.21, p = .001). No other significant amplitude differences were found. Accordingly, the average speech-induced suppression percent change was calculated collapsed across hemispheres and groups. The auditory evoked field amplitude was reduced by 59% for the *speak vowel* task relative to the *listen vowel* task. As shown in Figure 6, the M50 peak amplitude, measured in the left hemisphere, was negatively correlated with stuttering severity in the group of children who stutter (r = −.65, p = .03). However, the correlation result is reported for exploratory purposes only as its statistical significance did not survive Bonferroni correction for multiple correlations.

The latency of the auditory M50 was shorter for the *speak vowel* task (84.15 ± 16.31 ms) than the *listen vowel* task (97.27 ± 14.43 ms) in both children who stutter and fluently

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[3]Previous developmental studies have demonstrated a prolonged M50 in typically developing children (79.6 ± 7.8 ms) relative to adults (62.0 ± 1.9 ms) and an even further prolonged M50 in children with development disorders (85.9 ± 8.1 ms) (Oram-Cardy et al., 2004).

speaking children (F(1, 20) = 21.68, p < .001; Figure 7). On average, the M50 peak latency was 13.12 ms shorter for the *speak vowel* task relative to the *listen vowel* task. Children who stutter had delayed auditory M50 peak latencies (95.67 ± 17.07 ms) to vowel sounds, across tasks, compared to children who do not stutter (85.75 ± 14.84 ms) (F(1, 20) = 5.92, p = .02; Figure 8). As compared to the fluently speaking children, the children who stutter demonstrated a 9.92 ms delay in M50 peak latency.

Discussion

Our study is the first to provide evidence that speech-induced suppression of auditory fields is a process present in school-age children as it is in adults. Confirmation of this phenomenon in younger speakers allowed us to investigate whether differences existed in its manifestation in children who stutter relative to children who do not stutter. Consistent with findings in adults who stutter, children who stutter differed from fluent speakers in the peak latencies of evoked auditory fields to their own speech but showed no differences from fluent speakers in the amplitude of auditory fields for listening to or speaking a vowel. Rather, the findings advance our understanding of stuttering in children by demonstrating the importance of neural timing differences in auditory cortex for the processing of speech stimuli at a stage of development closer to the onset of this disorder than in adults. Task specific results are discussed below in relation to theories of the neural correlates of stuttering.

Amplitude

We examined evoked auditory fields to vowels during passive listening and active speech production. In the current study, children demonstrated a 59% reduction in the peak amplitude of the auditory M50 to vowel production versus vowel perception (Figure 5). The magnitude of speech-induced auditory suppression of the M50 in the current child cohort is substantially increased relative to our previously reported trend of a 6% reduction of the M50 to vowel production versus vowel perception in adults (Beal et al., 2010). We measured a statistically significant 22% reduction of the M50 for vowel-initial word production relative to vowel-initial word perception in the same adult cohort. We previously speculated that the increased magnitude of the suppression effect for word stimuli may be the result of the increased motor plan complexity of words over vowels. The 59% reduction of the M50 observed in the current child cohort, relative to the previously reported 6% reduction in adults, may be reflective of vowel production being a more complex, or at least a lesser established, motor task for a developing speech-motor system. Alternatively, the magnitude of the M50 reduction in our child cohort is consistent with previous studies of speech-induced auditory suppression of the M100 in fluent adult speakers (Beal et al., 2010;Heinks-Maldonado, Nagarajan, Houde 2006;Hirano et al., 1997;Houde et al., 2002;Ventura, Nagarajan, Houde 2009) and may reflect our ability to resolve a more consistent and robust measurement of this early component in children relative to adults.

Children who stutter did not differ from their fluent peers in the amplitude of the M50 during speaking. This finding is consistent with our previous observation that adults who stutter had similar M50 and M100 amplitudes for speaking relative to fluent adults (Beal et al., 2010). Therefore, neither adults nor children who stutter differed from their fluently speaking peers in the amplitude of their auditory evoked fields in response to actively produced self-generated vowel stimuli. Taken together, our findings suggest that for vowel production the mechanism of speech-induced suppression of evoked auditory field amplitude is typical in people who stutter across the development of the disorder.

As shown in Figure 6, the children who stutter showed a negative correlation between stuttering severity and left hemisphere M50 amplitude for *speak vowel* but not during *listen*

vowel. In other words, the children with the most severe stuttering had the smallest left hemisphere M50 amplitude during the *speak vowel* task. This result must be considered preliminary because it was not statistically significant following correction for multiple correlations. However, the correlation is interesting in light of the *efference copy hypothesis* of stuttering (Brown et al., 2005). The *efference copy hypothesis* predicts that auditory signals are further suppressed in people who stutter as a result of the well documented presence of increased speech-motor activity and reduced auditory signal in this population as measured by PET and fMRI (De Nil et al., 2008;Fox et al., 1996;Fox et al., 2000;Watkins et al., 2008). Although the children who stutter did not differ as a group from the fluently speaking children in our study, the children who stutter had a relationship between the left hemisphere M50 amplitude and stuttering severity in the presence of speech-motor activity. This finding suggests that children with more severe stuttering may engage speech-motor cortex to a greater degree, thereby further suppressing auditory activity, than their less severe stuttering peers. As the current study did not examine cortical speech-motor activity directly, further investigation is required to determine if increased cortical speech motor activity is a hallmark of the disorder in childhood.

Latency

The children who stutter had delayed M50 peak latencies in both hemispheres for the *listen vowel* and *speak vowel* tasks relative to the fluently speaking children (Figure 8). However, the children who stutter had similar M50 peak latencies to the fluently speaking children for the *listen tone* task. The finding of similar M50 latencies observed between children who do and do not stutter for the *listen tone* task is consistent with the previous literature investigating auditory responses to non-linguistic stimuli in adults who stutter (Beal et al., 2010;Biermann-Ruben, Salmelin, Schnitzler 2005;Hampton and Weber-Fox 2008). However, the M50 latency patterns observed in the current study of children who stutter differed from those observed in our previous study of adults who stutter for vowel stimuli (Beal et al., 2010). Relative to fluently speaking children, the children who stutter presented with prolonged M50 latencies, bilaterally, for vowel perception and production. Adults who stutter did not differ from fluently speaking adults for the M50 latencies in response to vowel stimuli but adults who stutter did have prolonged M50 latencies in both hemispheres in response to vowel-initial word stimuli relative to fluently speaking adults.

These findings suggest that a cortical timing deficit for the auditory processing of linguistic stimuli may play a role in the development and maintenance of stuttering in school-aged children and adults who stutter. Theories of speech development posit that auditory input of speech signals during listening and speaking contributes to the ongoing modification of internal representations of speech sounds (Guenther and Vladusich In press; Hickok and Poeppel 2004; Hickok and Poeppel 2007; Lotto, Hickok, Holt 2009; Shiller et al., 2009). As the auditory inputs in the two vowel tasks come from exogenous and endogenous sources, one interpretation of our findings is that the longer peak latencies during vowel perception and production in children who stutter are reflective of a deficiency in integrating auditory information for the purpose of improving internal representations of speech sounds. Other authors have suggested that children who stutter may have an inability to maintain internal representations of speech sounds and that this results in unstable motor planning and execution that can ultimately trigger stuttering moments during speech production (Civier, Tasko, Guenther 2010; Corbera et al., 2005; Max et al., 2004).

The M50 in the current child dataset and the M50 and M100 in the adult dataset, reported in Beal et al. (2010), were all localized to the auditory cortices. As such, it is reasonable to speculate about the general timing of cortical auditory events in children and adults who stutter. Whereas children and adults who stutter had similarly prolonged bilateral latencies for vowel perception relative to their fluently speaking peers, they differed substantially

from one another for vowel production. Children who stutter had prolonged bilateral latencies relative to their fluently speaking peers for vowel production. Although adults who stutter did not differ from their fluently speaking peers for vowel production, they did have shorter latencies in the right hemisphere relative to the left hemisphere for vowel production - a finding not observed in children who stutter. Kell et al. (2009) proposed that a primary structural deficit in the area of the left inferior frontal gyrus results in an in ability of people who stutter to integrate the auditory feedback information with internal representations of speech-motor programs thereby resulting in compensational adaptive changes in the right hemisphere. Our current findings of prolonged cortical auditory processing in children who stutter during vowel production taken together with our previous findings that mild stutterers engaged the right auditory cortex faster than more severe stutterers during vowel production further support the idea that the right faster than left pattern of cortical auditory processing in adults who stutter during vowel production is compensatory in nature.

Source Localization

The auditory M50 was localized to the auditory cortices for all tasks and participants. Small differences in the mean location for the *listen vowel* and *speak vowel* tasks were observed. As can be seen in Table 2, the largest systematic difference in mean location occurred in the control group in the *y*-plane of the left hemisphere which was 10 mm posterior for the *listen vowel* task relative to the *speak vowel* task. Given the known cytoarchitectural differences that span this distance of auditory cortex, it may be tempting to prescribe functional meaning to this change in position. However, given the limitations of source localization accuracy using MEG for such sources (which can be on the order of more than 10 mm) and the lower signal-to-noise ratio for response in the *speak vowel* task, further confirmation with a larger number of subjects may be needed to determine whether this posterior shift in location reflects activation of different neuronal populations within auditory cortex for the two types of stimuli. However, the amplitude and latency values measured at the source are consistent with those expected of the auditory M50 response in children and anatomical locations consistently within primary auditory cortex (Oram Cardy et al., 2004;Picton and Taylor 2007). Thus we are confident that the comparison of *listen vowel* and *speak vowel* source amplitudes for the purposes of determining the presence of speech-induced auditory suppression of the M50 response was valid across tasks and groups.

Conclusion

We demonstrated speech-induced suppression of the neuromagnetic auditory M50 response in children. We found that both children who stutter and their fluently speaking peers show evidence of speech-induced suppression for vowel stimuli. Children who stutter differed from children who do not stutter in that the auditory M50 was prolonged during vowel perception and production. This delayed M50 latency in children who stutter may reflect a deficiency in their ability to integrate auditory speech information for the purpose of establishing and improving internal representations of speech sound processes. By examining the neural correlates of auditory processing during passive listening and active generation in children who stutter, we have shown that faulty neural processes for speech may underlie stuttering early after the onset of the disorder. We have also differentiated the neurophysiology of early auditory processing in children who stutter from their same aged peers and adults who stutter. These results contribute to our understanding of this complex speech disorder closer to its onset as well as confirm the presence of speech-induced suppression in normal children.

Acknowledgments

Abbreviations

fMRI	functional magnetic resonance imaging
MEG	magnetoencephalography
PET	position emission tomography

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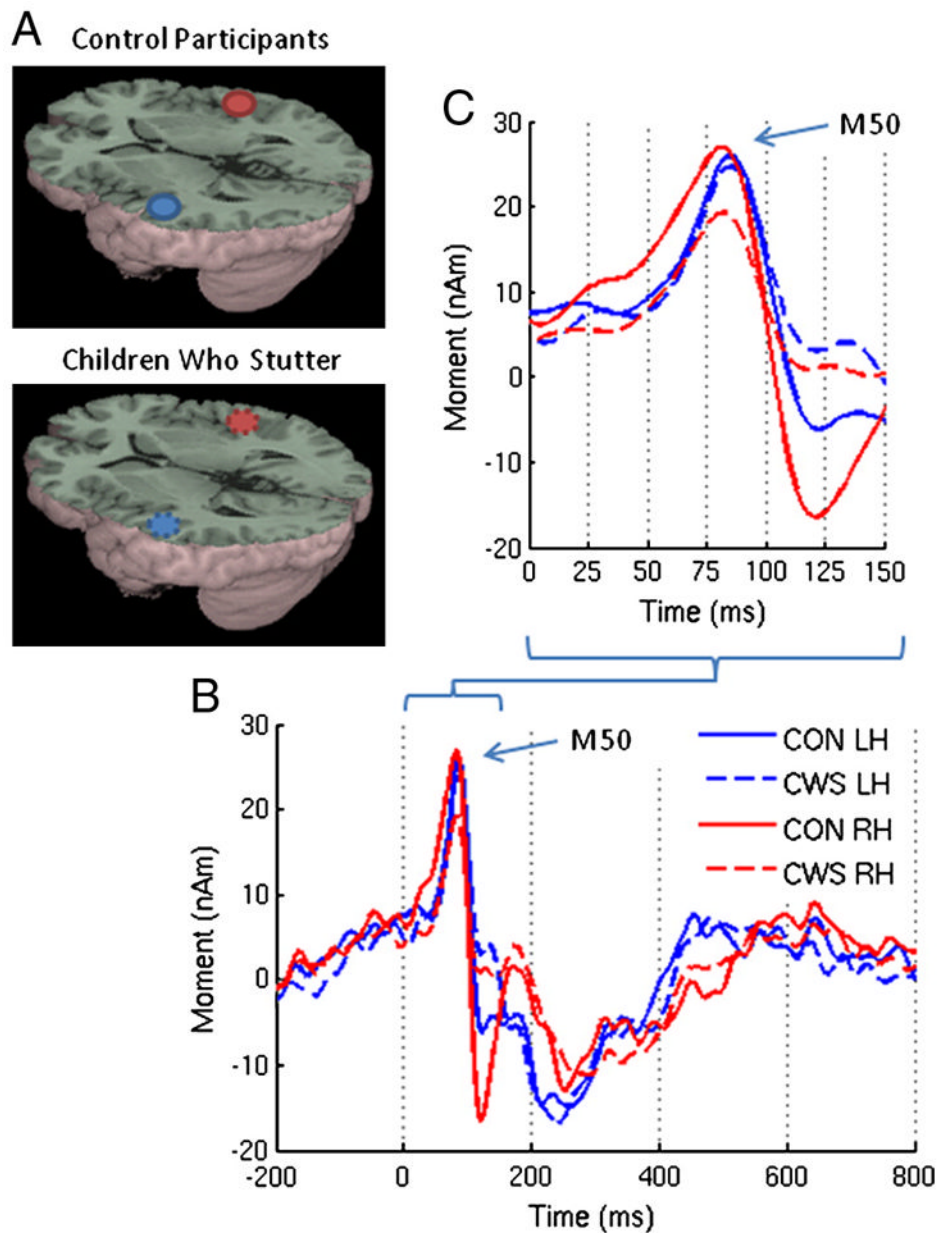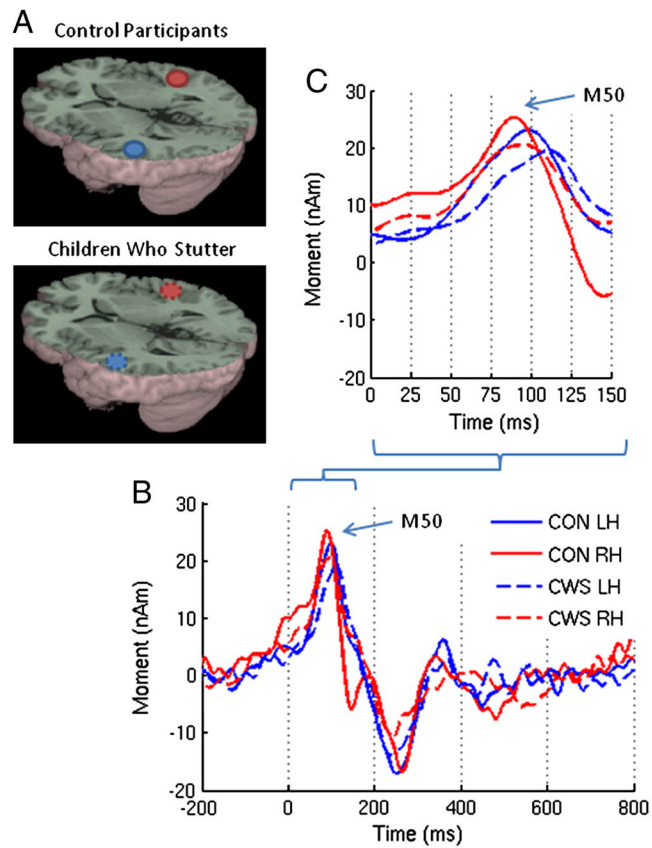
Figure 1.
(A) Group averaged source images of the auditory evoked magnetic fields in response to a 1kHz tone overlaid on the MNI canonical brain. The associated MNI coordinates are listed in Table 2. (B) Group averaged source magnitude variations from 200ms prestimulus to 800 ms post stimulus corresponding to those sources. (C) A detailed view of the early components. The solid and dotted lines represent the control participants and children who stutter respectively. nAm = nanoAmpere*meters; ms = milliseconds; Blue = left hemisphere (LH); Red = right hemisphere (RH).
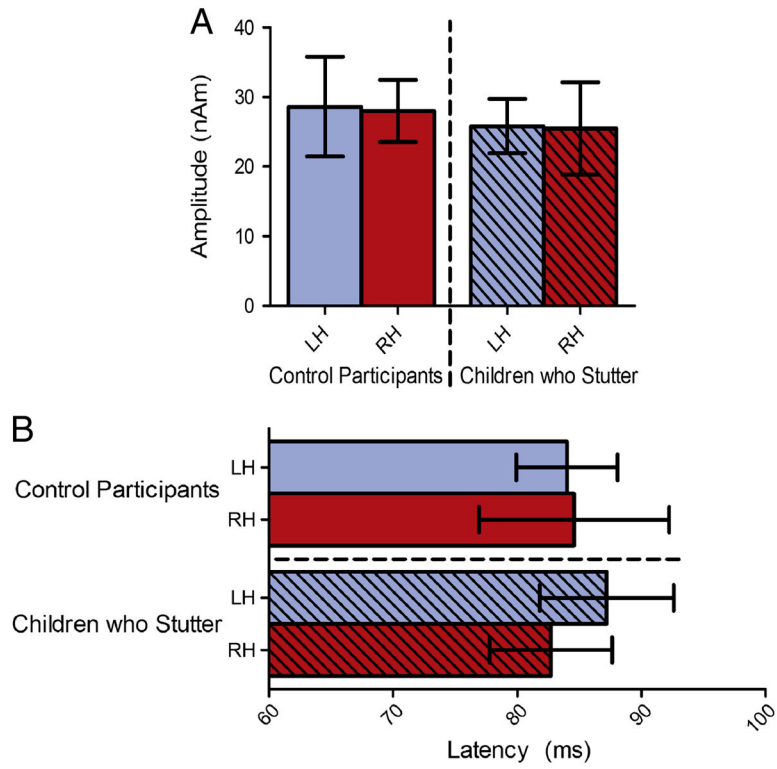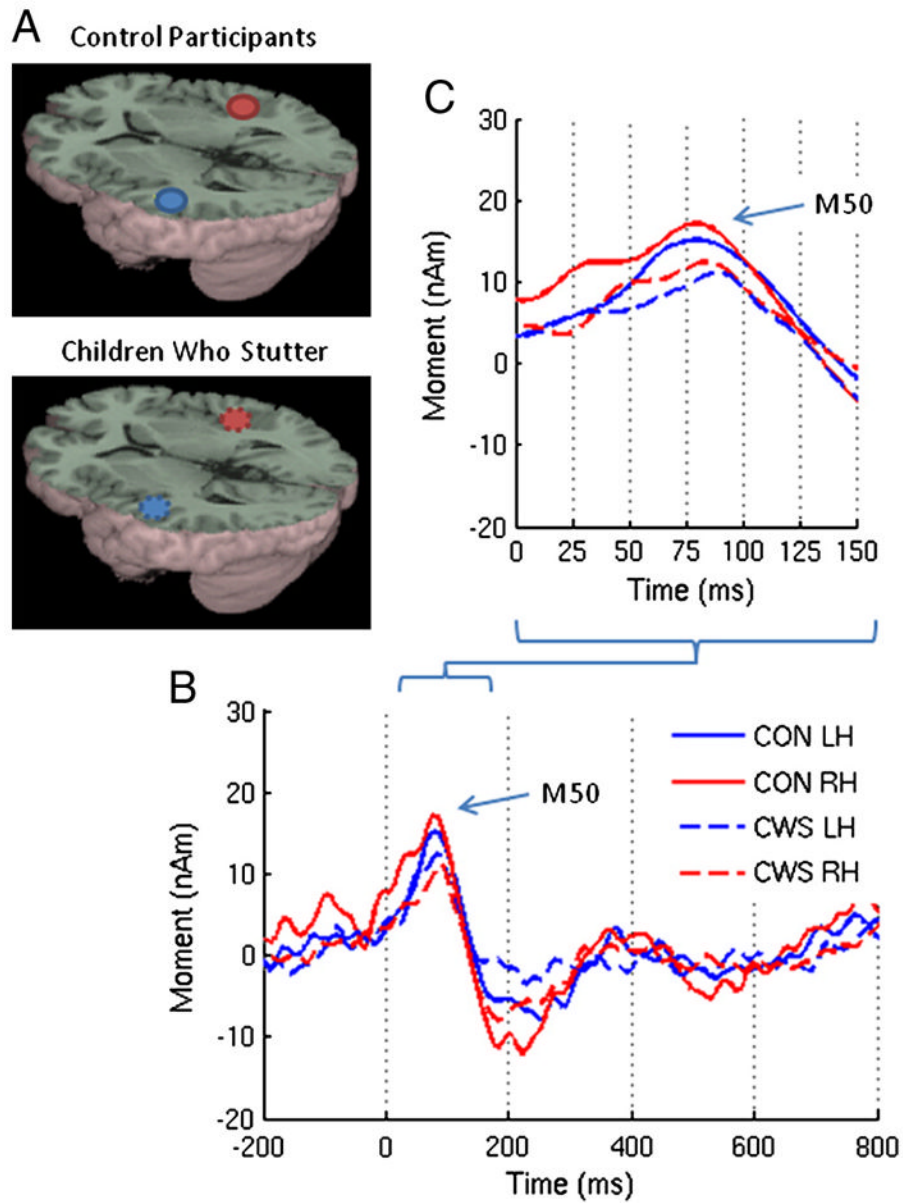
Figure 2.
The results of the *listen tone* task (A) amplitude and (B) latency analyses. No differences were found in the amplitude or latency of the M50 in response to a 1kHz tone in children who stutter relative to the control participants. Error bars represent the 95% confidence interval.
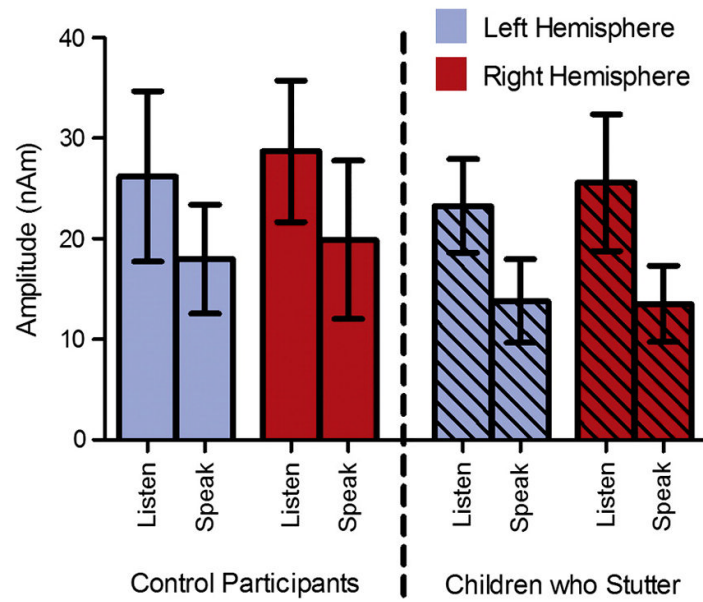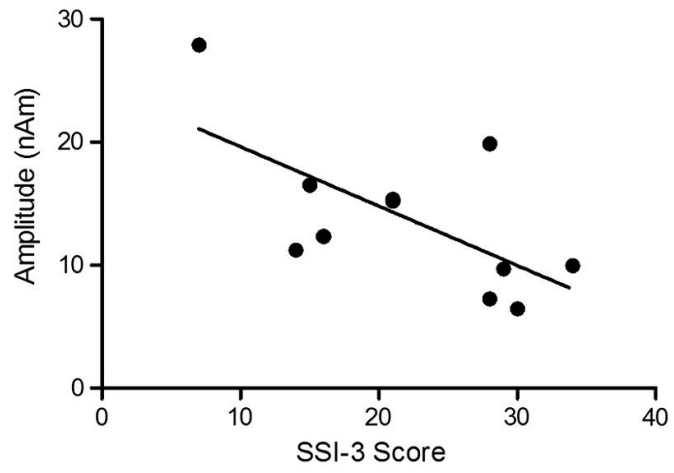
Figure 3.
(A) Group averaged source images of the auditory evoked magnetic fields for the *listen vowel* task overlaid on the MNI canonical brain. The associated MNI coordinates are listed in Table 2. (B) Group averaged source magnitude variations from 200ms prestimulus to 800 ms post stimulus corresponding to those sources and (C) a detailed view of the early components.
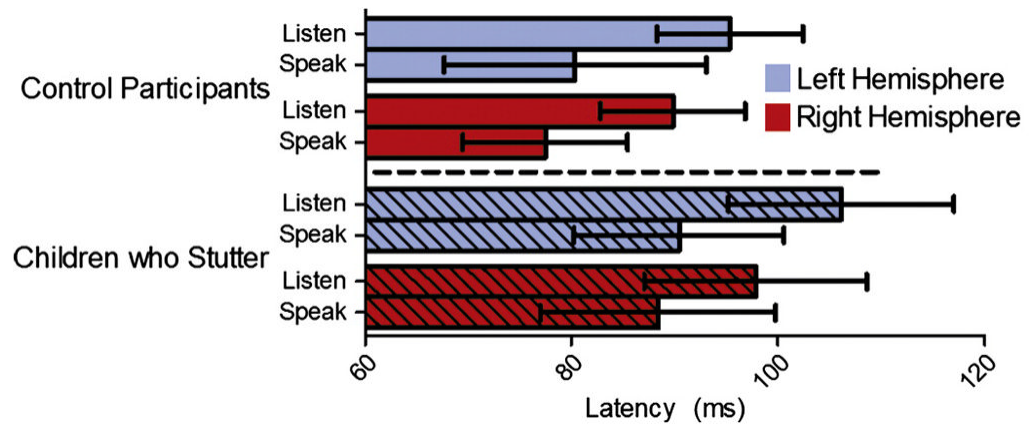
Figure 4.
(A) Group averaged source images of the auditory evoked magnetic fields for the *speak vowel* task overlaid on the MNI canonical brain. The associated MNI coordinates are listed in Table 2. (B) Group averaged source magntiude variations from 200ms prestimulus to 800 ms post stimulus corresponding to those sources and (C) a detailed view of the early components.

Figure 5.
The results of the *listen vowel* and *speak vowel* amplitude analysis. On average, the control participants and children who stutter demonstrated a 59% reduction in M50 amplitude for the *speak vowel* condition relative to the *listen vowel* condition. Error bars represent the 95% confidence interval.

Figure 6.
For children who stutter, left hemisphere amplitude for the *speak task* had a negative correlation with stuttering severity as measured with the SSI-3.

Figure 7.
The results of the listen and speak vowel task latency analysis. The children who stutter had
delayed M50 peak latencies for the *listen vowel* and *speak vowel* tasks relative to the control
participants. Error bars represent the 95% confidence interval.
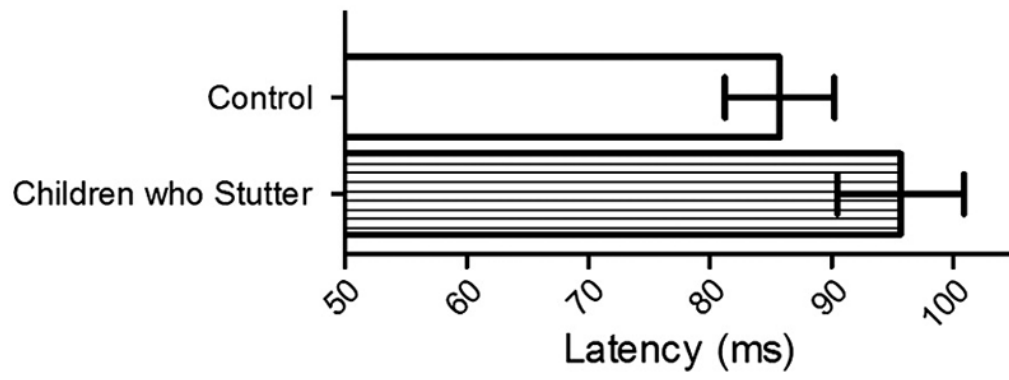
Fig. 8.
The children who stutter had a 9.92 ms delay in M50 peak latency for vowel tasks relative to the control participants. Error bars represent the 95% confidence interval.

Table 1

Means, standard deviations and ranges for participant characteristics.

	Control Participants (n = 11)			Children Who Stutter (n = 11)		
	Mean	SD	Range	Mean	SD	Range
Age (months)	119.18	22.46	74 – 144	114.18	18.07	92 – 148
PPVT-III	121.45	11.94	105 – 138	118.72	17.26	88 – 139
GFTA-II	104.36	2.98	97 – 109	102.45	6.15	87 – 108
SSI-III	-	-	-	22.09	8.40	7 – 34

Table 2

MNI coordinates for the M50 source locations and their respective pseudo-z threshold (Thresh.) values at $p < 0.001$ derived via non-parametric permutation testing adapted for beamformer source imaging (Nichols and A. P. Holmes, 2002; Singh et al., 2003).

	Control Participants							
	Left Hemisphere				Right Hemisphere			
	X	Y	Z	Thresh.	X	Y	Z	Thresh.
Tone	−53	−20	5	2.14	48	−20	−5	2.43
Listen /a/	−53	−32	5	1.64	48	−25	−5	1.99
Speak /a/	−53	−22	10	1.50	51	−23	0	1.63

	Children who Stutter							
	Left Hemisphere				Right Hemisphere			
	X	Y	Z	Thresh.	X	Y	Z	Thresh.
Tone	−55	−20	8	2.02	58	−18	2	1.76
Listen /a/	−55	−20	5	1.37	53	−20	5	1.54
Speak /a/	−55	−22	13	1.11	58	−15	8	1.15