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Auditory evoked fields to vocalization during passive listening and active generation in adults who stutter

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ABSTRACT

We used magnetoencephalography to investigate auditory evoked responses to speech vocalizations and non-speech tones in adults who do and do not stutter. Neuromagnetic field patterns were recorded as participants listened to a 1 kHz tone, playback of their own productions of the vowel /i/ and vowel-initial words, and actively generated the vowel /i/ and vowel-initial words. Activation of the auditory cortex at approximately 50 and 100 ms was observed during all tasks. A reduction in the peak amplitudes of the M50 and M100 components was observed during the active generation versus passive listening tasks dependent on the stimuli. Adults who stutter did not differ in the amount of speech-induced auditory suppression relative to fluent speakers. Adults who stutter had shorter M100 latencies for the actively generated speaking tasks in the right hemisphere relative to the left hemisphere but the fluent speakers showed similar latencies across hemispheres. During passive listening tasks, adults who stutter had longer M50 and M100 latencies than fluent speakers. The results suggest that there are timing, rather than amplitude, differences in auditory processing during speech in adults who stutter and are discussed in relation to hypotheses of auditory-motor integration breakdown in stuttering.

Introduction

Persistent developmental stuttering is a disorder of speech fluency prevalent in approximately 1% of the adult population (Bloodstein and Ratner, 2008). The disorder is characterized by frequent and protracted speech sound repetitions and prolongations as well as silent blocks that disrupt speech production and impede efficient communication. Adults with persistent developmental stuttering demonstrate a distinct pattern of functional neural activation during speech production relative to their fluently speaking peers. This pattern can be summarized as increased activation in speech motor related cortex and reduced activation in auditory related areas (Braun et al., 1997; Brown et al., 2005; De Nil et al., 2008; Fox et al., 1996, 2000). This observed pattern has led some researchers to propose that abnormal interactions between speech motor and auditory cortices may play a role in the aetiology of stuttering (Brown et al., 2005; Ludlow and Loucks, 2003; Max et al., 2004; Neilson and Neilson, 1987).

Integrative models of speech motor control posit that auditory-motor integration is a key component in the fluid execution of speech movement (Bailly, 1997; Guenther et al., 2006; Kröger et al., 2009). There is evidence suggesting that when a speech motor command is issued, a duplicate of that command, termed *efference copy*, is shared with auditory cortex and reconciled with auditory feedback for the purpose of self monitoring the speech motor output. A direct match of the auditory feedback with the efference copy results in suppression of the activity in auditory cortex (Christoffels et al., 2007; Curio et al., 2000; Houde et al., 2002; Numminen et al., 1999; Paus, 1996; Tourville et al., 2008). This mechanism is termed *speech-induced auditory suppression* and it is likened to the motor induced somatosensory suppression observed in limb movement research (Blakemore et al., 1998; Miall and Wolpert, 1996; Wolpert et al., 1995).

The nature of speech-induced auditory suppression in adults who stutter is uncertain. Stuttering has been associated with a reduced

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signal in auditory cortex during habitual speech production in positron emission tomography (PET) and functional magnetic resonance (fMRI) studies. Some PET and fMRI studies have reported reduced auditory activation in the left superior temporal gyrus only (De Nil et al., 2000; De Nil et al., 2008; Fox et al., 1996; Watkins et al., 2008), while others have observed decreased activity bilaterally in superior temporal gyri (Braun et al., 1997; Neumann et al., 2003; Stager et al., 2003; VanBorsel et al., 2003) in adults who stutter relative to fluently speaking control participants. The frequency of stuttered segments has been negatively correlated with activity in right superior temporal gyrus (Braun et al., 1997; Fox et al., 2000) and bilateral activity in the posterior superior temporal gyri (Neumann et al., 2003). It is possible to manipulate the frequency of stuttered speech segments within an individual who stutters such that they are transiently reduced via the use of fluency enhancing techniques. The application of such techniques has been shown to increase activation in the superior temporal gyri (Braun et al., 1997; De Nil et al., 2008; Fox et al., 1996; Stager et al., 2003). Increases in auditory activation have also been observed in adults who stutter following intensive fluency treatment programs (De Nil et al., 2003; Neumann et al., 2005).

A handful of theories have been proposed that may account for the multiple observations of increased motor activity combined with decreased auditory activity during speech production in adults who stutter relative to fluently speaking adults. Specifically, the differences in auditory cortical activity may result from increased suppression of auditory cortex in relation to over-active speech motor cortex, as proposed by the *efference copy hypothesis* (Brown et al., 2005), deficient neural representations of the motor command and auditory target (Max et al., 2004; Neilson and Neilson, 1987) or timing differences in the processing of speech (Biermann-Ruben et al., 2005; Ludlow and Loucks, 2003). As auditory-motor integration occurs at the millisecond level for speech, the low temporal resolution of fMRI and PET has limited the interpretation of these findings to date. Magnetoencephalography (MEG), on the other hand, is able to measure continuous neural activity with millisecond temporal resolution. The M50 and M100 are auditory evoked magnetic field components named in accordance with the millisecond latency at which each occurs. The M50 and M100 components have their sources in primary auditory cortex, on or near Heschl's gyrus (Godey et al., 2001; Herdman et al., 2003; Kotecha et al., 2009; Reite et al., 1994) and respond to the onset properties of an auditory stimulus (Biermann and Heil, 2000; Naatanen and Picton, 1987).

The amplitude of the M100 is known to be suppressed and delayed in response to tone stimuli presented during overt speech relative to silent reading (Houde et al., 2002; Numminen et al., 1999). The M100 suppression effect is even greater in response to one's own voice than it is to a tone presented during speech production (Houde et al., 2002). Such data support the idea that auditory suppression to self-generated speech sounds is greater than suppression to externally generated stimuli. Houde et al. (2002) proposed that a motor-to-auditory signal suppresses auditory cortex based on the achievement of the auditory target anticipated by the efference copy of the motor command. To date, speech-induced auditory suppression has only been investigated with regards to the M100 component of the auditory response to tone and vowel stimuli. The models of efference copy in speech production suggest the necessity of a very rapid integration of auditory feedback for the purpose of informing upcoming speech motor commands. However, we are not aware of any publications that have examined the impact of self-generated speech on the amplitude and latency of the M50 or of either component in association with word stimuli. Studying the M50 and M100 for vowel and word stimuli should provide important information on the speed and extent of auditory suppression in fluent speech production and stuttering.

Only one previous study has used MEG to specifically examine the auditory M100 response in adults who stutter. Salmelin et al. (1998) studied the M100 response to monaural stimulation with probe tones during self paced reading and found that the M100 was more suppressed on the right and less suppressed on the left in adults who stutter relative to controls. No group differences in the latency of the M100 to the probe tones were found. Salmelin et al. (1998) suggested that the data reflected differences in interhemispheric speech processing in stutterers. It is unknown if speech-specific suppression of the auditory M100 differs in adults who stutter relative to controls. However, previous MEG studies have revealed differences between adults who stutter and fluent speakers during speech planning. Specifically, adults who stutter have been found to activate speech motor regions in different temporal sequence relative to fluent speakers (Biermann-Ruben et al., 2005; Salmelin et al., 2000).

We used MEG to investigate evoked auditory responses to speech in adults who stutter and control participants to improve the understanding of cortical auditory processing in stuttering. Our study evaluated the spatiotemporal patterns of auditory evoked magnetic fields in adults who stutter during a variety of listening and speaking tasks relative to a group of matched fluently speaking peers for the purpose of elucidating the role of speech-induced auditory suppression in persistent developmental stuttering. Secondary to this main aim, we extended the current line of research on speech-induced auditory suppression to the earlier M50 component and to word stimuli. If increased cortical motor activity in adults who stutter underlies the reduced cortical auditory activity previously observed in PET and fMRI studies, then it is expected that the auditory M50 and M100 amplitudes will be more suppressed during speech production in this population relative to fluently speaking adults. Furthermore, if the neural timing differences in motor activity previously reported in MEG studies of speech planning continue during overt speech production, then it is expected that the latency of the M50 and M100 auditory responses will differ in adults who stutter relative to fluent speakers.

Materials and methods

Participants

Twelve adults who stutter between 21 and 45 years of age (mean = 32.1 years; s.d. = 7.9) and 12 fluently speaking adults between 24 and 49 years of age (mean = 32.9; s.d. = 7.4) participated in this study. All participants were men with normal speech (except for developmental stuttering in the stuttering group), language and hearing and no self-reported developmental or neurological history. All participants were right handed as tested with the Edinburgh handedness inventory (Oldfield, 1971) and spoke English as their primary language. Informed consent was obtained from all participants. The testing involved a pre-neuroimaging 1-hour session for training and stimuli recording (see Stimuli and procedures) followed by a 1-hour scanning session at the MEG and MRI facilities at the Hospital for Sick Children in Toronto. The Hospital for Sick Children's Research Ethics Board approved this study.

Stimuli and procedures

It was crucial that the stimuli presented for the passive listening tasks during MEG recording were produced by the participants themselves, in their own voice, as our research questions pertained to speech-specific suppression induced by self-generated vocalization. Therefore, prior to the neuroimaging session participants completed a stimulus collection and training session. Participants were trained to consistently produce the vowel /i/ and vowel-initial words at a constant volume of 70 decibels sound pressure level (dB SPL). The vowel-initial word stimuli were 200 different one- and two-syllable words controlled for linguistic complexity and word familiarity generated from the MRC Psycholinguistic Database at the University

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of Western Australia (http://www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm) (e.g., above, elbow, income). After successful training, the vowel /i/ and vowel-initial word stimuli were collected from each participant for playback of their self-produced stimuli during the MEG listening tasks described below (*listen vowel*, *listen words*). During the vowel and word stimuli recording sessions the speaking prompts were presented as in the speaking tasks described below (*speak vowel*, *speak words*). 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. The participants' 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 five independent tasks during MEG recording. Three tasks (*listen tone*, *listen vowel*, *listen words*) required the participants to listen attentively to acoustic stimuli while fixating on a static white cross on a black background. The stimuli for the listen tasks were presented binaurally via ear-insert phones at 70 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* and *listen words* tasks participants listened passively to trials of their recorded self-produced vowel /i/ and vowel-initial word stimuli respectively. The two remaining tasks (*speak vowel* and *speak words*) required the participants to speak aloud in response to a visual stimulus. The ear-insert phones remained in situ for the speaking tasks. Prior to the start of these speaking tasks, participants practiced producing the vowels and words with a constant volume of 70 db SPL as they had been previously trained to do during the training session described above. A sound pressure meter was used to measure the vocal intensity at a distance of 10 cm from the participants' mouths, thus approximating the distance from mouth to ear. In the *speak vowel* task participants were required to speak aloud the vowel /i/ 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. In the *speak words* task participants were required to read aloud vowel-initial words presented on a black background for 500 ms interspersed with the white cross. The order in which the tasks were completed was counterbalanced using a Latin square design. All tasks contained 200 trials with an interstimulus interval ranging from 2.5 to 3 s. 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

Auditory evoked magnetic fields were recorded continuously (2500 Hz 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 passive listening tasks and the participants' self-generated speech produced during the active generation tasks were recorded simultaneously with the changing magnetic fields of the scalp 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 auricle. Head movement was monitored online via fiducial movement and video surveillance. Fiducial locations were also used to facilitate coregistration of the MEG data with an anatomic MRI obtained for each participant in order to specify the sources of the magnetic fields. A 1.5-T Signa Excite MRI system (GE Medical Systems, Milwaukee, WI) and a standard quadrature head coil was used to obtain neuroanatomical images. A T1-weighted 3D inversion recovery-prepared FSPGR sequence (flip angle = 20°, TE = 4.2 ms, TR = 9 ms, prep time = 300 ms) was used to generate 124 1.5-mm-thick sagittal slices (256 × 256 matrix, 24 cm field of view).

Data analyses

Behavioural data were reviewed by the primary investigator to ensure participants performed the tasks correctly and that no misread or stuttered words were included in the analyses. 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 on the acoustic signals 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 et al., 2002; Tyler et al., 2005).

The identified onsets were used to epoch the MEG data from 200 ms prior to the auditory stimuli onset to 800 ms post onset. Individual trials were averaged and source analysis was performed using an event-related vector beamformer (Quraan and Cheyne, 2010) following the methodologies of Sekihara et al. (2001) to create volumetric images of source activity throughout the brain at selected time intervals (Cheyne et al., 2006; Herdman et al., 2003). Beamformer analysis was chosen because it is able to suppress large subject-generated noise artefacts in MEG recordings of auditory responses (Cheyne et al., 2007) which we expected to occur in the overt speaking tasks. It is known that binaurally elicited auditory evoked fields produced highly correlated sources that can result in suppression of beamformer output and concomitant errors in localization and amplitude (Dalal et al., 2006). 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) in order to image correlated sources in bilateral auditory areas. For generating source activity waveforms (virtual sensors) associated with single voxels identified for peaks of activity identified in the volumetric images, the single dominant current direction from the vector output of the beamformer was selected using a time window of 10 ms either side of the M50 and M100 peaks. Further details of this approach are provided in Quraan and Cheyne (2010).

Source plots for the M50 and M100 components were created for each individual participant via a co-registered anatomical MRI. In order to combine source localization results across subjects, pseudo-*t* source images co-registered to each individual 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. Significant peaks of activity in the group images were identified after thresholding images using a non-parametric permutation test (Nichols and Holmes, 2002) adapted for beamformer source imaging (Singh et al., 2003). Talairach coordinates of peak activations were determined from the normalized images using the MNI to Talairach conversion daemon (Lancaster et al., 2000). The peak voxel coordinate for each averaged source plot was noted. This coordinate was unwarped back to individual space and used to plot the time course at the peak amplitude voxel within a 10 mm radius of that location. The peak amplitude and latency of the moment signal

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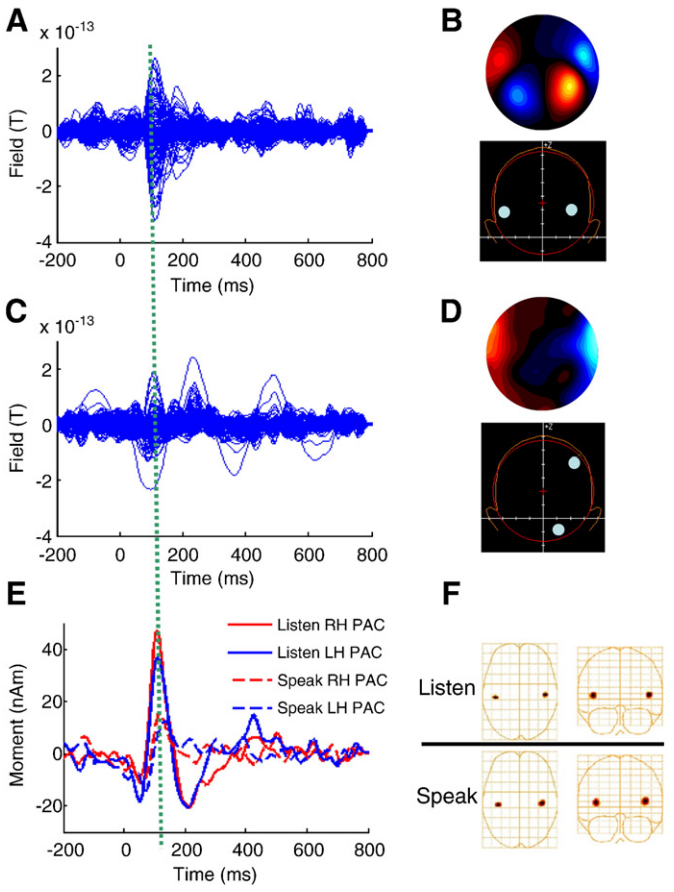

Fig. 1. Data from a representative single subject. (A) The evoked auditory response averaged over 200 trials, (B, top) the associated sensor field distribution pattern, and (B, bottom) the dipole source model are shown for the listen to vowel-initial word task. In addition, (C) the evoked auditory response averaged over 200 trials, (D, top) the associated sensor field distribution pattern, and (D, bottom) the dipole source model are shown for the speak vowel-initial word task. The noise artefact associated with the muscle movement for overt speech production is obvious in the signal data shown in C. The associated sensor field distribution is suggestive of tongue or jaw movement interference (D, top). As a result, an accurate dipole source model for the speak condition was not achieved (D, bottom). However, the event-related beamformer analyses accurately localized the sources to the left and right primary auditory cortex (G) and successfully separated the signal from the noise as shown in the virtual time course plots for each source (F). All source images were created at 100 ms (green line) and are shown in neurological convention (left is left). T = Tesla; ms = milliseconds; nAm = nanoampere*meters; LH = left hemisphere; RH = right hemisphere; PAC = primary auditory cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

from this time course were measured and extracted for averaging across participants for each task and group.

Statistical analyses of amplitude and latency data were completed separately for each component (M50 and M100) and each condition (tone, vowel and word). Analyses of the tone amplitude and latency data were completed using a 2-way mixed analysis of variance (ANOVA) to test for differences in either peak amplitude or latency of the components for the within group variable of hemisphere (left and right), between groups (control and adults who stutter) and interaction. Analyses of the vowel and word data were completed using 3-way mixed ANOVA to test for differences for the within group variables of hemisphere (left, right) and task (listen, speak), between groups (adults who stutter, controls) and any interactions. Group means of interest were tested post-hoc via dependent *t*-tests. To facilitate comparison of auditory suppression across conditions, we calculated the speaking induced suppression percent difference of the group mean amplitude values ($100\%^{*}(1-\text{amplitude}_{\text{speak}}-\text{amplitude}_{\text{listen}})$) (Ventura et al., 2009). Lastly, bivariate correlation analyses were conducted between the Stuttering Severity Index score and each of source amplitude and latency.

Results

Movement artefact

In comparison to the listen tasks, during the speak vowel and word tasks, large amplitude, low-frequency artefacts were present in the MEG sensor data in many participants (Figs. 1A and C), presumably due to muscle activity in the region of the mouth and lower face and/or small jaw movements. This resulted in distorted topography of the M50 and M100 responses in the averaged data and unsuccessful dipole fitting. Representative topographies and dipole fits are shown for the M100 response to the listen words and speak words tasks respectively (Figs. 1B and D, right). However, beamformer analysis applied to the speak tasks data was able to successfully localize sources of the M50 and M100 in similar anatomical locations to those obtained for the listen task data along with non-distorted temporal activity waveforms (Figs. 1E and F). This is consistent with previous reports on the ability of beamformers to localize auditory sources in the presence of large amplitude, motion artefacts generated in the region of the lower jaw in subjects who had highly magnetically noisy dental appliances (Cheyne et al., 2007).

Tone

The M50 and M100 components both had their sources in primary auditory cortex. The Talairach coordinates are listed in Table 1. No significant M50 or M100 amplitude differences were found for the

Table 1
Talairach coordinates for the M50 and M100 source locations.

		Control participants						Adults who stutter					
		Left hemisphere			Right hemisphere			Left hemisphere			Right hemisphere		
		x	*y*	*z*	*x*	*y*	*z*	*x*	*y*	*z*	*x*	*y*	*z*
M50	Tone	−40	−24	6	42	−22	6	−40	−24	10	40	−21	10
	Listen /i/	−42	−27	4	47	−17	3	−40	−24	6	42	−17	8
	Speak /i/	−35	−7	14	42	−12	12	−35	−6	16	40	−14	12
	Listen words	−42	−24	6	45	−19	6	−42	−22	3	45	−21	10
	Speak words	−37	−19	1	42	−19	6	−35	−11	17	40	−9	17
M100	Tone	−40	−22	6	45	−17	8	−40	−21	8	42	−17	8
	Listen /i/	−42	−24	6	45	−17	8	−40	−21	8	45	−17	8
	Speak /i/	−37	−19	6	42	−19	6	−35	−19	6	40	−26	11
	Listen words	−42	−22	6	47	−17	8	−40	19	6	42	−14	10
	Speak words	−37	−21	8	40	−19	10	−40	−14	12	40	−9	12

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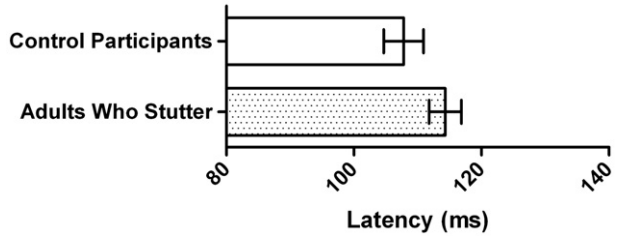

Fig. 2. M100 latencies for the tone task. The mean peak latency in milliseconds (ms) is plotted for the control group and the adults who stutter collapsed across hemispheres. Error bars correspond to the 95% confidence interval. Adults who stutter had significantly later M100 latencies in both hemispheres relative to controls.

tone condition. However, the M50 peak latency was slightly shorter in the right hemisphere ($x = 56.2$ ms, s.d. = 7.3 ms) compared to the left hemisphere ($x = 59.6$ ms, s.d. = 8.1 ms) across groups ($F(1, 22) = 4.88$, $p = .04$). As can be seen in Fig. 2, adults who stutter had longer M100 peak latencies in both hemispheres relative to controls ($F(1, 22) = 6.94$, $p = .02$). No significant correlations between stuttering severity and either amplitude or latency were found.

Listen /i/ and speak /i/

As shown in Fig. 3, the M50 and M100 components were localized to the primary auditory cortices for the listen and speak tasks in both groups. The Talairach coordinates are listed in Table 1. The time course data for the M100 sources are shown in Fig. 4.

No significant amplitude or latency effects were found for the M50. Although not significant, the M50 amplitude was reduced by an average of 6% during the speak task relative to the listen task across both control participants and adults who stutter. The M100 amplitude analysis revealed a hemisphere by task interaction ($F(1, 22) = 4.39$, $p = .05$) (Fig. 5). The interaction was explained by a stronger amplitude from the left relative to the right hemisphere for the listen to vowel task ($t(24) = 2.00$, $p = .03$). There was a task effect ($F(1, 22) = 95.45$, $p < .001$) due to the smaller amplitude of the speak task relative to the listen task regardless of hemisphere or group. On average, the amplitude of the M100 was reduced by 52% during the speak task relative to the listen task. The significant reduction in M100 amplitude during the speak task is clearly shown in the source time course data shown in Fig. 4.

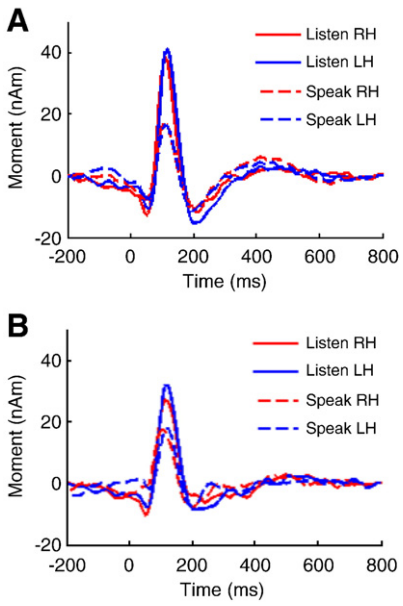

Fig. 4. The group averaged time course activity for the left (blue) and right (red) auditory cortices during the listen (solid) and speak (dashed) vowel tasks for the control group (A) and the adults who stutter (B). The mean peak amplitude is plotted in nanoampere*meters (nAm) on the *y*-axis and time in milliseconds (ms) along the *x*-axis. The amplitude of the M100 peak is suppressed during the speak vowel task relative to the listen vowel task. LH = left hemisphere; RH = right hemisphere. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The results of the listen to vowel and speak vowel task M100 latency analyses are shown in Fig. 6. A 3-way interaction for hemisphere by task by group ($F(1, 22) = 5.65$, $p = .03$) was found. In the left hemisphere there was little difference in latency between tasks or groups, while for the right hemisphere post-hoc tests revealed that the adults who stutter had significantly longer latencies for the listen task relative to the controls ($t(22) = 2.62$, $p = .02$). Additionally, adults who stutter had shorter latencies for the speaking task relative to the listen task in the right hemisphere ($t(11) = 2.61$, $p = .01$). No

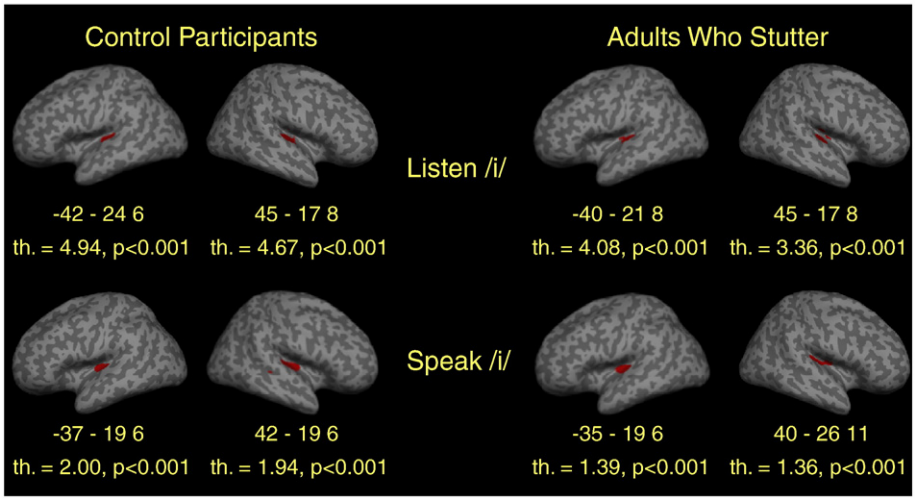

Fig. 3. Group averaged source images are shown for the listen and speak vowel tasks. The source locations for the vowel stimuli were representative of those for the tone and word stimuli. The statistical maps are overlaid on a surface based representation of the MNI canonical brain using the SPM surfrend toolbox (http://spmsurfrend.sourceforge.net). The surfaces were rendered using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) (Dale, Fischl, Sereno 1999; Fischl, Sereno, Dale 1999). Talairach coordinates and pseudo-*z* threshold (th.) values derived via non-parametric permutation testing adapted for beamformer source imaging (Nichols and Holmes 2002; Singh et al., 2003) are shown for each image.

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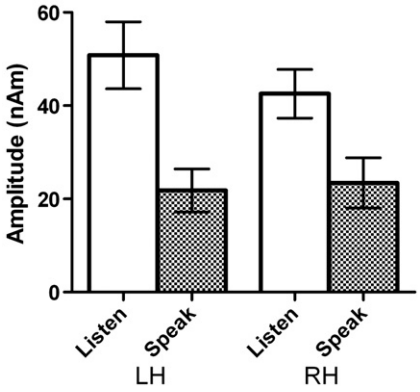

Fig. 5. M100 amplitudes for the listen to vowel and speak vowel tasks collapsed across groups. The mean peak amplitude is plotted in nanoampere*meters (nAm) on the *y*-axis. Both groups demonstrated suppressed M100 amplitudes for the speak vowel task relative to the listen to vowel task. The left hemisphere amplitude was slightly greater than the right hemisphere amplitude for the listen task. Error bars represent the 95% confidence interval. LH = left hemisphere; RH = right hemisphere.

correlations between stuttering severity and amplitude or latency reached significance.

Listen words and speak words

Similar to the vowel condition, the M50 and M100 source locations were localized to the primary auditory cortices for the listen and speak tasks in both groups (see Table 1 for the Talairach coordinates). The findings that participants had smaller M50 ($F(1, 22) = 4.42$, $p = .05$) and M100 ($F(1, 22) = 83.79$, $p < .001$) amplitudes during the speak task compared to the listen task are shown in Fig. 7. The mean amplitude of the M50 was reduced by 22% and the M100 was reduced by 57%.

The results of the listen to words and speak words task latency analyses are shown in Fig. 8. A task by group interaction was found for both the M50 ($F(1, 22) = 5.30$, $p = .03$) and M100 ($F(1, 22) = 7.54$, $p = .01$) due to the adults who stutter having a longer latency for listen than the controls. The Stuttering Severity Index score approached a significant positive correlation with peak M100 latency for speak words in the right hemisphere ($r = .527$, $p = .08$).

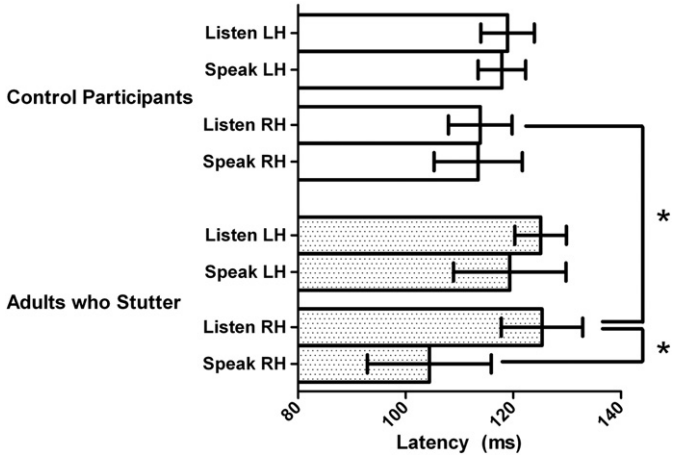

Fig. 6. M100 latencies for the listen to vowel and speak vowel tasks. The mean peak latency in milliseconds (ms) is plotted on the *x*-axis. The adults who stutter had an earlier right than left hemisphere response for the speak task. The adults who stutter also had later latencies in both hemispheres for the listen task relative to the control participants. Error bars represent the 95% confidence interval. LH = left hemisphere; RH = right hemisphere.

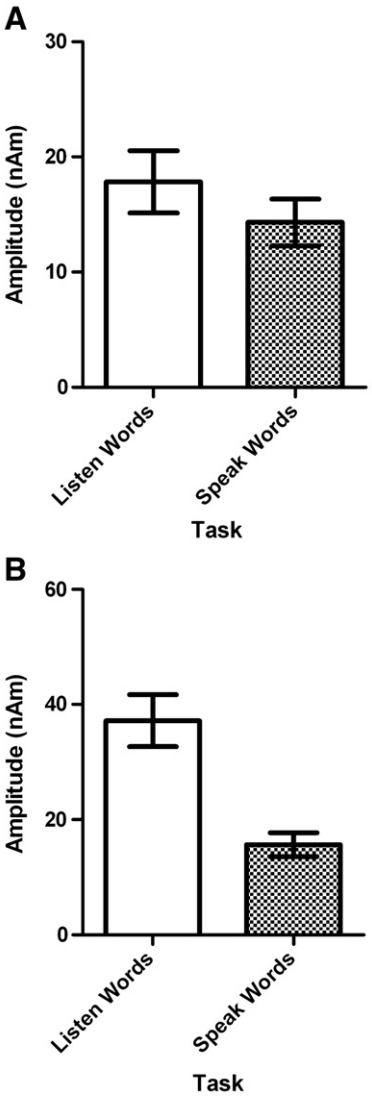

Fig. 7. M50 (A) and M100 (B) amplitudes for the listen to words and speak words tasks collapsed across hemispheres and groups. Peak amplitude is plotted in nanoampere*-meters (nAm) on the *y*-axis. Participants had a smaller M50 ($F(1, 22) = 4.42$, $p = .05$) and M100 amplitude during the speak task compared to the listen task ($F(1, 22) = 83.79$, $p < .001$). Error bars represent the 95% confidence interval.

Discussion

Our MEG study confirmed the phenomenon of speech-induced suppression of the auditory M100 for vowel stimuli and showed that both the M50 and M100 are suppressed for word stimuli. More importantly, the data showed that adults who stutter do not differ from controls in the amount of speech-induced suppression of the auditory M50 or M100 amplitude. Rather, our results revealed significant differences in the timing of cortical auditory processing in adults who stutter relative to controls under a variety of stimuli. The findings advance our understanding of stuttering by demonstrating the importance of neural timing differences in auditory cortex for the processing of both speech and non-speech stimuli in this population. Task-specific results are discussed below in relation to theories of the neural correlates of stuttering.

Amplitude

We examined auditory responses to speech stimuli, including vowels and words, during passive listening and active speech

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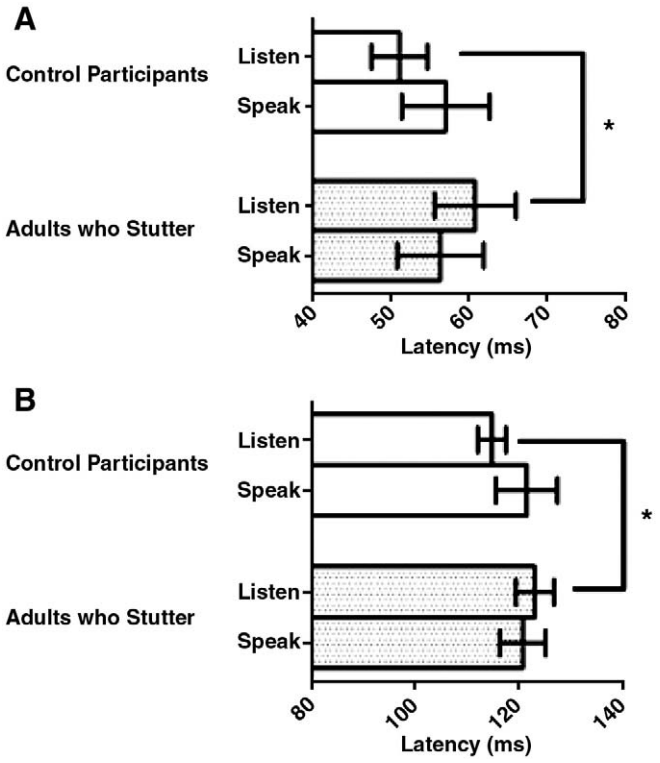

Fig. 8. M50 (A) and M100 (B) latencies for the listen to words and speak words tasks. Peak latency is plotted in milliseconds (ms) on the *y*-axis. The adults who stutter had longer M50 and M100 latencies for the listen task relative to the control participants. Error bars represent the 95% confidence interval.

production. Both the adults who stutter and the control group had reduced M100 peak amplitudes during active vowel production relative to passive listening (Fig. 5). This finding is highly consistent with other studies of speech-induced auditory suppression in fluent speakers and supports the theory that this is a normal process by which vocalization evoked auditory responses are reduced during self-generated speech relative to simply listening to playback of speech (Christoffels et al., 2007; Guenther et al., 2006; Heinks-Maldonado et al., 2006; Hirano et al., 1997; Houde et al., 2002; Tourville et al., 2008; Ventura et al., 2009). The impact of overt speech on the M50 peak amplitude was not consistent. The M50 was reduced in amplitude, for both groups, only during active production of the vowel-initial word stimuli (Fig. 7A). The magnitude of the M50 speech-induced suppression was markedly reduced relative to that of the M100 for both the vowel (6% compared to 52%) and word (22% compared to 57%) tasks. The amount of M100 speech-induced suppression is consistent with that observed in other studies of the auditory M100 in fluent control participants (Heinks-Maldonado et al., 2006; Houde et al., 2002; Ventura et al., 2009). The suppression effect to word stimuli for the M50 component may reflect greater suppression with increased motor plan complexity and a resultant increase in the number or magnitude of efference copy messages shared with auditory cortex. However, this would predict that the M100 suppression effect would also differ between vowels and words which was not the case. Further investigation is therefore required to determine the extent to which self-generated speech reliably attenuates components of the auditory evoked response earlier than 100 ms. However, our current results suggest that such suppression effects are not specific to the M100 component. To our knowledge, our findings represent the first time that the speech-induced suppression effect has been determined as early as the M50 as previous studies only investigated the M100 component.

A novel and central finding of the current study is that adults who stutter did not differ from the control group in the amount of speech-induced auditory suppression of the auditory M50 or M100 amplitude. The lack of a group difference in the amount of speech-induced suppression in the M50 and M100 is problematic for the *efference copy hypothesis* of stuttering (Brown et al., 2005) as it is currently proposed. Brown et al. (2005) posited that the efference copy signal itself has an inhibitory effect and that the lack of auditory activation observed in adults who stutter during habitual speech production on fMRI and PET studies is due to over-active motor activity. The main premise of the Brown et al. (2005) hypothesis is that the increased motor activity observed in adults who stutter during speech results in increased efference copy signal overly inhibiting the activity in the auditory cortex. Based on this hypothesis it would be expected that the M50 and M100 would be more suppressed in adults who stutter. However, our data clearly showed no difference in the amount of speech-induced auditory suppression in adults who stutter relative to fluent speakers. The *efference copy hypothesis of stuttering* is unable to account for the equal magnitude of speech-induced auditory suppression in the M50 and M100 auditory responses between adults who stutter and control participants observed in the current study.

We also examined the amplitude of auditory responses to non-speech stimuli during passive listening. The data showed that the amplitude of the M50 and M100 responses to 1 kHz tones did not differ in adults who stutter compared to fluent speakers. This finding is consistent with the previous literature (Biermann-Ruben et al., 2005; Hampton and Weber-Fox, 2008). The similarity of the auditory M50 and M100 amplitudes between adults who stutter and fluent speakers across stimuli (e.g., non-linguistic, linguistic) and tasks (listening, speaking) indicates that adults who stutter activate similar neuronal populations in auditory cortex with comparable amplitude as their fluently speaking peers while processing early auditory information. Thus, the current amplitude data suggest that the reduced auditory activation in adults who stutter during speech production observed in the seconds-long blood–oxygen level dependent response measured by fMRI (De Nil et al., 2008) and minutes-long tracer uptake in PET (Braun et al., 1997; Fox et al., 1996; Fox et al., 2000) are not associated with reduced auditory neuronal recruitment in the earlier stages of processing as measured by MEG.

Latency

Our results revealed differences in the timing of cortical auditory processing in adults who stutter relative to fluent speakers for both the vowel and word stimuli. Adults who stutter differed in the latency of the M50 and M100 dependent on the hemisphere and task. Adults who stutter demonstrated a significant earlier right hemisphere M100 latency compared to the left hemisphere latency pattern for processing their own voice during speaking relative to listening for the vowel stimuli, whereas fluent speakers showed no left–right latency differences across listening and speaking tasks (Fig. 6). A similar trend was found for the word stimuli. The finding of a right faster than left pattern for auditory processing of self vocalization in adults who stutter is particularly interesting in light of previously reported functional biases involving the right hemisphere in adults who stutter. A number of neuroimaging studies have noted biased right hemisphere activation in motor speech production areas in adults who stutter (De Nil et al., 2008; Fox et al., 1996, 2000). Right auditory cortex activation is increased in adults who stutter following participation in an intensive treatment program (De Nil et al., 2003) and is negatively correlated with stuttering severity (Braun et al., 1997; Fox et al., 2000) suggesting that it is associated with compensation. Our current data showed a trend for adults with mild stuttering to engage the right hemisphere earlier for the word stimuli than those with more severe stuttering. Taken together with previous findings of favoured right

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hemisphere activity, it may be the case that the right-earlier-than-left engagement of the auditory cortex by adults who stutter during overt speech reflects a compensatory change in sequencing of neural events in response to inefficient access to the neural representations for speech sounds. However, further investigation is required to determine if our observed changes in neural timing are not an inherent aspect of stuttering itself.

Our observation that the sequence of neural timing in auditory cortices is different in adults who stutter relative to fluent speakers is consistent with previously reported differences in the neural timing of the speech motor system prior to overt production in adults who stutter. Biermann-Ruben et al. (2005) reported that adults who stutter activated the left inferior frontal area and right Rolandic operculum in response to speech stimuli with different timing than fluent speakers. Similarly, but within the same hemisphere, Salmelin et al. (2000) showed that the normal activation sequence of left inferior frontal (articulatory planning) areas followed by left lateral central and dorsal premotor (motor preparation and execution) areas following presentation of a word for the purpose of repeating it was reversed in adults who stutter. Our findings suggest that the timing differences within the speech production system continue after overt production has occurred.

Adults who stutter had delayed auditory M50 and M100 peak latencies across most of the passive listening tasks relative to control participants (Figs. 2, 6, and 8). The only exception was for the non-speech tone task, for which no M50 latency group differences were found. The M50 and M100 are cortical auditory responses to the spectral and amplitude properties of sound stimuli and possibly reflect thalmo-cortical and corticocortical interaction (Liegeois-Chauvel et al., 1994; Naatanen and Picton, 1987; Reite et al., 1978). Our data suggest a fundamental difference in the way adults who stutter process sound information at the cortical level. For example, non-speech auditory processing delays have been previously linked to other populations with speech and language impairments. Oram-Cardy et al. (2008) reported that the peak latencies of the right hemisphere M50 and M100 predicted overall language ability in a group of children with autism and specific language impairment and were correlated with impaired language comprehension. In our study, stuttering severity did not correlate significantly with tone latency. This may point to a developmentally sensitive time period for which responses to non-linguistic tone stimuli correlate with linguistic behavioural measurements. Further, adults who stutter took longer to activate bilateral auditory cortices during passive listening to vowels and vowel-initial words. These observations may reflect difficulty extracting place-of-articulation features of speech for the purpose of updating the neural representations of speech sounds. Adults who stutter may have deficient, or difficult to access, neural speech sound representations. This could lead to the possibility of neural timing differences within either the feedforward or feedback components of an integrated model of the motor control system (Guenther, 1994, 1995; Guenther et al., 2006; Kröger et al., 2009) in adults who stutter. As speech is a rapid and dynamic motor process it follows that the underlying neural circuits supporting it must respond in a timely, precise and sequential manner to ensure its correct production (Ludlow and Loucks, 2003; Tsao and Weismer, 1997). The neural timing differences observed in the current study may reflect inefficient access to the neural representations of speech sounds in the brain. A failure to develop stable and accurate neural representations in childhood or to maintain these representations sufficiently across the lifespan has been theorized to play a role in stuttering (Max et al., 2004; Neilson and Neilson, 1987).

Conclusions

The amplitude and latency results presented here advance our understanding of cortical auditory processing in adults who stutter. The amplitude data demonstrated the speech-induced suppression effect for the auditory M100 and, to a lesser extent, the M50. We showed, for the first time, that adults who stutter do not differ from fluent speakers in the amount of speech-induced suppression. Rather, our data revealed differences in the timing of cortical auditory processing in adults who stutter relative to fluently speaking adults to a variety of stimuli. The latency data may suggest deficient or difficult to access neural representations of speech sounds in adults who stutter.

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