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Brain activation abnormalities during speech and non-speech in stuttering speakers

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Abstract

Although stuttering is regarded as a speech-specific disorder, there is a growing body of evidence suggesting that subtle abnormalities in the motor planning and execution of non-speech gestures exist in stuttering individuals. We hypothesized that people who stutter (PWS) would differ from fluent controls in their neural responses during motor planning and execution of both speech and non-speech gestures that had auditory targets. Using fMRI with sparse sampling, separate BOLD responses were measured for perception, planning, and fluent production of speech and non-speech vocal tract gestures. During both speech and non-speech perception and planning, PWS had less activation in the frontal and temporoparietal regions relative to controls. During speech and non-speech production, PWS had less activation than the controls in the left superior temporal gyrus (STG) and the left pre-motor areas (BA 6) but greater activation in the right STG, bilateral Heschl's gyrus (HG), insula, putamen, and precentral motor regions (BA 4). Differences in brain activation patterns between PWS and controls were greatest in the females and less apparent in males. In conclusion, similar differences in PWS from the controls were found during speech and non-speech; during perception and planning they had reduced activation while during production they had increased activity in the auditory area on the right and decreased activation in the left sensorimotor regions. These results demonstrated that neural activation differences in PWS are not speech-specific.

Keywords

Stuttering; Speech perception; planning; production; non-speech; functional magnetic resonance imaging (fMRI); auditory-motor interaction; forward model

Introduction

Stuttering is a developmental disorder affecting speech fluency, present in 1% of the adult population and in 5% of preschool-age children (Bloodstein, 1995). Functional neuroimaging studies of connected speech in stuttering speakers have shown disparity in the level and extent of activation between the left and right hemispheres in the motor and auditory regions (Braun et al., 1997; Fox et al., 1996; Neumann, 2007). Some differences include over-activation in the right frontal operculum and insula during both stuttered and fluent speech production (Braun et al., 1997; Fox et al., 2000), decreased activation in auditory association areas in the temporal

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lobe during stuttering (Braun et al., 1997; Fox et al., 1996), and increased motor and cerebellar activation during speech production (Braun et al., 1997; Fox et al., 2000).

Behavioral studies have shown differences from controls during non-speech movements in stuttering individuals including: orofacial non-speech and finger flexion movements (Borden, 1983; Max et al., 2003), finger tapping (Smits-Bandstra et al., 2006), and finger movement sequencing (Forster and Webster, 2001). Stuttering subjects also have difficulty making precise movements using afferent sensory information for motor execution (De Nil and Abbs, 1991; Loucks and De Nil, 2006). Difficulties in motor execution and sensorimotor integration may affect other vocal tract gestures that do not involve speech sounds in persons who stutter.

Using positron emission tomography, Braun et al. (1997) compared stuttering and fluent adults while subjects were humming and moving their jaw, lips and tongue. Differences in the cerebral blood flow patterns mimicked those found during stuttering although to a lesser degree: cerebral blood flow was increased in premotor, primary motor and somatosensory cortices on the left while increases in the primary and secondary auditory cortices were greater on the right in stuttering subjects. The authors concluded that these differences in brain function were independent of stuttering and might indicate that brain function in these regions was fundamentally different in persons who stutter. Others reported that cerebral blood flow differences from controls that occurred during stuttered overt reading in stuttering subjects, also occurred during covert stuttered reading (Ingham et al., 2000).

Recent anatomical studies have found structural brain differences from fluent controls in persons who stutter. Structural MRI studies using diffusion tensor imaging (DTI) showed differences in stuttering adults relative to controls in the major white matter tract underlying the rolandic fissure interconnecting the auditory and sensorimotor regions in the left hemisphere (Sommer et al., 2002). When children with persistent stuttering and those who had recovered were compared with fluent controls using DTI, the white matter tract in the superior longitudinal fasciculus in the left side differed (Chang et al., 2008). Others have shown atypical cerebral asymmetries (Foundas et al., 2001; Foundas et al., 2003) and aberrant sulcal morphology (Cykowski et al., 2007) in adults who stutter. Such anatomical differences may lead to abnormalities in the interaction between speech production and auditory and sensorimotor integration in persons with chronic stuttering, and affect brain function for both speech and non-speech vocal tract gestures. Further, brain function differences in these regions may occur not only during speech production, but also during perception and planning processes for speech and non-speech vocal tract gestures (Biermann-Ruben et al., 2005; Salmelin et al., 2000).

In normally fluent speakers, auditory-motor mapping is evidenced by motor activation during speech perception (Pulvermuller et al., 2006; Watkins and Paus, 2004; Wilson et al., 2004), and reduced neural activation in the superior temporal gyrus during speech production compared to during speech perception (Houde et al., 2002). The suppression of self-generated responses in the auditory region during speech production is support for a motor-to-sensory efferent feedforward mechanism, reported in humans, monkeys, and singing crickets (Eliades and Wang, 2003; Houde et al., 2002; Poulet and Hedwig, 2003a).

Auditory modulation during speech production may allow speech without consciously relying on auditory feedback. The DIVA speech model (Directions into Velocities of Articulators; Guenther, 2006) posits that a ventral motor region sends a feedforward signal to both motor and auditory regions, to compare the expected sensory consequences of motor execution, with the resulting sensory output. The auditory region may be activated when there is a mismatch, sending corrective signals to motor areas (Guenther et al., 2006). Given that previous studies on persons who stutter found increases in motor activation and decreases in auditory activation

during speech production (Braun et al., 1997; Fox et al., 2000), an aberrant interaction between the auditory and speech regions may be present in this group.

In this study, we examined whether patterns of brain activation indicate sensorimotor integration abnormalities in stuttering speakers during motor execution of auditory targets, for both speech and non-speech production. We posited that functional abnormalities would be present during vocal tract gestures which normally do not elicit stuttering, to demonstrate that any difference in brain activation could not be the result of stuttering.

We theorized that the white matter differences previously found in the superior longitudinal fasciculus underlying the rolandic fissure interfere with the frontal-temporoparietal link in the left hemisphere in stuttering speakers and hypothesized the following group differences would occur during the perception, planning and production of speech and non-speech vocal tract gestures: 1. During auditory perception of both types of gestures, the stuttering speakers will have attenuated activation in the frontal motor and temporal-parietal auditory/sensory regions; 2. During gesture planning, stuttering speakers will have attenuated responses in motor planning regions such as preSMA and insula, and the sensorimotor integration areas in the temporoparietal regions; 3. During gesture production, stuttering speakers would have increased monitoring in the auditory regions on the left due to impaired feedforward mechanisms and increased activation in the motor regions on the right as has previously been found during stuttered speech (Brown et al., 2005).

Finally, some have suggested that there are sex-linked genetic bases for susceptibility of stuttering (Kidd et al., 1981; Suresh et al., 2006), and Ingham et al. (2004) found that the rate of stuttering was related to blood flow measures only on the right in males and bilaterally in females. Therefore, we examined whether males and females differ in their brain activation comparisons with controls, and hypothesized that the females would have bilateral differences in brain activation while the males would have more right-sided differences during speech and non-speech production (Ingham et al., 2004).

Methods

Participants

20 healthy adults (11 females) (mean age = 36.35, SD=10.69) and 20 stuttering adults (9 females) (mean age= 35.75, SD=11.29) who were right handed on the Edinburgh handedness inventory (Oldfield, 1971), native North American English speakers, and normal on speech, language, and cognitive testing (within 1 standard deviation of the age-adjusted mean) participated in this study. Stuttering severity in the stuttering participants was assessed using the Stuttering Severity Instrument (SSI-3) (Riley, 1972), while they engaged in conversation, monologue, and reading tasks in front of a small audience. The SSI scores varied from very mild to severe (mean=24.5, SD=6.35). To establish measurement reliability of the SSI score ratings, a random sample of speech recordings from 7 stuttering and 3 control participants were scored independently by two trained raters. An intra-class correlation (ICC) analysis was conducted on the stuttering ratings; The ICC coefficients were derived using the following equation: r= (Between group mean squares-Within group mean squares)/Between group mean squares + (n-1)*Within group squares), where n was the number of samples taken to compare within and between judges. ICC is considered more robust to the effects of systematic bias, and addresses correspondence as well as agreement in the data when considering reliability, which is not the case with Pearson correlation. In our case, we took 10 random speech samples to measure intra-rater reliability, hence n equaled 10. The ICC for the overall SSI measurement was 0.98, for stuttering frequency measurements during conversation/monologue speech 0.86, and during reading the ICC was 0.99.

All subjects were required to be free of neurological or medical disorders, passed audiometric screening, and had normal structural MRI scans as confirmed by a radiologist. All subjects signed an informed consent form approved by the Internal Review Board of the National Institutes of Neurological Disorders and Stroke. All were paid for their participation.

Procedure

Auditory and visual stimuli were delivered using Eprime software (version 1.2, Psychology Software Tools, Inc.) running on a PC, which synchronized each trial with functional image acquisition. Sound was delivered binaurally through MRI-compatible headphones (Silent Scan™ Audio Systems, Avotec Inc., Stuart, FL). The auditory stimuli were set at a comfortable volume level for each subject before the experiment and remained constant throughout the experimental runs. Subjects' productions were monitored and recorded using an MR-compatible microphone attached to the headphones (Silent Scan™ Audio Systems, Avotec Inc., Stuart, FL).

Each trial started with a perception task involving binaural presentation of either a sequence of two nonsense speech syllables or a sequence of two non-speech oral sounds (Figure 1). All the stimuli were previously recorded, using the same female speaker. Five different stimuli pairs were randomly presented for the speech and non-speech conditions during the perception phase. The speech stimuli were pairs of meaningless consonant-vowel-consonant speech syllables /bem/-/dauk/, /hik/-/lʌ d/, /saip/-/kuf/, /lok/-/chim/, and /raig/-/sot/, devoid of lexicality but following the rules of English phonology. The non-speech stimuli were pairs of sounds of orofacial and vocal tract gestures: cough-sigh, sing ("/a/" on a tone)-raspberry, kiss-snort, laugh-tongue click, whistle-cry. All non-speech stimuli could be easily reproduced by each subject, yet involved complex oral motor sequencing, without phonemic processing typical of speech processing. The non-speech and speech stimuli were similar in duration ($\bar{x}_{\text{speech}}$ = 820 ms (s.d.= 136), $\bar{x}_{\text{non-speech}}$ = 916 ms (s.d.= 142)) and root-mean-square power ($\bar{x}_{\text{speech}}$ = .15 (s.d.= .04), $\bar{x}_{\text{non-speech}}$ = .12 (s.d.= .07)), with no statistically significant difference ($p > .05$). The speech and non-speech targets did differ, however, in acoustic and motor complexity; speech included more transients and smaller articulatory gestures, whereas non-speech involved less complex gestures.

The perception phase was followed by a planning phase, when the subjects were visually cued that their upcoming production of the two stimuli should either be in the same order (right arrow) or in the reversed order (left arrow) from the presented pair. Subjects were instructed beforehand not to make any oral movements during this time period. This design separated motor planning from motor production, as the onset of production was signaled by a fixation cross replacing the arrow from the planning phase. The cross served as the "go" signal for subjects to produce the previously planned speech or non-speech response (Figure 1). Each of the auditory stimulus was presented during a 4 second silent period, followed by 2.7 seconds of scanning. The planning and production responses also took place during the transient silence of 4 seconds, each immediately followed by 2.7 seconds of scanning (see section below for more detail).

All subjects underwent a training session on the day of the experiment to familiarize them to the stimuli and tasks. Both groups of subjects were able to produce both speech and non-speech stimuli without difficulty. The majority of stuttering participants did not stutter at all in either the speech or non-speech task. Although a few stuttered utterances did occur in some of our stuttering subjects, these were excluded from analysis by monitoring each of their productions on-line during the experiment, as well as reviewing recorded responses post-experiment for unclear responses. The time points associated with a stuttered trial were then deleted from further analysis. Ten speech and ten non-speech trials were randomly presented in each run, and a total of three runs were completed for each subject, resulting in 60 perception (only the

first of the two perception trials were taken for analysis), and 60 production responses; both containing 30 speech and 30 non-speech stimuli.

Image Acquisition

All images were obtained from a 3.0 Tesla GE Signa scanner equipped with a standard head coil. Subjects' head movements were minimized using padding and cushioning of the head inside the head coil. Gradient echo-planar pulse sequence was used for functional image acquisition (TE=30ms, TR=6.7s, FOV=240mm, 6 mm slice thickness, 23 contiguous sagittal slices). By using an event-related, sparse sampling design (Birn et al., 1999; Eden et al., 1999; Hall et al., 1999) the presentation of auditory stimuli, and the planning and production phases took place while the scanner was transiently silent before scanning 4 seconds later. Sparse sampling minimized scanner noise and movement related susceptibility artifacts. In this experiment, the scans were collected over 2.7 seconds within a TR of 6.7 seconds, leaving 4 seconds of silent period for stimulus delivery and task performance (Figure 1). High-order shimming before echo-planar image acquisition optimized the homogeneity of the magnetic field across the brain and minimized distortions. A high-resolution T1-weighted anatomical image was also acquired for registration with the functional data, using a 3D inversion recovery prepared spoiled gradient-recalled sequence (3D IR-Prep SPGR; TI=450 ms, TE=3.0ms, flip angle=12 degrees, bandwidth=31.25mm, FOV=240 mm, matrix 256×256 mm, 128 contiguous axial slices).

Data Processing

Image preprocessing and all subsequent data analysis was carried out using Analysis of Functional Neuroimages (AFNI) software (Cox, 1996). The first four volumes were excluded from analysis to allow for initial stabilization of the fMRI signal. To correct for small head movements, each volume from the three functional runs were registered to the volume collected closest to the high-resolution anatomical scan using heptic polynomial interpolation. The percent signal change in each voxel was normalized by dividing the hemodynamic response amplitude at each time point by the mean amplitude of all the time points for that voxel from the same run, and then multiplying by 100. These functional images from each run were then concatenated into one 3D+time file, and subsequently spatially smoothed using a 6-mm full-width half-maximum Gaussian filter.

A rest period of 6.7 seconds with scanning preceded the first perception presentation to reduce any possible effects of motor planning and execution on the perception response. In addition, only data from the first of the two perception trials were used for perception analysis. This reduced possible effects of motor planning on the perception data, because the planning task depended on hearing the second perception stimulus. The subjects also had to wait for the arrow onset approximately 4.7 seconds later to begin planning their production, as the arrow direction informed them of whether their upcoming production would have the same or a reversed order.

The amplitude coefficients for perception (speech and non-speech) and production (speech and non-speech) for each subject were estimated using multiple linear regression. This created statistical parametric maps of *t* statistics for the linear coefficients. Statistical images were thresholded at $t > 3.1$ at $p < .01$ (corrected). Correction for multiple comparisons was achieved using Monte Carlo simulations, for which we selected a voxel-wise false-positive *p* threshold of .001 and a minimum cluster size of four contiguous voxels (345 mm^3) to give a corrected *p* value of .01. Each individual's statistical map was transformed into standardized space (MNI 27 T1 weighted MRI from single subject) by using a 12 parameter affine registration.

Analyses

Comparisons of stuttering versus controls during perception, planning, and production—For group analyses, the *t* statistical maps of each condition were derived and entered into a mixed effects ANOVA, where group (stuttering, controls), task (perception, planning, production) and mode (speech versus non-speech) were fixed factors and subjects was a random factor. Contrasts between conditions of interest used pair-wise *t*-tests, resulting in statistical maps for each contrast (thresholded at p<.01, corrected, see above).

ROI analyses—ROIs were cytoarchitectonically defined, using atlas maps in standard space in the inferior frontal (BA 44, BA45) (Amunts et al., 2004), sensorimotor (OP4, BA 4, supplementary motor area (SMA)) (Eickhoff et al., 2006; Zilles et al., 1995), and inferior parietal regions (supramarginal gyrus (SMG), angular gyrus) (Caspers et al., 2006), using maximum probability maps and macrolabel maps (Eickhoff et al., 2005) implemented in AFNI (Cox, 1996). The posterior superior temporal gyrus (pSTG), and insula were also regions of interest, but as no cytoarchitechtonic maps were yet available for these regions, the talairach daemon database (Lancaster et al., 2000) was used to define their regional boundaries. These ROIs encompass regions known to be part of the auditory dorsal stream for speech processing, as well as those reported to be part of the speech production network (Bohland and Guenther, 2006; Guenther et al., 2006), which are co-activated during perception and production tasks (Okada and Hickok, 2006; Wilson et al., 2004).

The ROIs were used as masks to extract the percent signal change values (at $t > 3.3$, $p < .01$, corrected) from each individual's functional maps to compare speech versus non-speech activation between groups. Repeated measures ANOVA was used to examine the between factor of Group (stuttering, control), and the within subjects factors of ROI (BA44, BA45, OP4, BA4, preSMA, pSTG, SMG, angular gyrus, insula), laterality (left, right), strategy (imitation, encoding), and mode (speech, non-speech) for each task condition (perception, planning, production). If ROI interacted with group effects at $p < 0.0167$, then post hoc tests between groups were conducted for each ROI at $p < 0.006$ to correct for multiple comparisons.

To examine for possible gender differences, we additionally conducted post-hoc analyses of group differences within each sex. This was done by conducting repeated measures ANOVAs in ROIs that showed overall control versus stuttering group differences, to determine whether these differences were gender-specific.

Results

Perception of speech and non-speech in stuttering versus normally fluent controls

During perception, whole brain analysis ($p < 0.01$, corrected for multiple comparisons) showed stuttering individuals had consistently less BOLD response relative to controls in the bilateral superior temporal gyrus (BA 41), particularly on the left, and bilateral precentral motor (BA 6,4), angular gyrus, SMA, and cerebellum on the right, as well as in the right thalamus (table 1). These findings were similar for both speech and non-speech tasks (figure 2).

The ROI analysis revealed a group effect showing an overall greater percent signal change in controls compared to stuttering ($F_{1,38} = 5.28$, $p = .026$). There were no group differences in the response to speech and nonspeech stimuli ($F_{1,38} = .36$, $p = .056$), and no differences in the laterality of the response ($F_{1,38} = .17$, $p = .68$). When the groups were compared within each ROI, with the factors speech/nonspeech, and side as repeated measures, lesser signal change was found for stuttering individuals compared to controls in the preSMA ($F_{1,38} = 8.96$, $p = .005$), whereas the motor region 4p ($F_{1,38} = 7.601$, $p = .009$) approached significance (figure 3A). There were no significant interactions between ROI and the other factors.

In a post-hoc comparison of sex specific differences, we found a significant group difference between the stuttering and control males in the preSMA ($F_{1,18}$ =7.212, p=0.015) but not between the stuttering and control females ($F_{1,18}$ =2.707, p=0.117). No sex-specific differences occurred in 4p: neither in females ($F_{1,18}$ =4.094, p=0.058) nor in males ($F_{1,18}$ =2.723, p=0.116) when examined separately.

Planning of speech and non-speech in stuttering versus normally fluent controls

During planning, whole brain analysis showed stuttering individuals had less BOLD signal change than the controls throughout the cortex, including the bilateral motor regions, bilateral inferior parietal regions including the angular gyrus, bilateral cerebellum, left cingulate gyrus, and the right thalamus (figure 4, table 2). These findings were similar for both speech and non-speech tasks, although the regions showing differences were somewhat greater in extent for non-speech relative to speech. No differences were found between the two planning conditions (encoding versus imitation).

In the ROI analyses, an overall group effect was present, with greater percent signal change in the controls than in the stuttering individuals ($F_{1,38}$ = 7.72, p= .008), and a significant ROI × group interaction ($F_{1,38}$ = 3.08, p= .001). The two groups did not differ significantly in their response to speech versus nonspeech planning ($F_{1,38}$ = 3.44, p= .071) nor in their response to encoding versus imitation ($F_{1,38}$ = 2.53, p= .120). They did not differ in the laterality of the response ($F_{1,38}$ = .12, p= .731). When stuttering and controls were further compared within ROIs using repeated measures ANOVA, with repeated factors mode (speech versus nonspeech), strategy (encode versus imitation), and side (left, right), significantly decreased percent signal change occurred in the stuttering individuals compared to controls in the angular gyrus ($F_{1,38}$ = 8.89, p= .005), and insula ($F_{1,38}$ = 10.28, p= .003) (figure 3B). Differences approached significance in the preSMA ($F_{1,38}$ = 7.64, p= .009), pSTG ($F_{1,38}$ = 7.12, p= .011) and OP4 ($F_{1,38}$ = 5.81, p= .021). In preSMA, the strategy (encode versus imitation) × group interaction approached significance ($F_{1,38}$ = 6.49, p= .015), with stuttering individuals showing greater percent signal change during encoding than imitation compared to controls. There were no other significant interactions in the other ROIs.

In a post-hoc analysis of sex specific differences, group differences in the angular gyrus and insula were significant in females (angular gyrus, $F_{1,18}$=6.232, p=0.022, insula, $F_{1,18}$=0.106, p=0.024), but not in males (angular gyrus: $F_{1,18}$=1.254, p=0.278, ins $F_{1,18}$=1.122, p=0.304). Group differences occurred in the pSTG between males ($F_{1,18}$ = 6.479, p= 0.020), but not between the females ($F_{1,18}$ =1.563, p=0.227). Group differences found in OP4 and preSMA were not significant when compared separately within each gender.

Production of speech and non-speech in stuttering versus normally fluent controls

Initially, we compared the BOLD response from the “repeat” trials with the “reverse” trials, and found no significant differences (p>0.05). Therefore the BOLD responses from both response types were combined for the production analysis.

During production, whole brain analysis showed the normal controls had higher activation compared to stuttering individuals in the bilateral precentral gyri (BA 6), left STG/MTG (BA 41/42), inferior parietal lobule (BA 2, 40), and the right cerebellum (see table 3 for complete list of regions). Only on the production tasks, stuttering individuals had significantly greater activation than the controls in several regions: the bilateral precentral gyri (BA 4), bilateral transverse temporal gyri near Heschl’s gyrus (HG; BA 41), right STG (BA 22), left cerebellar culmen, and bilateral putamen. These findings were similar for both speech and non-speech conditions (figure 5, table 3) (statistical parametric maps thresholded at p < .01, corrected for multiple comparisons).

In the ROI analyses, there was a significant ROI × group interaction ($F_{1,38}$ = 2.70, p= . 005), and a significant ROI × side × group interaction ($F_{9,342}$= 3.34, p= .001). There were no significant group × mode (speech, non-speech) interactions ($F_{9,342}$ = 0.27, p= .60). The group differences were further examined within each ROI with ANOVA with the repeated factors mode (speech, nonspeech), strategy (encode, imitation), and side (left, right). There were no ROIs that reached significance at p=.006. With a lower threshold, normally fluent controls had greater percent signal change in the angular gyrus ($F_{1,38}$ = 6.72, p= .013), while stuttering individuals had greater percent signal change in the motor area 4p compared to controls ($F_{1,38}$ = 4.48, p= .041). A post-hoc correlation analysis between stuttering severity scores (SSI) and motor 4p activation revealed a significant positive correlation on both the left (r= .635, p= .006) and the right 4p (r= .684, p=.002) (figure 6). When stuttering frequency during conversational speech and reading were examined separately, stuttering in neither of these tasks were significantly correlated with left (r=0.23 for conversational speech, r=0.03 for reading) or right 4p (r=0.04 for conversational speech, r=−0.13 for reading).

A post-hoc comparison found that the stuttering and control males differed significantly in the angular gyrus ($F_{1,18}$ =3.452, p=0.026), and neared significance in females ($F_{1,18}$ =4.342, p=0.052). The group differences found in the 4p region were not significant when compared between females ($F_{1,18}$ =2.623l, p=0.123) nor between males ($F_{1,18}$ =1.705, p=0.208).

A significant side × group interaction occurred in the OP4 ($F_{1,38}$ = 11.77, p= .001) (figure 7), and pSTG ($F_{1,38}$ = 5.88, p= .020) and insula ($F_{1,38}$ = 4.76, p= .035) approached significance. In these regions, a consistent pattern of greater left laterality occurred in normally fluent controls, while stuttering individuals had equal, or greater signal change on the right hemisphere compared to the left.

When the side × group differences were examined within each gender, the laterality differences remained significant in the pSTG ($F_{1,18}$ =10.387, p=0.005), and insula ($F_{1,18}$ =5.900, p=0.026) and neared significance in OP4 ($F_{1,18}$ =4.306, p=0.053) between stuttering and control females, while group differences between males were significant for OP4 only ($F_{1,18}$ =9.058, p=0.008), whereas differences in pSTG ($F_{1,18}$ =1.264, p=0.276) and insula ($F_{1,18}$ =1.256, p=0.277) were not significant.

Discussion

This fMRI study compared stuttering and normally fluent control subjects' brain activation patterns during perception, planning, and overt production of speech and nonspeech vocal tract gestures. We posited that brain activation differences during tasks that do not elicit stuttering would provide information on fundamental differences in brain function between stuttering and fluent controls in sensorimotor integration for vocal tract oral motor gestures with auditory targets. During perception and planning phases, stuttering individuals compared to controls showed less activation in several motor regions (4p, preSMA, and insula) and the angular gyrus, but during production had greater activation in the primary motor and auditory regions, similarly for speech and non-speech.

For each task, we hypothesized group differences based on predicted possible deficit in auditory-articulatory mapping that affects perception, planning, and production in stuttering speakers. For example we expected decreased motor area activation during perception in stuttering individuals, indicating inadequate auditory-motor mapping during perception, even when stuttering is not present.

Motor regions are normally activated during speech perception tasks (Pulvermuller et al., 2006; Watkins and Paus, 2004; Wilson et al., 2004), indicating that speech perception involves an internal representation of the articulatory gesture that produces it. In our normally fluent

subjects, we replicated the auditory-motor co-activation in STG, area 4, and area 6 regions during perception. The stuttering individuals, however, showed consistently less activation in the angular gyrus and the motor regions during perception, particularly in 4p and preSMA. They also showed less left STG activation during both speech and non-speech perception, similar to previous results of Fox et al. (1996) and Braun et al. (1997).

Using perception tasks, Salmelin et al. (1998) also showed functional differences in the auditory cortex in stuttering individuals, with unusual inter-hemispheric responses when probed with monaural tones during silent reading, mouth movement, reading aloud, and reading in chorus (Salmelin et al., 1998). The ratio of left to right hemisphere source strengths differed between groups, the stuttering subjects showed more sensitivity on the right for all tasks except for the reading aloud condition, when they had more leftward sensitivity similar to controls. The controls showed delayed and attenuated auditory responses during overt production tasks compared to silent reading and mouthing, while the stuttering group did not show this kind of suppression of auditory responses during overt production (Salmelin et al., 1998). These findings are in line with our results that show increases in activation in the left STG region during production, and attenuated auditory-motor co-activation during perception in the stuttering subjects.

Similarly, the ROI analysis during perception showed reduced activation in the stuttering group primarily in motor regions; the premotor preSMA and primary motor 4p area. Only males differed significantly in the preSMA and neither male nor female groups differed significantly in 4p. As our perception task always preceded planning and production, this task likely involved short-term memory and motor planning processes in addition to perception. The group differences in the preSMA may reflect the influence of these processes in addition to perception. Perhaps differences in planning were more pronounced between male stuttering speakers and controls than between female stuttering speakers and controls.

During the planning phase, group differences occurred although this phase did not involve overt sound production similar to Ingham et al. (2000). Here, brain activation differences during speech planning in stuttering individuals are not secondary to stuttering. The whole brain analysis showed reduced activation in the stuttering group in the motor and parietal (including the angular gyrus), thalamus, and cerebellar regions and the ROI analysis showed significantly less percent signal changes in the insula, preSMA, and angular gyrus compared to controls. Sex comparisons revealed that these group differences were driven by differences between stuttering and control females in the insula and angular gyrus. The decreased activation in these regions during speech planning suggests brain function differences during the pre-articulatory phase of production in the stuttering group.

The regions less active in stuttering individuals during planning are those active for the preparation of motor responses. Among these, the angular gyrus is a well-known sensorimotor integration area important for recognizing intention to move (Farrer et al., 2008), motor planning (Sirigu et al., 2004), and adjustment (Grea et al., 2002). Some have suggested this region involves the internal representations needed for sensorimotor integration (Hickok and Poeppel, 2007; Wolpert et al., 1998), sensorimotor prediction (Blakemore and Sirigu, 2003), on-line movement control (Desmurget et al., 1999), and movement adjustment in the presence of sensory perturbation (Grea et al., 2002). Structurally, the parietal region including and surrounding the angular gyrus was shown to be interconnected with the ventral premotor and inferior frontal regions using tractography in humans (Catani et al., 2005; Rushworth et al., 2006) and retrograde tract tracing in monkeys (Petrides and Pandya, 1984). Perhaps differences in parietal activation may affect frontal-temporoparietal interactions for planning motor gestures with auditory targets.

During overt production, we predicted increased activation in the left posterior superior temporal gyrus (pSTG) in the stuttering group, reflecting less modulation of this region, and compensatory activation in the right hemisphere. The voxel-wise whole brain analysis showed *greater* activation in stuttering individuals relative to controls in the right STG, bilateral Heschl's gyrus (HG), left insula, putamen, and precentral motor regions (BA 4), during both speech and non-speech production. This suggests state-related increases in activation in motor and auditory regions during speech production possibly the result of increased effort required during production in persons who stutter. No such increases were found during perception and planning.

The increased right STG activation and decreased left STG activation found in our stuttering group relative to controls during both speech and non-speech production are somewhat at odds with previous PET studies, where bilateral STG deactivation was found in stuttering individuals during stuttered speech and normalized with fluency (Braun et al., 1997; Fox et al., 1996). Our study measured brain activation for speech articulation without stuttering and used shorter speech utterances of two syllables in contrast with sentence reading and conversation known to elicit stuttering. In addition, we deleted those few scans with stuttered utterances from the analysis. This may account for the differences in our results from previous studies using speech conversation or oral reading with and without stuttering (Braun et al., 1997; Fox et al., 2000). Given the complexity of our design with 6 different conditions, and the short utterances, it was not reasonable to add a stuttering condition. It is a limitation that we only measured speech without stuttering in this study.

As previous studies used longer utterances, the reduced STG activations may have resulted from the occurrence of perception and planning as well as production effects during the task production. Possibly the reduced activation we found in stuttering individuals relative to controls during perception and planning may have been the basis for the reduced activation seen during production in these studies (Braun et al., 1997; Fox et al., 2000). When overt production was examined alone, a more specific pattern emerged to differentiate stuttering subjects from controls of unilateral decreases in the left STG, with bilateral HG and right STG increases.

The increased BOLD signal found in the bilateral HG and right STG in stuttering individuals reflects increased neural activity in this region during production. Reductions in auditory activation during overt vocalization has been demonstrated in fluent speakers using MEG data from humans (Houde et al., 2002; Numminen et al., 1999), electrophysiological responses in monkeys (Eliades and Wang, 2003, 2005; Muller-Preuss and Ploog, 1981) and corollary discharge in invertebrates (Poulet and Hedwig, 2003a; Poulet and Hedwig, 2003b). In this study, we cannot be certain whether the increases in activation in the auditory regions in the stuttering group were inhibitory or excitatory in nature. During motor control, a functioning internal anticipatory model ("forward model") allows matching predictions about the sensory consequences of a motor act with the intended motor plan (Kawato and Wolpert, 1998; Miall and Wolpert, 1996; Wolpert et al., 1995). During speech modulation from the motor areas to the sensory regions may reduce cortical responses to auditory feedback (Blakemore et al., 1999; Webb, 2004). Decreased left STG activation in the face of increased activation in the right homologue and in primary auditory regions bilaterally during production in stuttering may suggest aberrant functioning in the internal forward model on the left side in persons who stutter. On the other hand, increases in the right STG and bilateral HG may be compensatory for the reduced activation of the left STG.

Another possibility is that the increased right STG and primary auditory activation may be an inherent deficit in itself. Namely, the auditory modulation may preferentially occur in the right rather than left STG in stuttering, and the over-activity in the primary auditory regions may

reflect over-reliance on auditory feedback during production. A dysfunctional forward model as a possible mechanism underlying stuttering pathophysiology, has been proposed by others (Brown et al., 2005; Max et al., 2004).

If a deficit in a forward model for motor control is implicated in stuttering, this would suggest a more generalized deficit in goal-directed movement in stutterers, not limited to speech. Our present data support this concept, showing no difference in stuttering individuals' performance between speech and non-speech conditions across all tasks. These findings are consistent with past studies that showed generalized differences in various goal-directed movements in stuttering individuals including orofacial non-speech and finger flexion movements (Borden, 1983; Max et al., 2003)..

Increases also occurred in the insula, and putamen for stuttering individuals relative to controls during production, similar to findings by Watkins et al. (2008). Increases in these regions in stuttering individuals were only observed during production and not during perception or planning. Differences in laterality of activation, where stuttering individuals had decreased left laterality or increased right activation, also were limited to production. On ROI analysis, significant group by side differences occurred in an opercular region overlapping BA 43; the stuttering group showed a less lateralized response compared to the strong left lateralized response seen in controls. This difference was also present when males and females were examined separately. Interestingly, this region overlies the region where white matter deficit was reported in stuttering adults (Sommer et al., 2002) and children (Chang et al., 2008). In female stuttering speakers, activity was less lateralized to the left in the pSTG and insula compared to control females.

The motor 4p activation during production, particularly on the right, correlated with stuttering severity. The coordinates of our 4p region in both hemispheres agrees well with those reported to be over-activated in stuttering speakers during oral reading based on a meta-analysis of 5 neuroimaging studies (Brown et al., 2005) and is close to the putative larynx/phonation area (LPA) in the cortex (Brown et al., 2008). While there was significant correlation between stuttering severity as measured with SSI and activation in the bilateral 4p, the same was not true between 4p activation and stuttering frequency during conversational speech and reading, when these two tasks were examined separately. The likely reason for this is that SSI includes duration of stuttering as well as occurrence of secondary physical concomitants during stuttering, information that is not included in stuttering frequency measurements alone. This suggests that the bilateral motor activation may be the result of increased effort associated with stuttering in more severe stuttering speakers, resulting in deficits in not only speech but also non-speech voluntary vocal control present in stuttering speakers.

Increased activation in the putamen in stuttering subjects is consistent with others' results (Watkins et al., 2008), and was previously correlated with stuttering severity (Braun et al., 1997). The basal ganglia is of interest in relevance to stuttering due to known dramatic effects of dopaminergic agents on stuttering (Ludlow and Braun, 1993; Maguire et al., 2000; Maguire et al., 2004), and because acquired stuttering occurs commonly following damage to the basal ganglia (Ludlow et al., 1987), with the putamen and caudate most often injured (Ludlow and Loucks, 2003). The basal ganglia-thalamocortical motor circuits through the putamen has been proposed to play a key role in stuttering (Alm, 2004). Here activation in the left caudate also correlated with stuttering severity, and reduced following speech therapy (Giraud et al., 2008). An early PET investigation showed decreased glucose metabolism in the left caudate during both stuttering and fluent conditions (Wu et al., 1995). More detailed investigation on cortico-striatal-thalamic loops is warranted in this group.

Some of our findings were gender specific. Ingham et al. (2004) found that stuttering severity correlated with right sided activity in the males and bilateral activity in the females. In our study, during symptom-free speech and non-speech tasks, females who stuttered had more bilateral differences from controls than their male counterparts during production, and stuttering versus control group differences in the AG and insula were driven by the females results during planning. Although group differences during perception were only significant in males in the preSMA, the overall picture appears to indicate that group differences were driven by a great degree by findings in the stuttering females than in the stuttering males.

In conclusion, we have shown that stuttering individuals have similar differences in brain activation from controls during speech and non-speech tasks, suggesting that their disorder may not be speech-specific. We found evidence consistent with functional activation abnormalities in regions relevant to auditory-motor integration in stuttering individuals, across perception, planning, and production tasks, for both speech and non-speech. The frontal and temporoparietal regions were largely decreased relative to controls during perception and planning in the absence of stuttering and may represent a trait abnormality, while increased activation was found in the right STG, bilateral HG, insula, bilateral precentral, SMA, and the putamen during production, possibly reflecting the state of overt production even when fluently produced. Reduced activation in the left auditory region in stuttering individuals during production may reflect decreased efferent input to this area from the motor articulatory region, possibly as a result of white matter differences previously found underlying this region. The functional data here are in agreement with structural difference in stuttering that alters brain function for speech and non-speech perception, planning, and execution.

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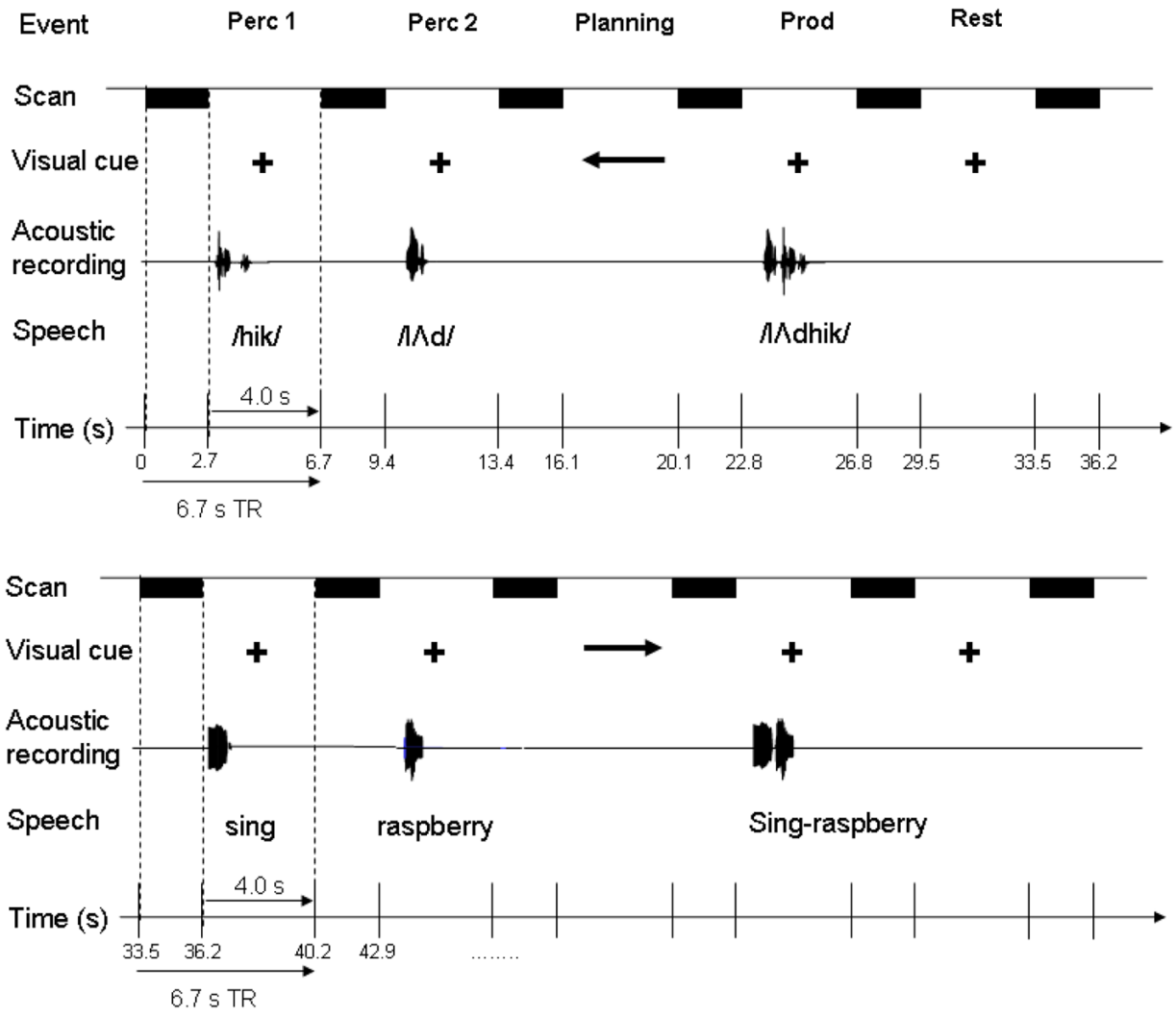

Figure 1.

Experiment outline. Here one speech trial (upper panel) and one non-speech trial (lower panel) are illustrated. Speech and non-speech trials were randomly presented. Each trial consisted of two perception (perc 1, perc 2), planning, production (prod), and rest, each presented/ performed during a 4 second silent period, which was followed by 2.7 seconds of scanning. Note that only the first of the two perception responses (scan following "perc 1") was used for perception analysis. See text for more detail on the experiment paradigm.

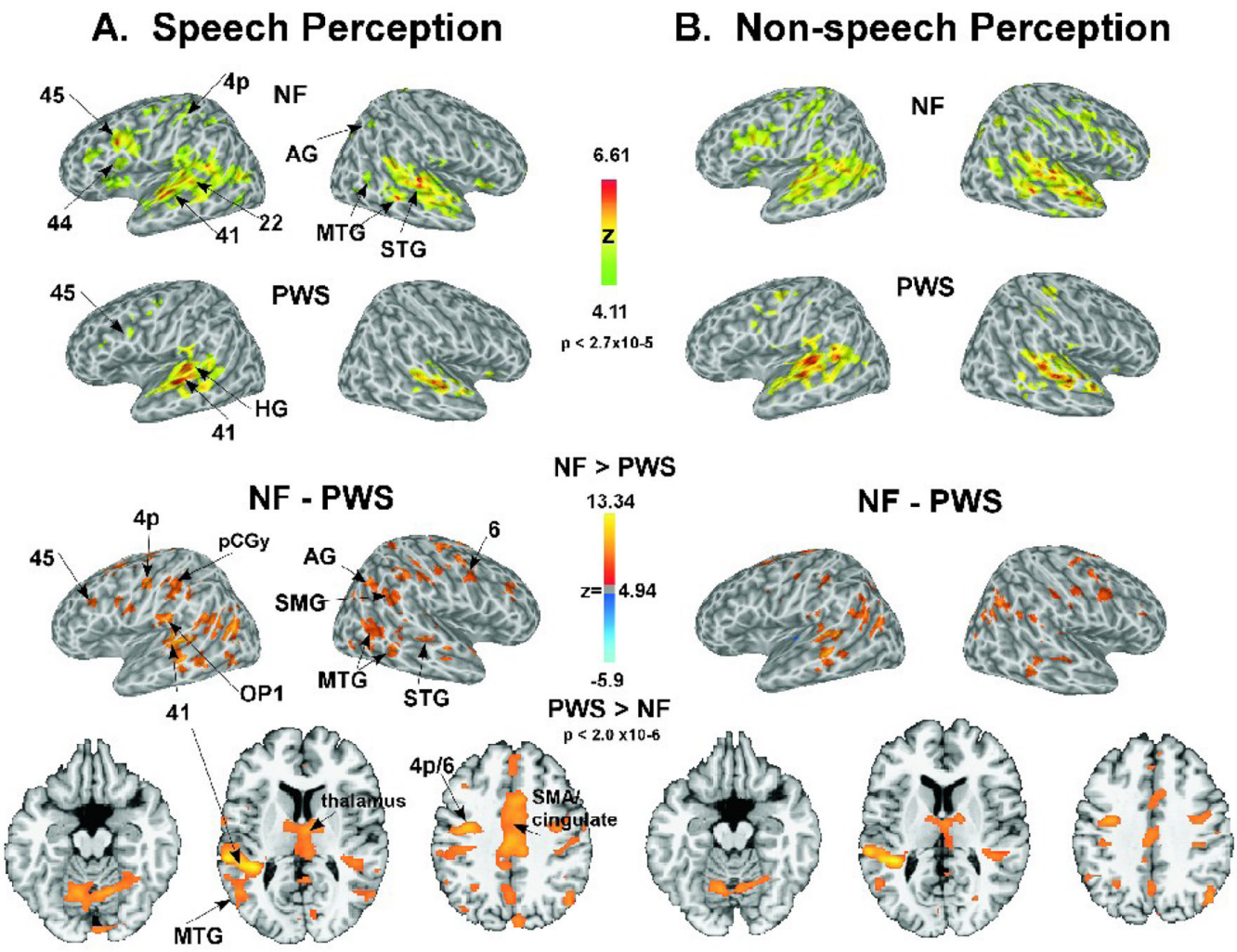

Figure 2.

Main effect of speech (A) and non-speech (B) perception shown for normally fluent (NF) and people who stutter (PWS). C. Contrast between NF and PWS show consistently greater activation for NF relative to PWS (warm color range) for both speech and non-speech perception. The statistical parametric maps shown here are thresholded at $p < 7.8 \times 10^{-6}$.

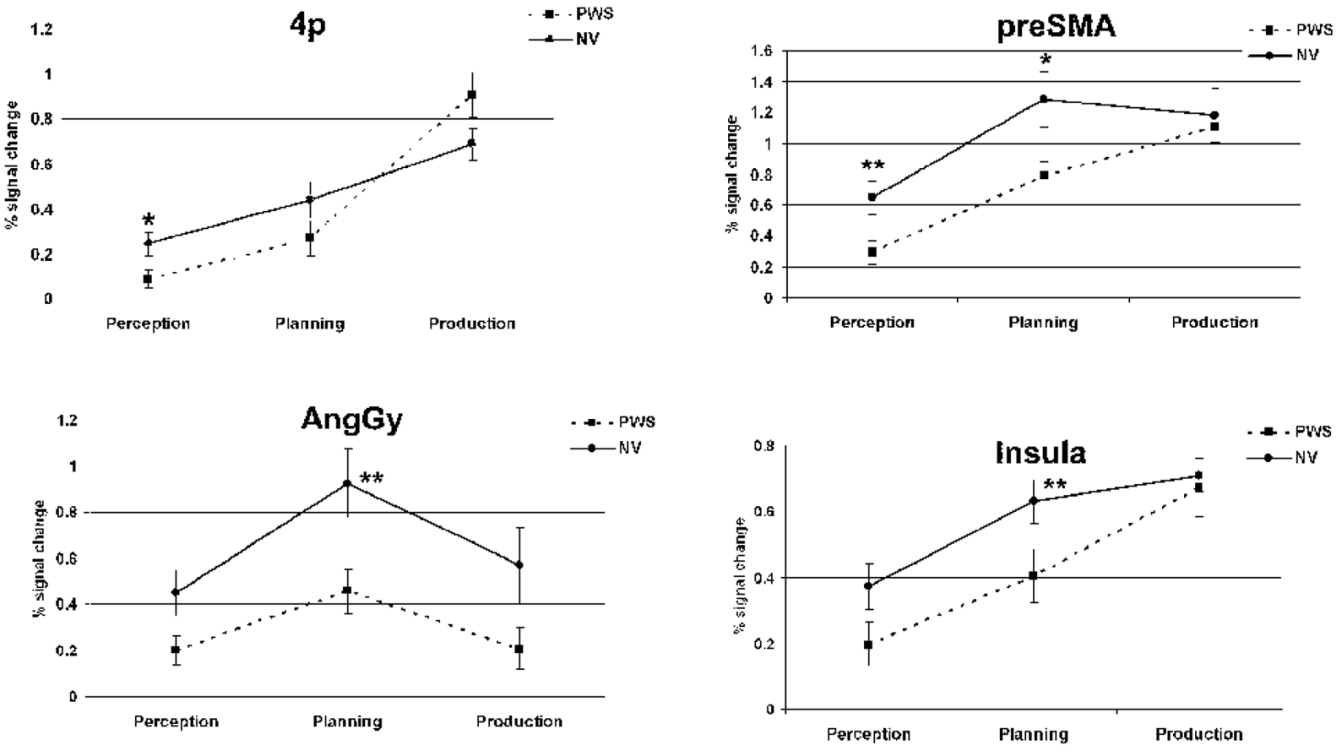

Figure 3.
Group differences in mean percent signal change values across task (perception, planning, production) are shown in the ROIs 4p, preSMA, insula, and angular gyrus. The ROI analyses revealed the strongest group differences during perception and planning tasks. * $p<0.05$ ** $p<0.01$

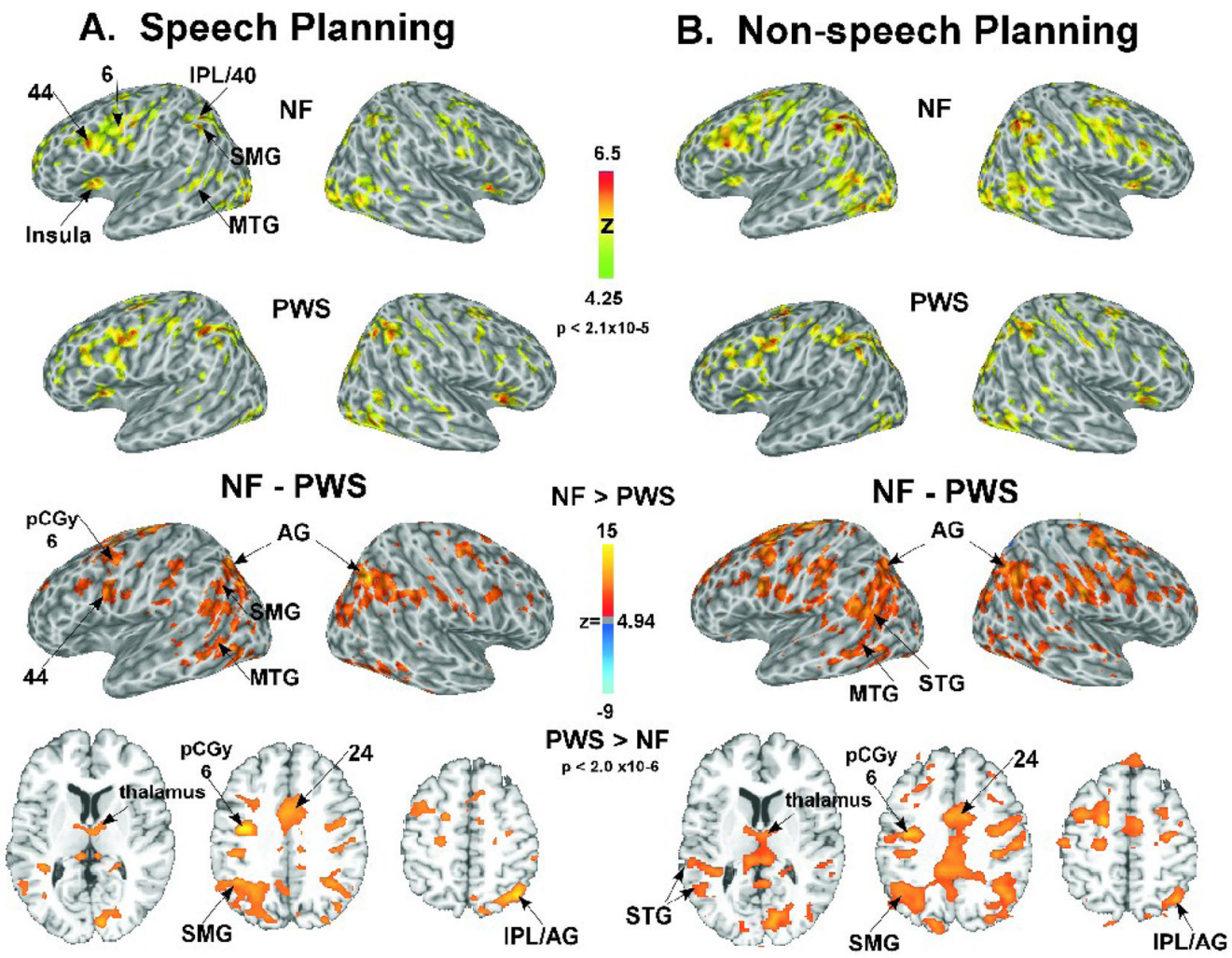

Figure 4.

Main effect of speech (A) and non-speech (B) planning shown for normally fluent (NF) and people who stutter (PWS). C. Contrast between NF and PWS show consistently greater activation for NF relative to PWS (warm color range) for both speech and non-speech planning. The statistical parametric maps shown here are thresholded at $p < 7.8 \times 10^{-6}$.

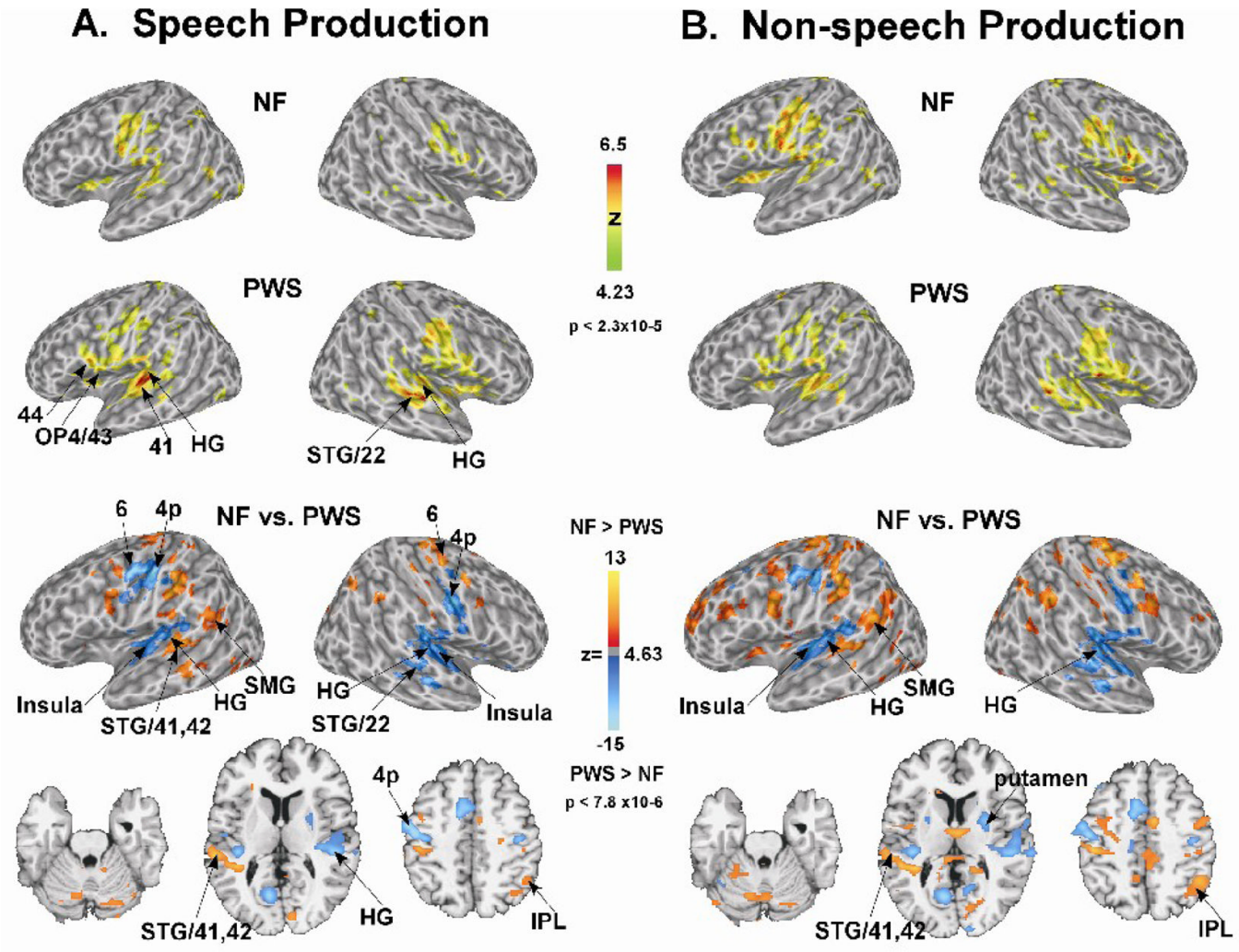

Figure 5.

Main effect of speech (A) and non-speech (B) production shown for normally fluent (NF) and people who stutter (PWS). C. Yellow-red colors depict regions with greater activation in NF relative to PWS, whereas light blue-blue colors depict regions with greater activation in PWS relative to controls. The statistical parametric maps shown here are thresholded at $p < 7.8 \times 10^{-6}$.

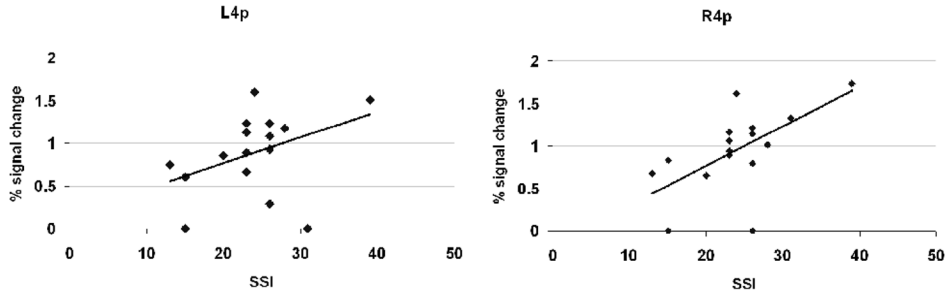

Figure 6.
Correlation between BOLD percent signal change and stuttering severity as measured through the stuttering severity instrument (SSI-3) was significant in the bilateral motor region 4p ($p < 0.005$).

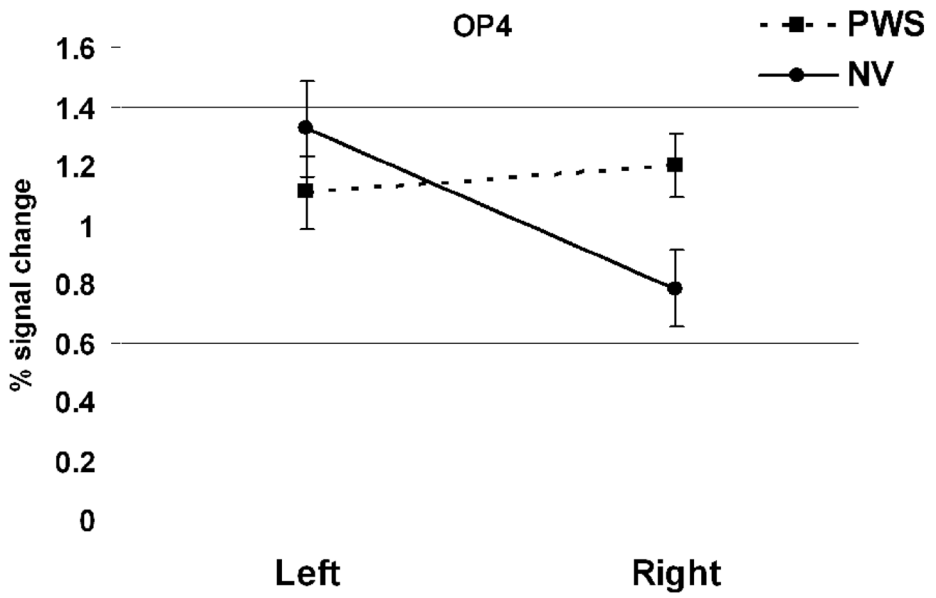

Figure 7.
Significant laterality effect was shown in OP4, a sensorimotor region during production only. Here normally fluent subjects showed a marked left laterality whereas the stuttering group showed a slight activation increase on the right side ($p < 0.001$).

Table 1

Differences between stuttering speakers and controls in speech and non-speech perception.

Region	Approx. BA	x	y	z	Peak t
		Speech Perception: PWS < controls			
Left precentral gyrus	6, 4	−33	−9	34	9.59
Right precentral gyrus	6, 4	41	−13	54	8.32
Right SMA	6	3	−13	70	7.59
Left STG	41	−37	−39	10	13.34
Right STG	41	42	−37	11	7.08
Left MTG	19	−46	−63	13	10.26
Right MTG	21	59	−42	−1	7.75
Right AG	39	45	−67	36	7.66
Right cuneous	19	31	−79	30	8.07
Right thalamus	N/A	3	−11	10	8.06
Right cerebellum (VI)	N/A	15	−57	−16	9.47
		Non-Speech Perception: PWS < controls			
Right MFG	6	49	3	42	7.74
Left precentral gyrus	6	−31	−9	34	9
Right SMA	6	11	−19	72	6.14
Left STG	41	−37	−39	10	13.43
Right STG	41	39	−37	12	7.22
Left MTG	19	−48	−62	14	7.64
Right MTG	21	59	−43	0	7.82
Right AG	39	45	−67	36	8.22
Right thalamus	N/A	3	−11	8	7.55
Right cerebellum (VI)	N/A	18	−56	−17	7.24

Regions, stereotaxic coordinates (talairach), and peak t score values for activation differences between stuttering and control groups during speech and non-speech perception.

Table 2

Differences between stuttering speakers and controls in speech and non-speech planning.

Region	Approx. BA	x	y	z	Peak t
		Speech Planning: PWS < controls			
Left precentral gyrus	6	−35	−9	34	14.52
Right precentral gyrus	4, 6	37	−13	54	12.13
Left cingulate gyrus	24	−1	1	36	12.05
Right IPL/AG	7	39	−63	46	12.03
Left precuneus/IPL	19	−31	−69	40	10.26
Right thalamus	N/A	5	−31	10	9.15
Right cerebellum (crus 1)	N/A	21	−71	−25	10.12
Left cerebellum (VI)	N/A	−13	−61	−20	9.31
		Non-Speech Planning: PWS < controls			
Left cingulate gyrus	24	−19	−1	44	14.4
Right IPL/AG	7	39	−61	46	14.26
Left precuneus/IPL	19	−33	−71	40	11.82
Right postcentral gyrus	2	47	−19	28	11.94
Right thalamus	N/A	3	−11	10	10.48
Right cerebellum (crus 1)	N/A	21	−70	−25	11.39
Left cerebellum (VI)	N/A	−23	−59	−24	10.69

Regions, stereotaxic coordinates (talairach), and peak t score values for activation differences between stuttering and control groups during speech and non-speech planning.

Table 3

Differences between stuttering speakers and controls in speech production.

Region	Approx. BA	x	y	z	peak t
		Speech Production			
PWS < Controls					
Left precentral gyrus	6	−33	−9	32	12.67
Right precentral gyrus	6	27	−27	62	13.03
Right cingulate gyrus	24	9	1	36	11.76
Left STG	42	−55	−31	10	11.2
Left MTG	22	−61	−32	0	9.22
Left IPL	2, 40	−39	−25	29	11.5
Left SMG	40	−47	−50	22	6.88
Right lingual gyrus	18	17	−85	−14	10.31
Right cerebellar tonsil (IX)	N/A	17	−41	−38	8.52
Right cerebellar vermis	N/A	3	−53	−10	8.45
PWS > Controls					
Left precentral gyrus	4	−41	−17	38	15.11
Right precentral gyrus	4	48	−9	30	12.32
Left cingulate gyrus	32	−11	10	38	11.22
Left SMA	6	−7	−3	52	11.96
Right IFG	47	44	14	−3	7.39
Left insula	13	−44	−14	5	8.5
Right insula	13	37	−8	15	8.28
Left HG	41	−35	−29	10	10.3
Right HG	41	43	−27	12	12.84
Right STG	22	55	−27	5	9.45
Right MTG	22	51	−33	3	7.74
Right IPL	40	51	−31	22	12.47
Left posterior cingulate gyrus	17	−9	−65	12	12.38
Right putamen	N/A	24	0	8	6.74
Left cerebellar culmen	N/A	−30	−54	−19	7.34

Regions, stereotaxic coordinates (talairach), and peak t score values for activation differences between stuttering and control groups during speech production.

Table 4

Differences between stuttering speakers and controls in non-speech production.

Region	Approx. BA	x	y	z	peak t
		Non-Speech Production			
PWS < Controls					
Left precentral gyrus	6	−35	−9	34	14.88
Right SMA	6	7	−31	66	15.27
Left middle frontal gyrus	10	−27	49	18	9.21
Left STG	42	−33	−41	12	13.01
Left IPL	2, 40	−38	−28	29	11.07
Right IPL	40	45	−51	44	9.59
Left SMG	40	−49	−49	22	9.99
Left lingual gyrus	18	−23	−77	−2	8.22
Right lingual gyrus	18	17	−85	−12	14.53
Right thalamus	N/A	3	−11	10	9.57
Left cerebellar vermis	N/A	−1	−51	−10	10.71
Left cerebellum (Crus 1)	N/A	−19	−73	−28	8.98
Right cerebellum	N/A	−21	−69	−26	9.04
PWS > Controls					
Left precentral gyrus	4	−41	−17	38	12.92
Right precentral gyrus	4	60	−6	20	7.68
Left cingulate gyrus	32	−9	13	40	12.49
Left insula	22	−39	−21	4	12.15
Left insula	13	−39	−21	4	12.15
Right STG	22	63	−27	6	12.91
Right MTG	22	51	−35	3	9.96
Right IPL	13	52	−31	21	12.45
Right IPL	40	45	−51	44	9.59
Left putamen	N/A	−23	1	7	5.81
Right putamen	N/A	25	2	7	9.2
Left cerebellar culmen	N/A	−31	−54	19	7.98

Regions, stereotaxic coordinates (talairach), and peak t score values for activation differences between stuttering and control groups during non-speech production.