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The neural substrates for atypical planning and execution of word production in stuttering

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ABSTRACT

Using an fMRI-based classification approach and the structural equation modeling (SEM) method, this study examined the neural bases of atypical planning and execution processes involved in stuttering. Twelve stuttering speakers and 12 controls were asked to name pictures under different conditions (single-syllable, multi-syllable, or repeated-syllable) in the scanner. The contrasts between conditions provided information about planning and execution processes. The classification analysis showed that, as compared to non-stuttering controls, stuttering speakers' atypical planning of speech was evident in their neural activities in the bilateral inferior frontal gyrus (IFG) and right putamen and their atypical execution of speech was evident in their activations in the right cerebellum and insula, left premotor area (PMA), and angular gyrus (AG). SEM results further revealed two parallel neural circuits—the basal ganglia-IFG/PMA circuit and the cerebellum-PMA circuit—that were involved in atypical planning and execution processes of stuttering, respectively. The AG appeared to be involved in the interface of atypical planning and execution in stuttering. These results are discussed in terms of their implications to the theories about stuttering and to clinical applications.

Introduction

There is accumulating evidence that atypical planning and execution processes are associated with stuttered speech. First, studies of stuttering speakers' motor execution showed aberrant coordination among articulatory, laryngeal, and respiratory systems during both stuttered and fluent speech (e.g., Loucks and De Nil, 2006; Loucks et al., 2007; Max et al., 2003; Namasivayam and van Lieshout, 2008). Second, studies of linguistic factors related to the speech planning process revealed altered semantic, syntactic, and especially phonological processing in both child and adult stuttering speakers, even in the absence of any speech production requirements (e.g., Cuadrado and Weber-Fox, 2003; Kleinow and Smith, 2000; Ratner and Sih, 1987; Sasisekaran et al., 2006; Weber-Fox, 2001; Weber-Fox et al., 2004). Finally, there is also evidence indicating an atypical interface between planning and execution processes (e.g., Blomgren and Goberman, 2008; Dworzynski et al., 2004; Savage and Howell, 2008; Snyder et al., 2009). That is, failure in speech fluency may result from dyssynchrony between cognitive-linguistic formulation of a speech plan and the motor execution of the linguistic plan (Howell, 2002, 2004; Howell and Sackin, 2002). However, it is still unclear what the neural substrates for atypical planning or execution are and how the neural substrates for the two atypical processes interact with each other.

Previous brain imaging studies have revealed widely distributed neural differences between stuttering and non-stuttering speakers, such as the the over-activation in the right frontal operculum/anterior insula and the right cerebellum, absent activation in the bilateral auditory areas, and increased or decreased activation in the motor areas and the basal ganglia (Brown et al., 2005; De Nil et al., 2008, 2000; Fox et al., 2000; Ingham et al., 2000, 2004; Neumann et al., 2003; Wu et al., 1995). However, it is not clear which of the above neural differences are associated with atypical planning, execution, or

Abbreviations: AG, the angular gyrus; BA, Brodmann area; CFI, Comparative Fit Index; CHAID, Chi-squared automatic interaction detector; CRT, classification and regression tree; FDR, false discovery rate; FLDA, Fisher linear discriminative analysis; fMRI, functional magnetic resonance imaging; GLM, general linear model; IFG, the inferior frontal gyrus; MEG, magnetoencephalography; MFG, the middle frontal gyrus; PGFI, Parsimony Goodness of Fit Index; PMA, the premotor area; RMSEA, Root Mean Square Error of Approximation; ROI, region of interest; SEM, structural equation modeling; SFG, the superior frontal gyrus; SSI-3, Stuttering Severity Instrument-III; STG, the superior temporal gyrus.

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interface between them. Thus far, only three brain imaging studies have provided some relevant results. Using MEG, Biermann-Ruben et al. (2005) showed that both the left inferior frontal and the right rolandic areas of stuttering speakers played similar roles in speech perception and production. Ingham et al. (2000) found similar types of neural differences between stuttering and non-stuttering speakers during imagined stuttering (i.e., speech planning without execution) and overt stuttering. These two studies seem to suggest that stuttering speakers differ from non-stuttering speakers in their brain activations regardless of the stage of speech process. On the other hand, Chang et al. (2009) recently found that during speech planning, stuttering speakers had less activation in the frontal and temporoparietal regions relative to controls, whereas during speech production, stuttering speakers had less activation than the controls in the left temporal and the premotor areas but greater activation in the right temporal and bilateral insula, putamen, and primary motor regions. This result, however, cannot be directly compared to those of the other two studies because it is unknown how the Go/no-Go paradigm used in Chang et al. (2009) might have altered the underlying processes of word production.

The purpose of the present study was to simultaneously examine the neural substrates for atypical planning and execution and the interaction between them. To do that, we needed to separate the planning and the execution processes experimentally. According to the well-known model of spoken word production (Levelt et al., 1999), a key process of planning is to retrieve and assemble syllable-sized motor programs. Thus, the computational load of the planning process should vary with the number of syllable-sized motor programs that need to be retrieved and assembled. On the assumption that multisyllable words require more syllable-sized motor routines than monosyllable words, Shuster and Lemieux (2005) used word length to vary the computational load of planning. It should be noted, however, that their study did not control for utterance length and syllable frequency. In our study, we used word length to vary computational load and at the same time controlled for the utterance length (through repeated production of the same syllable, Bohland and Guenther, 2006) and syllable frequency. Fig. 1 shows the tasks we used and the analytical approach that can reveal the neural subtrates for atypical planning process of stuttering.

Following the planning process is the execution process. According to previous literature (Blomgren and Goberman, 2008), the motor execution process of articulation includes both temporal (syllable production rate) and spatial (utterance length) control of articulatory movement. Thus, in this study, we controlled the syllable-size and onset-complexity of the spoken words, and varied the length of utterance and syllable production rate. It was assumed that the executional load would be higher for the production of long utterance at a high production rate than for that of short utterance at a low production rate. As shown in Fig. 1, brain regions that showed significant task × group interaction effects would be considered as the neural subtrates for atypical execution process of stuttering.

In sum, the purpose of the present study was to examine the neural substrates for stuttering speakers' atypical planning and execution of word production and their interaction. We used a pattern recognition technique—the classification trees analysis—to identify neural substrates for the planning and execution processes that could discriminate stuttering speakers from controls. After the identification of relevant brain regions, we then used structural equation modeling (SEM) to examine functional connectivity between the neural substrates for atypical planning and execution.

Materials and methods

Participants

Twelve stuttering participants (10 males) and 12 non-stuttering controls (7 males) were recruited for the present study. All participants were native Chinese speakers, and right-handed as assessed by Edinburgh Handedness Inventory (Oldfield, 1971). All stuttering participants started stuttering during childhood, and none of them had received treatment during the year prior to this study. The severity of these stuttering participants ranged from very mild to

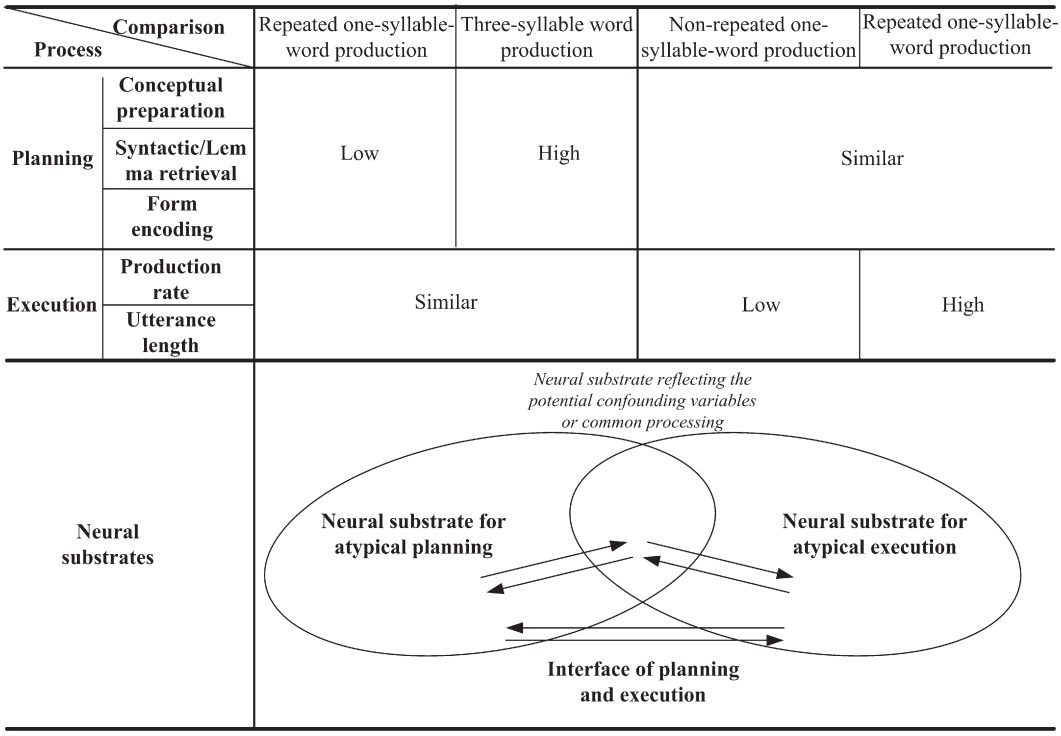

Fig. 1. Framework of the experimental design. The lables "low," "high," and "similar" indicate hypothesized computational and executional load during spoken word production.

severe (M = 24.55, S.D. = 6.82) as diagnosed by the Stuttering Severity Instrument-III (SSI-3) (Riley, 1994). Case history showed no other language, motor, or neurological problems with these stuttering speakers. Participants' mean chronological age was 24 years (ranging from 20 to 29 years), and their mean educational level was 17 years (ranging from 15 to 19 years). Non-stuttering controls were university students. These participants did not have any language, motor, or neurological problems. Their chronological ages and educational level were matched with the stuttering speakers (M = 24 years [22–29]; M = 15.5 years [16–19]). Both stuttering and non-stuttering samples were the same as those reported in Lu et al. (in press). More detailed information about these participants can be found in that report.

Tasks and materials

In order to control for the orthographical variations, we used a picture-naming task to examine word production process. One hundred and eighty simple line drawings of common objects were selected from a standardized picture database (Zhang and Yang, 2003). The common names of these pictures are all high-frequency words ($>5\times10^{-5}$). These words include the whole range of complexity of the syllable onset. Moreover, the drawings were presented in an order so that a name's ending phoneme would not have similar phonetic features as the beginning phoneme of the name for the next picture. This was done to avoid potential influence of the refractory processes when accessing the same phonetic unit. These pictures were randomly split into three groups (60 pictures per group) for three naming conditions (see below). In order to ensure that these three groups were equivalent in their level of conceptual familiarity, visual complexity, and semantic difficulty, these pictures were rated by a separate group of 30 participants who were not involved in the present study. Results confirmed the equivalence of these three groups of pictures. For the baseline condition, we randomized the pixels of the pictures used in the naming condition to create 180 nonsense unnamable pictures that had the same overall luminance as those in the naming conditions.

The three naming conditions were naming with a one-syllable word (the non-repeated condition), repeating the one-syllable word three times (the repeated condition), and naming with a three-syllable word (the three-syllable condition). Participants were required to name each of the pictures overtly within 3000 ms. Our design allowed us to make the following comparisons: the repeated condition vs. the three-syllable condition to examine the planning process and the non-repeated condition vs. the repeated condition to examine the execution process.

There were three scanning runs, one for each naming condition. The scanning sequence was counterbalanced across participants. During the scanning, participants lay supine within the MR scanner with their head secured in foam padding for the duration of each experimental run. An MRI-compatible earphone was used to reduce the background noise. A detailed description of the experimental procedures can be found in Lu et al. (in press).

Image acquisition

A 1.5T whole-body Siemens Magnetom Sonata Maestro Class (Siemens, Erlangen, Germany) equipped with the standard clinical head coil was used to collect the functional and anatomical images. The participant's head was restrained with additional padding between the earphone and the head coil. Functional whole-brain T2*-weighted images were acquired using a single-shot gradient-recalled echo-planar imaging sequence (TR = 3000 ms; TE = 50 ms; flip angle = 90°; FOV = 220 mm) with a matrix size of 64 × 64 (in-plane resolution = 3.4 × 3.4 mm) based on blood oxygenation level dependent effect. We acquired a total of 132 volumes, each containing 20 contiguous 6 mm slices collected in the transversal plane with interleaved slice acquisition in each experimental run. For anatomical data, standard whole-brain, high-resolution 3D structural images were acquired after the functional scans using a T1-weighted, three-dimensional, MP-RAGE sequence (TR = 1970 ms; TE = 3.93 ms; flip angle = 15°; FOV = 220 mm; matrix 256 × 256; 96 slices; slice thickness = 1.7 mm, sagittal plane; resolution = 0.48 × 0.48 mm).

Data preprocessing

The preprocessing of the imaging data was performed with the AFNI software package (http://afni.nimh.nih.gov/afni, Cox, 1996). The images of the first two time points in each run were discarded to control for hemodynamic delay effects. The images were slice-timing and motion corrected (Cox and Jesmanowicz, 1999). Motion parameters were estimated and each time series underwent realignment through this process. After the estimated motion parameters were visually inspected, participants with extreme motion (>4 mm translation, 5° rotation) were eliminated. These values were based on their match with the voxel size with consideration also for expectations of the spatial resolution of BOLD responses and the inherent variability between participants in brain anatomy (Johnstone et al., 2006). Two non-stuttering and three stuttering participants were discarded during this process. The remaining participants' functional image time series were then smoothed with a low pass filter and an Isotropic Gaussian blur (full-width, half-maximum = 6 mm).

Feature selection

In fMRI-based classification studies, various functional properties of the brain derived from neuroimaging data can be used as the features for classification. For task-related fMRI, both the original time series and activation maps have been used for discrimination of brain disorders (e.g., Kontos et al., 2004; Shinkareva et al., 2006; Zhu et al., 2008). The general linear model (GLM)-based statistical value and region-of-interest (ROI)-based feature extraction method are preferred (Bogorodzki et al., 2005; Diana et al., 2008; Lee et al., 2009; Martinez-Ramon et al., 2006; Serences and Boynton, 2007).

We first used the GLM approach to convolve the stimulus function with a canonical hemodynamic response function and estimated the regression parameter (β) corresponding to each task. We then performed statistical group contrasts to identify brain regions that showed significant task × group interaction effects and defined them as ROIs. Finally, the differences in the β value (percent signal change) between conditions (i.e., three-syllable vs. repeated one-syllable words, repeated vs. non-repeated one-syllable words) were computed and extracted from each ROI as the classification features.

GLM analysis and statistical group-contrast procedure

The preprocessed data were then subjected to the GLM analysis, and regression coefficients β corresponding to each of the tasks were obtained. The β was then converted into percent signal change (the regression coefficient was divided by the corresponding baseline constant then multiplied by 100; see http://afni.nimh.nih.gov/sscc/gangc/TempNorm.html), and individual images were resampled into Talairach coordinates space before group analysis using the AFNI hand landmarking procedure.

For group analysis, a mixed-model ANOVA procedure was applied on the percent signal change obtained from the GLM analysis at the voxel level in order to identify ROIs showing significant task × group interaction effect. Correction for multiple comparisons was established using a voxel-cluster threshold technique for an overall corrected level of significance (alpha) of 0.05 (individual voxel $p<0.01$, minimum cluster threshold required >220 mm^3) based

on the results of a Monte Carlo simulation at the cluster level (Forman et al., 1995; Xiong et al., 1995).

Feature extraction

To index the activation level of each ROI (as defined based on the ANOVA described above) for each condition and each individual, we used the AFNI program to calculate the average percent signal change in a sphere with a 3 mm radius, centered at the coordinates of the maximum value within the activated cluster. Classification features were then obtained by calculating the differences between conditions for the planning and the execution processes.

Classification analysis

The extracted classification features were fed into SPSS software (Rel. 13.0. 2004, Chicago: SPSS Inc.) to run the analysis of classification. Two classification algorithms, classification trees and Fisher linear discriminative analysis (FLDA), were used in order to validate the classification accuracy. FLDA has been widely used in fMRI-based pattern recognition (e.g., Carlson et al., 2003; LaConte et al., 2003; Mourao-Miranda et al., 2005). FLDA works most efficiently if the smallest group has significantly more cases than the number of variables and when groups are approximately of equal size. These assumptions, however, are not always true for fMRI studies of patient populations. As an alternative to FLDA, classification trees analysis is a non-parametric technique that makes no distributional assumptions and is not affected by outliers, colinearities, or distributional error structures (Breiman et al., 1984). Thus, the classification trees method is especially suitable for detecting neural bases of brain disorders (Feldesman, 2002; Godefroy et al., 1998; Kreisler et al., 2000; Ripley, 2002; Zimmerman-Moreno et al., 2008).

Cross-validation

Leave-one-out cross-validation was used to estimate the performance of our classifiers (Zhu et al., 2008). The flow chart of leave-one-out cross-validation is shown in Fig. 2. Suppose there are N samples in total. The leave-one-out cross-validation trains classifier N times, each time leaving out one of the samples from training, but using the omitted one to compute classification error. Generalization rate, sensitivity, and specificity can be defined on the basis of results of leave-one-out cross-validation to quantify the performance of a classifier.

$$\text{Generalization Rate} = (\text{TP} + \text{TN})/(\text{TP} + \text{FN} + \text{TN} + \text{FP})$$

$$\text{Sensitivity} = \text{TP}/(\text{TP} + \text{FN})$$

$$\text{Specificity} = \text{TN}/(\text{TN} + \text{FP})$$

where TP (true positive) is the number of stuttering speakers correctly predicted, TN (true negative) is the number of controls correctly predicted, FP (false positive) is the number of controls classified as stuttering speakers, and FN (false negative) is the number of stuttering speakers classified as controls. Thus, the sensitivity indicates the proportion of stuttering speakers correctly predicted, while the specificity indicates the proportion of normal controls correctly predicted. The generalization rate is the overall proportion of samples correctly predicted.

SEM

For the SEM procedure, the same ROIs (3 mm spheres) as those in the classification analysis were used. The extracted features for SEM were the averaged time series of voxels within the ROI for each condition and each participant. Principle components analysis was then used to identify an "average" pattern of responses in each region across all participants in stuttering and non-stuttering groups (Büchel et al., 1999; Fletcher et al., 1999).

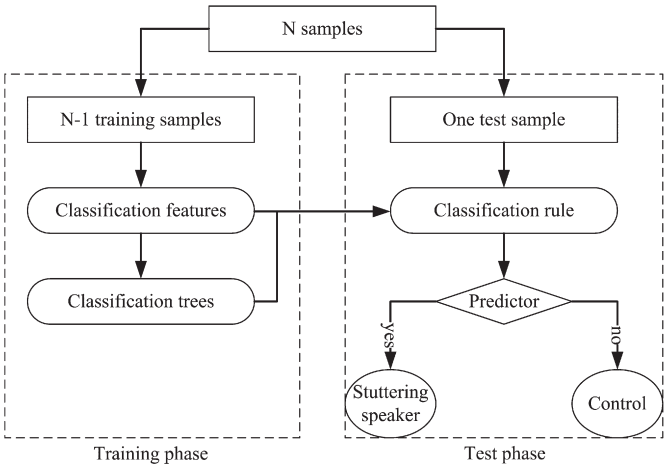

Fig. 2. Flow chart of leave-one-out cross-validation for classification analysis (see Zhu et al., 2008).

LISREL 8.7 (www.ssicentral.com) was used to estimate the parameters for the SEM model. It used an iterative maximum likelihood algorithm to calculate path coefficients and to achieve the best match between the covariance matrix reproduced by the model and the observed variance-covariance structure from the data (Jöreskog, 1996; Jöreskog and Sorbom, 1996). The overall fit indices included χ^2, the Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), and Parsimony Goodness of Fit Index (PGFI) (de Marco et al., 2009). Besides the overall fit indices, the reported t value for each path coefficient in the model should be greater than a certain critical value to reject the null hypothesis that the coefficient is 0. We used a path coefficient threshold of 0.05 (False discovery rate [FDR] corrected). The model-searching and group comparison methods were the same as those reported previously (Lu et al., in press).

Results

GLM and statistical group-contrast results

Since we were primarily interested in brain regions showing task×group interaction effects, the activation patterns and their group differences in a single task are not reported in the main body of this article. Instead, they are available as Supplemental materials (see Supplemental text, Fig. S1, and Tables S1 and S2).

Task×group interaction effects for the planning process

Brain regions showing significant interaction effects between subject groups (stuttering vs. non-stuttering) and condition (production of three-syllable words vs. repeated one-syllable words) included the left premotor area (PMA, BA6), post-central gyrus (BA3), anterior superior temporal gyrus (STG, BA38), insula (BA13), right posterior STG (BA22), lingual gyrus (BA18), culmen of the cerebellum, and bilateral inferior frontal gyrus (IFG, BA45/47) and putamen (see Fig. 3(a) and Table 1).

Task×group interaction effects for the execution process

Fig. 3(b) and Table 1 illustrate brain regions that showed significant interaction effects between subject group and condition (repeated vs. non-repeated one-syllable words). Specifically, they included the left IFG (BA45), left PMA (BA6), left angular gyrus (AG, BA39), bilateral insula (BA13), and right cerebellar tonsil.

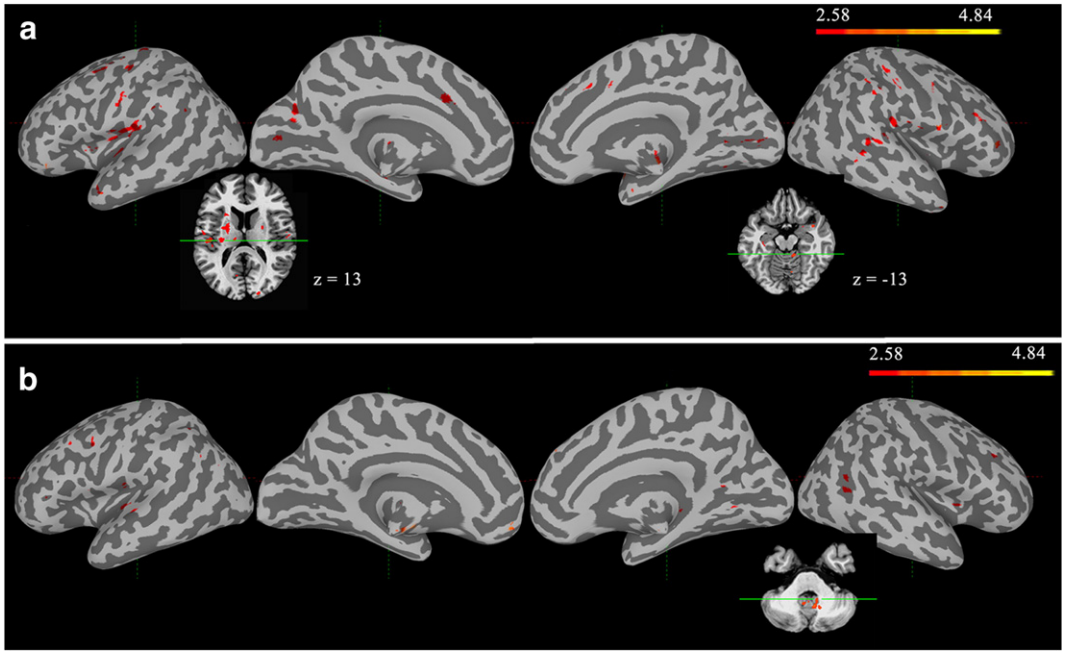

Fig. 3. Brain regions showing task × group interaction effects for the planning (a) and execution (b) processes. $p<0.01$, corrected.

Classification results

As mentioned earlier, data for 19 participants (10 stuttering speakers and 9 controls) were available for the classification analysis. First, the classifier was trained with all of the 19 samples to obtain the classification rules for prediction. Then a 19-round leave-one-out cross-validation (18 samples for training and 1 sample for testing) was conducted to estimate the predictive ability of the classifier. Classification results showed that the generalization rate, sensitivity, and specificity of classifiers computed from the leave-one-out cross-validation were all 100%. The contribution from various brain regions to the classifiers and the structure of the classification trees are shown in Figs. 4(a), (b), (d), and (e). These regions included the bilateral IFG and the right putamen for the planning process and the left PMA and AG, right insula, and cerebellum for the execution process.

In order to investigate whether the discriminative ability of the classifiers was specific to the learning algorithm of classification, we compared the above results computed from the classification and regression tree (CRT) method with those of other often-used tree-construction method, such as the Chi-squared automatic interaction detector (CHAID)/Exhaustive CHAID. The accuracy level was the same for all methods, although the latter two methods showed that significant contributions came from the bilateral IFG, but not the right putamen for the planning process, and from the left AG and the right cerebellum, but not the right insula and the left PMA for the execution process. We also compared the results of classification trees with those of FLDA. They were quite similar in their high accuracy in classification, ranging from 94.7% to 100% for their generalization rate, sensitivity, and specificity for both planning and execution processes.

For further validation, we randomly selected some other brain regions (see Supplemental text) that did not show task × group interaction effects and extracted the classification features to see whether they were able to accurately separate stuttering speakers from controls. Such analysis can help us determine whether the high-level discrimination ability we found was specific to the brain regions we selected. Results showed that the brain regions that did not show interaction effects could not satisfactorily distinguish the stuttering speakers from the controls.

Table 1
Brain regions with significant interactive effects for the two processes.

Brain region	Planning process			Execution process		
	Volume	*x*, *y*, *z*	*z* value	Volume	*x*, *y*, *z*	*z* value
L_PMA (BA6)				271	−45, 5, 40	2.82
L_IFG (BA45)	*128*	*−46, 27, −4*	*2.81*	*183*	*−43, 24, 9*	*3.54*
R_IFG (BA45)	380	60, 5, 5	2.83			
L_Precentral gyrus (BA4/6)	473	−35, −6, 53	2.89			
L_Postcentral gyrus (BA3)	358	−19, −32, 50	3.77			
L_Angular gyrus (BA39)				523	−51, −65, 32	2.97
L_STG (BA38)	*128*	*−50, 1, −18*	2.82			
R_STG (BA22)	539	47, −36, 4	3.1			
R_Lingual gyrus (BA18)	320	43, −28, 17	3.88			
L_Insula (BA13)	1648	−47, −20, 16	3.09	356	−41, −19, 4	3.04
R_Insula (BA13)				*199*	*35, 2, 8*	*3.26*
L_Putamen	1807	−29, −20, 13	3.16			
R_Putamen	401	30, −5, −6	3.31			
R_Culmen	291	11, −38, −13	2.85			
R_Cereb tonsil				606	11, −45, −32	2.84

The coordinates were in LPI direction, Talaraich space. $p<0.05$, volume > 220 mm^3 corrected. Italicized areas did not survive the thresholding. IFG, the inferior frontal gyrus; PMA, the premotor area; STG, the superior temporal gyrus; L, left; R, right.

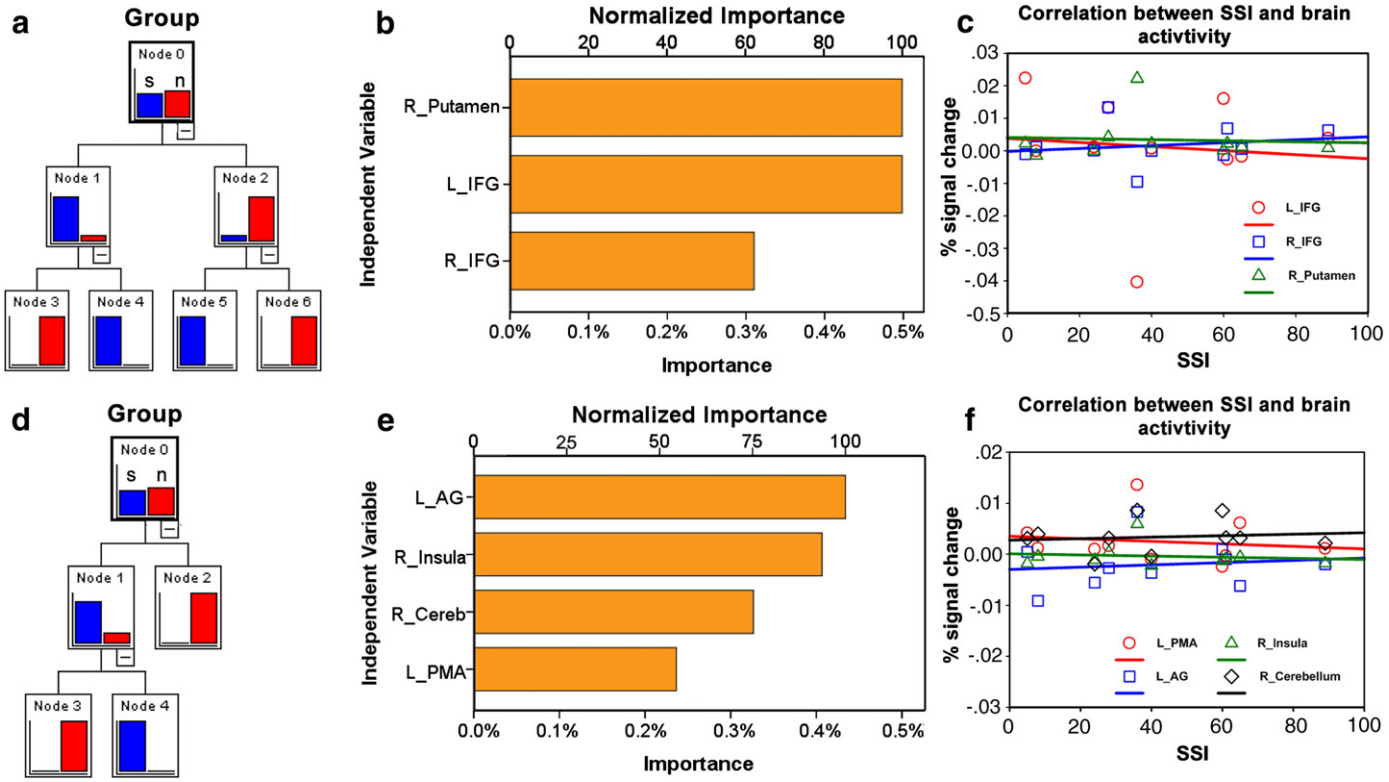

Fig. 4. Results of the classification trees analysis. Panels (a) and (d) show the two classifiers for the planning and execution processes, respectively. Important brain regions included in the classifiers are shown in panels (b) and (e). Panels (c) and (f) show that the brain activity in brain regions involved in both classifiers were not significantly correlated with stuttering severity level ($p>0.05$). s, stuttering speakers; n, non-stuttering controls; IFG, the inferior frontal gyrus; PMA, the premotor area; AG, the angular gyrus; Cereb, the cerebellum; L, left; R, right.

Finally, we attempted to use the classifiers to discriminate stuttering participants with different levels of stuttering severity as assessed by SSI-3. However, the classifiers failed to show adequate discrimination. Moreover, there were no significant correlations between level of stuttering severity and percent signal change in each brain region (see Figs. 4(c) and (f)).

SEM results

The SEM procedure was used to investigate the interactions between the neural substrates for atypical planning and execution. It produced a model that best fit the data of both non-stuttering speakers ($\chi^2=0.24$, $df=7$, $p=1.00$; RMSEA = 0.0; PGFI = 0.19, CFI = 1.00) and stuttering speakers ($\chi^2=0.045$, $df=7$, $p=1.00$; RMSEA = 0.0; PGFI = 0. 19, CFI = 1.00). The standardized path coefficients for the best fitting model in each participant group are presented in Table 2.

The overall connection patterns for the two groups were compared using the omnibus test. There were significant group differences in path coefficients ($\chi^2_{diff}=483.54$, $df=29$, $p<0.0001$). Further tests on the individual path coefficients revealed that stuttering speakers had weaker negative connections from the bilateral IFG to the left PMA than did controls (see Fig. 5). Moreover, stuttering speakers did not have a connection from the left IFG to the left putamen, and had a weak positive connection to the right putamen, which were both strongly negative in non-stuttering controls. In terms of the connections around the putamen, non-stuttering controls had a connection from the right putamen to the left putamen and connections from the bilateral putamen to the right IFG, all of which were absent in stuttering speakers.

Stuttering speakers had an additional positive connection from the left IFG to the left AG and a weak positive connection from the right IFG to the left AG. The projection from the left AG to the left putamen was negative in stuttering speakers, but positive in controls. The projection from the left AG to the right insula was weaker in stuttering speakers than in controls. Meanwhile, the right insula further received a negative projection from the right IFG in stuttering speakers, which was significantly different from the positive projection in controls, although neither reached statistical significance. Stuttering speakers showed stronger connections from the right insula to the left putamen and the PMA than did controls. Stuttering speakers also showed a weaker negative connection from the left PMA to the left AG relative to that of controls.

The PMA in controls, but not in stuttering speakers, further received a negative projection from the right cerebellum. In contrast, the PMA in stuttering speakers, but not in controls, projected a stronger negative projection to the right cerebellum.

Discussion

Previous studies have documented atypical linguistic planning, motor execution, and their interface among stuttering speakers. However, the neural substrates for them are not clear. Moreover, it is quite possible that some stuttering speakers have atypical planning, but not atypical execution, whereas others show a reversed pattern. Therefore, it is necessary to investigate the separate neural substrates for atypical planning and execution. Using an fMRI-based classification approach, the present study revealed that statistical values extracted from the brain regions involved in atypical planning or execution could accurately discriminate stuttering speakers from non-stuttering controls. We further found that this high-level discrimination ability was found regardless of classification methods. Among the brain regions involved in the task × group interaction effects, the bilateral IFG and the right putamen demonstrated the most significant contributions to atypical planning, whereas the left AG and PMA, the right insula, and the cerebellum contributed the

Table 2
Standardized path coefficients and results of group comparisons based on the best-fitting models for stuttering speakers and non-stuttering controls.

Paths			Non-stuttering		Stuttering		Group comparison	
			Standardized path coefficients	$p<$	Standardized path coefficients	p	χ^2_{diff}	$p<$
L_IFG	→	R_IFG	−0.40	0.106	−0.14	0.280	0.28	0.597
L_IFG	→	L_Angular	−0.25	0.263	0.26	**0.002**	10.01	0.002
L_IFG	→	L_PMA	−0.58	**0**	−0.51	**0**	17.53	0.000
L_IFG	→	L_Putamen	−1.23	**0**	0.02	0.819	8.87	**0.003**
L_IFG	→	R_Putamen	−0.75	**0**	0.37	**0.001**	40.12	**0**
L_IFG	→	R_Cereb	0.53	**0**	0.11	0.284	1.65	0.199
R_IFG	→	L_Angular	1.15	**0**	1.33	**0**	42.75	**0**
R_IFG	→	L_PMA	−0.87	**0**	−0.53	**0.005**	7.18	**0.007**
R_IFG	→	R_Cereb	0.17	0.199	0.04	0.842	0.23	0.632
R_IFG	→	R_Insula	0.02	0.984	−0.31	0.216	28.85	**0**
L_Putamen	→	R_Putamen	0.00	0.976	0.40	0.122	1.34	0.247
L_Putamen	→	R_IFG	−1.76	**0**	−0.30	0.117	31.50	**0**
R_Putamen	→	L_Putamen	−1.34	**0**	−0.01	0.921	15.18	**0**
R_Putamen	→	R_IFG	−1.04	**0**	0.60	0.047	9.40	**0.002**
R_Putamen	→	L_Angular	−0.08	0.735	−0.90	**0**	6.12	0.013
R_Putamen	→	R_Cereb	0.27	0.053	−0.07	0.571	4.38	0.036
L_Angular	→	L_Putamen	1.46	**0**	−0.39	**0.003**	22.13	**0**
L_Angular	→	R_Putamen	0.25	**0**	0.01	0.984	0.27	0.603
L_Angular	→	L_PMA	0.36	0.013	0.97	**0**	0.00	1.000
L_Angular	→	R_Cereb	0.11	0.427	0.47	**0.009**	1.22	0.269
L_Angular	→	R_Insula	3.32	**0**	0.89	**0**	17.69	**0**
R_Insula	→	L_Putamen	1.61	**0**	0.49	**0**	7.88	**0.005**
R_Insula	→	L_PMA	1.44	**0**	0.69	**0**	41.89	**0**
R_Cereb	→	L_Putamen	0.15	0.578	−0.15	0.100	0.82	0.365
R_Cereb	→	L_PMA	−0.57	**0**	0.04	0.780	15.24	**0**
L_PMA	→	L_Putamen	0.28	0.564	0.31	**0.003**	0.07	0.791
L_PMA	→	R_IFG	0.05	0.819	−0.14	0.115	0.97	0.325
L_PMA	→	R_Cereb	−0.05	0.698	−0.42	**0**	8.54	**0.003**
L_PMA	→	L_Angular	−1.80	**0**	−0.47	**0**	22.11	**0**

IFG, the inferior frontal gyrus; PMA, the premotor area; Cereb, the cerebellum; Angular, the angular gyrus; L, left; R, right. Bold numbers indicate statistical significance at $p<0.05$ (FDR corrected for multiple comparisons).

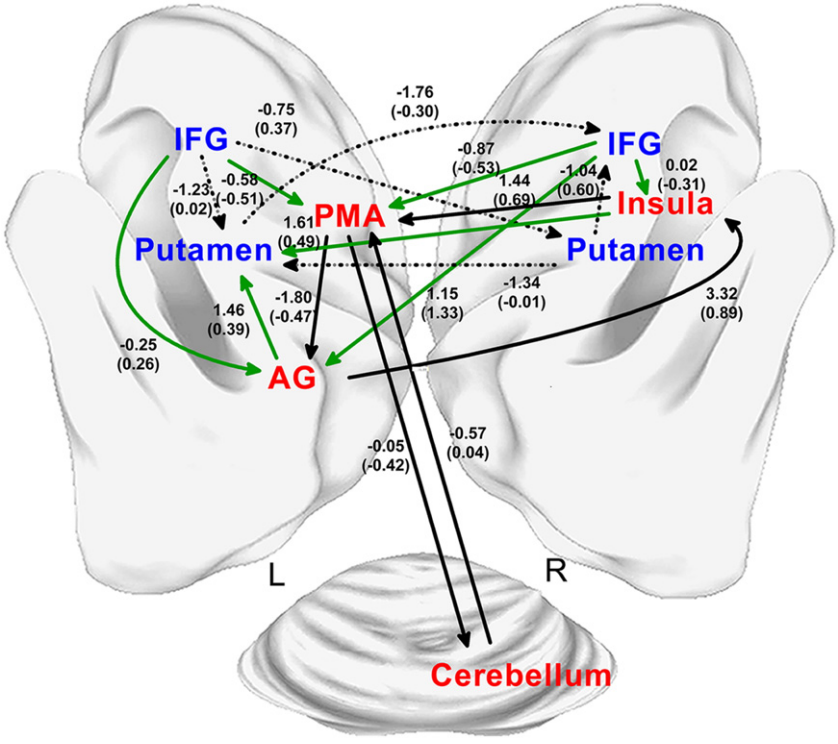

Fig. 5. Results of comparisons on individual path coefficients between stuttering and non-stuttering speakers in the interactions between neural substrates for atypical planning and execution. The arrows show directional inter-regional influence within the SEM model. The dash lines indicate connections among the neural substrates for planning, the solid black lines indicate connections among the neural substrates for execution, and the solid green lines indicate interactions between neural substrates for the two processes. The numbers indicate the path coefficients for controls and stuttering speakers (in bracket). The abbreviations are the same as those in Fig. 4.

most to atypical execution. No brain regions were shared by the two classifiers. The SEM analysis further revealed altered effective connectivity among these brain regions, revealing aberrant neural interactions between atypical planning and execution in stuttering.

We also found that the two classifiers for stuttering could not differentiate severity levels of stuttering and that neural activity in our ROIs was not significantly correlated with stuttering severity level. We interpret these results to mean that the neural activity of these brain regions is the common neural feature for all stuttering speakers regardless of their severity levels. In previous research, researchers tried to use correlation analysis to separate stuttering-related neural system from that for normal speech (e.g., Braun et al., 1997; Fox et al., 2000). Their results have been inconsistent (Braun et al., 1997; Fox et al., 2000; Giraud et al., 2008; Ingham et al., 2004). By separating the planning and execution processes, our results can help to shed light on the possible reasons for the inconsistenies. In the following paragraphs, we discuss the neural substrates associated with atypical planning, execution, and their interface among stuttering speakers.

The neural substrates for atypical planning process in stuttering speakers

We found that both the left classic Broca's area (IFG, BA45) and its right homologous area (BA45) showed high level discimination ability in separating stuttering speakers from non-stuttering controls in the planning process. The contribution from the left IFG to the discrimination of stuttering is consistent with the altered anatomical structure (i.e., reduced grey matter volume and fractional anisotropy) in this region among stuttering children (Chang et al., 2008). However, among previous functional imaging studies, some reported the involvement of the left IFG in stuttering (e.g., Braun et al., 1997; De Nil et al., 2008; Lu et al., 2009; Neumann et al., 2003; Watkins et al., 2008; Wu et al., 1995), whereas others did not (Chang et al., 2009; Fox et al., 2000; Ingham et al., 2000). This discrepency may have resulted from the fact that previous studies did not separately examine planning and execution processes in which the left IFG may play different roles. Evidence on normal speech indicates that the left IFG is mainly involved in syllabification (Schuhmann et al., 2008) or phonetic encoding (Papoutsi et al., 2009), both of which are related to the internal construction of motor plan of speech acts (Moser et al., 2009; Schnur et al., 2009). Thus, our results not only confirmed the involvement of the left IFG in stuttering, but also strongly suggested a key role of the left IFG in atypical planning process in stuttering. The right IFG, on the other hand, is found to be mainly involved in inhibition of speech acts that are generated in the left IFG (Xue et al., 2008). That is, it will temporarily “brake” some, but not all, movement preparation when selection is required (Chikazoe et al., 2007; Coxon et al., 2009). Moreover, due to the fact that response inhibition and performance monitoring come into play at various phases in a single act (Chevrier et al., 2007), the right IFG-related inhibition is more likely to function in planning than in execution, when the left IFG experiences problems. Therefore, the widely reported overactivation in the right IFG of stuttering speakers may reflect the compensatory effect for the planning deficit of its left homologous area.

According to previous research on normal speech, the putamen is also a node of the network for phonetic encoding and syllable sequence organization during word production (Bohland and Guenther, 2006; Indefrey and Levelt, 2004). The putamen’s involvement in stuttering has also been well documented. For example, lesion of this subcortical area could lead to stuttering, but not aphasia (Soroker et al., 1990). The putamen showed both functional and anatomical differences between stuttering and non-stuttering speakers (Lu et al., in press; Watkins et al., 2008). Although the specific role of the putamen in stuttering is not clear, studies have indicated that the basal ganglia are involved in storing and updating the routinces of articulation, and have influence on the improvement of proficiency of sequence act (Exner et al., 2002; Gentilucci et al., 2000). Therefore, it is likely that the putamen, along with the bilateral IFG, is associated with the dysfunction of building and improving the performance of motor plan in stuttering speakers.

The neural substrates for atypical execution process in stuttering speakers

In a previous meta-analysis, the right IFG and anterior insula were, as a whole, considered to be one of the neural signatures of stuttering (Brown et al., 2005). Our results, however, suggest that their roles in stuttering may be different. During normal speech, the insula was found to constribute to the actual coordination of articulatory movement (Ackermann and Riecker, 2004). Importantly, the right insula also has a similar role as the left tempo-parietal region, i.e., the AG (BA39), in aiding the coordination and evaluation of task performance across behavioral tasks with varying perceptual and response demands (Eckert et al., 2008). This is especially true when one relies on prior knowledge to process speech in the face of degraded or corrupted inputs (Shahin et al., 2009). Thus, for stuttering speakers, the failure of fluent speech may require the right insula and the left AG to adjust the articulatory behavior. Indeed we found neural differences in these two brain regions between stuttering speakers and controls. They appear to be neural features of stuttering during atypical execution process. Our findings are also consistent with that of Chang et al. (2009) showing abnormal activity in the right anterior insula of stuttering speakers during speech production, but not during speech perception and planning. Therefore, it is reasonable to conclude that whereas the right IFG is associated with atypical planning of stuttering, the right anterior insula is associated with atypical execution.

Previous research has reported the involvement of the PMA in stuttering (e.g., Braun et al., 1997; Fox et al., 2000; Watkins et al., 2008), but has not specified its association with atypical motor execution. Interestingly, a study using intraoperative functional mapping in awake patients showed that there may be a well-ordered functional organization in the PMA: The ventral part might be involved in planification of articulation, and the dorsal part might be involved in the naming network (Duffau et al., 2003). This functional organization pattern has not been discussed in terms of stuttering. Our results are consistent with this organization pattern by localizing the neural features for atypical execution in the dorsal part of the PMA.

Two other findings related to the execution process are worth discussing. First, previous research identified the overactivation of the right cerebellum as a neural signature of stuttering (Brown et al., 2005) and as specific to stuttered speech (Braun et al., 1997; Fox et al., 1996). Although the participants in this study produced fluent speech during the experiment, we also found overactivation in the right cereblum. Because both stuttered (previous data) and fluent speeches (our data) involve overt production, and the right cerebellum did not show neural abnormality in covert naming task (Lu et al., 2009), we think that its overactivation is likely related to the actual motor execution.

Another discrepency between our results and those of prevoius studies was that the overactivation was not located in Vermis III of the cerebellum. This discrepency may be related to differences in the neural substrates for planning and execution. For example, Chang et al. (2009) reported that different parts of the right cerebellum showed neural differences between stuttering and non-stuttering speakers during perception, planning, and production of both speech and non-speech. In the present study, we found that different parts of the cerebellum were involved in planning and execution. The part that is related to the execution process seemed to be a reliable discriminative neural signature of stuttering.

The interaction between the neural substrates for atypical planning and execution in stuttering

Stuttering speakers showed weaker negative connectivity from the left IFG to the left PMA relative to that of controls. This connectivity has been found to be a key path for the transformation of linguistic plan to motor commands (Indefrey and Levelt, 2004). Thus, an alteration of this connectivity directly reflects aberrant interactions between the neural substrates for atypical planning and those for execution in stuttering. This finding also confirmed previous reports about altered directional influence of the left IFG on the left motor cortex (Lu et al., 2009) and the reversed activation sequence of the left IFG and the motor cortex in the brain of stuttering speakers during word production (Salmelin et al., 2000). In addition, a similar alteration in effective connectivity was found between the right IFG and the left PMA. Thus, stuttering speakers seem to have difficulty transforming the inhibitory information from the right IFG to the motor cortex. This result further supports the conclusion that the interaction between planning and execution may be aberrant, leading to stuttering. Taken together, whereas the dyssynchrony/aberrant interaction between planning and execution may result from either aberrant planning or execution, the dyssynchrony/aberrant interaction itselft seems likely to be one of the immediate factors that contributes to stuttering.

The altered connection from the IFG to the PMA in stuttering speakers may have resulted from dysfunctional modulation from other neural circuits that exert poweful influence on the cortical activity. Corresponding to this assumption, we found altered connections between the basal ganglia and the bilateral IFG in stuttering speakers (see Fig. 5). These results are consistent with our previous finding that stuttering speakers showed altered effectivie connectivity and anamolous anatomy in the basal ganglia-thalamocotircal circuit (Lu et al., in press), and the alteration in connectivity had negative influence on the IFG and frontal motor areas (Lu et al., 2009). Alm (2004) hypothesized that the core dysfunction in stuttering may be the impaired ability of the basal ganglia to produce timing cues for the initiation of the next motor segment in speech. Therefore, these alterations in neural connections suggest that the basal ganglia may not receive sufficient input from the left IFG and are unable to project the timing information to their cortical target, which may in turn negatively influence the IFG-PMA connection. Taken together, the connection from the basal ganglia to the cortex is likely to play a mediating role in stuttering.

Besides the alterations in the basal ganglia-IFG/PMA circuit discussed above, stuttering speakers also had an altered connection in the cerebellum-PMA circuit. They seem to miss a connection from the right cerebellum to the left PMA. This finding confirms a previous report that the connection between the right cerebellum and the motor cortex was abnormal in stuttering speakers (Lu et al., 2009). Because the cerebellum-PMA connection has been found to subserve the online sequencing of syllables into fast, smooth, and rhythmically organized larger utterances (Ackermann, 2008), the left PMA of stuttering speakers may lack the control-related input from the right cerebellum. Correspondingly, we also found an additional back-projection from the left PMA to the right cerebellum among stuttering speakers, which was absent among non-stuttering controls. This back-projection may be closely related to the widely reported over-activation of the right cerebellum in stuttering speakers (e.g., Braun et al., 1997; Fox et al., 1996; Ingham et al., 2000). The alteration in the cerebellum-PMA circuit indicates that when producting rapid rhythmic speech, the motor cortex of stuttering speakers may be out-of-control even when the linguistic plan is intact. Therefore, the altered connectivities in the basal ganglia-IFG/PMA circuit and the cerebellum-PMA circuit seem to be two parallel aberations in stuttering speakers, that correspond to the neural substrates for atypical planning and execution, respectively.

Our SEM results further showed that in stuttering speakers the left AG is the neural interface for atypical planning and execution because it received planning-input from the bilateral IFG and execution-input from the left PMA, and then projected the integrated information to the left putamen to modulate linguistic planning and to the right insula and then onto the left PMA to modulate motor execution. This role is consistent with previous evidence that the AG is involved in the self-monitoring network for speech and plays an integrative role in motor control (Bernstein et al., 2008; Christoffels et al., 2007; Penhune et al., 1998; Shahin et al., 2009). Compared to non-stuttering speakers, stuttering speakers showed stronger positive connections from the left and right IFG, but weaker negative input from the left PMA. These results suggest that in stuttering speakers the left AG receives either unnecessary or insufficient planning information, and insufficient feedback about motor execution. This confusion may lead the left AG to exert rather weak modulation projection to the planning and execution processes. Indeed, we found that stuttering speakers showed a negative projection to the left putamen, and a weaker projection to the right insula, as compared to positive and stronger projections in controls. Moreover, the right insula had weaker projections to the left putamen and PMA in stuttering than non-stuttering speakers. Therefore, the alteration in effective connectivity around the left AG may be closely associated with the dyssynchrony between linguistic planning and motor execution in stuttering speakers.

Implications of the findings

In prevous literature about stuttering, there have been various hypotheses about the relations between cognitive dysfunction and neural abnormality in stuttering. For example, the EXPLAN theory focuses on the coordination or 'interlocking' of linguistic planning and execution stages at the language–speech interface (Howell, 2002; Watkins et al., 2008), and puts an emphasis on the cerebellum in organizing motor plans for output (Howell, 2004). The dual premotor systems theory of stuttering focuses on the role of the basal ganglia and the SMA in internal timing control of speech act sequence and the role of the cerebellum and the PMA in external timing control (Alm, 2006). However, these theories have suffered from a lack of empirical neural imaging evidence. Our results provide direct evidence for the EXPLAN theory in that the disfluency occurring in linguistic planning and motor execution stages has distinct neural substrates, and the dysfunctional neural interactions among these neural substrates may be responsible for the dissynchrony in the language–speech interface. Moreover, there seems to be two parallel neural circuits that are involved in stuttering: the basal ganglia-IFG/PMA circuit involved in atypical planning and the cerebellum-PMA circuit in atypical execution. These findings seem consistent with the dual premotor systems theory. Therefore, the present study was able to map the theoretical hypotheses onto actual neural structures and their connections, and to reveal the correspondence of the neural substrates to the specific cognitive dysfunctions of stuttering.

Our results not only contribute to theory building regarding stuttering, but also have implications for therapy methods of stuttering. For various reasons, stuttering has been mainly viewed and studied as a unitary problem (see Yairi, 2007). Although some classification systems have been offered, none has received wide recognition or has been routinely applied in research or therapy (see Yairi, 2007). However, the motivation in subtyping stuttering is strong not only in clinical spheres but also in research domain. The method used in the present study was based on the classification of individual participants, by which researchers can examine whether every stuttering speaker has aberrant planning or execution function. Therefore, brain-based classification has the potential for subtype investigation of stuttering speakers and clinical diagnosis.

Limitations

First, this study had a limited sample size. The classification approach needs to be confirmed with a larger sample. Second, the present results and conclusions were based on the task-related classification features. Although this approach has its advantages when examining specific cognitive processes, conclusions from such an approach should be replicated by data from task-free classification features (e.g., from resting state).

Conclusion

Our results revealed different neural substrates for atypical planning and execution in stuttering speakers as well as altered interactions between them. By providing empirical neuroimaging evidence, these results have significant implications for theoreties about the neuropathology of stuttering. The methods used in this study also have implications for clinical applications. They can assist in stuttering disagnosis, treatment-effect assessment, and subtype discrimination.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.expneurol.2009.10.016.

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