Neural anomaly and reorganization in speakers who stutter

A short-term intervention study

Chunming Lu, PhD
Chuansheng Chen, PhD
Danling Peng, BS
Wenping You, PhD
Xuhui Zhang, MS
Guosheng Ding, PhD
Xiaoxiang Deng, BS
Qian Yan, MS
Peter Howell, PhD

Correspondence & reprint requests to Dr. Lu: luchunming@bnu.edu.cn or Dr. Peng: pdl3507@bnu.edu.cn

ABSTRACT

Objectives: The aim of the current study was to differentiate between neural activity that represents neural anomalies that are responsible for persistent developmental stuttering (PDS) from the activity that is a result of compensating for stuttering. This was done by investigating alterations to the intrinsic functional architecture of speech-language processes of patients with PDS before and after a short-term intervention.

Methods: The resting-state functional connectivity (RSFC) and cortical thickness were examined before and after the intervention. The structural data were used to validate the functional results. Fifteen stuttering patients who received intervention (PDS+), 13 stuttering patients who did not receive intervention (PDS−), and 13 fluent controls participated.

Results: Before the intervention, both groups of PDS patients showed significant RSFC and cortical thickness reductions in the left pars-opercularis (PO) and RSFC increases in the cerebellum, as compared to fluent controls. The intervention was effective in reducing stuttering in PDS+ patients and lowering their RSFC in the cerebellum to the level of fluent controls. The intervention effect was specific to the PDS+ group (it was not evident in the PDS− group). The intervention did not change RSFC and cortical thickness in the left PO, which remained at its preintervention level.

Conclusions: The results suggest that the left PO is a locus where the intrinsic functional architecture of speech-language processes is altered in PDS patients, suggesting an etiologic role of this region in PDS. The cerebellum showed intervention-induced neural reorganization, suggesting a compensatory response when stuttering occurs. *Neurology*® 2012;79:625–632

GLOSSARY

AFNI = Analysis of Functional NeuroImages; **BA** = Brodmann area; **EPI** = echoplanar image; **IC** = independent component; **ICA** = independent component analysis; **IFC** = inferior frontal cortex; **MFG** = middle frontal gyrus; **OASES** = Overall Assessment of the Speaker's Experience of Stuttering; **PDS** = persistent developmental stuttering; **PDS−** = stuttering patients who did not receive intervention; **PDS+** = stuttering patients who received intervention; **PO** = pars-opercularis; **ROI** = region of interest; **RSFC** = resting-state functional connectivity; **SMA** = supplementary motor area; **SSI-3** = Stuttering Severity Instrument version III; **TE** = echo time; **TR** = repetition time.

Persistent developmental stuttering (PDS) is a common speech deficit that afflicts about 1% of the adult population.[1] Decades of neuroimaging research have revealed various functional and structural anomalies in people with PDS.[2–10] However, these studies cannot differentiate between neural anomalies that are responsible for PDS and those that are a result of compensating for stuttering.[8,9] This is because long-term compensation can result in both functional and structural changes in the brain of PDS patients. Another limitation in previous research is that most studies have mainly examined task-specific neural anomalies in PDS.[6,11–13] It is likely that the core neural causes of stuttering are task-independent. The aim of the current study was to differentiate etiologic and compensatory neural anomalies by establishing resting state functional connectivity (RSFC) in groups of PDS and fluent speakers[14,15] and establishing whether

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Supplemental data at www.neurology.org

Supplemental Data

From the State Key Laboratory of Cognitive Neuroscience and Learning (C.L., D.P., X.Z., G.D., X.D.), Beijing Normal University, Beijing, PR China; Department of Psychology and Social Behavior (C.C.), University of California, Irvine; Institute of Psychology (W.Y.), Chinese Academy of Science, Beijing; Stuttering Therapy Center (Q.Y.), Beijing, PR China; and Division of Psychology and Language Sciences (P.H.), University College London, UK.

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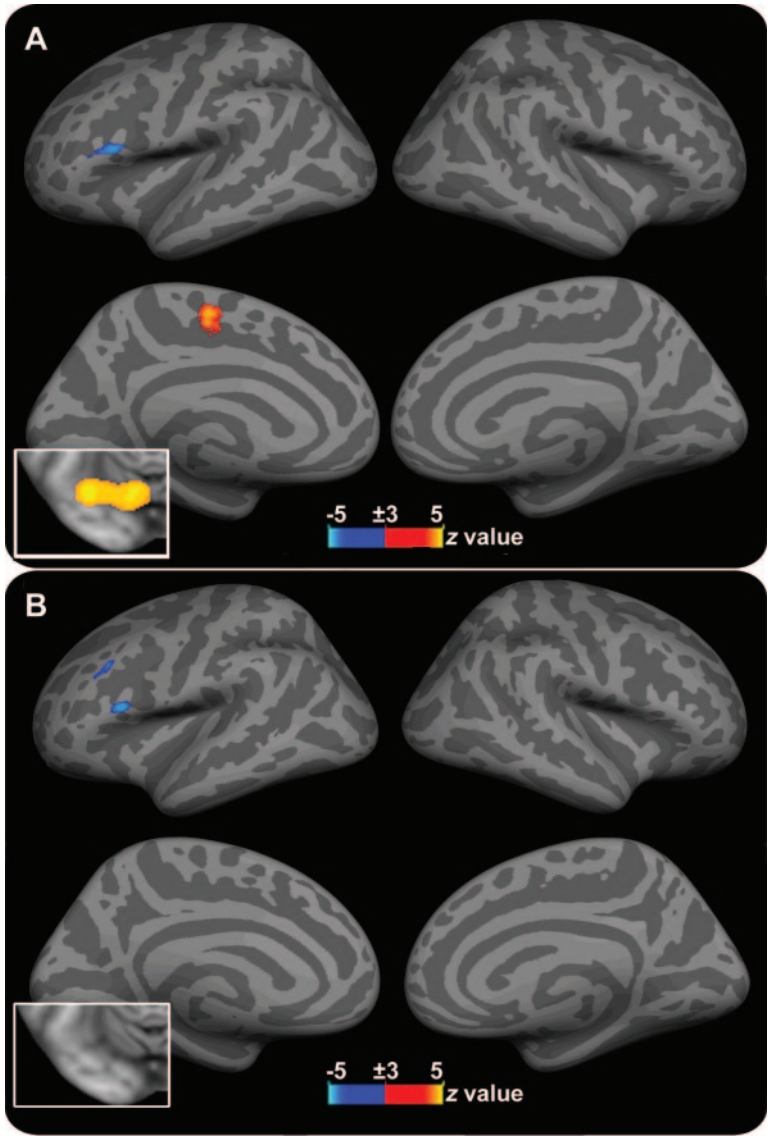
or not a short-term behavioral intervention[16–18] changed RSFC in the PDS group who received the intervention (PDS+). Cortical thickness was examined as a validation of the RSFC results.

METHODS **Participants.** Fifteen PDS+ patients (mean age 24 ± 2.43 years), 13 PDS− patients who received no intervention (mean age 29 ± 6.06 years), and 13 fluent controls (mean age 24 ± 1.45 years) were recruited. The PDS− group was included to validate that the changes in the PDS+ group were due to intervention-induced reorganization of the RSFC. All participants were male. The 3 participant groups were matched with regard to educational level and handedness scores (table e-1 on the *Neurology*® Web site at www.neurology.org).

Figure 1 **Regions with resting-state functional connectivity reductions (blue) or increases (red) in persistent developmental stuttering (PDS) patients relative to fluent controls**



(A) PDS+ patients vs fluent controls; (B) PDS− patients vs fluent controls. $p < 0.05$, corrected.

The only significant difference among the 3 participant groups was age ($F_{2, 38} = 7.73$, $p = 0.002$). Consequently, age was included as a covariate in all analyses to control for any potential statistical effects it had.

Inclusion criteria for all groups of participants were 1) native Mandarin speakers; 2) no personal or family history of psychiatric or neurologic disorders except for PDS in the stuttering patients, which was established by interview; and 3) handedness score of greater than +40, which is a cutoff for right-handedness, on the Edinburgh Handedness Inventory.[19] All participants met all these criteria except that 1 PDS+ patient had a handedness score of +38. General demographic, educational, and medical details were obtained by interview. A spontaneous speech sample of at least 300 syllables and a reading of a standard 300-syllable text were recorded from all participants. Any physical concomitants were noted independently by 2 research assistants while these recordings were made.[20]

Additional inclusion criteria for all PDS patients were that they were not involved in any treatment programs and started to stutter before teenage, both of which were established by interview. They also had a standard Stuttering Severity Instrument version III (SSI-3) score of at least mild,[20] based on the data obtained at the 2 recordings. Another clinical assessment performed on the PDS patients was the Overall Assessment of the Speaker's Experience of Stuttering (OASES).[21] All clinical assessments for the PDS patients were performed before and immediately after the intervention.

Fluent control participants met the objective inclusion criterion of %SS ≤3% to support their self-report that they did not stutter. %SS was estimated on the 2 recordings obtained at each attendance. Additionally, no physical concomitants were observed for the control participants by the research assistants. The main clinical and demographic characteristics of the patients and controls are summarized in table e-1.

Standard protocol approvals, registrations, and patient consents. The study was approved by the ethics committee of the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University. Written informed consent was obtained from each participant before the experiment.

Procedures. ***Behavioral intervention.*** The intervention on PDS+ patients was supervised by a therapist in the laboratory over 7 consecutive days, 3 sessions per day and 9 blocks of speech material per session.[22,23] Two-syllable words were selected from a standard database (5,670 in total).[24] The words were randomly divided into 189 blocks (each word appeared twice giving 60 words per block). For the first block in each session, PDS+ patients were required to repeat aurally presented words read by a man in standard Mandarin. The next 2 blocks of the corresponding session required PDS+ patients to read aloud visually presented words that were written in Chinese pinyin. There was no time limit in either task. At the end of each day, a random selection of the audiorecorded performances was played to the patients for feedback. The PDS+ patients were also required to practice on their own the newly learned speaking pattern. Changes in severity were assessed at the end of the intervention. The fluent controls and PDS− patients did not perform any language or speech improvement exercises during the intervention period.

Imaging data acquisition. Imaging data were acquired on a Siemens TRIO 3T scanner at the MRI Center of Beijing Normal University from all participants at first attendance and after 1 week (the PDS+ patients had undergone the intervention during this week). Participants lay supine within the scanner with

their head secured by foam padding. An MRI-compatible earphone was used to reduce the scanner noise.

Functional scans. Participants were instructed to close their eyes, relax, and remain stationary. The axial gradient-recalled echoplanar images (EPI) were acquired first in an 8-minute task-free scan. The parameters were as follows: repetition time (TR) = 2,000 msec; echo time (TE) = 30 msec; flip angle = 90°; slice thickness = 4 mm; in-plane resolution = 3.1 × 3.1 mm^2; number of interleaved slices = 33.

Structural scans. Structural images were obtained from each participant with a high-resolution T1-weighted magnetization-prepared rapid gradient echo sequence: TR = 2,530 msec; TE = 3.30 msec; flip angle = 7°; slice thickness = 1.3 mm; in-plane resolution = 1.3 × 1.0 mm^2; number of interleaved sagittal slices = 128.

Functional image data analysis. ***Independent component analysis of RSFC.*** Imaging data were preprocessed using the Analysis of Functional NeuroImages (AFNI) software (http://afni.nimh.nih.gov/afni). The preprocessed data were then subjected to independent component analysis (ICA) using the FMRIB Software Library's Melodic software (http://www.fmrib.ox.ac.uk/fsl/melodic/index.html). Finally, following previous research,[25] a modified quantitative procedure was used to select the independent component (IC) for each participant that matched most closely the spatial map of the speech-language network. The detailed parameters are described in appendix e-1 (section 1).

Group differences in RSFC patterns before intervention. The selected ICs from the PDS+ and PDS− patients were first compared in a second-level random-effects analysis (independent 2-sample 2-tailed t test). This was used to confirm that the PDS− patients could be used as a no-intervention control for the PDS+ patients. Then, RSFC patterns were compared between the PDS patients (PDS+ and PDS−) and fluent controls (independent 2-sample 2-tailed t test, $p < 0.05$, corrected by Monte Carlo simulation, individual voxel $p < 0.001$, cluster volume >327 mm^3).[26,27]

Intervention-induced RSFC reorganization. In order to examine the potential reorganization of the RSFC arising from intervention in PDS+ patients, the selected ICs from these patients were compared across the intervention (pre- vs postintervention) in a second-level random-effects analysis (paired 2-sample t test). The same procedure was applied to PDS− patients and fluent controls to confirm the stability of RSFC when there was no intervention ($p < 0.05$, corrected).

Structural image analysis. ***Cortical thickness measurements.*** Cortical surface reconstruction and thickness measurements were performed using the FreeSurfer toolkit (http://surfer.nmr.mgh.harvard.edu/). Details of the analytical procedures are provided in appendix e-1 (section 2).

Group differences in cortical thickness before intervention. A surface map was generated by computing independent 2-sample 2-tailed t tests that checked for an effect of group differences on cortical thickness between PDS+ and PDS− patients, and between the PDS patients (both PDS+/PDS−) and fluent controls ($p < 0.05$, corrected by Monte Carlo simulation, individual vertex $p < 0.0001$, surface area >50 mm^2).

Intervention-induced cortical thickness changes. Cortical thickness differences between pre- and postintervention in all 3 participant groups were computed, separately, by 2-sample 2-tailed t test ($p < 0.05$, corrected).

Correspondence between functional and structural results. The clusters that showed group differences (between PDS patients and controls) in RSFC or cortical thickness analyses were defined as regions of interest (ROIs). To do this, the RSFC ROIs were first superimposed onto the cortical thickness ROIs in order to estimate extent of anatomic overlap between them. Second, the AFNI program was used to calculate the averaged RSFC strength (z value) or cortical thickness over all voxels which survived the statistical threshold within the ROIs for each group. Correlations between the RSFC strength and cortical thickness were computed to assess the correspondence between the functional and structural results.

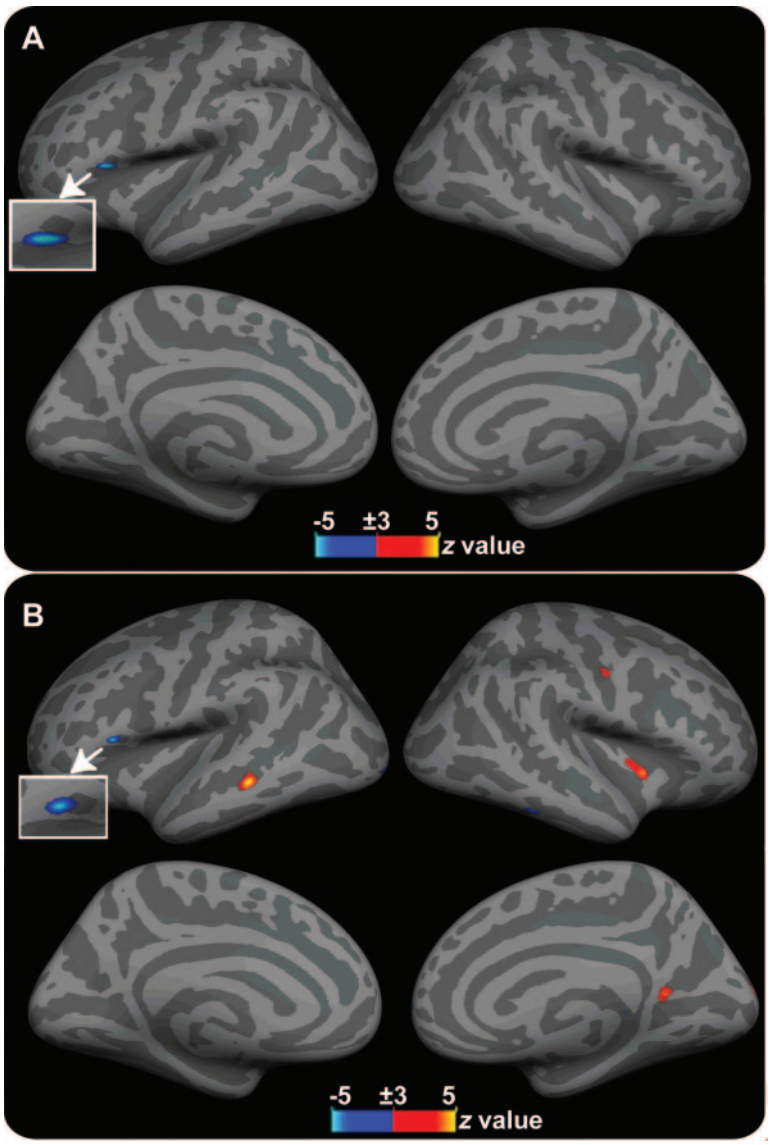
Table 1 Regions with RSFC and cortical thickness alterations in PDS patients relative to fluent controls before the intervention

Brain area	Position[a] x	y	z	z Value	Cluster volume, mm^3
RSFC alterations					
PDS+ < fluent					
Left par-opercularis (BA44)	−54	18	18	−3.526	329
PDS+ > fluent					
Left supplementary motor area (BA6)	−5	−18	50	3.814	354
Left cerebellum	−5	−69	−11	4.346	3,700
PDS− < fluent					
Left par-opercularis (BA44)	−54	14	18	−3.719	662
Left middle frontal gyrus (BA9)	−50	30	29	−3.733	432
PDS− > fluent					
None					
Cortical thickness alterations					
PDS+ < fluent					
Left par-opercularis (BA44)	−44	21	7	−4.414	107.33
PDS+ > fluent					
None					
PDS− < fluent					
Left par-opercularis (BA44)	−50	21	8	−3.198	58.25
PDS− > fluent					
Right precentral gyrus (BA4)	45	−6	31	2.951	60.68
Right precuneus	14	−52	13	3.341	108.68
Left middle temporal gyrus (BA21)	−56	−36	−7	3.441	125.16
Right insula (BA13)	36	6	−1	3.234	145.87

Abbreviations: BA = Brodmann area; PDS = persistent developmental stuttering; RSFC = resting-state functional connectivity.
[a] The coordinates are standard Talairach space.

RESULTS **RSFC differences before intervention.** As expected, no statistically significant differences in RSFC were found between PDS+ and PDS− patients before intervention, suggesting that the PDS− group was a satisfactory no-intervention control group. Relative to fluent controls, PDS+ patients showed significantly lower RSFC strength in the left pars-opercularis (PO, Brodmann area [BA]44) (see blue areas in figure 1A) and greater RSFC strength in the left part of the supplementary motor area (SMA,

Figure 2 Regions with cortical thickness reductions (blue) or increases (red) in persistent developmental stuttering (PDS) patients relative to fluent controls



(A) PDS+ patients vs fluent controls; (B) PDS− patients vs fluent controls. $p < 0.05$, corrected.

BA6) and left cerebellum (see red areas in figure 1A). Similarly, compared to fluent controls, PDS− patients showed a RSFC reduction in the left PO (BA44) and the middle frontal gyrus (MFG, BA9) (see blue areas in figure 1B). The detailed results are summarized in table 1.

Cortical thickness differences before intervention. No statistically significant differences were found in cortical thickness between PDS+ and PDS− patients before intervention. Comparisons between PDS+ patients and fluent controls revealed a reduction of cortical thickness in the left PO (BA44) of PDS+ patients (see the blue area in figure 2A and table 1). Compared to fluent controls, PDS− patients showed reduced cortical thickness in the left PO (BA44) (see blue regions of figure 2B) and increased cortical thickness in the left middle temporal gyrus (BA21), right precentral gyrus (BA4), right precuneus, and right insula (BA13) (see red regions of figure 2B and table 1).

Correspondence between functional and structural results. The left PO showed an anatomic overlap between RSFC and cortical thickness reductions in PDS patients (indicated in figure 3A). Furthermore, a statistically significant correlation between cortical thickness and RSFC strength was found in the preintervention data across all participants ($r = 0.346$, $p = 0.027$) (see figure 3B).

Intervention effect. ***Behavioral change.*** The mean scores and standard deviations of %SS, SSI-3, and OASES in PDS+ patients before and after the intervention are shown in table e-1. All 3 indexes showed significant changes after intervention for both overt stuttering behavior (%SS, $t = 8.015$, $p < 0.0001$; SSI-3, $t = 5.82$, $p < 0.001$) and covert stuttering experiences (OASES, $t = 5.26$, $p < 0.001$). As expected, no such changes were found in PDS− patients.

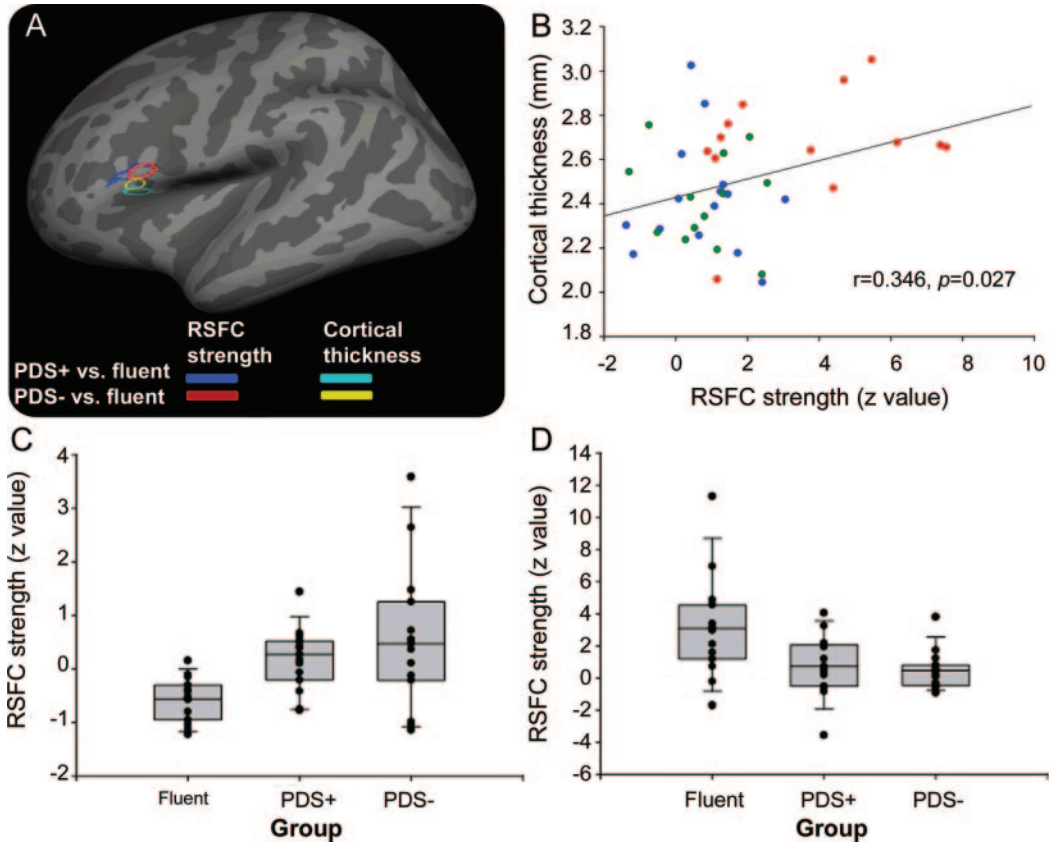
Intervention-induced RSFC reorganization. Comparisons between pre- and postintervention data from the PDS+ patients revealed that the left cerebellum (x, y, z = −5, −70, −15, $z = 4.327$, cluster volume = 363 mm^3, declive of vermis) showed significant changes (figure 4A). The cluster extended to the left declive of the cerebellum. The change correlated significantly with the decrease in stuttering severity when the change of duration of stuttering events and physical concomitants were regressed out (figure 4C).[20] As expected, no significant changes in RSFC were found for either PDS− patients or fluent controls.

Intervention-induced cortical thickness changes. As expected, the short-term intervention did not affect structural data of any of the participant groups.

DISCUSSION The left PO appears to be an anomalous region in PDS patients. It showed significant differences in RSFC and cortical thickness between PDS patients and fluent controls, which were resistant to behavioral intervention. The midline of the cerebellum (declive of vermis) may be a site responsible for reorganization of the intrinsic functional architecture of speech-language processes in PDS because it showed significant changes in RSFC from pre- to postintervention in PDS+ patients, but not in controls and PDS− patients. These interpretations are discussed below.

There were reliable RSFC and cortical thickness reductions in the left PO in PDS patients. This finding is consistent with previous reports of functional[28]

Figure 3 Correlations between resting-state functional connectivity (RSFC) strength and cortical thickness and individual RSFC patterns



(A) The detail of the anatomic overlap of the RSFC and cortical thickness reduction in the left pars-opercularis (PO). (B) Correlations between cortical thickness and RSFC strength across all participants in the left PO. Red, blue, and green dots represent fluent, PDS+, and PDS− participants, respectively. (C, D), Black dots show the RSFC pattern of each participant in the left supplementary motor area and middle frontal gyrus, respectively. Note the large overlap between the PDS patients and the fluent controls.

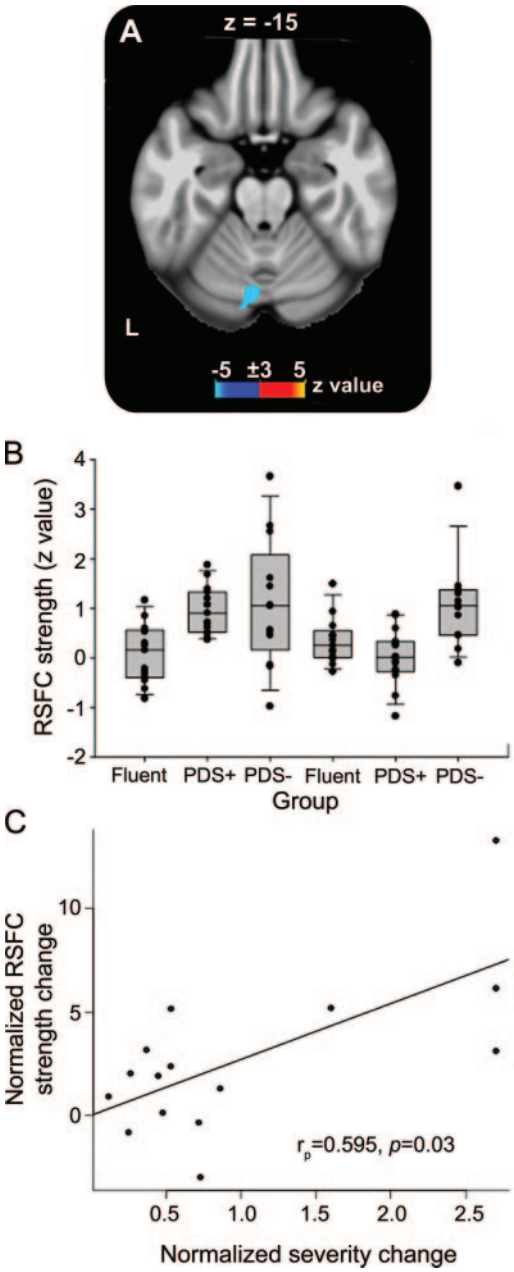
and structural anomalies or disconnections in this region in PDS patients.[3,17,29,30] Other studies have also shown functional anomalies and structural disconnections in regions that surround, or are connected with, the left PO in such patients.[5,6,8,31] Moreover, the reduced gray matter volume and functional anomalies in the left IFC seem to be associated with high risk of childhood stuttering,[9,30] whereas the reduced white matter integrity around the left PO seems to be associated with the persistence of stuttering.[17,30] Thus, there is likely a functional and structural alteration to the architecture of speech-language processes in the left PO of PDS patients.

Convergent evidence has shown that the degree of activation of the left PO in normal speakers and damage to the left PO in aphasic speakers are associated with performance on speech production tasks.[32] This region is particularly associated with lexical selection,[32] phonologic processing,[33] and phonetic encoding.[34] The anomaly of the left PO in PDS further supports the view that this region plays a vital role during speech production.

The significant correlation between the functional and structural results indicated that the anomaly of the left PO of PDS patients may reflect the fasciculus connections or alterations of neurodevelopment-related neurotransmission. It is known that RSFC reflects synchronization among spontaneous neural activity in distant brain regions, and corresponds well to the fasciculus connections and underlying white matter microstructure.[35] RSFC is considered to be a quantitative index of brain maturation in both healthy populations and those with neurodevelopmental disorders.[36] The conclusion that there is a left PO anomaly is also consistent with previous evidence which shows that the structural anomaly of PDS is neurodevelopment-related.[17,29,30]

A further observation is that overactivations were not found in the right frontal operculum/anterior insula.[2] The overactivations have been suggested as compensations to stuttering. Such compensatory activity would not be evident in our study because we scanned PDS patients and controls at rest.

Figure 4 Intervention effect



(A) Intervention-induced resting-state functional connectivity (RSFC) changes in persistent developmental stuttering (PDS)+ patients, $p < 0.05$, corrected. Note that no significant RSFC changes were found between pre- and postintervention data in PDS− and fluent control groups. (B) The black dots show the RSFC pattern of each participant before and after intervention, in the left cerebellum. The box shows the mean level of the RSFC strength in each group. The left 3 and right 3 boxes show RSFC strength before and after intervention, respectively. Note that most of the PDS+ patients showed plasticity. (C) Significant partial correlation between the change of RSFC in the cerebellum and that of stuttering severity in PDS+ patients when the change of duration of stuttering event and the physical concomitance were regressed out. All the changes have been normalized through dividing each individual's change by group mean. It should be noted that similar analysis on the left PO showed no significant results.

Several additional brain regions emerged in both the functional and structural comparison between PDS patients and fluent controls. For example, as compared with controls, the left SMA proper showed statistically significant differences in RSFC in PDS+ patients, but not in PDS− patients, whereas the left MFG showed the opposite pattern. Although both regions have previously been found to be involved in speech,[37] the current results suggest significant individual variability in these 2 brain regions (figure 3, C and D), as has been reported previously.[3] The issue of individual variability merits further investigation.

After behavioral intervention, both the overt stuttering behavior (%SS and SSI-3 scores) and covert stuttering experiences (scores on OASES) decreased significantly in PDS+ patients, indicating improvement in fluency. Meanwhile, a significant decrease of RSFC strength after the intervention occurred in the left declive and vermis area of the cerebellum among PDS+ patients, but not among the fluent controls and PDS− patients. Further examinations of individual participants' RSFC pattern showed that most of the PDS+ patients showed plastic changes (figure 4B). Furthermore, the change of RSFC was significantly correlated with the change of stuttering severity when the change of duration of stuttering events and physical concomitants were regressed out.[20] Overactivations along the midline of the cerebellum in PDS patients have been reported previously,[2,6,11,38] and were taken to suggest a compensatory mechanism because of a lifetime of stuttering. This assumption is consistent with the evidence that the bilateral cerebellum closely cooperates with the left PO in the sequencing of subsyllabic aspects of the sound structure of verbal utterances.[39] Thus, our results allowed the decrease of RSFC strength in the cerebellum to be associated with neural reorganization of the intrinsic functional architecture of speech-language processes arising from the behavioral intervention.

There are several differences between the present results and those of previous studies. First, one previous study revealed that the overactivations immediately after intervention were more widespread and distributed more bilaterally than before intervention.[18] These authors reasoned that the increased overactivations may reflect improved neural compensation. However, our results mainly showed decreased involvement of brain regions in the language network after intervention. One potential explanation for this discrepancy is that the current results were obtained at resting state, and neural compensation was not necessary. Thus, the effective intervention did not necessitate neural compensation that increased brain activations or connections among brain regions.

Another possibility is that the well-documented right hemispheric overactivations reflected neural compensation for the left hemispheric alteration of the speech-language network during prolonged stuttering. Stuttering persisted because of the inefficiency of the neural compensation. While intervention decreased stuttering severity effectively, it might also help the brain to reorganize the speech-language network so as to repair the anomaly efficiently, resulting in decreased activation in the other brain areas. If this was true, the reorganization process shown in this study perhaps reflected neural plasticity resulting from behavioral learning rather than a temporal adaptation effect under fluency-enhancing conditions.[12,13] However, further long-term follow-up studies are needed to confirm this hypothesis.

Finally, it should be noted that the RSFC approach has limitations. For fMRI-based RSFC, the scanner noise may lead to change of brain function, especially for stuttering patients. The participants were interviewed after scanning to ensure that there had been no change in their psychological state. However, the participant groups may have responded differently (i.e., the benchmark resting state could have differed across participant groups leading to differences in RSFC). These and other results need to be replicated with silent techniques such as fNIRS and EEG.

AUTHOR CONTRIBUTIONS

Dr. Lu designed and performed the study, analyzed the data, and wrote the manuscript. Dr. Chen designed the study and wrote the manuscript. Prof. Peng designed the study and wrote the manuscript. Dr. You acquired and analyzed the data Ms. Zhang acquired and analyzed the data. Dr. Ding acquired and analyzed the data. Ms. Deng acquired and analyzed the data. Ms. Yan acquired and analyzed the data. Dr. Howell wrote the paper.

DISCLOSURE

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