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Disrupted Intrinsic Local Synchronization in Poststroke Aphasia

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Abstract: Evidence has accumulated from the task-related and task-free (i.e., resting state) studies that alternations of intrinsic neural networks exist in poststroke aphasia (PSA) patients. However, information is lacking on the changes in the local synchronization of spontaneous functional magnetic resonance imaging blood–oxygen level-dependent fluctuations in PSA at rest.

We investigated the altered intrinsic local synchronization using regional homogeneity (ReHo) on PSA (n = 17) and age- and sex-matched healthy controls (HCs) (n = 20). We examined the correlations between the abnormal ReHo values and the aphasia severity and language performance in PSA.

Compared with HCs, the PSA patients exhibited decreased intrinsic local synchronization in the right lingual gyrus, the left calcarine, the left cuneus, the left superior frontal gyrus (SFG), and the left medial of SFG. The local synchronization (ReHo value) in the left medial of SFG was positively correlated with aphasia severity ($r = 0.55$, $P = 0.027$) and the naming scores of Aphasia Battery of Chinese ($r = 0.66$, $P = 0.005$). This result is consistent with the important role of this value in language processing even in the resting state.

The pathogenesis of PSA may be attributed to abnormal intrinsic local synchronous in multiple brain regions.

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Abbreviations: ABC = aphasia battery of Chinese, AQ = aphasia quotient, BOLD = blood–oxygen-level dependent, CQ = cortical quotient, fMRI = functional magnetic resonance imaging, KCC = Kendall's coefficient of concordance, PQ = performance quotient, PSA = post-stroke aphasia, ReHo = regional homogeneity.

INTRODUCTION

Poststroke aphasia (PSA) is a significant clinical problem that is usually caused by left hemisphere lesions.[1] Numerous functional neuroimaging are available for the investigation of the language architecture and the neurobiological mechanism underlying PSA.[2]

Glucose metabolism studies have shown that dominant hemisphere temporoparietal hypometabolism is responsible for language deficit and is related to the severity of aphasia.[3,4] Functional magnetic resonance imaging (fMRI) signals that depend on the differential magnetic properties of oxygenated and deoxygenated hemoglobin are designated as the blood–oxygen-level dependent (BOLD) signal. The BOLD contrast mechanism directly reflects the neural responses elicited by a specific state, stimulus, or task.[5] Task-related fMRI have most widely been used to map the (re)reorganization of language substrates in aphasia.[6] Resting-state fMRI, in the absence of explicit stimulus, encodes physiologically meaningful indicators of the BOLD variation over time or over dynamic fluctuation of intrinsic brain activity, based on the fact that coherent low-frequency fluctuated BOLD signals widely exist in different but functionally related brain regions.[7,8] In the resting state, dominant frontoparietal and default mode networks exhibit impaired remote regional functional connectivity in aphasia.[9–12] Poststroke aphasia is assumed to produce language deficits by remote cortical and local cortical dysfunctions. The aberrance of intrinsic local synchronization in the brain would also be responsible for the effect of an individual cortical lesion.

Therefore, we utilized a regional homogeneity (ReHo) approach to examine the intrinsic local synchrony changes in aphasic patients. ReHo measures local synchronization in the spontaneous BOLD fluctuations of ''nearest neighbor'' voxels.[13] Consequently, ReHo can feasibly be used to detect aberrance of brain intrinsic local synchrony.[14] We hypothesized that aphasic patients at rest would show abnormal ReHo in certain regions. These abnormalities may be potential neuromarkers for aphasia patient diagnosis. Moreover, we further examined the correlations between the abnormal ReHo values and the aphasia severity and language performance for aphasia.

METHODS

Subjects

Seventeen PAS patients (all right-handed, 6 females; mean ± SD age, 53.53 ± 14.06 years old) were recruited from admission at the Fuzhou Hospital (see Table 1 for demographic information). Patients were recruited retrospectively according

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TABLE 1. Demographics for Subjects

Demographics	Aphasia	Healthy Controls	*P* Value
Group size (n)	17	20	–
Handedness (left/right)	0/17	0/20	–
Gender (male/female)	11/6	12/8	0.90*
Age, y	53.53 ± 14.06	54.05 ± 8.43	0.98†
Education, y	8.71 ± 1.26	8.45 ± 1.47	0.58‡

Values are mean ± SD.
* Chi-square test.
† Mann Whitney *U* test.
‡ Two-sample *t* test.

to the following criteria: (i) first ever stroke occurred in the left hemisphere; (ii) age >18 and < 85 years; (iii) Chinese native speaker; (iv) aphasia persistent at day 1 poststroke; and (v) right handed. Participants were excluded if they had the following: (i) any past or current neurological disorders or family history of hereditary neurological disorders; (ii) a history of head injury resulting in loss of consciousness; (iii) alcohol or substance abuse; (iv) claustrophobia; and (v) incompatible implants. All patients experienced a single left hemisphere stroke (see Figure 1 for the lesion overlap map) and underwent MR imaging for an average of 9.9 ± 5.4 (± SD) days after stroke (see Table 2 for stroke-related clinical characteristics). All patients were Chinese native speakers and were right handed.

All patients received a comprehensive evaluation, including history and neurological examination, neuropsychological testing, and neuroimaging. Aphasia was diagnosed based on the Aphasia Battery of Chinese (ABC),[15] which is the Chinese standardized adaptation of the Western Aphasia Battery.[16] The ABC provides the aphasia quotient (AQ), performance quotient (PQ), and cortical quotient (CQ).[17] The AQ reflects a global measure of aphasia severity and type of aphasia. The PQ represents the nonlinguistic function of the brain. The CQ gives an overall picture of cognitive status.[18] Demographic and stroke-related clinical characteristics are shown in Table 2.

In total, 20 age-, gender-, and education-matched healthy controls (HCs) (all right-handed, 8 females, mean ± SD age, 54.05 ± 8.43 years old) were included in this study. The HCs were volunteers recruited through advertisement. These HCs had no history of neurological disorders or psychiatric illnesses and no gross abnormalities on brain MR images.

This study was approved by the local ethics Committee of the Fuzhou Hospital and was conducted in accordance with the approved guidelines. All participants provided informed consent to participate in the investigation.

Data Acquisition

All data were analyzed using a 3.0T Siemens Vision Scanner (Erlangen, Germany) equipped with high-speed gradients on the recruitment day. The following parameters were axially used for T1 anatomical imaging: repetition time/echo time (TR/TE) = 2300/2.98 ms, matrix = 512 × 512, flip angle = 9°, voxel size = 0.5 × 0.5 × 1 mm^3, and 176 slices without inter-slice gap. With the same locations as the anatomical slices, functional images were acquired using an echo-planar imaging sequence with the following parameters: TR/TE = 2000/30 ms, matrix = 64 × 64, flip angle = 90°, inter-slice gap = 4.0 mm, voxel size = 3.8 × 3.8 × 4 mm^3, and slices = 31. 31. Each participant underwent fMRI scan for 6 minutes, and 190 volumes were obtained. The participants were instructed to rest with their eyes closed, not to think of anything in particular, and not to fall asleep during scanning.

Data Preprocessing

Functional image preprocessing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF) (http://www.restfmri.net)[19] and SPM8 tool kits (http://www.fil.ion.ucl.ac.uk/spm). We removed the first 10 functional volumes, because of the unstable signal and inability of the subjects to adapt. We adjusted the remaining images for temporal and spatial differences. We removed the functional image data with translation or rotation parameters that exceeded ± 1 mm or ± 1°. We also calculated individuals mean frame-wise displacement by the translation and rotation parameters of head motion according to the formula in

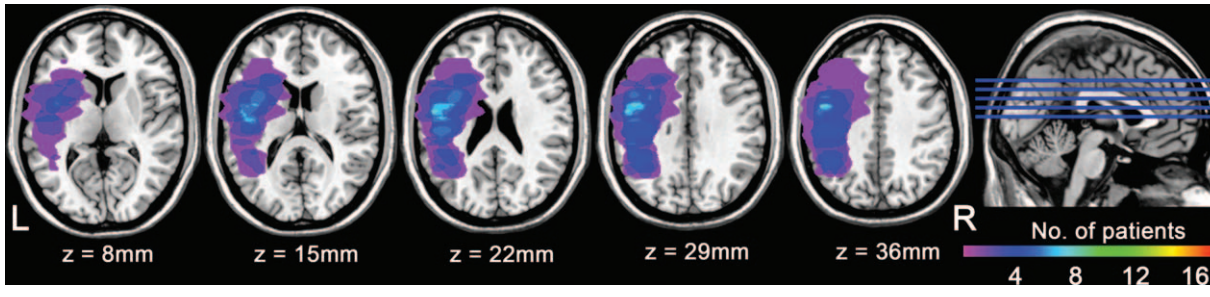

FIGURE 1. Distribution of the lesion areas of all patients. The lesion areas overlap across patients were rendered on the brain. Colors represent number of patients with a lesion to a specific voxel.

previously proposed issues.[20] No significant differences were found in the mean frame-wise displacement ($P = 0.16$) between groups. We then warped the functional images into a standard stereotaxic space at a $3 \times 3 \times 3\,mm^3$ resolution, using the Montreal Neurological Institute echo-planar imaging template. We removed linear trends from time courses and temporal band-pass filtering (0.01–0.08 Hz).

ReHo Analysis

We used Kendall's coefficient of concordance (KCC) to measure the regional homogeneity, for the similarity of the time series within a functional cluster.[13] We defined 27 nearest neighboring voxels as a functional cluster. The regional homogeneity of time series of the K voxels was calculated by the following equation:[13]

$$W = \frac{\sum_{i=1}^{n}(R_i)^2 - n(\bar{R})^2}{\frac{1}{12}K^2(n^3 - n)}$$

where W was the KCC among the K voxels, ranging from 0 to 1, $R_i = \sum_{j=1}^{K} r_{ij}$ was the sum rank of the ith time point, and r_{ij} was the rank of the jth voxel, ith time point. $\bar{R} = ((n+1)K)/2$ was the mean of R_i; K was the number of time series in a measured functional area ($K = 27$, the sum of given voxel and its 26 nearest voxels); n was the number of ranks (n = 180). We used the RESting-state fMRI data analysis Toolkit (REST) software (http://sourceforge.net/projects/resting-fmri) to calculate the time series of every voxel and its nearest voxels for regional homogeneity 1 by 1, to obtain the individual ReHo map. For further comparison within and between groups, the individual ReHo map was z score standardized. The ReHo value subtracts the mean from the value at each voxel and divides the value at each voxel by the standard deviation.[14,21] Finally, the standardized ReHo maps were spatially smoothed with a 4−mm full-width Gaussian filter at half maximum.

Statistical Analysis

One-sample t test was performed for within-group comparison. We conducted individual standardized ReHo maps in each group to 1-sample t test. For visual inspection, ReHo patterns of each group were obtained by an uncorrected significant threshold.

To investigate differences in intrinsic local synchronization between aphasia patients and healthy controls, the 2-sample t test was performed on the individual standardized ReHo maps. We included age, gender, and education level as covariates. The significance threshold was set at a false discovery rate (FDR) corrected $P < 0.05$.

Finally, we used Pearson correlation to determine whether the abnormal ReHo regions are correlated with the clinical scores for ABC in aphasia patients. Based on the result of the 2-sample t tests, we exacted the mean z value of every patient in the region of interest, which was the abnormal region in aphasia. We then computed the Pearson correlation coefficient among these ReHo values and the clinical scores for ABC. As these analyses were exploratory, we used an uncorrected statistical significance level of $P < 0.05$.

RESULTS

Demographics and Clinical Characteristics

The PSA patients and HCs did not significantly differ in age (2 sample t test, $P = 0.98$), gender (chi-square test,

TABLE 2. Stroke-Related Clinical Characteristics for Patients

No	Gender	Age (Y)	Educ. (Y)	Aphasia Type	Type of Stroke	Site of Lesion	Size of Lesion (cm^3)	Initial Aphasia Severity	Time Poststroke (D)	PQ	CQ	Understanding	Repetition	Naming	Reading & Writing	Applying	Structure
1	M	51	10	Conduction	Ischemic	Frontal, limbic	119.22	40.6	14	10.1	35.7	106	100	48	17	43	12
2	F	71	10	Conduction	Hemorrhagic	Frontal, parietal, insular	145.58	46.2	16	29.1	61.5	186	100	33	128	54	73
3	M	33	9	Broca's	Ischemic	Temporal, occipital	101.62	25.4	5	3.1	19.9	82	76	8	9	6	12
4	M	44	8	Anomic	Ischemic	Frontal, parietal	70.38	60.6	16	33.7	74.0	200	100	94	156	60	80.5
5	M	60	9	Anomic	Ischemic	Temporal, occipital	159.56	34.7	11	6.0	27.9	91	86	39	14	18	16
6	F	47	9	Anomic	Ischemic	Frontal, insular	177.86	42.3	2	33.5	64.2	190	100	10	142.5	60	92.5
7	M	63	8	Anomic	Ischemic	Temporal, occipital	68.57	53.2	5	28.2	63.9	183	100	66	107.5	56	81
8	F	65	6	Anomic	Ischemic	Temporal, occipital	125.14	50.2	9	35.4	70.2	193	100	46	167	60	87
9	F	77	10	Conduction	Ischemic	Subcortical, insular	75.80	32	7	18.2	39.7	110	92	12	72	40	43
10	M	54	7	Anomic	Ischemic	Temporal	48.74	51.8	17	30.5	66.3	198	95	60	135.5	56	76.5
11	M	37	7	Anomic	Ischemic	Temporal, occipital	46.86	61	3	35.0	75.5	200	100	96	177	60	72.5
12	M	69	9	Anomic	Ischemic	Frontal, temporal	1.68	57.4	15	36.4	74.3	184	100	86	172.5	60	91.5
13	M	38	9	Anomic	Hemorrhagic	Frontal, temporal, insular	122.78	27.7	17	15.9	34.2	89	90	3	68.5	24	50.5
14	F	57	8	Conduction	Ischemic	Temporal	32.15	37.2	8	16.9	35.5	101	85	0	44.5	42	54
15	M	64	11	Conduction	Ischemic	Frontal, temporal, limbic	20.01	34.2	14	18.6	41.7	121	88	19	63.5	46	45.5
16	M	51	10	Conduction	Ischemic	Temporal, occipital	225.77	25	3	12.7	30.0	96	74	2	37	42	20
17	F	29	9	Broca's	Ischemic	Temporal, limbic	76.55	15.4	7	13.9	28.4	137	2	6	26	34	56

CQ = cortical quotient, Educ = education, F = female, M = male, PQ = performance quotient.

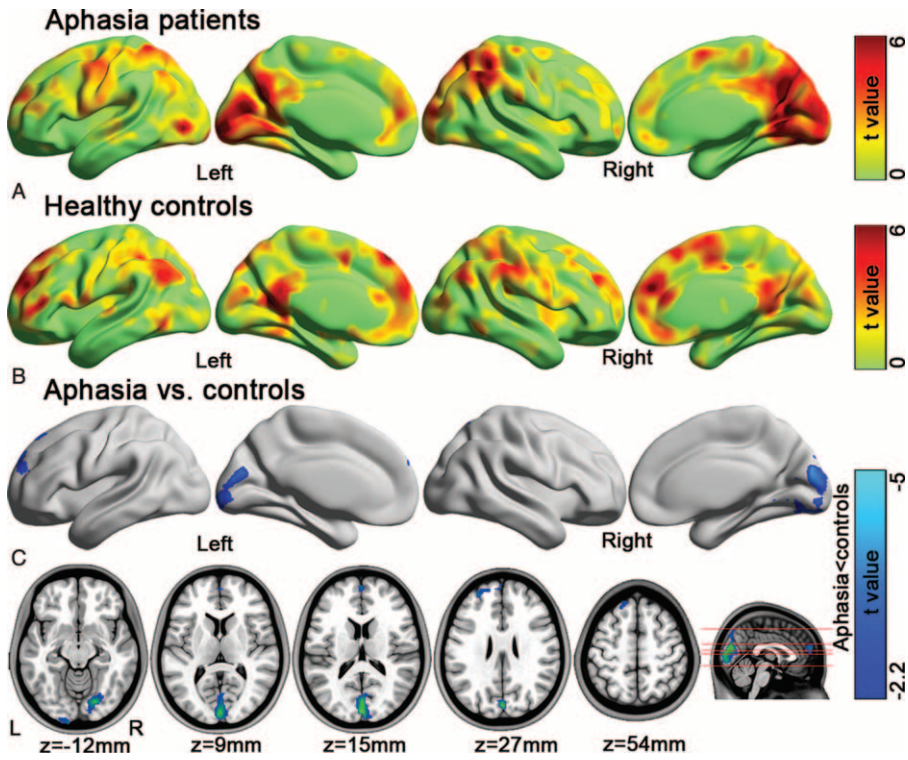

FIGURE 2. Comparison of intrinsic local synchronization patterns between groups. For visual inspection, ReHo maps of each group were obtained by uncorrected 1-sample *t* test (A for the aphasia patients group, and B for the healthy controls group). The results are presented on inflated surface maps by BrainNet Viewer (www.nitrc.org/projects/bnv). (C) The ReHo map of statistically significant differences between aphasia patients and HC by 2-sample *t* test ($P < 0.05$ FDR-corrected). The results are presented on inflated surface maps (*upper*) and axial maps (*lower*). Cold colors indicate ReHo decreases (aphasia<controls). Numbers below in each axial map refer to the *z* plane coordinates of the MNI space. Letters L and R correspond to the left and right sides of the brain, respectively. Further details of these regions are presented in Table 3. FDR = false discovery rate, HC = healthy controls, MNI = Montreal Neurological Institute, ReHo = regional homogeneity.

$P = 0.90$), and years of education (Mann–Whitney *U* test, $P = 0.58$) (Table 1). The scale score of patients included the following: understanding, repetition, naming, reading and writing, apply, structure, AQ, PQ, and CQ (Table 2). A manually drawn outline of the lesion on the T1 image of patients is illustrated in Figure 1.

ReHo Group Comparison

Within-group comparison of intrinsic local synchronization patterns, which are merely for visualizing, are shown in Figure 1 (1-sample *t* test, uncorrected for visual inspection). Visual inspection indicated that the posterior cingulate cortex/precuneus, medial prefrontal cortex, and bilateral angular gyrus exhibited significantly higher ReHo than other brain regions, which were consistent with our previous study.[22] The ReHo pattern was very similar to the so-called default mode network.[23] In addition, other brain regions, including the bilateral supplementary motor area, anterior cingulate gyrus, middle occipital gyrus, and cuneus and fusiform gyrus, have higher ReHo values.[22]

Compared with HC, the PSA patients showed significantly decreased ReHo in right lingual gyrus, left calcarine, left cuneus, left superior frontal gyrus (SFG), and left medial SFG (SFGmed) ($P < 0.05$, FDR-corrected) (Figure 2 and Table 3).

TABLE 3. Brain Regions With Decreased ReHo in Aphasia Patients

Brain Region	MNI Coordinates (*x*, *y*, *z*) (mm)	*T* Value	Voxel Size
Right lingual gyrus	(18, −81, −12)	−4.21	66
Left calcarine	(0, −93, 12)	−4.96	195
Left cuneus	(0, −93, 15)	−5.07	76
Left superior frontal gyrus	(−15, 45, 48)	−3.80	29
Left medial superior frontal gyrus	(−3, 60, 21)	−3.80	55

x, *y*, *z*, coordinates of primary peak locations in the Montreal Neurological Institute (MNI) space.
T value, statistical value of peak voxel showing ReHo differences between the groups.

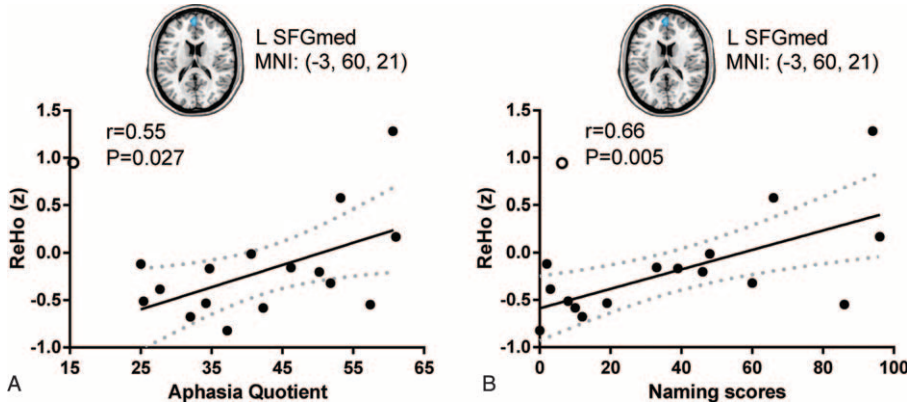

FIGURE 3. Correlations between the ReHo value in left medial of superior frontal gyrus and clinical characteristics. The ReHo value in left medial of superior frontal gyrus were positively correlated with correlated with AQ scores ($r = 0.55$, $P = 0.027$) and naming scores on ABC ($r = 0.66$, $P = 0.005$). Filled circles denote data points included in the correlation; open circles denote outliers. Solid line and dashed lines represent the best-fit line and 95% confidence interval of Pearson correlation, respectively. ABC = aphasia battery of Chinese, AQ = aphasia quotient, ReHo = regional homogeneity.

Correlations Between ReHo and Clinical Characteristics

The linear Pearson correlation between disturbed ReHo values and stroke-related clinical ABC scores in PSA patients was calculated. The ReHo value in left SFGmed was positively correlated with AQ scores ($r = 0.55$, $P = 0.027$) and naming scores on ABC ($r = 0.66$, $P = 0.005$) (Figure 3). We found no significant correlation between the others brain regions and local clinical symptoms' ABC scores (Table 4).

DISCUSSION

To the best of our knowledge, this is the first resting-state fMRI to examine the disruption of intrinsic local synchronization (or local connectivity) in PSA patients. Aphasic patients exhibited significantly decreased local synchronization in the visual cortex associated with language and semantic processing and the anterior part of DMN than HCs. Furthermore, the correlation analyses revealed that the local synchronization in the left SFGmed was positively correlated with naming score of ABC, indicating the impairment of production for language ability.

Decreased ReHo was also observed in the right lingual gyrus. The lingual gyrus is associated with language and semantic processing,[24] which is considered an essential element of human language. Previous task-related fMRI study demonstrated the activation of lingual gyrus in semantic and visual lexical decision task and silent reading.[25] Given that PSA is often accompanied by cognitive and expressive communication impairment and social communication barriers,[26] the decreased intrinsic local synchronization of lingual gyrus may contribute to the impairment of visual-spatial recognition, attention, working memory, and language expression. In addition, the patients with apraxia of speech exhibited abnormal lingual kinematics during consonant production and increasing word length.[27] The present findings suggest that lingual gyrus is closely related to normal integrative functions of language in aphasia not only during task, but also at rest.

TABLE 4. Association of ReHo With Clinical Scores in Aphasia Patients

	Association With Brain Region† (*r*)				
Clinical Scores	**R. LING**	**L. CAL**	**L. CUN**	**L. SFG**	**L. SFGmed**
Aphasia Quotient	−0.09	−0.20	−0.18	−0.08	0.55*
Performance Quotient	−0.06	−0.34	−0.35	0.01	0.30
Cortical quotient	−0.06	−0.29	−0.29	−0.04	0.42
Understanding	−0.06	−0.26	−0.27	−0.01	0.43
Repetition	−0.23	−0.34	−0.33	−0.41	0.37
Naming	0.11	0.06	0.10	0.01	0.66**
Reading and writing	−0.01	−0.29	−0.30	−0.06	0.30
Applying	−0.18	−0.38	−0.39	0.01	0.33
Structure	−0.02	−0.32	−0.33	0.17	0.20

CAL = calcarine, CUN = cuneus, L = left, LING = lingual gyrus, R = right, SFG = superior frontal gyrus, SFGmed = medial of superior frontal gyrus.

† Brain regions with ReHo reduction in aphasia patients.

* $P < 0.05$.

** $P < 0.01$.

Decreased ReHo in aphasic patients was also found in the left cuneus and calcarine [Brodmann's 18 (BA 18)]. Visual and auditory pathways are crucial to language and memory. The left calcarine was highly activated during processing of pseudowords and real words.[28] Furthermore, decreased task-related brain activation in the left calcarine is found in dyslexic patients, indicating reading disability in the semantic system.[29] In addition, word condition could activate the cuneus, which is associated with auditory processing.[30] These data, along with the present findings, suggest that the left cuneus and calcarine (BA 18) are closely related to language and semantic processing in aphasia.

Local synchronization was significantly decreased in the left SFG, which is considered as a key region in the language network.[31] Aphasic patients showed a significantly decreased intrinsic remote FC in bilateral SFG and medial frontal gyrus.[11] As for the language area, the gray matter and fractional anisotropy of SFG were lost in PSA.[32] The SFG was also thought to be included in the salience network, which was an important system in cognitive control and an essential factor in PSA recovery.[33] According to these previous studies and the present findings, the left SFG plays an important role in aphasia.

Compared with the HCs, aphasic patients showed decreased local synchronization in the left SFGmed, which was a key hub of DMN.[23] In addition, a significant positive correlation was found between the ReHo of the left SFGmed and naming score on ABC in the aphasia group. Damage in the SFGmed was related to the impairment on phonemic verbal fluency and speech in aphasic patients.[34] Moreover, the medial frontal area was thought to be associated with automatic propositional speech, semantic variant, and word generation in primary progressive aphasia.[35] Aphasic patients showed abnormal FC in the medial frontal in DMN, which likely plays a crucial role in motor aphasia.[11] In a recent study, transcortical motor aphasia, characterized by comprehension, intact repetition, and object naming, was associated with the damage to the left medial frontal area.[34] Furthermore, medial frontal cortex was functionally connected to the inferior parietal lobe, which is a key region in language processing by remote regional FC.[36] In addition to remote dysfunction, the current finding of intrinsic local dysfunction may provide new insights into how the medial of superior frontal areas affect the language system in PSA patients. The role of left SFGmed in language response may partially contribute to the pathogenesis of aphasia.

This study has several methodological limitations. First, the sample size is relatively small for conduction steady evidence for abnormal local synchronization in aphasia. Second, the healthy subjects were not tested with ABC for language performance. In addition, a longitudinal study is needed to examine whether the pretreatment intrinsic local synchronization would serve as a predictor for prognosis of recovery of aphasia following anomia treatments. The resting-state functional connectivity has been used for prognosis of recovery of aphasia.[2] Finally, constructing functional connectome will provide new ways of conceptualizing the mechanisms of aphasia.

In summary, patterns of intrinsic local synchronization are altered in PSA patients at rest. These patients exhibit significantly decreased local synchronization in the visual cortex, which is associated with language and semantic processing in the anterior part of DMN linked to language comprehension. Furthermore, the local synchronization in left SFGmed is associated with aphasia severity and naming score of ABC, thereby indicating the impairment of production for language ability. These results from local neural dysfunction may provide a novel way of investigating the neuro-pathophysiological PSA mechanisms.

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