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ORIGINAL PAPER

Abnormal Functional Connectivity Density in Post-Stroke Aphasia

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Abstract

Post-stroke aphasia (PSA), which refers to the loss or impairment of language, is typically caused by left hemisphere lesions. Previous neuroimaging studies have indicated that the pathology of PSA may be related to abnormalities in functional integration. In this study, we used resting-state functional magnetic resonance imaging (rs-fMRI) to examine functional connectivity density (FCD) in PSA. We compared short- and long-range FCD between individuals with PSA ($n=17$) and healthy controls (HC, $n=20$). We then performed Pearson's correlation analysis on the FCD values from the affected brain regions and the speech scores in the PSA group. Compared with HCs, individuals with PSA showed increased short-range FCD in the contralesional temporal gyrus, the inferior frontal gyrus, the thalamus, the insula, and the mesial temporal gyrus [hippocampus/parahippocampus (HIP/ParaHIP)]. PSA demonstrated an increased long-range FCD in the contralesional mesial temporal gyrus (HIP/ParaHIP). PSA also displayed decreased short-range FCD in the ipsilesional part of the frontal gyrus, the caudate, the thalamus, the fusiform gyrus, and the mesial temporal gyrus (HIP/ParaHIP), and decreased long-range FCD in the ipsilesional superior temporal gyrus, the fusiform gyrus, and the mesial temporal gyrus (HIP/ParaHIP). The decreased long-range FCD in the left superior temporal gyrus in PSA subjects was positively correlated with the spontaneous speech score. The altered FCD observed due to disrupted functional connectivity after stroke may lead to language production, semantic processing, and cognitive impairments. Our findings expand previous functional studies on stroke and provide new evidence of the intraregional and interregional interactions at the voxel level in the pathophysiology of PSA.

Keywords Post-stroke aphasia · Resting-state functional magnetic resonance imaging · Functional connectivity density

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Abbreviations

PSA	Post-stroke aphasia
fMRI	Functional magnetic resonance imaging
FCD	Functional connectivity density
ABC	Aphasia battery of Chinese
AQ	Aphasia quotient
PQ	Performance quotient
CQ	Cortical quotient
FC	Functional connectivity

Introduction

Stroke affects up to 10 million people each year, of which 21–38% are affected by aphasia (Pedersen et al. 1995, 2004; Kauhanen et al. 2000). Post-stroke aphasia (PSA) is a multimodal disorder that affects auditory comprehension, reading, language formulation, and writing, and is primarily caused by left- hemisphere lesions (Wade et al. 1986; Pedersen et al. 1995). PSA severely affects the functional outcome, social interactions, and quality of life of patients because of communication deficits (Saeki et al. 1995; Kauhanen et al. 2000). From an anatomical perspective, PSA arises from the damage of left-lateralized temporo-parieto-frontal perisylvian language networks (Bates et al. 2003; Hickok and Poeppel 2004a; Kiran 2012; Zhu et al. 2014; Boes et al. 2015). Although the fine-grained language architecture of PSA has been extensively studied, the alterations in brain activation and connectivity coherence remain poorly understood (Siegel et al. 2016; Pillay et al. 2017).

Previous cross-sectional studies found that PSA exhibited hypometabolism on ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) and gray matter loss on the MRI image of the left frontal gyrus, insula, and temporal gyrus (Peelle et al. 2008; Rogalsky and Hickok 2011). A task-related fMRI study of written word and picture semantic processing has found that semantic judgments induced bilateral brain activation in the middle temporal gyrus in aphasia (Robson et al. 2014). In addition, activations of the right hemisphere, mainly comprised frontal regions found in task-based fMRI studies in different phases implicated dynamic process of language recovery in patients with aphasia (Saur et al. 2006). However, in aphasia research, task-related fMRI was limited in terms of designing a language paradigm, which can be successfully completed by patients with PSA regardless of their clinical severity (Klingbeil et al. 2017; Sandberg 2017).

In recent years, resting-state fMRI has emerged as an alternative to mapping human brain function. Rs-fMRI has been used to demonstrate altered fronto-parietal network (FPN) (Zhu et al. 2014) and default mode network (DMN) (Wang et al. 2014) as well as the entire functional connectome (Yang et al. 2017) in aphasia. Stroke-induced distributed brain network disruptions in interhemispheric integration and intrahemispheric segregation predict post-stroke behavioral outcomes (Siegel et al. 2016). In addition, longitudinal data elucidated widespread network dysfunction in language specific networks (Harvey et al. 2013; Nair et al. 2015; Sandberg 2017). Furthermore, a compensatory mechanism for language deficits exists due to recruitment of right hemisphere areas homologous to left hemisphere language areas (Pascual-Leone et al. 2005; Stockert et al. 2016). Thus, converging rs-fMRI studies suggest that the alteration in functional connectivity in language specific networks is highly related to language processing deficits in patients with PSA. Brain networks possess several densely connected nodes, which serve as functional hubs and play a pivotal role in transferring information among modules; the abnormal connectivity of these hubs contributes to the development of neuropsychiatric disorders (Bullmore and Sporns 2012).However, the potential effects of PSA on the major functional brain hubs remain unclear.

In previous rs-fMRI studies, seed-based analysis relied on a priori selection of specific seed regions and whole-brain functional networks based on prior templates. These methods ignore the alterations in the whole brain network. Recently, a novel functional connectivity density (FCD) mapping approach was developed to assess the distribution of functional hubs in an unbiased whole brain manner (Tomasi and Volkow 2010). Different from the seed-based or whole-brain functional network approach, FCD method can measure the amount of FC for each voxel, thereby allowing the identification of short- and long-range functional hubs by calculating short- and long-range FCD (Tomasi and Volkow 2010, 2011b). Determination of short-range FCD facilitates observation in the central roles of voxels in the functional specialized systems. Long-range FCD would have the power scaling with the functional integration of the whole-brain networks (Sepulcre et al. 2010; Tomasi and Volkow 2010). Thus, FCD can capture the altered cortical and subcortical functional hubs without arbitrary selection of seed regions and can avoid network structure heterogeneity stemming from different templates (Tomasi and Volkow 2010, 2011a). FCD mapping provides a simple, direct, and robust index for identifying hubs with connection number changes at the voxel level. This method has been used to investigate abnormal functional integrations in various psychiatric and neurological diseases (Ding et al. 2014; Zhang et al. 2016; Zou et al. 2016).

This study aimed to: (i) obtain insights into how the altered functional pathogenesis affects functional connectivity in PSA; and (ii) investigate if the altered functional connectivity measures in PSA are correlated with subjects' clinical measures. Voxel-wise analysis was performed to measure the short- and long-range FCDs of PSA and HCs. On the basis of the altered FCD brain regions, correlation analysis was conducted on the PSA group with their respective clinical scores.

Methods

Subjects

A total of 17 participants with PSA (11 males and 6 females; age: 53.53 ± 14.06 years old) were used in this study. The lesions were secondary to single left hemisphere ischemic ($n = 15$) or hemorrhagic ($n = 2$) stroke (lesion size: 28.85 ± 42.84 cm^3). For this study 20 age-, gender-, and education-matched control subjects (12 males and 8 females; age: 54.05 ± 8.43 years) participated. Individuals with PSA were recruited from admission at Fuzhou Hospital. The inclusion criteria were as follows: (1) first stroke occurred in the left hemisphere; (2) native Chinese speakers; (3) persistent aphasia at day 1 post-stroke; and (4) pre-morbid right handedness assessed with the Edinburgh Handedness Inventory (Oldfield 1971). The exclusion criteria were as follows:

(1) family history of hereditary neurological disorders; (2) any other major systemic, psychiatric, or neurologic illnesses; (3) substance abuse that could interfere with cognitive function; (4) claustrophobia; and (5) contraindications to MRI.

All participants with PSA received a comprehensive evaluation, including medical history, neurological examination, neuropsychological testing, and neuroimaging. None of the participants received medication that affects the central nervous system at the time of the study. Aphasia was diagnosed based on the Aphasia Battery of Chinese (ABC), which is the Chinese standardized adaptation of the Western Aphasia Battery (Gao et al. 1992; Lu et al. 2013). ABC provides the following information: aphasia quotient (AQ), performance quotient (PQ), and cortical quotient (CQ) (Liu et al. 2015). AQ reflects the global measure of severity and type of aphasia. AQ (range 0–100) is derived from linguistic subtests on spontaneous speech, auditory comprehension, repetition, and naming. The normative and cut-off scores of AQ are 97.11 ± 2.43 (mean ± SD) and 93.25, respectively. PQ (range 0–40) combines scores of reading/writing, praxis, and construction. The normative scores of PQ is 22.20 ± 11.13. CQ (range 0–100) provides an overall assessment of the cognitive status. The normative and cut-off scores of CQ are 95.57 ± 3.01 and 90.85.

Written informed consent was obtained from all the subjects prior to the investigation. The study was conducted in accordance with the protocol and guidelines approved by the Ethics Committee of the Hospital of Fuzhou.

Data Acquisition

The participants underwent scanning via a 3.0T Siemens Vision Scanner (Erlangen, Germany), with an echo-planar imaging (EPI) sequence with the following parameters: TR/TE = 2000/30 ms, matrix = 64×64, flip angle = 90°, interslice gap = 4.0 mm, voxel size = $3.8 \times 3.8 \times 4$ mm^3, slice number = 31. For each participant, the rs-fMRI scan lasted for 6.33 min, and 190 volumes were obtained. The following brain sequences were also acquired: 3D T1-weighted fast field echo (TR/TE = 2300/2.98 ms, matrix = 512×512, flip angle = 9°, voxel size = $0.5 \times 0.5 \times 1$ mm^3, 176 axial slices without interslice gap). All subjects were instructed to keep their eyes closed, relax, think of nothing in particular, and avoid falling asleep.

Lesion Mapping

We constructed a lesion overlap image for all aphasic participants, as shown in supplementary Fig. S1. A radiologist (Y.L.) manually traced the outline of the lesion on individual 3D T1 images by using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron), to create a lesion mask for each participant with PSA. After the spatial normalization process, the union of all individual lesion masks was used to construct a group lesion mask for all participants with PSA.

Functional Image Preprocessing

The rs-fMRI data were preprocessed using Data Processing Assistant for Resting-state fMRI (http://www.restfmri.net) (Yan and Zang 2010). The first ten volumes of each subject were discarded to allow for magnetization equilibrium and saturation effects. The remaining 180 consecutive volumes were corrected for slice timing and realigned to the first volume to correct the head motion. Subject movement was determined to ensure a head motion of < 1 mm translations and 1° rotations. The mean frame-wise displacement (FD) was calculated (Power et al. 2012), to reflect the volume-to-volume changes in the head position. No difference was observed in the mean FD of the groups (Mann Whitney U-test, $p = 0.19$). The images were then spatially normalized to the standard EPI template and resampled to a voxel size of $3 \times 3 \times 3$ mm^3. No spatial smoothing was applied to avoid artificially introducing a local spatial correlation (Achard and Bullmore 2007). Several nuisance covariates (Friston-24 parameters of head motion, global signal of the entire brain, averaged signals from the cerebrospinal fluid and white matter) were regressed out from the data. Linear detrending and band-pass filtering (0.01–0.08 Hz) were performed to reduce the effects of low-frequency drift and high-frequency noise (Cordes et al. 2001; Foerster et al. 2010).

Functional Connectivity Density Mapping

The preprocessed data were used to compute the global FCD (gFCD) and short-range FCD maps. An in-house script using MatlabR2014a (MathWorks, MA) based on the method originally proposed by Tomasi and Volkow (2010) was implemented. Short-range FCD and gFCD were computed on a voxel-wise basis for all gray matter voxels for both the left and the right hemispheres. Voxels contained in the lesion mask (in PSA subjects) were excluded for short-range FCD and gFCD calculations. Because FCD has been described elsewhere in more detail (Tomasi and Volkow 2010), we have only briefly described it here. First, for every voxel time series, we defined the number of functional connections, k_i, by computing the Pearson's correlation coefficients between voxel (say with co-ordinates i, j, k) with every other voxel time series. Two voxels with a correlation coefficient threshold of $r > 0.6$ were considered to be strongly connected (Tomasi and Volkow 2010). This threshold was selected because a correlation coefficient that is < 0.4 increases false-positive rates, whereas a coefficient > 0.7 results in FCD maps with low sensitivity because of the reduced dynamic range. For a given voxel, the gFCD was the number of gray matter voxel time series, excluding the lesion area that had a correlation coefficient > 0.6. A simple approach based on a parallel algorithm was developed to accelerate the gFCD computation.

The computation of the short-range FCD at voxel *i* was similar to the gFCD calculation, although the operation was restricted within its local cluster. To determine the local cluster of voxel *i*, three-dimensional searching algorithm developed in the interactive data language was utilized. This algorithm searches for neighboring voxels in a three-dimensional space on the basis of the voxel coordinates. This calculation was repeated for all voxels that were adjacent to the neighbors of that given voxel in an iterative manner until no new neighbors could be added to the list. In the present study, 27 ($3\times3\times3$) nearest neighboring voxels were defined as a cluster and the given voxel was at the center of this cluster.

By contrast, the long-range FCD was computed using the following equation: long-range FCD_i = $gFCD_i$ − short-range FCD_i (Tomasi and Volkow 2012a, b).

Previous studies have shown a reduction in CBF in PSA subjects, particularly in the lesion and its neighboring regions. Hypoperfusion, known as the condition of diminished (but not abolished) baseline cerebral blood flow (CBF), was observed within the damaged hemisphere of stroke survivors, yet this hypoperfusion may be more pronounced within the peri-lesional regions (Hillis 2007; Treger et al. 2008; Brumm et al. 2010). To quantify these changes, researchers have used contralateral and ipsilateral regions to calculate the various parameters of interest. Because FCD method has utilized the blood oxygenation level dependent (BOLD) signal, the resulting fMRI signal is sensitive to changes during hypoperfusion (Ogawa et al. 1990; Henson 2002). Therefore, in this study, we computed the FCD (both short-range and long-range) for each hemisphere separately.

Quantification of Short- and Long-Range FCD

FCD map for each subject was rescaled by its average FCD [i.e., $FCD_{rescaled}$ = FCD (x,y,z)/mean (FCD)] to reduce the effect of individual variability and increase normality. Finally, spatial smoothing was performed on each volume by convolving with an 8-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel (Tomasi and Volkow 2012a, b).

Statistical Analyses

A two-sample t-test was employed on the Statistical Parametric Mapping 8 toolkit to test for the differences in the short- and long-range FCD, respectively. We regressed out confounding covariates, including the mean FD, age, gender, and education. As lesion size has tight correlation with average homotopic connectivity (Siegel et al. 2016), we also regressed out the lesion size. We determined the mean z-value in the abnormal region in the participants with PSA according to the two-sample t-test result. The significance threshold was set to a false discovery rate (FDR) corrected p value < 0.05.

Pearson's correlation analysis was used to determine the relationship between the altered FCD mapping parameters and the speech performance of the participants with PSA. We then computed the Pearson correlation coefficient among these FCD values and the speech scores in the ABC (repetition score, naming score, reading and writing score, AQ, PQ, CQ and spontaneous speech score). Bonferroni correction was used for the multiple comparisons when performing correlation analysis. The statistical level of $p < 0.05/7$ (Bonferroni corrected) was considered as significant.

Results

Demographic and Clinical Features

The demographic and clinical characteristics of the PSA and HC groups are summarized in Table 1. No significant group differences were observed in gender (χ^2-test, $P = 0.90$), age (two sample t-test, $P = 0.98$), and level of education (Mann Whitney U-test, $P = 0.58$). All participants with PSA had an ischemic ($n = 15$) or hemorrhagic ($n = 2$) stroke in the left hemisphere (lesion size: 28.85 ± 42.84 cm^3). The lesion overlap images for all patients with aphasia are shown in supplementary Fig.S1.

Head Movement Parameters

The framewise displacement (FD) across time points (Power et al. 2012) was calculated for each participant to examine the confounding influence of head motion on connectivity measures. Mean FD was not significantly different between patients with PSA and HCs ($p = 0.17$, two-tailed two-sample t-test).

Abnormal Short-Range FCD

Compared with the HCs, the participants with PSA exhibited significantly increased short-range FCD in the right temporal gyrus (TG), the inferior frontal gyrus (IFG), the thalamus (THA), the insula (INS), and the hippocampus/parahippocampus (HIP/ParaHIP). Decreased short-range FCD was observed in the left middle frontal gyrus (MFG), the medial superior frontal gyrus (SFGmed), the caudate (CAU), the thalamus (THA), the fusiform gyrus (FFG), and the hippocampus/parahippocampus (HIP/ParaHIP) in subjects with PSA (Table 2; Fig. 1).

Table 1 Demographic and clinical information of subjects

Characteristics	Aphasia (n = 17) M ± SD	HC (n = 20) M ± SD	Aphasia vs. HC *p* value
Handedness (left/right)	0/17	0/20	–
Gender (n: male/female)	11M/6F	12M/8F	0.77[a]
Age (years)	53.53 ± 14.06	54.05 ± 8.43	0.89[b]
Education (years)	8.71 ± 1.26	8.45 ± 1.47	0.58[c]
Time post-stroke (days)	9.72 ± 5.30		
Lesion size (cm^3)	30.60 ± 42.23		
ABC scores		–	–
Aphasia Quotient (AQ)	40.88 ± 13.57 97.11 ± 2.43* 93.25#	–	–
Auditory comprehension score	145.12 ± 47.16 193.08 ± 7.96*	–	–
Repetition score	87.53 ± 23.67 96.64 ± 4.72*	–	–
Naming score	36.94 ± 33.50 95.84 ± 3.81*	–	–
Performance quotient (PQ)	22.20 ± 11.13	–	–
Reading/writing score	90.44 ± 60.91	–	–
Praxis score	44.76 ± 16.41 59.91 ± 0.29*	–	–
Construction score	56.68 ± 28.32 86.04 ± 8.42*	–	–
Cortical quotient (CQ)	49.60 ± 19.55 95.57 ± 3.01* 90.85#	–	–

Data values are mean ± SD

HC healthy subjects

*Normative scores (mean ± SD) for healthy controls (see Ref. Agosta et al. 2014)

#Cut-off scores based on the receiver operating curve analyses. (see Ref. Agosta et al. 2014)

[a]Chi-square test

[b]Mann Whitney U-test

[c]Two sample t-test

Abnormal Long-Range FCD

We found that individuals with PSA displayed increased long-range FCD in the right hippocampus/parahippocampus (HIP/ParaHIP). In addition, our results showed decreased long-range FCD in the left superior temporal gyrus (STG), the fusiform gyrus (FFG), and the hippocampus/parahippocampus (HIP/ParaHIP) (Table 3; Fig. 2).

Correlation Between Abnormal FCD and Clinical Characteristics

The decreased long-range FCD in the left superior temporal gyrus was positively associated with the spontaneous speech score (r = 0.6393, $p = 0.0057$, Bonferroni corrected) (Fig. 3). We found no other significant correlations between the FCD values in other brain regions and the clinical speech characteristics.

Discussion

This study is among the first to examine aberrant FCD in individuals with PSA. Patients with PSA exhibited significantly increased FCD (either short- or long-range FCD) in the contralesional temporal gyrus, the inferior frontal gyrus, the basal ganglia, and the mesial temporal gyrus (hippocampus/parahippocampus) and decreased FCD (either short- or long-rang FCD) in the ipsilesional regions that are part of the frontal gyrus, superior temporal gyrus, the basal ganglia, and the mesial temporal gyrus (hippocampus/parahippocampus). Furthermore, the altered long-range FCD in the left

Table 2 Regions showing abnormal short-range FCD volume in patients

Brain regions	MNI			Cluster size (voxels)	*T* value[a]
	x	*y*	*z*		
Aphasia > HC					
ParaHIP.R	27	− 24	− 15	98	5.85
ITG.R	54	− 30	− 15	54	5.78
IFG.R	33	30	6	70	5.61
INS.R	39	18	− 12	34	5.61
HIP.R	30	− 21	− 15	122	5.40
STG.R	48	− 9	0	21	5.05
MTG.R	60	− 9	− 20	80	5.04
THA.R	18	− 21	15	44	4.13
Aphasia < HC					
CAU.L	− 15	21	− 3	24	− 5.25
FFG.L	− 33	− 24	− 30	101	− 4.72
THA.L	− 9	− 24	15	45	− 4.67
HIP.L	− 15	− 36	3	23	− 4.43
SFGmed.L	0	33	45	35	− 4.39
MFG.L	− 42	3	54	18	− 4.02
ParaHIP.L	− 27	− 27	− 18	63	− 3.57

x, y, z, coordinates of primary peak locations in the Montreal Neurological Institute (MNI) space

T value, statistical value of peak voxel showing FCD differences between the groups

HC healthy controls, *ParaHIP* parahippocampus, *ITG* inferior temporal gyrus, *IFG* inferior frontal gyrus, *INS* insula, *HIP* hippocampus, *STG* superior temporal gyrus, *MTG* middle temporal gyrus, *THA* thalamus, *CAU* caudate, *FFG* fusiform gyrus, *SFGmed* superior frontal gyrus, medial, *MFG* middle frontal gyrus

L left, *R* right

[a]Negative value represents lower FCD; positive value represents higher FCD

superior temporal gyrus was positively correlated with the spontaneous speech score of ABC, indicating that speech performance and word fluency were impaired. These findings suggest that the altered brain function may be related to specific brain areas with disrupted intraregional and interregional interactions in individuals with PSA.

Decreased FCD in the Ipsilesional Hemisphere

Decreased short-range FCD observed in the ipsilesional middle frontal gyrus (MFG) and medial superior frontal gyrus (SFGmed) were in accordance with a previous FC finding in motor aphasia (Wang et al. 2014). The MFG was functionally connected to the inferior parietal gyrus (IPS), which is a crucial node in language processing (Yeo et al. 2011). Damage to the left MFG was associated with transcortical motor aphasia and characterized by comprehension and intact repetition deficits (Chapados and Petrides 2013). The SFGmed is known as a key region of language network, where the damage was related to the impairment on verbal fluency and speech in PSA (Brownsett et al. 2014). Significant atrophy on MRI and degeneration of metabolism on FDG-PET in the left frontal lobe were correlated with the progression of aphasia (Josephs et al. 2006; Mesulam 2013; Yang et al. 2018). Overall, the current study indicated that the MFG and SGFmed may be vulnerable in PSA and the decreased functional connectivity in these regions might be responsible for the symptoms of language comprehension and word processing impairments.

PSA also demonstrated decreased short-range FCD in the ipsilesional caudate (CAU) and the thalamus (THA), which are highly interconnected subcortical regions with Broca's and Wernicke's area (Kelly et al. 2010; Tomasi and Volkow 2012c). These regions contribute to lexical retrieval during word generation (Crosson et al. 2001). Recent longitudinal and cross-sectional studies in primary progressive aphasia have described atrophy and hypometabolism caused by hypoperfusion extended beyond the left frontal and temporal lobes into insula and basal ganglia (Whitwell et al. 2013; Tetzloff et al. 2018). Our findings suggest that the aberrant local information integration capability in the CAU and THA might be the underlying mechanism for the symptoms of impaired word generation.

Our results also showed decreased long-range FCD in the ipsilesional superior temporal gyrus (STG), which is the language-relevant domain—Wernicke's area ventrally located (Hickok and Poeppel 2004b). The aforementioned findings imply that the left STG is a subpart of the temporo-frontal language network that supports semantic processing and syntactic processing (Vigneau et al. 2006; Friederici 2011). The posterior subparts of the left STG provide crucial gateways for semantic word processing, and its dysfunction could underlie the impairment in semantic ability (Mesulam 1998; Tomasi and Volkow 2012c). Given that the anterior parts of the left STG provide a core substrate for cross-modal translation and multi-modal integration in semantic representation, the damage to the anterior STG would result in semantic dysfunction (Patterson et al. 2007; Visser and Lambon Ralph 2011). Therefore, we suggest that the decreased long-range FCD in the left STG manifests the impaired integration of interregional information in broadly related language networks. Furthermore, our results showed that the decreased long-range FCD in the left STG was positively correlated with the spontaneous speech score, which reflects speech processing ability and word fluency (Wagenaar et al. 1975). Our correlation analysis suggested that more severe speech deficit is associated with high level interregional deactivation between the left STG and the broadly distributed brain networks. Basing on current research and previous works, we implied that the decreased interregional

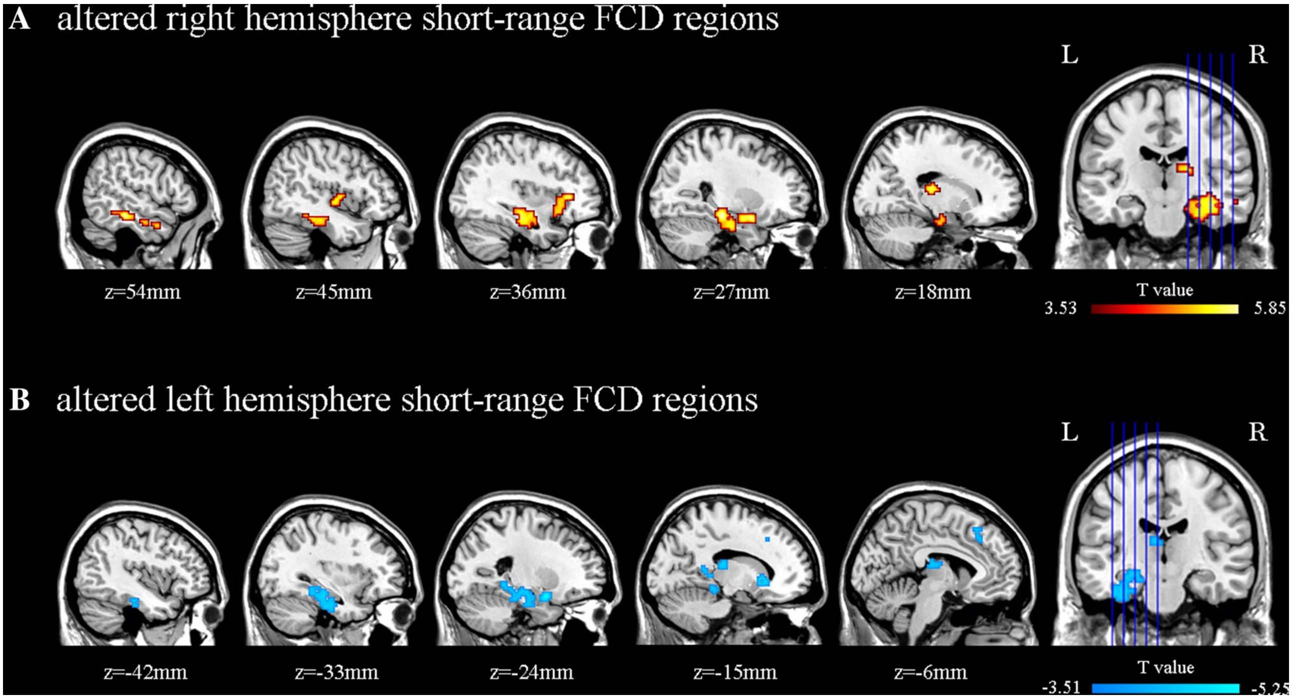

Fig. 1 Brain Regions showing significant differences in short-range FCD between aphasic patients and controls. All comparisons were performed using a two-sample t -test (FDR corrected $p<0.05$). **a** Warm colors indicate regions with increased short-range FCD value in post-stroke aphasia. **b** Cold colors indicate regions with decreased short-range FCD value in post-stroke aphasia. Numbers below each axial slice refer to the z-plane coordinates of the MNI space, respectively. Letters L and R correspond to the left and right sides of the brain, respectively. Further details of these regions are presented in Table 2

Table 3 Regions showing abnormal long-range FCD volume in patients

Brain regions	MNI			Cluster size (voxels)	*T* value[a]
	x	*y*	*z*		
Aphasia > HC					
HIP.R	33	− 12	− 12	67	5.50
ParaHIP	30	− 24	− 15	20	4.36
Aphasia < HC					
STG.L	− 24	6	− 21	20	− 5.95
HIP.L	− 27	− 18	− 18	72	− 5.88
ParaHIP.L	− 30	− 21	− 18	75	− 5.66
FFG.L	− 20	− 33	− 15	22	− 4.06

x, y, z, coordinates of primary peak locations in the Montreal Neurological Institute (MNI) space

T value, statistical value of peak voxel showing FCD differences between the groups

L left, *R* right

HC healthy controls, *HIP* hippocampus, *ParaHIP* parahippocampus, *STG* superior temporal gyrus, *FFG* fusiform gyrus

[a]Negative value represents lower FCD; positive value represents higher FCD

connection of the left STG would lead to insufficient integration of semantic processing modules in PSA.

Individuals with PSA exhibited decreased short-range and long-range FCD in the ipsilesional fusiform gyrus (FFG). The right FFG is thought to underlie our ability for face recognition (Adamson and Troiani 2018), whereas the left fusiform gyrus connecting with the temporo-parietal network supports word-form processing (McCandliss et al. 2003; Buxbaum and; Joseph 2012). A previous PET study found that the left FFG is related to word recognition and reading in language processing (Sharp et al. 2004a). Meanwhile, fMRI studies reported that the region activated lies in the left anterior FFG in word tasks (Buchel et al. 1998; Cohen et al. 2002). Combined with previous findings, the present study suggests that the left anterior FFG exhibiting abnormal intraregional and interregional functional organization might be related to the word recognition and reading dysfunction of patients with PSA.

Our results indicated that patients with aphasia exhibited left-lateralized decreased short-range and long-range FCD in the HIP/ParaHIP which is traditionally considered as a structure exclusively involved in memory circuit, and is correlated with severe dementia in the semantic variant of primary progressive aphasia (Chan et al. 2001; Tan et al. 2014). In addition to episodic memory, the HIP/ParaHIP is

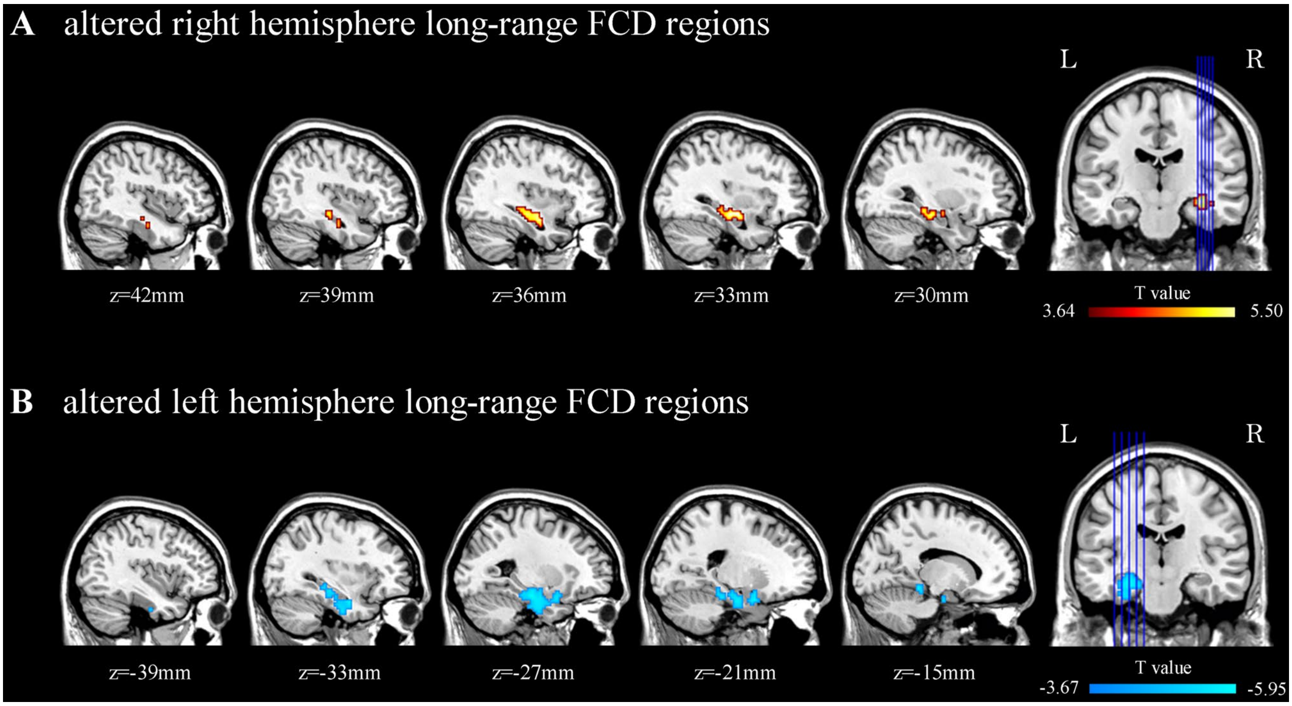

Fig. 2 Brain Regions showing significant differences in long-range FCD between aphasic patients and controls. All comparisons were performed using a two-sample t-test (FDR corrected $p<0.05$). **a** Warm colors indicate regions with increased long-range FCD value in post-stroke aphasia. **b** Cold colors indicate regions with decreased long-range FCD value in post-stroke aphasia. Numbers below each sagittal slice refer to the x-plane coordinates of the MNI space, respectively. 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

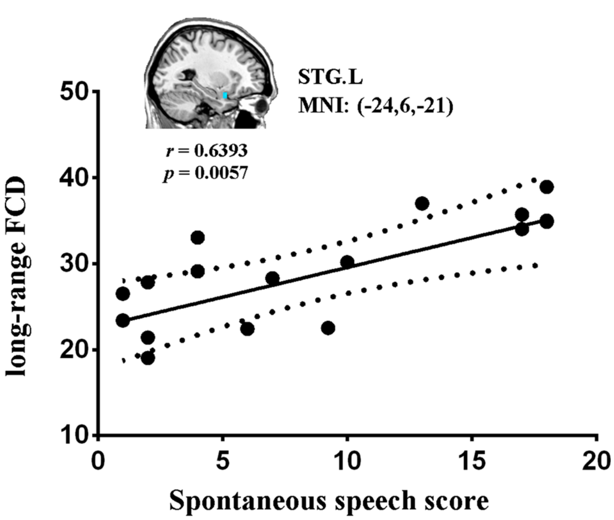

Fig. 3 Correlations between the abnormal FCD and clinical scores in aphasic patients. The altered long-range FCD value in the left superior temporal gyrus was positively correlated with the spontaneous speech score ($r=0.6393$, $p=0.0057$, Bonferroni corrected) in the Aphasia Battery of Chinese. The solid line and dashed lines represent the best-fit line and 95% confidence interval of Pearson's correlation, respectively. *P* posterior, *A* anterior

associated with spatial navigation and scene construction (Maguire and Mullally 2013; Maguire et al. 2016). Given the well-established role of HIP/ParaHIP in memory, we would expect that the decreased FCD may attribute to memory deficit due to the left hemisphere regional hypoperfusion caused by stroke.

Increased FCD in the Contralesional Hemisphere

The regions with increased short-range FCD were located in the contralateral temporal gyrus, which is a critical component of the language network (Kiran 2012). The temporal gyrus neuroanatomically subdivides into the inferior, middle, and superior temporal gyri. As a subpart of temporo-parieto-frontal perisylvian language network, the ITG was found to make distinct contributions for the semantic processing of speech (Sharp et al. 2004b). The MTG is also considered to be language relevant (Turken and Dronkers 2011), subserving lexical and semantic aspects in particular (Patterson et al. 2007). Additionally, the STG, where the traditional language processing area, namely Wernicke's area, is located, plays a vital role in speech production and semantic processing (Snijders et al. 2009; Friederici 2011). Several studies have concluded that the temporal gyrus is the vital area of semantic processing because it connects many regions indispensable for semantics (Tippett

2015). In the subacute phase, recruitment of right hemisphere homologous areas has been observed as a mechanism of successful compensation to obtain the best possible level of recovery (Geranmayeh et al. 2014). Increased intrinsic intraregional brain connectivity in the right temporal gyrus and decreased long-range FCD in left STG may be indicative of the recruitment of the homologous temporal cortex that compensates for language deficits by contributing to semantic processing.

Right-lateralized IFG also displayed increased short-range FCD. The posterior IFG in language-dominant hemisphere is traditionally referred to as Broca's region and plays a central role in language production (Friederici 2011). Massive damage to this area leads to Broca's aphasia, which is characterized by severe language production deficit (Ackermann and Riecker 2004). The homologous region in the right hemisphere is involved in certain aspects of speech (Botez and Wertheim 1959). Furthermore, functional imaging studies reported increased right IFG activity in recovery from aphasia (Naeser et al. 2005; Winhuisen et al. 2005). We conclude that the enhanced local connectivity in homologous IFG will help to compensate for particular aspects of speech production deficit.

We also observed increased short-range FCD in the right thalamus, which is related to language behavior in a circle of thalamus-cortical language areas. Thalamic lesions can produce word-emission difficulties and aphasic disorders (Jonas 1982). A previous word generation task-related fMRI study revealed that the increased activity was more wide spread in the right thalamus than in the left thalamus (Crosson et al. 2003). Considering the decreased short-range FCD in the left thalamus, we suggest that increased short-range FCD in the right thalamus may indicate a shift to right hemisphere homologous area for intraregional deactivation in word generation in patients with PSA.

Increased short-range and long-range FCD were also observed in right-lateralized HIP/ParaHIP. Previous studies suggested that the "engagement" of contralesional HIP/ParaHIP may mediate the functional recruitment of the right hemisphere homologous regions (Liegeois et al. 2004; Menke et al. 2009). The observed upregulation FCD in the right HIP/ParaHIP could be associated with the integration of regionally and broadly related brain networks. Overall, the present and previous results indicate that the function in the left HIP/ParaHIP is affected in aphasia, and the enhancement of information integration in the contralesional HIP/ParaHIP may be conducive to memory ability.

Limitations

This study presents several limitations. First, our sample size was modest; as such, our power to detect clinical imaging correlation within the PSA group was limited. Further studies should employ a larger sample size. Second, studies have shown that the association between disturbed interhemispheric connectivity and aphasia severity occurs predominantly within the temporo-parietal regions (Siegel et al. 2016) and the frontal regions (New et al. 2015; Yang et al. 2016). However, given that the precise relationships between interhemispheric connectivity and aphasia severity remain to be studied, further works must use a large sample size and various analytical techniques and consider the homogeneity of patients. Finally, we did not perform any task activation study to directly identify cortical regions related to specific tasks and did not ascribe the differences to PSA directly. Although PSA subjects may not be able to perform the given tasks due to difficulty in performing language-related tasks, continuous analysis by task-related fMRI focusing at language function in individuals with PSA must be conducted. The results must be compared with resting-state fMRI results.

Conclusion

We used an unbiased voxel-based analytical method to demonstrate short- and long-range FCD in PSA. Individuals with PSA showed decreased FCD in brain regions involved in the basal ganglia, the mesial temporal gyrus, and part of the frontal gyrus and increased FCD in the contralesional basal ganglia, the temporal gyrus, the inferior frontal gyrus, and the HIP/ParaHIP. These regions were considered important brain nodes for PSA beyond the language network extended into the areas responsible for memory, cognitive, and executive functions. Our study indicates that the intraregional and interregional functional connectivity disruption after stroke, may lead to the impairment of language production, semantic processing, and other cognitive functions. In addition, the aberrant long-range FCD in the left STG was positively correlated with the spontaneous speech score. Hence, reduction in interregional connectivity in the left STG may be responsible for impairments in semantic processing and word fluency. Our findings may provide novel evidence that focal damage not only directly interrupts the language function but also indirectly affects other functional brain networks that are responsible for complicated clinical syndromes in various aspects of stroke.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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