

Evidence of cortical reorganization of language networks after stroke with subacute Broca's aphasia: a blood oxygenation level dependent-functional magnetic resonance imaging study

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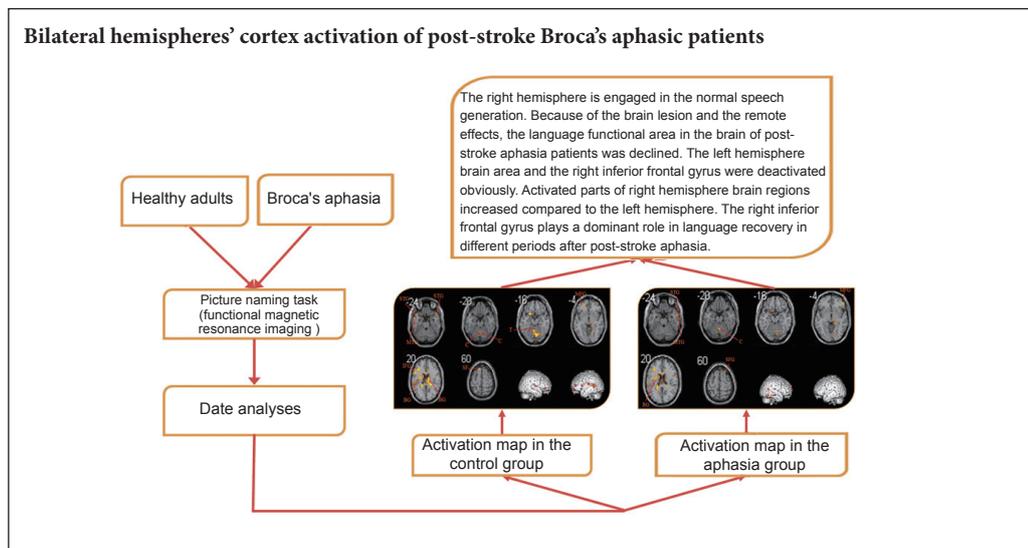
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Graphical Abstract



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Abstract

Aphasia is an acquired language disorder that is a common consequence of stroke. The pathogenesis of the disease is not fully understood, and as a result, current treatment options are not satisfactory. Here, we used blood oxygenation level-dependent functional magnetic resonance imaging to evaluate the activation of bilateral cortices in patients with Broca's aphasia 1 to 3 months after stroke. Our results showed that language expression was associated with multiple brain regions in which the right hemisphere participated in the generation of language. The activation areas in the left hemisphere of aphasia patients were significantly smaller compared with those in healthy adults. The activation frequency, volumes, and intensity in the regions related to language, such as the left inferior frontal gyrus (Broca's area), the left superior temporal gyrus, and the right inferior frontal gyrus (the mirror region of Broca's area), were lower in patients compared with healthy adults. In contrast, activation in the right superior temporal gyrus, the bilateral superior parietal lobule, and the left inferior temporal gyrus was stronger in patients compared with healthy controls. These results suggest that the right inferior frontal gyrus plays a role in the recovery of language function in the subacute stage of stroke-related aphasia by increasing the engagement of related brain areas.

Key Words: nerve regeneration; functional magnetic resonance imaging; cortical functional connectivity; language regions; neuroplasticity; Perisylvian language regions; brain activation; right hemisphere; picture-naming task; neural regeneration

Introduction

Language, which is considered the most distinct function of high-level cognition in human beings, is controlled by an intricate system involving many brain regions across both hemispheres. In the 95% of humans, the left hemisphere is the main domain implicated in language function (Szaflarski et al., 2011). Wernicke and Broca's areas in the left hemisphere are predominant components of language perception and speech production processes (Aminoff and Daroff, 2014). From the 1980s onwards, studies have produced evidence implicating the right hemisphere in language. An important demonstration of this is the 'Wada test' (a unilateral amobarbital injection) in chronic aphasia patients, and showed the right hemisphere engaged in the language process (Krashen, 1973; Rapport et al., 1983). Additionally, aphasia patients with a left hemisphere lesion may exhibit improved language function, while those who suffer a stroke in the right hemisphere may lose all language ability (Cambier et al., 1983).

Aphasia—the acquired loss of language ability—is one of the most common and debilitating cognitive consequences of stroke, affecting approximately 20–40% of stroke survivors and impacting approximately one million individuals in the US alone (Siirtola et al., 1977; Pedersen et al., 1995; Berthier, 2005). The stroke incidence in China is about 205–584 per ten thousand, and includes one third of patients with speech disorders (Tsai et al., 2013). The incidence of aphasia in the elderly population is increasing dramatically in China (Tsai et al., 2013), and motor aphasia is one of the most common types of post-stroke aphasia. Patients with Broca's aphasia usually retain greater comprehension *vs.* expressive capacity, which decreases their ability to communicate with others (Hamilton, 2016). This, along with a high degree of dependence in daily life can lead to loneliness, passiveness, and depression (Hamilton, 2016), as well as further serious psychological problems. Thus, aphasia represents a heavy burden to families and society.

Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have been widely used to explore brain functional networks (Bottini et al., 1994; Jang and Jang, 2016; Park and Park, 2016). For instance, these tools have been used to explore the role of the right hemisphere in language in healthy and aphasia groups (Bottini et al., 1994). Data from follow-up studies of aphasia patients suggest that dynamic changes can occur in the bilateral hemispheres, such as spontaneous recovery of language (Müller et al., 1999; Saur et al., 2006; Winhuisen et al., 2007), as well as functional changes in the brain following language therapy at specific recovery stages (Rochon et al., 2010; Szaflarski et al., 2011; Mattioli et al., 2014). These data highlight the involvement of the right hemisphere in post-stroke language function. However, evidence from neuroimaging studies has been somewhat inconsistent (Finger et al., 2003; Hillis, 2007), especially with regard to (1) aphasia type, (2) fMRI task, and (3) changes during aphasia recovery. With regard to aphasia type, Thomas et al. (1997) showed that the activation pattern in the bilateral hemisphere in indi-

viduals with Broca's aphasia tended to shift towards the left hemisphere a few months after onset, while patients with Wernicke's aphasia did not show this tendency. With regard to fMRI task, Hamilton et al. (2011) investigated the relationship between bilateral hemisphere activation in aphasia patients during language tasks by calculating 240 activation foci from 104 aphasia patients and 197 foci from 129 controls using fMRI and PET. They found that activation in the right inferior frontal gyrus was reliably associated with language production tasks, while that in the right middle temporal gyrus was associated with comprehension tasks. Finally, some studies have revealed inconsistencies in the development from the acute to chronic phase of aphasia. Saur et al. (2006) used fMRI with a parallel auditory comprehension task to assess changes as participants progressed from the acute to the chronic stage of aphasia. In the acute phase (mean: 1.8 days), they observed weak activation in the perilesional structures in the left hemisphere. In the subacute phase (mean: 12.1 days), they found that activation of the bilateral hemispheres corresponded with the peak values in the right Broca-homologues. In the chronic phase (mean: 321 days), shifting of the activation peak back to the left hemisphere was associated with further language improvement. A recent review by Anglade et al. (2014) described neuroplastic reorganization in the bilateral hemispheres of aphasia patients in different stages, suggesting that activation in the left and right hemispheres varies with time from onset. Non-invasive stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have enabled further exploration of the mechanisms underlying recovery in the left and right hemispheres. Low-frequency rTMS has been used to inhibit the right-hemisphere homotopic language area in a patient with chronic aphasia, improving language ability (Chieffo et al., 2014). Additionally, a study using longitudinal rTMS combined with PET showed that language-related brain areas in the left hemisphere are essential during aphasia recovery; the right hemisphere is also activated, but it is not critical to promote language improvement (Winhuisen et al., 2007). However, the role of the bilateral hemispheres during aphasia recovery is still unclear. Naming, as an essential function in daily life, is reported to be the earliest spontaneous post-stroke language function. Thus, naming may be a useful tool for examining activation in language-related areas in patients with subacute Broca's aphasia.

Although many treatment techniques have been used to treat individuals with Broca's aphasia, including behaviorally-based speech and language therapies and non-invasive brain stimulation, it is difficult for these patients to recover speech-language function (Hamilton et al., 2011; Koyuncu et al., 2016). A more comprehensive understanding of the mechanisms of aphasia will thus be useful in developing more efficacious treatment options. In this study, we used blood oxygenation level-dependent fMRI to evaluate bilateral cortex activation in patients with Broca's aphasia 1 to 3 months after stroke.

Participants and Methods

Participants

Ten patients with aphasia (three females and seven males) were recruited from the Department of Rehabilitation at the Third Affiliated Hospital of Sun Yat-sen University in China between December 2013 and April 2016. The control group contained ten healthy volunteers (three females and seven males). The two groups were matched in terms of age (aphasia group: 40–70 years, mean \pm SD: 55.89 \pm 13.37 years; control group: 45–70 years, 55.89 \pm 11.78 years) and years of education (aphasia group: 11.9 \pm 1.4 years; control group: 12.2 \pm 0.9 years). The demographic data from the two groups are presented in **Table 1**.

In this study, we only included individuals presenting with stroke-induced aphasia who had no previous history of aphasia and no prior history of speech, hearing, or neurological disorders. At enrollment, the duration of onset was 1–3 months post-stroke. The ten patients were diagnosed with Broca's aphasia *via* the Western Aphasia Battery (Wang, 1997a, b). We established that they had no severe cognitive impairments *via* the Mini Mental State Examination (Cockrell and Folstein, 1988) (22.7 \pm 1.3 scores). All participants met the diagnostic criteria for cerebral infarction or cerebral hemorrhage (Chinese Neurosurgical Society, 1996), as established at a national cerebrovascular conference. Single unilateral left-hemisphere lesion was confirmed by head computed tomography (CT) or (MRI) imaging. The exclusion criteria for aphasia patients included vision and hearing disabilities, MRI contraindication, dysarthria, and stuttering before onset. We also excluded participants with lesions involving bilateral hemispheres and individuals who were not cognitively fit to complete the study.

The normal control group contained age-matched healthy adults without vision or hearing disabilities and without MRI contraindication.

The two groups comprised exclusively right handed native Mandarin speakers (Li, 1983). The study protocol was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University in China (No. [2015]2-78). All participants provided written informed consent prior to engaging in the study.

Stimuli

We extracted a set of black and white line drawings from the normalized data set used by Snodgrass and Vanderwart (Snodgrass and Vanderwart, 1980). We randomly chose 27 images (**Supplementary Figure 1**), including animals and common objects, for use in the picture-naming task. Before the scanning sessions, we used a different set of pictures to train the participants in the procedure and ensure that they understood the fMRI paradigm.

Picture-naming task

The experiment had a block design such that a 30-second task (overt picture-naming) period alternated with a 30-second rest (fixation) period. We used E-prime software to present the stimuli on a computer screen (Psychology

Software Tools, Inc., Pittsburgh, PA, USA). Three trials comprised a session, and there were three sessions in total. Each session lasted 3 minutes and 6 seconds. Between each session, a fixation cross was shown in the center of the screen for 6 seconds. In the picture-naming condition, a picture cue was shown for 2 seconds. Afterwards, a fixation cross was presented in the center of the screen for 7 seconds, during which the participants were asked to name the object depicted by the picture. After a response had been made, a blank screen was presented for 1 second. This acted as a buffer between adjacent target pictures. The task sequence is shown in **Figure 1**.

fMRI image acquisition

We used a GE Signa 1.5 Tesla scanner (version 5.6) (General Electric Company, Milwaukee, WI, USA) with a gradient Echo Planar Imaging sequence to acquire image data. Scanning parameters for conventional T1-weighted imaging, transverse sections: reaction time = 530 ms, echo time = 13 ms. Scanning parameters for T2-weighted imaging, transverse sections: reaction time = 4,500 ms, echo time = 102 ms. FLAIR sequence scanning parameters: reaction time = 8,800 ms, echo time = 120 ms, flip angle = 90°. Slice thickness of scanning = 5 mm, slice gap = 1 mm, field of view = 240 \times 240 mm, matrix = 320 \times 256. Transverse sections were based on the orbitomeatal line, with a total of 12 slices. Coronal sections were vertical to the orbitomeatal line, with a total of 9 slices. 3D image scanning parameters: fast spoiled gradient recalled sequence, echo time = 1.8 ms, reaction time = 8.5 ms, flip angle = 15°, field of view = 240 \times 240 mm, matrix = 256 \times 192, slice thickness = 1.4 mm. For BOLD-fMRI images, we used a gradient recalled echo-echo planar imaging sequence, with a scanning time of 186 seconds. Scanning parameters were: reaction time = 3,000 ms, echo time = 40 ms, flip angle = 60°, field of view = 240 \times 240 mm, matrix = 64 \times 64, slice thickness = 7 mm, slice gap = 2 mm. Scan range: AC-PC line as baseline, for a total of 12 slices. The top edge included the frontal lobe and parietal lobe. The bottom edge was located around the tentorium cerebelli.

Image postprocessing

Brain structure and functional images were produced using Viewforum (General Electric Company, Milwaukee, WI, USA). The DICOM images were transformed to img. We used SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK) for data analysis. We used the Talairach Client (www.talairach.org, the University of Texas Health Sciences Center San Antonio (UTHSCSA), San Antonio, TX, USA) to transform the active brain area into Talairach coordinates. Finally, we located the Brodmann (BA) areas.

Assignment of brain activity

We measured the volume and intensity of the active brain regions. We used group analysis methods to calculate activation at a group level. In our individual level analysis, the threshold of brain activity was $P < 0.005$, and the activity volume was set at 10 voxels. The level result in each group

was analyzed *via* a one-sample *t*-test. We used two-sample *t*-tests ($P < 0.05$, voxel = 10) to compare activities in the two groups.

Results

Brain activation in normal control participants in the picture-naming task

When comparing the picture-naming condition with the fixation condition (task > baseline) in normal participants at an individual level, we found brain activation predominantly in the left hemisphere, and both the left and right inferior frontal gyri were activated in all participants. In addition, the left middle, superior frontal, and superior temporal gyri, as well as the right superior temporal gyrus, were activated in 90% of participants. Comparing these conditions (task > baseline) on a group level, multiple brain areas were engaged during the picture-naming process. We found substantially stronger activity in the left compared with the right hemisphere. Activated regions included the bilateral inferior frontal and superior temporal gyri, insula, basal ganglia, left anterior central gyrus, thalamus, and superior frontal, middle temporal, and middle frontal gyri (Figure 2 and Table 2).

Brain activation in Broca's aphasia patients in the picture-naming task

Whole-brain analyses of patients on an individual level revealed: (1) Activation in the visual processing cortices related to visual perception in both the left and right hemispheres (middle frontal, middle temporal, lingualis, and fusiform gyri) in all patients. (2) Areas activated during picture-naming were located in the left inferior frontal gyrus (*i.e.*, Brodmann area 44), right inferior frontal gyrus, and bilateral superior temporal gyrus. (3) All patients showed less activation volume in the left compared with the right hemisphere, although this was not significant. Group level analysis showed a significant decrease in brain activation (mainly in the left basal ganglia and insula) in the left hemisphere compared with controls. The activated brain areas in the right hemisphere were the superior temporal, fusiform, superior frontal, middle temporal, parahippocampal, and middle frontal gyri. The activated bilateral areas are presented in Figure 3 and Table 2.

Activation in Broca's aphasia vs. control group

When comparing the activated areas in the two groups, we found that, in the control group, the left hemisphere was dominant during the picture-naming process, specifically the anterior and posterior frontal area. Compared with the control group, we mainly observed a decrease in the left hemisphere, including the left posterior central, middle frontal, inferior frontal, and superior frontal gyri in the patient group. Simultaneously, the right inferior frontal and middle frontal gyri were more strongly activated in the controls compared with the patients. For the patients, the bilateral temporal-parietal lobes played an important role in the picture-naming task (Table 2).

Activation volume of left and right hemispheres

Comparing the activated volume between the aphasia and

control groups revealed that the activated volume was significantly less in the right hemisphere than in the left hemisphere ($t = 2.715$, $P = 0.024 < 0.05$). No statistically significant difference was found in the aphasia group ($t = -1.975$, $P = 0.098 > 0.05$). The activated volume in the ipsilateral left hemisphere was significantly less in the aphasia group than in the control group ($t = 3.583$, $P = 0.004 < 0.01$). We did not find any differences between the two groups in terms of the activated volume of the right hemisphere ($t = 1.931$, $P = 0.070 > 0.05$) (Table 3).

Discussion

Language region changes induced by stroke

In many clinical cases, post-stroke aphasia is associated with infarction near the left middle cerebral artery. Indeed, the bulk of behavioral and imaging aphasia studies have examined patients with language deficits that are attributable to lesions in this vascular territory. The notion that language is represented in the brain by a network of functionally distinct interacting processing centers dates back to the 19th century with the pioneering discoveries of Broca and Wernicker. Initially, the language network was envisioned as comprising a simple expression area and an understanding area. For most healthy individuals, language is predominantly but not exclusively represented in a network of regions in the left hemisphere surrounding Broca's area and Wernicke's area. The idea that lesions leading to aphasia are located in the left side of the brain corresponded with this classical model. Strokes that result in aphasia typically damage this left perisylvian network (the regions around fissure of Sylvius). Current models of language representation also emphasize the role of dorsal and ventral processing streams, and indicate that post-stroke aphasia can result from damage to either or both stream.

Advances in functional neuroimaging have yielded a number of insights into the changes that occur in brain activity during language tasks in patients with post-stroke aphasia. Stroke recovery mechanisms mainly involve neural plasticity, *i.e.*, the activation of regions peripheral to the lesion area or the contralateral brain regions. Similarly, post-stroke aphasia recovery mechanisms involve neural plasticity. Most studies investigating language reorganization in patients with large perinatal vascular lesions have suggested that the right hemisphere network mirrors that of the normal left hemisphere, both in the classical language areas (Staudt et al., 2002; Tillema et al., 2008) and other regions, such as the cerebellum (Lidzba et al., 2008). However, increased activity in peripheral regions has been noted in aphasia patients with small lesions. Interestingly, a study (Sebastian et al., 2016) found that improvements in naming accuracy from the acute stage to the chronic stage of aphasia following stroke corresponded with increased connectivity within and between language regions in the left and right hemispheres. These findings point to the importance of reorganizing patterns of brain activity and connectivity after stroke to make relevant connections in the language network.

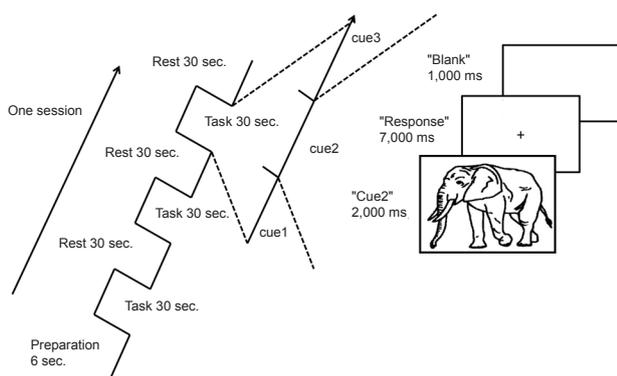


Figure 1 Timeline of task design in one session.

Each session contained three trials. Each trial comprised 30 sec of the picture-naming task and 30 sec of rest. In each task condition, three picture cues were presented one at a time. A 7-sec fixation was shown after the image, and the participants were asked to name the object during this period. At the beginning of each trial, a 6 sec fixation cross was shown. sec: Seconds.

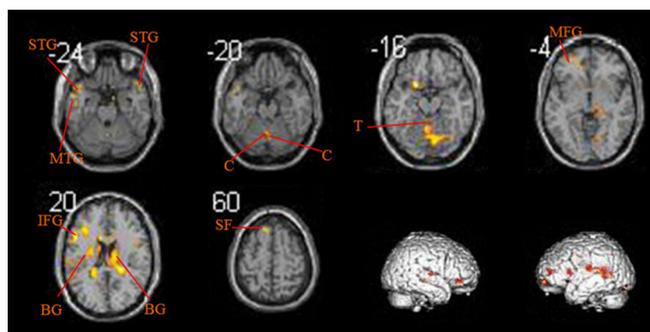


Figure 2 Activation map of the whole-brain analyses related to the main task effect by functional magnetic resonance imaging (task > baseline) in control group.

Activations denoted in yellow/red represent brain regions that were positively correlated with the picture-naming task. IFG: inferior frontal gyrus; MFG: middle frontal gyrus; SFG: superior frontal gyrus; STG: superior temporal gyrus; MTG: middle temporal gyrus; T: thalamus; BG: basal ganglia; C: cerebellum.

How and where brain regions involved in language transfer may depend in part on the stage of neural development at the time of injury after stroke. The mechanisms by which language reorganizes are still not well understood.

Findings of the present study

In this study, we examined the topography of language reorganization by studying healthy adults and patients with Broca’s aphasia. We found differences in the features of brain activation in the two groups.

Language-related brain activation in healthy controls

Naming is an important mode of expression. Picture-naming is commonly used in fMRI studies. Picture-naming requires the perception of the object depicted in the picture, as well as the extraction of information about the object, including: (1) visual analysis of the object; (2) matching the results of the visual analysis with the structural features of objects stored in memory; (3) search for a semantic description of the object, followed by speech coding; (4) speaking the name of the

Table 1 Demographic data from patients with Broca’s aphasia and normal controls

	Aphasia group	Control group
<i>n</i>	10	10
Gender (male/female, <i>n</i>)	7/3	7/3
Age (year)	55.89±13.37(40–70)	55.89±11.78(45–70)
Educational level (year)	11.9±1.4	12.2±0.9

Age and educational level are expressed as the mean ± SD.

Table 3 Activated volume in bilateral hemispheres of both groups

Group	Left hemisphere (voxels)	Right hemisphere (voxels)
Control	1,006.00±635.62**	248.33±197.07#
Aphasia	754.60±423.80	414.33±332.23

Data are expressed as the mean ± SD, with 10 participants in each group. ***P* < 0.01, vs. aphasia group (two-sample *t*-test); #*P* < 0.05, vs. left hemisphere (one-sample *t*-test).

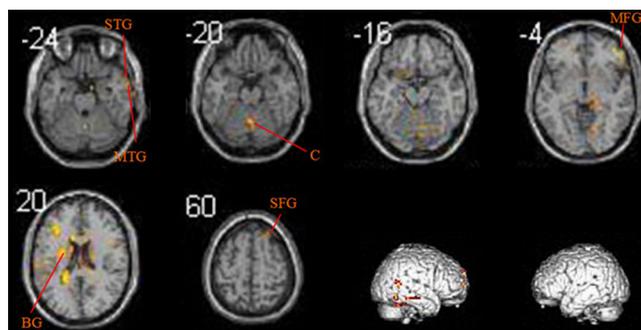


Figure 3 Activation map of the whole-brain analyses related to the main task effect by fMRI (task > baseline) in the aphasia group.

Activations denoted in yellow/red represent brain regions that were positively correlated with the picture-naming task. MFG: Middle frontal gyrus; SFG: superior frontal gyrus; STG: superior temporal gyrus; MTG: middle temporal gyrus; BG: basal ganglia; C: cerebellum.

object under the control of motor voice-related brain areas (Menke et al., 2009).

Cabeza and Nyberg (2000) reported that the visual process used during picture-naming is related to the left middle frontal gyrus, bilateral middle temporal gyrus, and the lower-middle part of the occipitotemporal cortex. The middle frontal, temporalis medius, and fusiform gyri, as well as the occipital lobe, are engaged during visual processing of an object. Among these, the left fusiform gyrus may participate in image recognition (Xue et al., 2006). Broca’s area is known for its input and output functions. Broca’s area covers not only the left pars opercularis gyri, but also the middle frontal and anterior central gyri (Catani et al., 2005, 2007). Previously, we found significant activation in the left inferior frontal, left middle frontal, left anterior central, and left superior frontal gyri during picture-naming in healthy adults (Xie, 2011), which supports the viewpoint that Broca’s area, along with multiple frontal areas, is engaged in phonologic and semantic processes.

fMRI studies have shown that the bilateral superior temporal cortex is activated during phoneme extraction.

Table 2 Activation during picture-naming task in aphasia and control groups (task > baseline)

Regions (Brodmann area)	Side	MNI coordinates			t value	Cluster size (k)
		x	y	z		
Control group						
Inferior frontal gyrus (45)	L	-57	12	21	6.17	59
Superior temporal gyrus (41)	L	-51	-30	9	5.76	42
Precentral gyrus (43)	L	-42	-3	33	6.49	41
Insular (13)	L	-39	-27	3	8.82	32
Thalamus	L	-21	-27	0	4.89	27
Basal ganglia	L	-21	12	-12	7.62	27
Superior frontal gyrus (11)	L	-18	60	-9	10.11	24
Middle temporal gyrus (22)	L	-63	-42	3	4.7	14
Middle frontal gyrus (46)	L	-36	39	3	3.72	10
Inferior frontal gyrus (9)	R	42	6	27	7.32	64
Basal ganglia	R	18	15	0	5.19	42
Insular	R	30	21	3	3.99	25
Superior temporal gyrus (21, 41)	R	63	-15	-3	4.61	10
Aphasia group						
Basal ganglia	L	-27	27	3	5.43	26
Insular (13)	L	-27	27	3	4.55	14
Superior temporal gyrus (22)	R	54	-51	12	6.12	31
Fusiform (37)	R	39	-54	-15	5.87	28
Superior frontal gyrus (9)	R	6	54	33	4.36	16
Middle temporal gyrus (20, 21)	R	54	-36	-15	6.54	13
Middle frontal gyrus (10)	R	24	-75	36	6.03	12
Patients < control						
Posterior central gyrus (3, 43, 40)	L	-60	-18	33	4.3	529
Middle frontal gyrus (9, 10, 46)	L	-33	30	21	3.07	76
Inferior frontal gyrus (47, 9, 45)	L	-21	12	-15	3.61	62
Superior frontal gyrus (10, 11)	L	-27	51	-3	2.61	27
Inferior frontal gyrus (9)	R	42	6	27	2.46	20
Middle frontal gyrus (6)	R	27	3	39	1.9	19
Patients > control						
Superior parietal lobule (7)	L	-30	-54	45	4.12	112
Cuneus (7)	L	-18	-78	30	2.77	111
Thalamus	L	0	-12	-3	1.99	19
Inferior Temporal Gyrus (20)	L	-51	-27	-15	2.3	13
Precuneus (7, 31, 39)	R	12	-72	39	3.38	86
Superior parietal lobule (7)	R	30	-54	42	2.46	55
Inferior parietal lobule (40)	R	36	-48	36	2.09	54
Superior temporal gyrus (38)	R	48	15	-21	2.73	16

Multiple comparisons: Family-wise error (FWE) cluster-corrected at $P < 0.05$ determined by Monte Carlo simulation.

Additionally, the left superior temporal cortex is implicated in phonological function. The left middle temporal gyrus and inferior temporal gyrus are correlated with semantic processes, and are connected *via* Brodmann area 37 (Xie, 2011). In this study, the left superior temporal gyrus, inferior parietal lobule, and middle temporal gyrus were activated in most of the healthy control participants. These areas might be involved in phonologic coding and semantic extraction.

The main goal of this study was to investigate the pattern of neural change in sub-stage aphasia patients *via* fMRI, as support for the subacute stage of aphasia post-stroke (Saur et al., 2006). The right hemisphere takes part in the language network in the subacute stage. As a result of this study, we

obtained four main results: (1) the right hemisphere was more strongly activated during the picture-naming process in normal participants; (2) the right hemisphere was engaged in the picture-naming process in normal participants; (3) activation decreased significantly in the left hemisphere, rather than the right hemisphere in Broca's aphasia patients; (4) weak connections were present among visual perception areas in Broca's aphasia patients when processing the picture-naming task.

Roles of the right hemisphere in the picture-naming process

The role of the right hemisphere in language processing has been a subject of intense focus in recent years. Many studies

have shown that the right hemisphere can process language (Crosson et al., 2005), while others have argued that the right hemisphere does not engage in the language process, as the right hemisphere does not appear to contribute to speech and language recovery in isolation from the left hemisphere (Blank et al., 2003; Naeser et al., 2004). Furthermore, some studies have demonstrated that parts of the right hemisphere activate, while others inhibit language recovery at an individual level (Benvenuti et al., 2012). In our study, the right hemisphere was activated in all 10 normal participants, although the activation intensity was weaker than that in the left hemisphere. This result indicates that the left hemisphere is dominant with respect to speech and language function in the normal population. Meanwhile, we found activity in the right hemisphere in the region that mirrors Broca's area. Noppeney et al. (2005) reported similar findings. Cogan et al. (2014) recorded brain activity while participants performed a word repetition task. Their results showed that the bilateral brain, including the bilateral inferior frontal gyrus, supramarginal gyrus, superior temporal gyrus, middle temporal gyrus, somatosensory cortex, motor cortex, and premotor area, exhibited a higher level of brain activation during language sensory-motor transformation. However, the connection between the bilateral hemisphere and the relationship between the right hemisphere and language processes will benefit from further investigation.

In sum, the language functional area is a whole brain network, where, in addition to Broca's area, the left superior frontal gyrus, middle frontal gyrus, inferior parietal lobule, right inferior frontal gyrus, superior temporal gyrus, and middle temporal gyrus play a role in language expression.

Role of the right hemisphere in picture-naming in aphasia patients

We found that activated brain areas in aphasia patients were reduced significantly compared with healthy participants, which is consistent with a previous study (Menke et al., 2009). Our data showed that the visual processing cortices were activated in all participants, such as the fourth visual cortex (BA17–20), left middle frontal gyrus (BA9), lingual gyrus (BA19), and fusiform gyrus (BA37). Nevertheless, the intensity of activation was lower than that in normal participants. This indicates that aphasia patients may have weak connections among visual perception areas that process object information. For instance, they may be able to obtain the shape of an object visually, but may find it difficult to match the specific information stored in the brain with the object (Warrington and James, 1988).

Aphasia is caused by brain lesions that directly or indirectly hinder normal language function (Price et al., 2001). The speech deficit caused by a specific lesion in Broca's area is mild and recovery may be faster than that for the lesions seen in our patient group. Indeed, the lesions leading to a severe speech deficit generally include, in addition to Broca's area (Mohr et al., 1978), the left pars opercularis, left middle

frontal gyrus, and left central motor cortex (Catani et al., 2005, 2007). In our study, 10 patients in the aphasia group were diagnosed as having moderate to severe aphasia, and they experienced multiple brain lesions including Broca's area. Thus, we were not surprised to find that bilateral brain activated volumes were lower in patients compared with controls. We found a significant decrease in volume in the left hemisphere of patients, but not in the right hemisphere. The activated volume in the right hemisphere was reduced in aphasia patients, although this was not statistically significant. Specifically, we found decreased activation in the inferior frontal gyrus, parahippocampal gyrus, and middle frontal gyrus in the right hemisphere. However, we observed normal and increased activation in other right hemisphere brain areas. Thus, language-related areas in the right hemisphere appear to be affected by distant effects of left hemisphere lesions.

Some studies have reported that the right inferior frontal gyrus is strongly activated in aphasia patients. In this population, language function is improved when the right inferior frontal gyrus is inhibited (Naeser et al., 2004). However, right hemisphere activation could promote recovery (Blank et al., 2003). Interestingly, previous studies have not shown decreased activation in the right inferior frontal gyrus in early stage aphasia patients compared with control participants. Thus, this finding is not consistent with previous results that focus on chronic aphasia patients rather than those in the early stages. This finding suggests that the right inferior frontal gyrus plays different roles during language recovery. One of the possible mechanisms is the involvement of the right inferior frontal gyrus in normal language processes. The distant effect of the lesion would decrease activation in the early stage of recovery. As the recovery process continues, the right inferior frontal gyrus compensates for the original language function. In contrast, in the chronic phase, activation in this region would be too high to inhibit lesion recovery in the left hemisphere through the corpus callosum. This is a valuable question for future investigations with increased samples and a longitudinal design, which could evaluate the mechanisms of reconstruction of functional paths in different recovery phases.

Limitations

There are a number of potential limitations that affect the interpretation of our study. First, we found a high degree of consistency in the activated brain regions in the healthy control group. However, the activated brain regions in the patient groups varied considerably. This is likely because that degree of damage varied among individuals. Additionally, the patients underwent the experiment at different time points post-stroke (1–3 months post stroke). Thus, they were likely at different points in the recovery process, which have different brain activation features. Second, all patients were right handed, so our findings about brain activation features may only be applicable to right-handed individuals with Broca's aphasia. How the brain changes after stroke in left-handed individuals with Broca's aphasia

is a topic for future study. Last, due to limited performance data collected during scanning, it was difficult to completely rule out the effect of variable task performance on the final results.

Implications of the current literature for further research regarding mechanisms of plasticity and reorganization

In this study, we found that individuals with subacute Broca's aphasia exhibited a decrease in left hemisphere and right inferior frontal gyrus activation during a picture-naming task. Additionally, we observed relative increases in certain activated brain regions in the right hemisphere in the patient population. Our findings are consistent with a comprehensive neuropsychological model of recovery mechanisms underlying the progression of aphasia. The reorganization that occurs in the early stages of Broca's aphasia may be different from that in chronic aphasia. Our data indicate that future research examining temporal changes during aphasia recovery may be beneficial, particularly for guiding non-invasive stimulation therapies (rTMS, tDCS), which are based on brain activation patterns and corresponding functions, in the early stages of post-stroke aphasia.

Conclusions

To the best of our knowledge, this is the first study to use functional imaging to examine brain activation in patients with subacute Broca's aphasia during a picture-naming task. Our results show that language expression is associated with multiple brain areas. The right hemisphere is engaged in normal speech generation. We found that brain lesion and associated remote effects led to a decrease in activity in language functional areas in post-stroke aphasia patients. Particularly, the left hemisphere and right inferior frontal gyrus showed a clear decrease in activation. However, activation in sections of the right hemisphere increased in this population, compared with healthy controls. The right inferior frontal gyrus plays multiple roles in language recovery during different periods in post-stroke aphasia. Further investigation regarding the mechanisms of aphasia will likely lead to improved treatments options, thus reducing family and social burden.

Declaration of patient consent: *The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.*

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