Neural Plasticity

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Lead Guest Editor: Cynthia K. Thompson
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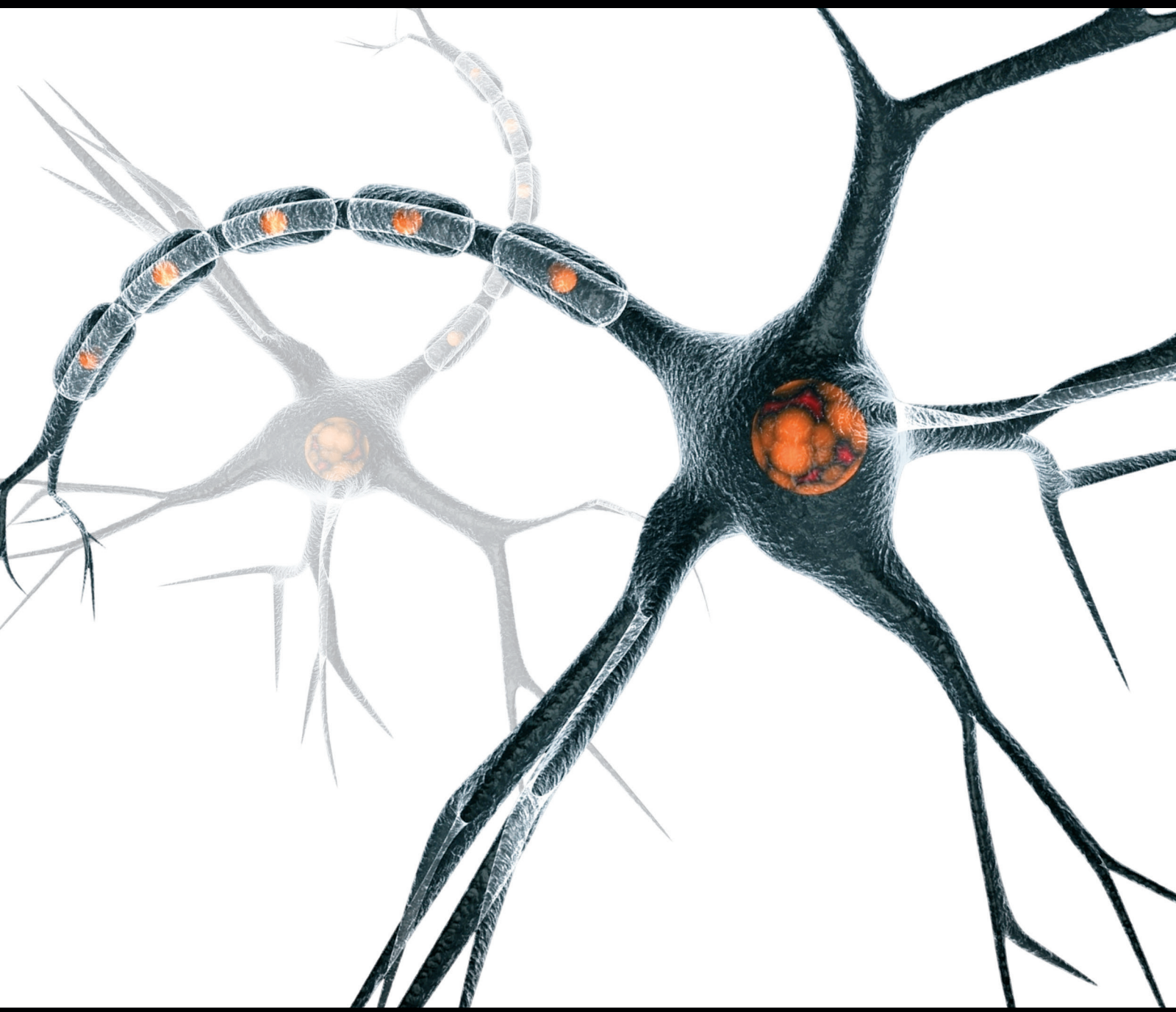

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Contents

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Research Article

Right Hemisphere Grey Matter Volume and Language Functions in Stroke Aphasia

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The role of the right hemisphere (RH) in recovery from aphasia is incompletely understood. The present study quantified RH grey matter (GM) volume in individuals with chronic stroke-induced aphasia and cognitively healthy people using voxel-based morphometry. We compared group differences in GM volume in the entire RH and in RH regions-of-interest. Given that lesion site is a critical source of heterogeneity associated with poststroke language ability, we used voxel-based lesion symptom mapping (VLSM) to examine the relation between lesion site and language performance in the aphasic participants. Finally, using results derived from the VLSM as a covariate, we evaluated the relation between GM volume in the RH and language ability across domains, including comprehension and production processes both at the word and sentence levels and across spoken and written modalities. Between-subject comparisons showed that GM volume in the RH SMA was reduced in the aphasic group compared to the healthy controls. We also found that, for the aphasic group, increased RH volume in the MTG and the SMA was associated with better language comprehension and production scores, respectively. These data suggest that the RH may support functions previously performed by LH regions and have important implications for understanding poststroke reorganization.

1. Introduction

Research shows that undamaged tissue in both the contralesional (usually right) and ipsilesional (left) hemispheres of the brain is recruited to support recovery in stroke-induced aphasia (see reviews by [1–7]). Neuroimaging studies show that in early stages of recovery, the right hemisphere (RH) is active during language tasks; however, a shift in activation to the left hemisphere (LH) regions has been found across tasks, including word repetition, rhyme judgment, auditory word/sentence comprehension, semantic association, and reading [8–12]. Functional neuroimaging studies conducted with chronic aphasic individuals also confirm a primary role of ipsilesional tissue in recovery, finding significant correlations between recovery of language function and activation in the LH during confrontation-naming tasks [13, 14].

Other studies, however, have found RH recruitment, even in late stages of recovery [15–23]. Patients studied by Musso and coworkers [18] with lesions in the LH superior temporal gyrus (STG) showed activation in the RH STG during a sentence comprehension task, which positively correlated with off-line performance on a measure of auditory verbal comprehension. Similarly, Perani et al. [20] reported patients with damage to the LH inferior frontal gyrus (IFG)

who showed activation of the RH homologue of this region when performing a verbal fluency task. In keeping with these findings, a recent meta-analysis of 12 neuroimaging studies in chronic stroke-induced aphasia [24] showed that, although aphasic individuals evince activation in the LH (i.e., the IFG and middle temporal gyrus (MTG), similar to healthy controls, as well as the left middle frontal gyrus (MFG) and insula), they also show the right hemisphere activation across a variety of language tasks (i.e., in the postcentral gyrus (PCG) and MTG).

Evidence of RH recruitment to support language recovery also comes from studies examining treatment-induced neural plasticity in chronic aphasia, showing increased RH activation associated with treatment gains [17, 25–31]. Recently, Kiran et al. [29] examined neural activation and effective connectivity within the left language network and right homologous regions following language treatment in eight chronic aphasic individuals. The results showed posttreatment increases in neural activity, bilaterally, in picture naming and semantic feature verification tasks. Importantly, effective connectivity maps in individuals with aphasia revealed that the LH IFG and the connection between the RH IFG and the RH MFG, respectively, most consistently modulated as a function of rehabilitation. Several other studies have shown similar patterns of posttreatment increases in the RH regions on picture naming (see [13, 32]) as well as semantic (compared to orthographic and phonological) processing tasks [33, 34]. Thompson et al. [35] also found a bilateral posttreatment upregulation of activation in the temporoparietal region in six chronic aphasic individuals who showed treatment-induced improvement in syntactic processing. These data indicate that the RH regions are engaged in language processing following damage to LH language networks. However, whether or if engagement of the RH is associated with maximally effective language processing has been questioned.

Some research suggests that rather than benefitting language processing, RH recruitment may be maladaptive and reflect inefficient language processing, finding, for example, either no association between increased RH activation and performance on a verb generation task [36] or a correlation between RH frontal activation and production of inaccurate responses on a picture-naming task [37]. An inefficient/maladaptive role of the RH has also been suggested by brain stimulation studies, showing that inhibitory repetitive transcranial magnetic stimulation (rTMS) applied to the RH regions (i.e., the IFG) improves language function ([38–41]; also see [6] for review), putatively secondary to inhibition of the maladaptive RH regions, which thereby facilitates LH processing (but see [42–44] for evidence suggesting that excitatory stimulation directed to the RH positively impacts language performance in chronic aphasic individuals). These and other studies have led to the assertion that recruitment of ipsilesional, rather than contralesional, tissue into the language network may result in greater language gains. Some recent neuroimaging studies also suggest that the contribution of the RH to recovery from aphasia may not reflect restoration of language processes, but rather the engagement of domain-general networks responsible for attention and cognitive control [45, 46], or processing of perceptual aspects of verbal stimuli [47].

One way to estimate the functionality of cortical tissue is to examine the density of grey matter (GM) tissue, with the assumption that greater GM volume is associated with greater functionality and lesser (i.e., cortical atrophy) associated with decreased function [48, 49]. Studies on the recovery of motor function in chronic stroke have found both increases and decreases in GM volume in motor regions of the brain in patients following recovery (versus healthy controls). Zhang et al. [50] examined 26 hemiparetic individuals (with partial or complete recovery) and 25 age-matched controls on motor tasks before and after physical therapy. They found reduced cortical volume in the ipsilesional motor region for all patients compared to controls with no GM changes in contralesional motor areas. However, in another study, Gauthier et al. [51] found increased GM volume in RH motor regions, homologous to lesioned tissue in the LH, associated with recovery of function in 85 individuals with chronic stroke (also see [52]).

Few studies have examined GM volume in patients with cognitive impairments resulting from stroke. Stebbins et al. [53], using voxel-based morphometry (VBM, [54]), reported significant GM volume reductions (mostly in the thalamus) for stroke patients ($n = 91$) with cognitive impairment (compared to those without). In another study, Xing et al. [55] reported increased GM volume (compared to healthy, unimpaired control participants) in the right temporoparietal cortex (i.e., the supramarginal gyrus (SMG) and STG) in individuals with chronic stroke-induced aphasia. They further showed that GM volume was positively associated with overall aphasia severity as well as performance on production subtests of the *Western Aphasia Battery-Revised* (WAB-R; [56]) (i.e., spontaneous speech, repetition, and naming). Although the study was not longitudinal, the authors interpreted the results as suggesting a compensatory role of the right posterior regions in chronic aphasia. In addition, by partialing out participant variables (e.g., age, gender, level of education, and handedness) as well as the effect of lesion volume on language performance, the authors found the right hypertrophic temporoparietal regions, suggesting that these regions play a role in language recovery.

The present study examined RH GM volume in individuals with chronic stroke-induced aphasia and cognitively healthy people using voxel-based morphometry (VBM; [54]), a voxel-wise neuroimaging technique used for measuring variables associated with brain anatomy (e.g., GM volume). We compared group differences (healthy versus aphasic participants) in GM volume in the entire RH and in RH regions-of-interest (ROIs) where aphasic individuals exhibited a significant relation between GM volume and language performance. Given that lesion site is a critical source of heterogeneity associated with poststroke language ability, we then used voxel-based lesion symptom mapping (VLSM; [55]) to examine the relation between lesion site and language performance in the aphasic participants. Finally, using results derived from the VLSM analysis as a covariate (following Xing et al. [56]), we evaluated the relation between GM volume in the RH and language scores

Table 1: Demographic data for aphasic and age-matched healthy participants.

	N	Age (yrs)	Gender	Education (yrs)	Time poststroke (months)
AM controls	40	58.9 (±11.8)	22F; 18M	15.6 (±2.4)	N/A
AM NU	11	54.8 (±8.2)	5F; 6M	16.4 (±1.6)	
AM BU	17	58.2 (±13.4)	8F; 9M	15.4 (±2.8)	
AM JHU	12	63.7 (±11.7)	9F; 3M	15.0 (±2.3)	
All aphasics	40	59.4 (±12.4)	14F; 26M	16.1 (±2.2)	57.2 (±52.3)
NU	11	49.0 (±8.0)	4F; 7M	16.9 (±2.1)	49.3 (±32.5)
BU	17	62.1 (±12.2)	5F; 12M	15.0 (±2.3)	44.3 (±40.7)
JHU	12	65.1 (±10.6)	5F; 7M	16.8 (±1.5)	82.7 (±72.7)

across domains, including comprehension and production processes both at the word and sentence level and across spoken and written modalities.

In line with the aforementioned studies showing structural changes after LH stroke, we expected differences in GM volume in the RH in the aphasic participants compared to healthy controls (i.e., either decreased or increased volumes). We also predicted that if the RH supports language function, then a positive correlation between performance on language tasks and RH GM volume would be observed, independently of differences in lesion volume. Conversely, if the RH does not support language functions, we expected no correlation between language performance and RH GM volume in the group of aphasic participants.

2. Method

2.1. Participants. Forty participants with aphasia (14 female) resulting from a single-left hemisphere stroke and 40 cognitively healthy age-matched (AM) controls (18 female) were recruited for the study from three research sites: Northwestern (NU), Boston (BU and MGH), and Johns Hopkins (JHU) Universities. All were native English speakers, passed a pure-tone audiometric screening and evinced normal or corrected-to-normal vision (self-reported). All participants were right handed, with the exception of one aphasic speaker who was left handed prior to the stroke that affected his left hemisphere. Participants at each site were recruited as part of a large-scale study examining treatment-induced changes in brain function and, hence, were selected for specific language-deficit patterns: agrammatism (NU), anomia (BU, MGH), and dysgraphia (JHU).

Across sites, the aphasic and control groups were matched for age (t (77.9) = −0.166; $p > 0.05$), ranging from 35 to 81 (59.4 ± 12.4 yrs) and 24–80 (58.9 ± 11.8 yrs) for the two participant groups, respectively, and years of education (aphasic group mean = 16.1 ± 2.2; control group mean = 15.6 ± 2.4 (t (71.5) = −0.936; $p > 0.05$)). Within site, participant groups also did not differ in age (NU: t (20) = 1.678, $p > 0.05$; BU: t (31.7) = −0.882, $p > 0.05$; and JHU: t (21.8) = −0.293, $p > 0.05$), and years of education were matched between participant groups for all sites except JHU, where patients were more highly educated than the control participants (NU: t (19) = −0.571, $p > 0.05$; BU: t (22.7) = 0.398, $p > 0.05$; and JHU: t (18.9) = −2.275, $p = 0.035$). All participants completed written consent form approved by NU, BU, and JHU Institutional Review Boards (IRB). See Table 1 for demographic data.

Aphasic participants were at least eight months post onset of stroke (57.2 ± 52.3 months) and presented with aphasia based on administration of the *Western Aphasia Battery-Revised* (WAB-R; [57]) and a uniform set of cross-site language measures. The WAB Aphasia Quotient score (WAB-AQ) ranged from 25.2 to 98.4 (70.2 ± 20.5), with no significant differences between participants enrolled at NU and those enrolled at the other sites (NU versus BU: $t = 1.282$, $p > 0.05$; NU versus JHU: $t = -1.536$, $p > 0.05$), while aphasic participants enrolled at BU showed lower WAB-AQ scores than those at JHU ($t = -2.452$, $p = 0.021$). The type and severity of language impairment were characterized using a test battery, which included selected subtests of the *Northwestern Naming Battery* (NNB; [58]), *Psycholinguistic Assessments of Language Processing in Aphasia* (PALPA; [59]); and *Northwestern Assessment of Verbs and Sentences* (NAVS; [60]).

2.2. Language Measures. Language measures selected to examine participants' abilities across domains included the confrontation-naming (CN) and auditory comprehension (AC) subtests from the NNB to quantify single-word naming and comprehension. These subtests use the same sets of nouns and verbs for testing in both domains. From the PALPA, subtests 35, 40, and 51 were selected to evaluate oral reading of words with regular and irregular orthography (PALPA35), spelling-to-dictation of words with high and low frequency (PALPA40), and semantic association between written words (PALPA51), respectively. Finally, the Sentence Production Priming Test (SPPT) and the Sentence Comprehension Test (SCT) from the NAVS were used to evaluate production and comprehension of sentences of different complexity (same sentences tested across domains).

2.3. MRI Image Acquisition. A 3T Trio Siemens scanner at NU, a 3T Skyra at BU, and a Phillips Intera scanner at JHU were used to obtain anatomical T1-weighted scans. Across all sites, standard T1-weighted 3D MPRAGE scans were acquired in the sagittal plane (TR/TE = 2300/2.91 ms, Flip angle = 9°, 1 × 1 × 1 mm), together with a T2-weighted FLAIR sequence (TR/TE = 9000/90 ms, Flip angle = 150°, 0.86 × 0.86 × 5 mm), which was coregistered and resliced for resolution and orientation consistency with T1 images

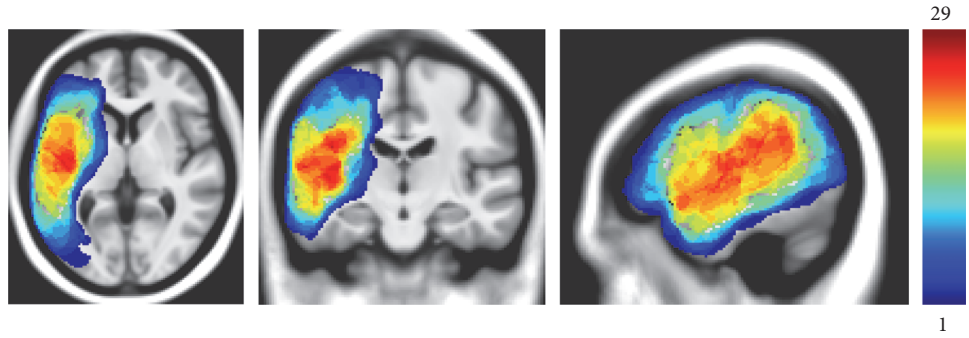


Figure 1: Lesion overlap map of 40 participants with aphasia, showing areas of overlap, from no overlap (blue) to maximum overlap (red; $N = 29$ participants).

by participant. Prior to the study, imaging sequences were equated across sites, with the same parameters used for data acquisition across scanners, and quality control was performed to ensure high-quality data from each site.

2.4. MRI Preprocessing (NUNDA Pipeline Description). Anatomical images were corrected for bias field inhomogeneities [61], and lesioned brain regions were masked out before being subjected to a standard voxel-based morphometry workflow using VBM8 toolbox (developed by Christian Gaser). Analysis steps included tissue segmentation, rigid registration, and DARTEL normalization to the template space (Template_1_IXI550_MNI152.nii). The normalized and modulated GM segments were smoothed by 8 mm FWHM Gaussian Kernel and masked using a right hemisphere (RH) GM mask of the T1 brain template.

2.5. Lesion Identification. The chronic stroke lesion mask was manually generated using MRIcron [62] in native space by trained professionals from each site. To delineate the borders of the necrotic tissue for each patient, intensity measures for white and grey matter (WM and GM) in the contralateral right hemisphere were used for each axial slice. The left hemisphere lesioned tissue was drawn on each slice using the pen tool of MRIcron, and then applying the minimum intensity to the outlined area using the intensity filter function. Additional manual correction was applied by visualizing the volume in all three planes simultaneously. All brains and lesions were normalized into Montreal Neurological Institute (MNI) space as part of the anatomical preprocessing pipeline provided by the Northwestern University Neuroimaging Data Archive (NUNDA; [63]) prior to VLSM analysis. Figure 1 displays a lesion overlap map for the aphasic participant group.

2.6. Data Analyses

2.6.1. Analysis 1: Between-Subject (Aphasic Participants, AM Controls) Differences in GM Volume. The group differences (healthy versus aphasic participants) in grey matter volume were examined in the entire RH and in selected region of interest (ROI). The ROIs were derived from the VBM Analysis 3 (see next). Specifically, for any cluster in which grey matter volume was found to be significantly associated with any of our seven language measures (VBM Analysis 3), we identified the ROI within which the peak voxel for that cluster resided. The so identified ROIs included the right supplementary motor area (SMA), MTG, insula, hippocampus, postcentral, and pallidum areas (see Figure 2). These ROIs were anatomically defined using the AAL atlas within the MarsBaR toolbox in SPM8 [64]. For each ROI, a linear regression analysis was conducted using R 3.2.3 [65], where the mean GM volume was used as a dependent variable, and group (healthy versus aphasic individuals) as an independent variable. Age and total intracranial volume (computed as the sum of grey and white matter and cerebrospinal fluid) were included as covariates in all regression models. Additionally, p values resulting from regression analyses were corrected for the number of ROIs examined using the Benjamini-Hochberg correction [66], with n being the total number of ROIs examined (6). Only Benjamini-Hochberg-corrected results are reported in the Results.

2.6.2. Analysis 2: The Effect of LH Lesion on Language Performance. A voxel-based lesion symptom mapping (VLSM) approach was used to analyze the relationship between lesions in the left hemisphere and language performance [55], using the VLSM toolbox (http://www.crl.ucsd.edu/vlsm) running under Matlab R2014a. (MathWorks Inc., 2014). The participants' lesion images (binary) and language scores (% correct) were entered into a VLSM analysis. For each voxel, aphasic participants were divided into two groups based on the presence (1) or absence (0) of a lesion in that voxel. Only voxels in which more than four (at least 10%) participants had lesions were included in the analysis. VLSM analyses were run with $n = 1000$ permutation tests, resulting in T-maps that reflected critical regions in the LH where lesioned tissue was associated with performance on a given language measure. The total lesion volume was automatically calculated from the lesion masks and served as a covariate in the analysis. Significant results were derived from voxel-wise t-tests using a threshold of $p < 0.05$ with permutation-based correction for multiple comparisons. Cluster level p values then underwent the Benjamini-Hochberg correction [66] for multiple comparisons (with n being the total number of VLSM analyses conducted, that is, seven, one for each language measure). Only corrected p

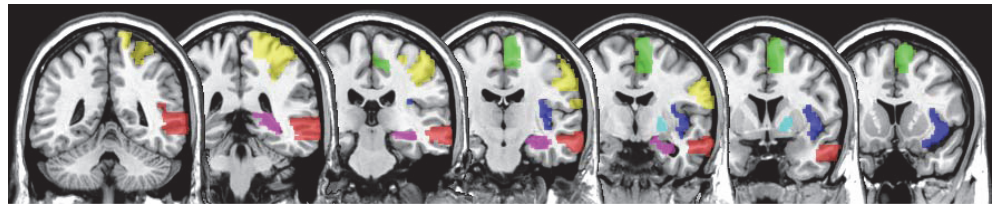


Figure 2: Six right hemisphere regions of interest (ROIs), derived from VBM analysis, used to evaluate between-group differences in the grey matter volume. SMA = green, MTG = red, insula = blue, hippocampus = violet, postcentral = yellow, and pallidum = cyan.

Table 2: Aphasic participants' scores on language measures.

Language domain		Test	All patients		BU		JHU		NU	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
Comprehension	*Aphasia severity*	WABAQ	70.2	20.5	62.2	24.3	80.6	16.1	71.3	13.0
	Spoken word comprehension	NNB AC	92.5	14.5	85.5	20.0	98.1	3.8	97.3	4.5
	Word semantic association	PALPA 51	64.0	20.1	54.1	23.7	73.3	16.2	69.7	13.6
	Sentence comprehension	NAVS SCT	71.4	17.3	71.0	19.6	78.9	17.9	63.9	8.5
Production	*Spoken word production*	NNB CN	70.5	29.7	59.6	37.4	76.6	21.6	80.7	17.8
	Oral reading	PALPA 35	65.1	34.3	56.4	41.3	68.5	28.0	76.0	25.9
	Spelling-to-dictation	PALPA 40	37.1	26.8	35.1	32.5	42.8	20.7	33.8	24.2
	Sentence production	NAVS SPPT	39.4	31.5	30.0	34.5	54.0	31.7	40.6	22.2

values are reported in the text. Additionally, effect sizes for significant comparisons were calculated using the following formula, based on the T-statistics (t) and the degrees of freedom (df) $\sqrt[2]{(t^2/(t^2+\mathrm{df}))}$.

2.6.3. Analysis 3: The Effect of RH GM Volume on Language Performance. The relationship between grey matter volume in the right hemisphere and language performance on the seven language domain measures was analyzed by performing voxel-wise multiple linear regression using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8) in Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm). The segmented, modulated, normalized, and smoothed GM images and language scores (% correct) were entered in each regression model, resulting in T-maps that showed regions where GM volume was significantly associated with language performance. As pointed by Xing et al. [56], when determining the contribution of GM volume in the RH to language performance, it is important to account for the contribution of LH lesioned tissue to the performance on the same language measure, as any correlation found between RH GM volume and language performance may be influenced by the effect of the LH lesion size/site on the participants' performance. In order to account for this, as in Xing et al. [56], the "proportion of critical area of damage" (PCAD) was entered as a covariate together with age and the total intracranial volume (computed as the sum of grey and white matter, and cerebrospinal fluid) in the VBM analysis to partial out their effects on language performance. The PCAD was computed by intersecting the map derived from the group VLSM with each participant's lesion, divided by the VLSM map volume. The PCAD, then, ranged from 0 (when there was no overlap between a patient's lesion and the group map) to 1 (when there was total overlap, with all voxels lesioned in the group map also lesion for the patient). Group T-maps derived from VBM analyses conducted on language measures were then thresholded by determining the minimum cluster size based on a $p < 0.001$ voxel-level threshold and on an estimate of image smoothness in AFNI [67], following the evidence of a disproportionately high rate of false-positive results yielded by family-wise (FWE) cluster-level correction in SPM [68]. The group residuals derived from the SPM T-maps were run through the 3dfwhmx function in AFNI, which uses the latest version of the autocorrelation function, to derive an estimate of image smoothness, and thresholded at a conservative $p < 0.001$ voxel level using the 3dClustSim function, to determine the appropriate cluster size threshold for each regression analysis. T-maps were also multiplied by a GM mask to ensure significant clusters would be restricted to grey matter and by the Automated Anatomical Labeling (AAL) atlas to obtain MNI coordinates for every peak in every significant cluster. The AAL template was then overlaid onto each binarized T-map using MRIcron [62] to identify the region corresponding to each peak coordinate. Cluster p values were finally corrected for multiple comparisons (with n being the number of regressions performed, that is, seven, one for each language measure) using the Benjamini-Hochberg correction [66]. As for VLSM, effect sizes for each VBM regression analysis were computed as described above, and only corrected p values are reported in the text.

3. Results

3.1. Language Measures. Participant scores derived from administration of language measures across language domains are shown in Table 2. Within the comprehension domain, participants performed well on spoken word comprehension (NNB AC: 92.5 ± 14.5), while scores obtained

Table 3: Results of VLSM analyses by language measure.

Language measure	Test	LH regions (AAL)	Cluster size	Peak coordinates px	py	pz	t value	df	p (perm) correction	Benjamini-Hochberg correction	Effect size
Spoken word comprehension	NNB AC	*Putamen* IFG STG Rolandic operculum	949	−32	−17	0	5.15	35	0.026	0.068	0.656
Word semantic association	PALPA51	*Putamen* Insula STG/MTG Caudate	796	−33	3	−9	4.49	34	0.015	0.068	0.61
Sentence comprehension	NAVS SCT	*MTG* STG	1040	−44	−23	0	4.98	35	0.029	0.068	0.644

Note. Table 3 summarizes regions where lesion volume was significantly associated with language performance in the comprehension domain. The results are presented at a threshold of $p < 0.05$, based on cluster size and the permutation method. In addition, the permutation-corrected p values were corrected for the total number of language measures examined ($n = 7$) using the Benjamini-Hochberg procedure. Significant peak regions are reported with the corresponding coordinates, T and p values, degrees of freedom, and effect sizes, as well as AAL regions included in the significant cluster; LH: left hemisphere; IFG: inferior frontal gyrus; STG: superior temporal gyrus; MTG: middle temporal gyrus.

on semantic association and sentence comprehension were lower on average and more variable (PALPA51: 64.0 ± 20.1; NAVS SCT: 71.4 ± 17.3). Within the production domain, aphasic participants scored better on spoken word production and oral reading (NNB CN: 70.5 ± 29.7; PALPA 35: 65.1 ± 34.3) than on spelling-to-dictation (PALPA40: 37.1 ± 26.8) and sentence production (NAVS SPPT: 39.4 ± 31.5).

3.2. Between-Subject (Aphasic Participants, AM Controls) Differences in GM Volume. Between-subject analysis of GM volume for the entire RH showed no significant differences between the aphasic participants and age-matched controls. The results of the ROI analyses revealed between-group differences in the right SMA ($p = 0.054$), where patients showed reduced GM volume compared to healthy participants. To follow up on this result, a median split was used to divide patients into two groups, that is, those with good (>65% correct) ($n = 21$) and poor (<65% correct) ($n = 19$) production ability, based on a composite score (the average percentage correct across the three production measures: spoken word production, oral reading, and sentence production). A between-group (healthy controls, good performers, and poor performers) analysis was run on the mean RH GM volume in the SMA, with age and total intracranial volume included as covariates. The results showed a significant difference between healthy controls and poor performers in GM volume within the RH SMA ($p = 0.004$), while no difference was found between healthy controls and good performers ($p = 0.294$).

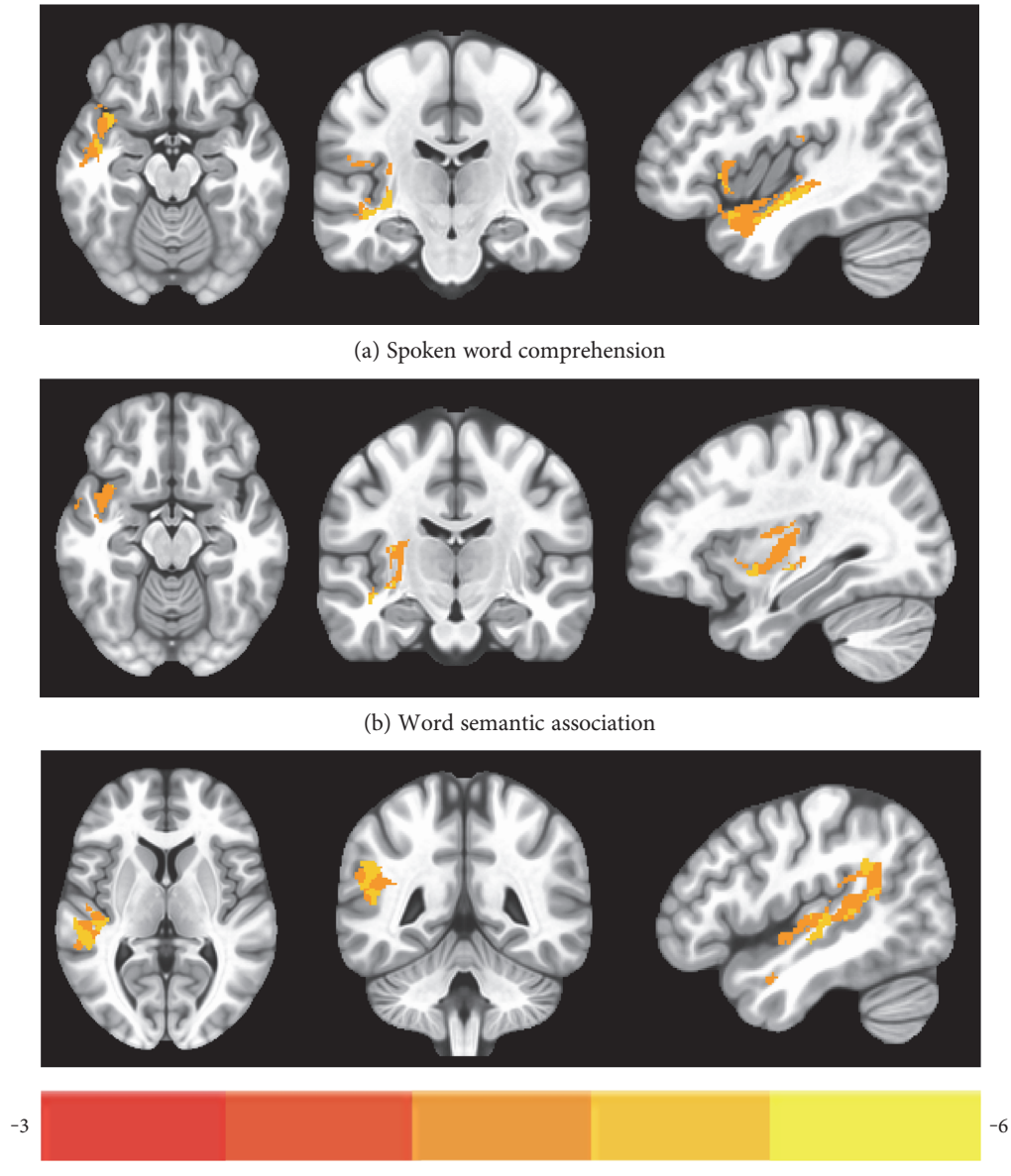
3.3. Effect of the LH Lesion on Language Performance (VLSM Results) in Aphasic Participants. The following results were derived from the VLSM analysis and illustrate the relation between LH lesion and language performance. The results of VLSM analyses are reported in Table 3. Figure 3 displays the relationship between LH lesion site and performance on each language measure.

For measures assessing comprehension, VLSM analysis of *spoken word comprehension* revealed a trend toward a negative relationship between lesions in the left IFG, STG, putamen, and rolandic operculum and spoken word comprehension scores ($p = 0.068$). Similarly, *word semantic association* performance was negatively associated with lesions in the left IFG, STG, and putamen, as well as in two unlabeled clusters spatially contiguous to the insula and caudate ($p = 0.068$). Finally, for *sentence comprehension*, a trend toward a negative relationship was observed with lesions in the left MTG and STG ($p = 0.068$).

VLSM analyses of production measures revealed no significant relationships between lesions and performance on *spoken word production*, *oral reading*, *spelling-to-dictation*, or *sentence production* (all corrected ps > 0.1).

3.4. Effect of the RH GM Volume on Language Performance (VBM Results) in Aphasic Participants. The following results were derived from the VBM regression analysis and illustrate the relation between RH GM volume and language performance where the relations between LH lesioned tissue and language performance (as derived from the VLSM analyses) were taken into account and entered as nuisance variables. VBM maps indicating RH regions in which GM volume was significantly positively associated with language performance are shown in Figure 4. The results of VBM analysis for the aphasic participants are reported in Table 4.

The voxel-wise linear regression of *spoken word comprehension* on GM volume revealed a significant positive relationship between single-word comprehension scores and GM volume in the right MTG and insula. VBM analyses conducted on measures of *word semantic association* and *sentence comprehension* did not yield any significant clusters. For production measures, the voxel-wise linear regression of *spoken word production* on the GM volume revealed a significant positive relationship between word production scores and GM volume in the right SMA and insula.



(a) Spoken word comprehension

(b) Word semantic association

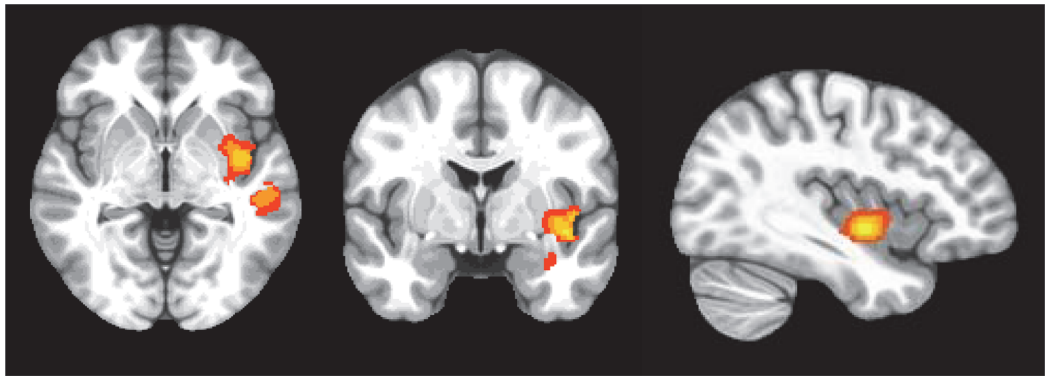
(c) Sentence comprehension

Figure 3: VLSM maps showing left hemisphere regions that were significantly associated with language performance. Panels (a–c) display lesions correlated with comprehension measures: (a) spoken word comprehension, (b) word semantic association, and (c) sentence comprehension. All voxels shown in color survived a threshold of $p < 0.05$, based on cluster size and the permutation method. The color bar reflects the range of t values from minimum (red) to maximum (yellow).

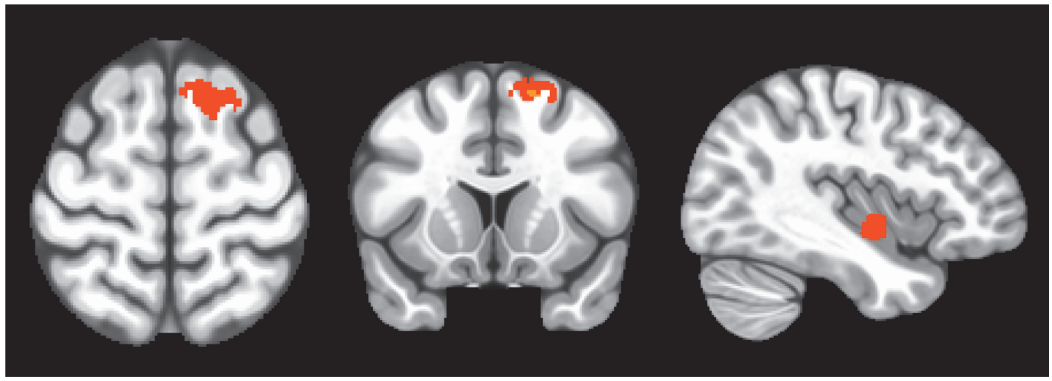
Similarly, *oral reading* and *sentence production* performances were positively related with GM volume within the right SMA, whereas *oral reading* performance was also associated with GM volume in the pallidum and hippocampus. Finally, for *spelling-to-dictation,* a positive relationship between GM volume and performance was observed in the right hippocampus and postcentral region.

4. Discussion

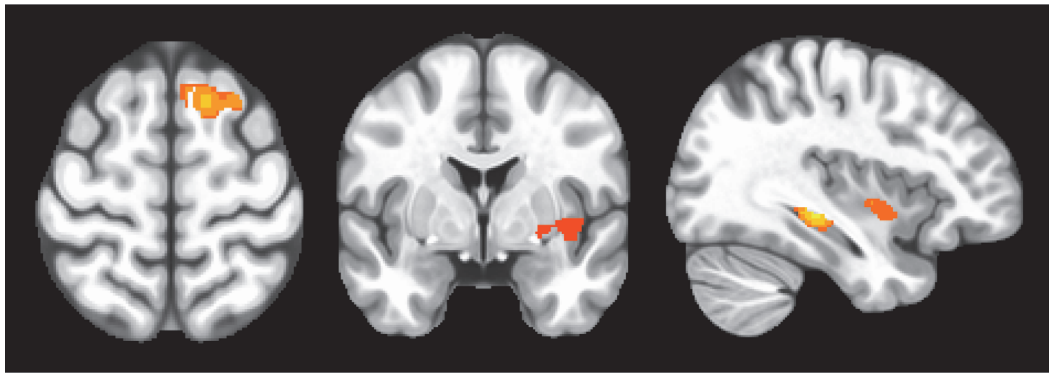
This study examined the right hemisphere (RH) grey matter (GM) volume in a group of 40 individuals with stroke-induced chronic aphasia using voxel-based morphometry (VBM). We first compared values derived from the patient group to those derived from 40 age-matched healthy controls, finding reduced GM volume in the RH supplementary motor area (SMA) in aphasic individuals compared to healthy age-matched controls. Follow-up analyses also revealed a significant difference in SMA GM volume only between healthy controls and aphasic individuals with more severe impairment in language production, while no difference emerged between patients with milder language production deficits and healthy individuals. Next, we evaluated the relation between RH GM volume and language performance in the aphasic participant group, controlling for the left hemisphere lesion site, using VBM. The results revealed two findings: (1) better word comprehension was associated with increased RH GM volume in the middle



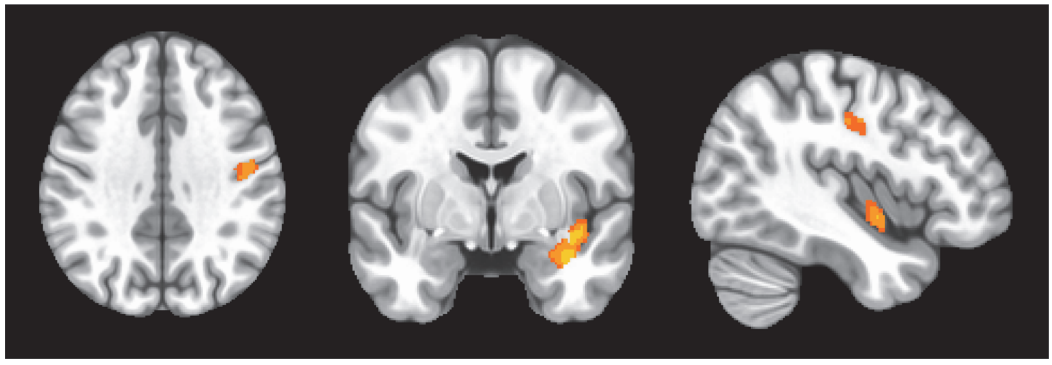
(a) Spoken word comprehension



(b) Spoken word production

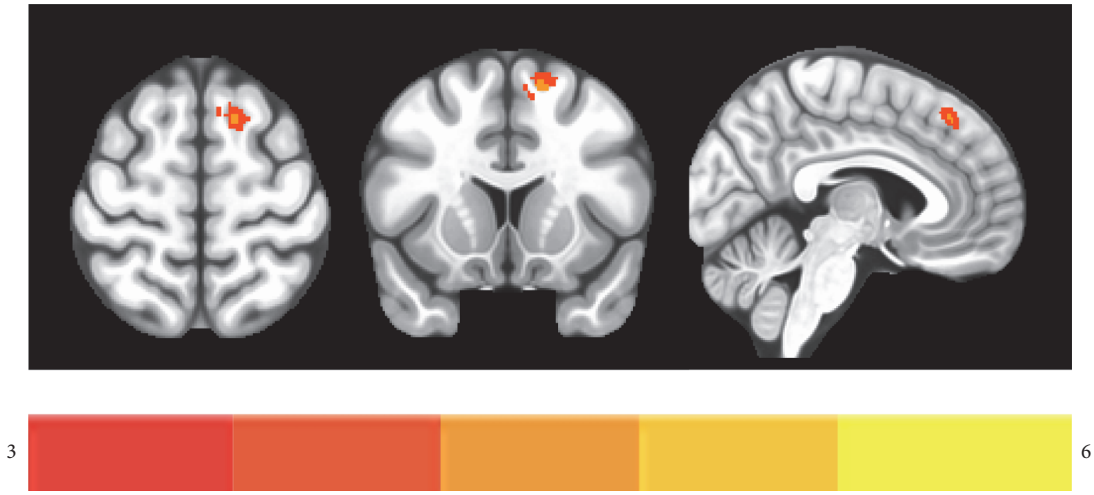


(c) Oral reading



(d) Spelling-to-dictation

Figure 4: Continued.



(e) Sentence production

Figure 4: VBM maps showing right hemisphere regions where GM volume was significantly associated with language performance. Panel (a) shows the relationship between RH gray matter volume and spoken word comprehension. Panels (b–e) display the relationship between RH gray matter volume and production measures: (b) spoken word production, (c) oral reading, (d) spelling-to-dictation, and (e) sentence production. All voxels shown in color survived a threshold of $p < 0.05$, cluster-level FWE corrected. The color bar reflects the range of t values from minimum (red) to maximum (yellow).

Table 4: Results of VBM analyses by language measure.

Language Measure	Test	RH regions (AAL)	Cluster size	Peak coordinates px	py	pz	t value	df	FWE correction	Benjamini-Hochberg correction	Effect size
Spoken word comprehension	NNB AC	Insula	1458	40.5	−4.5	−7.5	5.861	35	0.0000	0.0000	0.70
		MTG	732	55.5	−25.5	−4.5	4.646		0.0000	0.0001	0.62
Word semantic association	PALPA51	No sig. clusters									
Sentence comprehension	NAVS SCT	No sig. clusters									
Spoken word production	NNB CN	SMA	545	13.5	16.5	61.5	4.302	35	0.0001	0.0002	0.59
		Insula	267	40.5	−7.5	−7.5	4.106		0.0002	0.0003	0.57
Oral reading	PALPA35	SMA	502	13.5	15	61.5	4.549	34	0.0001	0.0001	0.62
		Pallidum	430	25.5	−1.5	−4.5	3.861		0.0005	0.0005	0.55
		Hippocampus	294	33	−28.5	−6	5.274		0.0000	0.0001	0.67
Spelling-to-dictation	PALPA40	Hippocampus	503	36	−1.5	−22.5	4.593	35	0.0001	0.0001	0.61
		Postcentral	258	49.5	−12	36	3.981		0.0003	0.0004	0.56
Sentence production	NAVS SPPT	SMA	275	13.5	15	58.5	4.625	34	0.0001	0.0001	0.62

Note. Table 4 summarizes regions where GM volume was significantly associated with language performance in both comprehension and production domains. The results are presented at a threshold of $p < 0.05$, based on $p < 0.001$ voxel-level threshold and a minimum cluster size (665–708 mm^3) determined by an estimate of image smoothness. In addition, cluster p values were corrected for the total number of language measures examined ($n = 7$) using the Benjamini-Hochberg procedure. Significant peak regions are reported with corresponding coordinates, T and p values, degrees of freedom, and effect sizes; RH: right hemisphere; SMA: supplementary motor area; MTG: middle temporal gyrus.

temporal gyrus (MTG) and insula, and (2) better word and sentence production was associated with increased RH GM volume in the SMA.

Language comprehension was evaluated using standardized measures of spoken word comprehension, semantic association, and sentence comprehension. The spoken word comprehension measure examined participants' ability to comprehend single words (nouns and verbs) from an array of semantically or argument structure-related items, respectively. Accordingly, failure on this task reflects inability to either link spoken words to objects/actions or to access semantic knowledge [58]. The semantic association task also examined word comprehension, although from the visual modality, requiring participants to select semantically related words. To perform the sentence comprehension (i.e., sentence-picture matching) task, individuals needed to access

lexical and semantic information stored in long-term memory and integrate it into syntactic structure.

The VBM analysis shows that GM volume in the right MTG and insula was positively associated with performance on *spoken word comprehension,* but no association was found between the RH GM volume and the other two comprehension measures, that is, *semantic association* and *sentence comprehension* in any region. Lesion-deficit patterns derived from VLSM showed that lower performance on both word comprehension and semantic association measures were associated with a lesion in the left IFG and STG, whereas lower sentence comprehension scores were associated with lesions in the left STG and MTG. However, given that VLSM analyses yielded results that were only marginally significant after applying a correction for multiple comparisons, the discussion will focus primarily on the results of the VBM analyses, and VLSM results will be discussed within the context of the explanation of the VBM results.

The finding of an association between performance on spoken word comprehension and GM volume in the right temporal cortex suggests that the RH temporal region may support lexical access during word processing. This finding is in line with neuroimaging studies showing increased RH activation in temporal lobe regions with improved lexical-semantic (compared to orthographic and phonological) processing in aphasic participants [33]. The results are also consistent with studies showing increased posttreatment activation bilaterally in the MTG (in addition to the frontal cortex) on a semantic feature verification task, which also requires access to semantic knowledge [24, 29]. Moreover, when looking at the results of the lesion-deficit analyses for spoken word comprehension and semantic association tasks, within the context of the aforementioned RH results, damage in the left IFG and STG likely affected lexical selection and storage of lexical representations, respectively. This is consistent with studies showing an association between damage to temporal lobe structures and comprehension/semantic deficits in aphasic individuals [69, 70].

In addition to recruitment of the RH temporal lobe, the VBM analysis showed that performance on spoken word comprehension was also associated with GM volume in the insula. Neuroimaging studies have shown activation in the left insula during phonological discrimination tasks [71, 72], although its role in word processing is debated, as several neuroimaging studies have found activation of the insula using a variety of language tasks including naming and word generation ([73–75], see [76] for a review). However, a role for the insula in word comprehension has been suggested in functional connectivity studies, showing significant connections between the insula and the temporal lobe, namely the STG and MTG [76].

Notably, we observed no relationship between GM volumes and sentence comprehension in the right hemisphere. According to most studies with cognitively healthy people, sentence comprehension is supported by a primarily left lateralized temporofrontal network (see [77] for a neurocognitive model of sentence comprehension; also see [5]), with neuroimaging studies showing increased activation in the left frontal and posterior temporal cortex when comparing sentences with plausible versus implausible meanings [78], grammatical versus ungrammatical sentences [79], or syntactically complex versus simple sentences [31, 80, 81]. These findings suggest that the left temporal and frontal tissue is recruited when strategic, combinatorial, and/or memory processes come into play during sentence processing [82]. In the present study, the absence of a sentence-level comprehension effect in the RH as well as our VLSM lesion-deficit results, revealing a significant negative correlation in the left STG and MTG and sentence comprehension, that is, poorer sentence comprehension was associated with lesions in these regions, consistent with previous findings [31, 70, 83, 84], reflect a reliance on the left hemisphere for sentence comprehension for our patients [1].

Turning to language production, spoken word and sentence production, oral reading, and spelling-to-dictation were tested using standardized measures. Language production engages many of the same processes involved in comprehension, including semantic mediation, phonological processing, and in the case of sentence production, integration of semantic, and syntactic information. However, production also engages motor planning, articulatory, and associated processes.

For *spoken word production*, *sentence production*, and *oral reading*, we found increased RH GM volume in the right SMA associated with better performance. This finding is in line with the results of several neuroimaging studies, which have found significant SMA activation in production tasks in healthy speakers in both silent (covert) and overt production tasks (see [85] and [3] for review; [86–88]). Although SMA activation often is associated with motor planning and articulatory processes, some authors suggest that this region also is involved in lexical selection and word form encoding [89, 90]. Positive correlations between GM volume in the RH SMA found in the present study across production (but not comprehension) tasks support this, suggesting that the right homologue of the SMA may be recruited to support production processes in individuals with aphasia resulting from stroke.

In addition, the VBM analysis showed that performance on word production was associated with increased GM volume in the insula. Neuroimaging studies examining naming and word generation in healthy speakers have found LH insula activation (see [76] for a review). Previous lesion-deficit correlation analyses also have found an association between lesions in the insula and performance on verbal fluency [54], speech initiation, and motor planning [91, 92]. In addition, the insula has been shown to have strong connections to the LH prefrontal cortex, including the MFG and SMA [76], suggesting that in our patients, lesions affecting the LH insula and its connections with the LH SMA, the RH homologous frontal regions may result in recruitment of the RH insula and SMA for production processes. Alternatively, the RH SMA and insula may support these processes independent of lesioned tissue in the homologue LH regions.

Lastly, performance on the *spelling-to-dictation* measure was associated with GM volume in the right hippocampus

and postcentral areas. Associations between performance on this task and GM volume in the RH hippocampal structures are in line with studies indicating a role of the hippocampus in healthy language learning [93–95], as well as with studies showing a positive correlation between treatment outcome and GM volume in the LH [96, 97] or bilateral hippocampus during recovery from stroke. Although—as previously acknowledged—the present study does not directly reflect "recruitment" of RH regions as part of recovery from aphasia, and the findings of a relation between GM volume and structures supporting healthy learning may not be coincidental. Further studies are necessary to investigate the role of the hippocampus as a structure supporting recovery in stroke-induced aphasia. Similarly, recruitment of the RH postcentral area may be implicated in recovery from aphasia. Previous neuroimaging studies in aphasic individuals have found RH postcentral gyrus activation across a variety of language tasks [24, 29].

Overall, our VBM results are inconsistent with those reported by Xing et al. [56]. Whereas Xing et al. found that GM volumes in right temporoparietal areas are related to speech production, but not comprehension, we found the opposite pattern. We found strong correlations between GM volumes in right temporal cortex and comprehension, but not production, and in the domain of production, we found that increased GM volume within the frontal region was associated with better production. It should be noted that the tasks used to test both comprehension and production differed across studies. To evaluate comprehension, Xing et al. [56] used data derived from WAB comprehension subtests and to evaluate production, spontaneous speech data and performance on a repetition task were used, whereas we used linguistically controlled, standardized comprehension and production tasks designed explicitly to elicit both comprehension and production of written and spoken words and sentences. We suggest that controlled tasks designed to measure specific language processes may better reflect neural recruitment patterns associated with recovery from aphasia.

To the extent that GM volume reflects functionality, the positive association between word comprehension and production ability and GM volume in the RH MTG and SMA, respectively, suggests that these regions may play a compensatory role in language recovery in aphasia. Although the precise mechanisms underlying RH GM volume are not completely understood, this finding is in keeping with one theory of language recovery—that RH regions are recruited to perform language functions when the LH is damaged. Notably, however, theories of language recovery suggest that RH compensation occurs in regions homologous to LH damaged regions. For example, in one study, Turkeltaub et al. [24] showed that people with lesions in the left IFG were more likely to recruit the right IFG than those without lesions in that area. Similarly, Buckner et al. [98] reported results of a single-stroke patient who showed activation in the right inferior prefrontal region during a word-stem completion task to compensate for lesioned tissue in the left frontal region, activated by healthy speakers. Also, see studies by Musso et al. and Perani et al., for similar patterns [18, 20]. However, the present data do not completely support this idea. Whereas, our patients with word comprehension impairments evinced lesions within the LH MTG, perhaps leading to recruitment of RH MTG, and our patients with sentence comprehension impairments evinced LH STG and MTG lesions, but no increases in GM volume were found in any RH regions. Further, our patients with production impairments did not present with LH SMA lesions but nevertheless showed increases in GM volume in the RH SMA, a nonhomologous region. One explanation for this latter finding is that the LH SMA is highly connected to regions within the LH that were damaged in our patients, perhaps leading to recruitment of its RH homologue.

In the absence of longitudinal data, however, we refrain from making strong claims regarding the relation between RH GM volume and recovery. Although RH regions may be recruited to support functions previously performed by LH regions, it is possible that RH recruitment may be maladaptive, as suggested by some repetitive transcranial magnetic stimulation studies (rTMS; see [6] for review). It also is possible that individual differences among participants before (rather than following) stroke may explain the RH GM volume differences we found between aphasic and healthy individuals. Although difficult to accomplish, longitudinal research in which individuals are tested prior to and following stroke could help to address this alternative hypothesis. Research examining GM volume in poststroke patients over time also will provide further insight into the extent to which GM changes are associated with language change. Indeed, the present data are part of a larger longitudinal study examining brain behavior changes associated with treatment (versus no treatment), and the results of which will be informative regarding neural recovery trajectories associated with improved language performance and yield a more comprehensive understanding of both structural and functional plasticity associated with language recovery in stroke aphasia.

5. Conclusion

This study examined the relation between the right hemisphere grey matter volume, left hemisphere lesion site, and both spoken and written comprehension and production of words and sentences in chronic stroke-induced aphasia. To the extent that RH grey matter volume reflects neural shifts associated with recovery from left hemisphere brain damage, our results indicate that right hemisphere regions, both homologous and nonhomologous to the left hemisphere lesioned regions, are recruited to support language, with unique recruitment patterns associated with language domain. Although further research is needed, the present findings have important implications for understanding poststroke neural reorganization.

Conflicts of Interest

The authors declare no conflicts of interest regarding publication of this paper.

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Research Article

Intrahemispheric Perfusion in Chronic Stroke-Induced Aphasia

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Stroke-induced alterations in cerebral blood flow (perfusion) may contribute to functional language impairments and recovery in chronic aphasia. Using MRI, we examined perfusion in the right and left hemispheres of 35 aphasic and 16 healthy control participants. Across 76 regions (38 per hemisphere), no significant between-subjects differences were found in the left, whereas blood flow in the right was increased in the aphasic compared to the control participants. Region-of-interest (ROI) analyses showed a varied pattern of hypo- and hyperperfused regions across hemispheres in the aphasic participants; however, there were no significant correlations between perfusion values and language abilities in these regions. These patterns may reflect autoregulatory changes in blood flow following stroke and/or increases in general cognitive effort, rather than maladaptive language processing. We also examined blood flow in perilesional tissue, finding the greatest hypoperfusion close to the lesion (within 0–6 mm), with greater hypoperfusion in this region compared to more distal regions. In addition, hypoperfusion in this region was significantly correlated with language impairment. These findings underscore the need to consider cerebral perfusion as a factor contributing to language deficits in chronic aphasia as well as recovery of language function.

1. Introduction

Recovery of language in chronic stroke-induced aphasia involves recruitment of undamaged tissue in the contralesional (typically right) and/or the ipsilesional hemisphere of the brain [1–4]. Although it has been suggested that ipsilesional, and even perilesional, tissue is best suited to support recovery, there are several factors that influence recruitment of undamaged tissue during functional recovery, including poststroke alterations in vascular physiology.

Emerging evidence from multiple sources suggests that restoration of cerebral blood flow (the rate at which blood perfuses a neural region) is critically associated with functional recovery. Blood delivers oxygen and glucose to the brain that is required for aerobic metabolism supporting neural activity [5]. In hyperacute stages of stroke, cortical spreading depression originating from the infarction site causes the lesion to expand [6], which affects symptom severity [7]. In addition, perilesional tissue becomes inflamed [8]. A settling of these events (e.g., lesion stabilization, reduced inflammation) contributes to recovery of function in acute stroke-induced aphasia, when perfusion is most likely to reverse to prestroke levels, either spontaneously or through pharmacological interventions [9, 10].

Prestroke perfusion levels, however, may not be regained in all regions of the brain, leaving uninfarcted tissue hypoperfused well past the acute stage. Using arterial spin labeling MRI, Richardson et al. [11] found reduced perfusion values in the left (ipsilesional) hemisphere compared to the right hemisphere in 17 patients with chronic aphasia [11, 12] (see Table 1 for a review of studies of perfusion in chronic aphasia). Notably, negative correlations between perfusion and lesion volume were reported, with larger infarcts corresponding to greater interhemispheric differences in perfusion. However, the duration of aphasic symptoms (time since stroke) did not correlate with reduced perfusion, suggesting a stable state of chronic hypoperfusion in chronic aphasia [11].

Regions of hypoperfused but otherwise intact tissue can create what are essentially functional lesions in chronic stroke, where the neurons are viable but unable to sufficiently support processing [13–15]. Evidence from animal models indicates that although neurons survive with perfusion levels greater than about 10% of normal, neuronal function is compromised when perfusion levels are below roughly 30% of normal [13, 16]. In human adults, normal cerebral blood flow in gray matter ranges from 37 to 64 mL/100 g/min, and lower perfusion may preclude normal functioning [14]. Consideration of hypoperfused regions, therefore, offers an important refinement to the traditional lesion method used to make inferences about structure-function correspondences in the brain [17], in that impaired language functioning may result not only from regions directly lesioned by stroke, but also from "hibernating" hypoperfused regions [18–20]. For example, Love et al. [15] reported hypoperfusion of otherwise spared tissue in the left angular and supramarginal gyri associated with impaired reading in a chronic aphasic patient.

Hypoperfused neural tissue also may not be viable for support of language recovery; rather, regions with lesser reductions or uncompromised cerebral blood flow (rCBF) may be better candidates for treatment-induced upregulation of neural activity. For example, Thompson et al. [19] found that baseline perfusion was higher (i.e., nearer normal levels) in regions that showed upregulation of neural activity in patients who underwent treatment for agrammatism. Fridriksson et al. [20] found a similar pattern in 30 patients who received treatment for anomia: pretreatment perfusion levels in undamaged regions within the left hemisphere language network (excluding infarcted and perilesional regions) predicted patients' naming accuracy, suggesting that higher baseline cerebral blood flow may be related to the potential for a better treatment outcome.

Reduction in cerebral blood flow also alters hemodynamic autoregulation aimed at maximizing the delivery of oxygen by increasing the blood volume or oxygen extraction fraction [21]. This has a fundamental effect on the shape and timing of the hemodynamic response used to measure blood oxygenation level-dependent (BOLD) task changes [12]. If not taken into account, an abnormal hemodynamic response may lead to underestimation and/or inaccurate measurement of the BOLD signal in functional magnetic resonance imaging (fMRI) [19, 22, 23]. Bonakdarpour et al. [24] found that three of five individuals with chronic stroke aphasia showed a delayed hemodynamic response (delayed blood flow) in left perisylvian, relative to the left occipital, cortex during a lexical decision task. No such delay was seen in right perisylvian regions. Likewise, increased time-to-peak was seen in the five patients in left perilesional tissue during an overt naming task, but not in homologous right hemisphere regions. These delays correlated positively with lesion size (longer delays were seen in individuals with larger lesions) and negatively with aphasia severity as estimated using the Western Aphasia Battery-Revised (WAB-R) [25] (longer delays in individuals with more severe aphasia).

One region suggested to be particularly important for recovery of function is perilesional tissue. In rodent models, perilesional tissue undergoes neurophysiological changes, such as vascular proliferation and remodeling (angiogenesis) [26–29], reduced dendritic complexity, spine density, and synapses [26, 28, 30], and elevated rates of axonal sprouting [31, 32]. Hypoperfusion and reduced glucose metabolism also are prevalent in perilesional space [31, 33]. Notably, reversal to more normal neurophysiology within this region has been shown to coincide with recovery of function in animals as well as in acute phases of aphasia recovery in humans [34–37]. Presently, however, few studies have examined perfusion and/or reperfusion in perilesional tissue in chronic aphasia. Furthermore, within the aphasia literature there has been little research focused on what constitutes perilesional tissue and/or its role in recovery of language. In one study, Richardson [22] found reduced perfusion levels in individuals with chronic aphasia in a perilesional region of interest (ROI), defined as tissue from 3 to 8 mm surrounding the lesion, compared to its right hemisphere homologue.

In sum, prior evidence underscores the importance of examining perfusion in individuals with aphasia into the chronic stage, to augment understanding of the neural basis of language processing following stroke, and to determine the relation between perfusion and recovery of function. This paper examined perfusion in a group of individuals with chronic aphasia induced by left hemisphere ischaemic stroke and a cohort of healthy control participants. We tested between-subjects (aphasic versus healthy participants) differences in perfusion values in the left versus right hemisphere as well as in 38 ROIs in each hemisphere of the brain. We also examined perfusion in the patient group in perilesional ROIs, compared both to right hemisphere homologous regions and to remaining gray matter tissue in the left hemisphere (i.e., unlesioned, outside of the perilesional region). Perfusion was also examined in relation to scores on behavioral language tests reflecting overall aphasia severity, single word production (i.e., naming) and comprehension, spelling, and sentence production and comprehension ability. Finally, we examined perfusion in relation to individual and stroke-specific factors, including sex, age, education, lesion age (i.e., time post stroke), and lesion size (volume).

Overall, we expected reduced perfusion values in left hemisphere (ipsilesional) regions, but not in right hemisphere tissue in participants with aphasia relative to healthy controls. Also, based on prior studies with this clinical population, we expected perilesional perfusion to be reduced compared to the remainder of the left hemisphere and to

Table 1: Studies of perfusion in chronic aphasia.

Study	Sample size (n)	Time since stroke	Diagnosis	Treatment protocol	MRI method	Task	Key findings
Love et al., 2002	1	16 years	Anomia, difficulty in reading	—	PASL	Resting state	(i) Hypoperfusion in L angular gyrus, L supramarginal gyrus; neither region infarcted
Peck et al., 2004	3	8–48 months	Nonfluent aphasia	2 with intention treatment; 1 with attention treatment	BOLD TTP	Category member generation	(i) From pre- to posttreatment, average difference across patients in TTP between R auditory cortex and R motor cortex decreased, corresponding to shortened posttreatment response times, and approached the average value for controls
Fridriksson et al., 2006	1	18 months	Aphasia (incl. moderate anomia)	—	PWI/BOLD	Overt picture naming	(i) Delayed TTP in resting state PWI in LH versus RH (ii) Abnormal HRF in activated areas during naming
Bonakdarpour et al., 2007	5	>2 years	Agrammatic aphasia	—	BOLD TTP	Lexical decision	(i) Increased TTP in L perisylvian cortex (3 of 5 individuals) relative to healthy controls (ii) No differences in R perisylvian or L or R occipital cortex
Brumm et al., 2010	3	2–11 years	Expressive aphasia	—	PASL	Resting state	(i) Hypoperfusion in L penumbra (2 voxels); noninfarcted regions of L hemisphere
Thompson et al., 2010	6	6–146 months	Agrammatic aphasia	Treatment of Underlying Forms (TUF)	PASL	Resting state	(i) Regions with upregulated BOLD response (auditory sentence-picture verification task) following treatment showed faster TTP (ii) After treatment, 4 patients decreased TTP in L angular gyrus; 3 decreased TTP in L superior parietal cortex; 4 decreased TTP in R superior parietal cortex
Richardson et al., 2011	17	4–246 months	Aphasia (not specified)	—	PASL	Resting state	(i) Hypoperfusion in L penumbra (8 mm); noninfarcted regions of L hemisphere (ii) Larger lesion correlated with reduced perfusion
Fridriksson et al., 2012	30	6–350 months	13 Broca's; 10 anomic; 3 conduction; 2 Wernicke's; 1 Trans-cortical motor; 1 global	Anomia treatment	PASL	Resting state	(i) Pretreatment perfusion levels in residual language network regions, that is, not infarcted and not perilesional (15 mm), predicted posttreatment improvement in picture naming (ii) Pretreatment perfusion levels in infarcted and perilesional tissue did not predict posttreatment improvement
Bonakdarpour et al., 2015	5	6–96 months	2 Broca's aphasia; 3 anomia	—	BOLD TTP	Overt picture naming	(i) Increased TTP in L hemisphere naming regions relative to healthy controls (ii) No difference in percent signal change

PASL: pulsed arterial spin labeling; PWI: perfusion weighted imaging; TTP: time to peak (of the hemodynamic response function (HRF)); SMA: supplementary motor area.

Table 2: Participant information (mean and standard deviation).

Group	Age (years)	Sex	Education (years)	Lesion age (months)	WAB-AQ[1]
Aphasia ($n = 35$)	57.7 (10.5)	21 M/14 F	15.8 (2.1)	59.3 (53.0)	66.2 (22.7)
Controls ($n = 16$)	32 (8.5)	8 M/8 F	17.7 (1.7)	—	—

[1]WAB-AQ: Western Aphasia Battery-Aphasia Quotient.

correlate with lesion volume and aphasia severity, but not with lesion age, sex, education, or age.

2. Method

2.1. Participants. We tested 35 participants with aphasia subsequent to a single left hemisphere ischaemic stroke and 16 healthy adult controls (see Table 2). Participants with aphasia, presenting with anomia, dysgraphia, and agrammatism, were recruited from three research sites, Northwestern University ($n = 9$), Boston University and Massachusetts General Hospital ($n = 21$), and Johns Hopkins University ($n = 5$), respectively, as part of a large-scale NIDCD funded Clinical Research Center. Healthy controls were recruited from the greater Chicago area and tested at Northwestern University. The study was approved by the Institutional Review Boards of all three universities and all participants provided informed consent.

All participants were right-handed native English speakers. Participants with aphasia were older (range = 41–79 years; M = 57.7 years) than the healthy controls (range = 24–57 years; M = 32.3 years; two-sample, unequal variance t-test: $t(36) = 9.19$, $p < .0001$) and had fewer years of education (M = 15.8 versus M = 17.7 years; two-sample unequal variance t-test: $t(32) = 3.33$, $p = .001$). Participants with aphasia passed vision and hearing screenings (pure-tone audiometric screening at 40 dB, 1000 Hz) and had no other diagnosed brain disorders and no history of drug or alcohol abuse. Healthy controls had self-reported normal or corrected-to-normal vision and hearing and no history of speech, language, or learning disorders or substance abuse.

Participants with aphasia were all in the chronic stage and were at least twelve months post-stroke-onset (M: 59.3 months, SD: 53.0, range: 12–209 months). The diagnosis and overall severity of aphasia were based on administration of the Western Aphasia Battery-Revised (WAB-R) [25]; WAB-AQ scores ranged from 11.7 to 95.2 (M: 66.2, SD: 22.7). We also characterized each participant's language abilities using a battery of language tests, which included measures of spoken and written comprehension and production of words and sentences. Single word production and comprehension were tested using 26 items from the Confrontation Naming (CN) and Auditory Comprehension (AC) subtests of the Northwestern Naming Battery (NNB) [38] (10 low frequency nouns from the "Other" category on the NNB and 16 verbs). We used the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) [39] to evaluate spelling-to-dictation of words with high and low frequency (subtest 40). Finally, the Sentence Production Priming Test (SPPT) and the Sentence Comprehension Test (SCT) from the Northwestern Assessment of Verbs and Sentences (NAVS) [40], which include 30 items each to test canonical and noncanonical structures, were used to evaluate production and comprehension of sentences of different syntactic complexity.

These tests provided the basis for five language domain scores that we used in our data analysis: single word production, single word comprehension, spelling, sentence comprehension, and sentence production. To obtain domain-specific severity scores, the proportion correct score for each domain was converted to a z-score based on the group mean and standard deviation, and the five z-scores were averaged to yield a composite language score for each participant. We correlated these domain and composite scores with z-transformed WAB-AQ scores (see Table 3 for scores by participant), with results showing strong correlations between measures: naming: $r(33) = .85$, $p < .0001$; word comprehension: $r(33) = .77$, $p < .0001$; spelling: $r(31) = .71$, $p < .0001$; sentence comprehension: $r(33) = .61$, $p < .0001$; sentence production: $r(33) = .79$, $p < .0001$; and composite language score: $r(33) = .93$, $p < .0001$. Spelling scores were not available for two participants.

2.2. Data Acquisition. Images were collected on four different 3.0T systems: a Siemens TIM Trio with a 32-channel head coil (Northwestern University), a Siemens Prisma with a 64-channel head/neck coil (Northwestern University), a Skyra with 20-channel head/neck coil (Boston University), and a Philips Intera with a 32-channel head coil (Johns Hopkins). Prior to the study, imaging sequences were equated across sites, using the same parameters in all scanners. Resting CBF maps were collected using a pseudo-continuous arterial spin labeling (pCASL) sequence [41] with two-dimensional gradient echo-planar readout (EPI): field of view (FOV) = 220 mm, in-plane resolution = 3.4×3.4 mm^2, 25 slices, thickness = 4 mm with 1 mm gap, and TE/TR = 11 ms/4500 ms. The labeling plane was situated 90 mm below the center of the imaging volume, and labeling pulses were applied for 1.5 s. The postlabeling delay was set to 1900 ms to balance between potential slow flow and adequate signal to noise ratio [42]. Sixty pairs of interleaved control and tag images were acquired for signal averaging. In addition to the ASL scan, high resolution T1-weighted anatomical images were acquired using an MPRAGE sequence [43]: FOV = 256 mm, TE/TR/TI = 2.91 ms/2300 ms/900 ms, 176 sagittal slices, and resolution of 1 mm^3.

2.3. Data Processing. Perfusion-weighted images from the pCASL scan were processed using a pipeline incorporating commands from Statistical Parametric Mapping (SPM8, Wellcome Trust Center for Neuroimaging, London, UK), and code developed in-house with Matlab R2013a (Mathworks,

Table 3: WAB Aphasia Quotients (AQ), language domain scores, and composite language scores (as z-scores) for each participant with aphasia.

Participant	WAB-AQ[1]	Composite language	Naming	Spelling	Word comprehension	Sentence comprehension	Sentence production
BU01	.92	.74	1.18	.33	.54	.41	1.23
BU02	−1.81	−1.39	−1.64	−1.20	−2.45	−.56	−1.12
BU03	−.63	−.55	−1.19	−.63	.54	−.56	−.93
BU04	.35	.25	.84	1.38	.29	−.75	−.54
BU06	.02	−.35	.39	−.63	.54	−.94	−1.12
BU07	−.80	−1.07	−.74	−1.12	−.46	−1.91	−1.12
BU09	1.28	1.30	1.07	1.78	.54	1.39	1.72
BU10	.63	.61	.73	.89	.29	1.00	.15
BU11	1.14	1.11	.84	−1.20	.29	1.77	1.53
BU12	−1.15	−.99	−.85	−1.20	−1.20	−.56	−1.12
BU13	1.17	1.42	1.18	1.78	.54	1.77	1.82
BU14	−.08	.16	−.40	.97	.54	−.56	.25
BU15	.92	.11	.84	−1.12	.54	.03	.25
BU17	.36	.02	1.07	−.63	.54	−.56	−.34
BU18	.52	.49	.39	.25	.29	1.39	.15
BU20	−2.34	−1.26	−1.64	−1.04	−1.20	−1.31	−1.12
BU21	−2.40	−1.78	−1.64	−1.20	−4.20	−.73	−1.12
BU22	−.04	.14	−.73	.57	−.46	1.19	.14
BUc01	.85	1.08	1.07	1.46	.54	1.58	.74
BUc04	1.11	1.23	1.18	1.05	.54	1.77	1.62
BUc05	−1.49	−1.00	−1.64	−1.12	−.95	−.17	−1.12
JH06	1.00	.46	−1.08	1.46	.29	1.00	.64
JHc04	−1.02	−.46	−1.07	−.47	.54	−.17	−1.12
JHc05	−.38	−.45	−.17	−1.04	.04	.03	−1.12
JHc06	1.03	.48	.05	.17	.54	−.17	1.82
JHc07	.41	.22	.28	1.05	.29	.03	−.54
NU03	.42	.56	.84	.57	.54	.03	.84
NU04	−.56	−.09	−.74	−.39	.29	−.36	.74
NU05	.35	−.10	.39	−.23	.54	−.94	−.24
NU06	1.00	.46	1.29	−.47	.54	.41	.55
NU08	−.59	−.58	−.51	−1.12	.29	−.56	−1.03
NU13	−.29	−.65	−.63	−1.20	−.71	−1.53	.25
NUc01	.44	.41	1.18	−.07	.54	−.17	.55
NUc02	.22	.05	.84	.81	.54	−1.33	−.63
NUc03	−.56	−.48	−.97	−.87	.04	.03	−.63

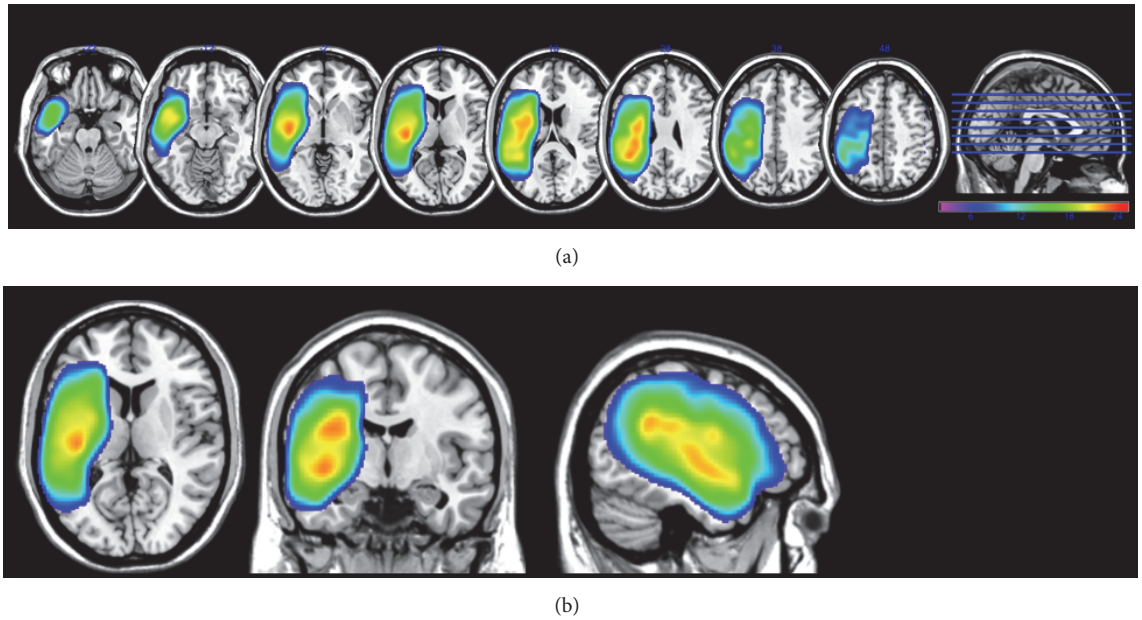
[1]WAB-AQ: Western Aphasia Battery-Aphasia Quotient.

Natwick, MA) and implemented on the Northwestern University Neuroimaging Data Archive (NUNDA) [44]. Briefly, the raw EPI images were first aligned to the first image of the time-series to extract 6 motion-related measures for the time-series. The motion parameters and signal from voxels containing 99% CSF were regressed out of the time-series to remove motion-related and physiological fluctuations in the signal [45]. Perfusion-weighted time-series were generated using pairwise subtraction, and outliers were removed based on the following criteria [46]: (a) translation greater than 0.8 mm; (b) rotation greater than 0.8°; (c) global signal or noise greater than 2 times the standard deviation. An average of 7 pairs of images was discarded from each ASL scan based on these criteria. The final perfusion-weighted time-series were then converted into quantitative flow (f) maps in units of mL/100 g/min using the following equation:

$$f = \frac{\lambda \cdot \Delta M}{2\alpha M_0 \cdot T_{1b} \cdot \left(e^{-\mathrm{PLD}/T_{1b}} - e^{-(\tau+\mathrm{PLD})/T_{1b}}\right)}, \quad (1)$$

where λ is the blood/tissue partition coefficient = 0.9 mL/g [47], ΔM is the perfusion-weighted signal, α is the inversion efficiency = 0.85 [41], M_0 is the equilibrium signal of tissue, PLD is the post-labeling delay, τ is the labeling duration, and T_{1b} is the T_1 of blood = 1664 ms [48].

Due to the low resolution of CBF maps, partial volume effects are prominent and need to be corrected before any further analysis. This was implemented as another NUNDA



(a)

(b)

Figure 1: Lesion overlap map for 35 participants with aphasia, by axial slices (a) and with a three-dimensional view (b), using the neurological convention (left hemisphere is on the left). The color bar indicates the degree of overlap from minimal overlap (violet; $N = 2$ participants overlapping) to maximum overlap (red; $N = 25$ participants overlapping). The overlap map was spatially smoothed (3 mm).

pipeline based on the following equation derived from positron emission tomography CBF studies [49]:

$$f_{GM} = \frac{f_{uncorr} - P_{WM} \cdot f_{WM}}{P_{GM}}, \quad (2)$$

where f_{uncorr} is the uncorrected flow value, P_{GM} and P_{WM} denote gray and white matter probability in the voxel, extracted from tissue segmentation of the high resolution anatomical image, and f_{GM} and f_{WM} are the corresponding tissue-specific flow values. f_{WM} was extracted from voxels containing 99% white matter. To minimize artifactually high CBF due to division by small numbers, the above calculation was limited to voxels containing at least 30% gray matter. The partial volume corrected CBF maps were then spatially normalized to MNI space using the transformation matrix calculated from the high resolution anatomical image.

2.4. Lesion Volume. Lesion volume was derived from lesion maps, developed by manual drawings measured using MRIcron software (http://www.sph.sc.edu/comd/rorden/mricron). To delineate the borders of necrotic tissue in each patient, we first determined intensity measures for white and gray matter (WM and GM, resp.) in the contralateral (right) hemisphere for each axial slice. The minimum right hemisphere WM intensity was determined. Left hemisphere lesioned tissue, on each slice, was drawn using the pen tool of MRIcron. Then the minimum WM intensity was applied to the outlined area using the intensity filter function. Additional manual correction was applied using lesion outlines in multiple corresponding coronal and sagittal views. Total lesion volume was calculated by summing the number of lesioned voxels in the left hemisphere for each participant. In our analyses the size of each voxel was 1 mm^3 and therefore lesion volume is reported in mm^3. Composite axial T1 MR images showing lesion location and overlap for the 35 participants in the study are shown in Figure 1.

2.5. Regions of Interest (ROIs). ROIs were defined based on the Harvard Oxford atlas thresholded at minimum of 25% gray matter, as well as from the Automated Anatomical Labeling (AAL) atlas. The list of ROIs ($n = 76$, 38 per hemisphere) is given in Table 4. Second, two perilesional ROIs and their right hemisphere homologues were created by dilating the lesion to 6 mm (0–6 mm) and 12 mm (6–12 mm) beyond its boundaries and subtracting the original lesion volume.

Because CBF is a physiological parameter that fluctuates with many factors such as vasoactive agents in food, beverages, and drugs and varies widely between subjects, all CBF values were normalized to the mean CBF of each individual's right occipital lobe ROI, assuming that CBF in this region is not compromised by a left hemisphere stroke resulting in aphasia. Importantly, raw perfusion values in this region did not differ significantly between patients (M = 68.8, SD = 25.5) and controls (M = 77.6, SD = 18.0), based on a one-way ANCOVA adjusting for age ($F(1, 48) = 2.55$, $p = .12$).

Mean CBF within each ROI was only computed from voxels with 30% or more gray matter, as these are the only voxels that survived the partial volume correction step detailed above. In addition to correcting for partial volume, the ROIs also accounted for the lesion mask (voxels where the lesion value is set to 1 were excluded) and the field of view of the perfusion scan (an FOV mask was created to exclude all voxels not covered by the perfusion scan). Thus lesions

Table 4: (a) Mean raw perfusion values (and standard deviation) for each region of interest (ROI) for patients and healthy controls in the left and right hemisphere. (b) Mean right-occipital-normalized perfusion values (and standard deviation) for each region of interest (ROI) for patients and healthy controls in the left and right hemisphere.

(a)

Region of interest (ROI)	Left hemisphere			Right hemisphere		
	Controls	Patients	% diff	Controls	Patients	% diff
Inferior frontal gyrus, orbital part[1]	74.75 (12.84)	59.98 (23.92)	80%	78.07 (14.77)	71.53 (22.73)	92%
Frontal pole	75.04 (14.11)	68.46 (25.16)	91%	77.08 (16.00)	73.40 (25.03)	95%
Superior frontal gyrus	60.75 (16.51)	67.09 (28.58)	110%	62.66 (17.06)	74.22 (26.20)	118%
Middle frontal gyrus	68.85 (14.09)	62.28 (26.49)	90%	71.39 (16.35)	76.07 (29.97)	107%
IFG, pars triangularis	76.61 (15.53)	58.49 (29.30)	76%	82.37 (20.38)	71.97 (24.18)	87%
IFG, pars opercularis	72.03 (19.32)	50.57 (25.74)	70%	72.87 (19.82)	70.91 (23.61)	97%
Precentral gyrus	62.83 (13.81)	63.10 (22.87)	100%	63.90 (12.72)	77.83 (26.56)	122%
Temporal pole	69.53 (9.78)	51.17 (19.35)	74%	72.23 (10.69)	62.88 (18.99)	87%
Superior temporal Gyrus, anterior	60.67 (19.02)	41.56 (23.52)	69%	62.89 (22.44)	62.60 (23.19)	100%
Superior temporal gyrus, posterior	69.25 (16.40)	45.70 (19.07)	66%	71.41 (17.42)	68.82 (23.58)	96%
Middle temporal gyrus, anterior	65.34 (14.08)	46.73 (25.43)	72%	70.86 (16.02)	61.06 (21.72)	86%
Middle temporal gyrus, posterior	71.00 (14.54)	50.23 (26.53)	71%	73.47 (14.60)	62.30 (24.03)	85%
Inferior temporal gyrus, anterior	53.68 (16.01)	44.55 (26.86)	83%	53.61 (12.95)	45.52 (24.79)	85%
Inferior temporal gyrus, posterior	62.21 (16.40)	48.26 (19.22)	78%	54.44 (10.75)	50.62 (21.34)	93%
Inferior temporal gyrus, temporooccipital part	62.11 (12.94)	47.26 (22.41)	76%	67.39 (16.01)	53.72 (17.41)	80%
Postcentral gyrus	65.27 (14.88)	61.51 (21.92)	94%	65.52 (13.60)	76.04 (23.83)	116%
Superior parietal lobule	64.03 (14.48)	57.39 (22.92)	90%	60.59 (14.89)	69.38 (25.58)	115%
Supramarginal gyrus, anterior	65.10 (16.58)	47.49 (18.24)	73%	63.63 (13.51)	63.00 (21.94)	99%
Supramarginal gyrus, posterior	69.63 (17.40)	48.53 (21.63)	70%	68.57 (12.42)	66.65 (23.02)	97%
Angular gyrus	68.04 (16.70)	46.28 (25.04)	68%	65.94 (11.83)	66.88 (23.02)	101%
Lateral occipital cortex, superior	72.13 (18.07)	60.48 (24.44)	84%	73.05 (14.42)	73.41 (25.21)	100%
Lateral occipital cortex, inferior	77.21 (19.52)	59.67 (36.35)	77%	75.67 (18.08)	70.25 (27.28)	93%
Frontal medial cortex	68.35 (18.82)	57.89 (24.42)	85%	70.51 (18.57)	62.23 (24.21)	88%
Supplementary motor area (SMA)	59.08 (18.25)	62.57 (29.89)	106%	57.70 (16.41)	68.00 (24.91)	118%
Paracingulate gyrus	62.97 (13.94)	55.45 (18.16)	88%	66.20 (15.71)	61.56 (21.89)	93%
Anterior cingulate	61.74 (15.48)	55.41 (18.20)	90%	62.87 (15.38)	59.95 (19.52)	95%
Posterior cingulate	69.11 (16.05)	61.06 (23.29)	88%	70.68 (17.48)	67.99 (23.89)	96%
Precuneus	63.33 (17.26)	57.12 (22.06)	90%	63.91 (18.19)	63.07 (22.55)	99%
Parahippocampal gyrus, posterior	56.73 (24.49)	48.47 (17.98)	85%	56.53 (24.01)	55.70 (19.94)	99%
Temporal fusiform cortex, posterior	46.23 (10.08)	47.19 (18.14)	102%	45.85 (10.27)	46.93 (18.16)	102%
Temporal occipital fusiform cortex	49.67 (15.59)	45.64 (21.72)	92%	49.40 (12.85)	51.23 (21.74)	104%
Occipital fusiform gyrus	61.41 (16.06)	54.07 (29.00)	88%	61.51 (15.54)	58.79 (26.45)	96%
Frontal operculum cortex	60.12 (13.76)	37.58 (25.39)	63%	58.17 (12.15)	58.39 (21.55)	100%
Parietal operculum cortex	63.33 (14.96)	37.37 (16.72)	59%	61.32 (15.02)	59.44 (19.41)	97%
Planum temporale	75.43 (19.61)	50.39 (29.98)	67%	72.83 (19.65)	69.98 (24.90)	96%
Hippocampus	52.66 (10.83)	49.05 (17.47)	93%	54.57 (10.63)	50.49 (18.15)	93%
Cerebellum V	48.40 (19.89)	44.93 (17.66)	93%	50.52 (19.65)	41.83 (17.54)	83%
Cerebellum VI	54.17 (17.05)	47.90 (19.77)	88%	54.07 (15.33)	46.84 (18.76)	87%

(b)

Region of interest (ROI)	Left hemisphere					Right hemisphere				
	Controls	Patients	F	p	% diff	Controls	Patients	F	p	% diff
Inferior frontal gyrus, orbital part[1]	.98 (.15)	.95 (.44)	.40	ns	97%	1.02 (.15)	1.10 (.33)	.85	ns	107%
Frontal pole	.98 (.13)	1.05 (.37)	.21	ns	107%	1.00 (.10)	1.12 (.32)	1.49	ns	112%
Superior frontal gyrus	**.79 (.16)**	**1.03 (.42)**	**4.12**	**.048**	**131%**	**.81 (.16)**	**1.12 (.34)**	**7.91**	**.01**	**138%**
Middle frontal gyrus	.90 (.13)	.95 (.36)	.98	ns	106%	.93 (.14)	1.14 (.34)	3.12	.08	123%
IFG, pars triangularis	1.01 (.20)	.93 (.44)	.00	ns	92%	1.06 (.15)	1.11 (.39)	.93	ns	104%

(b) Continued.

Region of interest (ROI)	Left hemisphere					Right hemisphere				
	Controls	Patients	F	p	% diff	Controls	Patients	F	p	% diff
IFG, pars opercularis	.93 (.16)	.80 (.41)	.16	ns	86%	.94 (.14)	1.08 (.34)	1.89	ns	115%
Precentral gyrus	.82 (.11)	.98 (.37)	1.90	ns	120%	**.83 (.12)**	**1.18 (.33)**	**10.87**	**.002**	**141%**
Temporal pole	**.92 (.17)**	**.78 (.27)**	**5.32**	**.03**	**85%**	.96 (.20)	.97 (.28)	.61	ns	100%
Superior temporal gyrus, anterior	**.78 (.17)**	**.62 (.30)**	**6.74**	**.01**	**80%**	.80 (.19)	.95 (.30)	3.93	.05	118%
Superior temporal gyrus, posterior	**.91 (.17)**	**.71 (.29)**	**8.42**	**.01**	**79%**	.94 (.19)	1.04 (.27)	.84	ns	111%
Middle temporal gyrus, anterior	**.86 (.17)**	**.69 (.28)**	**6.97**	**.01**	**80%**	.93 (.16)	.93 (.28)	.06	ns	100%
Middle temporal gyrus, posterior	**.93 (.15)**	**.75 (.29)**	**7.13**	**.01**	**80%**	.96 (.14)	.93 (.23)	.06	ns	96%
Inferior temporal gyrus, anterior	.71 (.21)	.67 (.36)	.00	ns	94%	.72 (.21)	.67 (.28)	.07	ns	93%
Inferior temporal gyrus, posterior	.81 (.17)	.74 (.29)	.21	ns	91%	.72 (.16)	.77 (.27)	.05	ns	107%
Inferior temporal gyrus, temporooccipital part	.81 (.11)	.71 (.23)	.17	ns	87%	.88 (.13)	.80 (.16)	.00	ns	92%
Postcentral gyrus	.85 (.13)	.97 (.40)	.76	ns	114%	**.86 (.14)**	**1.16 (.34)**	**10.83**	**.002**	**136%**
Superior parietal lobule	.83 (.13)	.89 (.39)	.12	ns	107%	**.78 (.14)**	**1.05 (.35)**	**8.28**	**.01**	**134%**
Supramarginal gyrus, anterior	.84 (.13)	.76 (.34)	.72	ns	90%	.83 (.14)	.95 (.25)	2.61	ns	114%
Supramarginal gyrus, posterior	.90 (.13)	.76 (.33)	3.94	.05	84%	**.90 (.15)**	**1.01 (.26)**	**4.06**	**.049**	**112%**
Angular gyrus	**.88 (.14)**	**.72 (.37)**	**5.29**	**.03**	**81%**	.87 (.13)	1.01 (.28)	1.35	ns	117%
Lateral occipital cortex, superior	.93 (.09)	.93 (.34)	.08	ns	100%	**.95 (.10)**	**1.10 (.26)**	**4.25**	**.045**	**116%**
Lateral occipital cortex, inferior	.99 (.07)	.85 (.30)	3.64	.06	86%	.98 (.07)	1.02 (.14)	.17	ns	105%
Frontal medial cortex	.88 (.18)	.88 (.35)	.05	ns	100%	.91 (.17)	.95 (.31)	.14	ns	104%
Supplementary motor area (SMA)	.77 (.20)	.96 (.44)	2.84	.10	125%	**.75 (.17)**	**1.03 (.34)**	**6.96**	**.01**	**138%**
Paracingulate gyrus	.82 (.13)	.84 (.24)	.97	ns	103%	.86 (.14)	.92 (.23)	1.26	ns	107%
Anterior cingulate	.80 (.12)	.85 (.27)	.61	ns	106%	.82 (.13)	.91 (.25)	2.12	ns	111%
Posterior cingulate	.90 (.13)	.92 (.31)	.03	ns	103%	.91 (.13)	1.02 (.29)	.68	ns	112%
Precuneus	.82 (.12)	.86 (.24)	.38	ns	105%	.82 (.12)	.93 (.20)	1.04	ns	114%
Parahippocampal gyrus, posterior	.73 (.25)	.73 (.21)	.23	ns	100%	.73 (.27)	.84 (.25)	.02	ns	114%
Temporal fusiform cortex, posterior	.60 (.09)	.71 (.20)	1.84	ns	117%	.60 (.09)	.70 (.18)	.01	ns	117%
Temporal occipital fusiform cortex	.64 (.12)	.66 (.20)	.41	ns	104%	.64 (.11)	.74 (.14)	.06	ns	116%
Occipital fusiform gyrus	.79 (.12)	.79 (.28)	.05	ns	99%	.79 (.11)	.85 (.22)	.02	ns	107%
Frontal operculum cortex	.79 (.15)	.60 (.41)	3.91	.05	77%	.76 (.12)	.89 (.26)	3.01	.09	117%
Parietal operculum cortex	**.83 (.16)**	**.61 (.33)**	**6.48**	**.01**	**74%**	.80 (.18)	.91 (.26)	.47	ns	114%
Planum temporale	**.98 (.18)**	**.81 (.53)**	**5.54**	**.02**	**83%**	.95 (.19)	1.06 (.30)	.01	ns	112%
Hippocampus	.70 (.17)	.75 (.27)	.48	ns	106%	.72 (.17)	.76 (.21)	.26	ns	105%
Cerebellum V	.61 (.14)	.66 (.14)	.75	ns	108%	.64 (.15)	.62 (.15)	.36	ns	96%
Cerebellum VI	.69 (.10)	.71 (.18)	.17	ns	103%	.70 (.11)	.70 (.24)	.68	ns	101%

Bold cells: significant group differences ($p < .05$).
[1]Region from Automated Anatomical Labeling (AAL) atlas; all others from Harvard-Oxford Atlas.
% diff: percentage of normal (control participants) perfusion values for people with aphasia by ROI.
Note. Means and standard deviations of normalized perfusion values. F and p values derived from one-way ANCOVA, with age as a covariate.

were excluded from the analysis, as otherwise they might substantially lower the CBF values in the left hemisphere. Indeed, mean CBF across participants in lesioned voxels was substantially lower (M = 17.95, SE = 2.1) than in nonlesioned voxels in the left hemisphere (M = 59.78, SE = 3.1).

2.6. Data Analyses. To test whether perfusion laterality differs broadly between patients and healthy controls, we conducted a 2 (hemisphere: left versus right as a within-subjects factor) × 2 (group: patient versus healthy control as a between-subjects factor) Repeated Measures Analysis of Covariance (RMANCOVA) with age as a covariate. Note that this analysis did not include all voxels from each hemisphere; rather, we included only the data from the 38 regions of interest (ROIs) that were the focus of our investigation. Follow-up tests were one-way ANCOVAs adjusting for age.

The level of statistical significance in all inferential analyses (here and those described below) was $p \leq .05$.

We also tested perfusion values from each of the ROIs (ROI: 76 levels, as a within-subjects factor) with group (patients versus controls) as a between-subjects factor and age as a covariate. Given the large number of ROIs and brain regions included in this analysis, we conducted analogues of protected t-tests to protect against inflated experimentwise Type I error [50]. Simulations have shown that this approach provides adequate Type I error rate protection, while affording better power than other approaches when conducting multiple tests [51]. In the present analysis, this approach consisted of using repeated measures analyses and only testing for group differences within individual regions if there was a significant ROI × group interaction. For the follow-up tests, we used one-way ANCOVA, adjusted for age, comparing patients against controls in each ROI.

2.6.1. Perilesional ROI Analyses. Analyses of perilesional perfusion were also conducted for the patients only, with three RMANOVAs. First, a 2 (perilesional space: 0 to 6 mm versus 6 to 12 mm) × 2 (region: left perilesional versus right homologue) test was performed on data from 35 patients comparing perfusion in the perilesional area of the left hemisphere to a homologous contralateral area in the right hemisphere. A second analysis compared perfusion in perilesional space to that in the remainder of the left hemisphere (i.e., the remainder of the entire hemisphere, not restricted to the 38 ROIs in our other analyses) using a 2 (perilesional space: 0 to 6 mm versus 6 to 12 mm) × 2 (left hemisphere region: perilesional versus the remainder of the left hemisphere) RMANOVA. For the 0–6 mm perilesional space, the remainder of the left hemisphere excluded the lesion and the 0–6 mm space; for the 6–12 mm perilesional space the remainder excluded the lesion and perilesional tissue from 0 to 12 mm. The third analysis examined all three regions across both hemispheres using a 3 (perilesional space: 0–6 mm, 6–12 mm, and 12+ mm) × 2 (left versus right hemisphere) RMANOVA.

2.6.2. Associations between Perfusion and Language and Demographic Variables. First, we computed a difference score for each of the 38 bilateral ROIs as well as perilesional ROIs (i.e., 0–6 mm and 6–12 mm), subtracting left hemisphere perfusion values from right hemisphere perfusion values, such that positive scores indicated lower perfusion in left hemisphere tissue compared to the right. These difference scores then were correlated with composite language scores with partial correlations adjusting for lesion volume. Given that we computed these partial correlations for 38 ROIs, we applied a Holm correction [52] for multiple comparisons. If the partial correlation was significant with the correction applied, we followed up with additional partial correlations between the perfusion difference score and each of the five language domain scores (word production, word comprehension, spelling, sentence comprehension, and sentence production). Finally, we computed partial correlations, adjusting for lesion volume, between mean perfusion values (normalized to the right occipital lobe) for each hemisphere separately (excluding the lesion and the 0–6 mm perilesional ROI) with language composite and domain scores and demographic variables (WAB-AQ, age, sex, education, and lesion age), and computed the simple correlation between perfusion and lesion volume itself.

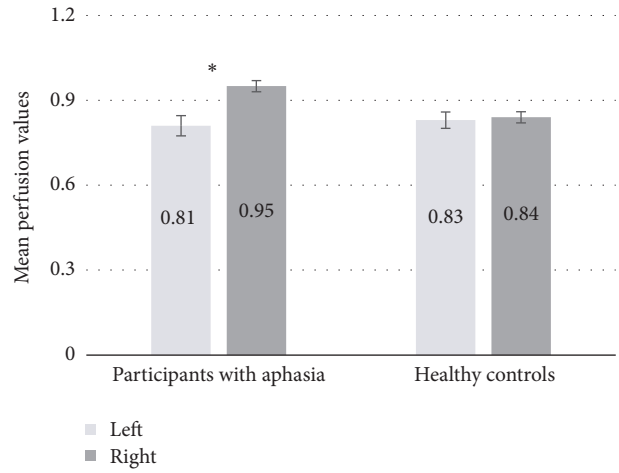


Figure 2: Mean right-occipital-normalized perfusion values for participants with aphasia and healthy controls, averaged across the 38 ROIs for the left and right hemispheres. Error bars are standard error. ∗ indicates a significant left versus right difference ($p < .05$).

3. Results

The RMANCOVA examining hemisphere by group effects (including age as a covariate) showed a significant group × hemisphere interaction ($F(1, 48) = 11.27$, $p < .01$) (Figure 2). Follow-up RMANOVAs demonstrated no significant difference between the perfusion values (over the 38 ROIs) for the left (M = .83, SD = .08) and right hemispheres (M = .84, SD = .08) in healthy control participants ($F(1, 14) = 1.62$, $p = .22$); however, for the aphasic participants, perfusion values over the 38 ROIs in the right hemisphere (M = .95, SD = .17) were significantly higher than in the left hemisphere (M = .81, SD = .21) ($F(1, 33) = 4.02$, $p = .05$). In addition, one-way ANCOVAs revealed a difference approaching conventional levels of significance with higher perfusion values for the patients compared to the healthy controls in the right ($F(1, 48) = 2.84$, $p < .10$), but not in the left hemisphere ($F(1, 48) = .45$, $p = .51$).

The RMANCOVA examining perfusion differences between participant groups by ROI, with age as a covariate, revealed a significant interaction of group × ROI ($F(75, 3525) = 3.87$, $p < .001$). As mentioned above, we used an analogue of protected t-tests to protect against inflated experimentwise Type I error. That is, for this set of analyses, if the group × ROI interaction had not been significant we would not have tested for group differences in each of the individual ROIs. Given that the interaction was significant, we proceeded by testing for group differences within individual ROIs. As shown in Table 4(b) and Figure 3, the groups differed significantly on 16 of the total 76 ROIs across hemispheres. Age-adjusted perfusion value differences between

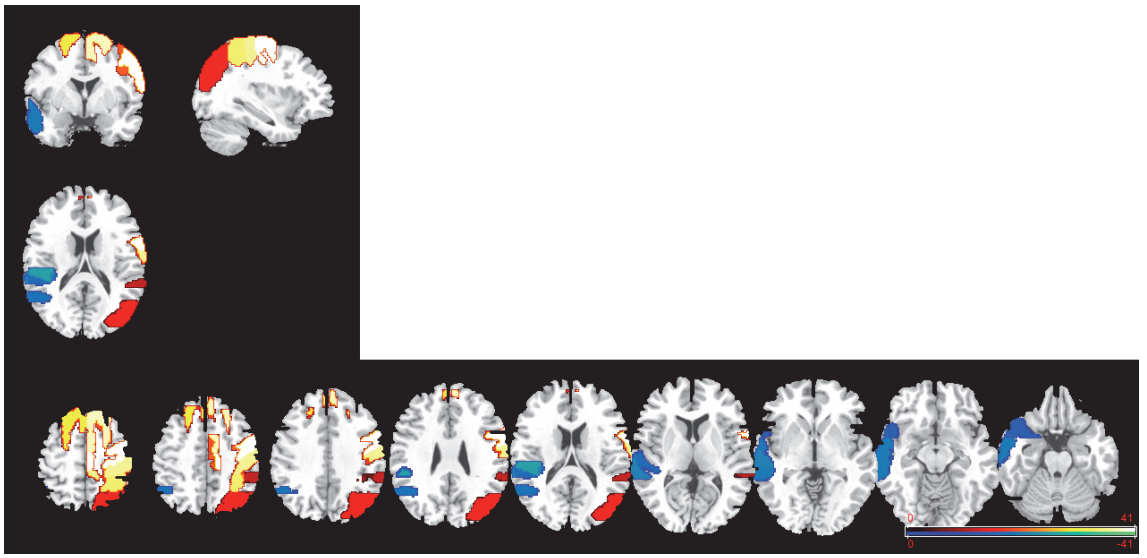


Figure 3: ROIs with greater perfusion (hyperperfusion; red-yellow color scale) and lesser perfusion (hypoperfusion; blue-green color scale) in patients relative to control participants, in three-dimensional and axial slice views (left hemisphere is on the left). Only regions that differ significantly across groups (patients versus controls; $p < .05$) are indicated.

the patients and control participants in the left hemisphere were significant in nine ROIs, with lower values for patients in eight of these regions: the anterior and posterior superior and middle temporal gyri, the temporal pole, the angular gyrus, the planum temporale, and the parietal opercular cortex. The superior frontal gyrus showed the opposite pattern with higher values for patients. Age-adjusted perfusion value differences in the right hemisphere were significant in seven ROIs, all in the direction of higher perfusion for the patients: superior frontal gyrus, precentral gyrus, postcentral gyrus, superior parietal lobule, posterior supramarginal gyrus, superior lateral occipital cortex, and supplementary motor area (SMA).

3.1. Perfusion in Perilesional ROIs. The 2 (dilation of perilesional space: 0–6 mm versus 6–12 mm) × 2 (region: left perilesional versus right homologue) RMANOVA revealed a significant dilation × region interaction ($F(1, 34) = 52.60$, $p < .001$) in the aphasic patient group. For the 0–6 mm dilation there was significantly greater perfusion in the homologous right hemisphere space (M = .99, SD = .23) than the left perilesional hemisphere region (M = .77, SD = .21; $t(34) = 7.64$, $p < .001$). Perfusion was also significantly greater for the 6–12 mm dilation in the homologous right hemisphere space (M = .97, SD = .21) than the left perilesional hemisphere region (M = .92, SD = .23; $t(34) = 2.32$, $p = .027$). The interaction reflects a larger left versus right difference for 0–6 mm than 6–12 mm.

The 2 (dilation of perilesional space: 0–6 mm versus 6–12 mm) × 2 (region: left perilesional versus the rest of the left hemisphere) RMANOVA revealed a significant dilation × region interaction ($F(1, 34) = 53.29$, $p < .001$). Comparisons between the perilesional region and the rest of the left hemisphere (M = .94, SD = .22) was significant for the 0–6 mm ROI (M = .77, SD = .21) ($t(34) = 5.62$, $p < .001$), but not for the 6–12 mm perilesional region (M = .92, SD = .22) ($t(34) = .34$, ns). Perfusion also was significantly lower in the 0–6 mm ROI than in the 6–12 mm ROI ($t(34) = 7.57$, $p < .0001$).

Finally, we conducted an overall 3 (dilation: 0–6 mm, 6–12 mm, rest of hemisphere) × 2 (hemisphere: left versus right) RMANOVA (Figure 4). The interaction between dilation and

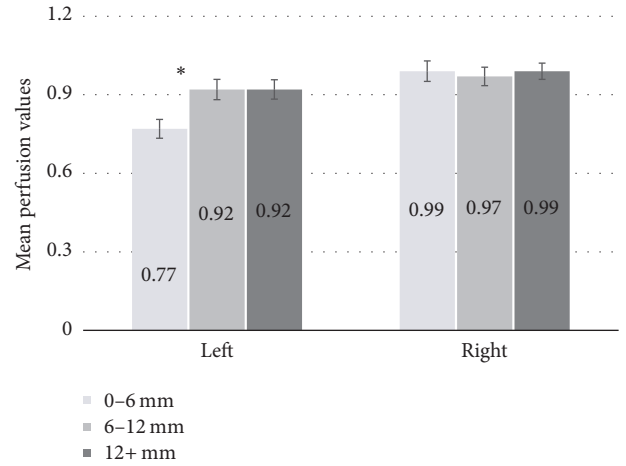


Figure 4: Mean right-occipital-normalized perfusion values for participants with aphasia for the left perilesional tissue and the corresponding right homologous regions in the 0–6 mm, 6–12 mm, and remaining (12+ mm) ROIs. Error bars are standard error. * indicates a significant difference ($p < .05$). Significance is not indicated for left versus right differences (all ROIs are significant between hemispheres).

hemisphere was significant ($F(2, 68) = 34.8$, $p < .0001$). Follow-up t-tests are consistent with the previous analyses, with perfusion in the left hemisphere lower than in the right hemisphere at each dilation (all ps $< .05$). In addition, within the left hemisphere, perfusion in the 0–6 mm region was lower than in the 6–12 mm region ($p < .05$), and perfusion was no different for the 6–12 mm region than the remaining left hemisphere tissue. No within-hemisphere contrasts reached significance in the right hemisphere.

3.2. Relationship between Perfusion, Language Performance, and Patient Variables. Correlational analyses for each ROI difference score (i.e., right minus left hemisphere perfusion values) and composite language scores, adjusting for lesion volume, showed significant negative correlations (i.e., greater difference scores and poorer language performance) in 6 ROIs: anterior inferior temporal gyrus ($r = -.354$, $p = .04$), postcentral gyrus ($r = -.360$, $p = .037$), supplementary motor area (SMA; $r = -.419$, $p = .014$), paracingulate gyrus ($r = -.353$, $p = .04$), anterior cingulate gyrus ($r = -.344$, $p = .046$), and posterior cingulate gyrus ($r = -.360$, $p = .037$). However, no correlation remained significant when the correction for multiple comparisons was applied. Accordingly, we did not follow up on these analyses with correlations between the perfusion difference scores and the five language domain scores.

With respect to the perilesional regions of interest, correlations between the composite language score and perilesional difference scores (i.e., right homologous perilesional ROI minus left perilesional ROI values), with lesion volume included as a covariate, revealed a significant negative correlation for 0–6 mm ($r = -.469$, $p = .007$), but not for 6–12 mm ($r = -.288$, $p = .11$). Thus, we calculated partial correlations with the five language domain scores separately only for the 0–6 mm perilesional ROI, adjusting for lesion volume. Results revealed significant negative associations between perfusion difference scores for the 0–6 mm ROI and single word production ($r = -.354$, $p = .032$), sentence comprehension ($r = -.427$, $p = .015$), and sentence production ($r = -.451$, $p = .01$). No other partial correlations reached significance (all rs $\leq |.30|$, all ps $\geq .097$). These effects are summarized in Table 5.

Finally, partial correlations (adjusting for lesion volume) between average perfusion values in nonperilesional tissue across each hemisphere (in the left, excluding the infarcted region and the 0–6 mm perilesional region; in the right, also excluding regions homologous to the lesion and the 0–6 mm perilesional ROI) and composite language scores for the patient group were not significant for the left hemisphere ($r = .14$, $p = .45$) or the right hemisphere homologous region ($r = .004$, $p = .98$). Likewise, correlations between average perfusion and demographic variables including age, sex, education, and lesion age (in months) revealed no significant correlations or partial correlations (correcting for lesion volume) for either hemisphere (all rs $\leq |.26|$, all ps $\geq .12$). However, a significant negative correlation between perfusion and lesion volume was found for the left ($r = -.37$, $p = .027$) but not the right hemisphere ($r = -.27$, $p = .112$).

4. Discussion

This paper examined perfusion values, normalized to the right occipital lobe, in people with chronic stroke-induced aphasia compared to cognitively healthy, right-handed, non-brain-damaged control participants. We focused our investigation on 38 regions of interest in each hemisphere. Results showed that whereas healthy controls evince no significant between-hemisphere differences in normalized perfusion values, averaged across our ROIs, the aphasic participants' values differ significantly between the left and right hemisphere. However, rather than showing left (ipsilesional) hemisphere hypoperfusion, as predicted, the patients showed normalized perfusion values similar to healthy controls in the left hemisphere, with no significant difference found between the two participant groups. Conversely, the aphasic group showed hyperperfusion in the right (contralesional) hemisphere, with overall perfusion values significantly greater compared to controls. Furthermore, for the aphasic group, right hemisphere perfusion was significantly higher than left hemisphere perfusion. These findings are broadly consistent with those reported by Richardson et al. [11], who found lower perfusion values in the left compared to the right hemisphere in participants with aphasia. However, patient perfusion values were not compared to a healthy control group, precluding the finding that between-hemisphere differences may have resulted from greater than normal right hemisphere perfusion in their patient group rather than lesser than normal left hemisphere perfusion.

Notably, not all regions in the left hemisphere were normally perfused in the patient group, and not all regions in the right hemisphere were hyperperfused. Within the left hemisphere, 8 regions showed a pattern of significant hypoperfusion, and one region showed increased perfusion. The remaining 29 regions did not differ between patients and controls. The lack of an overall effect of left hemisphere hypoperfusion likely reflects this variability, such that focal hypoperfusion was averaged out across the full set of 38 ROIs. In the right hemisphere, perfusion was significantly higher in the patient group compared to healthy controls in 7 regions, but no right hemisphere regions were hypoperfused. The remaining 31 regions did not differ significantly between patients and controls.

Note that this pattern of variable hypo- and hyperperfusion does not appear to be a consequence of our decision to normalize the raw perfusion values to the right occipital lobe. First, the raw perfusion values for the participants with aphasia and the healthy controls did not differ significantly in this region, suggesting that normalization did not introduce a systematic bias across groups.

One interpretation of the unexpected finding of hyperperfused regions in the right hemisphere is that autoregulation of blood flow is adaptive to vascular lesion, with upregulation in undamaged regions. Blood typically directed automatically, for example, to the left hemisphere middle cerebral artery (MCA), is shifted elsewhere, potentially to the left anterior cerebral artery (ACA) or the right MCA. If this were the case, however, we might expect all tissue supplied by these vessels to show equally greater perfusion, and perfusion

Table 5: Partial correlations, controlling for lesion volume, between perilesional perfusion and language ability for 35 participants with aphasia.

Difference Right-Left	Partial correlations controlling for lesion volume											
	Composite language		Naming		Spelling		Word comprehension		Sentence comprehension		Sentence production	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
0–6 mm	−.469*	.007	−.354*	.032	−.271	.13	−.299	.097	−.427*	.015	−.451*	.01
6–12 mm	−.288	.11	na		na		na		na		na	

Note. Difference scores were created by subtracting average perfusion in the perilesional area (left hemisphere) from the average perfusion in the analogous right hemisphere area. * $p < .05$.

in these regions would putatively be higher than that in regions supplied by other sources (e.g., the posterior cerebral artery (PCA)).

Although we did not examine every region supplied by these blood vessels, there may nonetheless be a pattern along these lines. In the left hemisphere, all of the regions found to be significantly hypoperfused are supplied by the MCA: the anterior and posterior superior and middle temporal gyri, temporal pole, angular gyrus, planum temporale, and parietal opercular cortex, whereas one left hemisphere region found to be hyperperfused is supplied by the ACA: the superior frontal gyrus. Regions supplied by the PCA were not abnormally perfused in either hemisphere. Furthermore, there were no hypoperfused regions supplied by the ACA and no hyperperfused regions supplied by the MCA or PCA. Thus, the overall pattern in the left hemisphere seems to be that, among the regions we examined, the regions supplied by the MCA are hypoperfused (or normal) and those supplied by the ACA are hyperperfused or normal, but regions supplied by the PCA show normal perfusion levels.

In the right hemisphere, regions either were normally perfused or showed perfusion levels significantly greater than that of the healthy controls. Of the (significantly) hyperfused regions, one is supplied by the MCA (the posterior supramarginal gyrus), three are supplied by the ACA (superior frontal gyrus, superior parietal lobule, and supplementary motor area), two are supplied by both the ACA and MCA (precentral and postcentral gyri, which are supplied by the ACA medially and the MCA laterally; our perfusion measures did not distinguish medial versus lateral aspects of these regions), and one is supplied by the PCA (superior lateral occipital cortex). The pattern in the right hemisphere thus appears complementary to the pattern in the left; that is, regions supplied by the MCA are hyperperfused (or normal). Similarly, as in the left hemisphere, hyperperfused regions are supplied by the ACA and regions supplied by the PCA are largely normal.

This appears to be consistent with a compensatory change leading to increased perfusion in regions supplied by the right MCA and bilateral ACA in response to reduced perfusion in regions supplied by the left MCA and may reflect right hemisphere vascular reserve engaged to absorb and distribute additional blood flow. However, this is not clear-cut in that hypoperfused regions in the left were not hyperperfused in the right hemisphere (except for the anterior superior temporal gyrus, which was significantly hypoperfused in the left hemisphere with hyperperfusion that approached significance in the right).

The functional significance of hyperperfusion in regions within the right hemisphere is also not completely clear. One interpretation is that this reflects maladaptive language processing, although correlations between perfusion difference scores (right-left hemisphere) and language performance (i.e., greater right hemisphere perfusion and poorer language ability) were not significant when corrected for multiple comparisons. Thus, it is unlikely that right hemisphere hyperperfusion alone reflects inefficient language function. Another more likely interpretation is that, because increased perfusion reflects increases in neuronal energy usage, perfusion value increases in our patients may be associated with generally increased cognitive effort. By virtue of a left hemisphere lesion, right hemisphere regions become more actively engaged. This interpretation is also supported by our observed bilateral hyperperfusion in the SMA (though the increased perfusion only approached significance in the left hemisphere). The SMA is one of several domain-general cognitive regions associated with the multiple-demand system in healthy people, which is engaged for language and other cognitive tasks when domain-specific resources are disrupted or unavailable [53, 54]. Notably, the pattern of hyperperfused regions is also in line with the Scaffolding Theory of Cognitive Aging (STAC) [55], which suggests that bilateral frontal regions (i.e., superior frontal and SMA) are engaged as a function of aging to compensate for neurocognitive decline and may also be available when brain damage compromises cognitive ability. Our results encourage further investigation in this direction.

When the brain is divided into regions based on rings of perilesional tissue, the results are less unexpected. Our findings showed that, on average, for perilesional areas, patients had significantly lower perfusion values in the left hemisphere than in homologous regions in the right hemisphere. However, within the left hemisphere, perfusion values became more normal in our participants with increasing distance from the lesion. Thus, even in chronic stages of aphasia a perilesional ring close to the lesion remains substantially hypoperfused. Importantly, relative perfusion values in the 0–6 mm (but not 6–12 mm) perilesional region correlated with language severity, even when accounting for lesion volume. The lesion-adjacent region may therefore not

only have a greater reduction in cerebral blood flow, but the extent of reduced blood flow in this region is also predictive of language impairment. For our participant group, perilesional perfusion (0–6 mm only) was significantly correlated with naming, sentence comprehension, and sentence production. We note, however, that this latter finding may reflect the language impairment patterns of our aphasic participants in that the majority of our participants were selected for naming impairments ($n = 21$ from Boston University), with 11 selected for impaired sentence production and comprehension (from Northwestern) and 5 selected for dysgraphia (from Johns Hopkins).

We note, however, that while our results speak to the importance of lesion-adjacent perilesional tissue for impaired language, we did not attempt to determine a precise boundary within which tissue may be underperforming, and beyond which tissue may be functioning normally. There is unfortunately no standard operational definition of what constitutes "perilesional" tissue [20]. Some previous studies have identified hypoperfused tissue in a 3–8 mm ring around the lesion [11], whereas others have reported reduced perfusion as far away as 15 mm from the lesion [20]. The problem here is twofold: an objectively determined anatomical method for determining hypoperfused tissue has not been identified, and any such method needs to account not only for fine-grained differences across brain regions (e.g., at the voxel level), but also for the possibility that perilesional rings may not adequately capture the functional impact of vascular lesions. Depending on the volume and location of the lesion, tissue surrounding it may include both normally perfused and hypoperfused tissue, such that averaging perfusion within the entire ring may lead to spurious results. It is possible, for example, that ribbons of hypoperfused tissue, extending distally from the lesion and including both perilesional and other cortical tissue, may better capture the cognitive effects of brain damage. In addition, lesion-adjacent rings may often include neural tissue that was involved in language processing prior to stroke as well as tissue that was not, thus, precluding determination of a clear relation between perfusion and language impairment. Further research is needed to identify the functional significance of reduced perfusion at various distances from the lesion, in particular regions within lesion-adjacent tissue, and in pathways following the vasculature.

Finally, we note that the only nonlanguage measure that correlated with perfusion in the remaining (undamaged and nonperilesional) portion of the left hemisphere was lesion volume. However, no correlation between lesion volume and perfusion in the right hemisphere region was found. Likewise, no correlations were found between perfusion (in either hemisphere) and lesion age (months after onset of stroke), chronological age, education, or sex. These results are consistent with prior findings in the literature and suggest that perfusion levels reach a stable steady state in individuals with chronic stage aphasia and are also not associated with general demographic variables.

While our results showed patterns of both hypoperfusion and hyperperfusion in chronic aphasia and link some of these perfusion changes to impaired language, questions remain. We did not address what this means for recovery of language in chronic stages of aphasia. With respect to hypoperfusion, the point at which reduced cerebral blood flow results in functional deficiencies or is indicative of a nonreversible state is unknown. Although animal models suggest that perfusion levels below 30% of normal constitute hibernating, nonfunctional tissue, we found correlations between perfusion and language impairment in the 0–6 mm perilesional ROI, where the mean normalized perfusion value was just below 80%. Correspondingly, we also do not know if hyperperfusion reflects language inefficiency, or what levels of perfusion impair (or improve) cognitive function. The regions with the greatest levels of right hemisphere perfusion were not consistently or significantly associated with language disability, and none of the right-occipital-normalized values within the ROIs we examined were more than 40% above those of the normal control participants. The time course by which certain regions of the brain become hyperperfused also is not known. It is possible that heightened perfusion levels in contralesional regions are an immediate consequence of stroke, though it could also be the case that such changes develop slowly over time, possibly reflecting attempts to compensate for left hemisphere brain damage.

5. Conclusions

In summary, we report two key findings regarding perfusion in chronic aphasia. First, we found a varied pattern of hypoperfused and hyperperfused regions across both the left and right hemispheres of the brain. These patterns suggest that autoregulatory shifts in blood flow in response to lesions within the distribution of the left middle cerebral artery may be associated with the abnormal perfusion patterns we observed; however this possibility requires further investigation. Notably, our findings do not strongly support the idea that perfusion changes (in particular right hemisphere hyperperfusion) reflect maladaptive language processing. Rather, we suggest that regions of increased perfusion reflect changes in domain-general cognitive effort. Secondly, we found that perilesional tissue within 6 mm of the lesion is particularly hypoperfused compared to regions more distal to the lesion. Importantly, the degree of hypoperfusion in this perilesional region correlates with performance on standard measures of language ability, when adjusting for lesion volume, with reduced perfusion corresponding to more impaired language. Critically, however, we suggest that perilesional rings may only crudely capture the effects of vascular lesions on perfusion due to heterogeneity of lesion location and volume as well as variability in the properties of lesion-adjacent tissue. Finally, the present results underscore the need to consider chronically altered cerebral blood flow as a contributing factor to the persistent language deficits in chronic aphasia, which might also serve as an additional avenue for targeted recovery of language function.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

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Research Article

The Cognitive Neuroplasticity of Reading Recovery following Chronic Stroke: A Representational Similarity Analysis Approach

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Damage to certain left hemisphere regions leads to reading impairments, at least acutely, though some individuals eventually recover reading. Previous neuroimaging studies have shown a relationship between reading recovery and increases in contralesional and perilesional activation during word reading tasks, relative to controls. Questions remain about how to interpret these changes in activation. Do these changes reflect functional take-over, a reorganization of functions in the damaged brain? Or do they reveal compensatory masquerade or the use of alternative neural pathways to reading that are available in both patients and controls? We address these questions by studying a single individual, CH, who has made a partial recovery of reading familiar words following stroke. We use an fMRI analysis technique, representational similarity analysis (RSA), which allows us to decode cognitive function from distributed patterns of neural activity. Relative to controls, we find that CH shows a shift from visual to orthographic processing in contralesional regions, with a marginally significant result in perilesional regions as well. This pattern supports a contralesional reorganization of orthographic processing following stroke. More generally, these analyses demonstrate how powerful RSA can be for mapping the neural plasticity of language function.

1. Introduction

A well-articulated network of cortical regions associated with single word reading has emerged over the past several decades [1–3], with the left ventral occipitotemporal cortex [4] and the left angular gyrus [5] identified as two critical nodes in the reading network. During the acute stage of stroke, damage to these regions is associated with severe impairments in the ability to read (e.g., [6–8]). These severe impairments often resolve during the transition from the acute to chronic stroke, with many individuals shown to at least partially recover over the years following damage (e.g., [9–15]).

These improvements in reading during the natural recovery from stroke have been argued to provide evidence for neural plasticity, with the damaged brain reorganizing to better support the impaired reading functions (e.g., [12, 13, 15, 16]). Neural plasticity could mean a variety of things: from *functional take-over* whereby the function previously performed by a damaged area shifts to a different brain region to *compensatory masquerade,* or a refinement of established but intact cognitive processes to perform a task [17]. Within the context of reading literature, both of these hypotheses have been proposed to account for the acute to chronic improvements following stroke.

According to the *functional take-over* hypothesis there is a region in the patient's brain whose associated function is different than the corresponding region in the undamaged population. The function of that region in the patient more closely matches the function of the damaged region in the undamaged population. As with much of the language recovery literature, there is debate over whether the region

that takes over the function is contralesional or perilesional (e.g., [18]). That is, some have argued that recovery of reading is associated with a retuning of the neural response of the homologous right hemisphere regions, such that this region now computes the function normally associated with the damaged tissue in the left hemisphere (e.g., [12, 16, 19]). Others have argued that the retuning occurs in the tissue just surrounding the lesion (e.g., [13, 15]).

Support for the *functional take-over* hypothesis largely comes from fMRI studies of reading in the damaged brain. For example, in unimpaired readers, it is typical for a region of the left ventral occipitotemporal, frequently referred to as the visual word form area (VWFA), to be more activated to words than baseline, with the region's response being case, font, and location invariant [4]. This pattern suggests that the region is involved in processing orthographic information about written words, that is, abstract information about the letter identities in the word and their order. When undergoing task-related fMRI, patients with damage to the VWFA typically show greater activation to words compared to baseline in the right hemisphere homologue of this region (e.g., [13, 15, 16, 19]) and/or in regions just adjacent to the lesion (e.g., [13, 15]). On the surface, the fact that patients show increased activation to words in regions not typically observed in the unimpaired population suggests that a reorganization of cognitive functions has occurred. Specifically, the orthographic function of the damaged region is hypothesized to be reorganized into other regions that do not typically carry out that function (e.g., [15, 16]).

There are alternative explanations for this reading recovery that do not require assuming functional take-over. Others have argued that the residual reading ability following damage to these regions is due to the refinement of alternative neural pathways for word reading that exist even in the undamaged brain, or a type of *compensatory masquerade*. For example, these patients have been argued to rely on the right hemisphere's normal capacity for visual word processing (e.g., [10, 20, 21]) or alternatively on left hemisphere reading pathways that do not involve the damaged regions (e.g., [14]). In these accounts, recovery over time results from participants learning to more efficiently use these alternative pathways, rather than a dynamic change in the neural organization of the reading system. According to the *compensatory masquerade* hypothesis, even after reading has partially recovered, the functions in the undamaged regions of the patient's brain are the same as the functions in the corresponding regions in the unimpaired population.

Changes in the location of word versus baseline activation in patient's brains may also be consistent with the *compensatory masquerade* hypothesis. Increases in activation in the patient could occur even without functional reorganization; instead they may reflect that the patient is engaging neural regions whose cognitive functions have not been altered by brain damage but that are being used in an atypical way for the task of reading (e.g., [22, 23]). For example, the right hemisphere activation may reflect that the word is being processed visually, but not orthographically. The same right hemisphere region may also process visual, but not orthographic, information about written stimuli in the unimpaired brain (e.g., [16, 24]). Impaired readers show greater activation in that region compared to baseline than the control participants because this visual processing is not well suited for word reading. Without the orthographic processes in the lvOT, impaired readers rely more heavily on these visual processes for word recognition, leading to more activation in the region. Alternatively, the right hemisphere activation may reflect engagement of cognitive processes that are not typically involved in reading for unimpaired readers but become part of the reading process after damage, processes like cognitive control, working memory, or response selection.

Support for this *compensatory masquerade* interpretation of changes in activation profile comes from several longitudinal studies of individuals with VWFA damage. Early in the course of recovery, patients show an increase in the activation of the right VWFA activation to words relative to baseline. As recovery continues and reading improves, less right VWFA activation is observed and greater perilesional activation is observed (e.g., [12, 13]). If, over time, the right VWFA takes on the functional properties of the damaged left VWFA, the opposite pattern would be expected, with more activity in the right VWFA as reading recovers.

This problem of interpreting what the meaning of changes in activation can tell us about the reorganization of cognitive functions is a larger problem in language recovery research. Similar fMRI results have been reported across different types of language impairments, with patients showing both greater perilesional and greater contralesional activation than controls (see [18, 25] for discussion). However, as with reading, early stages of language recovery are more linked to contralesional activation, while later stages of recovery are associated with perilesional activation [23]. Further challenging the idea that contralesional activation reflects functional reorganization is the finding that transcranial magnetic stimulation to contralesional areas in aphasic patients has surprisingly been shown to improve language production [26]. This finding has been interpreted to indicate that contralesional activation may reflect the engagement of a dysfunctional process that inhibits the ability to do the task. However, when a second stroke damages contralesional regions, whatever language has recovered is severely impacted, in both language production (e.g., [27–29]) and reading [30], suggesting that the contralesional region had been supporting the residual language capacity following the left hemisphere stroke.

With all of these difficulties in interpreting changes in activation, it is possible that traditional, univariate activation-based approaches to fMRI are not well suited to address issues of the reorganization of function following stroke. An additional concern is that it is not clear that the *functional take-over* necessarily predicts changes in activation between the patient and control populations. For example, both patient and controls may rely on the same brain regions during reading, but the function of the region is different between the two populations. Alternative methods for analyzing fMRI may be better at distinguishing the *functional take-over* and *compensatory masquerade hypotheses*.

The *functional take-over* and *compensatory masquerade hypotheses* clearly make testable predictions, given the appropriate analysis methods. According to the *compensatory*

masquerade, contralesional and perilesional regions in the patient's brain should be doing the same cognitive function as the corresponding regions in the control group. According to the *functional take-over* hypothesis, the function of those regions in the patient's brain should be different than the corresponding regions in the control group and more similar to the normal functions of the damaged region. To address this prediction, it is necessary to identify fMRI methods that can decode what function is being processed by a region, rather than just finding differences in activation level. Here, we use a multivariate approach to analyzing fMRI data, specifically representational similarity analysis (RSA, [31]).

Using RSA, we compare word-similarity measures derived from computation models of different reading-related functions to the patterns of activity distributed across a brain region for individual words. Following existing hypotheses about the neural plasticity of reading following damage, we focus on two levels of representation: low-level *visual* representations of the stimulus code all visual inputs into basic visual features such as oriented edges and *orthographic* representations segment words into a sequence of ordered letter identities and abstract away from low-level visual information like case, font, or location. Other levels of representation like *phonological* representations, which encode the sequence of sounds that correspond to the word being verbalized, and *semantic* representations, which denote the meaning of the word, are also involved in word reading but are outside of the scope of the current investigation.

These levels can be distinguished based on which stimuli are represented similarly. For example, the letters d and b are similar to each other at a visual level of representation, while d and D share fewer visual features. In contrast, at an orthographic level, d and D are examples of the same orthographic letter identity, while d and b are not and thus map onto different representations [32].

Several recent studies have used RSA logic to investigate levels of representation in reading in the unimpaired brain. Rothlein and Rapp [32] focused their investigation on the representation of single letters. They found that the left VWFA was selectively tuned to orthographic representations of letters and a right lateralized occipital region is tuned to low-level visual representation of letters. Fischer-Baum and colleagues [24] focused on whole word representations. They found that the VWFA processes orthographic information about words, while the right homologue processes visual information about the same stimuli. In addition, they found that distributed patterns of activity in the left angular gyrus implicates the region in orthographic processing, while the pattern of activity in the right angular gyrus did not correspond to any of the tested reading-related functions. These studies demonstrate how RSA can be used to decode reading-related functions from distributed patterns of activation.

In the current study, we will apply this approach to the question of the neural correlates of reading recovery. Specifically, we report an fMRI study that compares a single case of an individual, CH, with a chronic reading and writing impairment following a hemorrhagic stroke with a control group. Using RSA, we will determine the informational content of perilesional and contralesional regions in both the patient and the controls by comparing the similarity structure of the region's BOLD activation to individual words to a similarity structure predicted by computational models of representations during reading. In this way, we can adjudicate between the *functional take-over hypothesis* and the *compensatory masquerade hypothesis*.

2. Case Study

CH was a 52-year-old right-handed male with a left hemisphere lesion resulting from a hemorrhagic stroke in 2008. He started coming to the lab in December 2011, 37 months following his stroke. Data for the current project was collected between 2013 and 2015. Functional neuroimaging data was collected in July 2014. He has a Master's degree in Chemical Engineering and owned his own company prior to his stroke. As we show below, at the chronic stage, CH was able to read some familiar words despite serious difficulties in processing the identities of individual letters. Similar patterns have been reported previously in the literature [33] and have led researchers to posit an alternative reading pathway available to all readers [34]. Alternatively, during the course of recovery, CH's brain may have changed to allow for a different type of orthographic processing not available to other readers. These alternative accounts of CH's impairment are examples of the *compensatory masquerade* and the *functional take-over hypotheses,* respectively.

2.1. Lesion Localization. To localize CH's lesion, a T1-weighted structural image (TR/TE = 8.4/3.9 ms; FA = 8 degrees; matrix size = 256 × 256; FOV = 240 mm; slice thickness = 1.0 mm thick sagittal slices) was obtained. His lesion was segmented manually (following Schnur et al. [35]) and the structural scans, including the lesion mask, were warped and registered to an intermediate template using a symmetric diffeomorphic registration algorithm ([36]; see also http://www.picsl.upenn.edu/ANTS/). Figure 1 shows nine axial slices from CH's T1 scan. From the intermediate template, scans were then mapped to the "N27 Colin" normalized template in MNI space [37] and then resampled to 1 mm axial resolution using AFNI's 3dresample. Lastly, percent damage was calculated in Automated Anatomical Labeling (AAL) space [38] using VoxBo (http://www.voxbo.org).

CH's lesion included a large portion of the left hemisphere (38% of all left hemisphere voxels). Damage was most extensive in the parietal lobe, including nearly all of the left angular gyrus (90% damaged) and a large portion of the supramarginal gyrus (70% damaged), as well as portions of the left superior (49% damaged) and inferior parietal lobules (67% damaged). There were also extensive temporal damage, in the superior (51% damaged), middle (54% damaged), and inferior (20% damaged) gyri, the temporal pole (26% damaged), and occipital damage, in the superior (35% damaged) and middle (68% damaged) occipital gyri and the fusiform gyrus (18% damaged). Finally, the lesion extended anteriorly to the precentral gyrus (19% damaged) and the posterior portion of the left inferior frontal gyrus, specifically the pars opercularis (30% damaged).

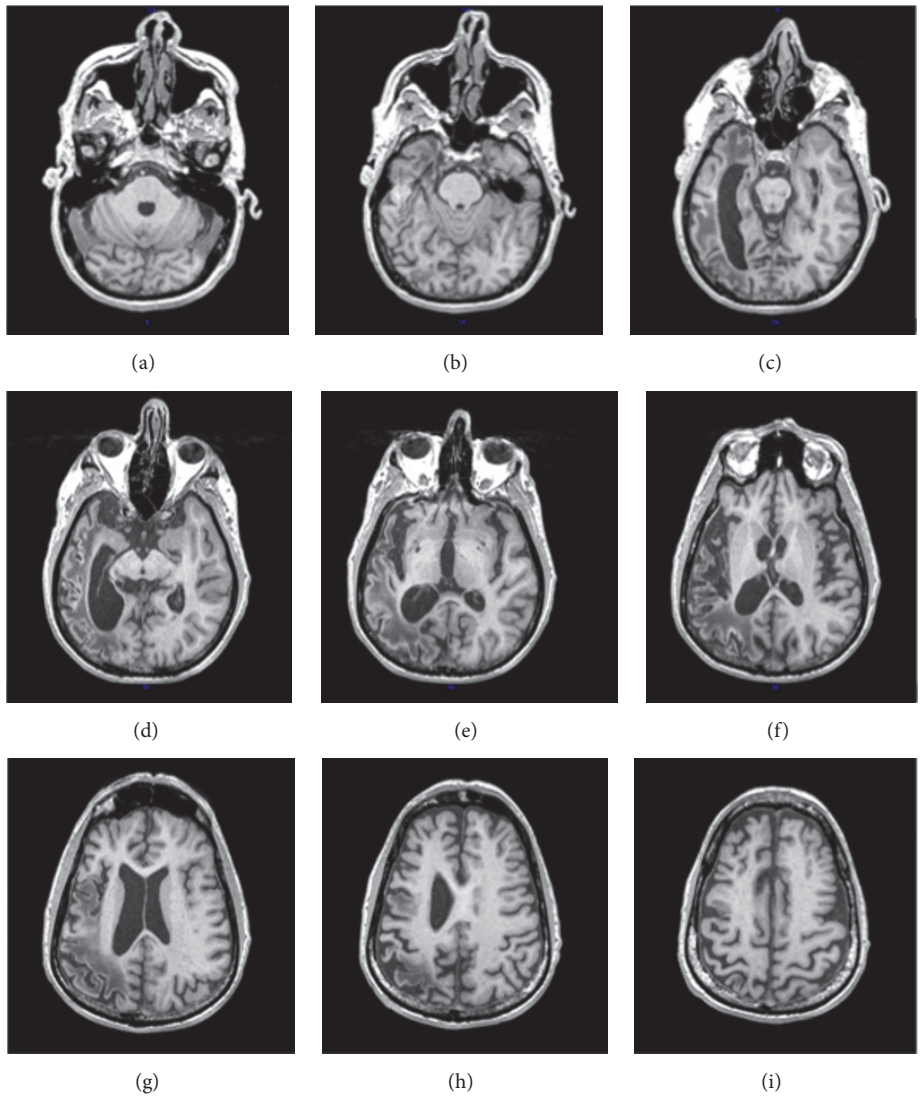

Figure 1: Visualization of CH's lesion from nine axial slices of his T1 scan with 10 mm between each slice going from inferior (a) to superior (i) location.

2.2. Behavioral Testing. CH received a standard battery of language and cognitive control tasks. His speech perception was assessed as part of a case-series study [39]. CH fell within age- and education-matched controls on both word and nonword minimal pair discrimination tasks, auditory lexical decision, and picture-word matching with auditory foils (p's > .20). In single word, picture matching task [40], CH was always able to correctly indicate when the picture and the word matched and also made no errors when the word and the picture were unrelated phonologically or semantically and only one error with phonological foils. However, he made many false alarms with semantically related foils (29/54, 54% correct), suggesting that he has a semantic impairment or an impairment in accessing semantics from the auditory modality.

There is some evidence that the semantic impairment in speech perception is multimodal. Speech production was also impaired. CH was given the Philadelphia Naming Test [41], on which he was only able to name 87/175 pictures. The majority of his errors (80%) are semantic in nature, evenly split between semantic errors and picture descriptions. He also performed below the control range (47/52) on the three pictures' version of the Pyramids and Palm Trees Test [42]. Therefore, CH appears to have an amodal semantic impairment.

CH also has a striking written language impairment, even on tasks that require processing single letters. CH's visual processing of letters appears to be largely intact. Low-level visual processing was evaluated by a task in which he had to directly copy visually presented letters in the same case. He was nearly perfect at this task (155/156; 99%). He was also able to judge whether a written symbol was a real letter or a pseudoletter (88/88; 100%). Following Schubert and McCloskey [43], this pattern suggests that CH has intact processing up to a visually processing level that stores shapes that correspond to familiar letters. However, on tasks that

require orthographic processing of single letters, that is, processing letter identity information that abstracts away from case, font, or modality, CH is quite impaired. He has difficulties naming visually presented letters (26/104; 25%) and copying visually presented letters in the opposite case (57/84, 68%). Therefore, we conclude that CH either has difficulties representing abstract letter identities at an orthographic level of representation that abstracts away from information about case or difficulties accessing these abstract letter identity representations at the orthographic level from the preceding level of representation involved in recognizing familiar letters.

CH also had difficulties processing abstract letter identities from other modalities of presentation. For processing letter identities from the tactile modality, foam letter magnets (approximately 1.75 inches tall) were handed to CH while his eyes were closed. CH had difficulty naming these tactilely presented letters (8/52; 15%) and had trouble copying these tactilely presented letters in the opposite case (10/22; 45%), suggesting that his impairment at the level of abstract letter identities was independent of the modality of input. CH also had difficulties processing letter identities from the auditory modality, for example, with difficulties in writing letters to dictation (13/52; 25%). Given that CH has difficulties processing abstract letter identity information from a variety of modalities, we assume that he has a general impairment in representing abstract letter identity information at an orthographic level of representation.

To assess his ability to read and write whole words, CH was given the same set of 80 high-frequency words between 3 and 7 letters long and 20 pronounceable pseudowords in four tasks: reading aloud, written spelling, oral spelling, and recognition of orally spelled words. This final task has been argued to tap into central reading processes while bypassing the visual system [44]. CH was unable to read or write any of the pseudowords (0/20 in all four tasks), suggesting that reading and writing pseudowords rely on processing individual letter identities at the orthographic level of representation impaired in this participant. He also was unable to orally spell any of the words or recognize a single orally spelled word (0/80 on both tasks) and was only able to correctly write 2 of the 80 word targets (2/80; 2.5% correct). CH's difficulty with processing abstract letter identities had a profound impact on his ability to write words and to recognize orally spelled words, suggesting that these tasks all rely on intact processing at an orthographic level of representation.

CH was also impaired at reading words aloud but was markedly better on this task than the other three, correctly naming 48/80 (60%) of the written words. To further assess CH's ability to read words, he was given the Johns Hopkins University Dyslexia Battery [45]. Overall, he correctly read 89/328 of the stimuli (27%). He was more accurate with words (30%) than nonwords (3%, $\chi^2 = 30.2$, $p < .0001$) and more accurate with high-frequency words (40%) than low frequency words (20%; $\chi^2 = 7.9$, $p < .01$). He showed no effects of spelling-to-sound regularity, reading regular-consistent words (33%), regular-inconsistent (33%), and exceptional words (30%) with the same level of accuracy ($\chi^2 = 0.1$, $p > .95$). This pattern suggests that whatever residual reading ability CH has, it is sensitive to lexical knowledge about the frequency with which words have been encountered, but not by knowledge of spelling-to-sound mappings, which would predict some nonword reading capacity and effects of spelling-to-sound regularity.

Note that this is likely an underestimate of his visual word processing ability. CH's difficulties in picture naming described above suggest language production problems mapping from a semantic system to the phonological system. This language production problem should contribute to CH's difficulties in reading words aloud, particularly since he is unable to read a single nonword [46]. An alternative test of his visual word processing ability is lexical decision, tapping into whether he can recognize that letter strings comprise familiar words. CH was given PALPA 25 which includes 60 words split evenly between high and low frequency and high and low imageability and 60 pseudowords. He was correct on 100/120 (83%) trials, below controls who are nearly perfect on this task, but well above chance. Nearly all of his errors with word stimuli (8/9) were made with words that were of both low imageability and low frequency, indicating, again, that his residual reading ability is limited in its scope to words that are high in frequency and/or imageability.

Further tests were carried out to test whether CH's preserved word processing could be attributed to certain frequent words being recognized perceptually as familiar objects. In one task, we had CH read the same set of 80 familiar words that were presented in UPPER case, lower case, and aLtErNaTiNg case, counterbalanced across a series of sessions. In another task, CH had to make lexical decisions to the same set of 120 words and 120 pseudowords under the same three conditions, counterbalanced across a series of sessions. The logic behind this case manipulation was that CH may have previously seen these words in upper or lower case but would have no previous perceptual experience with these words in alternating case (see [33, 47] for similar logic). If CH's ability to recognize these words depends on familiarity with the perceptual properties of the word, then his performance should be better with upper and lower case words than with alternating case words. Alternatively, if his ability to recognize these words depends on more abstract properties about letter identity and order, then his performance should not be influenced by the case manipulation. In both the reading aloud and lexical decision task, there was no difference in performance for the upper and lower case words than for the alternating case words (reading aloud: combined UPPER and lower case: 56/160 (35%), aLtErNaTiNg case: 27/80 (34%), $\chi^2 = 0$, $p = 1.0$; lexical decision: combined UPPER and lower case: 361/480 (75%), aLtErNaTiNg case: 183/240 (76%), $\chi^2 = .05$, $p > .82$).

Despite severe difficulties in orthographic processing for single letters, CH is able to process some written words. This pattern of performance is not predicted by most theories of visual word processing. Theories typically assume that central reading processes—activating long-term memories of the orthographic representations that correspond to familiar

words, semantic representations of the meaning of those words, and phonological representations of pronunciations for both familiar and unfamiliar words—are all necessarily mediated by a level that represents abstract letter identities [43, 48–50]. Furthermore, this pattern is inconsistent with the patterns that are frequently observed in acquired alexia. Most patients with severe problems processing letter identities from visual input also have difficulties in reading words (e.g., [21, 43, 51]), and intact letter identification with impaired whole word reading has been argued to be the basis of the letter-by-letter reading strategy frequently observed in individuals with alexia (e.g., [10, 16]). However, CH's pattern of performance is also not completely unprecedented. Howard [33] reported a similar case of an individual whose abstract letter processing ability was essentially at chance but who was able to read some words (30–40%). While it may be rare, acquired reading deficits in which abstract letter identity processing is more extensively impaired relative to word reading appear to be possible.

Brunsdon and colleagues [34] use this pattern to argue for an alternative route to reading that does not depend on the same level of abstract letter identity representation responsible for processing case-free letter identities.[1] Instead, this theory posits a level of representation that identifies individual shapes as letters in a manner that abstracts away from font but not from case, which precedes the case-free abstract letter identity representations. Furthermore, this theory assumes that there can be direct mappings from these font- but not case-free representations onto stored long-term memory representations of the spellings of familiar words. Assuming damage to the level of case-free representations and this alternative route to recognizing familiar words can explain why CH cannot match letters across case but can read UPPER case, lower case, and aLtErNaTiNg case words equally well.

According to Brunsdon and colleagues [34], this route is available for all readers. Therefore, this argument is a version of the *compensatory masquerade hypothesis*, suggesting that analysis of patient performance reveals a reading pathway that exists even in the undamaged brain. Another possibility is that, over the course of recovery, CH has developed this alternative route, which is not part of the unimpaired reading system. This argument is a version of the *functional take-over hypothesis*, with the damaged brain reorganizing to allow for orthographic processing of familiar words in regions not typically associated with an orthographic function.

Whether CH's residual reading ability reflects *functional take-over* of the reading system or reveals a *compensatory masquerade* remains an open question. To address this issue, CH and group of controls underwent fMRI scanning while reading words. Using representational similarity analysis, we will evaluate whether, contralesionally or perilesionally, CH shows evidence of a change in reading function, specifically a shift in the neural locus orthographic processing, as would be predicted by the *functional take-over hypothesis*.

3. fMRI Study

3.1. fMRI Methods

3.1.1. Subjects. CH and 20 healthy, right-handed, English-speaking, adult volunteers (aged 18–30) with normal or corrected-to-normal vision participated in the study (controls are the same as those previously reported in [24]). All participants gave informed written consent. The study was approved by the Rice University Institutional Review Board. Participants were compensated $25 for their participation. The entire experiment took approximately 1.5 hours.

3.1.2. Data Collection. Subjects were fitted with a 12-channel head coil in a Siemens 3-T scanner at the Core for Advanced MRI (CAMRI) at Baylor College of Medicine. First, a T1 anatomical scan with 192 1 mm axial slices was collected from each participant. Then, participants underwent twelve function runs to measure BOLD activity during the experimental task. BOLD activity was measured using gradient-echo $T2^*$-weighted echo-planar imaging (EPI) of the whole brain. 34 slices were acquired axially, for a voxel size of 3.4375×3.4375× 4 mm (TR 2 s, TE 30 ms, and flip angle 90°).

3.1.3. Task. An event-related design was used. Each of a single list of 40 words (5 proper names, 35 critical words for the analysis) was presented in random order exactly once during each of 12 functional runs. Participants were instructed to press a button whenever a proper name was presented. On a given trial, a fixation cross was presented for 500 ms, followed by a word for 500 m with a trial onset asynchrony of 4 s. Words were presented in all capital letters in Arial font (size 36). On approximately 25% of the trials, a blank screen was presented instead of a word, in order to obtain an estimation of baseline activity [31]. Visual stimuli were presented on a projection screen with an LCD projector and viewed through a mirror attached to the head coil. The 35 critical words were chosen to be intuitively and computationally distinguishable between the four levels of representation tested in the previous paper—visual, orthographic, phonological, and semantic. To adjudicate between the *functional take-over* and *compensatory masquerade hypothesis*, we focus on only the visual and orthographic levels of representation.

3.2. Theoretical Similarity Matrices. For the set of 35 critical words, similarity matrices were calculated based on computationally explicit theories of representation at different levels in the reading system. For the *visual level of representation*, we used a binary silhouette of each word and computed the pixel-wise overlap of the two images [31]. *Orthographic similarity* was calculated on the basis of an open-bigram model [52], in which words are represented by multiletter units that reflect ordered pairs of letter identities that are not necessarily adjacent to each other in the word. This type of open-bigram model closely matches the nature of the orthographic code that has been previously proposed to reflect the representational content of the left VWFA [53]. We used the MatchCalculator tool, developed by Colin Davis, to calculate

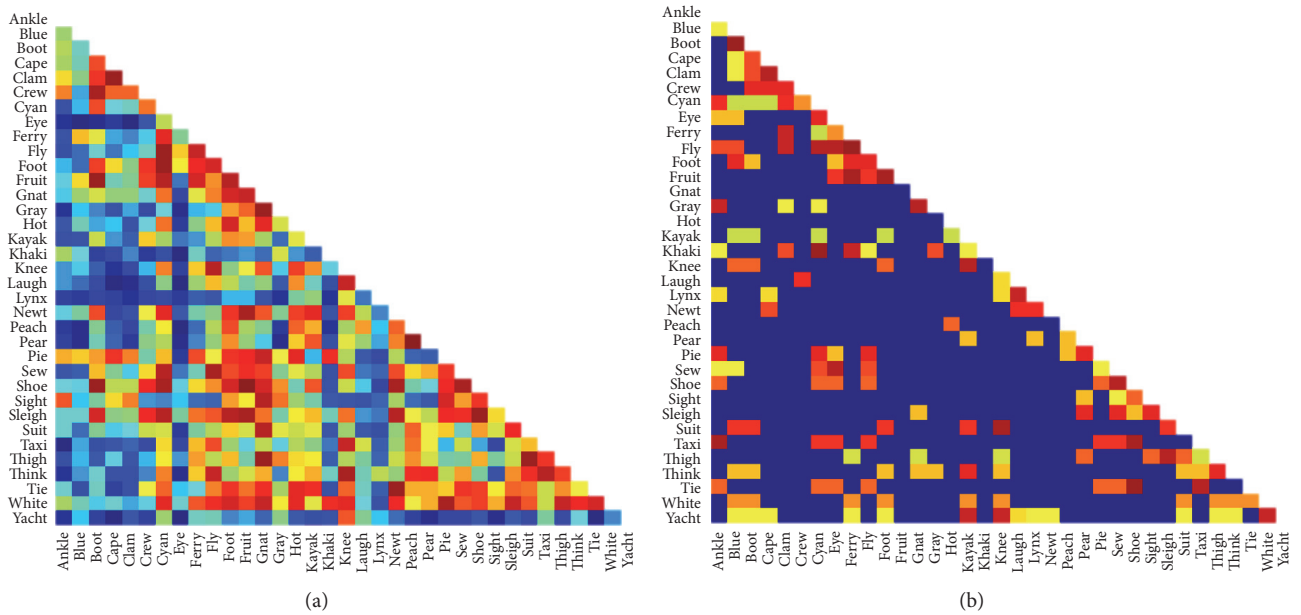

FIGURE 2: Lower off-diagonal for the two theoretical similarity matrices based on (a) visual and (b) orthographic levels of representation.

the similarity between words according to this theory (http://www.pc.rhul.ac.uk/staff/c.davis/Utilities/MatchCalc/)[2]. Figure 2 depicts a visual representation of the off-diagonal of the similarity matrices generated by these different theories of cognitive representation, in which an entry of i, j in a given matrix indicates how similar word i is to word j using a given metric. The Spearman correlation between the two similarity matrices was .12.

3.3. Data Analysis

3.3.1. fMRI Data Preprocessing. Data preprocessing was done using SPM12 (University College London, 2012) on T2*-weighted functional images. Preprocessing included motion correction, coregistration with the T1, and slice time correction. For the RSA, we chose to forgo spatial smoothing, since differences across adjacent voxels may contain valuable information in the RSA [31]. The segmentation step was carried out, producing forward and backward deformation fields to map to and from MNI space as well as a grey matter mask.

3.3.2. Univariate Analysis. To determine whether the experiment elicited a typical reading network in a standard fMRI analysis, we contrasted all words with fixation, using SPM12. Additional preprocessing steps were applied. Spatial smoothing was done using 8 mm full width at half maximum Gaussian smoothing kernel and the images were warped into MNI space at a resolution of $2 \times 2 \times 2$ mm with 4th-degree B-spline interpolation. For each participant, a 1st-level analysis used a contrast to compare all words, though not proper names, to a fixation baseline. Six motion parameters and scanner drift were included as covariates in the univariate analysis. A 2nd-level analysis used a Crawford's modified t-test [54] to determine if the t-maps that resulted from the 1st-level analysis for CH fell outside of the distribution of the control group.

3.3.3. Representational Similarity Analysis. For the RSA, no smoothing or normalization was applied during preprocessing. Beta-weights for each word in each run against fixation were obtained by a general linear model predicting BOLD response, which included the timing of each individual word (modeled as an event) deconvolved with a hemodynamic response function and six motion parameters and scanner drift as nuisance variables. By averaging the beta-weights across 12 trials per subject, we obtained 35 beta-weight maps for each subject, with each map reflecting the brain's response to each word in the experiment. These beta-weight maps were then mean centered within each subject. ROI analyses were applied to these 35 individual-word beta-weight maps for each participant. For each ROI, a vector of beta-weights for the voxels within that ROI was extracted for each of the 35 words. A similarity matrix of word-to-word similarity for this region was calculated based on a Spearman correlation of the beta-weight vectors for each word to every other word.[3] Each entry in the resulting similarity (correlation) matrix therefore represented how similar the distributed pattern of activity within the ROI is between two stimuli. The resulting similarity matrix of pairwise correlations was then compared with visual and orthographic similarity matrices described above, using a Spearman correlation of the off-diagonal values. We refer to the Spearman rho value for the correlation between the brain-based similarity matrix and

the visual similarity matrix as the *visual similarity index* and the Spearman rho value for the correlation between the brain-based similarity matrix and the orthographic similarity matrix as the *orthographic similarity index*. For each participant (both controls and CH) and for each ROI, two values were calculated—visual and orthographic similarity indices for the region.

3.3.4. Anatomical ROIs. A challenge to the RSA approach is selecting the appropriate regions of interest for the analysis. One option is data driven, selecting ROIs on the basis of the whole brain analysis, identifying regions in which CH shows more activation than controls and investigating the function of these regions in CH and controls. A second option is hypothesis driven, selecting regions anatomically, based on the hypotheses that reorganization is happening either in tissue just adjacent to the lesion (perilesionally) or in the right hemisphere homologues of damaged regions that are known to be relevant to reading in the undamaged brain. For the current study, we opted for the hypothesis driven approach to selecting ROIs. Because we are investigating only a single case study, the results of the whole brain analysis may be unreliable, with both type 1 and type 2 errors, making it a poor source for selecting ROIs. Additionally, as discussed above, it is not clear that the type of neural plasticity that we are investigating with RSA will result in changes in activation, especially if the function of a region switches from one reading-related function to another. Furthermore, the goal of the current study is to investigate specific claims about perilesional and contralesional reorganization, and there is no guarantee that we will find areas of increased activation in the whole brain analysis for a single subject in either of those critical regions. Therefore, we limited our ROIs to anatomical regions defined on the basis of specific hypotheses about the reorganization of function. Specifically, we looked at three types of region of interest—CH's lesion location in unimpaired participants, contralesional regions of interest, and perilesional regions of interest. We discuss the motivation for each type of ROI below.

One of the goals of the current study is to determine if the function that is normally computed by the region of cortex that is damaged in CH's brain has moved to a different region. Therefore, one ROI involves looking at the information processing capacity of the CH's damaged cortex warped onto the control participants. A lesion mask for CH was traced using MRIcron with "1" assigned to damaged voxels and "0" to other voxels and normalized to the MNI template brain using SPM12 and then warped into each subject's native space.

A second set of ROIs focused on decoding activation in contralesional regions. Specifically, we focus on regions that are (1) damaged in CH and (2) have been argued to have left-lateralized processing of orthographic information in control participants. We will then evaluate whether the right hemisphere homologue of these regions compute different reading functions in CH compared to controls. Fischer-Baum et al. [24] identified orthographic processing in the left VWFA and left angular gyrus (ANG), two regions partially damaged in CH. Therefore, left and right vOT and left and right ANG ROIs were used to analyze whether there is contralesional functional take-over in CH. The left and right VWFA ROIs were 12 mm^3 radius spheres centered on the MNI coordinates [±45, −57, −12] (based on Talairach coordinates for the VWFA form [55], MNI coordinates based on [56]) and were created using MRIcron [57] and left and right ANG were taken from the Automated Anatomic Labeling (AAL) Atlas [38].

A third set of ROIs focus on functional take-over in cortical regions adjacent to the lesion. Given CH's large lesion, we subdivided his perilesional space into five regions of interests. These masks were created by identifying undamaged voxels from different Automated Anatomical Labeling (AAL) regions. The *fusiform* mask was all of the voxels outside of CH's lesion mask in the left fusiform gyrus. The *inferior temporal* mask was all of the voxels outside of CH's lesion mask in the left middle and inferior temporal gyri. The *medial temporal* mask was all of the voxels outside of CH's lesion mask in the left hippocampus, parahippocampal gyrus, and amygdala. The *anterior temporal* mask was all of the voxels outside of CH's lesion mask in the left superior and middle temporal pole. Finally, the *parietal* mask was all of the voxels outside of CH's lesion mask in the left supramarginal gyrus, angular gyrus, superior parietal lobule, and inferior parietal lobule.

All masks were warped into each subject's native space at the resolution of the $T2^*$ image using normalize function from SPM12 and the backward deformation fields produced by the segment function in SPM12 during the preprocessing stage, with nearest neighbor interpolation. Second-level analyses were carried out across subjects for both similarity index values in each ROI. For each ROI, one set of tests focuses on determining the extent to which each ROI computes visual and orthographic information in the controls. A second set of analyses investigates whether the function of the region has shifted to orthographic processing in the CH, relative to controls. Our dependent measure is the difference between the orthographic and visual similarity indices in contralesional and perilesional ROIs. For this analysis, statistical analyses were carried out using a one-tailed Crawford's modified t-test [54] under the null hypothesis that CH's difference between the orthographic and visual similarity indices for a given region was not greater than the distribution of the control participants.

4. Results

4.1. Univariate Analysis. Figure 3 shows the results of the univariate analysis warped to CH's anatomical scan, with an uncorrected $p < .05$ comparing CH's words versus fixation analysis to the distribution of the controls words versus fixation analyses, using a Crawford's modified t-test. Bilaterally, CH shows more activation than controls in a number of regions: occipital cortex (calcarine sulcus and lingual gyrus), the insular and cingulate cortex, and the inferior frontal gyrus. In addition to these bilateral regions of activation, CH showed perilesional activation in the middle occipital

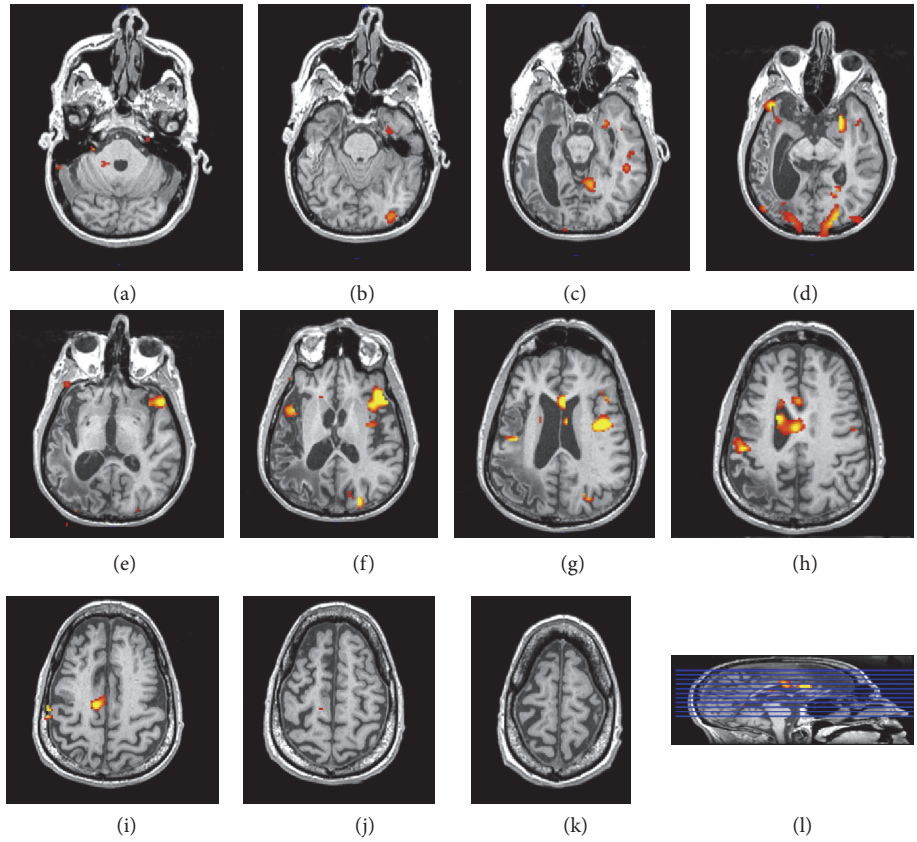

FIGURE 3: Results of the whole brain univariate analysis identifying regions where CH shows greater activation in words versus fixation than the control distribution plotted in CH's native space (uncorrected $p < .05$).

gyrus, the posterior middle temporal gyrus and the postcentral gyrus. He also showed contralesional activation to damaged left hemisphere regions typically associated with word reading, including the right midfusiform gyrus and the superior temporal gyrus. Finally, he showed greater activation to words than controls in other right hemisphere regions like the right parahippocampal gyrus and the superior frontal gyrus.

4.1.1. CH Lesion ROI. Figure 4 plots the average of the 20 control participants for each of the visual and orthographic similarity indices for the ROI based on CH's traced lesion. A one-sample t-test reveals that, in the CH Lesion ROI, both the visual (.013; $t(19) = 2.23$, $p < .05$) and orthographic (.030; $t(19) = 4.03$, $p < .001$) similarity indices are significantly different than zero. A paired t-test indicates that the lesioned region is marginally more involved in orthographic processing than visual processing ($t(19) = 2.01$, $p = .059$).

4.1.2. Contralesional ROIs. Control results for the ROIs used in this analysis are reported in Fischer-Baum and colleagues [24]. Table 1 reports the range of control orthographic and visual similarity index values for these contralesional regions, as well as the subsequent perilesional ROI analyses, along with CH's value for the orthographic and visual similarity index in each region and CH's rank among the control participants. Figure 5 shows the results of the analysis for the portion of the left and right ventral occipitotemporal cortex frequently referred to as the visual word form area and its right hemisphere homologue. For controls, a significant interaction between hemisphere and orthographic versus visual representation was observed in this region ($F(1, 19) = 11.3$, $p < .01$). Consistent with Dehaene and Cohen [4], in the left VWFA, the orthographic index (.024) was higher than the visual index (.006), while in the right VWFA the visual index (.021) was higher than the orthographic index (.003).

CH's lesion extends into this region in the left hemisphere. Under the contralesional version of the *functional take-over* hypothesis, we might predict that his right VWFA has reorganized, changing its function from visual to orthographic processing [16]. Figure 5(c) presents a box-and-whiskers plot for the distribution of the difference between the orthographic and the visual indices for all of the control participants in both the left and right VWFA ROIs. While, on average, the orthographic index is higher in the left VWFA and the visual index

Table 1: Range of the visual and orthographic similarity indices values along with CH's value and rank among the 21 participants (20 controls plus CH) for all 7 ROIs reported in the text.

	Visual			Orthographic		
	Control range	CH index	CH rank	Control range	CH index	CH rank
Contralesional VWFA	−.029–.100	−.032	21	−.050–.083	.032	6
Contralesional angular gyrus	−.034–.039	−.037	21	−.041–.053	.057	1
Perilesional fusiform	−.040–.068	−.003	17	−.049–.056	.033	8
Perilesional inferior temporal	−.042–.067	−.009	17	−.051–.085	.022	9
Perilesional medial temporal	−.038–.094	−.025	19	−.031–.067	.026	8
Perilesional anterior temporal	−.040–.057	−.004	11	−.041–.060	.013	11
Perilesional parietal	−.047–.057	.014	9	−.076–.120	.080	3

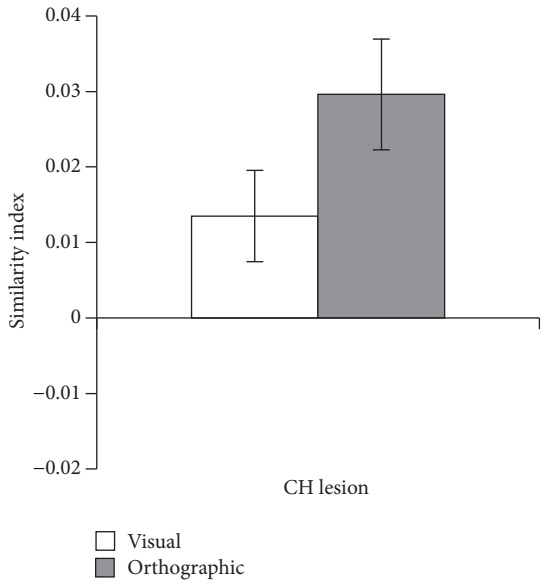

Figure 4: RSA results for the CH Lesion ROI. The graph reports the average (Spearman) correlation between each subject's brain-based similarity matrix with the two theoretical similarity matrices based on computational models of visual and orthographic representation. Error bars represent ±1 SEM.

is higher in the right VWFA, it is not true for all participants. The black dot depicts the difference between CH's orthographic and visual indices in his intact right hemisphere. Unlike the majority of control participants, CH shows more orthographic than visual processing in the right hemisphere homologue of the VWFA. CH ranks below all 20 control participants in terms of the visual similarity index and above all but 5 controls in the orthographic similarity index. Using a one-tailed, Crawford's modified t-test, we found that CH showed greater orthographic-relative-to-visual processing in the right hemisphere than controls ($t(19) = 2.09$, $p < .05$).

Figure 6 shows the results of the same analysis for the other contralesional ROIs, the left and right angular gyrus. For controls, neither the left nor the right angular gyrus shows any evidence of visual processing (p's > .27). However, there is evidence for left-lateralized orthographic processing, with the left angular gyrus (.019) having a significantly larger orthographic similarity index than the right angular gyrus (−.002; $t(19) = 2.45$, $p < .05$). As with the left vOT, CH's stroke has damaged a large portion of the left angular gyrus. We analyzed whether CH uses the right angular gyrus to process orthographic information. Figure 6(c) depicts the distribution of the difference between the orthographic and the visual indices for the 20 control participants in both the left and right angular gyrus using a box-and-whiskers plot, with a black dot indicating CH's orthographic minus visual similarity index for his intact right hemisphere. CH ranks below all 20 control participants in terms of the visual similarity index and above all 20 controls in the orthographic similarity index for this ROI. Unlike the control participants, CH had a much larger orthographic similarity index relative to his visual similarity index in the right angular gyrus. This value was significantly above the distribution of corresponding values in the control population ($t(19) = 3.13$, $p < .01$).

4.1.3. Perilesional ROIs. Figure 7 plots the results of ROI analysis for the five perilesional regions of interest, left hemisphere fusiform, inferior temporal, medial temporal, anterior temporal, and parietal regions adjacent to CH's lesion. Using a one-sample t-test, the visual similarity index was significantly different than zero for control participants in the fusiform (.013; $t(19) = 2.10$, $p < .05$), inferior temporal (.016; $t(19) = 2.80$, $p < .05$), and medial temporal (.017; $t(19) = 2.33$, $p < .05$) perilesional ROIs, but not for the anterior temporal or parietal ROIs (p's > .35). The orthographic similarity index was significantly different than zero for control participants in the medial temporal lobe (.016; $t(19) = 2.45$, $p < .05$) and marginally different than zero in the anterior temporal lobe (.014; $t(19) = 1.97$, $p = .064$), but not in the other ROIs (p's > .11).

Figure 7(c) depicts the distribution of the difference between the orthographic and the visual indices for the 20 control participants in all five perilesional ROIs, with the black dot indicating CH's difference value. There are marginally significant difference between CH's difference value and the distribution of the control difference values in the perilesional parietal ROI ($t(19) = 1.73$, $p = .050$) and medial temporal ROI ($t(19) = 1.49$, $p = .076$), but not in any of the other perilesional ROIs (p's > .12). The ranking results (Table 1) were similarly ambiguous; CH did not have either the lowest or

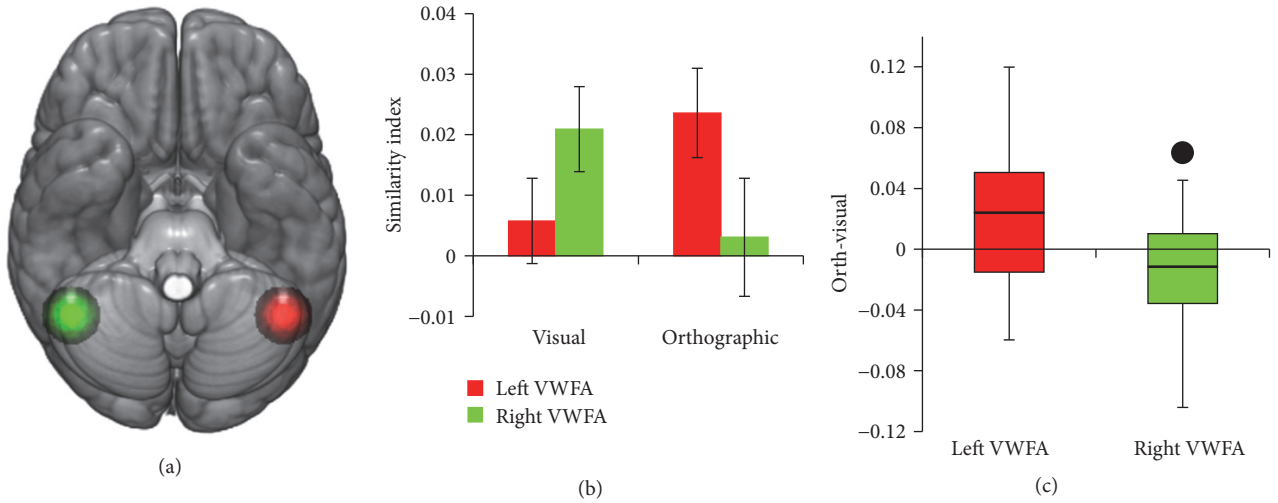

Figure 5: Results of the left and right VWFA ROI analyses. (a) shows the location of the left and the right VWFA regions of interest. (b) plots the average (Spearman) correlation between each control subject's brain-based similarity matrix (separately for the left and right VWFA ROIs) with the visual and orthographic similarity matrices. Error bars represent ±1 SEM. (c) depicts a box-and-whiskers plot for the distribution of the difference between the orthographic and the visual indices for all of the control participants in both ROIs, with the black dot in the right VWFA depicting CH's difference score.

the highest visual or orthographic similarity index in any of the regions. For the visual similarity index, he fell below the median in the fusiform (17/21), inferior temporal (17/21), and medial temporal (19/21) ROIs, at the median (11/21) for the anterior temporal ROI, and slightly above the median (9/21) for the parietal ROI. For the orthographic similarity index, he fell above the median for all but the anterior temporal ROI, in which his orthographic similarity index was the median value (11/21). His orthographic similarity index in the parietal perilesional ROI was higher than all but two of the control participants.

5. Discussion

Following a hemorrhagic stroke, CH was left with a severe written language impairment. Over several years, his familiar word reading improved, though he remained completely agraphic and had residual difficulties in processing abstract letter identity information for single letters. The goal of the current research is to investigate whether his residual reading ability was supported by *functional take-over*, whereby damaged functions have been reorganized into different brain regions, or whether it reflects a *compensatory masquerade*, whereby recovered reading depends on an alternative neural pathway that exists for all readers. By using an fMRI multivariate pattern decoding technique, we demonstrate that CH's brain shows evidence of functional take-over. Most clearly, we observe contralesional reorganization. We looked specifically at two right hemisphere regions that are homologous to the left hemisphere regions that are damaged in CH and have been shown to be important for orthographic information processing in controls. The results of our analyses suggest that CH is now using these right hemisphere regions to process orthographic information in manner that is distinct from the control participants.

As in previous research, we addressed this issue using functional MRI, scanning CH while he read words and comparing his results to a control sample (e.g., [13, 15, 16, 19]). Previous research has used this approach to identify cortical regions that show more of an increase in activation to written words relative to baseline for patients than controls. Taking this same analysis approach with CH, we found a familiar pattern of results. CH showed more activation than controls in a contralesional region close to the right hemisphere homologue of the VWFA, as well as more activation than controls in regions surrounding the lesion in the left hemisphere and additional bilateral frontal activation.

What differences in activation between patients and controls mean in terms of functional reorganization remains an open question [25]. While these activation instances are frequently interpreted as a shift in the locus of a cognitive function, they have also been argued to reflect engagement of processes not typically used by controls [22] or even dysfunctional processing that inhibits the patient's ability to perform the task [26, 58]. We, therefore, used an alternative to these traditional univariate activation-based approaches, a multivariate technique that allowed us to decode function from a distributed pattern of brain activity [31]. Specifically, using this analysis, we compare evidence for orthographic processing and visual processing in different cortical regions.

In unimpaired participants, there was clear evidence that CH's damaged cortex is involved in both visual and orthographic processing when reading words but, tentatively, is more involved in orthographic processing. It is worth noting that this analysis is carried out over a large region of interest and we are not concluding that this entire region is involved with both visual and orthographic processing of written

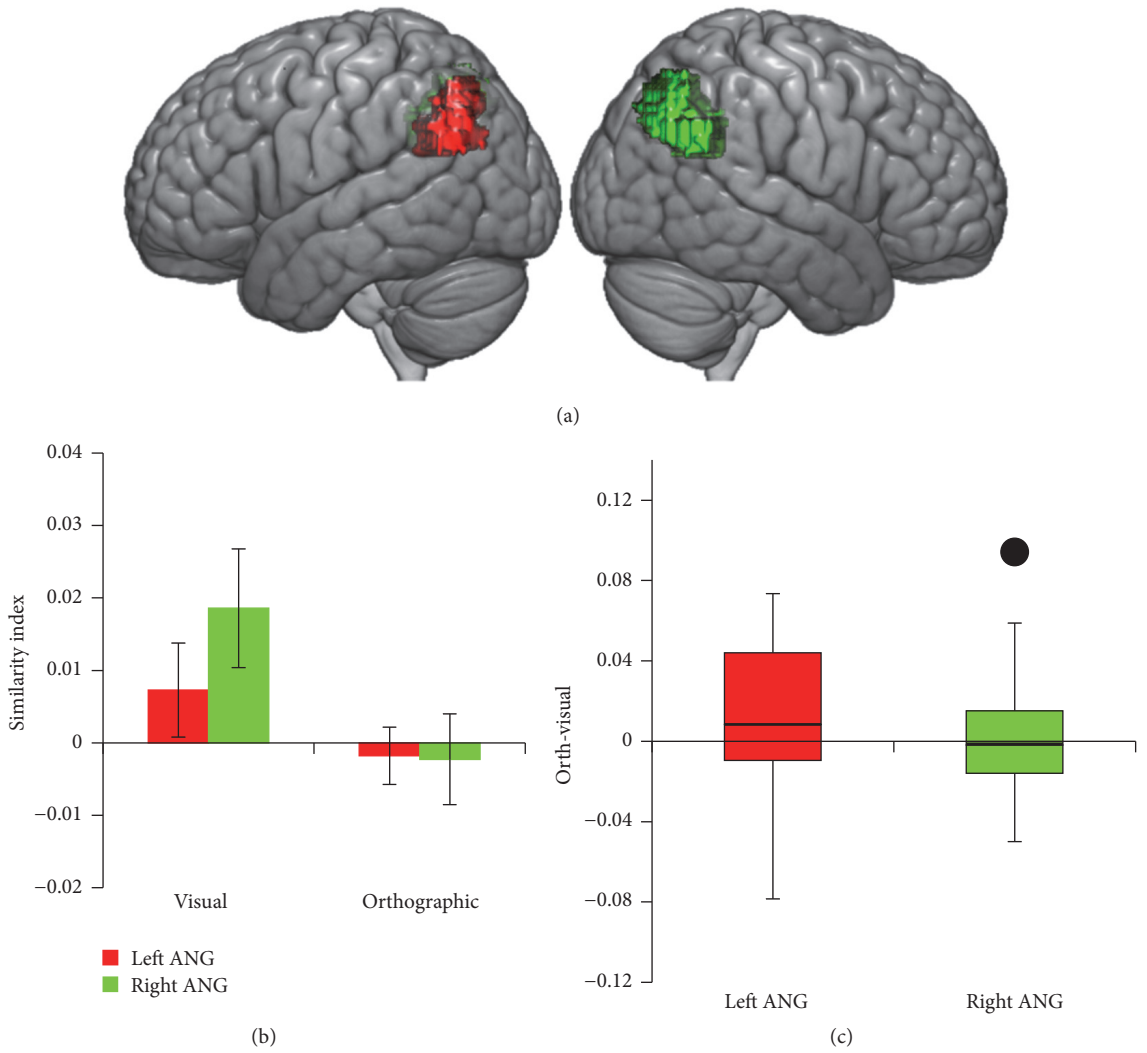

Figure 6: Results of the left and right angular gyrus (ANG) ROI analyses. (a) shows the location of the left and the right ANG regions of interest. (b) plots the average (Spearman) correlation between each control subject's brain-based similarity matrix (separately for the left and right ANG ROIs) with the visual and orthographic similarity matrices. Error bars represent ±1 SEM. (c) depicts a box-and-whiskers plot for the distribution of the difference between the orthographic and the visual indices for all of the control participants in both ROIs, with the black dot in the right ANG depicting CH's difference score.

words. Instead, it is likely that different subregions of the ROI are responsible for processing visual and orthographic information about written words. For example, CH's lesion does include damage to the middle and superior occipital gyri as well as the inferior temporal lobe and the angular gyrus. It is possible that visual processing in the occipital subregions of the large lesion ROI are responsible for the conclusion that the lesion ROI is involved in visual processing of written words, while the temporal lobe and angular gyrus subregions of the lesion ROI are responsible for the conclusion that the lesion ROI is involved in orthographic processing of written words.

Reorganization of the damaged orthographic function is clearest in the contralesional ROIs. We looked at two left hemisphere regions that are largely damaged in CH and in which controls show more evidence of orthographic than visual processing (left VWFA and left ANG). In the right hemisphere homologues of those regions, controls show either the opposite tendency (right VWFA) or no difference between orthographic and visual processes (right ANG). Unlike controls, CH shows a greater tendency to process orthographic information than visual information in both of these contralesional regions. CH uses these contralesional regions to compute a different function than that same region in controls. Furthermore, the function that CH is computing in these regions is similar to the function that controls are computing in tissue that CH no longer has following his stroke. This pattern of results is precisely the pattern that would be predicted if there is contralesional functional take-over, whereby the right hemisphere takes over the function of the damaged left hemisphere. At least in right hemisphere regions contralateral to the dyslexia-inducing lesion, there is evidence for functional reorganization in CH, with the

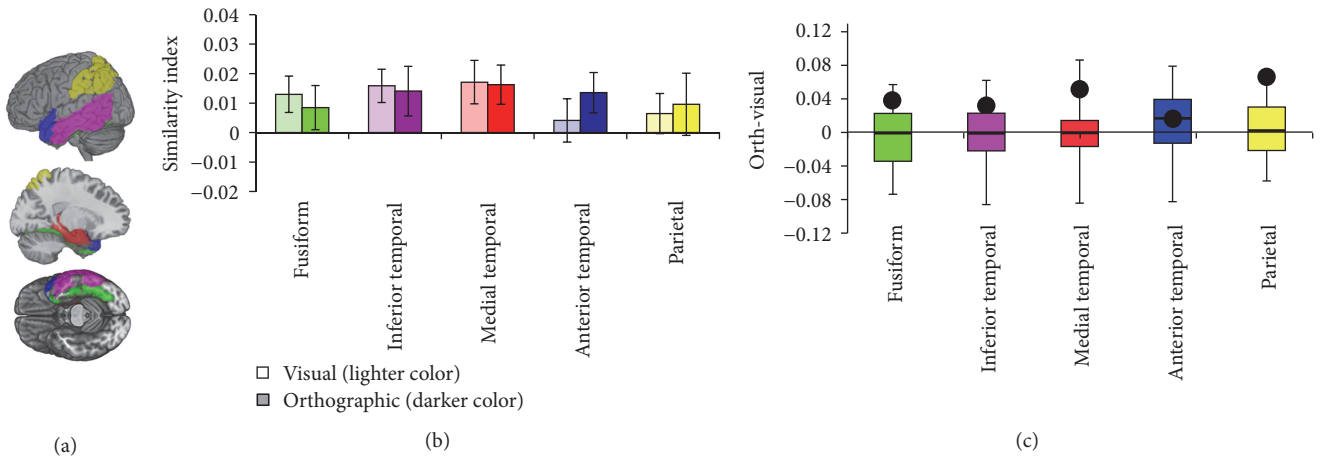

Figure 7: Results of the perilesional ROI analyses. (a) shows the location of the five regions of interest: fusiform (green), inferior temporal (purple), medial temporal (red), anterior temporal (blue), and parietal (yellow) regions. (b) plots the average (Spearman) correlation between each control subject's brain-based similarity matrix with the visual and orthographic similarity matrices. The white box indicates that for all 5 perilesional ROIs the lighter color is the visual similarity index and the grey box indicates that for all 5 perilesional ROIs the darker color is the orthographic similarity index. Error bars represent ±1 SEM. (c) depicts a box-and-whiskers plot for the distribution of the difference between the orthographic and the visual indices for all of the control participants in all five ROIs, with the black dot depicting CH's difference score.

region now processing orthographic information at least for familiar written words. Recall that CH's is still impaired at tasks, even with single letters, that require crossing case or modality. However, he remains relatively good at reading familiar words even when they are presented in an unfamiliar manner, like with alternating case. Therefore, we conclude that the orthographic information being processed in his right hemisphere supports the recognition of individual letters abstracting away from certain visual properties of the stimulus like font and location on the screen, but not other visual properties, like case.

In terms of the ranking data, the results were the clearest for the right ANG; CH has the highest orthographic similarity index value in this region relative to the 20 controls and the lowest visual similarity index value. However, one challenge in interpreting this pattern is that it is unclear what type of reading-related computation control participants are doing in this region. Specifically, it is possible that controls have an alternative reading pathway that goes through this region but that does not respond obligatorily during the fMRI task because controls read via a different pathway. If so, the increase in the relationship between the pattern of activity and the orthographic similarity metric in this region for CH might reflect the use of a preexisting system that is silent in the controls. The same argument cannot be made for the right VWFA. In control participants, the pattern of activity in the right VWFA correlates with the visual similarity metric, indicating that this region is engaged during reading and is doing visual processing. CH shows less visual processing and more orthographic processing in this region than controls. For this region, therefore, CH shows a clear shift in the normal reading function which cannot be explained by assuming a preexisting, but silent, reading pathway with orthographic processing in the right VWFA.

There is more limited support for this type of neural plasticity in perilesional regions. Regions that are superior/posterior to the lesion, in the perilesional parietal lobe, and medial to the lesion, in the medial temporal lobe, have a marginally greater tendency to process orthographic information in CH than in the controls. We therefore do not want to make any strong conclusions about whether or not CH shows perilesional reorganization of function. The role of contralesional and perilesional regions in recovery is an open question in the neural plasticity of language [18, 25]. In reference to this question, we can conclude that orthographic functioning in at least one individual is reorganized from the left to right hemisphere, with the possibility of additional perilesional reorganization in this individual.

However, there remain some limitations of the current study. First, the control group in this study is not ideal. CH is compared to a group of young adults. It is possible that the degree of orthographic and visual processing in the right hemisphere may depend on age. In general, aging has been associated with a reduction of hemispheric asymmetry [59]. While this reduction in hemispheric asymmetry has not been shown for reading specifically, it is possible that CH's right hemisphere responds differently to written words than the control group because he is older than the controls, not because he had a stroke. Age-matched control participants could address this concern.

Second, while the similarity index effects reported here are significantly different than zero, they are still exceedingly small. Similarity indices can vary between −1 and 1, but, at best, we observed values around .05 in the current study. These low correlations can partially be explained by noise in the data, but the values obtained in the current study are likely well below the noise ceiling (Nili et al., 2014). Therefore, we conclude that computational models used to compute the

similarity matrices are only approximations of the neural computations in the regions that we are investigating. The fact that, in controls, the left VWFA correlates higher with the orthographic than the visual similarity matrix suggests that the orthographic theory is closer to the actual neural computations of that region than the visual theory. However, the bigram model used here to compute orthographic similarity does not fully capture how words are processed in this region, potentially because it is not the correct theory of representation and processing at an orthographic level.

Third, this is a single case study of an individual who, despite having recovered some ability to read words, continues to have visual word processing difficulties well into the chronic state. We would not want to argue from this one case that all patients with acquired dyslexia show contralesional reorganization. For one thing, because this is an exploratory single subject analysis, we did not apply multiple comparisons correction for the ROIs tested. Therefore, it is possible that our results with this one subject reflect a type 1 error. A larger study, with more participants, in which we correct for multiple comparisons, is necessary to draw stronger conclusions about reorganization of the reading system following stroke. Furthermore, it is worth noting that CH has a greater residual reading impairment than many of the other cases whose reading recovery has been studied with fMRI (e.g., [12, 13, 15]). CH's continued impairment many years following the stroke may reflect limits to contralesional reorganization, and patients who make a more complete recovery may benefit from perilesional reorganization rather than contralesional reorganization. There are many open questions about how individual differences in neural plasticity following stroke related to differences in recovery. A large scale case-series investigation using the methods outlined above is necessary to address these questions.

Finally, because the current study is a single case investigation, we choose to select anatomical ROIs based on specific hypotheses about contralesional and perilesional reorganization, rather than functional ROIs based on regions that are more activated in CH than controls in the whole brain univariate analysis. As can be seen in Figure 3, there are a number of anterior regions in which CH shows greater activation than controls: bilateral inferior frontal gyrus and cingulate and insular cortex. One limitation of the current approach is we cannot interpret what this activity means, either in terms of reorganization of function or in terms of engagement of other cognitive processes like cognitive control or working memory. Future research, with a larger population, should apply this same logic of RSA to ROIs selected on the basis of regions in which patients show an increase in activation relative to controls. This approach will be able to interpret what functional changes underlie these increases in anterior activation.

The major contribution of this study is demonstrating how new decoding fMRI techniques can provide stronger evidence for functional reorganization of the reading network following stroke than traditional, univariate activation analyses. These new techniques for analyzing functional neuroimaging data for information, not activation, have proved to be powerful new tools in cognitive neuroscience [60–63]. Studies of language recovery would benefit from using these techniques. These techniques will allow us to map regions that shift their function following damage in a way that univariate, activation-based fMRI simply cannot. This study provides a proof of concept that representational similarity analysis can provide useful insights into functional reorganization following brain damage even with an individual subject. Going forward, we anticipate that representational similarity analysis will play a key role in addressing many of the open questions about the neural plasticity of language recovery: individual differences in neural and behavioral patterns of recovery, the relationship between spontaneous and treatment-induced recovery, and how patterns of recovery differ as a function of the domain of language impairment.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

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Endnotes

1. It is possible that CH's residual word reading is a version of word superiority effect observed in unimpaired readers, whereby briefly presented letters are easier to identify when embedded in words than when embedded in nonwords or shown in isolation [64, 65]. However, CH does not show a word superiority effect on letter identification. His letter naming performance is identical when letters are embedded in words (13/60; 22%) and nonwords (13/60; 22%) and comparable to his isolated letter naming ability (26/104; 25%). Another possibility is that this residual word reading reflects the patient's ability to guess which word is present given degraded, but not fully impaired, letter identity level information (e.g., [21]). This account would predict that CH should be more accurate at reading words with fewer neighbors, as it is easier to guess those words with limited orthographic information. However, when controlling for frequency, imageability, and length, CH's reading ability was not influenced by neighborhood size (many (>5) neighbors = 13/60; 22% versus few (≤1) neighbors = 12/60; 20%), providing evidence against this guessing account.
2. Given the design of our experiment, we cannot distinguish the font-free and case-free levels of representation proposed by Brunsdon et al. [34]. In our experiment, all of the words were presented in the same case, so we were unable to determine whether a given region treated

the same abstract letter identity in upper and lower case (e.g., g and G) identically. Given CH's behavioral pattern of impairment, with poor cross-case or cross-modality letter processing but relatively good reading even for words with alternating case, we expect that this orthographic similarity measure will track font-free but not case-free orthographic representations.

3. This procedure is slightly different than that used in other RSA papers. Specifically, other researchers have created representational dissimilarity matrices between two brain patterns by computing $1 - r$, where r is Pearson's correlation between two brain patterns. The choice of Spearman's correlation was motivated by concerns about nonlinearities in the relationship between beta-weights.

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Research Article

Right Hemisphere Remapping of Naming Functions Depends on Lesion Size and Location in Poststroke Aphasia

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The study of language network plasticity following left hemisphere stroke is foundational to the understanding of aphasia recovery and neural plasticity in general. Damage in different language nodes may influence whether local plasticity is possible and whether right hemisphere recruitment is beneficial. However, the relationships of both lesion size and location to patterns of remapping are poorly understood. In the context of a picture naming fMRI task, we tested whether lesion size and location relate to activity in surviving left hemisphere language nodes, as well as homotopic activity in the right hemisphere during covert name retrieval and overt name production. We found that lesion size was positively associated with greater right hemisphere activity during both phases of naming, a pattern that has frequently been suggested but has not previously been clearly demonstrated. During overt naming, lesions in the inferior frontal gyrus led to deactivation of contralateral frontal areas, while lesions in motor cortex led to increased right motor cortex activity. Furthermore, increased right motor activity related to better naming performance only when left motor cortex was lesioned, suggesting compensatory takeover of speech or language function by the homotopic node. These findings demonstrate that reorganization of language function, and the degree to which reorganization facilitates aphasia recovery, is dependent on the size and site of the lesion.

1. Introduction

One-third of stroke survivors suffer from loss of language ability [1, 2]. Recovery rates vary greatly, for reasons that are poorly understood [3]. The relationships between lesion site, activity pattern changes, and recovered language functions remain unclear.

1.1. Reorganization of Language Function after Stroke. In neuroimaging studies, patterns of increased activation during language tasks in chronic aphasia have been broadly consistent across studies. In a meta-analysis of neuroimaging studies, collapsing across a wide range of language tasks, we found that people with aphasia consistently overactivated perilesional regions in the left hemisphere, as well as right hemisphere regions that were homotopic to the left hemisphere language network [4]. In particular, people with lesions in the left inferior frontal gyrus (IFG) were more likely to recruit right IFG than those without lesions in that area. However, the behavioral and biological drivers of these changes, as well as the degree to which they promote, inhibit, or are even relevant to recovery, remain open questions.

The increased activation in the preserved left hemisphere in people with aphasia has generally been associated with overall better performance [5–8]. However, the relationship between lesion size, location, and ability to use these preserved regions has not been carefully examined. For example, particularly severe participants may have larger lesions or lesions in highly critical areas. If this is the case, then the relationship between left hemisphere activity and language performance may be indirect, in that both are actually dependent on the severity and size of the stroke itself, as well as the availability of left hemisphere tissue adjacent to the critical areas.

Within the right hemisphere, the relationship between plasticity and language performance is even less clear. A number of lines of evidence suggest that engagement of the right hemisphere serves overall to support aphasia recovery (for review, see [9]), suggesting a compensatory role for the right hemisphere homologues to language nodes. However, transcranial magnetic stimulation (TMS) studies show that inhibiting the right IFG pars triangularis (PTr) improves fluency, naming, and other language measures in people with left hemisphere stroke [10–15]. This suggests that the right IFG, specifically right PTr, may be limiting recovery in people with left hemisphere lesions. Furthermore, neuroimaging studies show that early engagement of the right hemisphere during the acute phase promotes recovery but that disengagement of the right hemisphere in later stages is related to ongoing successful recovery [16–19]. Increased activation in the right hemisphere during the chronic stage of aphasia is associated with naming errors [20] and overall worse performance, especially in picture-word naming and rhyme judgment [16, 21].

Unfortunately, the same concerns arise when examining the function of the right hemisphere as were raised for the left, specifically, confounding with lesion size and location. The usefulness of a shift from right to left hemisphere activation during the chronic stages likely depends on the availability of remaining healthy left hemisphere tissue [5]. Additionally, right hemisphere recruitment identified in neuroimaging studies may not be a consequence of plasticity at all. In neurologically healthy control subjects, right hemisphere activation has been shown to increase as a function of task difficulty [22, 23]. Furthermore, right hemisphere activity appears to be greater in participants with larger overall left hemisphere lesions [24], although this finding is only for some language tasks (picture naming, but not semantic judgment). Right hemisphere activity in people with aphasia, therefore, may actually be driven by the unique difficulty of the language tasks for people with aphasia. Right hemisphere activity may also reflect overactivation of any preserved tissue, of which there is less for people with large lesions, rather than actually remapping of function. However, the relationship between activity in the right hemisphere in people with aphasia, the rate of recovery, and actual plasticity remains unclear.

Beyond the general anatomical patterns of reorganization and their association with good or bad outcomes, the mechanisms underlying reorganization remain unclear. Such mechanisms may include behaviorally driven reorganization, as in the plasticity induced by speech-language therapy [18], or direct biological effects of the stroke itself. With regard to direct biological mechanisms underlying plasticity in language networks, relatively few specific hypotheses have been put forth. While some investigators, including ourselves, have previously described different patterns of reorganization (e.g., compensatory "takeover" by a new area), these descriptions do not generally hypothesize a specific biological basis for these changes. The great virtue of specific biological hypotheses is that they generate specific testable predictions, especially with regard to the timing of plasticity, the relationship of specific lesion features such as size and location to the pattern of reorganization, and the relationship of brain changes to behavioral outcomes.

One such biological hypothesis which has gained a great deal of traction in recent years is the interhemispheric inhibition model, which is commonly invoked to explain recruitment of homotopic right hemisphere processors, negative relationships between right hemisphere activity and language performance, and the beneficial effects of right PTr inhibition [25]. This hypothesis states that, in healthy people, there is transcallosal cross-hemispheric inhibition between language areas, similar to what has been demonstrated in motor areas [26, 27]. A stroke in the left hemisphere theoretically disrupts the interhemispheric inhibitory balance, leading to overactivation of right hemispheric language areas homotopic to the lesion. In the context of the interhemispheric inhibition theory, the overactivated right hemisphere is thought to maladaptively inhibit perilesional left hemisphere areas, resulting in worse outcomes [14].

In particular, the interhemispheric inhibition model makes at least three specific testable claims. First, larger lesions in the left hemisphere should be associated with more activity in the right hemisphere. Second, left hemisphere lesions should be associated with increased activity specifically in homotopic regions in the right hemisphere. Finally, increased right hemisphere activity in homotopic areas should be related to worse language abilities, even at the chronic stage. Some of the prior evidence regarding the latter two claims is outlined above. The predicted relationship between lesion size and right hemisphere recruitment is frequently mentioned in reviews on aphasia recovery either in the context of interhemispheric inhibition or based on the logical argument that if no left hemisphere tissue remains, the right hemisphere must be recruited for any recovery to occur [7, 28, 29]. However, the empirical evidence supporting this relationship is lacking and based primarily on small case series using methods that do not control for the accuracy of task performance [30].

1.2. Cognitive Models of Naming. Lexical-retrieval processes involve accessing concept knowledge and mapping phonological representations, stored in long-term memory [31] and these two stages are supported by distinct cortical regions. Phonological retrieval is ascribed to a ventral stream of processing, in which phonological representations in the posterior superior temporal lobe map onto semantic and conceptual information in the angular gyrus and anterior temporal lobes [32].

Postlexical output is the production stage, in which phonological representations are mapped to motor representations and speech occurs. Some dual-stream models assign this stage to the dorsal stream, in that the phonological representations in the superior temporal gyrus (STG) are mapped to motor sequence representations in the temporoparietal junction and posterior inferior frontal lobes [32].

1.3. Design of This Experiment. We tested these three predictions of the interhemispheric inhibition model in a cross-sectional study of people with chronic aphasia following left hemisphere stroke. The experiment used an fMRI task to

isolate covert (phonological retrieval) and overt (postlexical output) phases of picture naming; we first examined the general patterns of activity in our aphasia group compared to matched controls and the relationship between activity and overall lesion size. We then used the activity in the control group to define the normal brain network for naming in older people without language impairment or brain injury and tested how lesions at key nodes in this network affected activity throughout the rest of the brain, in particular within the remaining bilateral language sites. The goal of the study was to examine whether plastic changes in chronic aphasia would be related to the size and site of the lesion, with particular interest in right hemisphere plasticity occurring in regions that were homotopic to the left hemisphere lesions. We further tested whether any changes in activity associated with lesion site were related to naming performance, in order to assess whether these regions are successfully adapting to support language function or are inhibiting successful recovery.

2. Materials and Methods

2.1. Participants. Forty-nine chronic left hemisphere stroke survivors with a history of aphasia were recruited. Ten participants were then excluded based on fMRI task performance (<10% accuracy) resulting in a final sample of 39 participants in the aphasia group.

All participants in the aphasia group were native English speakers and testing occurred at least six months after their stroke (mean chronicity = 52.9 months). Participants were screened based on ability to follow testing instructions and had no history of other significant neurological illnesses. The distribution of lesions and individual demographic information for the aphasia group can be found in the Supplementary Material available online at https://doi.org/10.1155/2017/8740353.

Thirty-seven healthy control subjects, with no neurologic or psychiatric disorders, were also tested. Participants in the control group were matched to the aphasia group on age ($t(67.5) = -0.42, P > 0.60$), sex ($\chi^2(1) = 0.79, P > 0.30$), education ($t(73.0) = 0.85, P > 0.30$), and handedness ($\chi^2(3) = 3.1, P > 0.30$). Group means can be found in Table 1.

The study was approved by the Georgetown University Institutional Review Board, and written informed consent was obtained from all study participants prior to enrollment in the study.

2.2. Experimental Design. Visual stimuli consisted of 54 line drawings, with 92–100% name agreement based on norming in an independent sample of 55 older controls, representing one-, two-, and three-syllable words. To reduce individual differences in in-scanner performance, participants were presented with one of two 32-item sets during scanning based on the severity of their deficits. Fourteen participants whose naming and repetition deficits were severe in pre-MRI testing were given 32 one- and two-syllable items, while all other participants, including controls, were given 32 two- and three-syllable items during scanning. The one-syllable words also had overall higher frequency than the three-syllable words.

Table 1: Demographic information for the aphasia group and control group. Standard deviations are shown in parentheses. There were no differences between the groups on age, sex, education, or handedness.

	Aphasia group	Control group
Age (years)	59.8 (10.1)	58.7 (13.2)
Sex (male/female)	26/13	20/17
Education (years)	16.4 (2.8)	16.9 (2.6)
Handedness (right/left/ambidextrous/unknown)	33/4/0/4	33/3/1/0
Time since stroke (months)	52.9 (51.4)	—
WAB naming/word finding	7.1 (2.5)	—
WAB auditory-verbal comprehension	8.3 (1.5)	—
WAB repetition	7.0 (2.5)	—
WAB spontaneous speech	15.1 (4.9)	—

The fMRI task followed a slow jittered event related design. The trials were presented in a pseudo-randomized order. The task was a delayed naming task, which allows for the independent analysis of name retrieval and name production [33]. First, a single line drawing appeared centered on the screen, surrounded by a red border. This image remained on the screen for 7500–9000 ms, during which time the participant named the object in the image silently (covert naming). Then, the border around the image changed from red to green and remained on screen for 5500 ms. During this time, the participant was asked to produce the name of the object aloud (overt naming). Finally, the line drawing and the surrounding box disappeared and the participant fixated on a crosshair for 14000 ms. A slow event related design was chosen to allow for wash out of the hemodynamic response, which may be slower in stroke survivors [34]. Images were presented using E-Prime software (Psychology Software Tools Inc., Pittsburg, PA), and responses were recorded using a MRI safe microphone (Opto-acoustics, FOMRI-III). Before the scan, participants practiced the task on images not included in the fMRI task. If a participant produced the correct name at any point during the overt naming period, the item was counted as correct. Only trials in which the correct response was produced during the overt phase were included in the analysis. If a participant made an incorrect or no response during the overt naming phase of the trial, the entire trial (both covert and overt phases) was removed from further analysis.

Naming ability was tested using a 60-item version of the Philadelphia Naming Test (PNT) [35], made up of items independent of those used in the scanning task. Testing took place within one week of the MRI scan. We counted the total number of items on the PNT that were named correctly on the first attempt.

2.3. Scanning Parameters and Preprocessing. MRI data were collected on a 3.0 T Siemens Trio Scanner at the Georgetown University Medical Center. A high resolution T1-weighted MPRAGE was collected with the following parameters: repetition time = 1900 ms, echo time = 2.56 ms, flip angle = 9°, 160 contiguous 1 mm slices, field of view = 250 × 250 mm, matrix size = 246 × 256, and voxel size = 1 × 1 × 1 mm. Functional T2*-weighted images were acquired using a gradient-echo echo-planar pulse sequence, with the following parameters: repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, 38 contiguous 3.2 mm slices, field of view = 250 × 250 mm, and voxel size = 3.2 × 3.2 × 3.2 mm. The functional scan consisted of 32 trials, including an opening and closing screen, totaling approximately 15 minutes.

Lesion masks were created by manually tracing stroke damage on the T1-weighted images, in native space, in MRIcron [36], following a preestablished set of guidelines for determining lesion borders. Ventricular expansion was not included in the lesion. All lesion masks were checked by two board certified neurologists (Shihui Xing and Peter E. Turkeltaub) after the tracing and again after the lesion masks were warped to the template.

fMRI data were preprocessed and analyzed using FSL 5.0.6 [37]. Preprocessing included application of a high pass temporal filter, standard correction for head motion using MCFLIRT, interleaved slice timing correction, intensity normalization across volumes, and spatial smoothing to 5 mm FWHM. Registration and normalization were carried out to the MNI standardized brain provided by FSL. For each condition in each trial, a canonical double-gamma hemodynamic response function was constructed for the duration of the event. Motion parameters were then included as covariates in the model.

2.4. fMRI Analysis. First, we examined where participants in the aphasia group over- and underactivated relative to controls during covert and overt naming. In between-group contrasts, only areas that were significantly active ($z > 2.3$) in the aphasia group were included in the aphasia > control contrast, and vice versa. All whole-brain analyses were examined at cluster corrected $P < 0.01$, after a grey matter mask was applied.

2.4.1. Effects of Lesion Volume on Activity. We tested whether right hemisphere activity in people with aphasia is driven by the extent of overall damage in the left hemisphere. To do this, we quantified the size of the lesion, warped to template, for each individual. Lesion size was measured in mm^3 after warping to a standardized template and then entered as a voxelwise continuous predictor variable in a group analysis. Clusters identified as significant in this analysis are areas where activation, for either covert or overt naming, differed as a function of lesion size.

2.4.2. Regions of Interest Used to Examine Remapping. In order to examine how lesions within the normal language network affect naming ability, we identified regions of interest (ROIs) using the within-group contrasts from the control group. The peak voxel in each active cluster was identified, excluding primary visual cortex, for both the covert > fixation and overt > fixation contrasts. Then, 5 mm spheres were drawn around the peak voxel.

For each of the left hemisphere ROIs, aphasia group participants were grouped based on lesion status at the ROI. As these were very small ROIs, not large clusters, the distributions of percent lesions in the ROIs were highly bimodal, so an all or nothing approach was used: If a participant had a lesion that overlapped with the ROI in even one voxel, the participant was counted in the "lesion" group for that ROI. Then we tested whether lesions at each left hemisphere site led to worse naming performance on the PNT. Whole-brain analyses were then carried out, contrasting activity in these two groups (lesion versus intact at ROI site) of people with aphasia, while controlling for overall lesion volume.

Finally, we examined more closely the relationships between damage in sites normally active in controls and activity in the remaining nodes in the network. Regressions were carried out which tested whether lesion status in a left hemisphere ROI predicted activity levels in each of the other left and right hemisphere ROIs, controlling for lesion volume. ROIs in which activity was modulated by lesion status at another site were then further tested to see whether activity in that area related to naming ability.

3. Results

3.1. Whole-Brain Activity during Covert and Overt Naming. In the covert > fixation contrast (Table 2, Figures 1(a)-1(b)), the aphasia group showed greater activity than the control group mostly in bilateral basal ganglia, bilateral cerebellum, but also the right ventral central sulcus and right IFG. The aphasia group underactivated the left frontal pole, cingulate cortex, and bilateral clusters in the superior frontal gyrus compared to controls. In within-group contrasts, both groups showed significant activation in the visual cortex. The control group showed bilateral activation in the inferior parietal sulcus (IPS), while the aphasia group only showed significant activation in the right IPS. Likewise, the control group showed activation in the bilateral insula and pars opercularis (POp), as well as left PTr, while the aphasia group only activated the right PTr.

During overt naming (Table 3, Figures 1(c)-1(d)), the aphasia group overactivated dorsal regions bilaterally, in particular bilateral central sulcus, as well as right insula, right angular gyrus, and right Heschl's gyrus. The aphasia group underactivated, relative to controls, the left IFG, insula, superior temporal gyrus (STG), and cerebellum. In the within-group contrasts, both the aphasia group and control group activated the right superior temporal sulcus (STS), STG, temporal pole, and central sulcus. Only the control group activated these regions in the left hemisphere, while only the aphasia group showed activity in the right IFG.

3.2. Effect of Lesion Size on Activity. Next, we looked for regions, within the aphasia group, where activity during covert and overt naming was predicted by large lesions (Table 4, Figure 2). During covert naming, larger lesion size predicted widespread right hemisphere activity, especially

Table 2: MNI coordinates of activity in the covert naming > fixation contrast.

Group contrast	Peak z-value	x	y	z	Label
Aphasia > control	4.8	−22	16	8	Left basal ganglia
Aphasia > control	4.8	−20	−62	−28	Left lateral cerebellum
Aphasia > control	4.5	10	−40	−12	Right medial cerebellum
Aphasia > control	4.4	20	14	−2	Right basal ganglia
Aphasia > control	4.1	14	−62	−22	Right lateral cerebellum
Aphasia > control	4	−10	−28	0	Left thalamus
Aphasia > control	4.0	42	16	2	Right insula
Aphasia > control	4.0	65	10	0	Right ventral POp
Aphasia > control	3.9	62	−8	8	Right inferior central sulcus
Control > aphasia	3.9	−52	−40	60	Left IPS
Control > aphasia	3.7	−26	64	−2	Left frontal pole
Control > aphasia	3.7	26	54	26	Right superior frontal gyrus
Control > aphasia	3.5	−2	48	42	Left anterior cingulate cortex
Control > aphasia	3.1	−28	44	32	Left superior frontal gyrus
Aphasia group	8.1	36	90	0	Right visual cortex
Aphasia group	7.6	8	−84	−18	Right medial cerebellum
Aphasia group	6.8	10	0	6	Right thalamus
Aphasia group	6.6	−4	16	42	Left cingulate cortex
Aphasia group	6.2	50	20	−6	Right PTr
Aphasia group	6.2	−30	−92	4	Left visual cortex
Aphasia group	6.0	4	−34	−4	Right brainstem
Aphasia group	5.9	0	−22	6	Medial thalamus
Aphasia group	5.6	48	8	22	Right central sulcus
Aphasia group	5.2	30	−56	50	Right IPS
Aphasia group	5.2	−44	30	14	Left POp
Aphasia group	5.1	−16	6	6	Left thalamus
Aphasia group	5.1	50	18	−16	Right anterior STS
Aphasia group	5.0	18	−32	−8	Right posterior hippocampus
Control group	8.9	32	−92	12	Left visual cortex
Control group	7.2	0	28	36	Medial cingulate cortex
Control group	6.9	30	−66	54	Right dorsal IPS
Control group	6.6	−30	−60	48	Left dorsal IPS
Control group	6.6	38	22	−6	Right insula
Control group	6.5	−36	20	−4	Left insula
Control group	6.4	−50	28	24	Left dorsal POp
Control group	6.3	4	−36	−4	Right brainstem
Control group	6.3	54	16	−16	Right anterior STS
Control group	6.1	−48	12	24	Left ventral POp
Control group	6.0	48	10	24	Right central sulcus
Control group	6.0	54	38	12	Right POrb
Control group	5.9	−46	32	12	Left PTr
Control group	5.8	−32	56	14	Left frontal pole
Control group	5.7	28	−70	34	Right ventral IPS
Control group	5.5	−36	−50	44	Left ventral IPS

in the central sulcus, POp, and PTr, but also in bilateral visual cortex, cingulate, IPS, and basal ganglia. During overt naming, larger lesion size predicted activation in bilateral central sulcus, cingulate, and cerebellum, but activity was heavily right lateralized, especially in right PTr, posterior STS, and posterior STG.

We also looked for regions where activity was greater in participants with smaller lesions. There were no areas where

Table 3: MNI coordinates of activity in the overt naming > fixation contrast.

Group contrast	Peak z-value	x	y	z	Label
Aphasia > control	4.7	−28	−22	48	Left dorsal central sulcus
Aphasia > control	4.6	44	−66	0	Right visual cortex
Aphasia > control	4.6	24	0	66	Right dorsal central sulcus
Aphasia > control	4.0	−12	−26	64	Left middle cingulate cortex
Aphasia > control	4.0	−38	−10	48	Left central gyrus
Aphasia > control	3.9	40	−6	52	Right central gyrus
Aphasia > control	3.9	−14	10	42	Left anterior cingulate cortex
Aphasia > control	3.9	28	16	2	Right insula
Aphasia > control	3.8	40	−30	18	Right Heschl's gyrus
Aphasia > control	3.4	48	−34	24	Right angular gyrus
Aphasia > control	3.2	−32	−38	46	Left ventral IPS
Control > aphasia	5.2	−62	−4	−4	Left temporal pole
Control > aphasia	5.1	−62	−2	24	Left middle central sulcus
Control > aphasia	4.6	−10	−18	6	Left thalamus
Control > aphasia	4.5	−66	−40	4	Left posterior STS
Control > aphasia	4.1	−40	−14	−12	Left posterior insula
Control > aphasia	4.1	−4	−24	0	Left brainstem
Control > aphasia	4.0	−46	−30	6	Left posterior STG
Control > aphasia	3.9	−44	18	−6	Left PTr
Control > aphasia	3.9	−68	−30	8	Left middle STG
Control > aphasia	3.6	−16	−30	−16	Left hippocampus
Control > aphasia	3.4	−40	−82	−22	Left cerebellum
Aphasia group	7.7	54	4	36	Right central gyrus
Aphasia group	7.4	28	−80	−20	Right visual cortex
Aphasia group	7.4	6	6	52	Right cingulate cortex
Aphasia group	6.4	66	−22	−2	Right middle STG
Aphasia group	6.1	48	−34	2	Right posterior STS
Aphasia group	5.9	−46	−16	36	Left central sulcus
Aphasia group	5.6	12	−16	0	Right thalamus
Aphasia group	5.4	44	10	−6	Right PTr
Aphasia group	5.4	36	20	2	Right anterior insula
Aphasia group	5.4	56	−32	8	Right posterior STG
Aphasia group	5.3	−26	−94	12	Left visual cortex
Aphasia group	5.3	64	−40	22	Right angular gyrus
Aphasia group	5.1	40	−12	14	Right posterior insula
Aphasia group	5.0	−8	8	40	Left middle cingulate cortex
Aphasia group	5.0	38	−30	18	Right Heschl's gyrus
Aphasia group	4.9	32	−14	−10	Right middle hippocampus
Aphasia group	4.5	22	10	0	Right basal ganglia
Aphasia group	3.3	2	−54	−26	Right medial cerebellum
Aphasia group	3.3	−34	−20	48	Left central gyrus
Aphasia group	3.2	10	−28	−24	Right brainstem
Control group	8.5	−10	−104	−2	Left visual cortex
Control group	7.8	−50	−12	26	Left central sulcus
Control group	6.5	−16	−28	−12	Left middle hippocampus
Control group	6.5	22	−28	−10	Right middle hippocampus
Control group	6.4	68	−28	2	Right posterior STS
Control group	6.2	14	−18	2	Right basal ganglia

Table 3: Continued.

Group contrast	Peak z-value	x	y	z	Label
Control group	6.2	−64	−42	6	Left posterior STS
Control group	6.1	−2	2	58	Left middle cingulate cortex
Control group	6.0	−66	−2	−6	Left temporal pole
Control group	5.8	58	14	−16	Right temporal pole
Control group	5.6	−40	−30	8	Left Heschl's gyrus
Control group	5.3	66	−6	10	Right MTG
Control group	5.0	14	−24	−12	Right brainstem
Control group	4.1	−32	24	2	Left anterior insula
Control group	3.8	−46	8	22	Left dorsal POp
Control group	3.6	−36	4	2	Left middle insula

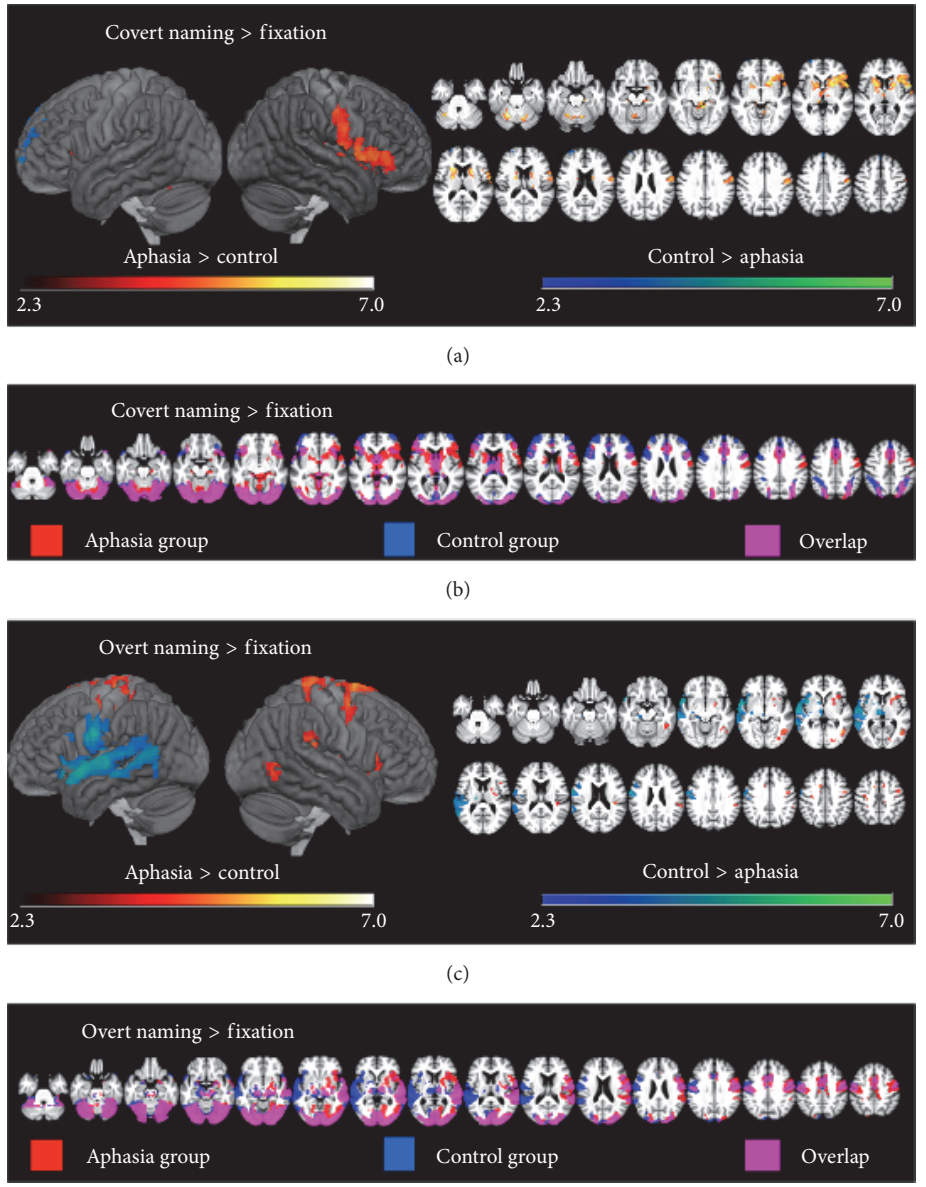
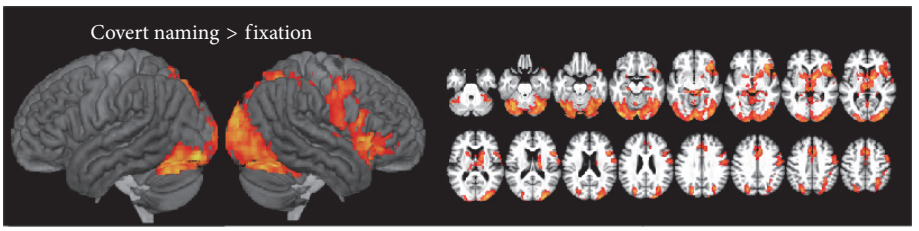


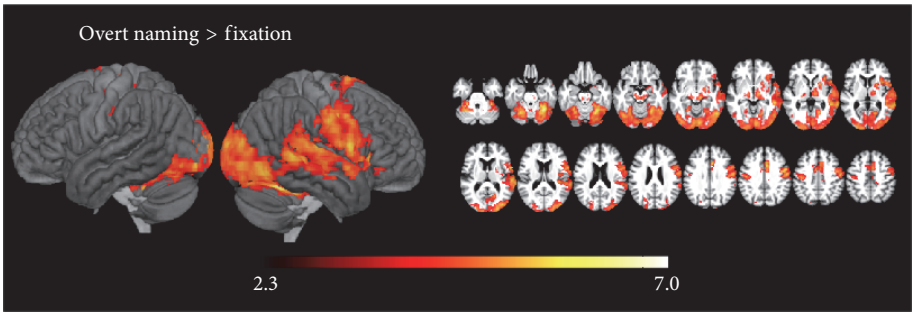
Figure 1: (a) Between-group contrasts showing activity during covert naming. (b) Within-group contrasts showing activity for both the aphasia and control groups during covert naming. (c) Between-group contrasts showing activity during overt naming. (d) Within-group contrasts showing activity for both the aphasia and control groups during overt naming.

Table 4: MNI coordinates of activity associated with large lesions, for both the covert naming and overt naming contrasts.

Task	Peak z-value	x	y	z	Label
Covert > fixation	5.5	4	−82	−16	Right visual cortex
Covert > fixation	5.4	34	−64	−24	Right cerebellum
Covert > fixation	5.3	−40	−88	−14	Left visual cortex
Covert > fixation	5.3	6	−32	−8	Right brainstem
Covert > fixation	5.1	12	0	2	Right basal ganglia
Covert > fixation	4.9	−26	−76	40	Left ventral IPS
Covert > fixation	4.8	30	−56	50	Right IPS
Covert > fixation	4.7	4	6	56	Right cingulate cortex
Covert > fixation	4.3	66	0	10	Left central gyrus
Covert > fixation	4.1	−18	8	4	Left basal ganglia
Covert > fixation	3.8	−24	−64	56	Left dorsal IPS
Overt > fixation	6.6	32	−58	−24	Right cerebellum
Overt > fixation	6.1	−26	−64	−28	Left cerebellum
Overt > fixation	5.4	4	4	52	Right cingulate cortex
Overt > fixation	5.4	68	−18	0	Right middle STS
Overt > fixation	5.3	66	2	10	Right PTr
Overt > fixation	5.1	52	−38	−6	Right MTG
Overt > fixation	4.3	−46	−16	36	Left central sulcus
Overt > fixation	4.3	22	8	0	Right basal ganglia
Overt > fixation	4.0	38	−12	14	Right posterior insula
Overt > fixation	3.9	−14	−34	54	Left cingulate cortex
Overt > fixation	3.8	−20	−20	0	Left external capsule
Overt > fixation	3.4	32	−14	−12	Right hippocampus



(a)



(b)

Figure 2: Regions where large left hemisphere lesions were related to greater activity during (a) covert naming and (b) overt naming.

activity was significantly predicted by smaller lesions at our threshold.

3.3. Lesions at ROIs and Behavior. Regions of interest were drawn based on peaks from the control group maps (Table 5). For covert naming, ROIs included the left and right IPS, left and right insula, and a left dorsal POp peak. Another peak in the left cingulate met requirements for an ROI, but only one participant in the aphasia group had a lesion in this area, so it was removed from further analysis. For overt naming, ROIs were selected in both the left and right motor cortex and STS.

We then tested whether lesion statuses in the left ROIs were related to naming performance in the scanner, using linear regression. Lesions in the left insula were related to worse naming, $t(37) = -2.4$, $P < 0.05$, but this effect did not hold when lesion size was introduced as a control variable, $P > 0.30$. Lesions in the left insula, dorsal POp, motor cortex, and STS had no relationship with naming performance in the scanner.

3.4. Effect of Lesion Location on Remapping and Whole-Brain Analysis. We then carried out whole-volume analysis using the aphasia group, testing whether lesion status at each left hemisphere ROI resulted in different patterns of activity in the rest of the brain, with lesion volume added as a nuisance variable. For covert naming, at a cluster corrected $P < 0.01$, there was no difference between people with left IPS lesions versus those without lesions at the IPS site.

People with left insula lesions showed less activity in the right middle and inferior frontal gyri, with peaks in the right middle frontal gyrus and right dorsal PTr. Participants with left POp lesions also showed less activation in nearly overlapping regions, including right dorsal POp (Figure 3, Table 6). The similarity of these results is likely due to the significant overlap between participants with left insula lesions and participants with left POp lesions.

We then took the cortical peak in this right hemisphere cluster, located in dorsal PTr, and extracted the activation levels for covert naming relative to baseline. The activation level in each participant with aphasia was transformed into a z-score centered on the control group mean. We carried out two tests, to examine whether activity in this area was related to PNT score, in the group with left POp lesions ($N = 16$) and in the group with intact left POp ($N = 23$), again controlling lesion size. There was no significant relationship between activity in the right peak activation and naming in either group (both P's > 0.25). The same analyses were also done, dividing participants based on lesion status at left insula (intact $N = 21$, lesion $N = 18$), but again no relationship was found for either group (both P's > 0.80).

No group differences in activity in the whole-volume analysis were identified based on lesion status at the two left hemisphere overt naming ROIs, left motor cortex and left STS, at this threshold.

3.5. Effect of Lesion Status in One ROI on Activity in Other ROIs. Finally, we tested whether lesion status in each left hemisphere ROI affected activity levels in all other, left and right hemisphere, ROIs derived from the healthy control sample, controlling for lesion size.

For covert naming, only one relationship was marginally significant. Participants with left insula lesions had marginally greater activity in the left POp, but this effect was unreliable at $P = 0.07$.

For overt naming, lesions in the left motor cortex were related to significantly greater activity in the right motor cortex, $t(36) = 2.91$, $P < 0.01$, while lesions in the left STS were associated with lower activity in right motor cortex, $t(36) = -2.24$, $P < 0.05$ (Figure 4).

We then tested whether right motor cortex over- or underactivation predicted naming performance in people with and without left motor lesions. As with the IFG analysis above, we calculated z-scores for activity in participants with aphasia, centered on the control group mean. For participants in the aphasia group with intact left motor cortex ($N = 15$), there was no relationship between right motor activity and naming, $t(12) = -0.28$, $P = 0.75$. However, for participants with left motor lesions ($N = 24$), right motor activity was positively associated with naming, $t(21) = 3.67$, $P = 0.001$.

4. General Discussion

This study addressed the relationship between stroke distribution and naming activity in chronic left hemisphere stroke survivors. Specifically, we examined whether overall size of the lesion, and damage of different nodes in the normal naming network, results in different patterns of brain activity. The analysis approach allowed us to test several current hypotheses regarding poststroke plasticity in language networks. Overall, the results support the prevalent notion that larger strokes result in greater usage of right hemisphere areas and further demonstrate that damage to different left hemisphere language nodes results in different patterns of activity in surviving nodes. The specific results, however, present challenges for the interhemispheric inhibition model and suggest that other mechanisms of behavioral and biological plasticity might better account for the data.

4.1. Residual Left Hemisphere Language Activity and Perilesional Recruitment. A striking finding from the overall group analysis was a failure of people with aphasia to activate normal left hemisphere brain areas associated with speech production, including the ventral sensorimotor cortex and the superior temporal cortex [38], during overt naming. These areas were robustly activated by the control group but not the group with aphasia, a difference confirmed in the direct between-group comparison. This finding cannot be related to direct lesion damage to these areas, as lesioned voxels were excluded from the analysis on a person-by-person basis. Rather, this pattern suggests a failure to activate spared left hemisphere speech production areas due to lesions elsewhere in the network. This explanation was not clearly supported by the ROI analysis, however, in which lesions in left hemisphere overt naming nodes did not relate to decreased activity in other spared left hemisphere nodes. Of note, because the ROIs were based on peak locations of activity in the control group, they were all located in the grey matter. It is possible the decreased activity observed in normal left hemisphere speech areas was primarily driven by

Table 5: Regions of interest drawn from the contrasts in the control group.

Contrast	Control group peak	x	y	z	Label	Subjects in aphasia group with lesions at ROI (out of 39 in total)
Covert > fixation	6.61	−30	−60	48	Left IPS	11
Covert > fixation	6.48	−36	20	−4	Left insula	18
Covert > fixation	6.38	−50	28	24	Left dorsal POp	16
Covert > fixation	6.91	30	−66	54	Right IPS	—
Covert > fixation	6.56	38	22	−8	Right insula	—
Overt > fixation	7.77	−50	−12	26	Left motor cortex/central sulcus	24
Overt > fixation	6.18	−64	−42	6	Left posterior STS	20
Overt > fixation	7.12	52	−10	26	Right motor Cortex/central sulcus	—
Overt > fixation	6.4	68	−28	2	Right posterior STS	—

Table 6: Areas where decreased activity was related to lesions in the left frontal lobe ROIs.

Lesion status ROI	Peak z-value	x	y	z	Label
Insula	−3.8	30	10	18	Right subcortical IFG
Insula	−3.6	46	22	32	Right superior frontal gyrus
Insula	−3.6	44	30	14	Right dorsal POp
Opercularis	−3.8	42	26	16	Right dorsal POp
Opercularis	−3.7	30	10	18	Right subcortical IFG
Opercularis	−3.2	48	26	30	Right superior frontal gyrus

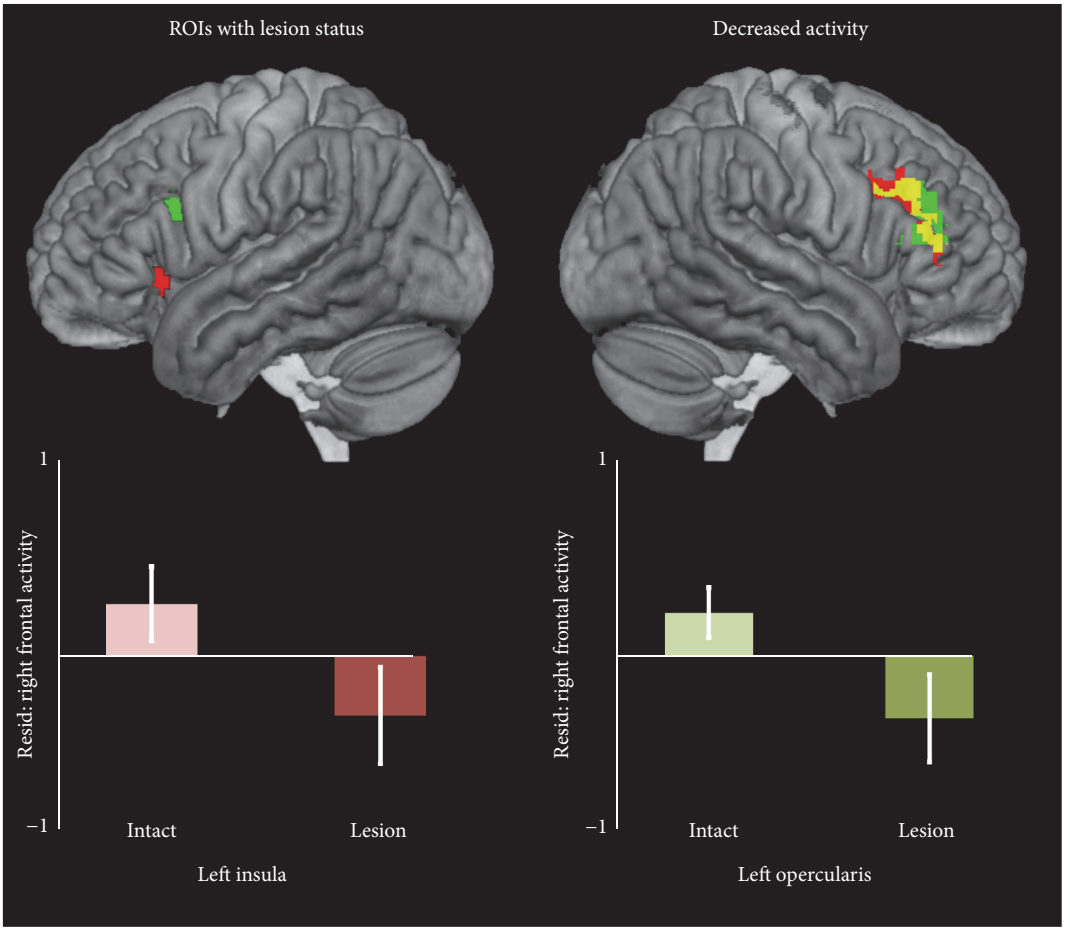


Figure 3: Lesions in the left insula and left opercularis were associated with less activity in the right middle frontal gyrus and right pars triangularis. Bar graphs show activity level in the right ROIs relative to the control sample, controlling for lesion volume.

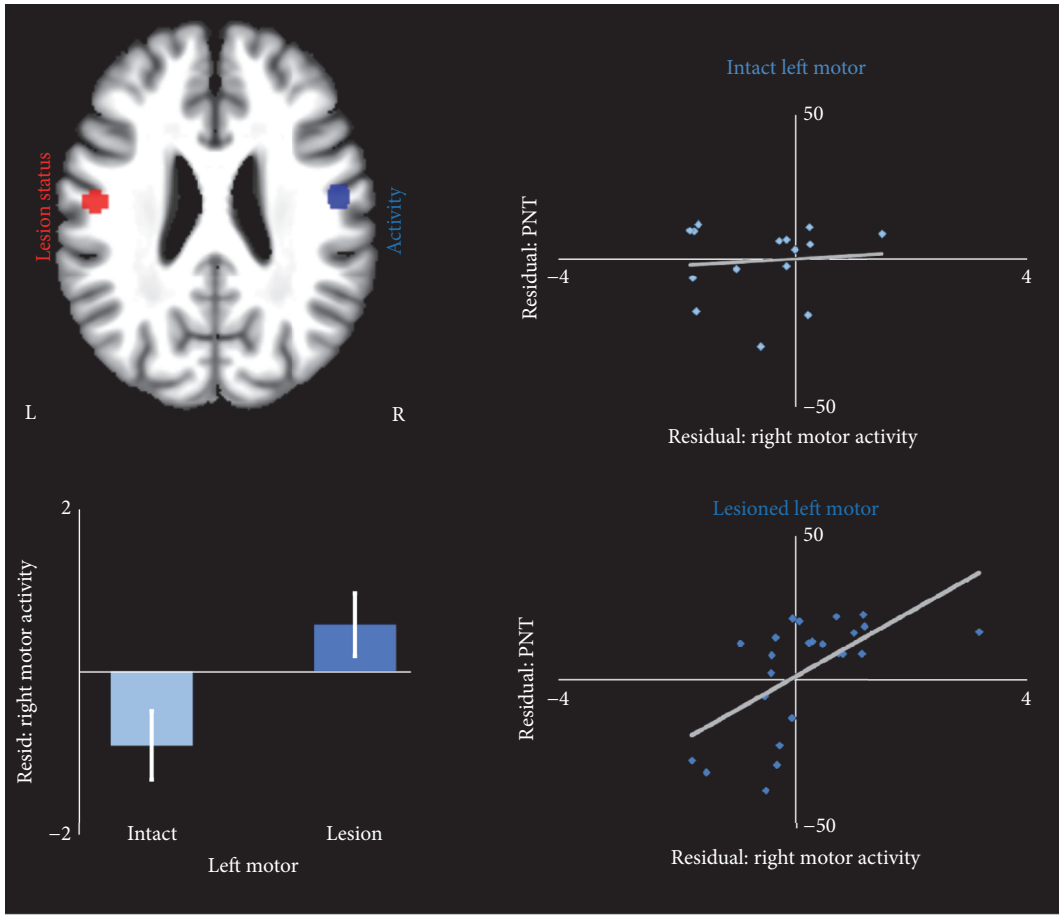


Figure 4: Lesions in the left motor cortex were associated with greater activity in the right motor cortex. The bar graph shows activity level in the right motor ROI relative to controls, controlling for lesion volume. Scatter plots show the relationship between activity and performance on the PNT, controlling for lesion volume, in the intact left motor group and in the group with lesions in left motor cortex.

disconnection from other network nodes due to white matter damage, which was not examined here. Regardless, the failure to activate normal left hemisphere areas involved in naming begs the question of whether and where compensation might be occurring in spared brain areas.

One prominent idea regarding poststroke language network plasticity proposes that left hemisphere perilesional areas surrounding the stroke that were previously involved in other functions are recruited into the language network to compensate for loss of language nodes [8]. In our voxelwise analysis, we found only weak evidence for these effects, with small areas of increased activity relative to controls in left dorsal frontal cortex during overt naming. We note that the analysis may not have been sensitive to these effects due to variability in stroke distributions. In the more sensitive ROI analysis, we found that lesions in the left insula were associated with marginally higher covert naming activity levels in the left dorsal POp, but this effect was weak and difficult to interpret given how few of our participants had one of these nodes lesioned and the other intact. Overall, this study provides little evidence either for or against perilesional compensation.

4.2. Lesion Size and Right Hemisphere Recruitment. Another prominent mode of proposed reorganization after stroke is the recruitment of homotopic areas in the right hemisphere. It has frequently been suggested that overall lesion size in the left hemisphere may relate to right hemisphere recruitment [7, 28, 29]. This proposed relationship is sometimes based on the interhemispheric inhibition model, even though a relationship between lesion size and contralesional recruitment is not supported by animal models, in which small sensorimotor lesions result in an increase in synaptogenesis and astrocytic volume contralateral to the stroke, while large lesions result in decreases in both of these measures, likely due to denervation-induced atrophy [37]. Alternatively, the proposed relationship between lesion size and right hemisphere engagement is sometimes based on the logical argument that people with relatively small lesions have sufficient viable left hemisphere tissue to support language and may not require right hemisphere compensation, whereas people with large lesions have little viable left hemisphere tissue and must rely on the right hemisphere to a greater extent. Although a positive relationship between lesion size and right hemisphere recruitment is frequently discussed

in the literature, there is surprisingly little direct empirical evidence of this relationship. One prior study examined the laterality indices of eight people with aphasia and found that large lesions were associated with greater right than left hemisphere activation during picture naming but not during a semantic decision task [17]. Here, we present strong support for this effect in both covert and overt naming in a large sample. Participants with larger lesions showed greater activity in right hemisphere areas homotopic to the normal left hemisphere language network. Notably, for overt naming, the specific pattern of activity related to lesion size in the right hemisphere (Figure 2(b)) closely mirrored the pattern of decreased activity relative to controls in the left hemisphere (Figure 1(c)).

The mechanisms underlying the increased activation of the right hemisphere in people with large lesions are unclear. This effect may not reflect plasticity at all but rather the increased effort required for language tasks by people with larger lesions. It is not unusual for more difficult tasks to elicit greater activity throughout the brain, including homotopic right hemisphere areas for language tasks [23]. Participants with large lesions likely exert greater effort in retrieving and producing the names of items and thus show overactivation during the task. Notably, activity in the bilateral visual cortex was also related to lesion size during both covert and overt naming here, suggesting that greater activity in general may be related to greater effort and longer looking times. Like other recent studies, we restricted our analysis to correct trials only in part to minimize these effort effects. However, even when producing a correct naming response, it is likely the people with large lesions may expend more effort than those with small lesions.

Similarly, it has recently been proposed that some right hemisphere overactivation observed in aphasia could be explained by recruitment of domain general attentional systems [39, 40] rather than language system reorganization per se. As above, the right hemisphere activity may similarly relate to the overall greater difficulty of language tasks for people with aphasia, although, under this hypothesis, the right hemisphere activity does not contribute to computations specific to language at all. Although this may explain part of the effect, we think it is unlikely to explain all right hemisphere overactivation in aphasia, given evidence here and elsewhere that activation of some right hemisphere nodes relates to the location of damage in the left and that the tasks that activate specific right hemisphere nodes are the same as those that activate the homotopic left hemisphere nodes in healthy controls [4].

Alternatively, explicit or implicit strategies used to compensate for deficits may result in recruitment of brain networks not used by healthy controls for language tasks, including the right hemisphere. As in the proposed overreliance on domain general systems, activity related to use of these strategies during scanning would not reflect any true plasticity in the language network. However, ultimately, reliance on domain general resources or alternate strategies in the long term could reinforce new neuronal connections and result in permanent neuroplastic changes in the network. In this case, differential activity could be observed even if the person does not actively use any alternate strategies during scanning. Melodic intonation therapy provides a clear example of an explicit compensatory strategy that can induce long lasting changes in network structure [41]. However, compensatory strategies need not be directly related to specific therapeutic experiences. For instance, a person who fails to retrieve the phonology of a word may attempt to visualize its spelling without any therapeutic training to do so. Changes in brain organization related to these type of strategic shifts may or may not relate to lesion size and location. For example, compensatory strategies involving pragmatic aspects of language or alternate forms of communication might be most used by people with large lesions and severe aphasia, potentially resulting in a relationship between lesion size and remodeling in brain areas involved in these functions. In the example of melodic intonation therapy, people with large frontal lesions causing nonfluent aphasias are most likely to receive this type of treatment [42], so this bias in exposure to intonation-based treatment could result in a relationship between left frontal strokes and right hemisphere changes that are behaviorally, rather than neurobiologically, driven. Spontaneous strategies such as mental visualization of word spellings could similarly relate to lesion location, assuming specific stroke distributions give rise to a pattern of deficits and preserved abilities that make these strategies advantageous. Importantly, however, reorganization related to strategic shifts should not necessarily occur in areas that are homotopic to the lesion.

4.3. Remapping in Homotopic Nodes. In contrast to the types of behaviorally driven plasticity described above, some neuroplasticity after stroke may occur as a direct biological result of the stroke itself. The interhemispheric inhibition model is the most prominent theory of biologically driven plasticity in the intact hemisphere after stroke. One prediction of this model is that remapping into the right hemisphere in aphasia should be homotopic to the lesion and not only driven by an overall lack of remaining left hemisphere tissue. A second predication is that as right hemisphere regions inhibit the remaining left hemisphere tissue, activity in the right should be associated with worse performance.

Contrary to this hypothesis, we found that lesions in the left POp and insula led to robustly decreased covert naming activity in the right PTr and in the MFG just dorsal to the POp, even when controlling for lesion volume. Furthermore, activity in this right frontal region was not related to naming ability. This finding also stands in contrast to a recent meta-analysis showing, across many studies using various language tasks, people with left IFG lesions were more likely to activate the right IFG [4]. There are several possible explanations for this discrepancy. First, the right hemisphere activity here is not perfectly homotopic with the lesioned nodes, although the difference in location, compared to the dorsal POp node, is very small. Second, we did not account for the proportion of the region affected by stroke. Greater right IFG activity might be more likely in people with a greater proportion of the left IFG damaged, while we treated all participants with lesions at the left insula (or POp) site as one group. However, a recent study using a semantic task found no relationship

between proportion of intact left IFG and right IFG activity [43], and as noted above, the animal literature shows that larger lesions can be associated with atrophy of contralateral cortex, rather than enhanced plasticity [44], corresponding with our findings here. Second, our study controlled for total lesion volume, which is rarely done in fMRI studies of aphasia, particularly in case studies or case series with few participants. It is likely that increased right IFG activity in prior studies is related to large lesions that include the left IFG and not specifically to lesions in the left IFG themselves. In support of this explanation, Figure 2 demonstrates that increased total lesion volume is associated with increased right IFG activity, among other areas. Finally, our study excluded participants with severe anomia, who could not correctly name at least 10% of the trials in the scanner. Other studies involving more severe patients, especially those that do not isolate activity related exclusively to correct trials, might reasonably produce a different result in the IFG. Therefore, questions for future study include whether homotopic remapping in the inferior frontal lobes is more likely in people with more severe aphasia and is related primarily to erroneous responses, as has previously been suggested in a small case series [20].

We did find evidence for homotopic remapping in motor cortex, in that left motor cortex lesions led to significantly greater right motor cortex activation during overt naming, controlling for total lesion volume. However, in contrast to the predictions of the interhemispheric inhibition model, overactivation of right motor cortex was associated with better naming performance in people with left motor lesions. These results join a growing body of literature suggesting that the right hemisphere may play a largely compensatory role, even in chronic stages of aphasia. Evidence for this begins in neuropsychological case studies, which have identified people who had recovered at least partially from aphasia following left hemisphere stroke and then redeveloped aphasia after a later right hemisphere disruption, whether due to intracarotid amobarbital injection or a second stroke [45–48]. These studies suggest that the right hemisphere can, to some degree, take over the language functions that the left hemisphere can no longer perform. A recent structural study found that greater grey matter volume in the right temporoparietal cortex related to better language production outcomes in chronic aphasia [49]. Other neuroimaging studies have shown positive relationships between right hemisphere activation and various language outcomes, supporting right hemisphere compensation [50–52]. Based on performance decrements after inhibitory TMS, other studies have also suggested that right hemisphere areas may be involved to some degree in phonology and naming in healthy people [53, 54]. Damage to left hemisphere language nodes may thus result in increased reliance on these right hemisphere language processors [55]. However, this explanation cannot account for the effects observed here, since the activity in right motor cortex related to naming performance only in people with left motor cortex lesions. This pattern strongly suggests a true compensatory relationship in which the right hemisphere node "takes over" for the corresponding lesioned left hemisphere area and demonstrates that specific biological mechanisms of plasticity beyond the interhemispheric inhibition model must be considered.

4.4. Alternate Biological Mechanisms of Right Hemisphere Recruitment. If not interhemispheric inhibition, what biological mechanism might explain recruitment of a homotopic node in the right hemisphere? The first possibility is that the interhemispheric inhibition hypothesis may be partially correct. It is possible that right hemisphere homotopic recruitment does result from transcallosal disinhibition but that this overactivation does not significantly suppress the surviving left hemisphere tissue. Behaviorally important right-to-left inhibition may simply never occur in language systems, may be restricted to particular areas such as the PTr, or may occur only in the case of relatively small lesions with some nearly homotopic left hemisphere tissue remaining to be inhibited [7].

However, other biological mechanisms might better explain compensatory recruitment of homotopic areas in the spared hemisphere after stroke. It has previously been noted that right hemisphere activity is maximal several weeks after a stroke causing aphasia [17]. If this activity resulted from direct disinhibition, the right hemisphere activity should occur immediately after the stroke. This kind of immediate right hemisphere recruitment has been observed after TMS-induced transient lesions [55, 56], but not after stroke. The gradual development of right hemisphere activation after stroke instead suggests a slower process, possibly relying on structural plasticity rather than a direct electrophysiological effect.

We suggest that axonal collateral sprouting from surviving neurons may provide an alternative neurobiological mechanism to explain both perilesional left hemisphere and homotopic right hemisphere recruitment in aphasia. This model is based on the principle that if two neurons send axons to the same target, they compete for synapses at the target. If one neuron dies, its axon degenerates and the surviving neuron's axon sprouts new collaterals near the target to take over empty synapses. Axonal collateral sprouting is observed throughout the central and peripheral nervous systems, for instance, in the development of ocular dominance columns and the delineation of motor units at the neuromuscular junction. It is known to play a role in reorganization after spinal cord injury [57] and brain injury, including stroke [58]. Competition has been shown to guide axonal sprouting in the sensory-motor spinal circuits in adult rats [59], and unbalanced endogenous activity dramatically affects receptor targeting in tracts crossing the corpus callosum [60]. Although not the only mechanism that can explain "take over" of prior functions by new brain areas, axonal collateral sprouting has previously been demonstrated to account for this phenomenon. For example, when dorsal route fibers to the hippocampus are destroyed in rats, ventral route fibers take over these connections over a period of months resulting in ultimate recovery of innervation patterns [61]. Further, axonal collateral sprouting is altered by the experience of the organism [62], providing a specific biological mechanism for function and neuroanatomic changes induced by speech-language therapy in people with aphasia.

Under this hypothesis, spared brain regions that share axonal targets with the lesioned tissue are the most likely to be recruited after stroke. This suggests that areas engaged to compensate might be predictable based on coconnectivity patterns before the stroke. Neighboring neurons are likely to share axonal targets, thus providing a basis for perilesional recruitment in the case of relatively small lesions. In some cases, such as motor areas innervating proximal limb muscles and the tongue, the homotopic cortex in the intact hemisphere likely shares axonal projection targets with the lesioned neurons and can take over the lost synapses, resulting in functional recovery [63, 64].

Our findings were near the mouth areas of motor cortex, and this mechanism might explain our findings of right hemisphere mouth-area motor recruitment during overt but not covert naming, corresponding with better naming performance specifically when the left hemisphere mouth area of motor cortex is lesioned. However, motor cortex has also been shown in other neuroimaging studies to play a role in covert naming and prearticulatory processes [65]. Furthermore, Geranmayeh and colleagues have argued that, regardless of the role of motor cortex in healthy people, upregulation of the region in people with aphasia is a marker of increased demands on domain general systems such as cognitive control and attention [66], and the relationship between activity and recovery is more related to those processes than anything language specific. It is possible that the diverse, nonspecific role of the motor cortex in speech production may also prime it to be uniquely plastic and available for taking over cognitive function through axonal sprouting, when the homotopic region is lesioned.

Regardless of the specific role of each region, the broader pattern of right hemisphere recruitment may result from a cascading effect from one homotopic right hemisphere node taking over synapses from its left hemisphere counterpart at a shared axonal target. When this node takes over the function of the lesioned left hemisphere node, the entire right hemisphere network connected to this one node may become involved in compensation, at least to a degree, resulting in broad patterns of increased activity. Alternatively, homotopic areas of each hemisphere's association cortices may share common cortical and subcortical axonal projection targets, and synaptic competition may account directly for broad patterns of right hemisphere recruitment. Modern connectomics may help to test these ideas. If supported by additional data, this hypothesis may provide clear predictions regarding the availability and location of alternate processing nodes based on the specific anatomical structures damaged by an individual's stroke.

4.5. Limitations and Future Directions. One unexpected finding was that while both people with aphasia and controls showed widespread activity during both covert and overt naming, the differences between the two groups was more widespread during overt naming. Most strikingly, the temporal lobe, in particular the STS and STG, was not significantly active in either group during covert naming. The posterior STS and STG are involved in phonological processes, which can include phonological retrieval [67], verbal working memory [68], and a sensorimotor speech interface for speech productions [69], so it was expected to be active during the covert naming phase of the experiment. In our experiment, however, no response was collected during the covert naming phase. If a trial was answered incorrectly during overt naming, both the covert and overt naming phases were removed from analysis. But, we do not have any measurable evidence of what was occurring for each participant during the covert naming phase. It is possible that some participants were less engaged in the task and only really attempted to name the object when cued to make an overt response and thus did not activate articulatory regions during the covert naming phase. In general, the use of a low-level control condition in the fMRI task allowed us to identify activity for word retrieval and production broadly but prohibited a detailed accounting of the precise nature of the processing in any given area of activity.

In this study, we identified regions where plasticity was dependent on the site of the lesion in left frontal and motor tissue. However, it remains unclear whether these relationships are mediated by the degree to which critical areas for naming are damaged or preserved. The language network in the left hemisphere involves many regions which are critical for different aspects of language. The degree to which a critical area for naming is destroyed by the stroke may determine whether plasticity of naming function is even possible, regardless of the lesion status at other regions of interest such as motor or inferior frontal cortex. A goal of future research is to identify regions in which damage has a catastrophic effect on naming ability and then model how damage in these regions affects others in the system, both perilesional and homotopic.

5. Conclusions

In this study we tested three central hypotheses of the interhemispheric inhibition model. We found an overall greater rightward shift of activity dependent on lesion size. Taking this overall effect into account, specific patterns of right hemisphere plasticity depended on the specific location of the stroke. Furthermore, right motor activation was positively associated with naming ability but only in people with left motor lesions. This finding suggests that lesion site needs to be accounted for when considering both the cause of right hemisphere overactivation and the role of right hemisphere activity, in people with aphasia. It is unlikely that any single biological mechanism explains all aspects of poststroke reorganization, and as noted above, complex interactions between biology and the environment are expected. We suggest that future work on aphasia recovery should be guided by specific behavioral and biological hypotheses that lead to specific experimental predictions for brain imaging and stimulation studies. Interhemispheric inhibition is one such specific biological hypothesis, but it cannot account for the entire range of observed neuroplastic effects in aphasia. The field must begin to entertain equally specific alternate hypotheses, such as synaptic competition, in order to move forward.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

The Role of the Cognitive Control System in Recovery from Bilingual Aphasia: A Multiple Single-Case fMRI Study

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Aphasia in bilingual patients is a therapeutic challenge since both languages can be impacted by the same lesion. Language control has been suggested to play an important role in the recovery of first (L1) and second (L2) language in bilingual aphasia following stroke. To test this hypothesis, we collected behavioral measures of language production (general aphasia evaluation and picture naming) in each language and language control (linguistic and nonlinguistic switching tasks), as well as fMRI during a naming task at one and four months following stroke in five bilingual patients suffering from poststroke aphasia. We further applied dynamic causal modelling (DCM) analyses to the connections between language and control brain areas. Three patients showed parallel recovery in language production, one patient improved in L1, and one improved in L2 only. Language-control functions improved in two patients. Consistent with the dynamic view of language recovery, DCM analyses showed a higher connectedness between language and control areas in the language with the better recovery. Moreover, similar degrees of connectedness between language and control areas were found in the patients who recovered in both languages. Our data suggest that engagement of the interconnected language-control network is crucial in the recovery of languages.

1. Introduction

Due to the increasing number of multilinguals in modern society, the incidence of language impairments induced by brain lesions (aphasia) in this population is growing rapidly [1, 2]. The rehabilitation of multilingual aphasic patients represents an important challenge for clinicians because (i) since the representation of first (L1) and second (L2) languages partly overlaps in bilinguals' brains, brain lesions do not necessarily affect L1 and L2 equally [3]; and (ii) recovery patterns for each language in multilingual aphasic patients vary considerably and so far are unpredictable [4].

Most of the current literature indicates that language recovery in bilingual aphasic patients depends on the degree of language mastery or language-specific factors [5–7]. For example, similarities in typology, phonological, morphological, lexical, and syntactic aspects between languages are shown to affect the pattern of recovery of languages in bilingual aphasic patients [1, 6]. Such an approach is also supported by evidence that changes in second language expertise and use are associated with an increase of connectivity within the language network of healthy subjects. However, growing evidence suggests that the control system may also play a key role in this process [5, 8, 9]. In healthy bilingual speakers, cognitive control system is strongly involved in language production [10] because language representations must be manipulated and monitored both within the language being spoken and across languages to select the appropriate vocabulary and syntax and to inhibit the nontarget language [11].

Abutalebi and Green [10], for instance, propose a "dynamic view" in which the pattern of language recovery in bilingual aphasia depends on the patient's ability to select and control language activation [10, 12]: (i) a parallel recovery, in

which both impaired languages improve to a similar extent, and, concurrently, occurs when both languages are inhibited to the same degree; (ii) an antagonistic recovery, in which the patient is able to speak in one language on one day while on the next day only in the other, occurs when inhibition affects only one language for a period of time and then shifts to the other language (with disinhibition of the previously inhibited language); (iii) a selective recovery, in which one language remains impaired while the other recovers, occurs if the lesion has permanently raised the activation threshold for one language; and (iv) a pathological mixing, in which the elements of the two languages are involuntarily mixed during language production, occurs when languages can no longer be selectively inhibited [9, 10, 13].

While this theory accounts for the large variability in recovery patterns of multilingual aphasia, there is only sparse evidence for any association between control function and language recovery since control functions are rarely specifically assessed in aphasic patients. Aglioti et al. [5] reported the case of a bilingual aphasic patient who showed a greater deficit in her more used L1 than in her less practiced L2, following lesions mainly involving the left basal ganglia. The authors suggest that the patient's deficit in L1 may be considered as a pathological fixation on a foreign language resulting from a deficit in switching between languages. However, the patient had a normal performance in the Wisconsin card-sorting test (WCS), a nonverbal task testing the ability to change from one criterion of choice to another. This result suggested that, in the absence of a remarkable impairment in control functions (shown in WCS which evaluated "shifting," a part of control functions), the patient's fixation behavior was mostly linguistic. Moreover, since the assessment of executive functions was conducted one year after the stroke, anatomo-functional plastic reorganization of the language and control networks could already have taken place and likely confounded the results. An earlier evaluation (e.g., at acute or subacute phase) following the stroke could have better shown whether this so-called pathological fixation on L2 and the L1 impairment has resulted from impairment in cognitive control function. Verreyt et al. [14] reported the case of an early French-Dutch bilingual aphasic who, following a lesion to the left thalamus, presented larger impairment in Dutch. By showing cognate facilitation and cognate interference effects in different lexical decision tasks and an impaired performance in the flanker task, the authors suggested that the differential pattern of impairment in language could be explained by a language-control deficit. In addition, Abutalebi et al. [9], in a longitudinal, single-case study of a chronic bilingual aphasic patient combining fMRI and dynamic causal modelling (DCM), showed an increased connectivity within the control and language networks for the treated and recovered language. In line with the Paradis's activation threshold theory, which holds that lesions that do not completely damage language areas but cause an imbalance in activating and inhibiting languages are responsible for aphasia in bilinguals [12], they found that the engagement of the areas mediating language control played a crucial role in language recovery in bilingual aphasic patients. They showed that connections between language and control areas were stronger in the language that recovered better, probably because it received more resources for its functioning.

The network underlying language control described by Abutalebi and Green [10] and Abutalebi et al. [9] includes the prefrontal cortex (mainly inferior prefrontal cortex including LIFGOrb (left inferior frontal gyrus pars orbitalis, BA47)), the anterior cingulate cortex (ACC) (BAs24, 32, 33), and the basal ganglia. This network is interconnected with language areas involved in word production (LIFGTri: left inferior frontal gyrus pars triangularis, BA45) and "basal temporal language area, BTLA" involved in semantic decoding during picture naming (posterior part of the left inferior temporal gyrus BAs19 and 37). In the bilingual brain, the prefrontal cortex is involved in word production in the less proficient language and in inhibiting responses from the more proficient language. Together with the anterior cingulate that detects response conflicts, it constitutes a control loop in which the identification of conflict triggers a top-down signal from the prefrontal cortex to modulate the nontarget representation (see [10, 15, 16]). The left caudate and the ACC are strongly connected to the prefrontal cortex [17] and work together with this structure to inhibit interferences from the nontarget language. The ACC signals potential response conflicts or errors to the prefrontal cortex (i.e., in the case that an erroneous language has been chosen) and the prefrontal cortex then seeks to avoid incorrect selection. Finally, the basal ganglia may subserve language planning, that is, the activation of a given language as a main function of the left caudate and the control of articulatory processes in the left putamen (see [18, 19]). Using linguistic and nonlinguistic switching tasks, it has been shown that the neuroanatomical bases of language control and domain-general cognitive control share the partially overlapping structures, although their involvement may vary [20, 21]. It is worth noting that understanding neural mechanisms underlying patterns of recovery has many implications for the therapeutic approach.

Based on the hypothesis of a key role for cognitive control in bilingual language production and in the recovery of bilingual aphasia, our study aims to test whether among the different control areas proposed by Abutalebi et al. [9], changes in certain connections between control and language areas influence the recovery of language (namely, between LIFGTri and LIFGOrb and LC and ACC). To this aim, we tested five late bilingual patients who suffered from aphasia following a focal left-hemispheric brain lesion. The patients were evaluated at two time points (subacute and chronic phases, three months apart). Three main analyses were conducted to examine the pattern of changes in patients' language and control functions, connectivity within language-control network, and possible correlation between behavioral performances and connectivity with language-control network.

(A) As a descriptive marker of behavioral improvement/changes in language and control functions, the patients were behaviorally evaluated for their pattern of recovery of language and executive functions using general aphasia evaluation (GAE), picture naming and executive tasks (linguistic and nonlinguistic switching).

(B) In order to investigate the connections within the language-control network, we used fMRI analyses and applied dynamic causal modelling in the fMRI picture naming task in L1 and L2 to examine whole brain activation patterns and the effective connectivity between the control areas (ACC, left caudate nucleus, and LIFGOrb) and the regions involved in language production (especially LIFGTri). We further examined whether global changes in connectedness within language-control network are associated with the recovery of languages.

(C) To directly assess the hypothesis advanced in the language-control model [9], we examined the correlations between the recovery of language functions and the changes in the strength of connections between the above-mentioned areas using group analyses. In fact, as Meier et al. [22] in a DCM study on chronic aphasic patients and a group of controls have found that language network parameters are specifically associated with naming abilities in picture naming task, we consider that there should be a difference in connection strength in L1 and L2 and also according to naming improvement across time.

We chose to evaluate bilingual aphasic patients during the subacute phase since this population has rarely been studied in the acute and subacute phases. This will allow us to better understand the contribution of the control system in the recovery of language in bilingual aphasia, especially during the period when spontaneous recovery process mainly takes place [6, 23]. In addition, in this phase, the spontaneous recovery and neural plasticity processes are ongoing and given that bilingual population is strongly relied on cognitive control system, we assume that the changes in cognitive control system and its interconnection with the language system probably play a role in the recovery of aphasia.

2. Methods

2.1. Participants

2.1.1. Aphasic Patients. We recruited right-handed late (age of acquisition (AoA) of L2 after 6 y/o) bilingual patients aged between 18 and 85 years old, who suffered from aphasia following a focal left-sided ischemic or hemorrhagic stroke. The following languages were included in the study: French (in each case as subjects' L1 or L2) and English, German, Spanish, or Italian. During the recruitment procedure, we excluded patients with a history of premorbid language impairment, several brain lesions, or severe aphasia.

A total of eleven patients were recruited for this project. However, only six patients completed all the steps of the study and, among them, five subjects fulfilled our criteria of the selection of regions of interest (ROIs) for the DCM analyses and therefore are reported in this paper. Five more patients performed the first session of the study and then declined to participate in the second session (see Section 2.3 for details of the steps of the study) and were therefore not included in the analyses. Among the five patients included in this paper (aged 61.6 (±6.9) years old and including two females), three patients were French (L1) and English (L2) and two patients were Italian (L1) and French (L2). All the patients were late bilinguals (AoA: 16.5 ± 5.1). The lesion of each patient is shown in a figure specifically designed for each of them (Figures 3(a)–7(a)). The study procedure was approved by the local Ethics Committees of Geneva University Hospital (CE 12-274) and Fribourg Cantonal Hospital (018/12-CER-FR).

Case Description

Patient 1. YL is a 61-year-old man who is a French (L1)-English (L2) bilingual. Mr. YL was born in French-speaking part of Switzerland. The language of teaching at school was French. Mr. YL estimates an advanced level of English for reading, speaking, and comprehension (all between 95 and 100% according to the self-evaluation scale of L2 level). Before the stroke, his language usage was mainly in French; he spoke 100% French with his family and 80% with his friends. He followed TV and radio programs only in French. However, his reading was 50% in French and 50% in English (readings in English are mainly work-related books and documents), and he used mainly English at his workplace (80%).

Mr. YL was admitted to Geneva University Hospital (HUG) with right sensorimotor hemiparesis, right facial palsy, and impaired comprehension and language production mainly manifested in L2 following a left frontotemporal ischemic stroke. A secondary hemorrhagic event in the ischemic area was seen three days after the ischemic event (Figure 3(a)). A first language evaluation showed a transcortical sensory aphasia; he presented mainly auditory comprehension problems and produced repeated semantic errors. However, spontaneous speaking was relatively fluent.

Patient 2. MR is a 65-year-old Italian (L1)-French (L2) bilingual woman. She was born in Italy to Italian parents and followed primary school in Italy. She moved to the French-speaking part of Switzerland at the age of 24, and then she has taken some courses to learn French. Before the stroke, she used Italian and French quite equally; she used French at work (100%), and Italian for TV or radio programs (100%). She used 50% in Italian and 50% in French to speak with her family and friends and to read books and journals.

MR was admitted to HUG for resection of a meningioma on the left greater wing of the sphenoid bone. Two days after the resection of the meningioma, she presented a right sensorimotor hemiparesis and a severe language production problem plus a lesser degree of comprehension problems in both languages, caused by an epidural hematoma with pressure over the operation site and ischemic changes in the left frontobasal area (Figure 4(a)). The initial language evaluation showed anomia in both L1 and L2.

Patient 3. CA is a 63-year-old woman who is an Italian (L1)-French (L2) bilingual. She was born in Italy to Italian parents and followed primary school in Italy. She moved to the French-speaking part of Switzerland at the age of 10; thereafter she started to learn French. Mrs. CA followed secondary school in Switzerland where the teaching language was

French. She has also basic knowledge in English and Spanish, which she has learned at school. Before the stroke, the main language of conversation was French with her husband and children (90%) and at work (75%) and she spoke Italian with her parents (100%).

She was admitted to HUG because of right hemiparesis and severe global aphasia due to a left basal ganglia hemorrhagic stroke with no evidence of midline shift (Figure 5(a)). Within a few days, global aphasia developed into severe anomia with hypophonia mainly affecting L2.

Patient 4. RG is a 49-year-old bilingual French (L1)-English (L2) male patient. He finished primary and secondary schools in the French-speaking part of Switzerland. He started to learn English at school at the age of 14. He used English quite frequently in his daily life; he used French and English equally at work (50% French and 50% English for teaching and customer care). He followed TV and radio programs and also read books and journals 50% in French and 50% in English. However, he spoke only in French with his friends and family. According to the self-evaluation questionnaire filled in by his wife, his language abilities were estimated as follows: speaking 50%, comprehension 70%, reading 85%, and writing 30%.

He was admitted to Fribourg Cantonal Hospital with a sudden right hemiparesis and anomia and no other language symptoms due to a left sylvian ischemic stroke (Figure 6(a)).

Patient 5. GH is a 79-year-old bilingual French (L1)-English (L2) male patient. He has learned English around the age of 18 when he first travelled to the US and England. He has then moved to Sweden and started to learn Swedish too. He has been working in Sweden for about 18 years teaching guitar in both English and Swedish. He then moved back to Switzerland at the age of 66. He then continued to teach playing guitar to children. He used both French and English in his teachings (50% French and 50% English). With his family he spoke only in French; however with his friends he spoke 50% in French and 50% in English. He followed TV and radio program mostly in French (75% in French and 25% in English) and he read books and journals only in French.

He was admitted to HUG with a paresthesia in his left arm and global aphasia. GH was a known case of auricular fibrillation before this acute event. The cerebral CT scan after the acute event confirmed an ischemic lesion in the left frontal, insula, and sylvian areas (Figure 7(a)). Within a few days, global aphasia developed into severe anomia and increased switching behavior.

More details of patients can be found in Tables 1 and 2 and Supplementary Data 1 available online at http://dx.doi.org/10.1155/2016/8797086.

2.1.2. Control Subjects. The data and results on the control subjects are presented in Supplementary Data 2 and 3.

2.2. Assessment of Premorbid Language Proficiency. Subjects were assessed using a questionnaire on their immersion in both L1 and L2, AoA, how long they had lived in a region where predominantly the second language was spoken, which language they spoke with their family members, in school, and in present activities (watching TV/listening to radio, reading books, and mental arithmetic), and if the language was acquired in school or out of school only. In the self-evaluation part, subjects (or their family members) had to indicate in percentages how well they would estimate their reading, speaking, comprehension, and writing skills.

2.3. Study Design. Patients were assessed at subacute (three to five weeks after stroke onset, T1) and chronic (three months after T1 evaluation, T2) phases. In both sessions we used the same procedures, listed as follows: (1) behavioral assessment of the severity of aphasia as well as a combination of language-control function evaluations; (2) in an fMRI recording session, the patients performed a language production task (picture naming) in each language (see Section 2.6.1 for picture naming task).

2.4. Behavioral Tasks. General aphasia evaluation (GAE): global severity of the aphasia and language capacities was assessed using a separate evaluation of language capacities in each language (i.e., L1 and L2 were evaluated separately, one day apart). This evaluation consisted of a brief test of object naming (ten objects to name), automatic speech (series: days of the week, counting from 1 to 25), word and phrase repetition, yes/no questions, object recognition, following oral and written instructions (simple, semicomplex, and complex commands), description, and verbal fluency. All these tests were extracted from the Bilingual Aphasia Test (BAT) [24] except for yes/no questions which were extracted from the Mississippi Aphasia Screening Test (MAST) [25]. This evaluation material has been already used in our previously published works, for example, [26]. As a result, a production index of maximum 52 scores (i.e., the sum of the scores obtained from production tasks including object naming, series, verbal fluency, word and phrase repetition, and description) and a total score (maximum 96 scores) was obtained.

Language-control functions were evaluated using the following:

(a) A linguistic switching task (adapted from Abutalebi et al. 2008 for aphasic patients [27]): forty images (black and white line drawing picture) of Snodgrass and Vanderwart [28] (all noncognate words) were used for each list. Eight pairs of lists were prepared (a combination of French as first or second language and the other four languages). The words of each pair were matched for word frequency. The subjects were asked to name, as quickly as possible, the images in L1 when the image appeared on the upper part and name the image in L2 when the image appeared on the lower part of the screen. After a fixation cross of 500 ms, the images were presented on the screen for 5,000 ms and were followed by a blank screen of variable duration of 3,000–7,000 ms (to provide a random duration of the interstimulus interval). Therefore, the subjects had at most between 8,000 and 12,000 ms to respond. However, only first-attempt correct responses within five seconds of the presentation of the image were scored as correct. Each trial was started manually

Table 1: Assessment of premorbid L2 proficiency.

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
First language (L1)	French	Italian	Italian	French	French
Second language (L2)	English	French	French	English	English
AoA (y/o)	10	24	10	14	18
Lived in region speaking L2	0	41	53	>1	>1
Family					
First language of mother	French	Italian	Italian	French	Swiss German
Language spoken with mother	French	Italian	Italian	French	French
First language of father	French	Italian	Italian	French	French
Language spoken with father	French	Italian	Italian	French	French
First language of partner	French	French/Italian	Italian	French	—
Language spoken with partner	French	Italian	French	French	—
Childhood (<7 y/o)					
Language taught in school	French	Italian	No info.	French	French
Language spoken with peers at school	French	Italian	No info.	French	French
Language spoken with family	French	Italian	Italian	French	French
Present					
Spoken at work	15% L1, 85% L2	100% L2	75% L2, 25% L1	50% L1, 50% L2	50% L1, 50% L2
Watching TV/listening to radio	100% L1	100% L1	50% L1, 50% L2	50% L1, 50% L2	75% L1, 25% L2
Speaking with friends	90% L1, 10% L2	50% L1, 50% L2	50% L1, 50% L2	L1	50% L1, 50% L2
Reading books	50% L1, 50% L2	50% L1, 50% L2	50% L1, 50% L2	50% L1, 50% L2	100% L1
Mental arithmetic	100% L1	75% L1, 25% L2	50% L1, 50% L2	L1	100% L1
Self-evaluation of L2 (0–100)					
Speaking	100	95	100	55	80
Writing	98	15	100	75	50
Comprehension	100	95	100	80	89
Reading	100	75	100	35	70

by the experimenter when the word "ready?" was presented on the screen. The first six trials of the task were cued with the language in which the image should be named (L1 or L2) written on the left of the image (Figure 1(a)). This task lasted between 10 and 12 minutes depending on patients' response time.

(b) A nonlinguistic switching task: four images (a red or blue circle or square) were presented on the upper or the lower part of the screen. Subjects were instructed to name, as quickly as possible, the color of the image when the image was presented on the upper part of the screen and to say the shape of the image when it was presented on the lower part of the screen. After a fixation cross of 500 ms, the images were presented on the screen for 5,000 ms and were followed by a blank screen of variable duration of 3,000–7,000 ms (to provide a random duration of the interstimulus interval). Therefore, the subjects had at most between 8,000 and 12,000 ms to respond. However, only first-attempt correct responses within five seconds of the presentation of the image were scored as correct. Each trial was started manually by the experimenter when the word "ready?" was presented on the screen. The first six trials of the task were cued with the category in which the image should be named (color or shape) written on the left of the image (Figure 1(b)). The task lasted around 10–12 minutes depending on patient's response time.

For all the tasks, instructions were given both written on the screen and orally, and the subjects performed a short training session just before starting the task. The evaluation of the language-control function was performed in the more proficient language (usually L1). Moreover, because of slowness of patients and fatigability, for all the tasks we did

Table 2: Demographic data.

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Age	61	65	63	49	79
Gender	M	F	F	M	M
Scholarity (years)	16	12	12	18	16
Lesion site	Left frontotemporal	Left frontobasal area	Left basal ganglia	Left sylvian	Left frontal-insula-sylvian
Lesion etiology	Ischemic + hemorrhagic stroke	Epidural hematoma	Hemorrhagic stroke	Ischemic stroke	Ischemic stroke
Time after stroke at T1 (days)	34	21	64	7	21
Time after stroke at T2 (days)	120	118	166	110	135
Language therapy between T1 and T2					
Language of therapy	L1	L2	L2	—	L1
Number & duration of therapy sessions	25 sessions (45 min./session)	1 session (30 min.)	41 sessions (45 min./session)	—	10 sessions (45 min./session)
Type of therapy	CAT CIAT	CAT	CAT	—	CAT

CAT: computer assisted therapy for anomia to improve lexical access.
CIAT: constraint induced aphasia therapy.

not record reaction times, and the analyses were focused on response accuracy.

2.5. Behavioral Data Analyses. Because of the limited number of patients, differences in lesion size and site, and variability of symptoms, we used primarily a multiple single-case approach for our analyses between T1 and T2. For comparison of the patients' scores in the two sessions, a McNemar Chi-squared test is used for each case. GAE, picture naming, and "combined production score" (i.e., the average response accuracy percentage in picture naming and production score of the GAE) are assessed as language performances. Specifically, we focused on the "combined production score" which could better represent language production performance.

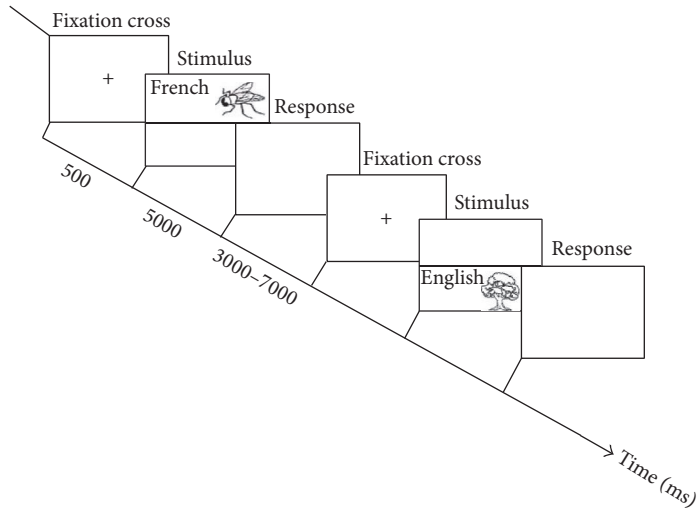
2.6. Functional Magnetic Resonance Imaging Task

2.6.1. Picture Naming in L1 and L2

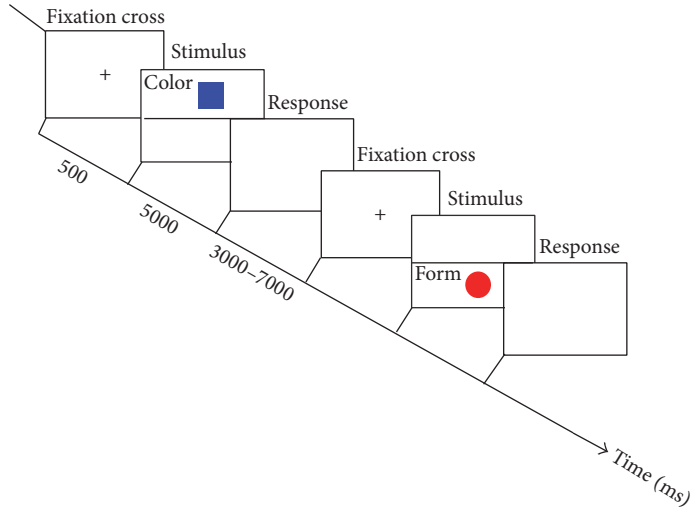
Stimuli. Five lists (one list per language) of 40 noncognate words (black and white line drawing pictures) were selected from Snodgrass and Vanderwart [28]. The words were matched for word frequency across all the lists.

Procedure. Each fMRI session started with a picture naming in L1; in this part, the subjects were instructed to name the pictures that appeared on the screen in their L1. After a fixation cross of 500 ms, the images were presented on the screen for 5,000 ms and were followed by a blank screen of variable duration of 4,100–6,100 ms (to provide a random duration of the interstimulus interval). Therefore, the subjects had at most between 9,100 and 11,100 ms to respond. However, only first-attempt correct responses within five seconds of the presentation of the image were scored as correct. Each task lasted around 7-8 minutes (a total of around 15 minutes for picture naming in both L1 and L2). After about 30 seconds of rest, the subjects started their second task in which they had to name the pictures in their second language. The first six trials of the task were cued with the language in which the image should be named (L1 or L2) written on the left of the image. For the fMRI tasks, a short training was performed before the subjects entered the scanner. In this training, which contained 10 trials, the subjects were presented with black and white line drawing pictures selected from Snodgrass list and were asked to name the pictures in their L1 or L2 to become familiar with the task.

2.7. FMRI Acquisition. Data of the aphasic patients were acquired using three different 3T scanners on two different sites; Site 1: Fribourg Cantonal Hospital (HFr) and Site 2: University Hospital of Geneva (HUG). The scanners which were used were (1) Discovery MR750; GE Healthcare, Waukesha, Wisconsin, with a 32-channel receive head coil (Site 1), (2) Magneton Trio, Siemens Medical Solutions, Erlangen, Germany, with a 12-channel receive head coil (Site 2), and (3) Magneton Prisma, Siemens Medical Solutions, Erlangen, Germany, with a 20-channel receive head (Site 2). Subjects were in a supine position with their heads stabilized by foam to reduce head movements. They wore headphones (MKII system from MR confon, Magdeburg, Germany) coupled with an MRI-compatible microphone (FOMRI-III system from Optoacoustics, Israel) to record oral response during the experiment. In the first scanner, visual stimuli were presented on an LCD screen (NordicNeuroLab, Bergen, Norway). In the other two scanners, the stimuli were displayed on a screen by a video projector (Hitachi CP-X1200 with long focal distance



(a) Linguistic switching task



(b) Nonlinguistic switching task

Figure 1: (a) Linguistic switching task. This task includes 40 trials. Only the six first trials were cued; the language in which the image should be named (L1 or L2) is written in the left of the image. (b) Nonlinguistic switching task. This task includes 40 trials. Only the six first trials were cued; the category in which the image should be named (color or form) is written in the left of the image.

Hitachi LL-504, Hitachi Ltd., Tokyo, Japan) through a mirror system. In all three cases, the stimuli resolution was 1024 × 768 with a refresh rate of 60 Hz. The E-Prime 2 software (Psychology Software Tools, Pittsburgh, USA) was used to show stimuli and record behavioral data.

2.8. MRI Acquisition. MRI acquisition parameters were optimized for each site. From the first site in Fribourg (Scanner 1), T1-weighted images were acquired with a FSPGR BRAVO sequence, voxel size: 0.86 × 0.86 × 1 mm, field of view (FOV) = 220 mm, number of coronal slices: 276, TR/TE = 7300/2.8 ms, flip angle = 9, phase acceleration factor (PAF) = 1.5, and intensity correction (SCIC). Functional T2*weighted echo planar images (EPI) with blood oxygenation level-dependent (BOLD) contrast were acquired with voxel size: 2.3 × 2.3 × 3 mm, FOV = 220 mm, 37 ascending axial slices, interslice spacing = 0.2 mm, TR/TE = 2000/30 ms, flip angle = 85, and PIAF: 2. In addition, a B0 field inhomogeneity mapping sequence was acquired to correct for geometrical distortion that occurred along the phase-encoding direction (using a Gradient Echo protocol) with the same scan coverage as the functional scan: number of slices = 37, FOV = 220 mm, $TR/TE_1/TE_2$ = 50/4.9/7.3 ms [29]. From the second site (scanners 2 and 3), T1 weighted images were acquired with an MP Rage sequence, voxel size: 0.86 × 0.86 × 1.1 mm, FOV = 220 mm, number of coronal slices: 208, TR/TE = 2500/2.94 ms for scanner 2 and 2500/2.97 for scanner 3, flip angle = 9, and PAF: 2. Functional T2*weighted EPI with BOLD contrast were acquired with voxel size: 2 × 2 × 3.5 mm, FOV = 240 mm, 29 ascending axial slices, interslice spacing = 0.35 mm, TR/TE = 2000/30 ms, flip angle = 85, and PIAF: 2. A B0 field inhomogeneity mapping sequence was also acquired

with the same scan coverage as the functional MRI sequences: number of slices = 29, FOV = 240 mm, and TR/TE_1/TE_2 = 400/5.19/7.65 ms. On average, a total of 248 volumes were acquired during the picture naming in L1 and picture naming in L2. Each fMRI acquisition session started with six seconds of dummy scans to ensure a steady-state magnetization of the tissues.

2.9. Functional MRI Preprocessing. We used the SPM8 software (Welcome Trust Centre for Neuroimaging, Institute of Neurology, University College London), running on MATLAB 2012b (MathWorks, Inc., MA, USA), to analyze functional MRI data (fMRI). FMRI images were preprocessed following the standard procedure proposed by Friston [30]. Preprocessing steps included a spatial realignment, unwrapping (using the FieldMap 2.1 toolbox [31]), slice timing (with middle temporal slice as reference), coregistration on T1 image, normalization on the Montreal Neurological Institute (MNI) space with $3 \times 3 \times 3\,mm^3$ voxel size, and smoothing with a Gaussian kernel of 8 mm full width at half maximum (FWHM). In order to exclude the brain lesion from the analyses, a mask file of the brain lesion of each subject was manually drawn on axial slices of the standard Montreal Neurological Institute's (MNI) brain template using the MRIcron software (https://www.nitrc.org/projects/mricron) and used during the preprocessing of data on SPM. The preprocessed volumes were submitted to fixed effects analyses at the subject level by applying the general linear model to each voxel [32]. Each stimulus onset was modelled as an event encoded in condition-specific "stick-functions" and convolved with a canonical hemodynamic response function. A separate model was built for picture naming in L1 and picture naming in L2. In addition, movement parameters were included as regressors of no interest. Time series from all voxels were submitted to a high-pass filter with a 1/250 Hz threshold, and an autoregressive function (AR (1)) was applied.

2.10. Dynamic Causal Modelling (DCM). DCM is a widely used method for investigating context-dependent causal interactions between brain regions and it describes the architecture of the network (i.e., the ROIs and the connections). In DCM, the brain is treated as a dynamic input-state-output system. A given experiment is considered as a designed perturbation of neuronal dynamics that is propagated throughout a network of interconnected nodes. Three sets of parameters are estimated in DCM: the direct influence of stimuli on regional activity (driving input), the intrinsic connections between regions, and the changes in the intrinsic connectivity between regions induced by adding or removing a modulatory influence (modulatory effect).

We based our analyses on this model, which has been defined by Abutalebi et al. [9]. Because of the variability of lesion site in our patients, in order to be able to compare changes in connectivity with the same model across all subjects/conditions, we have defined this model for all subjects and conditions. We have not selected a fully connected model (i.e., with all possible connections within the network) to avoid having a very complex model and overfitting of the data. In addition the structure of this model was designed based on *a priori* hypotheses already tested by previous works. Therefore, the selection of the ROIs and the intrinsic connections was based exactly on the work by this group. Accordingly, the following five ROIs were selected for the network: BTLA, LIFGTri (areas related to language processing), head of left caudate, ACC (areas involved in cognitive control function), and LIFGOrb as a part of both language and cognitive control systems. As per Abutalebi et al. [9], we also included only left-hemispheric regions as our main focus was the effect of control areas on the intrahemispheric reorganization of language areas (see Figure 2 for the model structure). The same model was used for all subjects (patients and controls) and for both testing sessions. Using TD-ICBM-MNI template atlas, we prepared the mask for the ROIs. Individual subject time series data from each subject's individual activation map threshold at $p < 0.05$ uncorrected were extracted from each 7 mm spherical ROI centered at the subject's local maximum inside the ROIs. For the patients, we have verified visually whether the ROIs were affected by the lesion. When the patients or control subjects did not fulfill our criteria (showing activation with threshold < 0.05 uncorrected in all 5 ROIs and/or absence of lesion in the ROIs) they were removed from the analyses. This way, we have removed one patient (as one of the ROIs was inside the lesion) and one control participant (as he did not show activation in one of the ROIs in the desired threshold) [33].

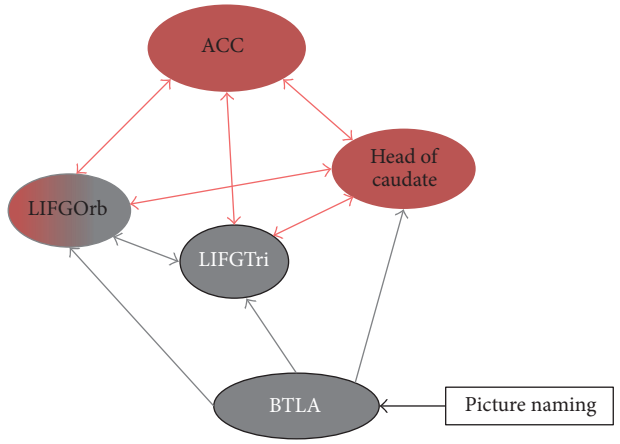


Figure 2: The structure of language-control network. This network was proposed by Abutalebi et al. (2009). Connections between brain areas involved in picture naming (in black) and control (in red). The modulatory effect of the experimental task (picture naming in L1 and L2) was added to the model on BTLA. ACC: anterior cingulate cortex, LIFGTri: left inferior frontal gyrus-pars triangularis, LIFGOrb: left inferior frontal gyrus-pars orbitalis, BTLA: basal temporal language area.

However, in order to take into account the modulatory effect of the language task on the network (which was not included previously in the model by Abutalebi et al.), we inserted the modulatory effect of the task over BTLA (as the sensory input of the network) [33] and LIFGTri as two different models. We compared the three models (two models with modulatory effect of picture naming on LIFGTri or BTLA and

a model with no modulatory effect) using a Bayesian model selection with a fixed effect strategy which assumes that the optimal structure is assumed to be identical across subjects, and the model with modulatory effect over the BTLA best explained fMRI activation through the different patients and controls (separately) during the naming in L1 and L2 according to this comparison. We therefore employed this model in all our subjects. The DCM model was deterministic, bilinear with one state per region. The analyses of DCM were performed using SPM12 and using the data preprocessed in SPM8.

2.11. FMRI Data Analyses. Considering the limited number of patients and the effect of the different scanners used in this study, we primarily performed the analyses at a single-case level. Patterns of brain activation in the four different conditions (picture naming in L1 and L2 at T1: subacute phase and T2: chronic phase) for each patient are shown in the figure representing the data related to the patient (Figures 3(b)–7(b)).

Regarding the DCM analyses, in order to investigate how connection strength changes over time for single intrinsic connections within the network, the differences in the strength of connection between L1 and L2 (L2 − L1) at each session are presented in a graph for each patient. These graphs represent the pattern of difference in connection strength in language-control network while performing picture naming in L1 and L2 across time (these graphs are shown in Figures 3(d)–7(d)).

At the group level, correlation analyses were performed with aphasic patients to investigate possible correlations between the changes in connection strength (especially for the connections between control and language areas) and the changes in combined production scores for each language separately.

3. Results

3.1. General Approach. (A) We first conducted McNemar Chi-squared tests comparing language performance (GAE and picture naming scores) in L1 and L2 and control function (linguistic and nonlinguistic switch task scores) across time; (B) using DCM on fMRI, we compared the strength of connectivity within the language-control network between L1 and L2 across time at single subject level; (C) at the group level, we then performed a correlation analysis between the recovery of language production scores and the changes in the strength of connection between language and control areas. A description of the main results of the analyses is provided here, and a complete reporting of the scores and results is provided in Table 3 and Supplementary Data 1.

3.2. Single-Case Analyses

3.2.1. Patient 1

(A) Behavioral Scores. At T2 (chronic phase), the combined production score showed improvement in L1 (χ^2: 12.7, p: 0.005) but no changes in L2. In addition, no improvement was found in linguistic and nonlinguistic switching tasks accuracy (Figure 3(c)).

(B) Changes in Connectivity in the Language-Control Network. For each single intrinsic connection within the network, the differences in connection strengths between L1 and L2 (L2 − L1) at each session are shown in Figure 3(d). At T1 (subacute phase), seven connection strengths were greater for L1 and eight connections had greater coupling values for L2. At T2 (chronic phase), however, the majority of connections (10 out of 15) had stronger coupling values for L1 compared to L2 (i.e., the following five connections had higher strength values in L2 at T2 (chronic phase): connections from LC to ACC, LIFGTri, and LIFGOrb, from LIFGTri to LC, and from BTLA to LIFGTri). The rest of the 15 connections had higher strength values in L1 at T2 (chronic phase). These changes in strength values indicated a globally higher connectedness inside the language-control network for L1.

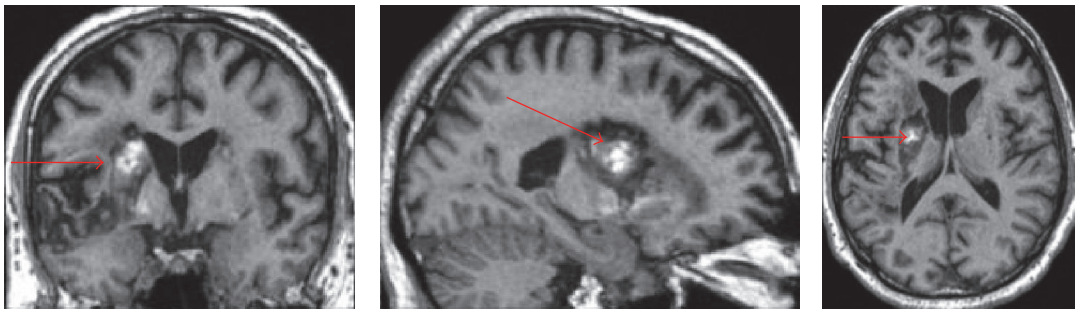
3.2.2. Patient 2

(A) Behavioral Scores. At T2 (chronic phase), the combined production score improved in both L1 (χ^2: 9.09, p: 0.002) and L2 (χ^2: 5.14, p: 0.023). However, no significant improvement was found in linguistic (χ^2: 3.2, p: 0.07) and nonlinguistic switching tasks (χ^2: 0.5, p: 0.47) (Figure 4(c)) (see Table 3 for details of the patient's performance).

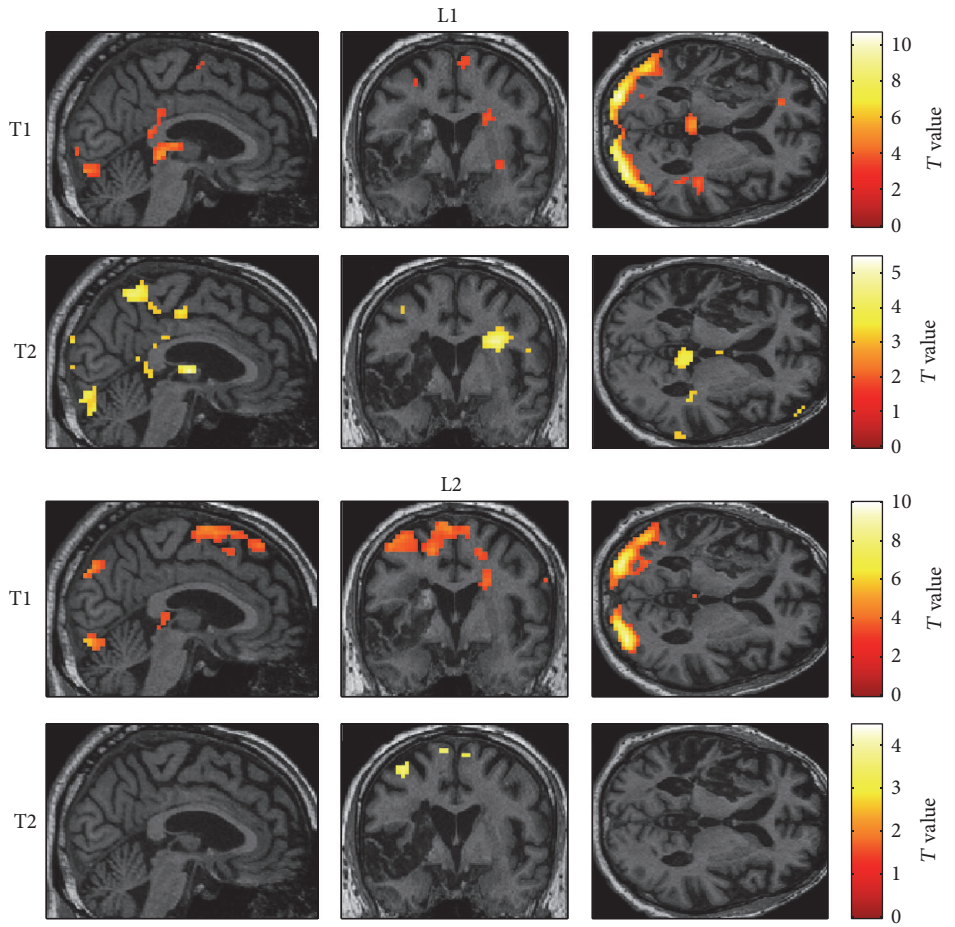
(B) Changes in Connectivity in the Language-Control Network. Regarding the DCM analyses for each single intrinsic connection within the network, the same approach was used as for patient 1 (Figure 4(d)). Importantly, a notable change was seen in the language-control network in the pattern of differences in connection strengths between L1 and L2 from T1 (subacute phase) and T2 (chronic phase): at T1, five connections had greater strength values for L1 and 10 connections had greater strength for L2. At T2 (chronic phase), seven connections had greater strength values for L1 and eight connections had greater strength values for L2. Across time, eight connections showed different patterns of difference between L1 and L2. In particular, the connections from ACC to LIFGTri, from LIFGOrb to LIFGTri, and from ACC to LC had higher strength values for L2 compared to L1 at T2 (chronic phase), while the connections from LC to ACC, LIFGTri, and LIFGOrb, from ACC to LIFGOrb, and from LIFGTri to AB47 showed greater strength values for L1 compared to L2 at T2 (chronic phase). Although reorganization happened in the connection strengths for L1 and L2 at T2 (chronic phase), there was a similar degree of connectedness within the language-control network for L1 and L2.

3.2.3. Patient 3

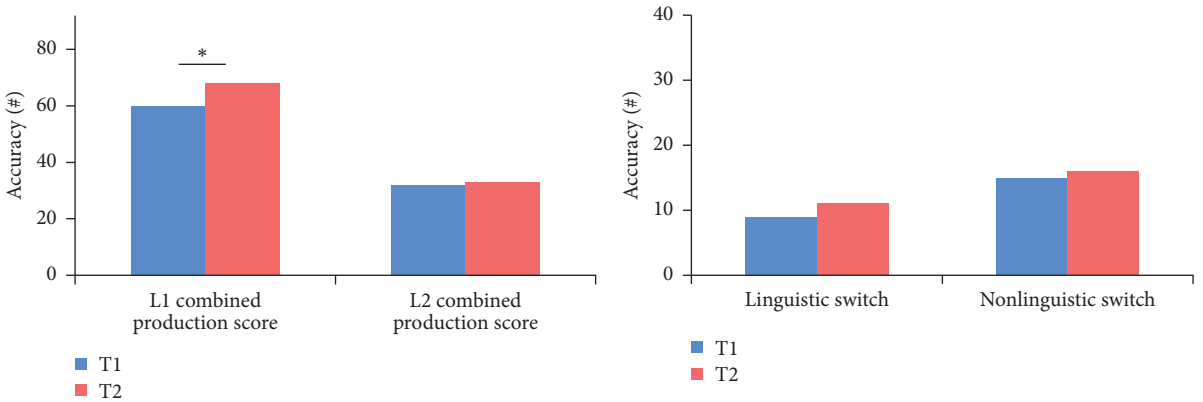
(A) Behavioral Scores. At T2 (chronic phase), the combined production score showed improvement in both L1 (χ^2: 25.07, $p < 0.0001$) and L2 (χ^2: 4.16, p: 0.041) at T2 (chronic phase). The patient also showed a significant improvement in both



(a) Lesion location

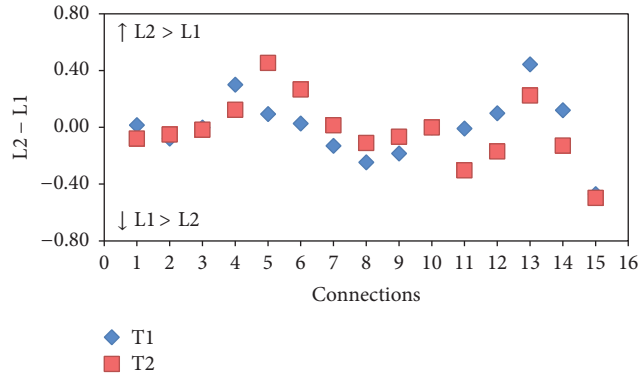


(b) Functional MRI naming task



(c) Behavioral results

Figure 3: Continued.



(d) DCM connections

Figure 3: Patient 1. (a) Ischemic stroke in left frontotemporal area in the T1-weighted MRI image at T1. (b) Pattern of brain activation in different conditions while picture naming, with an uncorrected $p < 0.001$ for the main effects. (c) Behavioral results of the combined production scores in both languages, linguistic and nonlinguistic switching scores across sessions. ∗ represents p value < 0.05. (d) Differences between L1 strength values and L2 strength values for each single connection across sessions. (1) ACC to LIFGTri. (2) ACC to LIFGOrb. (3) ACC to LC. (4) LC to ACC. (5) LC to LIFGTri. (6) LC to LIFGOrb. (7) LIFGTri to LC. (8) LIFGTri to ACC. (9) LIFGOrb to LC. (10) LIFGOrb to ACC. (11) LIFGTri to LIFGOrb. (12) LIFGOrb to LIFGTri. (13) BTLA to LIFGTri. (14) BTLA to LIFGOrb. (15) BTLA to LC.

linguistic and nonlinguistic switching tasks across time (χ^2: 17.05, $p < 0.0001$ and χ^2: 21.04, $p < 0.0001$, resp.) (Figure 5(c)) (see Table 3 and Supplementary Data 1 for details of the patient's performance).

(B) Changes in Connectivity in the Language-Control Network. The differences between L1 and L2 (L2 – L1) in the strength of single intrinsic connections within the network are shown in Figure 5(d). The raw differences in the strength of connections within the language-control network in this patient also indicated differing patterns in the connection strengths between L1 and L2 from T1 (subacute phase) and T2 (chronic phase) in half of the connections; notably, the connections from ACC to LIFGTri and forward and backward connections between LIFGTri and LIFGOrb showed greater connection strengths for L1 compared to L2 at T2 (chronic phase). However, forward and backward connections between LC and LIFGOrb and the connection from BTLA to LIFGTri and LIFGOrb had higher connection strength values for L2 compared to L1 at T2 (chronic phase). Overall, at T1 (subacute phase), seven connections had higher strength values in L1 while at T2 (chronic phase), nine connections had higher strength values in L1. Altogether, there was a similar degree of connectedness within the language-control network for L1 and L2 at T2 (chronic phase).

3.2.4. Patient 4

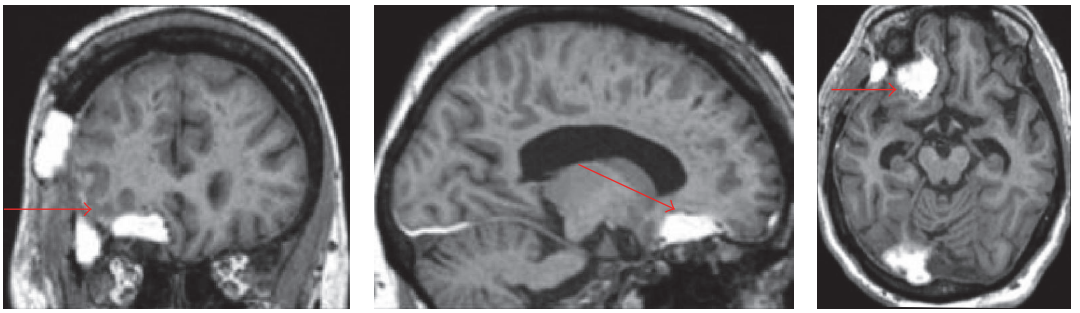
(A) Behavioral Scores. At T2 (chronic phase), the combined production score improved in L2 (χ^2: 8.16, p: 0.004) and no improvement was seen in L1 (already spared at T1 (subacute phase)). His performance in the linguistic switching task improved significantly (χ^2: 4.16, p: 0.041) and his nonlinguistic switching performance was spared at T1 (subacute phase) (Figure 6(c)).

(B) Changes in Connectivity in the Language-Control Network. At the single intrinsic connection level, the differences between L1 and L2 (L2 – L1) in strength of single intrinsic connections within the network for each session are shown in Figure 6(d). At T1 (subacute phase), around half of connections had higher strength values for L1 (eight out of 15), while at T2 (chronic phase), only three connections had greater values for L1 (i.e., connection from LIFGTri to LC, LIFGTri to LIFGOrb, and BTLA to LIFGOrb) and the rest of the connections showed higher coupling values for L2. These changes indicated a globally higher connectedness inside the language-control network for L2 at T2 (chronic phase).

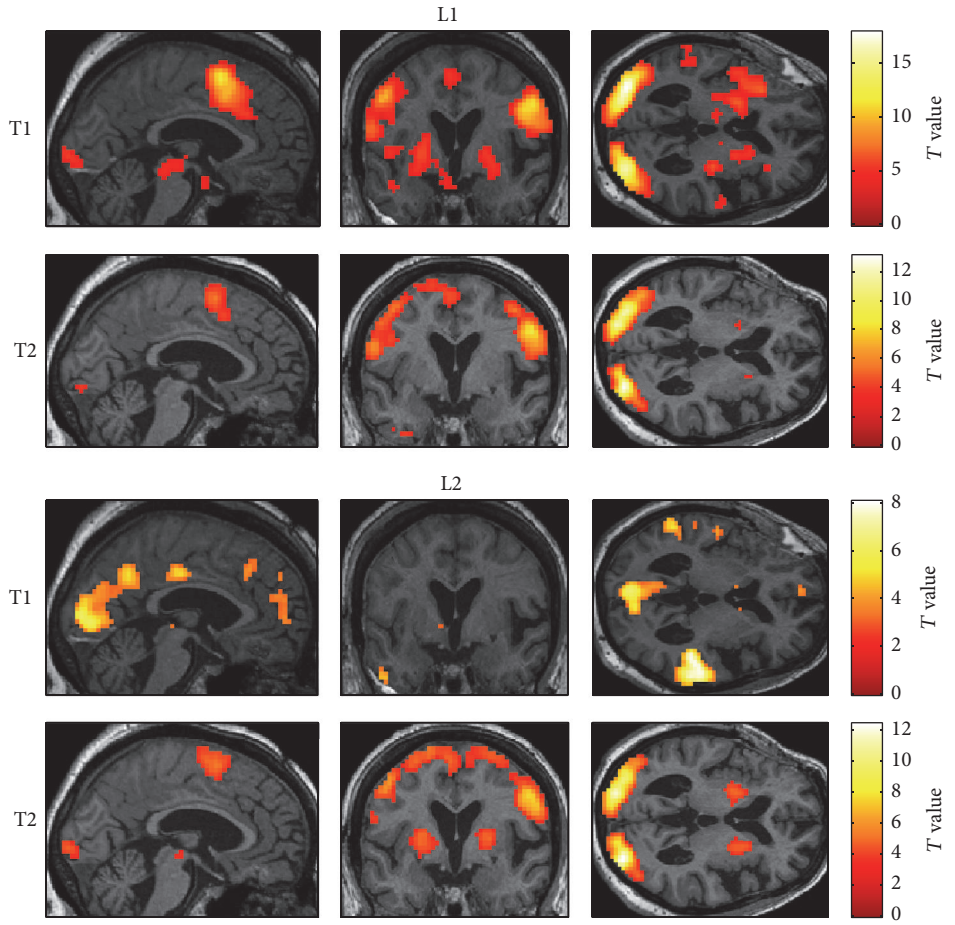
3.2.5. Patient 5

(A) Behavioral Scores. The combined production score improved in both L1 (χ^2: 9.09, p: 0.002) and L2 (χ^2: 12.07, p: 0.0005) at T2 (chronic phase), although the patient still made several language switching errors. However, no improvement was seen in the linguistic and nonlinguistic switching task performances (Figure 7(c); more details can be found in Table 3 and Supplementary Data 1).

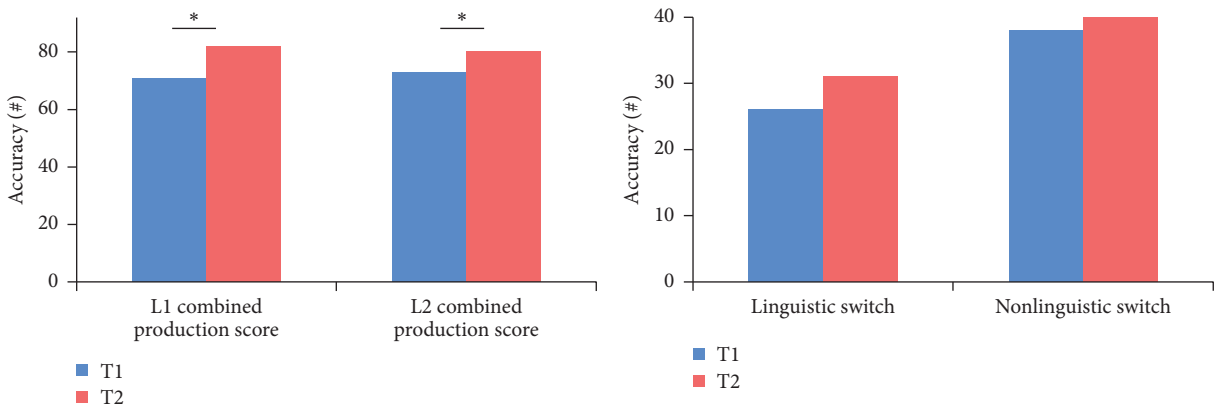
(B) Changes in Connectivity in the Language-Control Network. At the single intrinsic connection level, the differences between L1 and L2 (L2 – L1) in the strength of single intrinsic connections within the network for each session are shown in Figure 7(d). Importantly, several connections showed inverse patterns between T1 (subacute phase) and T2 (chronic phase); that is, four connections (from ACC to LIFGTri, ACC to LIFGOrb, LIFGTri to ACC, and LIFGTri to LIFGOrb) had higher strength values for L1 at T2 (chronic phase), and four connections (from LC to LIFGTri, LIFGOrb to ACC, LIFGOrb to LIFGTri, and BTLA to LIFGTri) had greater strength values for L2 at T2 (chronic phase). As with the changes



(a) Lesion location

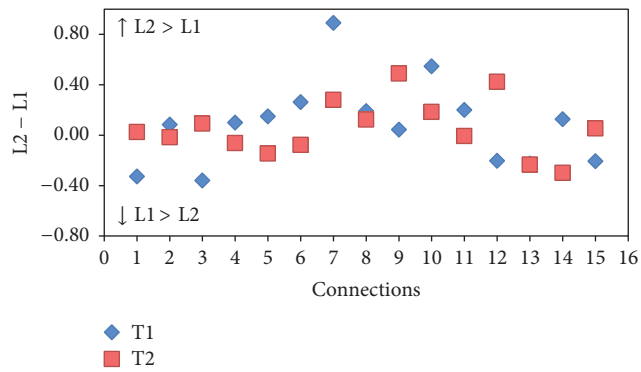


(b) Functional MRI naming task



(c) Behavioral results

Figure 4: Continued.



(d) DCM connections

Figure 4: Patient 2. (a) The T1-weighted MRI image at T1 shows an epidural hematoma with pressure over the operation site on the left frontobasal area. (b) Pattern of brain activation in different conditions while picture naming, with an uncorrected $p < 0.001$ for the main effects. (c) Behavioral results of the combined production scores in both languages, linguistic and nonlinguistic switching scores across sessions. $*$ represents p value < 0.05. (d) Differences between L1 strength values and L2 strength values for each single connection across sessions. (1) ACC to LIFGTri. (2) ACC to LIFGOrb. (3) ACC to LC. (4) LC to ACC. (5) LC to LIFGTri. (6) LC to LIFGOrb. (7) LIFGTri to LC. (8) LIFGTri to ACC. (9) LIFGOrb to LC. (10) LIFGOrb to ACC. (11) LIFGTri to LIFGOrb. (12) LIFGOrb to LIFGTri. (13) BTLA to LIFGTri. (14) BTLA to LIFGOrb. (15) BTLA to LC.

seen in patients 2 and 3, there was a similar connectedness within the language-control network in L1 and L2 at T2 (chronic phase).

3.3. Group Analyses of fMRI and DCM Analyses

3.3.1. FMRI Results. For the aphasic patients, the patterns of activation at each session of picture naming in L1 and L2 were presented for each patient separately; a threshold of uncorrected $p < 0.001$ was selected to visualize the main effects (Figures 3(b)–7(b)). As our main aim of the fMRI study was to perform DCM analysis based on a previously published model, we did not statistically compare the activations in the different conditions.

3.3.2. DCM Results

(C) Correlation Analysis between Language Production Recovery and Changes in the Strength of Connection. At the group level, in the aphasic patients, the changes in the strength of intrinsic connections between language and control areas (specifically between ACC, LC, and LIFGOrb from control subnetwork to LIFGTri in language subnetwork) were implemented to correlate with the changes in combined production scores.

In the aphasic patients, we found a significant correlation between changes in the combined production scores in L1 and changes in the strength of connection from ACC to LIFGTri (while performing picture naming in L1) (Spearman's rho: 0.921, p: 0.026). Moreover, changes in the combined productions score in L2 were negatively correlated to the changes in the strength of connections from LIFGTri to LIFGOrb (Spearman's rho: −0.900, p: 0.037).

3.4. Supplementary Analyses of DCM. To better compare the changes in the number of connections with higher strength values between the improved versus unimproved language across time, we concatenated the data of patients 1 and 4 (who improved language production in only one language). This combined analysis showed a higher number of connections in the improved language at T2 (chronic phase) (χ^2: 4.44, p 0.035).

4. Discussion

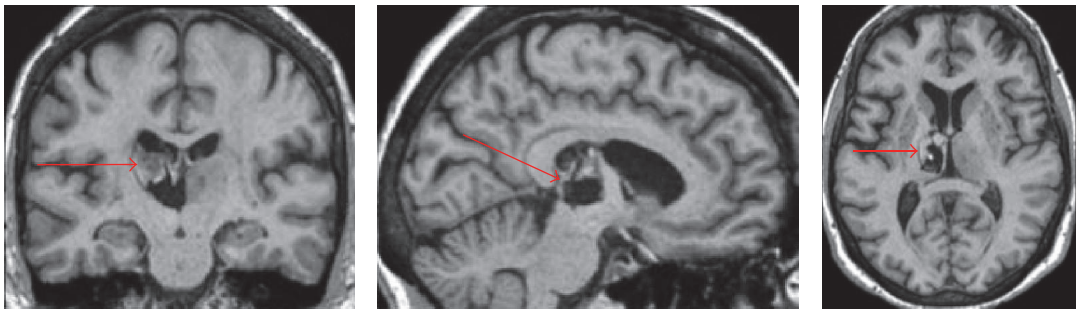
Using a longitudinal design, we examined language production recovery in five late bilingual patients suffering from poststroke aphasia at subacute and chronic phases following a stroke. From three weeks to four months following a stroke, (A) we monitored modifications in language and control performance to identify whether language recovery was linked with the recovery of control functions. Moreover, (B) using a DCM approach, we examined how the interconnections between language and control areas changed with the recovery of language production, and (C) we then investigated the possible correlation between changes in language production performances and changes in the strength of each single connection within language-control network across time.

Considering the changes in the combined production scores, three of our five patients recovered in both L1 and L2 (patients 2, 3, and 5), one patient recovered in L1 (patient 1), and one (patient 4) in L2 only (the latter patient already had a high accuracy score in L1 at the subacute phase). Two patients (patient 3 with recovery in both languages and patient 4 with recovery in L2) showed improvement in language-control functions (Table 4). No decrease in control functions was observed among the patients.

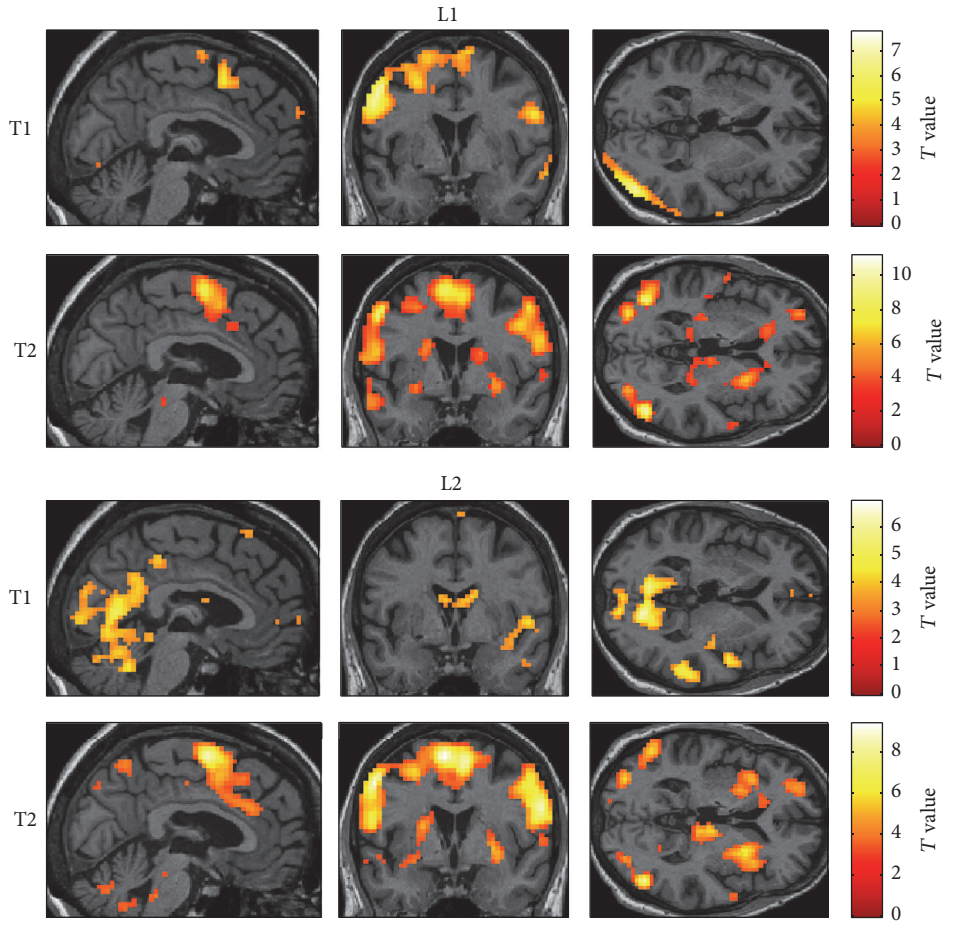
Descriptive analyses of the DCM suggested a relationship between the pattern of recovery of language production and changes in the strength of connections across time. In patient 1, who recovered only L1 production score across time, the majority of connections within language-control network (10

Table 3: General aphasia evaluation, picture naming, and control functions scores at T1 and T2.

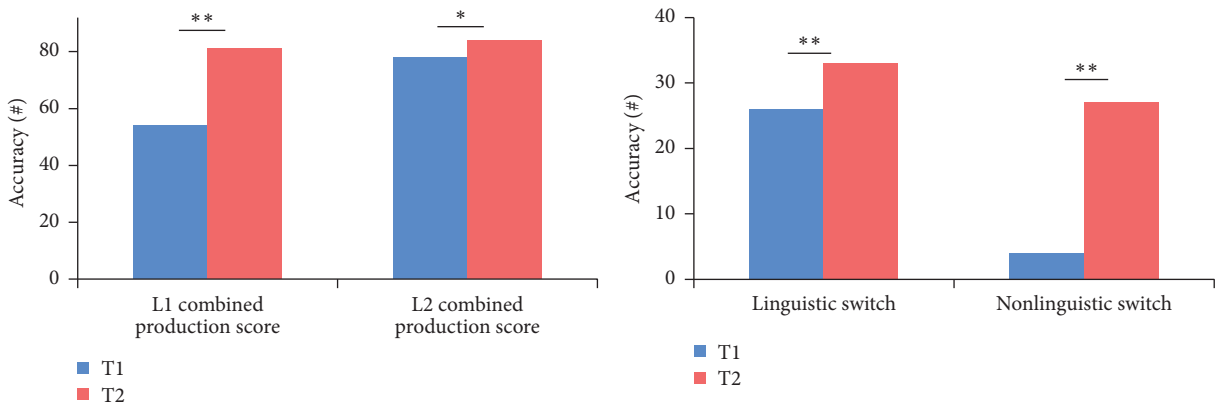
		General aphasia evaluation (GAE)													Language control	
Task	Session	Object naming (/20)	Series (/6)	Verbal fluency (/3)	Repetition (/13)	Yes/no questions (/20)	Pointing (/5)	Following commands (/8)	Reading commands (/11)	Description (/10)	Production score (GAE) (/52)	Total (/96)	Picture naming (/40)	Combined production score (/92)	Linguistic switch (/40) (number of switching errors)	Nonlinguistic switch (/40) (number of switching errors)
Subject 1	T1 L1	10	6	0	13	13	4	4	2	10	39	62	20	59	9 (7)	15 (13)
	T1 L2	4	4	0	13	16	4	1	3	10	31	55	1	32		
	T2 L1	13	6	0	13	17	5	6	8	8	40	76	28	68	11 (5)	16 (24)
	T2 L2	4	4	0	13	16	4	1	3	10	31	55	2	33		
Subject 2	T1 L1	16	6	0	13	16	5	4	9	10	45	79	26	71	26 (5)	38 (1)
	T1 L2	19	6	1	9	20	5	5	7	10	45	82	28	73		
	T2 L1	19	6	1	13	18	5	5	9	10	49	86	33	82	31 (4)	40
	T2 L2	20	6	0	13	16	5	5	9	10	49	84	31	80		
Subject 3	T1 L1	18	6	0	13	18	5	8	7	10	47	85	7/14	54/66	14 (11)	4 (15)
	T1 L2	18	6	0	13	20	5	7	4	10	47	83	31	78		
	T2 L1	20	6	1	13	20	5	8	11	10	50	94	31	81	33 (2)	27 (8)
	T2 L2	20	6	0	13	20	5	8	11	10	49	93	35	84		
Subject 4	T1 L1	18	6	2	13	16	5	8	11	10	49	89	39	88	30 (0)	38 (2)
	T1 L2	11	6	0	13	20	4	8	10	6	36	78	27	63		
	T2 L1	20	6	3	13	18	5	8	11	10	59	94	38	90	36 (1)	40 (0)
	T2 L2	12	6	3	13	18	4	8	11	8	42	83	31	73		
Subject 5	T1 L1	18	6	0	13	18	5	2	9	10	47	81	19	66	19 (17)	25 (3)
	T1 L2	12	4	0	13	20	5	4	8	10	39	76	19	58		
	T2 L1	18	6	0	13	18	5	4	11	10	47	85	30	77	19 (13)	29 (4)
	T2 L2	16	6	0	13	16	5	4	11	10	45	81	27	72		



(a) Lesion location

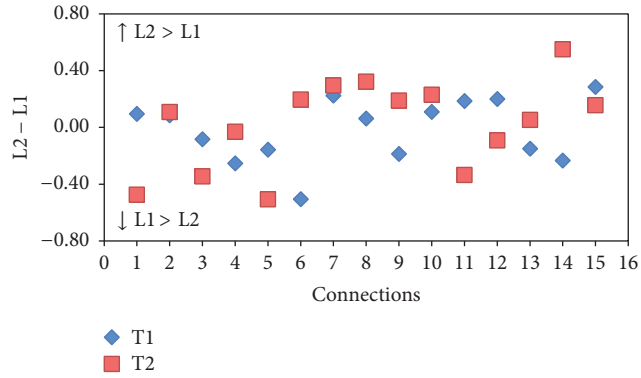


(b) Functional MRI naming task



(c) Behavioral results

Figure 5: Continued.



(d) DCM connections

Figure 5: Patient 3. (a) The T1-weighted MRI image at T1 shows a hemorrhagic stroke in the left basal ganglia. (b) Pattern of brain activation in different conditions while picture naming, with an uncorrected $p < 0.001$ for the main effects. (c) Behavioral results of the combined production scores in both languages, linguistic and nonlinguistic switching scores across sessions. $*$ represents p value < 0.05 and $**$ represents p value < 0.001. (d) Differences between L1 strength values and L2 strength values for each single connection across sessions. (1) ACC to LIFGTri. (2) ACC to LIFGOrb. (3) ACC to LC. (4) LC to ACC. (5) LC to LIFGTri. (6) LC to LIFGOrb. (7) LIFGTri to LC. (8) LIFGTri to ACC. (9) LIFGOrb to LC. (10) LIFGOrb to ACC. (11) LIFGTri to LIFGOrb. (12) LIFGOrb to LIFGTri. (13) BTLA to LIFGTri. (14) BTLA to LIFGOrb. (15) BTLA to LC.

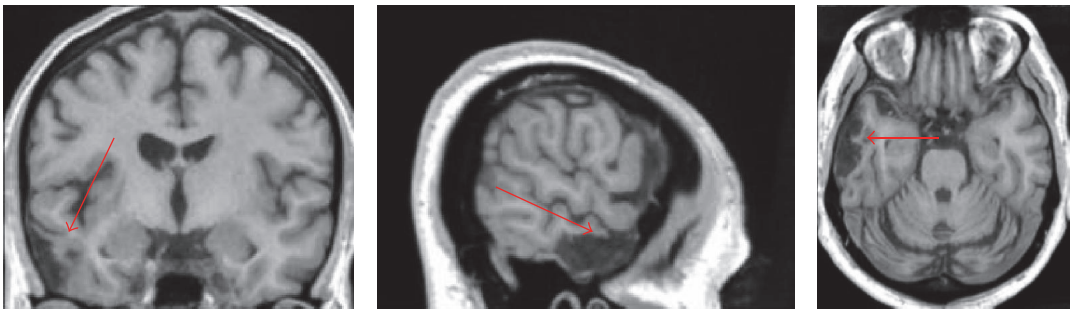
Table 4: Summary of the recovery patterns.

Subject	L1-combined production	L2-combined production	Linguistic switch	Nonlinguistic
Patient 1	↑	→	→	→
Patient 2	↑	↑	→	→
Patient 3	↑	↑	↑	↑
Patient 4	→	↑	↑	→
Patient 5	↑	↑	→	→

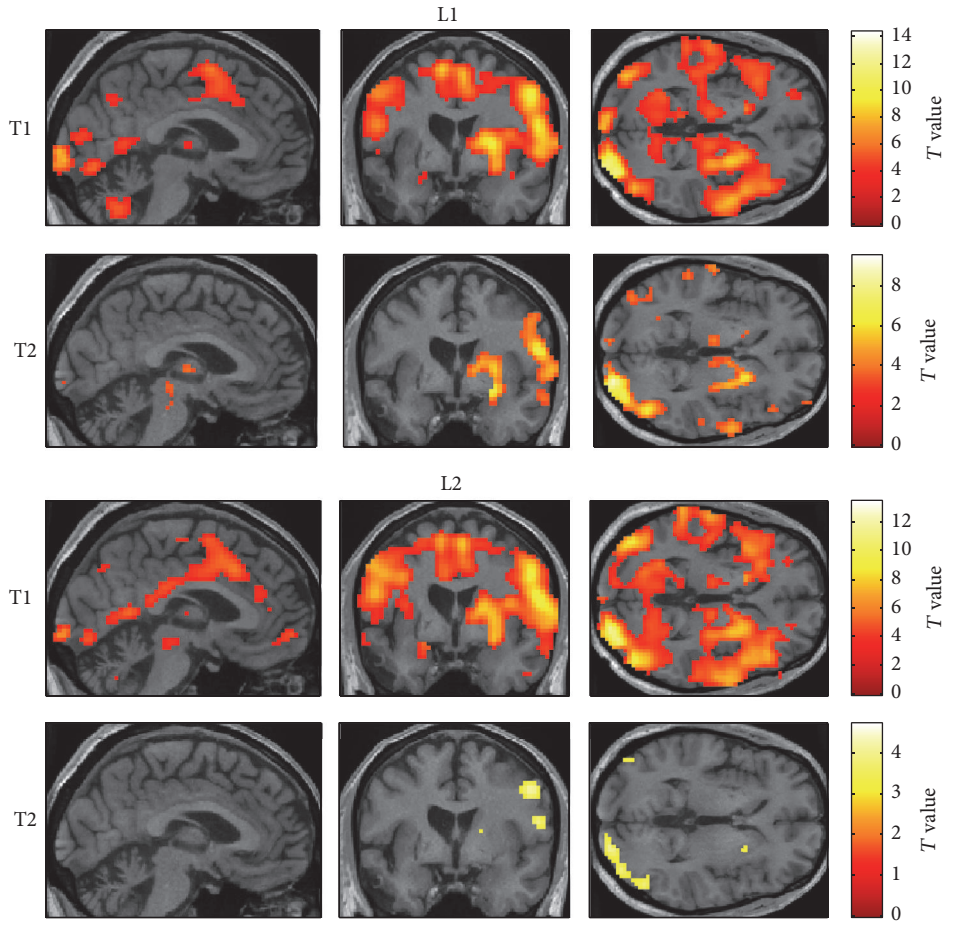
out of 15 connections) had higher connection strength values at the chronic phase, indicating a higher connectedness within the language-control network while picture naming in L1. The similar pattern of changes in the connectedness within language-control network took place in patient 4 who recovered only L2 (i.e., at the chronic phase he showed higher connectedness within language-control network while picture naming in L2). In these two patients with recovery of only one language, combined analyses revealed that improvement in production score in one language was associated with an increase in the number of connections with higher strength values at T2 (chronic phase) while performing the task in that specific language. In addition, showing a similar pattern of changes in the language-control network connectedness, patients 2 and 5 at T1 (subacute phase) in the majority of connections had higher coupling values for picture naming in L2, while at T2, the coupling values of 7 connections were higher in L1 and 8 connections had higher coupling values in L2 task. Also, patient 3 showed higher coupling values for the majority of connections for L1 picture naming at T1 (subacute phase), while at T2, the coupling values of 7 connections were higher in L1 and 8 connections had higher coupling values in L2 task. Taken together, in patients 2, 3, and 5 who recovered both L1 and L2, a redistribution of the connection strength occurred across time; the strength of the connections between language and control areas was similarly distributed at T2 (chronic phase) over the network during picture naming in L1 and L2. In the control group with main L2 exposure and usage in daily life, a higher connectedness was seen within the network for L1 compared to L2 (see Supplementary Data 2 and 3). We will discuss each of these results in turn.

Although the role of control functions in the recovery of bilingual aphasia has been suggested in several studies [8, 9], in our patients, at the behavioral level, the improvement in language-control functions alone could not explain their patterns of language recovery. The observed pattern of language and control recovery does not directly support Paradis' statement that when language-control function is intact, one can expect a parallel recovery of languages, and in the presence of language-control problems one may expect the weaker language in the premorbid stage to be impaired [34]. However, Green and Abutalebi [35] suggest that, along with premorbid proficiency, languages that were mostly used following stroke may become more proficient and easily manageable, especially in the case of reduced resources for controlling the use of two languages.

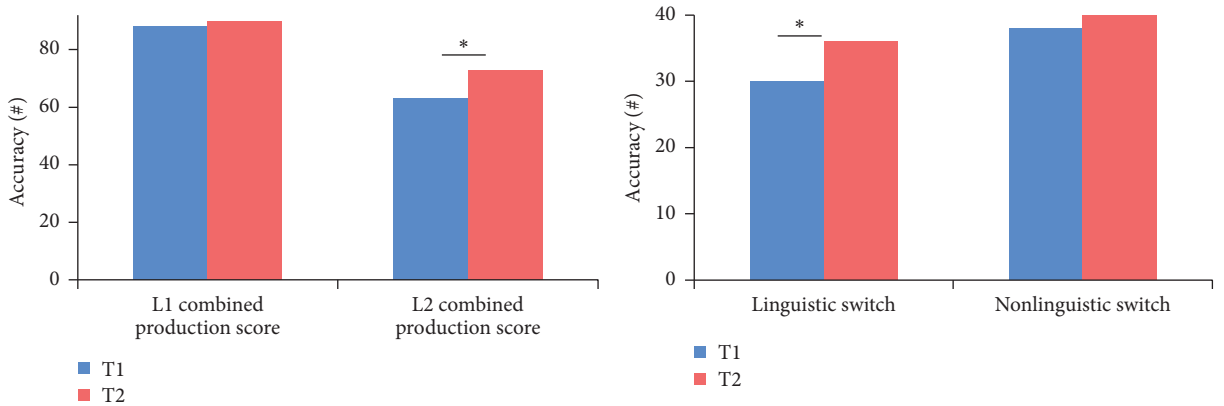
Our findings on the changes in the differences in connectedness between L1 and L2 within the language-control network are in line with the results of Abutalebi et al. [9],



(a) Lesion location

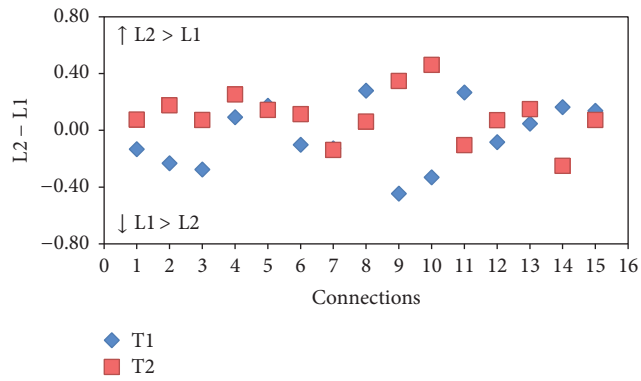


(b) Functional MRI naming task



(c) Behavioral results

Figure 6: Continued.



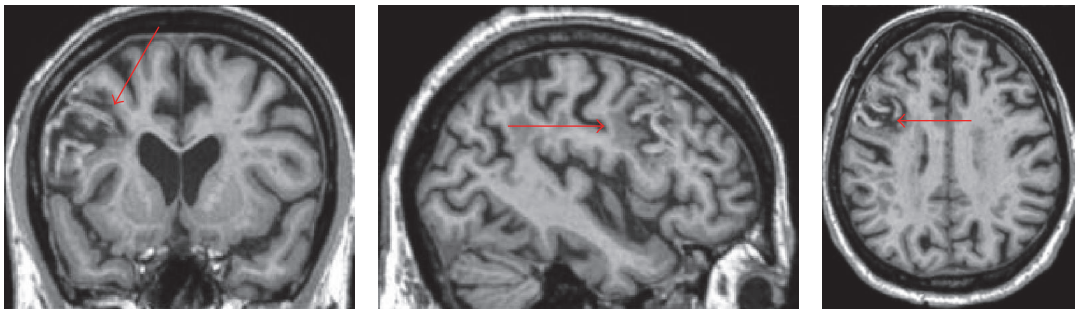
(d) DCM connections

Figure 6: Patient 4. (a) The T1-weighted MRI image at T1 shows a left sylvian ischemic stroke. (b) Pattern of brain activation in different conditions while picture naming, with an uncorrected $p < 0.001$ for the main effects. (c) Behavioral results of the combined production scores in both languages, linguistic and nonlinguistic switching scores across sessions. $*$ represents p value < 0.05. (d) Differences between L1 strength values and L2 strength values for each single connection across sessions. (1) ACC to LIFGTri. (2) ACC to LIFGOrb. (3) ACC to LC. (4) LC to ACC. (5) LC to LIFGTri. (6) LC to LIFGOrb. (7) LIFGTri to LC. (8) LIFGTri to ACC. (9) LIFGOrb to LC. (10) LIFGOrb to ACC. (11) LIFGTri to LIFGOrb. (12) LIFGOrb to LIFGTri. (13) BTLA to LIFGTri. (14) BTLA to LIFGOrb. (15) BTLA to LC.

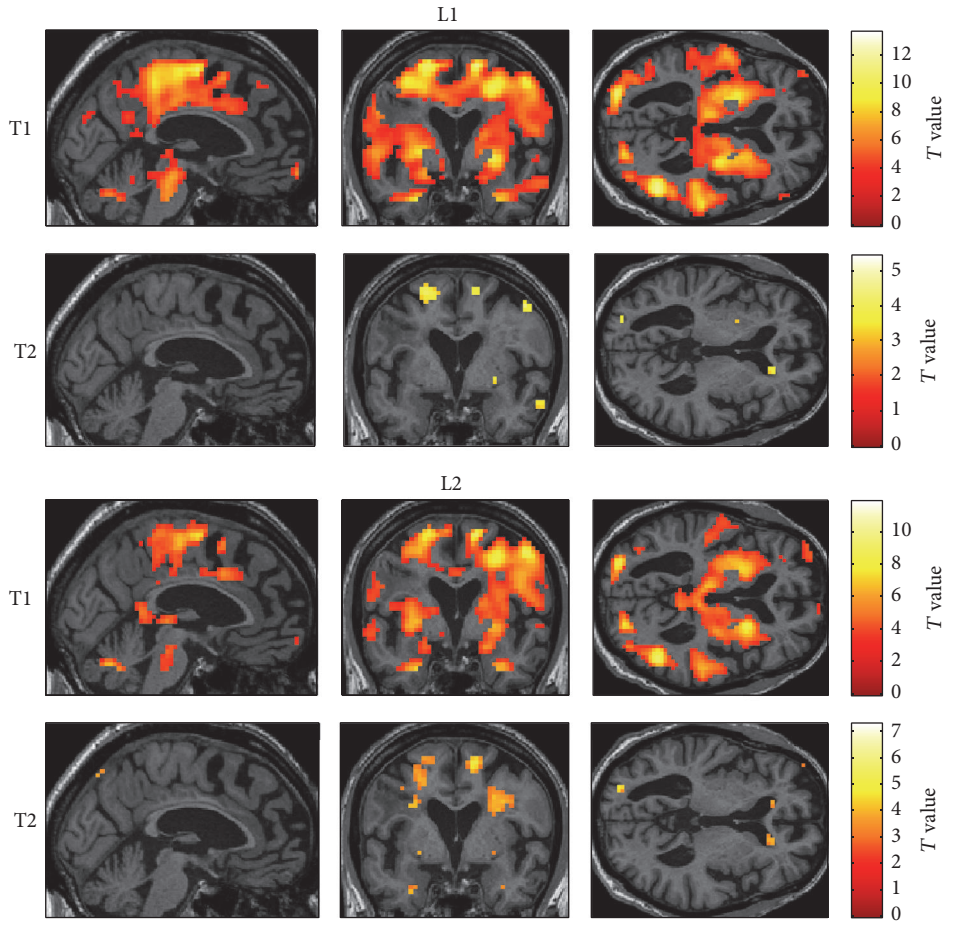
in the case of a bilingual aphasic patient for whom the language which recovered better showed increased connections between language and control networks. Our DCM results support a role for language-control interconnections in language recovery in bilingual aphasic patients [9, 10, 35] and are in line with the "dynamic view" of language production, which posits that patterns of language recovery are related to alterations in language control. Interestingly, for patients in whom both languages recovered (patients 2, 3, and 5), the two languages were connected to the control system to the same extent. Additionally, when one language recovered better, there was a greater engagement of language-control interconnections in this language. Previous studies of the association between global patterns of brain connectivity and the recovery of language functions have suggested that decreased functional connectivity between anterior and posterior areas of the default mode network (DMN) is associated with cognitive impairment. Accordingly, therapy-induced increases in functional connectivity between anterior and posterior areas of the DMN have been reported in a group of chronic monolingual aphasic patients [36]. In a further study, Sebastian and colleagues [37] evaluated the recovery of naming functions from acute to chronic phase and showed that the degree of functional connectivity between language-specific areas in both hemispheres was important for optimal recovery of naming functions.

Furthermore, our results suggest that a change in connection strength from ACC to LIFGTri during picture naming in L1 was associated with L1 recovery; the coupling between these two areas became stronger when L1 recovered. LIFGTri, along with the LIFG pars opercularis (BA44), is known to be involved in different steps of language production [38], namely, in syntactic encoding [39], speech praxis [40], and verb retrieval [41]. ACC is known to be involved in conflict and error monitoring, including domain-general control functions in healthy populations [42]. In the normally functioning bilingual brain, ACC, in connection with the prefrontal cortex, is a component of the circuit involved in inhibiting interference from the nontarget language [1, 18, 43] while in a healthy brain, this interference is caused mainly by the more proficient language (usually L1); our results could be explained by the fact that in the presence of language and control dysfunction (e.g., following a stroke), conflicts may arise between L1 and L2 even in the case of different proficiencies. Therefore, a higher engagement of the circuit between ACC and LIFGTri could possibly facilitate performance in the recovery of L1 by blocking the interference of information from L2.

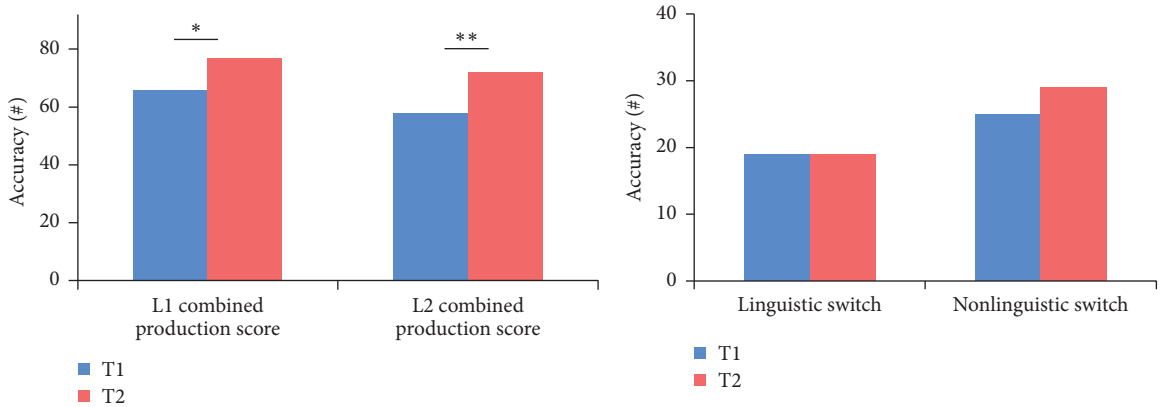
Analyses of the changes in connectivity strengths across time suggest that, in patients with L2 recovery (four out of five patients), the connection from LIFGTri to LIFGOrb becomes weaker for L2 compared to L1. This finding is also supported by the result of a correlation analysis showing that the recovery of combined production scores in L2 negatively correlates with changes in the strength of connection from LIFGTri to LIFGOrb. In other words, when L2 recovers, the coupling from LIFGTri to LIFGOrb decreases. These two regions are strongly anatomofunctionally interconnected as subregions of the inferior frontal gyrus [40]. LIFGTri is selected as the main language production area and LIFGOrb is a part of language-control network, which is involved in both language production and language-control processes (lexical semantic processes along with LIFGTri and selecting among lexical competitors) [44, 45]. The reason for the decrease of coupling from LIFGTri to LIFGOrb in L2 production could be explained by the Revised Hierarchical Model of lexical and conceptual representation in the bilingual brain [46, 47]. In this psycholinguistic model the conceptual system is common across languages, even in the less proficient L2. However, L1 is hypothesized to have privileged access to the conceptual system, favored by a strong connection between the areas involved in lexical and semantic processing (resp., LIFGTri



(a) Lesion location

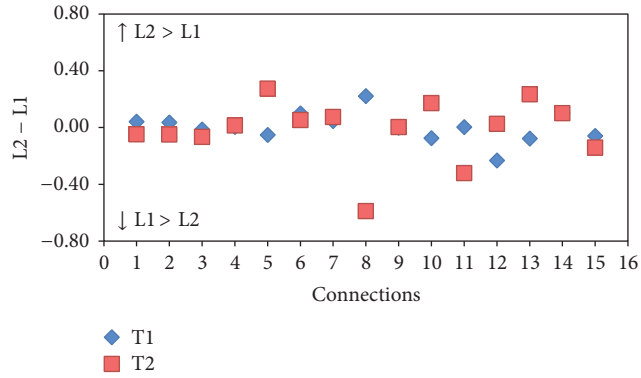


(b) Functional MRI naming task



(c) Behavioral results

Figure 7: Continued.



(d) DCM connections

Figure 7: Patient 5. (a) An ischemic lesion in the left frontal, insula, and sylvian areas in the T1-weighted MRI image at T1. (b) Pattern of brain activation in different conditions while picture naming, with an uncorrected $p < 0.001$ for the main effects. (c) Behavioral results of the combined production scores in both languages, linguistic and nonlinguistic switching scores across sessions. $*$ represents p value < 0.05 and $**$ represents p value < 0.001. (d) Differences between L1 strength values and L2 strength values for each single connection across sessions. (1) ACC to LIFGTri. (2) ACC to LIFGOrb. (3) ACC to LC. (4) LC to ACC. (5) LC to LIFGTri. (6) LC to LIFGOrb. (7) LIFGTri to LC. (8) LIFGTri to ACC. (9) LIFGOrb to LC. (10) LIFGOrb to ACC. (11) LIFGTri to LIFGOrb. (12) LIFGOrb to LIFGTri. (13) BTLA to LIFGTri. (14) BTLA to LIFGOrb. (15) BTLA to LC.

and LIFGOrb in our study). Hence, a weaker connectivity between these two areas may help in the process of L2 recovery.

The present study suffers from several limitations. First, we could not implement certain language and control tasks since they were too demanding for aphasic patients, especially in the acute and subacute phases. A comprehensive evaluation of language and control would have helped better understand the possible correlation between the recovery of control functions and the recovery of language performance following a stroke. Even though we narrowed our selection of tasks to a limited series of evaluation materials, half of the initially recruited patients dropped out of the second session of the study. Another limitation of this study was the small number of included patients; their results may not be easily applicable to all bilingual aphasic patients. In addition, we could not control the age of the patients in the study (the age of patients ranged from 49 to 79 years old). It is known that the age factor can affect behavioral performance, functional brain activity, and connectivity within brain areas as a result of alteration in neuronal activity and connectivity in aging brain [48, 49]. However, as the design is mainly within-subject the age does not seem to affect importantly the results. In addition, regressing out the effect of age from the analyses would not let any significant results due to the small sample size. Moreover, the use of different MRI scanners in this study restricted us in carrying out a direct group comparison of brain activation in different conditions. Finally, as obtaining an accurate measure of premorbid proficiency following their stroke was impossible, the evaluation of premorbid second language proficiency was restricted to a detailed questionnaire filled in by a family member or the patient himself.

It worth noting that, in the present study, only three patients followed language therapy sessions and the therapy was computer assisted to improve lexical access and in turn improve naming performances. One patient (patient 1) received therapy in his L1 (French) and he then improved in L1 production. This lack of improvement in L2 could be explained by the very low L2 usage and immersion by this subject. It has been previously suggested by Edmonds and Kiran [50] that the effect of therapy in less mastered language is more likely to transfer to the untreated language as the subject is more relied on borrowing word from the more proficient language. Another explanation of the absence of transfer of the effect of language therapy in L1 to the untreated L2 is the fact that he did not show improvement in control functions across time [8]. Patient 3 received therapy in her L2 (French), which she has been used and was immersed in an equal level as her L1 since 53 years ago. She improved in both L1 (Italian) and L2 across time. Her improvement in both languages can be explained by high immersion in both languages as well as improvement in the cognitive control functions. Patient 5 attended to a limited number of therapy sessions (10 sessions) in his L1 (French) and he improved in both L1 and L2 (English). In this patient, the recovery of both languages cannot be explained by the choice of therapy or the pattern of changes in cognitive control functions. Therefore, no consistent pattern of the effect of therapy and possible cross language transfer of the effect of therapy was found. Therefore, our interpretation of these results is not based on the language therapy. Moreover, because of the timing of the study sessions (at three weeks and around four months following the stroke), the process of spontaneous recovery should be still ongoing [6, 23]. Accordingly, this recovery takes place as the result of a combination of spontaneous recovery and language therapy.

5. Conclusion

Taken together, our findings supply additional evidence that the engagement of the interconnected language-control network is crucial for the recovery of languages. Furthermore,

we suggest that L1 recovery is improved by increased connectivity between ACC and LIFGTri, which prevents conflicts from the second language. However, L2 recovery requires a decrease in connectivity from LIFGTri to LIFGOrb in order to decrease the automatic activation of the L1 lexical system, which, according to the Revised Hierarchical Model, has stronger links with the conceptual system.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Adaptive Plasticity in the Healthy Language Network: Implications for Language Recovery after Stroke

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Across the last three decades, the application of noninvasive brain stimulation (NIBS) has substantially increased the current knowledge of the brain's potential to undergo rapid short-term reorganization on the systems level. A large number of studies applied transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) in the healthy brain to probe the functional relevance and interaction of specific areas for different cognitive processes. NIBS is also increasingly being used to induce adaptive plasticity in motor and cognitive networks and shape cognitive functions. Recently, NIBS has been combined with electrophysiological techniques to modulate neural oscillations of specific cortical networks. In this review, we will discuss recent advances in the use of NIBS to modulate neural activity and effective connectivity in the healthy language network, with a special focus on the combination of NIBS and neuroimaging or electrophysiological approaches. Moreover, we outline how these results can be transferred to the lesioned brain to unravel the dynamics of reorganization processes in poststroke aphasia. We conclude with a critical discussion on the potential of NIBS to facilitate language recovery after stroke and propose a phase-specific model for the application of NIBS in language rehabilitation.

1. An Introduction to the Study of Language Networks

The ability to associate sound patterns with meaningful concepts and articulate one's thoughts is a core feature of human communication. During successful language processing, rapid analysis of sound, meaning, and structure of spoken or written words is required. Since the days of Broca and Wernicke in the second half of the 19th century, researchers aimed at identifying key networks for language comprehension and production in the human brain. The first functional-anatomical models of language were solely based on the observation of behavioural deficits in patients with brain lesions and relied on postmortem analyses of damaged brain areas (e.g., [1, 2]; see [3] for review). The advent of modern electrophysiological and neuroimaging techniques like electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) in the late 20th century allowed for the direct correlation between mental operations and neural activity in the healthy human brain [4]. These approaches were complemented by the application of non-invasive brain stimulation (NIBS) that enables the researcher to probe the causal relevance of task-specific neural activity for different motor or cognitive functions. Moreover, when applied in a plasticity-inducing fashion, NIBS further allows for the investigation of rapid short-term reorganization on the systems level.

The capacity of the human brain to flexibly change the functional weight within a network is a core feature of adaptive reorganization and compensation after brain lesions. A profound understanding of language organisation and the brain's general potential for adaptive plasticity is mandatory for the interpretation of reorganization processes in the lesioned brain and might ultimately prove useful to optimize treatment strategies for language rehabilitation in patients with poststroke aphasia.

In this review, we will discuss how different NIBS approaches can be used to investigate adaptive plasticity in the healthy and lesioned language network and elucidate the potential of such approaches to enhance recovery of language function after stroke-induced brain lesions. First, some basic

mechanism of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) will be discussed. We will also introduce more recent NIBS approaches like transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS). With respect to the application of these techniques, the emerging field of computational neurostimulation [5] might substantially advance the experimental and clinical use of NIBS by establishing quantitative models that link stimulation dose to behavioural and clinical outcomes and provide insight into the physiological underpinnings of the stimulation effects [6].

In the second part of the review, we will focus on the combination of NIBS and neuroimaging or electrophysiological techniques in the healthy language network. Employing multimethod approaches allows for a comprehensive mapping of stimulation-induced effects on neural activity and connectivity locally and in distant connected network regions and provides insight into the adaptive short- and long-term effects induced by NIBS.

2. An Introduction to Noninvasive Brain Stimulation

The application of electrical currents to stimulate body parts dates back to Galvani (1737–1798) who pioneered the field of bioelectromagnetics with his discovery that the muscles of a dead frog's legs twitched when struck by an electrical spark, an observation that he referred to as "animal electricity" [7]. About 100 years later, Fritsch and Hitzig [8] demonstrated that electrical stimulation of different cortical areas caused involuntary muscular contractions of various body parts in dogs, thereby dethroning the doctrine that the brain was electrically inexcitable.

2.1. Transcranial Magnetic Stimulation (TMS). It took another 100 years after Fritsch's and Hitzig's discoveries until transcranial magnetic stimulation (TMS) was introduced as a noninvasive technique for electrical stimulation of the human cortex by Barker and colleagues in 1985 [9]. Strikingly, the principles of electromagnetism that underlie TMS were well known more than a century before its introduction, and the failure to develop TMS sooner was due to a lack of the necessary high-power electronics [10].

TMS is based on the principles of electromagnetic induction. A brief electric current produces a strong time-varying magnetic field in the TMS coil, and the time-varying magnetic field penetrates the scalp without attenuation to induce a flow of electric current in the stimulated tissue [11]. A single TMS pulse thereby causes electro-magneto-electric stimulation of neuronal axons, particularly in superficial regions of the cerebral cortex that can temporarily excite or inhibit the stimulated area [12]. A large number of previous studies have elucidated the physiological mechanisms of TMS in the human motor system (e.g., [11–14]). When applied over the primary motor cortex, TMS can depolarize corticospinal tract neurons and evoke contralateral hand muscle movements. The size of these motor evoked potentials reflects the excitability of the corticospinal system [11]. However, the physiological mechanisms of the TMS-induced neuronal excitation at the cellular level remain largely unclear. For instance, tissue resistivity and cerebrospinal fluid likely influence current flow, electric field direction, and magnitude [15, 16] and it remains illusive how the cellular and gyral shapes or grey matter boundaries influence stimulation effects [17].

An increasing number of studies used biophysical modelling and simulation of the electric field distribution induced by TMS or transcranial direct current stimulation (tDCS) to provide estimations of the spatial stimulation patterns induced by these techniques (see [18]). The results from these modelling studies might inform future applications of NIBS and thereby increase the spatial specificity of these methods.

The effects of TMS on cognitive functions can be probed on the behavioural level by changes in response speed or accuracy or alterations in neural responses mapped by M/EEG, PET, and fMRI. Behavioural TMS studies usually employ TMS bursts to characterize the functional relevance of task-specific activity patterns observed in neuroimaging studies, following the assumption that if a certain area is critical to a given task, then transient disruption of this region with TMS should impair task processing, which should lead to a measurable change in the dependent variable of interest [14, 19].

2.1.1. Complementary TMS Approaches: Online versus Offline TMS. Nowadays, a large number of different TMS protocols have become available, ranging from the application of single or double pulses to short or long bursts of repetitive TMS (rTMS) with different frequencies [20]. TMS is usually applied either before a task (i.e., offline) or during a task (i.e., online).

Online TMS is particularly suited to directly interfere with ongoing task processing and provide causal structure-function relationships [21–23]. The acute, transient effect of online TMS leaves the brain no time for functional reorganization and is thus not confounded by chronic processes of functional recovery [23, 24]. This is an important advantage of studying TMS induced perturbation relative to the investigation of structural brain lesions in clinical settings. In contrast to structural lesions that seldom conform to functionally homogenous neuroanatomical subsystems, TMS is more focal (average resolution of about 1–1.5 cm) and allows for the perturbation of different subregions within a larger area of interest [25]. The majority of online TMS studies in the language domain applied either single pulses or high-frequency 10 Hz bursts over one cortical area, although some designs also included double and triple pulses at higher frequencies, low-frequency bursts, or multifocal TMS over more than one region [26]. It remains to be determined why 10 Hz is efficient in disrupting language performance. One might speculate that this protocol modulates ongoing language-related oscillatory frequencies in the stimulated area, probably by inducing alpha entrainment.

Offline TMS, on the other hand, can be used to study processes of adaptive plasticity on the systems level [27, 28]. Offline TMS usually refers to the application of repetitive TMS (rTMS) that can suppress task-related activity for an extended time period (usually about 30–45 minutes). The offline approach bears some analogies to acute stroke,

because it may give rise to an acute adaptive reorganization within the nonstimulated functional nodes of the network to compensate for the TMS-induced suppression of neural activity in those components of the network that have been perturbed with TMS [28, 29]. Notably, some rTMS protocols like intermittent theta-burst stimulation can also facilitate motor cortical excitability [30] and probably also some cognitive processes in the healthy brain, including language [31] and working memory [32]. Such a protocol might thus prove useful to promote language recovery after stroke [33].

The neurophysiological mechanisms of plasticity-inducing rTMS protocols are poorly understood. A common assumption is that rTMS influences neural excitability by long-term potentiation- and depression- (LTP- and LTD-) like effects of synaptic processes [17, 34]. Such after effects of TMS can be mapped with neuroimaging and electrophysiological techniques and were reported to modulate behavioural performance in different language tasks (e.g., [35–37]; see below for details).

2.1.2. Stimulation Parameters for TMS Studies: Control Conditions and Intensity. A critical issue for all TMS studies is the appropriate choice of a control condition. Many studies rely on placebo stimulation (referred to as sham TMS) to control for unspecific side effects, such as the clicking sounds that are produced when the coil is discharged. However, placebo stimulation is usually easy to identify as ineffective for the participant, especially when compared to stimulation of core language areas, where high stimulation intensities can induce muscle twitches and discomfort caused by direct stimulation of nerves. Depending on the network under investigation, a neighbouring region that is not expected to contribute to the task of interest or a contralateral homologous region could be chosen as active control region.

Another important issue that needs to be taken into account when applying TMS is that the induced electric field decreases rapidly with increasing distance from the coil. Hence, only a few regions on the cortical surface can be directly stimulated with TMS while deep brain structures might only be indirectly targeted. The stimulation intensity itself also influences the effectiveness of the applied protocol. For instance, Brückner et al. [38] demonstrated that continuous theta-burst stimulation (cTBS) over the prefrontal cortex only impaired lexical decisions when applied at 90% of the individual active motor threshold, but not with the "standard" intensity of 80% of the active motor threshold [30].

2.2. Transcranial Direct Current Stimulation (tDCS). tDCS has been used to study plasticity in animals for a long time before it was reintroduced for application in the human brain by Nitsche and Paulus in 2000 [39]. Animal studies revealed that weak polarizing currents applied to the brain surface could produce lasting changes in cortical-evoked potentials and influence the activity of individual cortical neurons [40–42]. During tDCS, weak direct electrical currents of 1-2 mA are applied continuously to the scalp between two large sponge electrodes for usually up to 20–30 minutes [43].

Although the physiological effects of tDCS are not fully understood, it is argued that surface-anodal polarization of the cortex with the anode near the dendritic poles of radially oriented neurons increases the firing rates of spontaneously active cells, while cathodal polarization has the opposite effect [39]. Importantly, tDCS does not cause spontaneous firing but is thought to primarily work via a passive change in the resting membrane potential [44, 45] through voltage-gate ion channels [46, 47]. As the electric field diffuses rapidly in the head, the physiological action of the current is presumably near the surface [48]. Physical models suggest that approximately half of the applied current is shunted through the scalp [49] and another significant amount through the cerebrospinal fluid [50]. In this context, it should be noted that very recent (yet unpublished) data obtained from electrode recordings in a human cadaver by Buzsaki and colleagues suggested that up to 90% of the current had been redirected by the skin (see comment by Underwood [51]), questioning the effectiveness of tDCS and related techniques to stimulate brain tissue. However, it remains unclear whether such postmortem results translate to the conductivity of the living human brain.

The focality of tDCS is not known, but modelling studies indicate that a large area under the electrode is polarized [49]. It is generally assumed that the strongest tDCS effect should occur at the stimulated area under the electrode [52], but functional effects also engage distant neural networks [53], and the position of the second electrode probably affects the effects under the first one [54]. Common montages place both electrodes on the head in a bipolar arrangement, although in theory, the reference electrode can be placed anywhere on the body to ensure that it exerts no physiological effects of its own [6]. Given the overall low focality of tDCS, a direct structure-function relationship is hard to establish, especially with respect to the induced behavioral changes [55].

One important feature of tDCS is the ability to modulate cortical excitability for longer time periods [39]. For instance, plasticity related after effects of tDCS on the behavioural level were reported up to 6–12 months after the end of an intervention [56–58]. Moreover, tDCS is easy to apply and is less prone to side effects than TMS. Compared with TMS, the lower focality of tDCS might be tolerable if the primary aim is a general modulation in the overall excitability rather than a causal proof of structure-function relationships in specific brain regions. This makes tDCS an appealing tool for neurorehabilitation settings. Indeed, there is an increasing interest in the application of tDCS to augment brain function in "home use" settings [59].

A common assumption is that anodal tDCS increases the overall activity in a brain region while cathodal tDCS decreases it, which should in turn map onto the respective behavioural consequences (i.e., improvement versus disruption) [60]. Indeed, a large number of previous studies used tDCS to facilitate learning and consolidation in different motor and cognitive tasks in healthy subjects [61, 62]. In contrast to TMS, the tDCS intensity is usually not calibrated to the individual motor threshold but given at a constant intensity across subjects. However, a better understanding of the recruitment of different neuronal circuits by tDCS could substantially advance the application of individualized stimulation protocols to facilitate treatment in therapeutic

settings [63]. In this context, it remains to be determined whether stimulation paradigms that successfully modulate cortical excitability in healthy participants are also optimal in the diseased brain.

2.2.1. Online and Offline tDCS. Similar to TMS, tDCS can also be applied before a certain task (offline) or during task processing (online). Online tDCS may induce slight shifts in task performance when considering a whole session [43], although the effect is not sufficiently strong to efficiently disrupt task performance on the single-trial level. The physiological effects of online tDCS might differ from those mediating short and long-lasting after effects [46, 64, 65]. As argued above, the immediate tDCS effects are presumably mediated by membrane depolarization for anodal stimulation and membrane hyperpolarization for cathodal stimulation [41], while the after effects could be explained by long-term potentiation and long-term depression [42, 66, 67]. The effects of tDCS on task processing can be quantified with behavioural measures, neurophysiological parameters, or neuroimaging read-outs.

Two quantitative reviews challenged the overall reliability and efficacy of tDCS to modulate cognitive functions [68, 69]. However, some of their analyses were limited by the inclusion of studies with methodological variations and the overall small number of comparable studies included [70, 71] and should thus be interpreted with caution. Indeed, a reanalysis on the included tDCS studies in the language domain pointed towards significant and reliable effects of single session anodal tDCS in the healthy brain [71], while the effects of cathodal tDCS might be more variable [72, 73]. To draw strong conclusions on the reliability of different tDCS protocols in various cognitive domains, replication studies with similar experimental paradigms and stimulation parameters would be mandatory, which are rarely available to date [74, 75]. Such studies might inform future applications of various tDCS protocols in therapeutic settings.

2.3. Novel Transcranial Electrical Stimulation Techniques. Recently, two novel NIBS techniques have been introduced: transcranial alternating current stimulation (tACS) [76] and transcranial random noise stimulation (tRNS) [77]. In contrast to the tDCS induced alterations of spontaneous cortical activity, these approaches are presumed to modulate oscillations of cortical networks in a frequency specific (tACS) or random manner (tRNS) [78]. The ability to modulate cortical oscillations provides a causal link between neural oscillations and specific cognitive processes [79–81]. tACS is usually applied with sinusoidal currents, although other waveforms are also possible. Depending on the applied frequency, tACS can be used to synchronize or desynchronize cortical oscillations and induce plastic effects in the stimulated areas. Synchronization is expected if a single resonance frequency is applied while desynchronization should result from the application of several frequencies [79]. tACS is assumed to entrain ongoing brain oscillations if the applied frequency matches the ongoing oscillation frequency in the brain [82]. Similar to TMS and tDCS, the effects of tACS can be quantified on the electrophysiological, neural, or behavioural level. To assess stimulation induced entrainment of brain oscillations, tACS can be combined with EEG or MEG. Since tACS induces strong artefacts in the EEG data, most of the previous studies relied on an offline approach. Only very recently, first successful correction methods for tACS induced artefacts in online EEG recordings were introduced [83]. These approaches might help to increase the current knowledge of the task-specific functional relevance of oscillatory brain activity. A different strategy was used by Lustenberger and colleagues [84] who introduced an EEG-feedback-controlled approach for real-time modulation of transient brain oscillations with tACS during sleep. Epochs of tACS in the spindle frequency range were triggered by the detection of sleep spindles with the analysis of EEG recordings being restricted to stimulation free intervals after short tACS epochs. Feedback-controlled tACS caused an enhancement of cortical synchronization in the spindle frequency range that intensified the spindling process and improved motor memory consolidation. These results demonstrate the value of oscillation-triggered stimulation to boost cognitive processes.

Other previous studies showed that tACS applied at individual alpha frequencies could enhance alpha band power in the subsequent offline EEG [85], with the after effects lasting for up to 30 minutes after the end of the stimulation [86]. As with other NIBS techniques, stimulation intensity might have an important influence on the effects of the tACS protocol. For instance, Moliadze and colleagues [87] demonstrated a nonlinear dependency between the intensity of their tACS protocol and the observed effects on motor excitability. Specifically, low stimulation intensities given at 140 Hz over the primary motor cortex resulted in cortical inhibition, as assessed with increased motor thresholds during simultaneous recordings of motor evoked potentials with single pulse TMS. In contrast, high intensities facilitated cortical excitability and decreased motor cortical thresholds. Interestingly, there were no significant effects for intermediate intensities, presumably indicating that inhibitory and excitatory effects cancelled each other out at such intensities. How this translates to areas outside the primary motor cortex and cognitive functions remains to be determined.

Recent studies reported sustained beneficial after effects when tACS was applied over left frontal cortex during explicit word pair encoding [88] or working memory processing [89] or over left temporoparietal cortex during implicit associative language learning [90]. In the latter study, 6 Hz tACS during language learning significantly improved retrieval performance in a collective of healthy young and older participants. The beneficial tACS after effect was driven by superior performance of older subjects after effective versus sham tACS, providing the first evidence that tACS might enhance language learning in the aging brain [90]. These results are encouraging with respect to a possible application of tACS in neurorehabilitation settings in the future.

tDCS can also be combined with tACS, with the alternating current being superimposed onto a direct current. This technique is referred to as oscillatory tDCS (otDCS) and aims at directly modulating the ongoing rhythmic brain activity at the frequency of the applied current [80, 81]. A number of studies used otDCS to modulate memory encoding or

consolidation during sleep or wakefulness in the healthy brain [91–93]. For instance, Marshall et al. [91] applied anodal otDCS at 0.75 Hz after associative word learning to boost slow oscillations during sleep. This study showed a stimulation-induced increase in endogenous slow oscillatory activity and enhanced spindle activity. otDCS also improved declarative memory performance after sleep, demonstrating a causal role of slow oscillations in declarative memory consolidation. More recently, Ladenbauer and colleagues [94] found that otDCS enhanced slow oscillatory activity as well as fast spindle activity in older participants when applied during an afternoon nap. Moreover, otDCS improved picture memory retention after sleep. The authors concluded that otDCS during daytime naps might be used to counteract cognitive decline in aging.

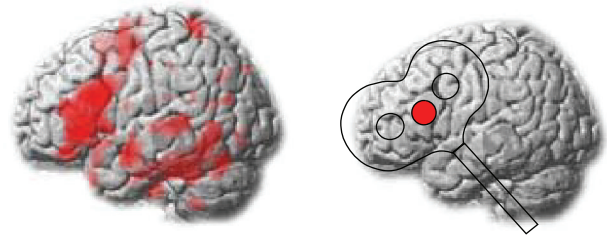
As implicated by its name, transcranial *random noise* stimulation (tRNS) is applied with a broad frequency spectrum (0.1–640 Hz) and a random noise distribution [77] to cover physiological brain oscillations. On the physiological level, it is assumed that tRNS might induce LTP-like cortical plasticity by augmenting the activity of neuronal sodium channels in the stimulated parts of the brain [78]. Research on tRNS is still in its infancy, but some studies demonstrated that this technique might have lasting facilitatory after effects on motor cortical excitability. Accordingly, increases in the baseline levels of cortical excitability were shown to outlast the stimulation for up to 60 minutes when 10 minutes of high-frequency (100–640 Hz) tRNS was applied to the primary motor cortex [77]. Plastic after effects of tRNS on corticospinal excitability were already reported after a minimal stimulation duration of 5 minutes, but the respective after effects lasted for only 10 minutes [95]. Preliminary evidence in the study of cognition further suggests that tRNS might facilitate perceptual learning when applied over the visual cortex [96] but might disrupt categorical learning when given over the right dorsal lateral prefrontal cortex [78], with (unknown) task specific effects being likely to contribute to the direction of the tRNS induced effects.

In summary, most of the previous studies applied tACS and tRNS in the motor, visual, or auditory system to directly modulate cortical rhythms, but some studies also reported modulation of higher cognitive functions after tACS and otDCS (reviewed in [79–81]) or, more recently, tRNS [97, 98].

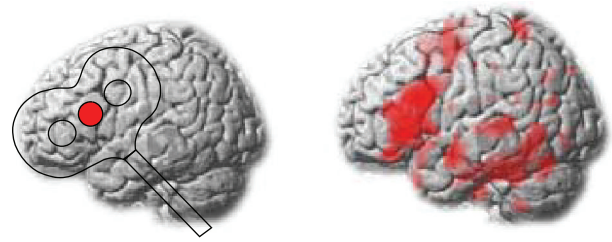
3. Combining NIBS with Neuroimaging Techniques

NIBS can be combined with functional neuroimaging to draw causal conclusions regarding the contribution of one or more specific brain regions to a given task or map NIBS induced changes on task-related activity and connectivity. An exemplified illustration of different combinations of TMS and fMRI is given in Figure 1. These combinations can also be used with tDCS, tACS, and tRNS. In a similar vein, the effects of NIBS can also be mapped with EEG or MEG, with the exception that the simultaneous combination of TMS and MEG is technically not feasible.

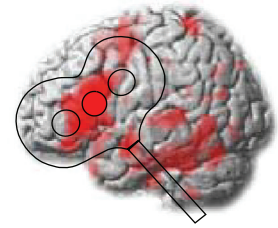
fMRI can be used prior to TMS to localize task-specific activity of interest and inform the subsequent application of



(a) fMRI preceding TMS: localization of neural activity



(b) TMS preceding fMRI: mapping lasting stimulation effects



(c) Concurrent TMS & fMRI: mapping immediate stimulation effects

Figure 1: Illustration of different combinations of transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI). (a) fMRI can be used to localize target areas for TMS application. Subsequently, TMS is applied to probe the contribution of these regions to a specific task. (b) TMS can also be applied prior to fMRI to probe its lasting neuromodulatory effects on the network level. (c) Simultaneous TMS and fMRI can be used to map the immediate consequences of TMS on brain functions.

TMS with respect to the stimulation site (Figure 1(a)). With this approach, TMS is used to probe the causal relevance of task-related activity observed with correlative neuroimaging measures. This approach has been used in most of the previous TMS studies in the language domain (for recent reviews see [26, 99]). A potential shortcoming of NIBS studies that solely focus on behavioural outcomes is that network effects can hardly be quantified unless multifocal NIBS is used. Moreover, the effects of NIBS might not necessarily map on the behavioural level and the contribution of remote effects in distant connected regions remains unclear. Although a common assumption of NIBS studies is that the strongest modulatory effect should occur at the targeted area, this might not necessarily hold true, especially for complex cognitive functions that depend on interactions of larger networks [22]. Indeed, remote effects outside the stimulated region have been reported to arise in neighbouring cortical regions close to the targeted area and in distant cortical and subcortical areas via intra- or interhemispheric connections

[100, 101]. These effects are well described in the motor system [100, 102, 103], although it is less clear whether physiological remote effects are able to interfere with behaviour [104].

Plastic stimulation-induced changes on the network level can be mapped with fMRI after TMS application (Figure 1(b)). For instance, a recent study in healthy volunteers revealed an improvement in the subjects' ability to control impulsive responses after rTMS had been applied to the presupplementary motor area [105]. This beneficial after effect was mediated by increased activation and connectivity of a cortico-subcortical network including right inferior frontal gyrus and subthalamic nucleus. These results illustrate that the behavioural consequences observed with NIBS over a certain area might not necessarily be mediated by the stimulated area itself, but by spatially remote areas, which are part of the same network. Here, the combination of NIBS and neuroimaging or electrophysiological measures is well suited to map subtle changes in neural responsivity on the network level. In this context, it should be noted that TMS can also be given simultaneously during fMRI to probe the direct, immediate effects of the stimulation on the neural and behavioural level (Figure 1(c)). However, this combination is technically challenging and only established in a few research centres so far. The author is not aware of any concurrent TMS-fMRI application in the study of language. For a comprehensive overview of previous simultaneous TMS-fMRI studies, the reader is thus referred to a recent review [106].

4. Mapping Adaptive Plasticity in the Healthy Language Network

To date, only a few studies in the language domain combined NIBS with neuroimaging (i.e., PET or fMRI) or electrophysiological approaches (i.e., EEG or MEG) to map NIBS induced changes on the network level. These studies will be discussed in the next sections.

4.1. Evidence from Transcranial Magnetic Stimulation. One of the earliest studies that used TMS and PET to investigate speech perception in the healthy motor system was conducted by Watkins and Paus [107]. These authors found increased excitability of the primary motor cortex (M1) lip areas as measured by increased amplitudes of the motor evoked potentials recorded from orbicularis oris muscle during speech listening. Interestingly, increased motor excitability was positively correlated with an increase in the regional cerebral blood flow in left posterior inferior frontal gyrus (pIFG) during speech listening, indicating that the excitability of the M1 lip representation is influenced by input from the pIFG during speech perception. Additionally, increased cerebral blood flow in the left temporoparietal junction, an area previously associated with audio-motor-mapping processes during speech production [108], was also positively correlated with increased M1 excitability during speech perception [107]. The increase in motor excitability of the speech production system could reflect covert imitation or internal speech that might improve comprehension of the percept [99, 109]. The notion of a causal contribution of left M1 to speech perception was supported by several other TMS studies [35, 110].

More recently, Möttönen et al. [111] combined TMS and EEG to investigate how TMS modulates mismatch negativity (MMN) responses to phonetic changes in auditory vowels during automatic speech discrimination. In that study, subjects received 15 minutes of low-frequency 0.6 Hz rTMS over M1. Afterwards, participants listened to oddball sequences with frequent ("da") and infrequent ("ba" and "ga") phoneme stimuli while watching silent movies. The authors reported decreased MMN amplitudes to infrequent phonemes after disruption of M1 lip area but not M1 hand area. Moreover, the disruptive effect of rTMS was functionally specific since disruption of M1 lip area did not change MMN responses to nonverbal piano tones. These results provide further evidence for a causal contribution of the M1 lip area to speech discrimination.

In a follow-up investigation [112] MEG was used to track TMS-induced changes in the dynamic interaction between auditory and articulatory motor cortices during processing of attended versus unattended speech sounds. Again, subjects received 15 minutes of low-frequency rTMS over left M1 lip area. This study revealed a strong influence of attention on auditory-motor interactions. The authors found that TMS induced disruption of the motor lip representation modulated early, left-lateralized articulatory-specific responses in the auditory cortex that occurred 60–100 ms after sound onset when lip-articulated speech sounds were attended. In contrast, when speech sounds were ignored, rTMS disruption of M1 lip area led to late, nonspecific bilateral responses in the auditory cortices that started 170 ms after stimulus onset. These results show that the articulatory motor cortex contributes to the auditory processing of speech sounds and that attention can facilitate the interaction between auditory cortex and articulatory representations during speech perception.

In summary, these studies support the critical role of articulatory-motor representations in speech perception, a central notion of the motor theory of speech perception [113]. Moreover, these results provide novel insight into the interaction between articulatory-motor regions and primary auditory as well as language specific regions during speech perception.

TMS has also been combined with fMRI to investigate adaptive plasticity during speech production. For instance, a recent study investigated the contribution of the right hemisphere to speech repetition after focal disruption of the left hemisphere in healthy volunteers [114]. In that study, effective or sham continuous theta-burst stimulation (cTBS) was given over either anterior or posterior inferior frontal gyrus (a/pIFG) prior to neuroimaging in three separate sessions. Subsequently, participants had to overtly repeat real words and pseudowords (letter strings without any meaning) during functional MRI. Compared with sham cTBS or cTBS of neighbouring aIFG, cTBS of pIFG resulted in a strong suppression of task-related activity in the stimulated area and a strong upregulation of the contralateral homologous area during pseudoword repetition. Additionally, dynamic causal modelling (DCM) of functional MRI data was employed

to investigate how TMS influences task-specific changes in the effective connectivity between homologous regions in the IFG. One important feature of DCM is that it provides a measure of both the strength and direction of neuronal interactions between prespecified regions of interest [115, 116]. Accordingly, effective connectivity analyses showed that right pIFG increased its facilitatory influence on left pIFG after left pIFG had been perturbed with cTBS. Critically, response speed became faster as the influence of the right pIFG on left pIFG increased, indicating that homologous areas in the right hemisphere can actively contribute to speech production after a focal left-hemispheric perturbation. These findings are compatible with the notion that increased activation of homologous right hemisphere areas might support aphasia recovery after left hemisphere damage (e.g., [117]; see discussion below).

In another recent study, Shinshi and colleagues [118] used TMS and MEG to investigate the role of the left pIFG in picture naming. In a first experiment, the authors showed that high-frequency 40 Hz triple pulse TMS over the left pIFG but not right pIFG significantly delayed naming latencies when applied 300 or 375 ms after picture presentation. The authors reasoned that TMS most likely disturbed the processes of syllabification during picture naming. To further elucidate the time course of picture naming, participants performed the same task during MEG. Interestingly, the authors found a significant correlation between the individual time period where TMS delayed picture naming and the individual time period when low gamma event-related desynchronizations peaked in left IFG, providing evidence for a critical contribution of these oscillations to picture naming.

Although the simultaneous application of TMS and MEG is technically not feasible since the TMS coil does not fit into the MEG helmet and TMS pulses might probably destroy the MEG sensors [119], another study successfully applied cTBS before MEG to modulate occipitoparietal alpha and gamma power during visuospatial attention processing [120]. In that study, offline inhibition of the frontal eye fields induced by cTBS caused a disruption of the attentional modulation of occipitoparietal alpha oscillations contralateral to the stimulated frontal eye field. This effect was explained by compensatory reorganization mechanisms in the dorsal frontoparietal attention network [120]. Such an approach would be of great interest to probe how inhibitory TMS over pIFG modulates neural oscillations during picture naming. This might provide new insight into the interactions and temporal dynamics between pIFG and other critical regions for picture naming such as posterior superior temporal gyrus.

TMS was also combined with neuroimaging and electrophysiological techniques to investigate language comprehension. For instance, in a number of studies, Andoh and colleagues investigated interhemispheric interactions during word recognition and auditory processing and at rest with consecutive TMS and fMRI [121–123]. In a first study, Andoh and Paus [122] combined high-frequency 10 Hz offline rTMS over left or right posterior superior temporal gyrus (pSTG) with subsequent fMRI to investigate auditory word comprehension. During fMRI, participants performed a word recognition task on native and foreign words. On the neural level, rTMS over either hemisphere resulted in an increase in the task-related activity in the nonstimulated homologous region. These changes were taken to reflect adaptive plasticity that compensated for the rTMS induced disruption of the respective other hemisphere. TMS-induced changes in task-related activity were accompanied by more specific modulations on the behavioural level. Hence, rTMS over left but not right pSTG selectively decreased response speed for native relative to foreign words. These results support the role of the left pSTG in lexical processing. However, it remains unclear whether the reported behavioural improvement was related to increased task-related activity in the contralateral right hemisphere or decreased activity at the site of stimulation in left pSTG [122]. In this context, future modelling studies might explore how changes in behavioural measures match TMS-induced modulations of effective connectivity measures between homologue regions.

In another study, Andoh and Zatorre [123] mapped TMS-induced modulations of interhemispheric interactions between auditory cortices with fMRI. Subjects performed a melody discrimination task during fMRI before and after cTBS over the right auditory cortex (AC). The authors reported increased task-related activity in the contralateral left AC after cTBS over right AC. The strength of the individual task-related upregulation of left AC was negatively correlated with behavioural performance. Hence, individual response speed decreased as activity in left AC increased and individuals with reduced contralateral activity did not exhibit any behavioural facilitation. Additionally, stronger interhemispheric connectivity between auditory cortices before cTBS was associated with faster response speed after cTBS. These results show how TMS modulates plastic short-term reorganization in the healthy auditory network. Similar mechanism might be observed after focal perturbation in the language system.

More recently, the same authors showed that rTMS over the right AC induces changes in functional connectivity in auditory and motor-related networks at rest [121]. To this end, healthy participants underwent resting-state fMRI prior to and after cTBS application over right and left AC and a control site in the vertex. The authors reported widespread changes in the functional connectivity in auditory and motor networks after cTBS of right AC in comparison to left AC. These network effects were underpinned by differences in the callosal tract integrity of auditory fibers, as evidenced by a negative correlation between the volume of the callosal auditory fibers and individual differences in the degree of cTBS-induced changes in functional connectivity between the auditory cortices. The authors concluded that their results support a role of the corpus callosum in mediating functional asymmetry. Together, their results emphasize the value of combining TMS and neuroimaging to map network effects of focal perturbations and investigate rapid short-term reorganization in auditory and language networks.

To map compensatory reorganization in the semantic system, two recent studies combined focal perturbation of the left anterior temporal lobe (ATL) with subsequent fMRI [124, 125]. In the first study, Binney and Lambon Ralph [124] found that cTBS over the left lateral ATL suppressed task-related

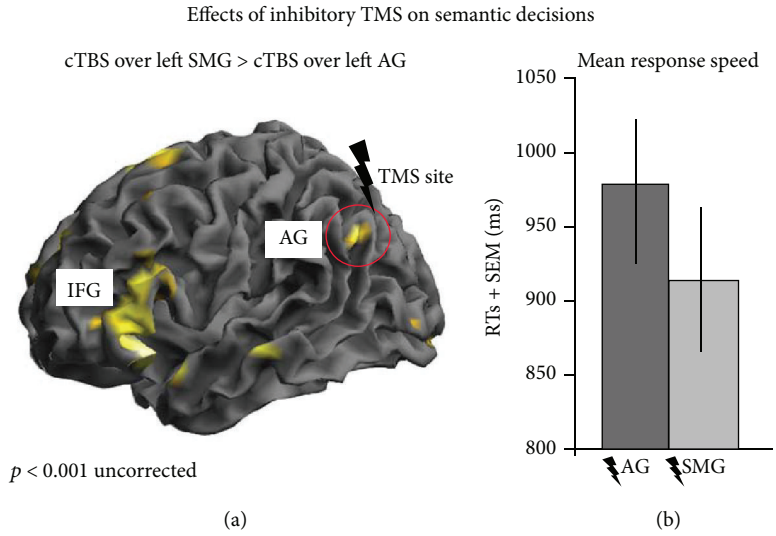


Figure 2: TMS-induced suppression of the semantic network during a word decision task in a representative subject. (a) Illustration of the strong remote effects induced by continuous theta burst stimulation (cTBS) given over the left angular gyrus (AG) prior to fMRI. Relative to cTBS over the neighboring supramarginal gyrus (SMG), cTBS of AG inhibited task-related neural activity during semantic decisions in the stimulated area as well as in the left inferior frontal gyrus (IFG) and in temporal regions. (b) Effects of cTBS on the mean reaction times (RTs) of semantic decisions. SEM = standard error of the mean.

semantic activity not only at the stimulated site, but also in other left-hemispheric areas of the semantic network, including the ventral ATL and ventrolateral prefrontal and posterolateral temporal cortex. Moreover, ATL suppression led to an extended, compensatory upregulation of the contralateral homologous region, indicating a high degree of adaptive plasticity in the semantic network. Congruent with the reported flexible adaptation of the semantic network, the second study from the same group [125] also found decreased activity in the left ventrolateral ATL after cTBS induced suppression of this region (relative to a control site in the occipital pole) and compensatory upregulation of the contralateral homologue. The upregulation of the right ATL was negatively correlated with task speed, indicating that subjects with shorter response latencies showed stronger right ATL activation. Additionally, effective connectivity analysis revealed that, after cTBS, the right ATL increased its intrinsic facilitatory influence on left ATL, demonstrating a flexible, bilateral organization of the semantic system with a strong degree of adaptive plasticity. In a behavioural experiment, cTBS also delayed task performance during synonym judgements, providing evidence for the functional relevance of this area for semantic processes. Together with the above-discussed study on pseudoword repetition [114], these results unravelled the compensatory potential of the right hemisphere during language production and comprehension and indicate a flexible, TMS-induced redistribution of the functional weight within a network for a specific language function.

Recently, we combined TMS and fMRI to investigate adaptive plasticity in the semantic network after focal perturbation of a key semantic area prior to task processing (Hartwigsen et al., unpublished data). That study revealed strong remote effects induced by cTBS of left angular gyrus (AG). Hence, cTBS suppressed neural activity not only at the stimulated site but also in remote semantic network areas, including left anterior inferior frontal gyrus and posterior middle temporal gyrus. Figure 2 provides an illustration of these effects in a representative participant. Note that this participant also showed a strong delay in the semantic response speed after perturbation of the left AG. This effect was not significant at the group level, which might be explained by a strong compensatory upregulation of neighbouring parietofrontal regions for phonological processing (i.e., left supramarginal gyrus and pIFG) across participants. These findings implicate that the effects of TMS over a key area for a specific language function can modulate task-specific neural activity in the whole network. Moreover, the upregulation of neighbouring networks might help to maintain task function, indicating a high degree of flexibility in the language network to compensate for a focal perturbation of a key region.

One of the few studies that combined TMS and EEG in a consecutive fashion investigated the neural basis of semantic comprehension [126]. In that study, high-frequency 10 Hz rTMS was given in 500 ms trains over either left or right Wernicke's area (CP5 electrode in the 10-20 EEG system) or a control site in the occipital cortex 750 ms before stimulus onset during a picture-word verification task. To avoid stimulation-induced artefacts in the EEG signal, recordings of event-related potentials were stimulus-locked. The authors found a selective delay of response speed for artificial but not natural items with rTMS over left Wernicke's area. These effects were anatomically specific as rTMS over the right Wernicke homologue or occipital cortex did not have any disruptive effect. Moreover, on the electrophysiological level, TMS increased the amplitude of the late positive complex in the central-parietal electrodes of the right hemisphere. These changes were taken to reflect a compensatory transfer of language function from the left to the right hemisphere

after disruption of the left hemisphere. The absence of any rTMS effect on natural items might indicate a more bilateral representation of sensory and perceptual features related to the processing of these items. These results show that adaptive plasticity and rapid short-term reorganization in the language network might also be mapped by changes in electrophysiological markers such as event-related potentials. Moreover, these results demonstrate a functionally relevant integration of right hemisphere activity into the normal language network subserving language comprehension on the word level [126].

In summary, the above cited studies stress the value of combining TMS with subsequent neuroimaging or electrophysiological techniques to map TMS induced changes in neural activity or oscillatory patterns and elucidate changes in inter- as well as intrahemispheric interactions after focal perturbation of task-specific key nodes.

4.2. Evidence from Transcranial Direct Current Stimulation. Very few studies combined tDCS with neuroimaging or electrophysiological techniques to investigate plastic changes in the healthy language network. Among these studies, Holland et al. [127] applied anodal tDCS over the left inferior frontal cortex (IFC) during concurrent fMRI to probe the role of the IFC in picture naming. Relative to sham tDCS, 2 mA of anodal tDCS significantly facilitated the response speed during picture naming. On the neural level, anodal tDCS significantly decreased task-related activity in inferior frontal regions, including the inferior frontal sulcus (IFS) and the ventral premotor cortex (PMv). Moreover, the observed individual behavioural facilitation was significantly correlated with the decrease in task-related activity in the stimulated left inferior frontal cortex. Although an association between a *decrease* in neural activity and behavioural *improvement* may sound counterintuitive at first glance, the authors argued that the underlying mechanism might be similar to neural priming effects reported in behavioural studies. Hence, anodal tDCS might have facilitated picture naming via regionally specific neural adaption in left inferior frontal cortex. Indeed, other studies also reported that beneficial behavioural effects of anodal tDCS were paralleled by a reduction in task-related activity in the left IFC ([128], see below for details).

In a recent follow-up investigation, Holland et al. [129] used dynamic causal modelling of functional MRI data to further elucidate tDCS-induced changes on task-related interactions in the left IFC during picture naming. In that study, the authors explored how anodal relative to sham tDCS changes task-related interactions between the left IFS and PMv. Results revealed that the previously observed significant decrease in task related activity of both frontal nodes with anodal tDCS was underpinned by an increase in the inhibitory feedback influence of IFS on PMv. These results presumably reflect neuronal adaption and more efficient task processing. Moreover, the individual variability in the feed-forward connection strength from PMv to IFS was positively correlated with the degree of facilitation in picture naming during anodal tDCS. According to the authors, their results indicate that anodal tDCS reduced noise in the naming system and thereby made the signal (i.e., the correct word related to a presented picture) easier to detect. This might indicate that the correct word was easier to select among the competing alternatives (the noise) in the mental lexicon with anodal tDCS. The authors further argued that anodal tDCS might have worked as a top-down mechanism that filtered out irrelevant signals by reducing "noisy" activity in left PMv. These results underline the important role of left IFS as top-down node and driver during speech processing. Moreover, these findings demonstrate the value of combining NIBS and modelling of fMRI data to provide insight into the interactions between task-specific regions in speech and language networks.

These results were complemented by a recent concurrent tDCS-fMRI study that probed the neural correlates of tDCS-induced facilitation over left IFG during word production [128]. In that study, 1 mA anodal or sham tDCS was applied in the MR scanner for 20 minutes. This included a resting state fMRI session and subsequent task-related fMRI with a semantic word generation paradigm. Relative to sham tDCS, anodal tDCS significantly improved semantic fluency by increasing the number of correctly produced responses for different visually presented categories. The beneficial behavioural effects were paralleled by a reduction in the task-related activity in the left ventral IFG. Functional connectivity analyses of resting-state fMRI data revealed increased coupling between the left IFG and other core areas for language processing, including left middle temporal gyrus and bilateral inferior frontal, inferior parietal, and prefrontal regions during resting-state fMRI. The authors suggested that tDCS modulated endogenous low-frequency oscillations in the language network that might have induced more efficient task processing in relevant network nodes and could thus explain the observed behavioural improvement. Accordingly, it was further speculated that the modulation of endogenous low-frequency oscillations was not restricted to the targeted area but also spread to functionally connected brain areas, which would explain the observed network effects. In this context, it would be of great interest to explore how tDCS influences the *task-related* effective connectivity between these regions. Moreover, a frequency specific modulation with tACS might further elucidate the functional relevance of endogenous oscillations.

The electrophysiological underpinnings of tDCS-induced facilitation on language production were investigated with combined tDCS and EEG by Wirth et al. [130]. To provide a comprehensive characterization of the effects of tDCS on event-related potentials as well as neural oscillations and behavioural parameters, the authors explored both direct (i.e., online) and after (i.e., offline) effects of tDCS. To this end, 1.5 mA of anodal or sham tDCS was applied for 30 minutes over the left dorsal prefrontal cortex. The task consisted of a semantic interference paradigm that prompted subjects to name repeatedly presented pictures of objects displayed in semantically homogenous (e.g., different fruits) or heterogeneous contexts (e.g., a fruit and an insect), with the presence of categorical similar objects inducing lexical-semantic competition. Anodal tDCS significantly reduced the semantic interference effect for homogenous contexts and thus facilitated picture naming latencies. In contrast, on

the electrophysiological level, this effect was underpinned by an enhanced semantic interference effect (i.e., increased event-related potentials) for left but not right temporal electrode sites. These results were taken to reflect a superior tuning of neural responses with language-related generators. Specifically, the authors suggest that the behavioural tDCS effect might be related to increased prefrontal inhibitory functions, reflecting increased processing efficiency. In contrast, the electrophysiological effect might have resulted from a network effect in the temporally distributed representational system. With respect to the after effects of anodal tDCS, the authors reported a significant reduction in delta activity at rest and during picture naming after offline tDCS over dorsal prefrontal cortex. Since activity in the slow-wave delta band might be regarded as a surrogate of neural inhibition [131], these effects were interpreted as neural excitation (i.e., disinhibition) and suggested to reflect a boost in neurocomputational resources. Future studies should explore whether the behavioural results are directly related to the observed electrophysiological changes. In this context, different tasks might be related to different oscillation frequencies that could be selectively modulated by tACS protocols.

The author is not aware of any previous study in the language domain that combined cathodal tDCS with fMRI or EEG to investigate the neural correlates of inhibitory stimulation. Only a few studies used cathodal tDCS to probe the effects of LTD-like plasticity on language learning. One of these studies compared the effects of repeated 20 minutes sessions of cathodal, anodal, or sham offline tDCS over the left primary motor cortex prior to action word learning over four consecutive days [132]. The action word learning paradigm included correct and incorrect couplings of pictures of concrete body-related actions (e.g., *shaving*) with meaningless pseudowords (e.g., *apef*). Correct couplings were more frequent than incorrect ones and subjects had to indicate via button press whether picture and word matched. The authors found that the number of novel action words successfully translated into German at the end of training was significantly reduced after cathodal versus sham tDCS. In contrast, anodal tDCS did not significantly affect task performance. This effect was anatomically specific, as tDCS over the left dorsolateral prefrontal cortex did not affect translations after language training. The effect was also functionally specific since tDCS did not disrupt non-action related object word learning in a control experiment. Additional analyses further explored the nature of the disruptive effect of cathodal tDCS: Relative to sham stimulation, cathodal tDCS significantly reduced success rates in vocabulary acquisition. Specifically, cathodal tDCS decreased the ability to associatively couple actions with novel words (i.e., to identify correct couplings), providing evidence for a causal involvement of left primary motor cortex in the acquisition of novel action-related words. The authors argued that the process of correct couplings between words and actions might strongly rely on synaptic strengthening between motor and language areas and might thus be particularly susceptible to a stimulation-induced downregulation of cortical excitability. Future studies should explore the network effects of cathodal tDCS on language learning with combined tDCS and neuroimaging. In particular, if the explanation of a task-specific synaptic strengthening was true, one might expect that cathodal tDCS over the primary motor cortex affects the interaction between motor and inferior frontal language regions during language learning.

Although the precise physiological mechanisms of the tDCS-induced modulation of (language related) neural activity remain unclear, the above described studies that combined tDCS with concurrent neuroimaging [127, 129, 133] implicate that the beneficial effects of anodal tDCS on different language functions might be explained by an increase in the efficiency of task processing locally in the stimulated areas as well as in interconnected language regions. It remains to be determined how anodal and cathodal tDCS affect other language functions.

5. Implications for Aphasia Recovery after Stroke

The above discussed studies demonstrate the value of combining noninvasive brain stimulation with electrophysiological and neuroimaging measures to map NIBS induced changes on the network level. Although the overall number of multimodal studies in the language system is scarce, first results implicate that a focal perturbation of a strategic language region changes the functional weight within in a network, which may result in a compensatory upregulation of neighbouring left-hemispheric regions or contralateral right-hemispheric regions. Moreover, NIBS induced changes on the behavioural level might be mediated via modulation of the interaction and effective connectivity within a network for a specific language function. These results provide important insight into the compensatory potential and flexible redistribution of the human language system and might be transferred to the lesion brain to increase the current knowledge of the dynamics of reorganization in the language network after brain lesions.

5.1. Current NIBS Approaches to Support Language Recovery after Stroke. Indeed, an increasing (yet still relatively small) number of studies have used NIBS to promote language recovery in poststroke aphasia (for recent reviews see [134, 135]). Most of these studies relied on low-frequency rTMS to suppress language-related activity in the "overactive" right IFG (see [136, 137]). More recently, language therapy was also combined with tDCS, as this technique is cheap and easy to apply and less prone risk to severe side effects than TMS. While the results from these studies are generally encouraging, the reported effect sizes are not striking and the potential benefit of TMS and tDCS in the neurorehabilitation of language functions remains elusive.

A Cochrane review that included 6 tDCS studies and a total of 66 patients came to the conclusion that there is currently no evidence for the effectiveness of anodal or cathodal tDCS to improve language functions in poststroke aphasia [138]. However, these results should be interpreted with caution since they were obtained from heterogeneous studies that differed with respect to aphasia type and severity, as well as stimulation parameters [137]. Indeed, a recent

meta-analyses including 6 inhibitory rTMS studies and 3 cathodal tDCS studies that aimed at inhibiting right-hemispheric regions in subacute or chronic patients with poststroke aphasia indicated positive effects of NIBS on naming accuracy [139].

It should be borne in mind that the use of NIBS to facilitate language recovery in patients with aphasia after stroke is still at its infancy and future studies with larger collectives are needed to provide a systematic investigation of the potential of different NIBS approaches to effectively modulate language functions across the time course of recovery.

To date, only very few studies investigated the neural correlates of NIBS induced modulation in the lesioned language network. For instance, a recent study by Heiss et al. [140] applied inhibitory rTMS over the contralesional right anterior IFG or vertex (control site) in a relatively large group of 29 right-handed and two left-handed aphasic patients in the subacute and chronic phase after left-hemispheric stroke. To this end, 10 sessions of 1 Hz effective or sham rTMS were combined with speech and language therapy. Concordant with other rTMS studies in patients with post-stroke aphasia [141–145], the authors reported improvement of language functions after rTMS over the IFG but not vertex in right-handed patients. PET measurements revealed a shift of language-related activity towards the left hemisphere in treated right-handers, while the vertex group maintained activation in the contralesional hemisphere. Interestingly, language improvement was also found in the two left-handed patients although PET scans demonstrated only a very small interhemispheric shift and a consolidation of active networks in both hemispheres. These results indicate that rTMS-induced suppression of "maladaptive" right-hemispheric activity might be beneficial to facilitate language recovery after stroke, probably via reshifting language activity towards perilesional left-hemispheric regions. This would be compatible with the notion that, after left-hemispheric stroke, the right hemisphere is released from transcallosal inhibition and might in turn suppress (beneficial) language-related activity in perilesional regions [134]. The beneficial effects of rTMS over the contralesional right IFG to improve picture naming abilities in patients with chronic poststroke aphasia were replicated in other studies by the same group [143, 146]. Recently, a first multicentre study on the efficacy of inhibitory NIBS over the contralesional hemisphere to support aphasia recovery was launched (see [147]).

To account for the large individual variability in response to various stimulation protocols reported in the literature and optimize individual montage for treatment in 12 patients with chronic nonfluent aphasia after stroke, Shah-Basak et al. [148] investigated different tDCS set-ups. Despite individual variability, best improvement was on average obtained after 10 days of cathodal stimulation given over the left frontal cortex during picture naming. Moreover, improvement of aphasia severity lasted for at least 2 months after the intervention, indicating that repeated individualized tDCS treatment might have lasting effects on language recovery after stroke.

In contrast, the beneficial effect of perilesional *facilitation* was explored by Szaflarski and colleagues [33] who demonstrated improved semantic fluency in 8 patients with chronic poststroke aphasia after intermittent theta-burst stimulation over the left IFG. The beneficial effect of facilitatory stimulation was underpinned by a leftward shift in language-related activation during subsequent fMRI.

Congruent with the previously observed improvement after perilesional facilitation [33], a recent study showed that anodal stimulation of the left primary motor cortex improves language recovery in patients with chronic aphasia after left-hemispheric stroke [149]. In that study, picture naming therapy over 2 weeks was combined with anodal or sham tDCS in two groups of aphasic patients. The authors reported significant improvement directly after treatment in both groups, with a slightly larger effect for trained items and a significantly larger effect for untrained items in the anodal tDCS group. Importantly, in a 6-month follow-up, treatment effects were significantly larger in the anodal tDCS group and transfer effects were only maintained in these patients. Moreover, functional communication was also more improved with anodal tDCS at both time points. Together, these results highlight the beneficial contribution of motor regions (or functionally connected areas) to language recovery and indicate that anodal tDCS effects might generalize to measures of functional communication that are highly relevant for everyday life.

Recently, the combination of contralesional inhibition and perilesional facilitation was established. For instance, Khedr and colleagues [150] reported significant language improvements after 10 repeated sessions of dual-site TMS combining inhibitory rTMS over the right Broca homologue with subsequent facilitatory TMS over the affected left-hemispheric Broca region in 13 patients with subacute aphasia (compared with 7 patients receiving sham rTMS). The beneficial effects of effective relative to sham TMS remained significant for 2 months after the end of treatment. Future studies in larger collectives should explore whether dual-site TMS proves more effective than unilateral TMS.

5.2. Open Questions and Future Directions. The above cited studies suggest that the combination of NIBS and language therapy might be promising to support aphasia recovery after stroke. Future studies in larger collectives should explore whether individual lesion size, location, and symptoms could be used to predict the efficacy of a specific individualized NIBS approach (cf. [148]). Indeed, it was suggested that the strong individual variation in response to different tDCS protocols might reflect differences in neural recovery mechanisms [151]. Of note, most of the previous studies investigated the beneficial effects of NIBS to support aphasia recovery on the behavioral level only. To increase the currently limited knowledge of (individual) recovery mechanisms, future studies should also elucidate the neural underpinnings of these effects in the reorganized brain.

As a first step, the results from studies in the healthy language network should be transferred to the lesioned brain to explore how NIBS can modulate neural activity and connectivity in the reorganized language system. In this context, it is worth to bear in mind that cognitive processes are not mediated by isolated neural areas but rather engage dynamic interactions among relevant regions [152]. In

particular, measures of functional and effective connectivity [153, 154] might capture NIBS induced changes in the causal network organization that might be more closely related to the neurobiological mechanisms by which NIBS changes a cognitive function compared to only analysing regional changes in neural activity [155]. Consequently, future patient studies should include the systematic application of both inhibitory and facilitatory NIBS protocols over perilesional as well as contralateral regions. Subsequent neuroimaging might elucidate mechanisms of plasticity in the reorganized language system. A better understanding of both the healthy and the lesioned brain's potential for adaptive plasticity would be mandatory to increase treatment efficiency in poststroke aphasia. Here, it is important to appreciate that recent tDCS results point towards altered functions of synaptic plasticity in the aging brain [156], which is of particular importance for the application of NIBS for neurorehabilitation purposes.

To provide further insights into the dynamics of network reorganization in the lesioned language network, longitudinal designs should explore the efficacy of different NIBS protocols across the time course of language recovery. This may include the application of different stimulation protocols during different phases of reorganization after stroke [157, 158]. These approaches should be informed by current models of language recovery after stroke. For instance, Saur et al. [117] argued that the contribution of perilesional and homologous right-hemispheric regions might change across the time course of recovery. Employing a longitudinal fMRI design, these authors reported that patients with poststroke aphasia after left-hemispheric stroke showed a global downregulation of language related activity in the acute phase after stroke. In the early subacute phase, language improvement was correlated with increased activity of the right hemisphere, with the strongest peak observed in the right Broca-homologue. In contrast, in the chronic phase, a normalization of language activity with a reshift towards the dominant left hemisphere was associated with further improvement. Although the role of the right hemisphere in language recovery after left-hemispheric stroke is still debated, this study implicates that an early, temporary recruitment of contralesional homologous regions may be beneficial, while longer-term language improvement is associated with a recruitment of perilesional left-hemispheric regions (see [159, 160]). Accordingly, Winhuisen et al. [161] argued that restoration of the left-hemispheric language network is more effective for language recovery after stroke, but in some cases, the right hemisphere is successfully integrated. Hence, the dynamic process of language recovery may involve a variety of plastic changes in both hemispheres [134]. With small left hemisphere lesions, complete or near-complete recovery may be achieved by recruitment of perilesional regions [162]. In contrast, for larger left hemisphere lesions, additional right hemisphere recruitment may subserve language functions, although such remodelled language networks might be less efficient than the premorbid left-hemispheric network [163]. Notably, additional factors such as premorbid laterality of language function and lesion site are important determinants of successful integration of right-hemispheric activity during poststroke reorganization in language networks [158].

A beneficial contribution of right hemisphere regions after left-hemispheric lesions further converges with the findings of the above discussed studies in healthy volunteers (cf. Section 4.1) that TMS-induced perturbation of the left hemisphere induced a compensatory upregulation and contribution of the right hemisphere during speech repetition [114] and language comprehension [122, 124–126]. This might indicate that the right hemisphere has the potential to support language functions of the dominant left hemisphere, probably by contributing more domain-general or supralinguistic functions such as (emotional) prosody and perceptual features of word stimuli. Indeed, it was argued that, in general, engaging the contralateral homologous area helps to preserve behaviour by taking over the specific function of the left hemisphere or contributing coarser computations for the same general processes [164, 165]. Notably, the beneficial effects of an acute flexible integration of homologous right-hemispheric regions after a left-hemispheric lesion might be restricted to the initial stages of adaptive compensation. Indeed, the effects of acute short-term plasticity induced by rTMS in the healthy network are most comparable with the immediate reorganization effects in the acute phase after stroke [163].

The above discussed results are summarized in a phase-specific NIBS approach to promote language recovery after left-hemispheric stroke in Figure 3. This model assumes that the contribution of left- and right-hemispheric regions to language recovery might change over time with an early beneficial contribution of right-hemispheric regions in the acute and early subacute phase after stroke and a stronger reshift of language-related activity to remaining left-hemispheric regions in later subacute and chronic phases.

It should be noted that although the majority of studies applied NIBS over the same regions across patients, irrespective of the individual lesion site and size, future studies might rely on individual recovery maps obtained from neuroimaging to identify target areas for NIBS across the time course of recovery. Most of the previous studies applied NIBS over the left or right anterior IFG to facilitate language recovery after stroke. However, at least with focal TMS, the effect might critically depend on the targeted subregion within the IFG (i.e., anterior versus posterior part) and the task under investigation. In this context, the systematic application of different NIBS protocols over various temporal regions should also be addressed. This should include the comparison of unifocal TMS effects with dual-site stimulation ([150], see above) and the systematic investigation of bilateral tDCS effects, for example, with the anode placed over a left-hemispheric language region and the cathode over the right-hemispheric homologue [166]. Other studies suggest that modelling the current flow on an individual basis might help to optimize NIBS effects at the target region and might thus be used to increase therapeutic efficiency in future studies [167].

Only recently, NIBS was combined with patient-relevant outcome measures such as improvement in functional communication ([149], see above). Such approaches are mandatory to assess the ecological validity of NIBS effects.

One remaining open question is related to the efficacy of novel modulatory techniques such as tACS and tRNS to

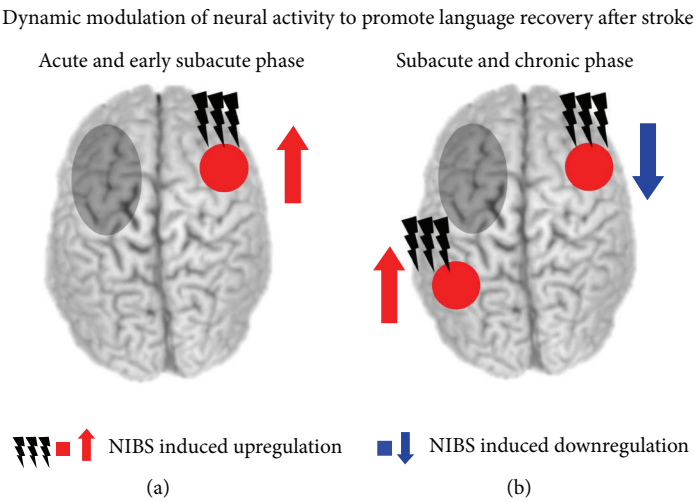


Figure 3: Illustration of a phase-specific stimulation approach to promote language recovery after left-hemispheric stroke. Note that the appropriate stimulation protocol might strongly depend on the site and size of the lesion and the individual deficits. (a) In the acute and early subacute phase, an upregulation of homologous right-hemispheric regions with facilitatory noninvasive brain stimulation (NIBS) might promote language recovery. (b) In the late subacute and chronic phase, patients might rather benefit from an inhibition of homologous right-hemispheric regions and an upregulation of ipsilesional regions by NIBS. Grey circles illustrate a stroke-induced lesion.

modulate language-related neural oscillations and thereby facilitate aphasia recovery. For instance, language recovery was associated with a decrease in the perilesional delta power in previous studies [168, 169]. Hence, future studies might probe whether NIBS induced modulation of abnormal slow wave patterns might be beneficial.

Finally, future studies in both the healthy and lesioned brain are mandatory to shed light on the biological mechanisms of plastic changes induced by different NIBS protocols. Here, simultaneous combinations of NIBS and electrophysiological or neuroimaging methods as well as the combination of NIBS and modelling approaches are particularly promising.

Competing Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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