

Plasticity of Language-Related Brain Function During Recovery From Stroke

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Background and Purpose—This study was undertaken to correlate functional recovery from aphasia after acute stroke with the temporal evolution of the anatomic, physiological, and functional changes as measured by MRI.

Methods—Blood oxygenation level–dependent contrast and echo-planar MRI were used to map language comprehension in 6 normal adults and in 2 adult patients during recovery from acute stroke presenting with aphasia. Perfusion, diffusion, sodium, and conventional anatomic MRI were used to follow physiological and structural changes.

Results—The normal activation pattern for language comprehension showed activation predominately in left-sided Wernicke's and Broca's areas, with laterality ratios of 0.8 and 0.3, respectively. Recovery of the patient confirmed as having a completed stroke affecting Broca's area occurred rapidly with a shift of activation to the homologous region in the right hemisphere within 3 days, with continued rightward lateralization over 6 months. In the second patient, in whom mapping was performed fortuitously before stroke, recovery of a Wernicke's aphasia showed a similar increasing rightward shift in activation recruitment over 9 months after the event.

Conclusions—Recovery of aphasia in adults can occur rapidly and is concomitant with an activation pattern that changes from left to a homologous right hemispheric pattern. Such recovery occurs even when the stroke evolves to completion. Such plasticity must be considered when evaluating stroke interventions based on behavioral and neurological measurements. (*Stroke*. 1999;30:749-754.)

Key Words: magnetic resonance imaging ■ aphasia ■ cerebral infarction ■ stroke outcome

The development of language in right-handed and most left-handed subjects involves many areas of the brain, including the superior temporal (Wernicke's area) and inferior frontal (Broca's area) gyri of the left hemisphere.¹ This view derives from many sources, including lesion studies and Wada tests.¹ Although knowledge of language processing during development remains rudimentary, the left hemispheric regions are believed to dominate language comprehension early in the process. If the left hemisphere becomes dysfunctional during development, neuroplasticity allows homologous regions in the right hemisphere to perform the same processes.² Recent neuroimaging studies with positron emission tomography (PET) of adult patients recovered from aphasia after left-hemisphere stroke have demonstrated right-sided activation for language processing.³ Similar results were reported for adult patients recovered from auditory agnosia.⁴ Functional recovery appears to be connected to activation of homologous regions of the contralateral hemisphere. Although some ipsilateral activation may also aid recovery, the possible bilateral representation before stroke has been raised as a possible explanation.⁵ Such previous studies were completed well after recovery from the clinical symptoms, leaving the temporal course of such changes uncharted.

Functional MRI (fMRI), a noninvasive method of measuring human brain function during cognition,⁶⁻⁹ has shown that a network of cortical areas contributes to language processing.^{10,11} For example, the difficulty of language comprehension during reading has been demonstrated to correlate with the degree of cortical activation.¹⁰ This association between task difficulty and fMRI activation has been generalized to other tasks including visuospatial processing.¹² This reading comprehension also includes brain activation associated with eye movement.¹³ Such cognitive paradigms are now being used to map eloquent cortical areas before surgical treatment of epilepsy.¹⁴ Such methodology allows the network of brain areas to be characterized not simply by network locations but also in terms of workload distribution between each location.

A modified¹⁰ simple sentence–reading paradigm for fMRI has been standardized in a group of normal subjects. Two separate clinical cases have been studied with fMRI to show the changes in activation patterns during the first months of the recovery period from stroke involving either Broca's area or Wernicke's area. The first patient with acute onset of expressive aphasia from left middle cerebral artery (MCA) stroke showed rapid recovery over the first few days. Although normal controls are useful, the question of language

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representation in a patient before stroke requires a study of the rare patient who has been mapped before stroke. The second patient was examined before and after stroke suffered during surgery for left temporal lobe epilepsy. The implications of these neuroimaging results are discussed in terms of recovered brain function and plasticity of large-scale networks.^{5,15,16}

Subjects and Methods

Informed consent followed the guidelines of the Institutional Review Board.

Control Group

Six healthy right-handed male college graduates (aged 26 to 31 years) served as control subjects.

Case 1

The patient was a 45-year-old right-handed man, on chronic anticoagulation medication for aortic valve replacement 7 years previously. He was a high school graduate with additional technical school training. He presented to medical attention with abrupt onset of a dense expressive aphasia and right-sided weakness. A left MCA stroke was suspected. Emergency CT showed no cerebral hemorrhage. Intravenous tissue plasminogen activator (tPA) was initiated within 3 hours of onset of symptoms. An MRI study was performed at 5 hours after onset of symptoms and more than 2 hours after commencement of thrombolytic therapy. Diffusion imaging confirmed the left MCA stroke, and perfusion imaging demonstrated persistent arterial occlusion. The patient recovered considerable language function over the next 3 days. Another comprehensive fMRI examination was performed at 76 hours and again at 6 months, by which time minor word-finding difficulties and a slight balance impairment were the only symptoms.

Case 2

The patient was a 34-year-old right-handed male college graduate with chronic epilepsy since sustaining a left-sided closed head injury at age 11 years. He had been poorly maintained on antiepileptic medication because of adverse effects. A CT examination demonstrated focal cortical calcification in the mid left superior temporal gyrus. When surgical intervention was contemplated to control his seizures to avoid the use of medications, fMRI using the language paradigm was performed before surgical placement of grid electrodes for cortical recording. Agreement between fMRI and cortical grid mapping was excellent, with Wernicke's area being placed about 2 centimeters posterior to the well-defined localized lesion in the left temporal lobe. The patient proceeded to surgery with limited resection of the small focal region of calcifications but not extending posteriorly into the area of language function documented by cortical electrodes. He awoke with a dense receptive aphasia. Functional MRI studies at 3 and 9 months, during which time language comprehension skills improved, were compared with the preoperative study. The pathology of the resected tissue diagnosed a ganglioglioma. The patient returned to work but still acknowledges having language difficulties since his surgery.

Imaging Protocol

All fMRI imaging was performed with a commercial quadrature head coil on either a 1.5- or 3.0-T whole-body scanner equipped with echo-planar imaging and large data-handling capabilities.^{8,9,17}

The comprehensive MRI protocol for patient studies, involving anatomic, diffusion, perfusion, and sodium imaging, has been reported elsewhere.¹⁸

Acquisition parameters for fMRI using gradient-echo echo-planar imaging at 3.0 T were as follows: TR=4000 ms; TE=25 ms; field of view (FOV), 40×20; voxel size, 3.1×3.1×3.0 mm³; slice thickness/gap, 3/1 mm; and n=18 slices. The 1.5-T parameters differed only in that TE was 50 ms and slice thickness was 5 mm.

The language comprehension paradigm^{8,10} consisted of 5 cycles of 2 conditions: (1) central fixation (rest condition, 30 s); and (2) silently reading simple sentences (mean length, 5.5 words) each followed by a question requiring a "true" or "false" answer indicated by pushing 1 of 2 finger switches (sentence condition, 30 s). The accuracy of responses (at least 79% in each session) to the comprehension questions assured that the patients were performing the required task. An additional condition, silent reading of word strings, is not reported because it produced similar results to the sentence-reading condition but provided no assurance of comprehension processing. This paradigm was chosen because it activates both Broca's and Wernicke's areas and can be used to detect changes in both expressive and receptive aphasias.

The fMRI data were analyzed using customized software,^{13,19} resulting in a 2-tailed paired *t* test comparison of the rest and active conditions of the paradigm for each voxel. The *t* test is a conservative statistical approach to analysis of fMRI data and emphasizes the most robust responses within the data. The volume of each activated region for each subject was measured as the number of voxels exceeding the chosen threshold ($t > 3.0$). This threshold minimized the number of randomly activated voxels while maximizing the number of reproducibly activated voxels for the subjects of the normal group. Higher thresholds did not change the patterns of activations, only decreasing the number of reproducibly activated voxels. Head motion was assessed by visual inspection of the images presented in a closed display loop. Three-dimensional display of the functional data was performed with software called AFNI¹⁹ to ensure that regions were appropriately labeled according to Talairach coordinates.²⁰ From our previous experience with eye movement¹³ and language¹⁰ paradigms in normal subjects, the areas of activation are Broca's area, Wernicke's area, supplementary eye fields, superior and inferior frontal eye fields, intraparietal sulcus, visual cortex, and prefrontal cortex. By counting the number of voxels in each region of interest, volumes of activation were determined. These volumes allowed hemispheric asymmetries to be expressed as the laterality ratio (LR) for each area: $LR = (\text{left} - \text{right}) / (\text{left} + \text{right})$, where LR equal to 1, 0, or -1 shows that activation is only in the left hemisphere, symmetrically distributed, or restricted to the right hemisphere, respectively.

Results

Normal Reading Comprehension

Figure 1 shows a representative activation map for the control subjects that identifies 8 regions bilaterally. This activation pattern represents a large-scale network^{15,16} that includes the 2 main language areas, Wernicke's and Broca's areas, which show left-sided asymmetry, irrespective of right- or left-handedness, as expected for adult language comprehension.^{1,5} The Table provides the means and standard deviations of these laterality ratios (LR) for these areas, showing that the asymmetry is particularly marked for Wernicke's area (LR, 0.8 ± 0.3) and less so for Broca's area (LR, 0.4 ± 0.4). By contrast, the activation associated with eye movement (superior frontal eye fields, inferior frontal eye fields, and intraparietal sulcus) showed laterality ratios close to 0, indicating bilateral symmetry.

Case 1

Structural Analysis

Selected anatomic, physiological, and metabolic images from the first (5 hours), second (76 hours), and third (6 months) MRI examinations after the abrupt onset of a dense expressive aphasia are shown in Figure 2. Although the T2-weighted image shows little change acutely (Figure 2a), an extensive cortical region of signal hyperintensity was present

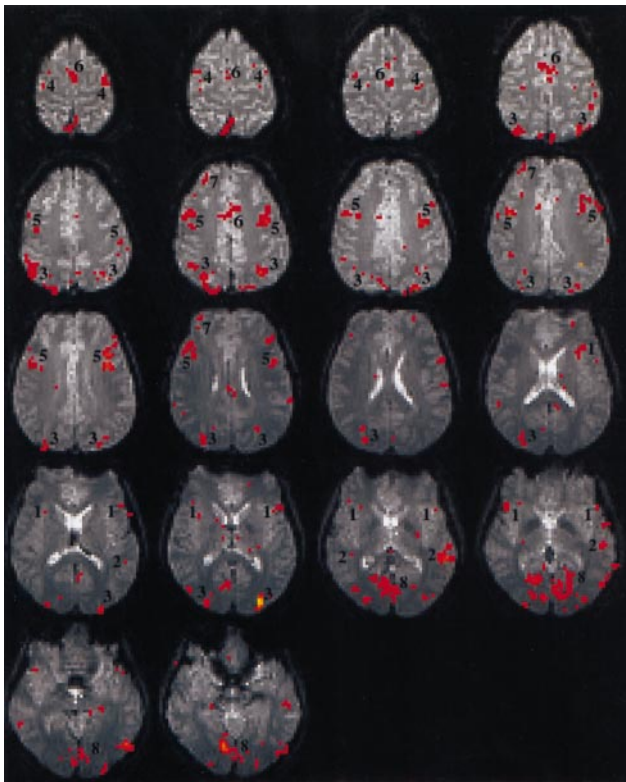


Figure 1. Representative axial activation map of a normal control for sentence reading comprehension showing the large-scale network of multiple active areas. Areas are labeled as 1, Broca's area; 2, Wernicke's area; 3, intraparietal sulcus; 4, superior frontal eye fields; 5, inferior frontal eye fields; 6, supplementary eye fields; 7, prefrontal cortex; and 8, visual cortex. Radiological convention (viewing the supine patient from the foot of the bed) has been used in all images, with the right-hand side of the subject on the left-hand side of the page.

on diffusion-weighted imaging (Figure 2b) that showed a reduced apparent diffusion coefficient (ADC [lesion], $0.58 \pm 0.09 \times 10^{-3} \text{ mm}^2/\text{s}$; ADC [normal gray matter], $0.97 \pm 0.09 \times 10^{-3} \text{ mm}^2/\text{s}$) from normal gray matter. Acutely, there was a persistent perfusion defect with prolonged tissue transit time (TTT [lesion], $>20 \text{ s}$; TTT [contralateral], 10 s). The tissue sodium image showed little change between the tissue sodium concentration of 45 mmol/L in the lesion and that on the contralateral side (Figure 2c). The subject was unable to perform the language paradigm during this examination at 5 hours after the event.

By 76 hours, considerable clinical recovery from the initial aphasia had occurred. The spin-echo images show markedly T2-hyperintense cortex along the left Sylvian fissure (Figure 2d) whereas little change occurred to the region of hyperin-

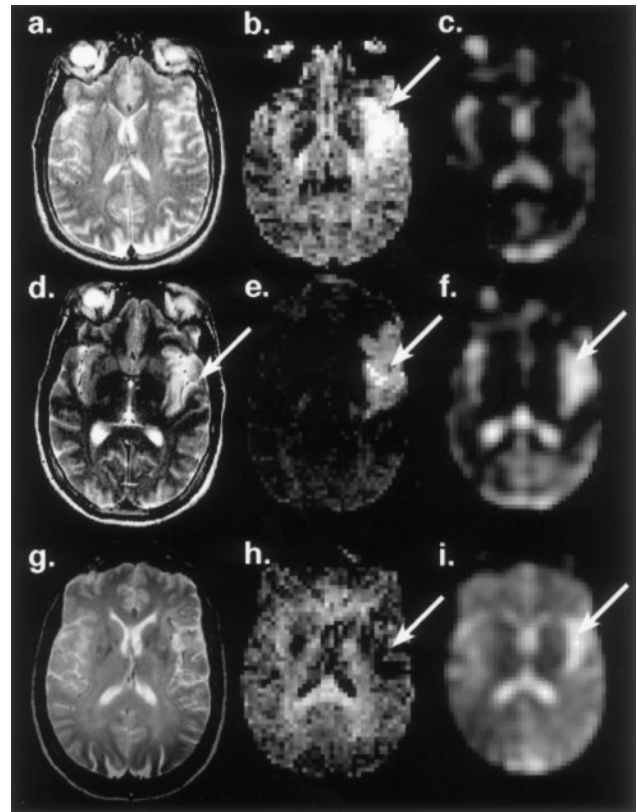


Figure 2. Images of patient 1 documenting the left-sided stroke (arrow) at 5 hours (top row), 76 hours (middle row), and 6 months (bottom row) after the event on representative slices of T2-weighted images (a, d, g), diffusion-weighted images (b, e, h), and sodium images (c, f, i). The lesion is diagnosed early by diffusion imaging. Infarction is documented by the elevated sodium levels by 76 hours.

tense signal on the diffusion-weighted imaging (Figure 2e), except for further reduction in ADC (ADC [lesion], $0.47 \pm 0.05 \times 10^{-3} \text{ mm}^2/\text{s}$; ADC [contralateral], $0.97 \pm 0.2 \times 10^{-3} \text{ mm}^2/\text{s}$). The sodium image (Figure 2f) showed increased TSC (TSC [lesion], 70 mmol/L; TSC [contralateral], 44 mmol/L) over an extensive area encompassing the abnormal ADC.

Selected images from the third MRI examination at 6 months after stroke, by which time the patient had only a few word-finding difficulties, are shown in Figures 2g, 2h, and 2i. The spin-echo images show markedly T2-hyperintense encephalomalacic change along the left Sylvian fissure and left inferior frontal region (Figure 2g). The region of signal hyperintensity on the diffusion-weighted imaging (Figure 2h) showed increased ADC as expected with old stroke (ADC

Laterality Ratios (\pm SD) for Activation in Wernicke's Area and Broca's Area for Reading Comprehension for Control Subjects (n=6) and Patients 1 and 2 at Different Times From Stroke

Brain Area	Control Subjects	Case 1		Case 2		
		76 hours	6 months	Before Stroke	3 mo	9 mo
Wernicke's area	0.8 ± 0.3	1.0	0.9	0.8	0.3	-0.6
Broca's area	0.4 ± 0.4	-0.8	-1.0	-0.2	0	0.2

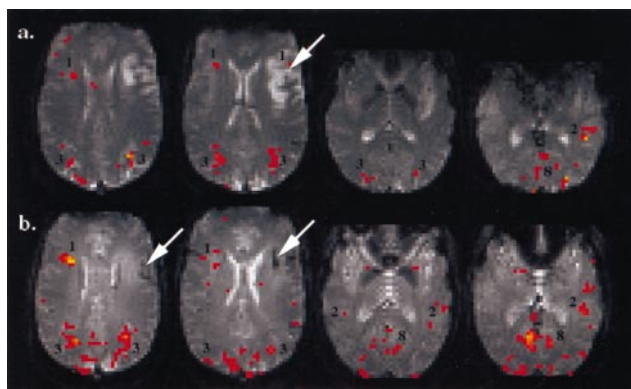


Figure 3. Activation maps of patient 1 at (a) 76 hours and (b) 6 months using the same paradigm and activation labels as in Figure 1.

[lesion], $1.86 \pm 0.32 \times 10^{-3}$ mm²/s; ADC [contralateral], $0.98 \pm 0.25 \times 10^{-3}$ mm²/s). The TSC abnormality (TSC [lesion], 74 mmol/L; TSC [contralateral], 49 mmol/L) was similar to the second examination. Thus, structural changes for patient 1 can be attributed definitively to a large stroke in the left MCA territory, as indicated by anatomic, diffusion, perfusion, and sodium imaging performed acutely and confirmed at follow-up, despite rapid clinical improvement over 3 days.

fMRI Analysis

The significant clinical recovery of patient 1 permitted fMRI studies with language to be performed at 76 hours and at 6 months, as shown in Figures 3a and 3b, respectively. The fMRI results show that this right-handed subject had an abnormal laterality ratio for Broca's area (the region affected by the stroke) by 76 hours, showing strong right dominance, in contrast to the normal left dominance. By 6 months, this abnormal cerebral dominance pattern progressed to being totally right-sided. Wernicke's area, which was structurally undamaged, was completely left dominant at 76 hours and remained strongly left dominant at 6 months. The changes involving several areas measured at 2 times support the hypothesis that clinical recovery was associated with rapid redistribution of the task over an existing large-scale network to allow rapid initial recovery within days, followed by consolidation of the new pattern over subsequent months. No new nodes of activation other than those observed in normal subjects were identified. Activation in areas related to eye movement were normal, indicating that not all of the areas activated during sentence reading had been disturbed by the lesion.

Case 2

Structural Analysis

Selected anatomic MR images before and at 3 months after stroke with resultant receptive aphasia are shown in Figure 4. Initially (Figure 4a and 4b), the epileptic lesion in the left temporal lobe was a focal region of hypointensity on T1- and T2-weighted images. At 3 months, an extensive cortical region of signal hyperintensity with encephalomalacia was present on T2-weighted images (Figure 4c). This corresponded to a T1-hypointense region (Figure 4d) consistent

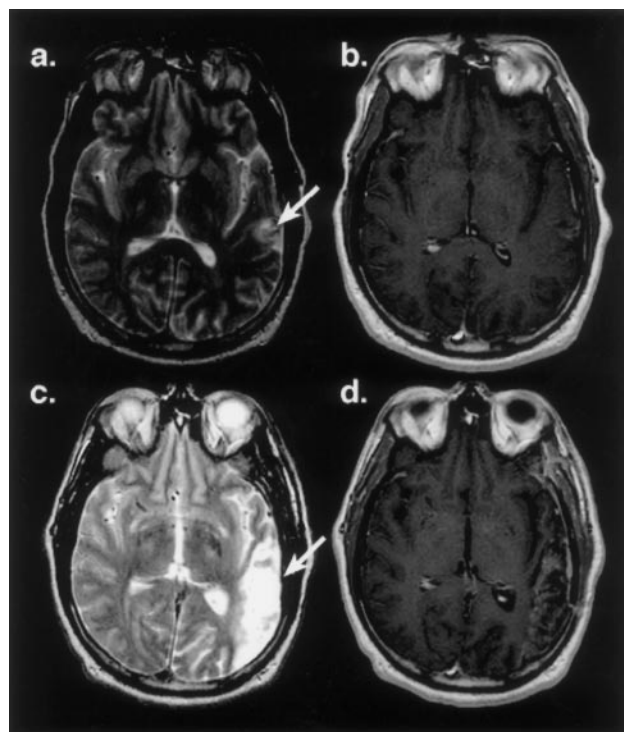


Figure 4. Images of patient 2 documenting the left-sided epileptic focus (arrow) before surgery (upper row) and after the stroke (arrow) at 3 months follow-up (lower row) using representative slices of T2-weighted images (a, c) and diffusion-weighted images (b, d).

with stroke. Differential damage to white matter surrounding the lateral angle of the frontal horn of the lateral ventricle and of the isthmus of the left temporal lobe have been related to the differential rates of recovery.²¹ The lateral angle was spared in patient 1, indicating that cingulate-supplementary motor area connections to the caudate nucleus were intact. In contrast, the isthmus of the left temporal lobe of patient 2 was at least partially involved in the stroke. Thus, patient 2 was confirmed as having a focal stroke in the superior temporal gyrus by anatomic imaging at 3 months after the event, during which time progressive recovery had occurred.

fMRI Analysis

The fortuitous availability of pre-event fMRI data from this subject afforded a rare glimpse of a documented shift in the hemispheric dominance after stroke. At 3 and 9 months, the subject participated in the same fMRI language study as used before surgery. The activation maps from these studies are shown in Figure 5. The laterality ratio of Wernicke's area changed progressively from strong left hemisphere dominance before the event to weak right dominance after 3 months and considerable right hemisphere dominance by 9 months. Although the stroke did not involve Broca's area, there was a slight shift from weak right dominance before the event to weak left dominance by 9 months. In general, the large-scale network seemed to be reestablishing function in an interactive way among its member nodes. No new regions of activation other than those observed in normal subjects were identified. Activation in the areas related to eye movement were normal, indicating again that not all of the areas

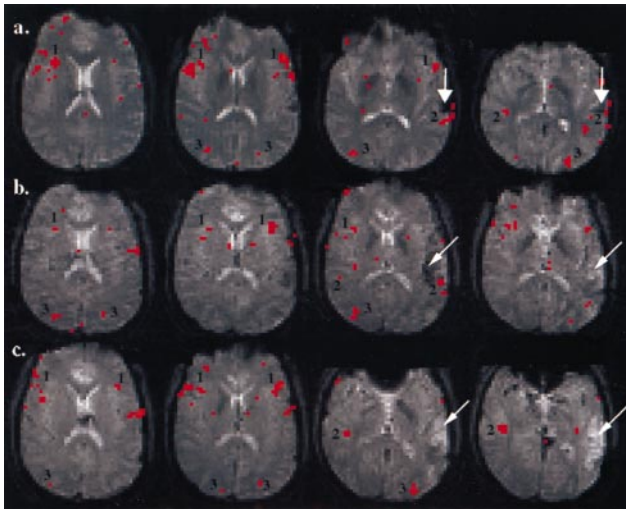


Figure 5. Activation maps of patient 2(a) before stroke with epileptic focus (vertical focus) and at (b) 3 months and (c) 9 months after stroke (oblique arrows) using the same paradigm and activation labels as in Figure 1.

activated during sentence reading were disturbed by the lesion. These observations support the hypothesis that recovery was associated with a redistribution of workload over the existing large-scale network, with consolidation occurring over many months.

Discussion

Because language function, like other higher level cognitive processes, is subserved by multiple brain areas,^{10,11} focal brain damage and subsequent recovery constitute a change to the large-scale network supporting such cognition. In the case of patient 2, with a long standing underlying disease process that may have influenced the development and maturation of the language network, we caution that this pattern of redistribution may not generalize to recovery patterns of patients with simple acute embolic stroke. However, the observations are that when a key node of a large-scale cortical network is damaged by a stroke, undamaged network components (namely, contralateral homologs) are increasingly recruited to increase their workload. Hence, as the workload of the remaining network is modified, a shift in cognitive workload can occur toward the contralateral hemisphere. There may also exist other patterns of compensatory cortical activation that have been observed in chronic patients years after stroke, such as increased activation in areas immediately adjacent to the lesion.⁵ Any of these long-term adaptations of a network constitutes a form of plasticity that is associated with recovery of language function after brain damage.⁵

The contribution of fMRI to the understanding of such phenomena is its ability to measure and characterize the activity of a large-scale cortical network and to noninvasively monitor any changes in its organization during the course of spontaneous or intervention-based recovery from stroke. The language paradigm used for these cases is a particularly useful one in that abnormal activation patterns were detected for both expressive and receptive aphasias. The evaluation of the effects of therapies to promote recovery from stroke,

whether they be pharmacological, surgical, or behavioral, can be guided by functional neuroimaging.

Involvement of contralateral areas of the brain after stroke in adults has been documented previously in aphasia recovery weeks after the event at low spatial resolution by cortical DC potential changes²² and in motor output recovery weeks to months after the event by magnetic transcranial stimulation,^{23,24} blood flow responses,²⁵ and motor-evoked responses.²⁵ The PET studies were performed months to years after recovery.^{3,4} The current study demonstrates a spontaneous redistribution of function to the right hemisphere that occurred within days and continued over months as performance normalized during recovery from aphasia. The results indicate the organizational flexibility of the cortical systems that underlie higher-level function.^{15,16} This information may be useful in designing future rehabilitation strategies that can exploit this flexibility.²¹ Given that even the adult has mechanisms of plasticity that can produce rapid functional recovery despite the evolution of infarction, functional neuroimaging is essential for distinguishing the success of acute stroke interventions from these innate compensatory mechanisms.

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