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Authors
Cramer, Steven C
Shah, Rajendra
Juranek, Jenifer
et al.

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Activity in the Peri-Infarct Rim in Relation to Recovery From Stroke

Steven C. Cramer, MD; Rajendra Shah, BSc; Jenifer Juranek, PhD; Kit R. Crafton, BS; Vu Le, MS

Background and Purpose—In the rim of tissue surrounding a cortical infarct, animal studies have described an increase in a number of growth-related processes that likely contribute to behavioral recovery. The current study hypothesized that in patients with good outcome after stroke, brain activation in peri-infarct tissue would be greater than normal.

Methods—In 15 patients with good recovery chronically after ischemic cortical stroke, activation within peri-infarct brain tissue was directly compared with activation within the same brain tissue of 13 control subjects.

Results—Although most patients did show activation within peri-infarct tissues, their activation compared with controls was reduced rather than increased. Evaluation of the T2*-weighted images underlying functional MRI mapping disclosed a significant gradient of increased T2* signal in peri-infarct tissues, likely attributable to tissue changes such as gliosis.

Conclusions—Among well-recovered stroke patients, cortical activation is present in the area surrounding a cortical infarct but is smaller than normal. A baseline derangement of the T2*-weighted signal underlying functional MRI (fMRI) is also present in this area, which might influence interpretation of fMRI findings. The relationship between increased tissue T2* signal and fMRI activation is not known and requires further study. **(*Stroke*. 2006;37:111-115.)**

Key Words: functional MRI ■ motor activity ■ neuronal plasticity ■ stroke

One aspect of brain function after stroke that has received limited study in humans is changes in the peri-infarct area surrounding a cortical stroke. Animal studies have described a wide range of molecular, cellular, and representational map changes in the peri-infarct area. Such changes occur at a greater than normal level, persist chronically, and often have been interpreted as important to post-stroke behavioral recovery.[1–3] Furthermore, in some cases, these events can be further amplified by therapeutic intervention, a phenomenon that has been associated with additional behavioral gains.[1,4] Consistent with these observations, studies in human stroke patients have found that the volume of threatened but surviving peri-infarct tissue is directly related to final clinical outcome.[5] Together, these observations suggest that restorative events in the peri-infarct area contribute to behavioral recovery after stroke.

A number of functional neuroimaging studies, using a range of methods, have described peri-infarct activation with chronic stroke.[6–10] However, the significance of these observations remains uncertain.[11] Peri-infarct activation has not been quantitatively evaluated in humans, although such analyses might provide additional evidence for a functional contribution of this area. This issue would be best addressed by determining whether activity in peri-infarct regions is greater after stroke compared with before, but such an approach is not possible. Instead, the current study addressed this issue by determining whether activation in peri-infarct regions of patients with cortical stroke is different from activation in the very same brain regions of healthy controls. The hypothesis of the current study was that among patients with good outcome after cortical stroke, activation in the brain tissue surrounding the stroke is greater than normal.

The blood oxygenation level-dependent (BOLD) method used to derive functional MRI (fMRI) measures relies on voxelwise signal changes on T2*-weighted images. With BOLD fMRI, neuronal activation is coupled with vascular responses such that increased activation reduces deoxyhemoglobin levels, which increases T2* signal, typically by 1% to 2% in motor system studies. Other pathological processes such as gliosis can also influence T2* signal.[12–15] Therefore, baseline resting T2* signal levels were also measured to gain further insight into the T2* signal fluctuations underlying peri-infarct fMRI activation.

Subjects and Methods

Subject Selection and Evaluation

Fifteen patients and 13 controls were studied. Entry criteria for patients, designed to increase the chance that fMRI sensorimotor probes would manifest in peri-infarct areas, were: (1) chronic unilateral ischemic cortical stroke visible on T1-weighted images,

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From the Department of Neurology (S.C.C., K.R.C.), University of Washington, Seattle; and Departments of Neurology, and Anatomy and Neurobiology, and the General Clinical Research Center (S.C.C., R.S., J.J., V.L.), University of California, Irvine.

Correspondence to Steven C. Cramer, MD, University of California, Irvine, UCI Medical Center, 101 The City Dr S, Building 53 Room 203, Orange, CA 92868-4280. E-mail scramer@uci.edu

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(2) stroke involved precentral or postcentral gyri, (3) stroke was associated with arm sensorimotor deficits at onset, and (4) very good motor recovery (Fugl–Meyer arm motor score >60/66) that had reached a plateau. Control subjects with no stroke and no active neurological disease were also enrolled. Consent was obtained in accordance with local human subjects committee. Immediately before scanning, subjects underwent detailed examination.

MRI Acquisition

Scanning was at 1.5 T and included: (1) T1-weighted high-resolution anatomical MRI with in-plane resolution 0.94 mm^2, 7-mm thickness, 14 axial slices below brain vertex that included the entire infarct, and (2) 2 fMRI runs that alternated 20 seconds of rest with 20 seconds of index finger movement that was either: (1) active, with index finger tapping 25° at the metacarpophalangeal joint at two thirds maximum tapping rate no faster than 2 Hz; or (2) passive, with index finger passively moved 25° at the metacarpophalangeal joint at 2 Hz. In patients, the affected body side was tested; in controls, the right side. An examiner at the subject's side during scanning observed and verified task performance. BOLD fMRI used T2*-weighted images with repetition time 2000, echo time 50, in-plane resolution 3.75×3.75 mm, the same 14 axial brain slices, 7-mm thickness, either 100 images/slice (5 rest–active cycles, for finger tapping) or 200 images/slice (10 rest–active cycles, for passive finger movement).

Data Analysis

Four anatomical region of interest (ROI) masks were created for each patient, the stroke and 3 peri-infarct rims, each of which contained only brain tissue (ie, no cerebrospinal fluid [Figure 1]). To generate these, first the stroke, which contained cystic and infarcted tissue, was outlined by hand on the high-resolution T1-weighted images then transformed into stereotaxic space, resulting in the stroke ROI. This was then dilated using a 3-voxel binary spherical structural element. The infarct was subtracted from this dilation leaving the rim 1 ROI, which was a rim of tissue immediately surrounding the infarct. Because of uncertainties regarding an MRI-based definition of the peri-infarct area,[16] 2 additional, larger peri-infarct rims were generated. The infarct was dilated twice, then the infarct and rim 1 were subtracted, resulting in the rim 2 ROI. Then the infarct was dilated 4×, from which the infarct, rim 1, and rim 2 were subtracted, resulting in the rim 3 ROI. For right hemisphere infarcts, activation maps and ROI masks were flipped to left. For each ROI, the total volume was determined, as was fraction of each ROI that was within cortical gray matter. To determine the latter, cortical gray matter was segmented of the T1-weighted images for each patient and control using the Functional Magnetic Resonance Imaging of Brain (FMRIB) automated segmentation tool along with a mask that removed deep gray matter structures.

Functional images were motion corrected to a single volume from the active task, followed by linear detrending and a voxelwise *t* test contrasting the rest and active states of each task, with results expressed as a Z-map. Studies with excess head motion, evident as a circumferential ring of activation or total absence of any activated voxels, were excluded. For each task, excess head motion was present in 2 patients and 1 control, leaving 13 patients and 12 controls per task.

A whole brain analysis identified activation clusters with size greater than that expected by chance ($Z>3$; $P<0.05$).[17] Activation maps were then spatially smoothed (4 mm filter) and converted to Talairach stereotaxic space[18] using the FMRIB Linear Image Registration Tool.

For each patient, their own 4 ROI masks were superimposed on: (1) their own finger-tapping activation map, plus (2) the finger-tapping activation maps of each control (Figure 1). Significantly ($Z>3$; ie, approximately $P<0.001$) activated voxels were then counted in each ROI. To verify results, secondary analyses were performed varying a number of assumptions, although primary analysis used finger tapping data at $Z>3$ threshold. First, analysis was repeated using data from passive finger movement activation maps. Second, analyses were repeated using 2 additional thresholds to define activation: $Z>2.3$ ($\approx P<0.01$) and $Z>4.2$ ($\approx P<0.00001$). Third, analyses were repeated using a ratio (number of voxels significantly activated in ROI/total number of significantly activated voxels in entire brain).

For each patient, the T2*-weighted images collected during the rest epochs of an fMRI run were further evaluated by measuring mean T2* signal in each of the 4 ROI masks. In patients and control subjects, mean T2* signal was measured in a mask of the entire brain that, for patients, excluded tissue in the 4 ROI masks.

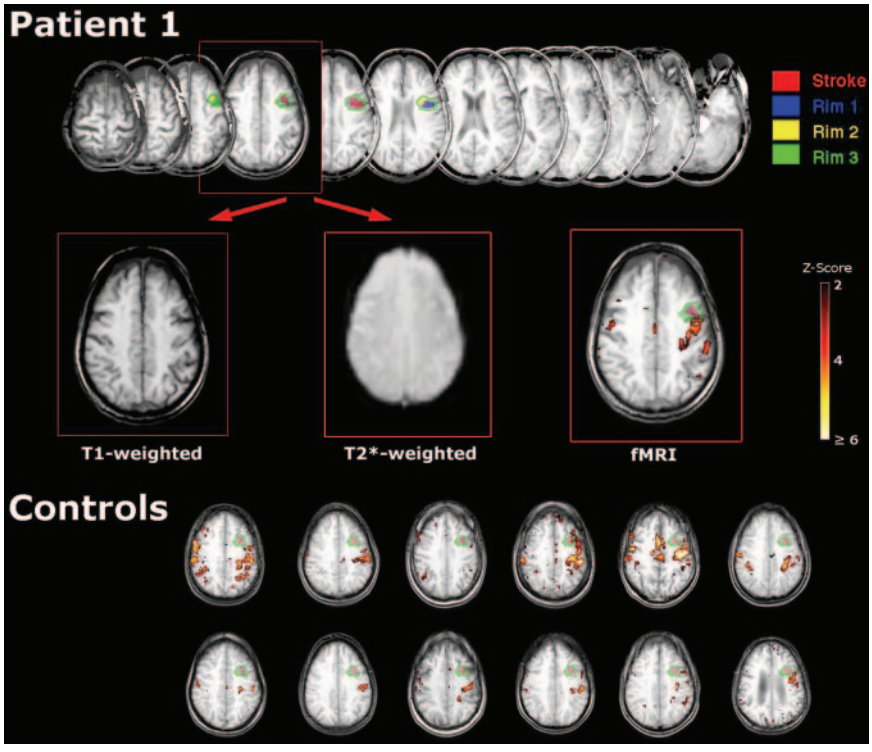

Figure 1. An example is provided of 1 of the patients plus the 12 control subjects during finger tapping. For patient 1, the top row shows the anatomical MRI with the stroke ROI plus 3 peri-infarct rim ROIs superimposed. For a representative slice that includes the infarct (Talairach z=+39), the second row shows the T1-weighted image, the T2*-weighted image, as well as the 4 ROIs for this patient superimposed on fMRI activation. For each of the 12 controls, respective fMRI maps were then analyzed after superimposing the 4 ROIs of patient 1. The third row shows the same representative slice (z=+39) for controls.

Statistics

The study hypothesis is that within the brain tissue surrounding an infarct, each patient will have increased activation volume compared with values measured in control subjects. If increased activation is defined as a larger activation volume than all 12 controls for a given task, then the probability of this by chance in 1 patient, based on a binominal distribution, is 0.647; that at least 2 of 13 patients will have larger activation than all controls, 0.264; for ≥3 patients, 0.073; and for ≥4 patients, 0.014. Thus, for the data to support the hypothesis in a given ROI at $\alpha=0.05$, ≥4 patients would need to have activation larger than all 12 control subjects. If increased activation is instead defined as patients consistently activate in the top 30% of controls, then the probability of observing this by chance in ≥2 patients is 0.943; and in ≥8 patients, 0.02. Other study comparisons used nonparametric statistics.

Results

In patients, acute motor deficits varied from mild to severe but by time of fMRI were mild (Table). Proprioceptive function was normal in 13 and mildly reduced in 2 patients. All patients received poststroke physiotherapy. The cervical internal carotid artery ipsilateral to stroke was without significant disease in 11 patients, 70% to 79% narrowed in 1, and occluded in 3. Six patients had a previous stroke that was distant from the cortical stroke of current interest. Patients were median 4.5 months poststroke (range 1.5 to 115) at time of fMRI. Excess head motion corrupted data from 2 of 15 patients and 1 of 13 controls for each fMRI task. Approximately half of the infarct was restricted to cortical gray matter (mean 44%; range 22% to 84%; Table).

Demographic and MRI Data

	Patients	Controls	*P*
n	15	13	
Age, y	57±13	49±18	NS
Gender	7 M/8F	7 M/6F	NS
Handedness	14R/1L	13R	NS
Fugl–Meyer arm motor score	64±2	66	<0.005
Pegboard performance^	0.72±0.32	0.93±0.09	<0.07
NIHSS score	1	0	<0.001
Modified Rankin scale	1	0	<0.0001
Side of stroke	8R/7L		
Activation volume (voxels)*			
Infarct	138±250	1029±862	0.0005
Rim 1	124±210	370±255	<0.005
Rim 2	262±379	755±511	<0.005
Rim 3	598±664	1590±1051	<0.05
Volume in mL of (and % in cortical gray matter of)			
Infarct	12.6±18.3 (44±21%)		
Rim 1	80±89 (33±12%)		
Rim 2	137±129 (26±7%)		
Rim 3	300±228 (25±5%)		
Distance (mm) from stroke edge to center of			
Rim 1	6.4±2.6		
Rim 2	17.4±6.8		
Rim 3	28.0±9.9		

Values are mean±SD, otherwise median. ^Pegboard performance is expressed as affected/unaffected hand for patients and left/right hand for controls; *activation is in voxels (98.4 mm^3) during index finger tapping thresholded with significance Z>3.

During tapping, 4 of 13 patients tapped slower than 2 Hz because two thirds maximum tapping rate was 1 to 1.4 Hz, and 1 patient tapped slower than instructed. As a result, mean patient tap rate was slightly slower than controls (1.7±0.4 versus 2.0 Hz; $P=0.04$). For 2 patients, middle finger movements rarely accompanied index finger taps. All 25 passive movement studies were performed at 2 Hz.

The data did not support the study hypothesis because 0 of 13 patients had activation that was larger than all 12 controls subjects in any of the 3 peri-infarct rims. Furthermore, 0 of 13 patients had activation that was among the top 30% of control values in any of the 3 peri-infarct rims. Within the infarct, stroke patients had activation (Table), likely attributable to partial volume averaging, that was subnormal, being 0, or less than all controls, in the same tissue in 7 of 13 patients during tapping and in 11 of 13 patients during passive movement.

Most (10 of 13) patients did activate in peri-infarct tissue during finger tapping. However, within each of the 3 peri-infarct rims, the mean activation volumes for patients were reduced versus the mean activation volume in controls within these same brain ROIs (Table). In the peri-infarct rims of the 3 patients who did not show such activation, 11 to 12 of 12 controls did.

Approaching the hypothesis by varying fMRI methods resulted in the same findings. Results during passive finger movement were nearly identical to results during finger tapping. Also, measuring activation volume as a ratio of total brain activation, rather than as voxel counts, overall had negligible effect on results. In addition, results using Z>2.3 or Z>4.2 as the threshold to define significant activation were nearly identical to above findings derived using Z>3.

Although patients showed a range of activation volumes in each rim, peri-infarct activation volume did not correlate with clinical status. Neither the Fugl–Meyer motor score nor the Purdue pegboard performance correlated with activation volume at Z3 threshold in any of the 3 peri-infarct rims. Note that patients with versus patients without carotid disease did not have a significant difference in activation volumes.

Among the 15 patients, there was a significant gradient of increased T2* signal intensity in the peri-infarct area. Mean T2* signal inside the infarct was 5% greater than signal inside rim 1 ($P<0.05$; 2-tailed signed-rank test), which was 1% greater than signal inside rim 2 ($P<0.05$), which was 3% greater than signal inside rim 3 ($P<0.005$; Figure 2). The total brain T2* signal in patients was not significantly different from rim 3 in patients or from total brain T2* signal in controls.

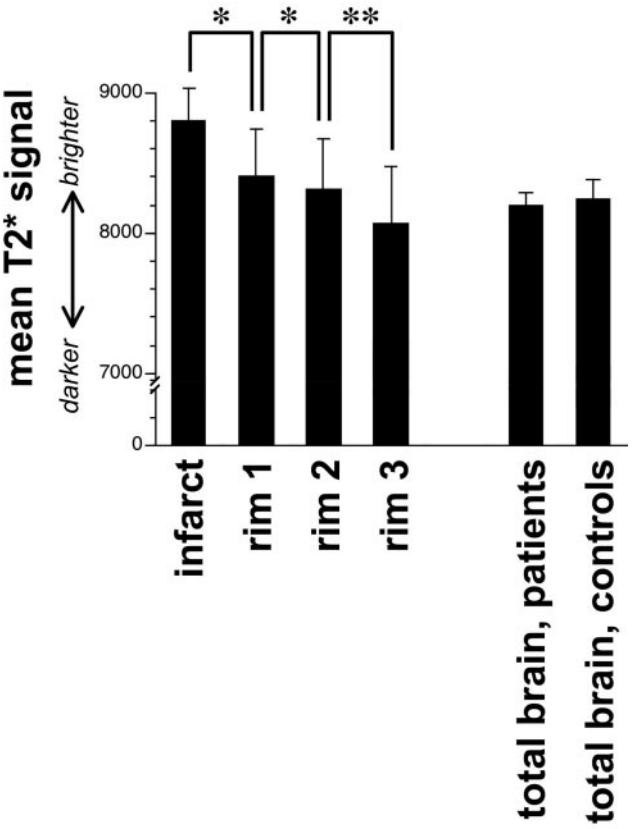

Figure 2. The mean (±SEM) T2* signal intensity is shown for each of the 4 ROIs across patients. Note that mean T2* signal in total brain of patients was not significantly different from rim 3 of patients or from total brain of controls. *$P<0.05$; **$P<0.005$ by signed-rank test.

Discussion

fMRI evaluated brain tissue surrounding an ischemic cortical infarct in patients with good behavioral recovery. Based on animal data, the study hypothesized that peri-infarct activation would be greater than normal. Although most patients did show peri-infarct activation, patients actually had significantly reduced peri-infarct activation compared with activation of the same brain tissue in healthy controls. In addition, peri-infarct tissue was found to have a gradient of significantly increased T2* signal, the MRI measure underlying fMRI mapping, and this change in tissue T2* might influence interpretation of fMRI findings. The relationship between these 2 findings is not known and requires further study.

Animal studies suggest that changes in the cortical areas surrounding an experimental infarct might be important to behavioral recovery. A range of events has been found to be increased compared with the normal state, and some remain increased chronically, such as levels of growth-related proteins[1,19] or expansion of representational maps.[2] Increased infarct rim activation is associated with return of behavioral function,[20] and interventions that amplify growth-related peri-infarct events are associated with improved outcome.[1,4]

Some data suggest that similar peri-infarct events contribute to behavioral recovery after stroke in human patients. The volume of threatened but surviving peri-infarct tissue is directly related to final clinical outcome,[5] possibly reflecting a restorative role by peri-infarct tissues. A number of functional neuroimaging methods have described peri-infarct activation chronically after stroke.[6–10] If fMRI activation is taken to reflect neuronal activity,[21,22] these animal and human observations suggest that peri-infarct activation increases in parallel with recovery after stroke.

The current study, using BOLD fMRI activation, tested this hypothesis, ie, that the volume of peri-infarct tissue activation is increased with good behavioral recovery. However, the main finding of the current study is that patients had decreased peri-infarct activation compared with controls. Furthermore, the volume of activation did not correlate with the final level of motor function. The findings do not support the hypothesis.

The other main finding in the current study is that T2* signal is increased in the area surrounding a cortical infarct. The T2* finding in patients likely represents a gradient in pathological processes such as gliosis, demyelination, ischemic injury, or Wallerian degeneration.[12–15] This increased T2* signal was found in tissue judged to be normal on T1-weighted images; even if infarct outlining by investigators was imprecise and rim 1 included some infarcted tissue, inclusion of infarcted tissue in rim 2 would be unlikely, and even this rim had mean T2* signal greater than rim 3. An alternative interpretation is that the reduced T2* signal with greater distance from infarct is attributable to increased hemorrhage, given that chronic blood reduces signal on T2*-weighted images.[23] However, stroke in the current patient cohort was ischemic without hemorrhagic conversion. The observed T2* signal gradient might be useful toward the study of peri-infarct events after stroke, eg, toward the goal of an MRI method for defining the peri-infarct zone.[16]

The relationship between peri-infarct tissue increased tissue T2* signal and reduced BOLD fMRI activation is not known. If there is no significant relationship, then the current data suggest that peri-infarct neuronal events, at least those captured by fMRI, do not increase to supranormal levels in humans with stroke. The basis for such a result might include loss of input to the peri-infarct areas from the region of infarct.[3] Methods that capture peri-infarct neuronal activity differently (eg, via electrophysiology)[24] might provide different answers. Peri-infarct abnormalities of neuronal–vascular coupling might be relevant, although data suggest that the latter is not likely a major factor after 4 weeks after stroke.[9] Peri-infarct activation might be an epiphenomenon that primarily reflects shifts in somatotopic maps. Such shifts might depend on topography of injury[25,26] and can sometimes take years to arise,[25] factors that might have influenced current findings. Extent of peri-infarct fMRI activation might be related to features of acute stroke diffusion–perfusion mismatch[27] not measured in the current study.

However, if increased baseline T2* signal does affect BOLD fMRI, then BOLD fMRI measurements might fail to actually test the hypothesis in the ≈3 cm (rims 1 and 2; Table) of brain surrounding a cortical infarct, ie, where T2* signal was found to have a gradient of increase. Other variables have been suggested to reduce BOLD fMRI activation such as increased age[28] or advanced arterial disease.[29] Specific studies are needed, possibly experimental studies in

animals, to determine whether and how changes in baseline T2* affect BOLD fMRI activation.

Weaknesses of the study include the need to flip images for patients with right hemisphere stroke. Disease in the internal carotid artery might have dampened activation in 4 patients, although activation in these 4 subjects was not significantly different from the other patients, and the main study finding was robust across the entire patient cohort using a range of methods to define significant activation. The slower tapping rate in 4 patients, while controlling for effort, might have had a very slight effect on activation volumes. Vasomotor reactivity, which might have provided insights into reduced fMRI activation,[30] was not measured. Study strengths include evaluation of a relatively uniform form of stroke pathology, cortical stroke with good behavioral outcome. All patients had involvement of a peri-Rolandic gyrus, increasing the chances that the fMRI motor and sensory probes would manifest in the peri-infarct areas.

The current study found that activation in the tissue surrounding a cortical infarct as measured with fMRI is present but reduced. The robustness of the findings was confirmed by varying a number of experimental details. The data do not support the hypothesis that peri-infarct activation is increased after cortical stroke. Importantly, the current study also found that T2* signal was significantly increased in tissue surrounding a cortical infarct. Any effect that increased tissue T2* has on BOLD fMRI activation might modify the interpretation, or perhaps the utility, of BOLD fMRI in certain brain regions of patients with stroke. However, the effect that increased T2* has on BOLD fMRI is not known and requires further study.

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