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Use of Functional MRI to Guide Decisions in a Clinical Stroke Trial

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Background and Purpose—An investigational trial examined safety and efficacy of targeted subthreshold cortical stimulation in patients with chronic stroke. The anatomical location for the target, hand motor area, varies across subjects, and so was localized with functional MRI (fMRI). This report describes the experience of incorporating standardized fMRI into a multisite stroke trial.

Methods—At 3 enrollment centers, patients moved (0.25 Hz) the affected hand during fMRI. Hand motor function was localized at a fourth center guiding intervention for those randomized to stimulation.

Results—The fMRI results were available within 24 hours. Across 12 patients, activation site variability was substantial (12, 23, and 11 mm in x, y, and z directions), exceeding stimulating electrode dimensions.

Conclusion—Use of fMRI to guide decision-making in a clinical stroke trial is feasible. (*Stroke*. 2005;36:e50-e52.)

Key Words: magnetic resonance imaging ■ motor activity ■ neuronal plasticity ■ stroke

Functional areas such as hand motor representation site do not have a precise correspondence with brain anatomy. Identifying functional areas requires some form of brain mapping.

Localizing functional areas underlies the effectiveness of some approaches to stroke therapy. Reports in rodents,¹ primates,² and humans³ have described motor gains after introducing such targeted stimulation after stroke. A recent clinical trial examined safety and motor effects of epidural motor cortex stimulation in chronic stroke patients (Lutsep et al, submitted data, 2004).

The underlying hypothesis of that trial was that stimulation of hand area of motor cortex, identified using functional MRI (fMRI), would increase physical therapy-derived motor gains. However, published fMRI data acquisition methods vary substantially. To address the hypothesis in the context of a multicenter study, therefore, implementation of a standardized fMRI protocol was necessary. The current report describes the approach and feasibility of this goal. In addition, fMRI examined effects of cortical stimulation on motor system function. To our knowledge, this is the first use of functional neuroimaging to guide decision-making in a stroke trial.

Materials and Methods

At each of 3 medical centers, patients with chronic ischemic stroke and arm paresis underwent fMRI scanning followed by randomization to 3 weeks physical therapy with/without epidural motor cortex

stimulation with an investigational device, followed by repeat fMRI. A full report of trial clinical/safety outcomes is reported elsewhere (Lutsep et al, submitted data, 2004).

At each site, patients underwent fMRI alternating 20 seconds rest and 20 seconds 0.25-Hz paretic index finger tapping, or, if this task could not be performed, wrist extension. These cycles were repeated for a total of 280 to 300 volumes. Each site used 1.5-T MRI (2=GE, 1=Siemens), repetition time=2000 ms, echo time=50 ms, in-plane resolution 3.75×3.75 mm, and field of view that included cerebral vertex to Sylvian fissure via 5-mm axial slices (interslice gap 0 to 1 mm).

Scans were digitally transmitted to a central laboratory where 2 investigators (R.R.B., V.C.B.) processed the images. Motion correction and in-plane spatial smoothing (6-mm full-width half-maximum, SPM99) were followed by linear detrending and generation of statistical maps contrasting movement with rest. Within 24 hours, images were reviewed by a single investigator (S.C.C.) who determined coordinates for the voxel of interest (VOI), ie, the voxel with the highest Z-score within the largest activation cluster, thresholded at $Z > 3$, on posterior precentral gyrus of the stroke-affected hemisphere. VOI location was indicated on coregistered high-resolution anatomical images. Images were prepared for each hospital's neuronavigational system and then transmitted.

For patients randomized to neurosurgery, an investigational epidural electrode (effective stimulation area 18×18 mm) was centered over the fMRI-identified VOI. The epidural stimulator was connected to a stimulator that was switched on during physical therapy and removed after 3 weeks. For all patients on protocol, fMRI scans were repeated after completion of therapy. Group maps⁵ were created for fMRI scans acquired before, and after, therapy.

Results

An fMRI scan was performed in 13 patients, with excess head motion contaminating 1. Of the remaining 12, 7 performed

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Demographic and fMRI Findings

No.	12
Age, y	61 (33–74)
Gender	6 M/6F
Arm affected	8R/4L
Handedness	9R/2L/1A
Months after stroke	23 (9–68)
Baseline arm motor Fugl–Meyer score	39 (24–48)
Stroke location	
Brainstem	1
Cortical	2
Subcortical	6
Cortical+subcortical	3
VOI, primary motor cortex	
Talairach x-coordinate	34 (28 to 40)
Talairach y-coordinate	–27 (–16 to –39)
Talairach z-coordinate	48 (40 to 51)

Median values, range in parentheses.

A indicates ambidextrous; F, female; L, left; M, male; R, right; VOI, voxel of interest.

index finger tapping during fMRI; 5 performed wrist extension. All 12 patients (Table) had an activation cluster involving stroke hemisphere posterior precentral gyrus, in which the VOI could be identified. The VOI was on posterior precentral gyrus in 7, central sulcus in 2, and 1 each for anterior postcentral gyrus, medial precentral gyrus, and precentral sulcus.

VOI location varied substantially across patients (Figure). Across all 12 patients, the range was 12 mm for Talairach (Tal)-x, 23 mm for Tal-y, and 11 mm for Tal-z, using absolute values for Tal-x. There were no significant differences in VOI Tal-x, Tal-y, or Tal-z coordinates between index finger tapping (n=7) and wrist extension (n=5, $P>0.25$, Wilcoxon test for each Tal coordinate). VOI location did not correlate with time after stroke or baseline arm motor Fugl–Meyer score.

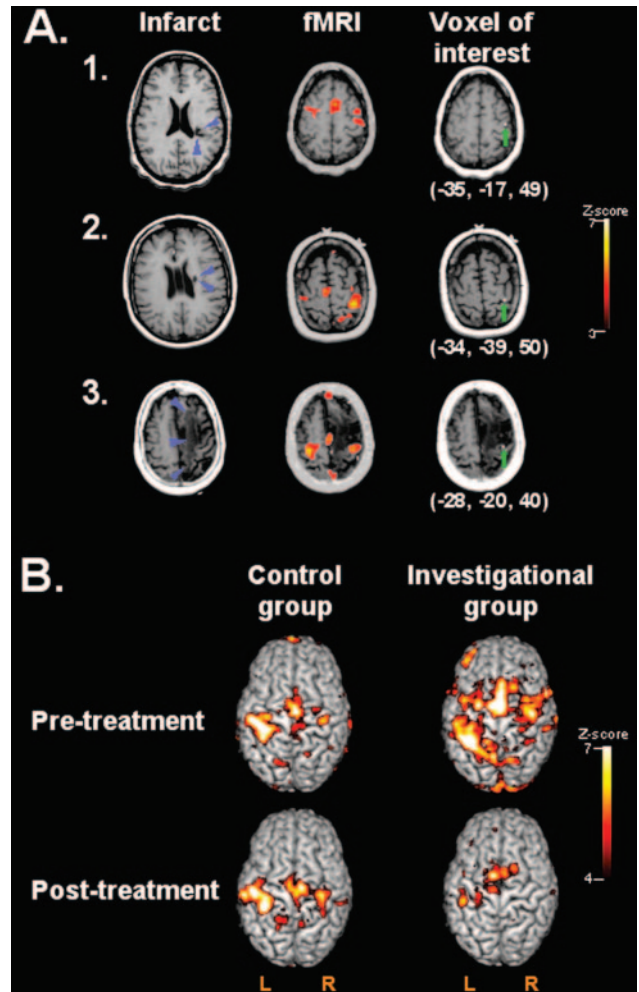
Of the 12 patients who passed fMRI screening, 2 did not meet additional clinical entry criteria. Four were randomized to the control group. Six were randomized to the investigational device, 2 of whom did not complete protocol, 1 because of infection and 1 because of a lead break.

Among these 6 patients, intraoperative motor evoked responses (MEP) were generally concordant with fMRI results. Using a range of MEP settings, VOI stimulation evoked movement in stroke-affected index finger in 3, ring finger in 1, deltoid in 1, and nowhere in the patient with the lead break.

After completion of the 3-week protocol, the 4 remaining investigational device patients showed significant arm motor improvement versus the 4 control patients (Lutsep et al, submitted data, 2004). Follow-up scans showed reduced fMRI activation volumes, particularly in investigational device patients (Figure).

Discussion

The current report describes successful and rapid implementation of fMRI to localize motor function in the context of a



A, Results in 3 patients during index finger tapping demonstrate anatomical variability in hand motor site. Blue arrowheads=infarct. Column 2=fMRI slice with VOI. Green arrow=VOI. Numbers=xyz-Talairach coordinates. Images flipped left–right for patients 1 and 3. B, Group fMRI maps.⁴ Activation showed small change in control patients (n=4) who underwent physical therapy only but larger reductions in investigational patients (n=4) who underwent physical therapy plus targeted subthreshold cortical stimulation. Baseline activation was larger in investigational patients even though the 2 groups were matched clinically (Lutsep et al, submitted data, 2004). Fixed-effects analysis found scan1–scan2 had significant ($Z>4$, $P<0.05$) foci in control patients, eg, 2004 mm³ in stroke hemisphere motor cortex (27, –26, 55) Larger foci were found in investigational patients, eg, 18 613 mm³ in stroke hemisphere parietal cortex (17, –55, 52) but not in stroke hemisphere motor cortex.

multicenter clinical trial. Implementation of other brain mapping methods in a clinical trial setting is likely also feasible.

Hand motor VOI showed substantial variation in location after stroke, as described previously.⁵ The range was similar to the range in healthy controls⁶ and approximated electrode size. These data emphasize the anatomical variability in human motor system functional organization.

Cortical stimulation was associated with reduced activation volume over time. This might correspond to motor learning,⁷ events seen during spontaneous stroke recovery,⁸ remote effects of stimulation,⁹ or thalamic plasticity.¹⁰

Strengths of the study include uniform image acquisition parameters and analysis methods, plus rapid data analysis across sites spanning a continent. Weaknesses include different MRI manufacturers and lack of correction for echoplanar imaging distortions. Use of >1 motor activation task increased heterogeneity of fMRI results but might have controlled for effort. MEP results were largely but imperfectly concordant with fMRI maps. Use of consistent MEP methods and correction of echoplanar-based distortions might have improved concordance.

Some restorative therapies undergoing development are systemic. Others target specific brain areas and benefit from use of brain mapping when the target is defined in functional rather than anatomical terms. In this regard, the current study aimed to evaluate a standardized fMRI protocol for rapid localization of hand motor function in the context of a multicenter clinical trial. The findings support the feasibility of this approach.

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