Title
Mapping individual brains to guide restorative therapy after stroke: Rationale and pilot studies

Journal
Neurological Research, 25(8)

ISSN
0161-6412

Authors
Cramer, Steven C
Benson, Randall R
Burra, Vijaya C
et al.

Publication Date
2003-12-01

DOI
10.1179/016164103771953899

Mapping individual brains to guide restorative therapy after stroke: Rationale and pilot studies

Steven C. Cramer*, Randall R. Benson†, Vijaya C. Burra†, David Himes‡, Kit R. Crafton*, Jeri S. Janowsky§, Jeffrey A. Brown¶, Helmi L. Lutsep§

*Department of Neurology, University of California, Irvine, Irvine, CA
†Department of Neurology, Wayne State University, Detroit, MI, ‡Northstar Neuroscience; Seattle, WA
§Department of Neurology, Oregon Health & Science University, Portland, OR
¶Department of Neurosurgery, Wayne State University, Detroit, MI, USA

Some treatments under development to improve motor outcome after stroke require information about organization of individual subject's brain. The current study aimed to characterize normal inter-subject differences in localization of motor functions, and to consider these findings in relation to a potential treatment of motor deficits after stroke. Functional MRI (fMRI) scanning in 14 subjects examined right index finger tapping, shoulder rotation, or facial movement. The largest activation cluster in left sensorimotor cortex was identified for each task, and its center expressed in Talairach stereotaxic coordinates. Across subjects, each task showed considerable variability in activation site coordinates. For example, during finger tapping, the range for center of activation was 7 mm in the x-axis, 19 mm in the y-axis, and 11 mm in the z-axis. The mean value for center of activation was significantly different for all three coordinates for all pairwise task comparisons. However, the distribution of activation site centers for the finger task overlapped with the other two tasks in the x- and y-axes, and with the shoulder task in the z-axis. On average, the center of activation for the three motor tasks were spatially separated and somatotopically distributed. However, across the population, there was considerable overlap in the center of activation site, especially for finger and shoulder movements. Restorative therapies that aim to target specific body segments, such as the hand, in the post-stroke motor system may need to map the individual brain rather than rely on population averages. Initial details are presented of a study using this approach to evaluate such a therapy.
[Neurol Res 2003; **25**: 811–814]

Keywords: Stroke; motor cortex; somatotopy; functional MRI; therapy; plasticity

INTRODUCTION

Stroke remains the leading cause of adult disability[1]. The most common impairment after stroke, and a major contributor to disability, is weakness[1,2]. Acute thrombolytic therapy can reduce long-term disability after stroke[3–5], however, few patients in the US reach a medical facility early enough to be eligible for such interventions[6]. Therefore, increased attention has been focused on improving neurological status with therapies administered in the subacute or chronic phase of stroke.

Animal studies have suggested a number of potentially useful therapeutic strategies for patients who have passed the acute phase of stroke. One such approach involves focal cortical stimulation, with the intent being to improve behaviors arising from the stimulated cortical region. Studies supportive of this approach are reviewed elsewhere in this journal.

Animal studies use direct cortical stimulation to target the cortical area in which the function of interest is localized. This is generally not possible in human stroke patients. In such a situation, one might hope to stimulate cortex with respect to anatomical landmarks. However, the human brain shows substantial variability in the localization of functions such as language and movement. Thus, across subjects, sites of functional organization do not correspond precisely to features of brain anatomy[7–11]. Moreover, even within subject, functional localization can change in relation to short-term and long-term experience, disease, age, and other variables[11–17].

The first purpose of the current report is to characterize, at the individual level, inter-subject variability in the localization of hand motor function, and to contrast these findings with localization of shoulder and face motor function. Results support the need to map individual subjects when localizing motor function, rather than rely on a single set of coordinates. The second purpose of this report is to provide initial details of a study that utilizes this approach in the treatment of patients with chronic stroke.

MATERIALS AND METHODS

Subjects

Fourteen healthy subjects were studied. Each was right-handed[18], free of neurological disease, and gave informed consent. This study was performed at the University of Washington, where it was approved by the human subjects committee.

Correspondence and reprint requests to: Steven C. Cramer, MD, University of California, Irvine, Department of Neurology, UCI Medical Center, 101 The City Drive South, Building 53 Room 203, Orange, CA 92868-4280, USA. [scramer@uci.edu] Accepted for publication June 2003.

0161–6412/03/080811–04

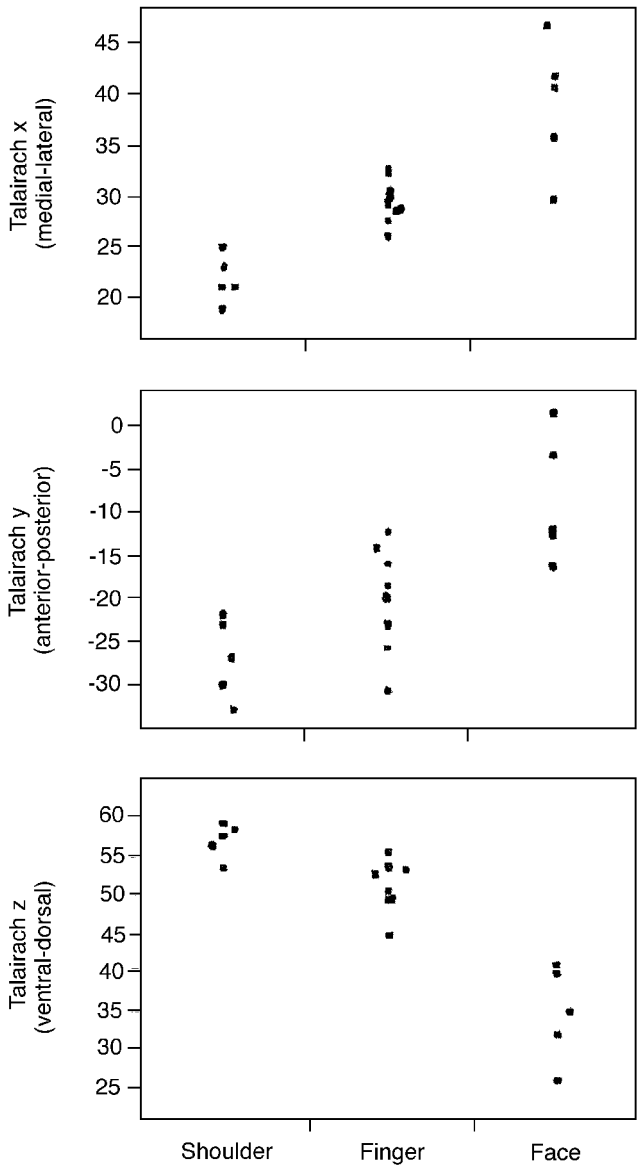

Figure 1: The left primary sensorimotor cortex activation site center of activation is presented for each subject and for each motor task performed during fMRI brain mapping. Activation center is presented in Talairach *x*, *y*, and *z* stereotaxic coordinates

Data acquisition

Each subject underwent functional magnetic resonance imaging (fMRI) that alternated rest with performance of one of the motor tasks. Detailed methods have been published previously[19]. In sum, subjects rehearsed each task prior to scanning. Imaging was performed at 1.5 Tesla. Scanning employed a gradient echo echo-planar pulse sequence with T2*-weighting for blood oxygenation level dependent contrast. Each of the three scans lasted 3:20 and alternated 20 sec rest with 20 sec of motor task performance. The first scan alternated rest with 2 Hz right index finger tapping; then rest *versus* 1 Hz right shoulder rotation; then rest *versus* 1 Hz contraction of the right corner of the mouth. Scanning parameters included TR 2000, TE 50, in-plane resolution 3.75×3.75 mm, 14 contiguous 7 mm axial brain slices, 100 images/slice, plus four TRs to establish steady state.

Data analysis

Images were motion corrected and linear detrended, after which a voxelwise *t*-test contrasted active with rest state for each of the three tasks, with results expressed as a Z-map. Results were spatially smoothed with a 4 mm Gaussian filter. Each Z-map was then converted to stereotaxic space[20] by registering to the standard image supplied with MEDx 3.3 software (Sensor Systems, Sterling, VA, USA) using FLIRT (www.fmrib.ox.ac.uk/fsl/). The activation cluster with the largest number of activated voxels in the area composed of left precentral plus postcentral gyri was identified and isolated in its entirety at the threshold of $Z = 4.2$ (approximately). The center of this cluster was identified, and its Talairach *x*, *y*, and *z* coordinates were noted. In the current report, absolute values are used for all coordinates.

A two-tailed, nonpaired *t*-test was used to compare coordinate values across tasks, without correction for multiple comparisons.

RESULTS

For the 14 subjects, mean age (± SD) was 51 ± 19 years. There were eight males and six females. Multiple factors such as head motion reduced the number of available scans to 10 for finger movement, five for shoulder movement, and five for facial movement.

Figure 1 shows scatterplots for the *x*-axis (higher numbers mean more lateral), *y*-axis (more negative numbers mean more posterior), and *z*-axis (higher numbers mean more dorsal) for each of the tasks. ANOVA testing identified a significant difference in the center of activation across the three tasks for each of the three coordinates ($p < 0.001$ for each). Comparing each pair of tasks found significant ($p < 0.05$) differences for *x*, *y*, and *z* coordinates.

Table 1 presents the mean values across subjects for the *x*, *y*, and *z* coordinate for the center of activation of each task. The decreasing *z*-axis values describe a somatotopic distribution going ventrally down the central sulcus, from shoulder to hand to face. Consistent with human central sulcus anatomy, this ventral progression is accompanied by increasingly lateral and anterior progression in the mean subject site of center of

Table 1: Center of activation coordinates for three motor tasks

	Finger	Shoulder	Face
n	10	5	5
Mean *x*	30 ± 2	22 ± 2	39 ± 6
Mean *y*	−20 ± 6	−27 ± 5	−9 ± 7
Mean *z*	51 ± 3	57 ± 2	34 ± 6
Range *x*	7	6	17
Range *y*	19	11	18
Range *z*	11	6	15

Mean (± SD) values are Talairach coordinates; both mean and range are in mm.

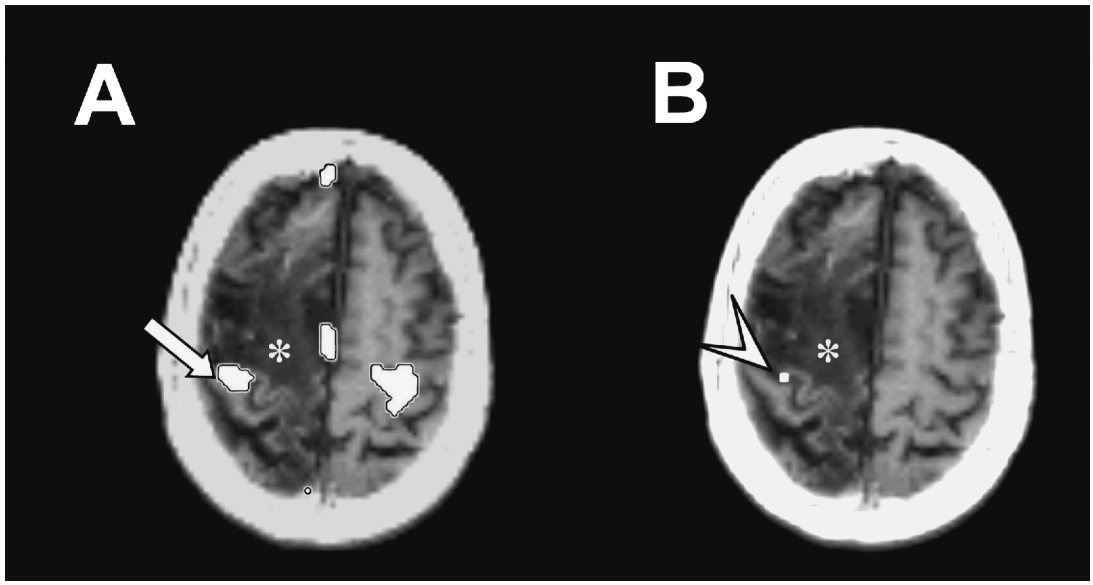

Figure 2: MRI images from a 69-year-old female patient studied 3.8 years after stroke, enrolled in a study assessing the safety and effects of epidural stimulation. The patient had moderate motor deficits, with left arm motor Fugl–Meyer score of 48 (normal = 66). **A:** The patient's fMRI scan. The patient alternated rest with 0.25 Hz left index finger tapping. Activated voxels with $z > 4$ have been colorized and superimposed upon in-plane anatomical images. The white arrow indicates the cortical activation cluster that contains the most strongly activated voxel in right (contralateral, stroke-affected) primary sensorimotor cortex. **B:** The patient's matching anatomical image. The voxel of interest has been colored white and is indicated by the arrowhead. It is located directly in the right central sulcus. In both images, the asterisk indicates the area of infarction

activation. The range is also presented in *Table 1*. The *y*-axis had the highest range for each of the three tasks.

DISCUSSION

Human brain mapping has provided many insights into changes in brain organization after stroke[21]. The current discussion, however, pertains to extending the utility of human brain mapping beyond this. Several authors have suggested that measuring features of cortical organization may be useful in the application of therapies that target patients with chronic stroke[22–24]. For therapies that aim to stimulate cortical regions in which a specific function is localized, brain mapping may be valuable for identifying the target of interest.

The current results describe a considerable range in the normal site of activation for each task (*Figure 1* and *Table 1*). Results are concordant with prior studies. Penfield and Boldrey[7], reporting in 126 operations on patients with conditions such as epilepsy or tumor, described a broad distribution in the area in which unipoloar stimulation induced finger movements, extending 55 mm along the central sulcus. Hlustick *et al.*[25] described the mean (± SEM) right primary motor cortex center of activation during fMRI of left finger movements by 11 controls. Results were presented for *x*-axis (34) and for *y*-axis (−13), the latter value reflecting analysis of only activated voxels anterior to the central sulcus. Lotze *et al.*[26] performed fMRI in 30 subjects during right or left hand movements. Apart from average group maps, the authors presented box plots showing linear distance from brain vertex to site of maximal activation. Indovina and Sanes[27] described the range of Talairach coordinates in left motor cortex during 2 Hz right finger movements. The range was 26–42 (*x*-axis), 12–24 (*y*-axis), and 49–65 (*z*-axis). These ranges are generally higher than the values found in the current report (*Table 1*), likely due to the use of a more liberal threshold ($p < 10^{-2}$, *versus* 10^{-5} in *Table 1*) to define significant activation.

These contrasts raise several caveats for efforts to noninvasively localize motor function. First, the threshold used to define activation influences variability detected. Second, results are influenced by whether analysis considers the entire activation cluster, or only those voxels on a specific gyrus. In 37 of 42 control subjects, 2 Hz index finger tapping activated a cluster that extended from precentral to postcentral gyrus[28]. The current study examined the center of the entire activation cluster rather than a subregion, and therefore likely included regions related to sensory processing. Third, the extent of variability identified may be influenced by the sample size studied. Finally, some of the differences between the above studies may relate to use of different activation tasks.

The current results show overall concordance with prior brain mapping studies and describe inter-subject variability. This method may be useful as a noninvasive assessment of cortical function for directing a stimulation-based therapy. This approach is currently being employed in a study to evaluate epidural stimulation in 18 patients with chronic motor deficits after stroke. Epidural stimulation to the motor cortex, applied to relieve chronic pain, has been described as improving

chronic motor deficits after stroke, as reviewed by Brown *et al*. in this issue. Consequently, an industry-sponsored study has been organized to assess the safety and efficacy of targeted subthreshold epidural cortical stimulation, in association with occupational therapy, in 18 patients with stroke-induced hemiparesis affecting primarily the upper extremity. The primary endpoint of this study is safety, defined as the proportion of patients who have any of the following outcomes between the time of enrollment and the time of epidural stimulation electrodes removal, which is approximately 23–28 days later: 1. death, 2. major medical morbidity, including myocardial infarction, pneumonia, wound infection, or deep venous thrombosis, 3. a generalized tonic clonic seizure, or 4. decrement in neurological status, defined as a decrease in 20% on either the Fugl–Meyer scale or the hand function subscore of the Stroke Impact Scale.

Entry criteria include age 20–75 and a history of paresis-inducing stroke >4 months prior. Deficits must be moderate–severe but nondevastating, as specified by an arm motor Fugl–Meyer score of 20–50 (normal = 66), and active wrist extension of at least 5. Twelve of 18 patients will be randomized to cortical stimulation, and 6 to no stimulation, with all patients receiving the same occupational therapy regimen.

In this study, neurosurgical placement of the epidural stimulator is guided by brain mapping. Patients undergo fMRI during performance of a motor task by the paretic hand. The choice of task is determined by the patient's motor status, with the most able patients mapped during 0.25 Hz index finger tapping, and those with poorest motor status mapped mapped during 0.25 Hz wrist movements. The most strongly activated voxel in contralateral (stroke-affected) sensorimotor cortex is used to direct placement of the epidural cortical stimulation device. An example of a patient study is shown in *Figure 2*. This approach considers inter-subject variability in localization of motor function by using features of brain function to guide this potentially restorative treatment.

CONCLUSION

Normal subjects show variability in the site of primary sensorimotor cortex activation. Animal studies suggest that simulating key motor areas might be a useful therapy for improving motor outcome after stroke. Mapping an individual subject's brain may therefore help to achieve best clinical effect from therapies that aim to stimulate a cortical region underlying a specific function.

REFERENCES

1 Gresham GE, Duncan PW, Stason WB, Adams HP, Adelman AM, Alexander DN, Bishop DS, Diller L, Donaldson NE, Granger CV, Holland AL, Kelly-Hayes M, McDowell FH, Myers L, Phipps MA, Roth EJ, Siebens HC, Tarvin GA, Trombly CA. *Post-Stroke Rehabilitation*, Rockville, MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, 1995

2 Rathore SS, Hinn AR, Cooper LS, Tyroler HA, Rosamond WD. Characterization of incident stroke signs and symptoms: Findings from the atherosclerosis risk in communities study. *Stroke* 2002; **33**: 2718–2721

3 The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; **333**: 1581–1587

4 Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM, Silver F, Rivera F. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: A randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *JAMA* 1999; **282**: 2003–2011

5 Sherman DG, Atkinson RP, Chippendale T, Levin KA, Ng K, Futrell N, Hsu CY, Levy DE. Intravenous ancrod for treatment of acute ischemic stroke: The STAT study: A randomized controlled trial. Stroke Treatment with Ancrod Trial. *JAMA* 2000; **283**: 2395–2403

6 Reed SD, Cramer SC, Blough DK, Meyer K, Jarvik JG. Treatment with tissue plasminogen activator and inpatient mortality rates for patients with ischemic stroke treated in community hospitals. *Stroke* 2001; **32**: 1832–1840

7 Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* 1937; **60**: 389–443

8 Whitaker HA, Selnes OA. Anatomic variations in the cortex: Individual differences and the problem of the localization of language functions. *Ann NY Acad Sci* 1976; **280**: 844–854

9 Van Essen DC, Drury HA, Joshi S, Miller MI. Functional and structural mapping of human cerebral cortex: Solutions are in the surfaces. *Proc Natl Acad Sci USA* 1998; **95**: 788–795

10 Rademacher J, Caviness VS, Steinmetz H, Galaburda AM. Topographical variation of the human primary cortices: Implications for neuroimaging, brain mapping, and neurobiology. *Cerebral Cortex* 1993; **3**: 313–329

11 Ojemann GA. The neurobiology of language and verbal memory: Observations from awake neurosurgery. *Int J Psychophysiol* 2003; **48**: 141–146

12 Kaas JH. The reorganization of sensory and motor maps in adult mammals. In: Gazzaniga M, ed. *The Cognitive Neurosciences*, Cambridge, MA: MIT Press, 1995: pp. 51–72

13 Cohen LG, Ziemann U, Chen R, Classen J, Hallett M, Gerloff C, Butefisch C. Studies of neuroplasticity with transcranial magnetic stimulation. *J Clin Neurophysiol* 1998; **15**: 305–324

14 Xerri C, Coq JO, Merzenich MM, Jenkins WM. Experience-induced plasticity of cutaneous maps in the primary somatosensory cortex of adult monkeys and rats. *J Physiol Paris* 1996; **90**: 277–287

15 Chen R, Cohen LG, Hallett M. Nervous system reorganization following injury. *Neuroscience* 2002; **111**: 761–773

16 Ungerleider LG, Doyon J, Karni A. Imaging brain plasticity during motor skill learning. *Neurobiol Learn Mem* 2002; **78**: 553–564

17 Nudo RJ, Plautz EJ, Frost SB. Role of adaptive plasticity in recovery of function after damage to motor cortex. *Muscle Nerve* 2001; **24**: 1000–1019

18 Oldfield RC. The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia* 1971; **9**: 97–113

19 Crafton KR, Mark AN, Cramer SC. Improved understanding of cortical injury by incorporating measures of functional anatomy. *Brain* 2003; **126**: 1650–1659

20 Talairach J, Tournoux P. *Co-planar Stereotaxic Atlas of the Brain*, New York: Thieme Medical, 1988

21 Rijntjes M, Weiller C. Recovery of motor and language abilities after stroke: The contribution of functional imaging. *Prog Neurobiol* 2002; **66**: 109–122

22 Dobkin BH. *Neurologic Rehabilitation*, Philadelphia: F.A. Davis, 1996

23 Cole TM, Lieberman JS. Neurorehabilitation research opportunities for improvement and restoration of function. In: Toole J, Good D, eds. *Imaging in Neurologic Rehabilitation*, New York: Demos Vermande, 1996: pp. 5–12

24 Cramer SC. Implementing results of stroke recovery research into clinical practice. *Stroke* 2003; **34**: 1752–1753

25 Hlustik P, Solodkin A, Gullapalli RP, Noll DC, Small SL. Somatotopy in human primary motor and somatosensory hand representations revisited. *Cereb Cortex* 2001; **11**: 312–321

26 Lotze M, Erb M, Flor H, Huelsmann E, Godde B, Grodd W. fMRI evaluation of somatotopic representation in human primary motor cortex. *Neuroimage* 2000; **11**: 473–481

27 Indovina I, Sanes JN. On somatotopic representation centers for finger movements in human primary motor cortex and supplementary motor area. *Neuroimage* 2001; **13**: 1027–1034

28 Cramer SC, Moore CI, Finklestein SP, Rosen BR. A pilot study of somatotopic mapping after cortical infarct. *Stroke* 2000; **31**: 668–671