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Anatomy and physiology predict response to motor cortex stimulation after stroke

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ABSTRACT

Objectives: Preclinical studies found that epidural motor cortex stimulation improved motor deficits after stroke, but a phase III trial in humans did not corroborate these results. The current retrospective analysis examined subjects randomized to stimulation in order to identify features distinguishing responders from nonresponders.

Methods: Anatomic (MRI measures of gray matter thickness and of white matter tract injury) and physiologic methods (motor evoked responses) were examined as predictors of treatment response.

Results: Among 60 subjects randomized to cortical stimulation, both anatomic and physiologic measures at baseline predicted behavioral response to therapy. Anatomically, those achieving the primary efficacy endpoint had a smaller fraction of the corticospinal tract injured by stroke compared to those who did not (44% vs 72%, $p < 0.04$), and rarely had severe tract injury. Physiologically, the primary efficacy endpoint was reached more often (67%) by those with preserved motor evoked responses (MER) upon cortical stimulation compared to those lacking MER (27%, $p < 0.05$). Those with an elicitable MER also had a lower rate of precentral gyrus injury (0% vs 33%, $p < 0.05$) by stroke, as compared to those lacking MER, and had higher gray matter volume compared to those lacking MER in regions including ipsilesional precentral gyrus.

Conclusions: In this clinical stroke trial, the more that the physiologic integrity of the motor system was preserved, the more likely that a patient was to derive gains from subsequent therapy, consistent with preclinical models. Functional and structural preservation of key brain substrates are important to deriving gain from a restorative therapy. *Neurology*® 2011;77:1076–1083

GLOSSARY

IQR = interquartile range; **MER** = motor evoked response.

Stroke remains a major source of human disability. An emerging group of therapies aims to improve function in the chronic phase of stroke, when behavioral deficits are fixed.[1] This is an issue of considerable impact, as at least 6.4 million such persons are alive in the United States alone.[2] A major question is how to distinguish patients who are likely to respond to a restorative therapy from patients who are not.

The current study considers this issue in relation to a phase III clinical trial[3,4] that examined behavioral effects of epidural cortical stimulation after stroke. Preclinical studies in rodents and in nonhuman primates suggested that this form of brain stimulation improved behavioral outcome.[5–9] Together, these studies described a biological model whereby epidural motor cortex stimulation promotes motor cortex plasticity and, as a result, improves motor behavioral status.

In the clinical trial, patients with chronic hemiparetic stroke underwent anatomic and physiologic assessment of the motor system and were then randomized to either epidural cortical stimulation plus physiotherapy or to no stimulation plus physiotherapy. The main study results were that the 2 treatment groups did not significantly differ in the proportion of subjects who

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reached the primary composite efficacy endpoint.[4] The hypothesis of the current analysis of these data is based on the model generated in the animal studies: the best behavioral gains from epidural motor cortex stimulation are found with greater anatomic and physiologic preservation of motor system integrity at baseline, i.e., prior to therapy initiation.

METHODS **Overall clinical trial design.** The current study analyzed data from a randomized, single-blind, multicenter clinical trial that compared the effect of 6 weeks of subthreshold epidural cortical stimulation + physiotherapy with physiotherapy alone on arm motor function in patients with chronic stroke,[3,4] which ran at 21 US sites from 2004 to 2008. After meetings with the Food and Drug Administration, the trial designated a subject as having reached the primary composite efficacy endpoint, intended to represent clinically meaningful improvement in both impairment and function of the affected arm/hand after therapy, if the subject had both ≥4.5 point improvement in the arm motor Fugl-Meyer score (range 0–66) and ≥0.21 point improvement in the Arm Motor Ability Test score (range 0–5) at 4 weeks following end of therapy.

Entry criteria for this trial included age ≥21 years; stroke that was ischemic, supratentorial, and >4 months old; moderate–severe arm motor deficits; and either wrist extension ≥5° or ability to repetitively grasp. Exclusion criteria included severe neglect, spasticity, or sensory deficit; depression; or modified Rankin Scale ≥4. Eligible subjects underwent baseline behavioral assessments and MRI. The MRI (1.5 or 3 Tesla) included a T1-weighted high-resolution anatomic and a fMRI scan that contrasted rest with any of 4 hand movements, as described elsewhere.[3] Subjects lacking activation over the perirolandic region were excluded. Subjects remaining eligible were then randomized to epidural cortical stimulation + physiotherapy vs physiotherapy alone.

Those subjects randomized to epidural cortical stimulation + physiotherapy were implanted with the epidural electrode and pulse generator; these subjects are the focus of the current analysis. Subjects received subthreshold cortical stimulation during rehabilitation therapy sessions, which occurred 5 days/week for weeks 1–4 and 3 days/week for weeks 5–6, and consisted of 2.5 hours of task-oriented physiotherapy.[3] The stimulating electrode was placed over the area of ipsilesional primary motor cortex activated on the baseline fMRI. Three times during the 6-week treatment protocol (baseline prior to therapy initiation, day 6 of therapy, and end of therapy), the electrodes were used to assess for presence of a motor evoked response (MER), allowing subject classification as MER present or absent. This was done by increasing stimulation current, up to maximum device output, to determine presence or absence of visible movement in any affected hand muscle.

Of the 94 stroke subjects randomized to the investigational group, 60 were used in the current study, with 34 subjects excluded because the T1-weighted MRI scan was missing, corrupted, or had excessive head motion artifact. Note that baseline deficits for these 60 subjects (Fugl-Meyer score 38.9 ± 5.8, mean ± SD) did not significantly differ from the overall 94 subjects randomized to stimulation (37.6 ± 6.1).

Image analysis. The baseline T1-weighted MRI were analyzed several ways. First, they were reviewed to 1) classify stroke topography (subcortical + cortical vs subcortical only) and 2) determine whether precentral gyrus was affected or spared by stroke.

The image was then flipped along the midline for stroke subjects with stroke in the right hemisphere, such that all images displayed the stroke in the left hemisphere. A stroke mask was generated for each patient by outlining the stroke lesion using MRICron, then binarized.

Next, the degree to which stroke injured the white matter tract descending from primary motor cortex was determined, as described previously[10]; this method for determining tract-specific injury has been found to be a significant predictor of behavioral gains in subjects with chronic stroke undergoing motor-based therapy.

Images were then examined using voxel-based morphometry (VBM5 toolbox) implemented in SPM5. VBM5 employs the unified segmentation approach using a single generative model integrating tissue classification, bias correction, and image registration. VBM5 toolbox was used to normalize masked images, then segment them to produce gray matter, white matter, and CSF masks in Montreal Neurological Institute stereotaxic space; proper normalization and tissue classification was confirmed individually for each subject. These final tissue maps were then modulated by multiplying by the Jacobian determinants, after which maps were smoothed at 8-mm full width at half maximum.

Statistical analysis. For each subject, SPM5 was used to analyze the smoothed modulated gray matter masks, with all analyses using threshold $p < 0.001$ without correction for multiple comparisons. One set of analyses examined gray matter in relation to physiologic integrity: a 2-sample t test compared gray matter volumes among the 9 investigational subjects with MER vs the 51 without MER. A second set of analysis examined differences in gray matter in relation to meeting the primary composite efficacy endpoint or not: a 2-sample t test compared gray matter volumes among the 20 subjects who reached this endpoint vs the 40 subjects who did not; note that because few differences were observed at threshold $p < 0.001$ for this comparison, a secondary analysis was performed using the exploratory threshold $p < 0.005$. A third set of analyses examined gray matter differences between 23 healthy controls and both MER groups. The healthy control MRIs were acquired at University of California Irvine according to the standard protocol.

For each analysis, age and total intracranial volume (sum of gray and white matter volumes) were added as covariates, i.e., as

Table 1 Baseline and outcome measures[a]

	Primary behavioral endpoint met	Primary behavioral endpoint not met	p
No.	20	40	
Age, y	59.6 ± 1.7	55.6 ± 2.6	0.18
Female/male	5/15	20/20	0.10
Dominant hand, left/right/ambidextrous	3/16/1	5/35/0	0.31
Affected arm, left/right	6/14	13/27	0.84
Hypertension, yes/no	16/4	24/16	0.15
Time poststroke, mo	58.6 ± 11.7	60.4 ± 10.4	0.91
Baseline arm motor Fugl-Meyer score (out of 66)	39.5 ± 1.5	38.6 ± 0.8	0.58
Final arm motor Fugl-Meyer score (measured 4 weeks following end of therapy)	48.5 ± 1.9	40.6 ± 1.2	0.0005

[a] Values are mean ± SEM.

nuisance variables. Note that adding field strength, enrollment site, and gender as additional nuisance variables had no effect on results, so these were not retained in final analyses.

Chi-square and Fisher exact test were used to analyze nominal variables, and a *t* test and Wilcoxon rank-sum test were used for continuous variables, as appropriate, in relation to behavioral outcome and in relation to MER status. All analyses were 2-tailed.

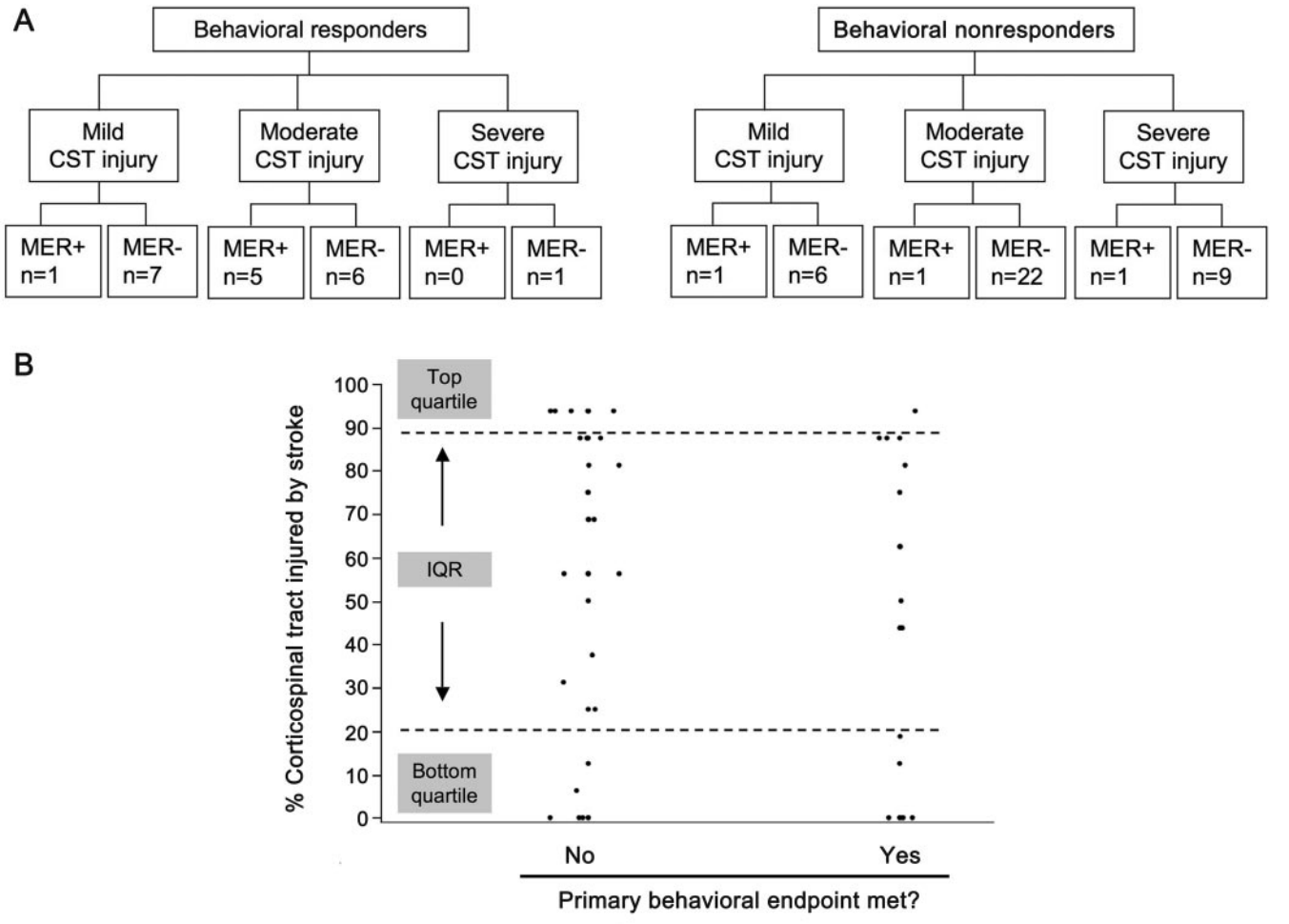
Standard protocol approvals, registrations, and patient consents. The trial whose data were used for the current analyses was clinicaltrials.gov NCT00170716. All data were obtained with approval from local institutional review boards.

RESULTS

Subjects. Table 1 presents baseline features for the 60 subjects randomized to epidural motor cortex stimulation in the clinical trial. Most (n = 53) were Caucasian. Of the 60, 20 reached the composite endpoint and 40 did not; also, 9 had a MER while 51 had no MER at any assessment. Note that for these 9 subjects, MER did not vary over time, being uniformly present at all 3 (baseline and both follow-up) assessments. Baseline features did not vary according to MER status or behavioral outcome (table 1). For VBM comparisons with stroke subjects, 23 age-matched (58.9 ± 3.3 years), gender-matched (12 female/11 male) healthy controls were also studied.

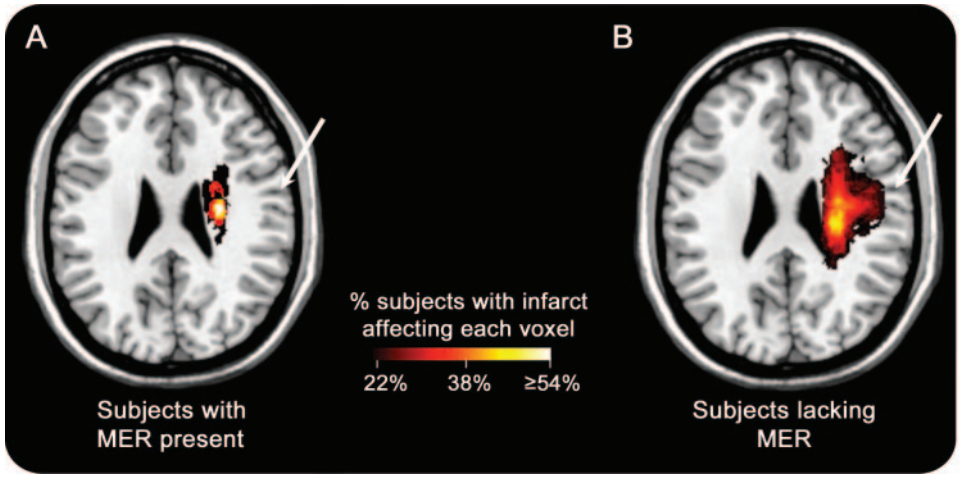
Anatomic status. ***Corticospinal tract injury.*** Extent of injury to the corticospinal tract descending from ipsilesional primary motor cortex correlated with behavioral outcome but not physiologic status. Thus, extent of tract injury was significantly lower in those reaching the primary composite efficacy endpoint (44% [0–80], median [interquartile range (IQR)]) as compared to those not reaching this endpoint (72% [33–92], $p < 0.036$). Though the distribution of values overlapped across the 2 groups, severe corticospinal tract injury (top quartile of injury values, see figure 1) was present in only one subject reaching the composite endpoint (5%) vs 25% of those not reaching this endpoint ($p = 0.08$,

Figure 1 Corticospinal tract injury in relation to behavior and motor evoked responses



(A) The relationship between behavioral response to therapy, corticospinal tract (CST) injury, and physiologic status. Mild corticospinal tract injury is defined as the bottom quartile across the entire cohort (≤20% of the corticospinal tract injured by stroke); moderate tract injury, the interquartile range (IQR) (21%–88% of the tract injured); and severe tract injury, the top quartile (≥89%). MER+ = motor evoked response present; MER− = motor evoked response absent. (B) Extent of CST injury is presented as a function of behavioral outcome. The dashed lines indicate the bottom quartile, IQR, and top quartile of tract injury.

Figure 2 Distribution of infarct locations



Infarcts were overlapped and superimposed on a normal brain template to show the distribution of infarct sites in (A) subjects with motor evoked response (MER) present and (B) subjects lacking MER. In both cases, infarcts in these hemiparetic patients were centered on the central sulcus (indicated by the arrow). This representative slice demonstrates that infarcts in subjects with preserved MER did not involve gray matter and in general spanned a much smaller area of white matter, as compared to infarcts in subjects lacking MER.

figure 1). Physiologic status did not vary with extent of tract injury, being 44% (22–88) for MER present vs 69% (19–88) for MER absent ($p > 0.5$).

Infarct location. Features of infarct location did not correlate significantly with behavioral outcome, but they did with physiologic status. Thus, the proportion of subjects reaching the primary behavioral endpoint did not vary in relation to depth of stroke ($p = 0.098$) or precentral gyrus involvement ($p = 0.093$). However, for subjects with MER, 100% of had a subcortical lesion, while for those lacking an MER, the lesion was subcortical in 41.2% and both cortical and subcortical in 58.8% ($p < 0.002$). Regarding precentral gyrus involvement, stroke involved this gyrus in none (0%) of the subjects with MER but in 33.3% of subjects lacking MER ($p < 0.05$).

Physiologic status. A significant difference in behavioral outcome was found in relation to physiology. Those subjects from whom an MER could be elicited had a significantly higher rate of reaching the primary composite efficacy endpoint (67%) as compared to subjects with MER absent (27%, $p < 0.05$). Moreover, MER, when present, were mainly in subjects reaching the primary composite efficacy endpoint who had moderate corticospinal tract injury (figure 1A). Overlap of binarized stroke masks (figure 2) indicates that infarcts in subjects with preserved MER spanned a much smaller area of white matter, compared to infarcts in subjects lacking MER.

Gray matter volume in stroke patients who did vs did not have MER. The anatomic underpinnings of these observations were examined with VBM. At baseline, patients with MER, as compared to patients without MER, exhibited increased gray matter volumes in brain areas that included ipsilesional precentral/postcentral gyri, bilateral anterior cingulate cortex, and contralesional anterior striatum (table 2 and figure 3). Conversely, patients with absent MER, as compared to patients with MER, showed increased gray matter volume in areas including contralesional precentral/postcentral gyri.

In order to better understand the nature of these observed differences in gray matter volume between stroke patients with MER vs stroke patients without MER, each of these 2 patient subgroups were compared with a cohort of healthy control subjects (n = 23).

In most cases, when subjects with MER had larger gray matter volume as compared to subjects without MER (table 2), this was due to above normal (subjects with MER significantly > healthy controls) gray matter volume in subjects with MER, a pattern observed within bilateral anterior cingulate, contralesional anterior striatum, ipsilesional precentral/postcentral gyri, and ipsilesional posterior putamen. One exception was noted, whereby subjects with MER had larger gray matter volume than subjects without MER due to below normal (healthy control > subjects without MER) gray matter volume in subjects without MER, within ipsilesional anterior putamen.

When subjects without MER had larger gray matter volume as compared to subjects with MER (table 2), this was due to above normal (subjects with MER absent significantly > healthy controls) gray

Table 2 Brain regions where gray matter volume differed according to MER status[a]

Cluster volume (mm^3)	MNI coordinates (x, y, z)	Anatomic locations
MER present > MER absent		
5,860	2, 33, 14	Contralesional > ipsilesional anterior cingulate
5,051	23, 16, 15	Contralesional anterior striatum
449	14, −24, 74	Contralesional dorsal/medial precentral gyrus
5,557	−35, −22, 68	Ipsilesional precentral > postcentral gyrus
2,201	−27, −9, 14	Ipsilesional posterior putamen
720	−54, 19, 32	Ipsilesional dorsolateral prefrontal cortex
798	−19, 9, 6	Ipsilesional anterior putamen
871	−59, −12, 47	Ipsilesional precentral and postcentral gyrus
MER absent > MER present		
1,734	27, −62, 2	Contralesional occipital lobe
1,006	43, 15, 27	Contralesional inferior frontal gyrus
670	17, −31, 50	Contralesional medial precentral and postcentral gyri
528	11, −45, 39	Contralesional precuneus
3,783	−35, −53, 3	Ipsilesional occipital
1,004	−39, −28, −16	Ipsilesional parahippocampal gyrus
828	−10, −51, 38	Ipsilesional precuneus

Abbreviation: MER = motor evoked response.
[a] Among the 60 subjects who received investigational brain stimulation during 6 weeks of physiotherapy, an MER could be evoked in hand muscles by brain stimulation in 9 (MER present) but could not be evoked in the other 51 subjects (MER absent). This table shows regions where the anatomical brain MRI, taken at baseline, prior to therapy, showed significant differences between these 2 groups.

matter volume in the subjects without MER, a pattern observed within bilateral precuneus and ipsilesional occipital lobe.

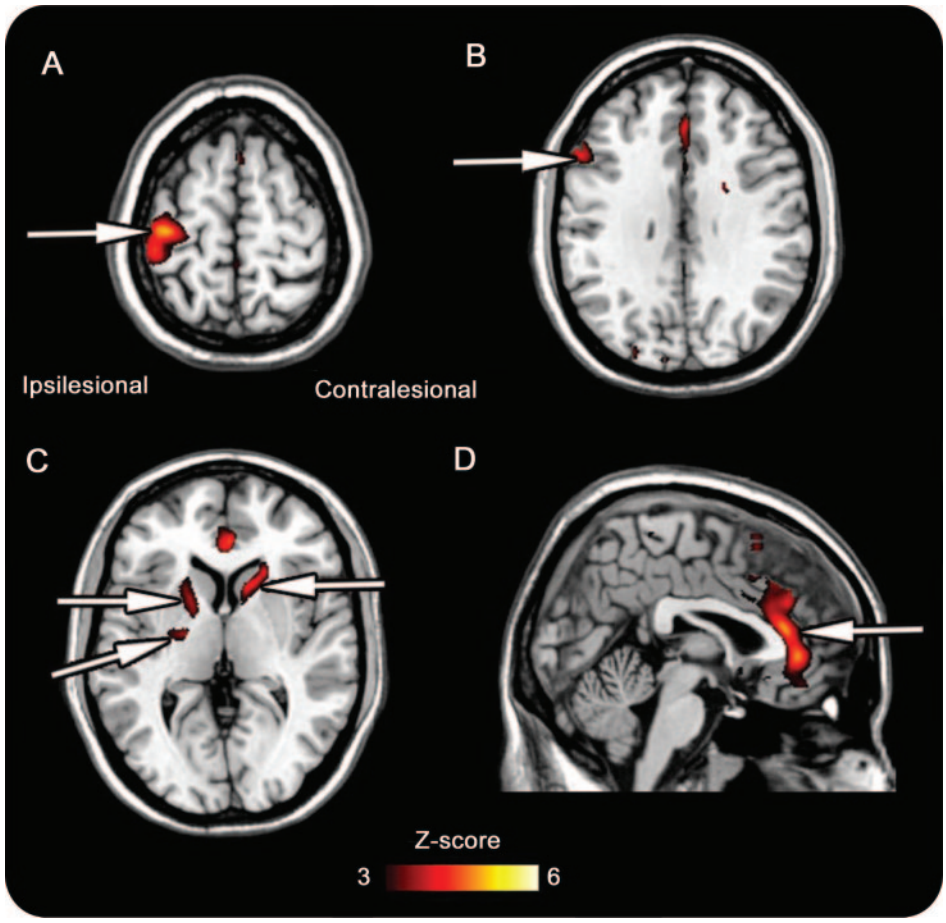
Gray matter volume in stroke patients who did vs did not reach the primary composite efficacy endpoint. There were few differences in relation to final clinical outcome when the data were analyzed at threshold $p < 0.001$. However, a secondary analysis using threshold $p < 0.005$ disclosed that the 20 subjects who reached the primary composite efficacy endpoint had a significantly larger volume of gray matter within contralesional anterior striatum, ipsilesional medial lentiform nucleus, and ipsilesional anterior temporal lobe. Comparison with healthy controls, as above, disclosed that this was due to above normal volumes in subjects who reached the composite endpoint, in the case of contralesional anterior striatum. Conversely, the 40 subjects who did not reach the primary composite efficacy endpoint, as compared to the 20 who did, had a significantly larger volume of gray matter within ipsilesional medial temporal lobe, ipsilesional midbrain, and contralesional medial frontal lobe. Comparison with healthy controls disclosed that this was due to above normal volumes in subjects who did not reach the composite endpoint, in all 3 regions.

DISCUSSION A series of preclinical studies in rodents and primates[5–8] concluded that epidural motor cortex stimulation was associated with behavioral gains after stroke, but a phase III trial[4] found that those randomized to stimulation + physiotherapy did not differ significantly in the proportion of subjects reaching the primary composite efficacy endpoint as compared to those randomized to physiotherapy alone. The current report focused on trial enrollees who were randomized to stimulation, and results support the current hypothesis, i.e., that both anatomic and physiologic measures at baseline distinguished responders from nonresponders.

The differences between behavioral responders and nonresponders provide a number of insights. Responders had significantly less injury to the corticospinal tract and were significantly more likely to have preserved motor system physiology; preserved physiology itself was significantly associated with subcortical stroke and supranormal gray matter volume in regions including primary motor and sensory cortex. These findings echo studies of natural stroke recovery, for example, where an association also exists between better outcome and less corticospinal tract injury.[11,12] Treatment-induced repair is thus affected by many of the same constraints as spontaneous recovery. Stroke topography might be a particularly important factor, as subcortical stroke differs from cortical stroke in ways such as pattern of poststroke plasticity[13,14] and of cortical excitability.[15] The current analysis found that stroke topography might influence response to therapy, consistent with a prior study of cortical stimulation,[16] and suggests that this might be mediated through the association between topography and physiologic integrity. The current results reinforce recent findings[17] that the best picture of brain substrate available for a restorative therapy may be provided by combining anatomic and physiologic assessments.

Regarding anatomic assessments, the current results might have value for development of biomarkers for stroke recovery therapeutics.[18] One set of markers relates to regional gray matter volume. Gray matter volume in bilateral basal ganglia was associated with better behavioral outcome; in primary motor cortex, with greater physiologic integrity. Gray matter volume is a useful predictor in other clinical contexts, such as in hippocampus for response to therapy in depression,[19] in anterior cingulate for response to cognitive behavioral therapy,[20] and in several cortical zones to predict clinical course in dementia.[21] Greater primary sensory cortex thickness

Figure 3 Areas where subjects with preserved physiologic integrity had increased gray matter volume



Arrows indicate brain regions where subjects with MER present had significantly increased gray matter volume, relative to subjects with MER absent. (A) Ipsilesional precentral > postcentral gyrus; (B) ipsilesional dorsolateral prefrontal cortex; (C) bilateral striatum; and (D) bilateral anterior cingulate.

has been linked with larger extent of functional plasticity,[22] suggesting a functional correlate to these anatomic findings. A second set of potential biomarkers relates to white matter injury. Of the 20 subjects reaching the composite endpoint, only 1 had severe corticospinal tract injury (figure 1). Extent of corticospinal tract injury predicts response to robotic therapy after stroke.[10] Such a measure might be useful as an exclusion criterion in some restorative stroke trials, for example, excluding those with severe tract injury. Increased technological refinements[23,24] support further development of anatomic measures as biomarkers for restorative trials after stroke.

The current report provides lessons useful for future translation of neuroplasticity-based trials.[25] Entry criteria differed between the animal and human studies: the rodent and primate studies required preserved motor evoked potentials[5–8] but the human trial did not. Human patients demonstrating an MER were 2.5 times more likely to achieve the primary composite efficacy endpoint. This highlights the importance of aligning patient selection with the biological model developed in preclinical studies,[26] though there were other differences between preclinical and clinical studies such as time poststroke and type of stroke injury.

The current analysis had several limitations. Extent of corticospinal tract injury, while significantly different between responders and nonresponders, showed substantial overlap across the 2 groups, limiting broader clinical trial application of this measure in current form, though the dichotomous measure "severe tract injury or not" might be promising. A slightly more liberal statistical threshold was needed to appreciate VBM differences between responders and nonresponders. Behavioral outcome varied with extent of corticospinal tract injury but not with infarct topography, while physiologic status varied with infarct topography but not extent of corticospinal tract injury. A larger extent of agreement might have been expected between these 2 analyses. Use of less sensitive visual methods rather than electromyographic methods to ascertain physiologic status might have contributed to this discrepancy, and

might also explain the observation that most subjects who were behavioral responders lacked MER, though other issues such as electrode placement or stimulus parameters might also have contributed. Nonetheless, these results together suggest that tract injury might have greater influence on behavioral response, while injury to cortex has a greater bearing on the likelihood of eliciting an MER with stimulation.

Injury and behavioral deficits caused by stroke are highly variable. Optimizing the efficacy of restorative therapies after stroke will require matching treatments with patients who have sufficient biological target. The current analysis identified anatomic and physiologic measures predictive of a favorable response to epidural motor cortex stimulation, and found these to be concordant with preclinical investigations. These findings might have value to the study of other restorative therapies after stroke.

AUTHOR CONTRIBUTIONS

Steve Cramer: contributed to drafting the manuscript, study design, data analysis, and statistical analysis. Sarvenaz Nouri: contributed to drafting the manuscript, study design, and data analysis.

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DISCLOSURE

S. Nouri reports no disclosures. Dr. Cramer has served as a consultant and/or on scientific advisory boards for GlaxoSmithKline, Pfizer Inc, PhotoThera, Stem Cell Therapeutics Corp, Asubio Pharmaceuticals, Inc., CytRx Corporation, Allergan, Inc., Grupo Ferrer S.A., and Johnson & Johnson; serves on the editorial board of *Neurorehabilitation and Neural Repair* and as an Assistant Editor for *Stroke*; and has received research support from Panasonic, GlaxoSmithKline, Stem Cell Therapeutics Corp., Northstar Neuroscience, Inc., and the NIH.

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