Motor Cortex Stimulation for the Enhancement of Recovery from Stroke: A Prospective, Multicenter Safety Study

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OBJECTIVE: Functional magnetic resonance imaging and transcranial magnetic stimulation studies suggest that human cortex shows evidence of neuroplasticity. Preclinical studies in rats and monkeys suggest that motor cortical stimulation can enhance plasticity and improve recovery after stroke. This study assesses the safety and preliminary efficacy of targeted subthreshold epidural cortical stimulation delivered concurrently with intensive rehabilitation therapy while using an investigational device in patients with chronic hemiparetic stroke.

METHODS: This is a prospective, multicenter, and nonblinded trial randomizing patients to rehabilitation with or without cortical stimulation. Patients aged 20 to 75 years who had had an ischemic stroke at least 4 months previously causing persistent moderate weakness of the arm were included. Functional magnetic resonance imaging localized hand motor function before surgery to place an epidural cortical electrode. Both groups then underwent rehabilitation for 3 weeks after which the electrode was removed. Outcome measures were obtained at baseline, during therapy, and at 1, 4, 8, and 12 weeks postprocedure.

RESULTS: Ten patients were randomized; six patients to surgery, four to the control group. No patient deaths, neurological deterioration, or seizures occurred. There were two infections from nonprotocol-related causes. Of the eight patients completing the treatment, the stimulation plus rehabilitation group improved significantly better than controls in the Upper Extremity Fugl-Meyer ($P = 0.003$ overall) and the hand function score of the Stroke Impact Scale ($P = 0.001$ overall).

CONCLUSION: The technique of cortical stimulation to enhance stroke recovery is well tolerated and safe.

KEY WORDS: Cortical stimulation for stroke recovery, Electrical stimulation, Motor cortex, Rehabilitation, Stroke

Stroke is the third leading cause of death and the most common cause of disability in the United States. There are approximately 700,000 strokes in the United States annually, with approximately 150,000 to 250,000 stroke survivors becoming severely and permanently disabled. There are over 5 million disabled stroke survivors. The most common neurological deficit among these stroke survivors is weakness, which contributes to poststroke disability. The only approved available treatment showing benefit for patients with residual motor deficits is physiotherapy. Unfortunately, many patients do not achieve complete recovery after rehabilitation therapy (10).

Spontaneous recovery does occur after stroke, possibly from recovery of marginally effective cortical areas with limited or temporary insult. Alternatively, neurological restoration may be from reorganization, in which adjacent brain areas take over the function of stroke-damaged areas. The latter mechanism falls under the concept known as neuroplasticity.

There is an extensive clinical literature on motor cortex stimulation for central and peripheral neuropathic pain syndromes beginning with the work of Tsubokawa et al. (24, 26) in 1991. The authors commented on the motor effects of cortical stimulation for treatment of neuropathic pain in this publication and in ensuing related publications, noting, "subjective improvement of motor deficits was also reported in most of these cases." Similar findings have also been seen in ensuing clinical studies for the treatment of central and neu-

ropathic pain syndromes. A number of laboratory investigations confirm these observations of enhanced motor recovery brought about by cortical stimulation during rehabilitation from stroke (1, 15, 21, 23).

This study tests the hypothesis that subthreshold cortical stimulation of primary motor cortex involved in producing residual motion in an impaired limb after a nonhemorrhagic cortical or subcortical infarction may enhance motor recovery. This feasibility study is designed to assess the safety of targeted subthreshold electrical motor cortex stimulation delivered to stroke patients concurrent with active rehabilitation. The primary objective is to establish the safety of this technique while also obtaining preliminary efficacy data.

METHODS

Overall Design

This is a prospective, randomized, multicenter study of the safety of subthreshold motor cortical electrical stimulation of patients with motor deficit resulting from a stroke that occurred at least 4 months before enrollment. The study was supported by Northstar Neuroscience (Seattle, WA). Patients were randomized into two groups: 1) a treatment group that underwent an electrode (a 3 × 3 grid electrode, Ad-Tech, Racine, WI) implant and subsequent epidural electrical stimulation (at 50 Hz, 50% of the current needed to evoke gross motor movement) using an investigational battery powered external pulse generator (Northstar Neuroscience, Seattle, WA) concurrent with 3 weeks of rehabilitation (the investigational arm) and 2) a group of control stroke patients who received the same 3 weeks of rehabilitation but did not undergo device implantation. For the patients receiving cortical stimulation, the stimulation device was turned on only during rehabilitation therapy sessions. At other times, the external stimulator was disconnected, and no stimulation was delivered. All patients received 16 weeks of assessments, including baseline, during 3 weeks of therapy, and for 12 weeks after the end of rehabilitation therapy.

Subjects

Subjects were recruited after approval of each institution's institutional review board and after an appropriate informed consent had been signed. The major inclusion and exclusion criteria are given in *Table 1*.

Protocol

Patients who, after preliminary screening, were deemed candidates for inclusion in this study then underwent functional magnetic resonance imaging (*f*MRI) using a protocol to evaluate the cortical activation associated with finger tapping or movement of the paretic hand at least 5 degrees at the wrist. These images were evaluated to determine whether the patient had sufficient activation to identity the primary motor cortex of the affected hemisphere. If an activation site within primary motor cortex was found, the voxel of greatest activa-

TABLE 1. Major inclusion and exclusion criteria

Major inclusion criteria:
    Patients 20 to 75 years.
    Ischemic infarct, either cortical or capsular, that occurred at least 4 months before enrollment and demonstrated on computerized tomography or magnetic resonance imaging.
    An Upper Extremity Fugl-Meyer Assessment score between 20 and 50, inclusive sufficient to allow active wrist extension of at least 5 degrees.

Major exclusion criteria:
    Another stroke preceded their index stroke and was associated with incomplete motor recovery.
    There was a history of spinal cord injury, significant traumatic brain injury (such that associated with loss of consciousness and memory loss), or a subdural or epidural hematoma.
    They had any history of seizures or were taking anticonvulsants to treat seizures.
    There was any significant central nervous system disease state.
    They were not considered candidates for surgery to implant the device.

tion within the largest motor cortex activation cluster was identified (4), and then the patient was randomized into either 1) the treatment group or 2) the control group. If no activation was seen, the subject did not continue with the study.

Surgery

The site for hand function was identified on the *f*MRI before surgery. On the day of surgery, fiducials were placed, and a T1-weighted MRI was performed (*Fig. 1*). This activation site was integrated into a neuronavigational workstation. General endotracheal anesthesia was induced. Patients were positioned supine with the head rotated to the side. Electromyography electrodes were inserted in the affected shoulder, arm, and hand for intraoperative cortical mapping. The site corresponding to hand function was mapped onto the scalp using neuronavigation. After this localization, an appropriate scalp incision was performed so that a circular 4 cm craniotomy could be centered over the center of the *f*MRI activation site. Once the bone flap was removed, this activation site was projected onto the exposed dura. In preparation for epidural cortical stimulation, the general anesthesia was allowed to lighten to the minimal necessary to keep the patient unconscious. Muscle paralyzing agents were not used except during induction. Transdural electrical stimulation at 50 Hz was then undertaken with the objective of evoking either gross motor movement or electromyographic activation of the hand/finger electrodes. This stimulation was intended to verify that the underlying cortex was capable of evoking peripheral muscle activity but not to supplant the role of *f*MRI in selecting the site for electrode placement. The initial electrode orientation
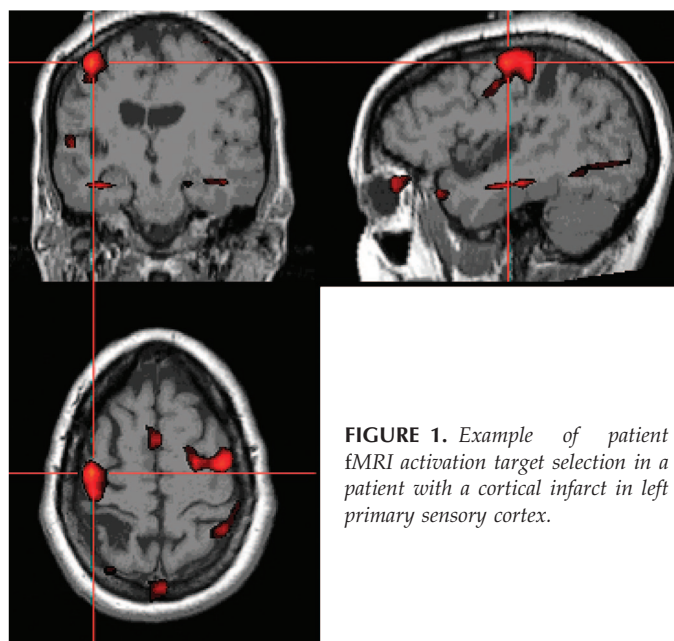
FIGURE 1. *Example of patient fMRI activation target selection in a patient with a cortical infarct in left primary sensory cortex.*

was estimated so that the long axis of the electrode was at right angles to the suspected trajectory of the central sulcus.

After completion of epidural stimulation, the investigational electrode grid was sutured to the dura with the center of the grid over the point deemed to be the center of the fMRI "hot spot" (4). The electrode lead was tunneled to a supraclavicular exit site and the bone flap replaced. Patients were observed in intensive care for 24 hours after surgery and discharged on the second postoperative day. Rehabilitation began 1 week later.

After the rehabilitation portion of the protocol was completed, the patient's craniotomy wound was reopened under general anesthesia for removal of the investigational device. This second surgery did not require recovery in the neurosurgical intensive care.

Control Patients

Patients in this group did not undergo device implantation but were started on the same rehabilitation protocol as the treatment patients.

Rehabilitation

All study patients were given the same active rehabilitation protocol, which required two 1.5 hour sessions per day, 5 days a week, for a total of 3 weeks. This occupational therapy was directed toward strengthening and improving function of the affected shoulder/arm/hand. All rehabilitation, with or without electrical stimulation, was provided under the direct supervision of a therapist.

Electrical Stimulation

At the beginning session each week of treatment, threshold for evoking gross movement in the contralateral hand was determined using stimulation parameters of 3 second trains of 50 Hz, 250 ms pulses starting at 1 mA and increasing until either movement was evoked or a maximum of 15 mA was reached.

At the beginning of each rehabilitation session, stimulation was turned on. Stimulation was set at either 50% of movement threshold (if movement was evoked) or 6.5 mA (if no movement was evoked) and supplied through the outermost two rows of electrodes, one side serving as cathode, the other side serving as anode, with the middle electrode row not being used for stimulation. Biphasic stimulation pulses were delivered with 250 ms first-phase durations and decaying exponential second phases. Stimulation was turned off upon completion of each rehabilitation session.

Outcome Measures

The numerous outcome measures chosen for this initial feasibility study are listed in *Table 2*. The primary focus was safety, and so patient status and potential adverse events were carefully monitored. Neurological status was measured via several scales, on numerous occasions. The most important scales used were the Upper Extremity Fugl-Meyer (UEFM) scale, the Stroke Impact Scale, and the Arm Motor Ability Test. Both patient groups were tested before randomization (baseline), during each week of treatment, and during follow-up physician visits at 1, 4, 8, and 12 weeks after the last rehabilitation session. Outcome assessments were unblinded.

Safety

The primary endpoint of this study was safety. Safety was defined by measuring the proportion of patients who had any of the following outcomes between the time of enrollment and the time that electrode was removed (approximately 23–28 d later): 1) death, 2) medical morbidity, including myocardial infarction, pneumonia, wound infection, or deep venous

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TABLE 2. Outcome measures

Measures of motor impairment:
    Upper Extremity Fugl-Meyer Scale
    Grip strength
    Action Research Arm test (ARM)
    9-hole Pegboard Test
    Tapping speed
Stroke scales:
    National Institutes of Health Stroke Scale (NIHSS)
    Stroke Impact Scale (SIS)
    Activities of daily living
    Functional Independence Measure (FIM)
Neurological measures:
    Neurological Function questionnaire
    Mental status
    Beck Depression Inventory

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thrombosis, 3) clinically definite generalized tonic-clonic seizure, or 4) decrement in neurological status, defined as a decrease in 20% on either the UEFM scale or the hand function subscore of the Stroke Impact Scale.

At baseline, the patient's medical condition was evaluated by assessing the history, performing a neurological examination, obtaining a laboratory screen, electrocardiogram, chest radiograph, electroencephalogram, and brain MRI. Neurological status was evaluated on the final day of rehabilitation. Any morbidity including seizure incidence was reported immediately for review by the study's independent data and safety monitor board.

Statistics

For safety measures, descriptive statistics were used. For assessment of neurological status, data were analyzed in two different ways; note that specific scores on the UEFM scale and Stroke Impact Scale hand subscale, and not percentage change, were used in these analyses. First, longitudinal effects were analyzed using repeated measures analysis of variance, examining the time × treatment group interaction. As an extension of examining longitudinal effects, an intention to treat analysis was performed using a mixed linear model, a generalization of standard linear model designed for analyzing repeated measurements, via the SAS Proc Mixed procedure (Cary, NC). Second, group characteristics were compared at three prespecified time points: study week 4 (1 wk follow-up after completion of treatment), the time point of greatest interest, as well as at baseline and at study week 16 (12 wk follow-up after completion of treatment). These comparisons used a t test for continuous data and Fisher's exact test for proportions. All statistical tests were conducted at the $P = 0.05$ significance level.

RESULTS

Patients

A total of 14 patients were enrolled, but 4 were excluded before randomization because they did not meet inclusion criteria. Ten patients met full inclusion criteria and were randomized, six patients to the treatment group and four patients to the control group. Two treatment patients were withdrawn from the study during week 1 of treatment because of complications in their treatment (see below). Eight patients (4 treatment, 4 control) completed the study (*Table 3*). Five patients were male. Three patients were female. Mean age was 58 years with a range of 33 to 74 years. There were no significant differences between treatment groups. All patients had suffered a cortical or subcortical ischemic cerebral infarction between 9 and 68 months before entering the study. The mean time between stroke and randomization was 28 months (range 9–68 mo). The infarction occurred in the right hemisphere for four patients and in the left hemisphere for four patients. Three surgery patients received implants on their right hemisphere, whereas one surgery patient received an implant on the left hemisphere.

Complications and Safety

No patient deaths occurred. No patient demonstrated new neurological deficits during the period of assessment. There were no seizures during study participation for any patient, in either study group.

Two complications occurred, both infectious. One acute infection resulted from a surgical protocol violation. Instead of being tunneled to a supraclavicular exit site, the lead was tunneled only to within 2 cm of the craniotomy wound. The second complication was an electrode lead breakage caused by tension on the electrode lead. Rather than risk reimplantation, the electrode was removed and the patient taken off active treatment. This patient subsequently fell and traumatically reopened the wound, resulting in an infection, which was treated effectively. Thus, of six surgical patients, two patients were excluded from the efficacy statistics.

Safety was also assessed by looking for a decline in motor status during the 16 weeks of study assessments, using the Fugl-Meyer arm motor score. Compared with baseline Fugl-Meyer score, none of the patients randomized to cortical stimulation had a 10% or greater decline at any of the follow-up

TABLE 3. Baseline patient characteristics[a]

	Overall (n = 8)	Investigational (n = 4)	Controls (n = 4)	P value
Sex	5 M, 3 F	2 M, 2 F	3 M, 1 F	1.0
Age (yr)	58 ± 16 (33–74)	58 ± 17 (34–74)	58 ± 18 (33–73)	1.0
Months since stroke	28 ± 20 (9–68)	18 ± 18 (9–33)	38 ± 24 (15–68)	0.2
Upper Extremity Fugl-Meyer	38 ± 7 (24–48)	36 ± 9 (24–43)	41 ± 5 (38–48)	0.4
Hand Stroke Impact Scale	24 ± 18 (0–60)	23 ± 26 (0–60)	26 ± 14 (5–35)	0.8
Beck Depression Inventory	8.3 ± 6.0 (1–18)	6.8 ± 5.9 (1–15)	9.8 ± 6.7 (3–18)	0.5
Modified Rankin	2.1 ± 0.6 (1–3)	2.0 ± 0.8 (1–3)	2.3 ± 0.5 (2–3)	0.6
Handedness	6 right, 2 left	4 right, 0 left	2 right, 2 left	0.4
Stroke affected brain hemisphere	4 right, 4 left	1 right, 3 left	3 right, 1 left	0.5

[a]M, male; F, female. Values are mean ± SD. The mean time from stroke to study enrollment was more than twice as long in the control group (15, 22, 46, and 68 months) as compared with the investigational group (9, 11, 18, and 33 months). However, this difference was not significant.

periods. However, one stroke patient randomized to the control intervention (physical therapy only) had a 16% decline during follow-up. As an additional means of addressing this issue, Fugl-Meyer scores were also compared from each visit to the next. None of the patients randomized to the cortical stimulation group had a 10% or greater decline in the arm motor Fugl-Meyer score at any of the follow-up visits. On the other hand, one control patient had a 16% decline at follow-up week 1, and another control patient had a 13% decline at follow-up week 4.

Efficacy Assessments

From baseline to study week 16, the UEFM score in the investigational study group (n = 4) improved by 10 points, compared with only 1.9 points for the control group ($P < 0.05$) (*Table 4*). Repeated measures analysis of variance was $P < 0.0001$ overall, $P = 0.08$ by time, and $P = 0.02$ for the group × time interaction. Scores for the UEFM results are presented in *Figure 1*, which demonstrates that patients in the investigational active treatment (rehabilitation with cortical stimulation) group improved to a significantly greater degree than control patients (rehabilitation only). Furthermore, patients in the active treatment group continued to improve through the 3 week treatment period into the 1 week follow-up assessment (study week 4). Improvements were maintained through the 12 week follow-up assessment (study week 16). In comparison, lesser improvements in control patients occurred within the first 2 weeks and then seemed to decrease over time (*Fig. 1*).

In an intention to treat analysis, scores were also analyzed using all available serially collected Fugl-Meyer data for all 10, rather than just 8, patients (i.e., including all available data from the 2 patients who dropped out of the study because of infection). The difference between treatment groups remained significant ($P = 0.027$).

Correlation between *f*MRI and Cortical Stimulation

Five of the six investigational patients were able to have muscle activity evoked in the contralateral arm/hand by direct epidural stimulation over the neuronavigationally deter-mined center of the *f*MRI "hot spot" at the time of craniotomy for electrode placement. Stimulation parameters for evoking distal, contralateral muscle activity are shown in *Table 5*. Because patients were under general anesthesia, the current levels were sometimes quite high. However, the type of evoked movements were characteristic of stimulation of primary motor cortex and often consisted of individual finger movements or simultaneous flexion of several fingers. In other words, the accuracy of the *f*MRI for identifying motor cortex in these patients was confirmed for five of six patients. Because the depth of anesthesia could not be controlled, the reason for the lack of response in the sixth patient could not be determined.

DISCUSSION

Stroke remains a major source of disability. There are currently few options to promote return of strength medically. Reports of motor gains during epidural stimulation of motor cortex for chronic poststroke pain suggested the current approach. The results suggest that this approach might provide significant gains. The safety assessments were significant for two infections, which, although explained by a protocol violation and a faulty electrode lead, nevertheless suggest the need to carefully collect safety data in any future studies of this approach.

Early clinical studies of the effectiveness of motor cortex stimulation focused on reduction in central pain arising from thalamic infarction or neuropathic pain arising from trigeminal nerve injury (6, 8, 11–14, 16, 18–20, 22, 24–27). The authors of these studies hypothesized that motor improvement was secondarily observed to occur because of improvement in the spasticity associated with the patient's stroke. Hosobuchi et al. (11) described a 53-year-old man with right hemiparesis, dysarthria, and bulbar pain 3 years after his stroke. Despite not achieving satisfactory analgesia from the motor cortex stimulation, this patient chose to have the stimulator internalized "because [he] was so pleased with the marked improvement in his motor weakness." In a later review, Katayama et al. (13) quantified the motor improvement that was observed with

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TABLE 4. Upper Extremity Fugl-Meyer (A) and Hand Stroke Impact Scale (B) results by study group[a]

(A) UEFM	Baseline score	Study week 4 (1 week follow-up) score	Study week 16 (12 week follow-up) score
Investigational	35.3 ± 7.8 (24.0–42.0)	45.5 ± 10.8 (30.0–53.0)	45.3 ± 9.7 (32.0–53.0)
Control	40.6 ± 5.3 (36.0–48.0)	44.5 ± 12.0 (34.0–60.0)	42.5 ± 8.9 (34.0–52.0)
P value[b]		0.12	0.047
(B) Hand SIS	Baseline score	Study week 4 (1 week follow-up) score	Study week 16 (12 week follow-up) Score
Investigational	26 ± 14 (5–35)	70 ± 40 (10–95)	69 ± 34 (20–95)
Control	23 ± 26 (0–60)	51 ± 29 (25–90)	46 ± 33 (25–95)
P value[b]		0.3	0.2

[a] UEFM, Upper Extremity Fugl-Meyer; SIS, Stroke Impact Scale.
[b] Comparison in improvement from baseline between investigational and control patients by *t* test. Values are mean ± SD.

TABLE 5. Stimulation parameters for evoking contralateral distal muscle activity by epidural stimulation over the functional magnetic resonance imaging identified area of motor cortex in six patients[a]

Subject	Frequency (Hz)	Pulse duration (ms)	Amplitude (mA)	Train duration (sec)
1	400	500	35	0.005
2	50	300	15	3
3	50	400	17.5	5
4	No MEP/movement			
5	50	250	15	3
6	400	500	30	0.005

[a] MEP, motor evoked potential.

motor cortex stimulation. In 19% of patients who underwent epidural cortical stimulation for pain control, motor cortex stimulation improved their hemiparesis. The benefit was thought to be unrelated to the extent of pain control. Garcia-Larrea et al. (8) reported that this effect might be caused by a "not quantified relief of spasticity during motor cortex stimulation" in "some" of their patients with strokes. Franzini et al. (7) observed diminished stroke-related dystonia and intentional myoclonus with motor cortex stimulation along with pain relief. Four patients experienced pain control associated with reduced intentional myoclonus. These findings are consistent with Katayama et al.'s clarification that there was a significant reduction in effective pain relief when there was moderate or severe weakness in the painful region targeted. Satisfactory pain control was achieved in 73% of the patients in whom motor weakness in the painful region was absent or mild but only in 15% of the patients who had moderate or severe weakness in the painful region (13). The effects of motor cortex stimulation are thus mediated through the motor system.

A number of centers have since undertaken preclinical studies to confirm the benefits observed anecdotally in motor recovery. Adkins-Muir and Jones (1) studied the effect of perilesional, subdural motor cortex stimulation on a skilled forelimb task in rats with ischemic cortical injury. Low-frequency intermittent stimulation during poststroke rehabilitation significantly improved the forelimb retrieval task. Performance levels persisted when tested 2 days after stimulation was discontinued. Dendritic density in layer V of the peri-lesion cortex also increased. Kleim et al. (15) investigated the hypothesis that after a focal ischemic cortical infarction, motor cortex stimulation combined with rehabilitation expands the cortical representation of contralateral forelimb movement. Rats with an ischemic cortical infarct underwent 50 Hz cortical stimulation at 50% of the threshold for limb movement while the accuracy of achieving reaching tasks was measured. Cortical stimulation significantly enhanced motor recovery and increased the area of peri-infarct cortex from which micro-

stimulation movements could be evoked. Teskey et al. (23) used an alternate model of cerebral ischemia and also implanted recording electrodes for measuring frontal evoked potentials. Addition of cortical stimulation to rehabilitative training improved behavioral status and enhanced evoked potentials and also reduced the amount of current required to elicit a movement in a stimulation frequency dependent manner.

Plautz et al. (21) used a primate model of cortical ischemic infarction to investigate the benefits of motor cortex stimulation. These authors mapped the proximal forelimb motor cortex (M1) region using intracortical microstimulation techniques. An infarct was created using bipolar electrocoagulation over the neurophysiologically identified M1 hand representation regions of the squirrel monkeys. After 3.5 to 5 months, spontaneous motor recovery had stabilized, although significant motor impairments persisted. Cortical stimulation was combined with rehabilitative training for 2 to 4 weeks. Pellet retrieval from small wells showed statistically significant gains although not to pre-infarct abilities. Cortical mapping showed that there was a significantly increased hand representational area, with newly emerged hand representations apparent adjacent to the infarct as well as at a considerable distance from the infarct. This study is important because is
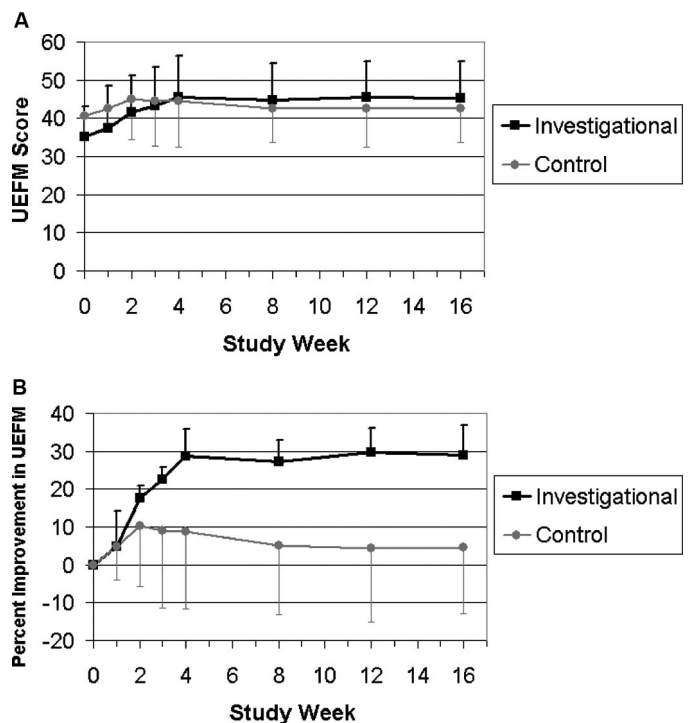

FIGURE 2. Changes in UEFM scores for the control and investigational patient groups. Group means and standard deviations. A, raw scores show greater gains in investigational group, but initial deficits were more severe in this group. Repeated measures analysis of variance was P < 0.0001 overall, P = 0.08 by time, and P = 0.02 for the group × time interaction. B, greater gains in investigational group can be appreciated by presentation of data as percentage improvement in the UEFM score.
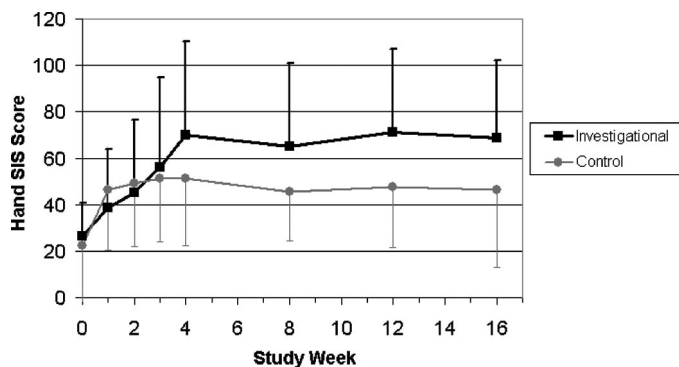
FIGURE 3. *Changes in Hand Function Subscore of the Stroke Impact Scale as a function of study participation for the control and investigational groups. Group means and standard deviations. Analysis of variance was P = 0.001 overall, P = 0.14 by group, P = 0.001 by time, P = 0.03 group by time.*
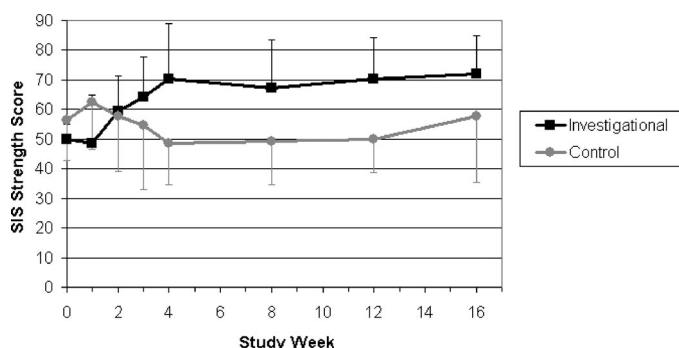

FIGURE 4. *Changes in Strength Subscore of Stroke Impact Scale as function of study participation for control and investigational groups. Group means and standard deviations. Analysis of variance was P < 0.0001 overall, P < 0.0001 by group, P = 0.06 by time, P = 0.02 group by time.*

demonstrates that poststroke motor gains can be achieved outside of the subacute poststroke period.

These findings support the hypothesis that increased motor cortical representation derives from enhanced synaptic function and restoration of cortical circuitry brought about by cortical stimulation with rehabilitation. These preclinical studies when combined with the extensive clinical literature of enhanced motor function that occurs during cortical stimulation for central pain provide the background for a clinical investigation of the safety of enhancing outcome after nonhemorrhagic stroke in humans (3).

Bezard et al. (2), in 1999, published a primate study assessing the potential risk of inducing epileptic seizures using chronic motor cortex stimulation parameters similar but for a greater duration than parameters proposed in this clinical trial. The primate study used chronic motor cortex stimulation parameters similar to what is used to relieve chronic pain. In this study, none of the primates developed epileptic seizures at the stimulation parameters (i.e., frequency and pulse duration of approximately 40 Hz and 90 μs, respectively, and at a subthreshold intensity for inducing muscle movement). Sei-

zures could only be induced at intensities approximately twice as high as necessary to evoke motor movement. Although cortical reorganization is hypothesized to be the explanation for this improvement, the precise mechanism for this enhancement of function is not yet known.

Another possible explanation is the inhibition during stimulation of regions that have developed hyperactivity after stroke and confound effective motor function or retraining. For example, Tsubokawa et al. (25) noted inhibition of thalamic hyperactivity by motor cortex stimulation in a cat deafferentation model wherein the spinothalamic tract had been sectioned. Garcia-Larrea et al. (8, 9) observed regions of increased blood flow when positron emission tomographic scans were performed during motor cortex stimulation of patients with central pain syndromes. The most significant increase in regional cerebral blood flow was seen in the ventral lateral thalamus, probably reflecting corticothalamic connections from motor areas. This could reflect direct enhancement of motor output or secondary enhancement of this region from inhibition of other regions. It is not yet clear how the hypothesis of thalamic electrophysiological inhibition fits in with these identified sites of increased regional cerebral blood flow.

It appears both from preclinical studies and the current study that the enhancement of function persists after withdrawal of cortical stimulation. This observation suggests that the motor improvement represents more than direct enhancement of surrounding marginally functional cortical neurons. It also suggests that the improvement is not simply an indirect result of inhibition of confounding regions of hyperactivity. During intraoperative cortical mapping, individual finger contractions occurred, movements that were not present before stimulation through voluntary effort. The combination of rehabilitation and stimulation may enhance the plasticity of marginally effective circuits, leading to improved voluntary function.

The primary goal of this study is to demonstrate the safety of this procedure. Most importantly, there was no deterioration in neurological function observed from the surgery to implant a cortical stimulating electrode. The two groups were well randomized (*Table 3*). Although a trend (*P* = 0.20) favored earlier time poststroke for enrollment of the experimental group, these subjects were more than a year beyond the 3 month interval poststroke generally considered to represent the main time of behavioral recovery plateau (5, 17). An additional weakness was the lack of blinding during outcome assessments in patients with versus without craniotomy. Blinding could be added to future studies in several different ways. For example, each investigational group patient could serve as his/her own control by comparing results when the device is switched on with results when device is switched off. Alternatively, raters blinded to patient treatment group could be used to assess motor status.

Two patients developed an infection during study participation, one in association with a protocol violation and the second in association with a faulty lead. These complications do not likely portend a high infection rate for future applica-

tions of the surgical approach when the procedure is performed according to dictated protocol. Furthermore, in future trials of this treatment, it is anticipated that the leads will not be externalized, reducing both the risk of lead fracture and infection. Some key clinical endpoints, such as the Fugl-Meyer motor score, demonstrated a statistically significant gain in relation to cortical stimulation. These are not trivial gains; however, the full clinical significance of these findings will be evaluated in future, larger studies that are focused on efficacy.

This safety study demonstrates that cortical stimulation can be safely performed in a population of patients with cerebrovascular disease who are at risk for surgical morbidity. Preliminary motor assessment data also show that intermittent cortical stimulation delivered during periods of rehabilitation activity does enhance upper extremity functional recovery when compared with control groups of patients who receive only rehabilitation. More extensive study is required to confirm and to clarify clinical efficacy (*Figs. 2*, *3*, and *4*).

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Acknowledgments

COMMENTS

This study provides an interesting contribution to the field in attempting to address an important problem for which there is not much to offer. Stroke is among the leading causes of disability in the United States. Physical therapy can be beneficial, but the benefits are limited and large numbers of patients are disabled. In this context, developing therapies aimed at improving the recovery from stroke are important.

The authors report a prospective randomized study to evaluate

safety of epidural motor cortex stimulation for motor recovery from stroke. They enrolled 10 patients randomized into a group of six undergoing stimulation and four control patients. The surgical group underwent the procedure guided by functional magnetic resonance imaging (fMRI) localization of the hand and neuronavigation, epidural implantation of a 3×3 grid centered on the fMRI hot spot, followed by externalization of the leads with 1 week of recovery and then stimulation at 50% of motor threshold while undergoing a 3-week rehabilitation as with the control group prior to removal of the implants. Patients were assessed for a total of 16 weeks with various scales. The outcome showed the control group improved average of 5% and stimulation group improved 29% which was statistically significant. Complications included two infections and there were no seizures.

Several factors can influence motor outcome after stroke. These include age, location of the lesion, co-morbidities, and the time elapsed since stroke. In the present study, the control group had more than double the time elapsed since stroke than the group undergoing cortical stimulation. The authors report the average time since stroke, as well as the patients with the shortest and longest time intervals since stroke. Evaluation of the data show that the patient with the shortest interval was at 9 months since stroke in the investigational group and 15 months in the control group. The patients with the longest intervals since stroke were 33 months in the investigational and 68 months in the control group. These large differences may partially influence the outcomes observed in the investigational group in relation to controls.

The authors have argued that the potential for motor recovery after a stroke is greatest in the first weeks after the event, making the issue of time since stroke less relevant since all patients were at least 9 months since the ictus. Nevertheless, late improvements in motor function can be seen with rehabilitation therapy, as also evidenced by the small improvements observed in the control group of the present study. Thus the issue of time since stroke is important and needs to be disclosed for all patients in conjunction with the respective outcomes.

The authors have provided an interesting contribution to the field. The primary endpoint of the study was assessment of efficacy of this new technique. Although two patients presented with infections in the postoperative period, no permanent neurological damage or seizures were associated with the therapy. Given the lack of alternatives for this very disabled population, the results presented by the authors indicate relative safety of motor cortex stimulation and emphasize the importance of conducting larger prospective trials.

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Sponsored by Northstar Neuroscience (Seattle, Washington), Brown et al. have demonstrated in a randomized, unblinded study improvements in motor function using subthreshold epidural cortical stimulation delivered concurrently with intensive rehabilitation therapy. The brain has a great deal more plasticity than we generally think. The anecdotal observation of functional improvement in patients with implanted motor cortical stimulators (MCS) for a variety of pain syndromes has led to some very interesting work in rehabilitation. Both clinical studies and animal studies have demonstrated considerable plasticity following stroke. This work is nicely outlined by the authors.

There is now considerable evidence that cortical reorganization to compensate for motor deficit occurs predominately through mechanisms involving enhanced activity of pre-existing networks (3, 7, 10).

The combination of rehabilitation training with stimulation whether peripheral, transcranial magnetic stimulation, or MCS seems to have the ability to enhance the behavioral gains (2, 5, 6, 13). The case for transcranial magnetic stimulation seems to be just as strong, if not stronger than MCS (8, 9, 11, 12). In addition, even peripheral stimulation may be of value (1, 4, 14).

Although a safety study, the efficiency observed is interesting. Significant improvements were seen in the upper extremity Fugl-Meyer and hand function scores of the Stroke Impact Scale. These improvements were not trivial, but they were also not particularly large. Many investigators thought that once they occur, these changes tend to be permanent, but this remains to be determined. It would be most interesting to follow up on these patients 1 year after rehabilitation to see if they maintain their improvement. Furthermore, if internalized, MSC could be equally effective in subsequent training episodes. Although this study was performed under intensive physical therapy, home-based self-administration also could be possible. Such a program might be quite effective if stimulation perimeter are subthreshold and could be routinely obtained while avoiding.

Since this study, the technology for MCS has significantly advanced. Follow-up studies have been performed and await publication. Although there is not a particularly strong placebo effect in these types of studies, bias can always be introduced in subjective evaluations. Blinded study will have to be performed at some point. With the advances in noninvasive techniques such as transcranial magnetic stimulation, a head-to-head comparison may be necessary before MCS receives widespread acceptance in the rehabilitation community. The authors are to be congratulated on this work and hopefully can provide us with long-term follow-up.

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Recovery from stroke remains an elusive goal that would have considerable impact on the lives of thousands of individuals who have been so disabled. In an aging population, the need for innovative strategies to stroke recovery is likely to increase. Brown et al. have demonstrated relative safety of MCS in a small cohort of stroke patients. This is a necessary first step in the investigation of a new therapy. The absence of significant adverse effects supports the previous data of safety in patients who have received MCS in the treatment of chronic pain.

However, the question of efficacy is still unresolved. The authors have been able to demonstrate a more robust improvement in the Fugl-Meyer scores of patients receiving stimulation. This is certainly a very exciting result. But, as the authors themselves correctly point out, because this study is not blinded, the possibility for a potent placebo effect is considerable. Also worrisome is the comment that two of the non-operated patients experienced spontaneous decreases in their scores during the period of the study. This seems unusual in a group of patients who are an average of 38 months out from their stroke and should have achieved stable scores. The small size of this study is such that an aberrant decline in one or two patients might well shift the outcomes considerably. A larger study with patient and evaluator blinding to stimulation will certainly be required.

The authors are to be commended for exploring this potentially groundbreaking area with appropriate care and precision. Their discussion intelligently explores potential mechanisms by which this treatment may be exerting an effect. As this treatment is investigated further we may learn quite a lot about cortical plasticity and its mechanism.

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