Rehabilitation for patients with aphasia typically focuses on behavioral and environmental interventions for the language disorder. Despite the extensive literature indicating that individuals with aphasia benefit from language treatment, most patients are left with residual deficits that affect their daily communication as well as their quality of life.

There is a growing interest in the use of novel biological therapies that might enhance language recovery and rehabilitation in patients with neurological impairments. Preclinical animal studies have shown that direct, focused subthreshold electrical stimulation to the forelimb representation of the cortex enhanced motor recovery in rodents and primates following focal brain lesions.[1-5] Based on feasibility studies in stroke patients with hemiparesis, cortical stimulation in conjunction with hand rehabilitation appears safe and possibly has some benefit in upper limb motor function compared to rehabilitation alone.[6] Interestingly, during participation in the motor recovery study, two individuals with Broca's aphasia provided anecdotal evidence of speech and language improvement.

Given the functional and anatomical relationship between language and motor systems in the brain, we hypothesized that cortical stimulation in conjunction with speech-language rehabilitation might also enhance recovery of language function in patients with Broca's aphasia. The purpose of this prospective, randomized, single-blind, feasibility study was to assess the safety and efficacy of targeted sub-threshold epidural cortical stimulation delivered concurrent with speech-language therapy in stroke survivors with chronic Broca's aphasia.

METHODS

Subjects: Eight right-handed individuals with chronic Broca's aphasia were enrolled and met study requirements. All participants had a single left-hemisphere ischemic stroke at least one year earlier. The first four subjects were randomly assigned to either the investigational or the control group. The second four subjects were matched on aphasia severity to the first four subjects and then assigned to the opposite group.

Intervention

The investigational group (N=4) received both the surgical protocol with stimulation system implant/cortical stimulation and the intensive therapy protocol. The control group (N=4) received identical intensive speech-language therapy, but without surgical implantation or cortical stimulation.

Surgical Protocol: The cortical stimulation target was identified by functional imaging. Placement of epidural electrodes was localized to the left premotor cortex in an area activated by overt speech. Subjects were surgically implanted with an investigational cortical stimulation device (Northstar Neuroscience, Seattle, WA) including an epidural electrode grid placed over the fMRI-determined site. A lead connected the grid to a pulse generator implanted in a subclavicular pocket, which could then be programmed externally. Electrical stimulation was set at 50% of threshold, defined as the level that affected language function or induced movement. The targeted subthreshold cortical stimulation was only delivered concurrent with intensive speech-language therapy.

Speech-Language Therapy Protocol: Both groups received 6 weeks of intensive speech and language therapy i.e. 3 hours a day, 5 days a week. Therapy included apraxia drills (30 minutes), cued naming tasks (30 minutes), choral reading of sentences (60 minutes), and conversation practice (60 minutes).

Outcome Measures: The primary speech and language recovery outcome measure was Western Aphasia Battery - Aphasia Quotient (WAB-AQ) with a 5 point improvement from baseline considered a successful outcome. Secondary outcome measures included the caregiver rating on the Communicative Effectiveness Index (CETI), and neurophysiological changes in brain activation with fMRI. Speech and language measures were taken at baseline, immediately post-treatment, and at 6 week and 12 week follow-ups. fMRI measures on three tasks, observation and imitation of speech sounds, audiovisual story comprehension, and oral reading of sentences, were taken at baseline and post-treatment.

RESULTS:

WAB-AQ:

Investigational subjects showed a mean WAB-AQ change from baseline of 8.0 points at both the post-therapy and 6-week follow-up endpoints, and 12.3 points at the 12-week follow-up. The control group's mean WAB-AQ change at post therapy and 6 week follow-up was 4.6 and 5.5 points, respectively. In contrast to the 12-week WAB increase for the investigational group, the mean WAB-AQ change for the control group decreased to 3.6 points at 12 weeks. There were no data for one control subject at the 12-week follow-up.

The change in WAB-AQ was examined for each pair of subjects, matched on severity of aphasia as defined by the baseline WAB-AQ score (see Table 1). The most severe subject had the greatest amount of change in the Investigational group with an increase of 20.3 points by the 12 week follow-up. This compares to a change of only -0.5 for the most severe subject in the control group. For the least impaired subjects (mild-moderate aphasia), neither the investigational nor the control subject achieved success defined as a 5 point change on the WAB-AQ. However, the investigational subject had greater changes than the control subject immediately post-treatment and at 6 and 12 weeks follow-up.

CETI:

Mean change from the rating at baseline by caregivers of subjects in the Investigational group was 17.1, 33 and 30.8 points at post-treatment, 6-week, and 12-week follow-up respectively. Although changes were also evident in the control group, these were not as great (10.9, 16.3 and 19.6 at post-treatment. 6-week, and 12-week follow-up respectively). These results mirror the trends seen with the WAB-AQ, that the communication changes post-treatment and during the maintenance period were greater in the investigational than the control group.

fMRI Results:

fMRI data collected during repetition and oral reading exercises before and after therapy were available for 6 of the 8 subjects (mild-moderate, moderate, and severe). For repetition, whole brain activation decreased in the investigational cases and increased in control cases for moderate and severe cases. Left dorsal premotor cortex activation increased for all patients, but much less so for the investigational patients. Activation decreased in left pars opercularis

(of the inferior frontal gyrus) for the investigational cases but increased for the control patients. For oral reading, activation decreased in the occipito-temporal cortex for the investigational cases but increased for the control cases.

CONCLUSIONS

Language therapy helps nonfluent aphasia, independent of cortical stimulation. However, epidural stimulation of the ipsilesional premotor cortex may augment this effect. The largest effects might be in the maintenance phase, after completion of the therapy. The neural mechanisms underlying these effects are not clear, but could relate to remodeling of existing pathways, manifested in the brain by decreases in the volume of activity and increases in its intensity in task-relevant brain regions. Although the number of patients enrolled in this trial precludes strong conclusions, epidural stimulation may possibly play a role in increasing the potential of the underlying cortex to remodel and maintain the changes. Further investigation of this novel therapy is warranted to confirm these findings and to further elucidate the mechanisms of the effects.

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Table 1.
WAB-AQ: Change from baseline to post-treatment and 6- and 12-week follow-up

Subjects paired by severity	Group (Baseline WAB-AQ)	Post-Treatment	6-Week F/up	12-Week F/up
Severe	Investigational (AQ=34.2)	15	10.6	20.3
	Control (AQ=30.8)	2.65	2.65	-.05
Mod-severe	Investigational (AQ=45.9)	6.45	14.6	17.4
	Control (AQ=40)	11.9	12.2	Lost to f/up
Moderate	Investigational (AQ=72.0)	7.00	2.50	7.80
	Control (AQ=59.9)	3.95	4.95	8.25
Mild-moderate	Investigational (AQ=82.3)	3.45	4.25	3.75
	Control (AQ=80.0)	-.15	2.35	2.45
All Subjects (Mean±St Dev)	Investigational (Mean AQ=58.6)	8.0±4.9	8.0±5.6	12.3±7.8
	Control (Mean AQ=52.5)	4.6±5.2	5.5±4.6	3.6±4.3