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Invasive Cortical Stimulation to Promote Recovery of Function After Stroke

A Critical Appraisal

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Background and Purpose—Residual motor deficits frequently linger after stroke. Search for newer effective strategies to promote functional recovery is ongoing. Brain stimulation, as a means of directing adaptive plasticity, is appealing. Animal studies and Phase I and II trials in humans have indicated safety, feasibility, and efficacy of combining rehabilitation and concurrent invasive cortical stimulation. However, a recent Phase III trial showed no advantage of the combination. We critically review results of various trials and discuss the factors that contributed to the distinctive result.

Summary of Review—Regarding cortical stimulation, it is important to determine the (1) location of peri-infarct representations by integrating multiple neuroanatomical and physiological techniques; (2) role of other mechanisms of stroke recovery; (3) viability of peri-infarct tissue and descending pathways; (4) lesion geometry to ensure no alteration/displacement of current density; and (5) applicability of lessons generated from noninvasive brain stimulation studies in humans. In terms of combining stimulation with rehabilitation, we should understand (1) the principle of homeostatic plasticity; (2) the effect of ongoing cortical activity and phases of learning; and (3) that subject-specific intervention may be necessary.

Conclusions—Future cortical stimulation trials should consider the factors that may have contributed to the peculiar results of the Phase III trial and address those in future study designs. (*Stroke*. 2009;40:1926-1931.)

Key Words: electrical stimulation of the brain ■ neuronal plasticity ■ recovery of function ■ stroke rehabilitation

Upper limb function is one of the best predictors of long-term disability after stroke.¹ Rehabilitation improves upper limb function and reduces disability.²⁻⁸ Nevertheless, despite extensive therapy, recovery is frequently incomplete.⁹ Improved rehabilitation methods are needed to achieve higher levels of recovery. One appealing approach is neuromodulation through invasive cortical stimulation to supplement the effects of rehabilitation. Studies in animals¹⁰⁻¹⁵ and humans,¹⁶⁻¹⁹ which combined rehabilitation with concurrent invasive cortical stimulation, have provided encouraging results. However, these results have been contradicted by a recent industry-sponsored Phase III trial that showed no advantage of the combination. We critique the relevant literature, discuss factors that contributed to this distinctive result, and provide guidance for future studies. It is, however, important to first understand mechanisms of recovery, rehabilitation, and brain stimulation.

Spontaneous, Rehabilitation-Based, and Stimulation-Based Stroke Recovery

Spontaneous recovery of upper limb function involves different mechanisms, including (1) peri-infarct reorganization²⁰; (2) recruitment of ipsilesional^{21,22} or contralesional areas²³; and (3)

shifts in interhemispheric interactions^{24,25} and bihemispheric connectivity.²⁶ Rehabilitation modulates one or more of these mechanisms, enhancing some and suppressing others, to improve function. For example, rehabilitative distal forelimb training in primates²⁷ and hand retraining²⁸ and language therapy in aphasia²⁹ in humans are associated with peri-infarct reorganization. Virtual reality training promotes ipsilesional sensorimotor activation.³⁰ Lastly, active-passive bilateral training³¹ and constraint-induced movement therapy⁸ help return interhemispheric balance. Nonetheless, despite extensive therapy, effect sizes for upper limb neurorehabilitation are small and residual deficits linger.^{9,32}

Brain stimulation, as an adjunct to other therapies, may magnify therapeutic outcomes. Its overarching aim is to increase ipsilesional excitability or decrease contralesional excitability.³³⁻³⁷ Noninvasive brain stimulation techniques, like high-frequency repetitive transcranial magnetic stimulation (rTMS),^{38,39} anodal transcranial direct current stimulation,⁴⁰ or intermittent θ -burst stimulation delivered ipsilesionally,^{41,42} or low-frequency rTMS,^{43,44} cathodal transcranial direct current stimulation,⁴⁵ or continuous θ -burst stimulation^{41,42} delivered contralesionally, improve hand func-

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Table 1. Different Types of Cortical Stimulation Used in Stroke Motor Rehabilitation

Mode and Depth	Duration	Frequency	Intensity	Location	No. of Sessions
rTMS					
Transcranial	10 minutes, ^{38,44,67,73} 8 minutes, ³⁹ 20 minutes, ^{70,81} 25 minutes ^{43,46,63}	1 Hz, ^{43,44,46,63,67,70,73,81} 3 Hz, ³⁸ 10 Hz ³⁹	80%, ³⁹ 90%, ^{63,70} 80%, ³⁹ 100%, ^{43,44,67,73,81} 120% ³⁸ MT Induced currents—1.45– 4.35 A/m ² (healthy brain); 1.85–7.42 A/m ² ⁶⁵	Contralesional M1, ^{43,44,46,63,67,70,73,81} ipsilesional M1, ^{38,39} contralesional PMC ⁴⁴	1 day, ^{39,44,46,63,67,70,73} 5 days, ⁴³ 8 days, ⁸¹ 10 days ³⁸
tDCS					
Transcranial	7 minutes, ⁸² 20 minutes ^{40,45,66,83}	NA	1 mA, ^{45,83} 1.5 mA ⁸²	Anodal over ipsilesional M1, ^{40,66,82} cathodal over contralesional M1 ^{45,83}	1 day, ^{40,66} 5 daily or 4 weekly, ⁸³ 30 sessions/6 weeks ⁸²
TBS					
Transcranial	600 pulses (intermittent), 300 pulses (continuous) ^{41,42}	(3 pulses at 50 Hz), applied at 5 Hz ^{41,42}	80% ^{41,42}	Intermittent over ipsilesional M1 and continuous over contralesional M1 ^{41,42}	1 day ⁴²
DCS					
Epidural	150 minutes ^{16–19}	50–101 Hz ^{16–19}	50% MT or 6.5 mA ^{16–19}	Ipsilesional M1 ^{16–19}	3–6 weeks

tDCS indicates transcranial direct current stimulation; TBS, theta-burst stimulation; DCS, direct cortical stimulation; MT, motor threshold; PMC, premotor cortex; NA, not applicable.

tion.^{43,44,46} See Table 1 for details about stimulation parameters of all common types of cortical stimulation used in stroke rehabilitation. However, the functional improvement from these stimulation methods alone is only 10% to 30% and is short-lasting.^{33,37,47} In the search for more effective and longer-lasting interventions, the combination of rehabilitation and brain stimulation seems reasonable. Safety and efficacy of the combination of implantable cortical stimulation and rehabilitation is supported by animal studies (Table 2).

Animal Studies of Rehabilitation Combined With Invasive Brain Stimulation

Although animal models do not mimic stroke per se, because the predisposing conditions of stroke typically are absent, they reduce covariates and allow mechanistic investigation. Efficacy of a combination of invasive cortical stimulation and rehabilitation was tested in squirrel monkeys. Artificial infarcts were induced that destroyed most of the distal forelimb representation in the primary motor cortex (M1). After spontaneous recovery, animals were rehabilitated on a complex distal forelimb task,¹⁰ whereas the contralateral peri-infarct cortex in M1 was directly stimulated using implanted subdural electrodes. Electrodes covered the proximal representations in peri-infarct M1 and also spanned the forelimb representation in the adjacent dorsal premotor cortex. See Table 2 for details about stimulation parameters. After training, performance approached preinfarct level. In rats too, cortical stimulation was deemed safe and effective over a wide range of stimulation parameters, although the greatest efficacy was demonstrated for frequencies between 50 and 100 Hz.^{11–13} Furthermore, monopolar cathodal stimulation proved to be most beneficial¹⁴ (Table 2). The mechanisms of recovery from combined rehabilitation and concurrent invasive cortical stimulation were enhanced synaptic potentiation in layer V,¹² expansion of distal forelimb representations,^{10,14}

and greater neuronal density^{11,13,15} in peri-infarct M1. In summary, studies in nonhuman primates and rodents provided evidence that cortical stimulation is safe, effective for rehabilitation, and induces peri-infarct reorganization.

Pilot Study of Combined Rehabilitation and Invasive Brain Stimulation in Humans

An initial case study¹⁷ was conducted on a patient with subcortical stroke. Using functional MRI (fMRI), the wrist area of activation in M1 was defined. A 3×3 array of electrodes was implanted epidurally over the fMRI location. Viability of descending pathways was confirmed by evoking movements. The paretic arm and hand were trained concurrent with subthreshold invasive cortical stimulation (Table 2). After 3 weeks of combined treatment, the patient was able to perform a pincer movement; additionally, the scores on the Upper Extremity Fugl-Meyer (UEFM) and Stroke Impact Scale improved significantly.

Phases I, II, and III of Combined Rehabilitation and Invasive Brain Stimulation in Humans

After the successful case study, a Phase I trial was conducted to evaluate the safety of the combined approach.¹⁶ Eight patients were divided into 2 groups; one received invasive cortical stimulation concurrent with rehabilitation of the paretic upper limb and the other received rehabilitation alone. Methods were the same as described earlier.¹⁷ During confirmation of the stimulation site, high current levels were needed to evoke movements because patients were under general anesthesia. After 3 weeks of combined treatment, one patient sustained a postoperative infection due to protocol deviation and another had electrode lead breakage. Overall, however, the intervention proved safe.

In the Phase II trial, 24 patients^{18,19} were divided equally into 2 groups like in Phase I.¹⁶ Rehabilitation lasted 6 weeks.¹⁹

Table 2. Studies of Concurrent Direct Cortical Stimulation and Physical Rehabilitation for Functional Recovery in Stroke

Study	Phase	Purpose	Electrode Type	Frequency Current Duration	Behavioral Results	Reorganization Results
Plautz et al (2003)	Primate	Feasibility and safety	Subdural (circular 1.5 mm ²)	50 Hz 50% MT 1 s	Improved distal forelimb function	Expansion of distal forelimb representation in peri-infarct M1
Kleim et al (2003)	Rodent	Compare different polarities	Subdural electrodes (0.4 mm ²)	50 Hz 50% MT 1 s	Higher reach accuracy in monopolar cathodal group	Increased functional peri-infarct cortex
Teskey et al (2003)	Rodent	Compare different frequencies	Subdural (0.4×3 mm ²)	0, 25, 50, 100, 250 Hz 50% MT 3 s	Frequency ≥50 Hz showed increased accuracy	Frequency ≥50 Hz showed increased polysynaptic potentiation
Adkins-Muir and Jones (2003)	Rodent	Compare different frequencies	Subdural (1×3 mm ²)	0, 50, 250 Hz 50–70% MT 3 s	50-Hz group improved most in accuracy	50 Hz group— increased MAP-2 reactivity in the perilesional cortex
Adkins et al (2006)	Rodent	Compare polarities and try epidural method of electrode implantation	Epidural (0.4×2 mm ²)	0, 100 Hz 50% MT 3 s	Reaching performance better in stimulated groups	Neuronal density increased in perilesional cortex in cathodal 100-Hz group
Adkins et al (2008)	Animal	Variation of Cortical stimulation effects based on impairment level	Epidural monopolar	100 Hz 40–50% MT	Reaching improved in moderately impaired rats, not in severely impaired rats	Moderately impaired rats showed increase in the efficacious synapses
Brown et al (2003)	Human-single case	Explore combined treatment in humans	Epidural	50 Hz 4.5 mA 100 s	Improvement on pincer movement, UEFM, and SIS	Not explored
Brown et al (2006)	Human-Phase I (8 patients)	Safety	Epidural (3×3 array of 2-mm electrodes)	50 Hz 50% MT or 6.5 mA 3 s	Improvement on UEFM and SIS—2 patients withdrawn	Not explored
Phase II (Huang et al, 2008; Levy et al, 2008)	Human (24 patients)	Efficacy and safety	Epidural (2×3 array of 3-mm electrodes)	50 and 101 Hz 50% MT or 6.5 mA 3-s pulse trains	Combined group showed greater improvement on UEFM and AMAT	Not explored
Phase III clinical trial	Humans (146 patients)	Effectiveness and safety	Epidural (2×3 array of 3-mm electrodes)	50 Hz 50% MT or 6.5 mA 250-μs pulse duration	Combined group not better than control group on UEFM and AMAT	Not explored

SIS indicates Stroke Impact Scale; AMAT, Arm Motor Ability Test; MT, motor threshold; MAP, microtubule-associated protein.

Frequency was 50 Hz or 101 Hz versus 50 Hz in Phase I (Table 2). During confirmation of the stimulation site, movements or sensations were elicited in the contralateral arm in 42% of the patients in the combined treatment group. Significantly more patients in the combined treatment group showed clinically meaningful improvement on the UEFM (combined treatment: 67%; rehabilitation alone: 25%). Half the patients in the combined treatment group reached the composite end point, ie, clinically significant improvement on UEFM as well as Arm Motor Ability Test at posttest¹⁹ and at follow-up.¹⁸ Thus, the Phase II trial supported greater efficacy of rehabilitation with concurrent invasive cortical stimulation than rehabilitation alone.

The results of Northstar Neuroscience's Phase III study were released in January 2008, which showed no advantage for combination of concurrent invasive cortical stimulation and rehabilitation. The trial enrolled 146 patients (combined=91, rehabilitation alone=55). Methods were the same as in Phase II. The proportion of patients in the combined treatment group, who (1) improved on the UEFM alone; (2) improved on the Arm Motor Ability Test alone; or (3) achieved the composite end point, was not significantly different than in the rehabilitation alone group. The findings of this Phase III trial seem surprising in light of positive findings in the previous studies. We discuss various aspects of the combination treatment that warrant future investigation.

Review of Factors That Need Further Investigation in Cortical Stimulation Trials

Localization of the Site of Stimulation

Invasive cortical stimulation trials have used fMRI to localize site of stimulation. However, there are important limitations of fMRI data collection and analysis in relation to rehabilitation. First, the fMRI task should correspond with the parts of the body targeted by rehabilitation. In all trials, fMRI was used to find the locus of hand/wrist/finger movement,^{16–19} but rehabilitation was aimed at improving coordination of shoulder, elbow, and distal joints during reach/grasp and self-care. Second, patients with stroke show greater head motion than healthy control subjects.⁴⁸ Head motion should be included as a covariate in analysis.⁴⁹ Third, besides fMRI, techniques like (1) morphological localization of M1 using craniometer landmarks; (2) phase reversal to localize the central sulcus; and (3) motor mapping⁵⁰ would provide a more accurate location for stimulation in future studies.

Targeted Pattern of Reorganization: Differences Between Animal Studies and Human Trials

Human trials have attempted to translate the results from animal studies in the hope of achieving similar success without accounting for the fundamental differences between patterns of reorga-

nization in animals and humans. First, animal trials use focal artificially induced lesions that usually lead to sparing in the adjacent cortex.^{10–15} However, in humans, the lesion typically is more diffuse, leading to lower survival of “peri-infarct” representations. Second, although human stroke recovery can be associated with peri-infarct reorganization,^{29,51–53} there is extensive evidence from studies of spontaneous improvement, non-invasive brain stimulation, and rehabilitation that indicate involvement of other mechanisms. These alternative mechanisms include recruitment of contralesional areas^{54–57} and surviving networks ipsilesionally^{3,57–61} and interhemispheric interactions.^{31,38,39,42,43,45,46,62,63} Varied mechanisms might be operative depending on the type and location of lesion and the stage of recovery. Thus, targeting patient-specific and stage-specific mechanisms of recovery in humans, instead of attempting literal translation from animal studies, promises to improve efficacy of cortical stimulation interventions.

Predicting the Effect of Cortical Stimulation: Importance of Assessing Descending Pathways’ Viability

Viability of descending projections is an important factor in stroke motor prognosis.^{55,64} Viability of pathways could be assessed presurgically by evoking movements using TMS or intraoperatively using epidural electrodes. Only 16% of patients in the combined treatment group in the Phase III trial showed evoked movements intraoperatively as compared with 100% and 42% of patients in the Phase I and II trials, respectively. Indeed, the subset of patients in Phase III, who showed evoked movements, demonstrated significantly greater improvement than patients in the rehabilitation alone group (Northstar, unpublished data, 2008).

Influence of Tissue Characteristics on Current Distribution: Need for Mapping the Induced Currents

Using MRI-derived finite head modeling for examining effects of TMS, it is shown that in patients with cortical stroke, (1) location of maximal current density is displaced; (2) magnitude of maximal current density is altered due to cerebrospinal fluid shunting; and (3) the site of stimulation is disjointed and multifocal around the infarct.⁶⁵ This will affect epidural more than subdural stimulation, thus making it more critical for human trials. In either case, modeling current distributions would optimize cortical stimulation paradigms and ensure that the desired brain region is targeted.

Lessons From Noninvasive Brain Stimulation Trials

Some investigators using noninvasive brain stimulation methods^{38,40} have speculated that although these techniques target affected^{38–40,66} or unaffected M1,^{44,45,63,67} they are nonfocal, possibly modulating other motor areas that critically contribute to the beneficial effects. If so, focal stimulation of M1 may be undesirable or even inefficient. Additionally, careful analysis of noninvasive brain stimulation studies in stroke indicates that dosage, frequency, and other parameters of stimulation are important factors to consider when predicting functional benefit.⁶⁸ Hence, a detailed exploration of the

focus and parameters of invasive cortical stimulation could possibly reveal results similar to those of noninvasive trials.

The impact of the type of behavioral coupling with stimulation should also be carefully considered. Pomeroy et al⁶⁹ discussed that rTMS of the affected M1 in conjunction with voluntary biceps and triceps contraction increased cortical excitability but failed to induce functionally significant changes. Possibly brain stimulation exerts a task-specific effect that fails to generalize. Consistent with this notion, Mansur et al found transfer of motor training to dexterity and reaction time tests but not to finger tapping⁴⁴ and Liepert et al saw differences in dexterity but not grip strength⁷⁰ after inhibitory rTMS of the unaffected hemisphere. Coupling a more general training paradigm with stimulation might produce generalized improvements.

Customizing stimulation to the neural activation, genomic polymorphisms, and an individual’s response to stimulation is likely also critical. Malcolm et al,⁷¹ in a study of rTMS of the affected hemisphere, found a subgroup of patients showing desirable effects from stimulation (“stimulation responders”). “Stimulation responsiveness” could be a consequence of genetic predispositions. For example, Kleim et al⁷² found that “absence of val66met polymorphism” in the brain-derived neurotrophic factor gene allows for training-induced cortical reorganization. Furthermore, “stimulation responsiveness” could also be artificially promoted by customizing cortical stimulation to the cortical activation and function of patients. Nowak et al⁷³ treated patients who showed contralesional recruitment of the dorsal premotor cortex in association with poor baseline function by using inhibitory 1 Hz rTMS over the contralesional M1. Thus, to predict the stimulation responsiveness, use of neurophysiological mapping or functional neuroimaging is critical.

Timing the Stimulation: Consider Ongoing Cortical Activity and the Different Phases of Motor Learning

Fluctuations in brain activity before or after stimulation can impact the effect of cortical stimulation. Homeostatic plasticity, as conceptualized by the Binstock-Cooper-Monroe theory,⁷⁴ proposes that learning, through long-term potentiation-inducing mechanisms, strengthens synaptic connections to a level such that the effect of a subsequent long-term potentiation-inducing protocol is occluded.⁷⁵ Thus, the specific timing between rehabilitation and cortical stimulation is critical. Additionally, state-dependency, ie, a targeted region’s varying response to stimulation based on its previous state of activity, should be studied in the context of combination of rehabilitation with stimulation.⁷⁶ Closed-loop systems that record brain activity and gate the timing of stimulation might maximize the consistency of brain stimulation effect.⁷⁷ Discontinuous patterns of invasive cortical stimulation could also be used to ensure that critical skill consolidation is not disrupted as witnessed with the use of TMS.^{78,79} Last, it is especially important to avoid intervening 2 training sessions with wakeful periods of declarative learning; instead, influence of sleep needs to be considered.⁸⁰

Conclusions

Clearly, combining cortical stimulation with rehabilitation to promote functional recovery after stroke is complex and various

obscure but important issues have to be considered. Localization, descending pathways' integrity, and pattern of reorganization to the target may need to be carefully individualized and guided by ongoing physiological monitoring in future invasive cortical stimulation trials. Lessons from noninvasive brain stimulation trials about task specificity and subject selection should also be understood to plan more valid designs in the future. The divergent findings of the Phase III trial compared with the Phase I, Phase II, and animal trials should also guide future noninvasive stimulation trials; lesion geometry—current modeling, integration of multiple site-localizing techniques, and monitoring of ongoing cortical activity could be helpful.

Disclosures

A.P.L. has served on Northstar Neuroscience's Medical Advisory Board and has received an honorarium for that work in the past.

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