

Novel Approaches of Non-Invasive Stimulation Techniques to Motor Rehabilitation Following Stroke: A Review

Shahid Bashir, Ph.D.

Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School

This review intends to synthesize our understanding of the effects of novel approach of non-invasive peripheral nerve and brain stimulation techniques in motor rehabilitation and the potential role of these techniques in clinical practice. The ability to induce cortical plasticity with non-invasive stimulation techniques has provided novel and exciting opportunities for examining the role of the human cortex during a variety of behaviors literature concerning non-invasive stimulation technique incorporated into stroke research is young, limiting the ability to draw consistent conclusions. In this review we discuss how these techniques can enhance the effects of a behavioral intervention and the clinical evidence for its use to date. (**Brain & NeuroRehabilitation 2014; 7: 71-75**)

Key Words: functional electrical stimulation, paired-associative stimulation, repetitive TMS, tDCS, plasticity

Introduction

Stroke is a common disorder that produces a major burden to society, largely through long-lasting motor disability in survivors. Recent studies have broadened the perception of the processes underlying recovery of motor function after stroke.¹ Our understanding of the extent to which different forms of cortical reorganization contribute to behavioral gains in the rehabilitative process, although still limited, has led to the formulation of novel interventional strategies to regain motor function following stroke.

To date, the best approach to reduce impairment in the upper limb of stroke survivors seems to be intensive physical therapy. However, results are limited and functional gains are often minimal. The goal of rehabilitation training is to minimize functional disability and optimize functional motor recovery in stroke, an aim thought to be achieved by modulation of plastic changes in the brain. Therefore, adjunct interventions that can augment the response of the motor system to behavioral training might be useful to enhance the therapy-induced recovery in stroke populations. In this context, new approaches appear to be an interesting option as an add-on intervention to standard physical therapies that represent powerful methods for priming cort-

ical excitability for a subsequent motor task, demand, or stimulation. Thus, the mutual use of these techniques can optimize the plastic changes induced by motor practice, leading to more remarkable and long-lasting clinical gains in rehabilitation.

Novel Plasticity Inducing Approaches as Add-on Intervention to Standard Physical Therapy Following Stroke

A number of different strategies have been developed to augment conventional therapies, most of which involve repetitive motor activity. Adding fifteen-minute sessions of repetitive wrist and hand exercises against increasing loads twice daily to the usual care regimen for subacute stroke patients resulted in increased grip strength and peak acceleration in the paretic hand over four weeks. This was not observed in the control group who were given transcutaneous electrical nerve stimulation.² Muellbacher et al.³ trained patients to perform repetitive pinching movements between the paretic index finger and thumb over several weeks until they became proficient in the task. Following this, the upper arm was anaesthetized with the aim of enhancing the effects of motor practice of the hand by depriving the motor cortex of sensory inputs from the upper arm. This led to greater improvements in pinch force and acceleration than following the exercises alone, and the increase in peak pinch force correlated significantly with the increase in motor evoked potential (MEP) ampli-

Correspondence to: Shahid Bashir, Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215, USA
Tel: 1-617-667-0203, Fax: 1-617-975-5322
E-mail: sbashir10@gmail.com

tude in the involved thumb muscle.³ Neither of these studies reported improved function as a result of these interventions, so the potential impact of repetitive simple movements on rehabilitation is unclear. It would be plausible to think of external stimulation induced plasticity as add-on to conventional therapies to facilitate recovery from stroke.

1) Functional electrical stimulation

An area of research that has gathered increasing evidence and is becoming mainstream is the use of functional electrical stimulation (FES) to reduce motor impairment in patients with hemiparesis following stroke. The basis of this approach is to both employ electrical stimulation to maintain and improve tone in weak muscles and increase muscle strength through peripheral mechanisms. In patients with pain and weakness in the upper limb and shoulder, stimulation of the posterior deltoid and supraspinatus muscles is effective in reducing glenohumeral subluxation and decreasing shoulder pain following stroke.⁴⁻⁶ Implementation of FES in patients with severe weakness has been recommended in recent best-practice guidelines (see National Stroke Foundation, 2010). Electrical stimulation of the wrist and finger extensors enhances upper limb motor recovery in acute stroke patients⁷ and increases function compared with a control group.⁸

Muscle activation measured by electromyography (EMG) was also used to trigger the FES to ensure that patients participate actively with at least weak voluntary movement. Greater improvements in strength and function than control interventions were demonstrated.⁹⁻¹³ Weak voluntary muscle contraction triggers electrical stimulation in the contracted muscle, which induces augmentation of muscle recruitment by either increasing peripheral sensation of that muscle as well as by increasing central voluntary control.

Recently, a combined orthosis-stimulation system was developed that enabled daily home-based stimulation-assisted training to increase hand function. While this was achieved, there was no control intervention for comparison.¹⁴ In contrast to the studies described above, peripheral stimulation has more recently been employed to induce central changes that might be beneficial for rehabilitation. Somatosensory stimulation in the absence of muscle contraction is able to influence cortical reorganization, and the application of peripheral nerve stimulation to chronic stroke patients with upper limb hemiparesis was tested in randomized crossover design study.¹⁵ Pinch

grip strength increased following a two-hour session of median nerve stimulation but not control stimulation, and patients reported improved ability to write and hold objects. This type of stimulation increased the amount of use-dependent plasticity seen in chronic stroke patients when tested using transcranial magnetic stimulation,¹⁶ supporting the hypothesis that somatosensory input is able to drive plastic changes in the motor cortex following stroke.¹⁶⁻¹⁸

A single session of peripheral nerve stimulation improved the ability of stroke patients to complete the Jebsen-Taylor Functional Hand Test¹⁹ but to date, no longitudinal studies have investigated the effects of repeated application of somatosensory stimulation in stroke patients.

2) Paired-associative stimulation

Paired associative stimulation (PAT) modulates motor cortical excitability in a manner similar to associative long-term potentiation (LTP) in animal experiments.^{20,21} In a recent study, PAT was applied daily for four weeks to increase the excitability of the corticospinal projection to paretic ankle dorsiflexors and evertors in a group of chronic stroke patients.²² In some subjects, this induced significant improvements in the gait characteristics such as cadence, stride length and time-to-heel-strike, even in the absence of gait training. Increased MEP amplitude and maximal voluntary contraction force was demonstrated in five of the nine subjects, but there was no overall group effect in this small sample. Although this study lacked a control group, it suggests that in some subjects the application of repeated sessions of dual stimulation can result in plastic changes in the motor cortex that lead to functional improvements.

3) Noninvasive brain stimulation (NIBS)

(1) Repetitive transcranial magnetic stimulation (rTMS)

There has been a rapid growth in the development of NIBS techniques in the past twenty years. There are several methods of brain stimulation devices used in clinical practice and their mechanisms of action are not completely understood. In recent years, several NIBS studies have shown promising results for a large range of neuropsychiatric disorders, such as depression, Parkinson's disease, dementia, cognitive disorders, cerebral palsy, and motor recovery following stroke.

As discussed above, stroke alters the balance between excitation and inhibition between the hemispheres. It suggests that down-regu-

lation of the unaffected primary motor cortex (M1) may facilitate motor recovery following stroke.²³ The ability of rTMS to modulate motor cortical excitability in a frequency-dependent manner has been exploited in studies investigating stimulation of either the affected or unaffected hemispheres of stroke patients. Low-frequency rTMS decreases cortical excitability²⁴ and has been applied to the unaffected motor cortex to decrease hyperexcitability in chronic stroke patients.²⁵ A single session of 1 Hz rTMS decreased cortical excitability and transcortical inhibition, and led to a short-lasting increase in pinch acceleration of the paretic hand, while no change was seen following sham stimulation. In contrast, a recent study applied 3 Hz rTMS in conjunction with routine rehabilitation in acute stroke patients, and found that real, but not sham, stimulation decreased disability over a two-week period, although there was no increase in motor cortical excitability as predicted.²⁶ These studies suggest that decreasing inhibition in the affected M1, and perhaps other motor related areas such as the dorsal premotor cortex, can unmask pre-existing, functionally latent neural connections around the lesion and contribute to cortical reorganization.²⁵ A case study highlighting the functional gains made after three weeks of motor cortex stimulation via implanted epidural electrodes during structured occupational therapy sessions adds further support to the hypothesis that cortical stimulation could contribute to recovery of motor function in stroke patients.²⁷

(2) Transcranial direct current stimulation (tDCS)

Non-invasive motor cortical stimulation with tDCS, which is believed to increase cortical excitability, has also been used during the performance of a motor training task.²⁸ Hummel et al.²⁹ studied stroke patients as they practiced an upper limb-training task, the Jebsen-Taylor Hand Function Test (JTT). When their performance had reached a plateau they received a session of stimulation while continuing to perform the JTT. Performance time decreased significantly after stimulation, but not after sham stimulation, with greater improvement in tests requiring fine motor control than tasks involving proximal arm control tasks. Stimulation increased the amplitude of MEPs recorded using recruitment curves and short-latency intracortical inhibition (SICI) a widely used paired-pulse transcranial magnetic stimulation measure to assess inhibition in human motor cortex was significantly reduced, suggesting that GABA receptor-dependent inhibitory processes were involved²⁹. The significant correlation between improvement in JTT time and increased recruitment curve

slope suggests that tDCS can influence motor cortical excitability and can improve skilled motor functions of the paretic hand in chronic stroke patients.

(3) Summary of Non-invasive brain stimulation

Overall, the data discussed above provide some encouraging information suggesting that NIBS might optimize the effect of standard physical therapy under certain circumstances. Beyond the obvious need for further clinical trials to corroborate the validity of this approach, attention must be directed in understanding the optimal way to combine motor training with NIBS. Crucially the next step is to determine the best parameters required to optimize the conditioning effects of NIBS on motor therapy, as well as the exact temporal window during which NIBS can be delivered in order to modulate brain plasticity and enhance the effects of the motor training.

Potential Role in Clinical Practice

Owing to the belief that functional connections among cortical and subcortical structures are essentially 'hard wired' and static, it was assumed that lesions in particular parts of the brain would result in permanent loss of function.³⁰ On the one hand, this perspective led to the bleak conclusion that efforts to rehabilitate stroke patients were doomed to fail. On the other hand, this view suggested that the behavioral correlates of specific cortical and subcortical regions could be determined in a straightforward manner by comparing the performances of normal subjects with the performances of patients who sustained lesions in particular structures. For many years, clinicians and researchers accepted this tradeoff between explanatory power and optimism regarding recovery. As time passed, however, it became clear that return of function often took place. Because such improvement was inconsistent with the localizationist perspective, later writers attempted to modify the original view by proposing the existence of 'parallel processing mechanisms', which assume responsibility for the functions of damaged areas.³⁰ In addition, some writers proposed that recovery resulted from routine physiological processes such as reduction of edema and resorption of blood and necrotic tissue.³¹ These latter accounts were called into question, however, by the finding that recovery sometimes occurs up to one year after onset.

Although newer explanations of restoration of motor function represented a necessary refinement of previous views, they still oversimplified the complexity of basic brain processes.³⁰

As a consequence of the mounting evidence against a strict doctrine of cerebral localization, the field has gradually undergone a paradigm shift toward more integrated views of the brain. Such views suggest that motor responses reflect the interactive functioning of diverse cortical regions that are linked by intricate networks of fibers.

The studies discussed above paint a cohesive picture of the process of motor recovery following stroke. In general, the adult human brain contains multiple somatotopically-organized pathways, which have the potential to transmit impulses to trunk and limb musculature when normal functioning is compromised. In addition, certain cortical regions demonstrate an intrinsic ability to assume responsibility for novel functions when customary circuits are interrupted. Although the cellular processes underlying these changes have not been fully explained, one promising line of research suggests that the loss of inhibitory influences leads to an expansion of the receptive fields of some neurons. This expansion allows previously dormant paths to conduct impulses to their final destinations. In general these studies have involved small sample sizes, lack appropriate control groups, and require complex training and/or equipment, and thus are not commonly used in mainstream rehabilitation.

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