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INTRODUCTION

It Takes Two: Noninvasive Brain Stimulation Combined With Neurorehabilitation

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Abstract

The goal of postacute neurorehabilitation is to maximize patient function, ideally by using surviving brain and central nervous system tissue when possible. However, the structures incorporated into neurorehabilitative approaches often differ from this target, which may explain why the efficacy of conventional clinical treatments targeting neurologic impairment varies widely. Noninvasive brain stimulation (eg, transcranial magnetic stimulation [TMS], transcranial direct current stimulation [tDCS]) offers the possibility of directly targeting brain structures to facilitate or inhibit their activity to steer neural plasticity in recovery and measure neuronal output and interactions for evaluating progress. The latest advances as stereotactic navigation and electric field modeling are enabling more precise targeting of patient's residual structures in diagnosis and therapy. Given its promise, this supplement illustrates the wide-ranging significance of TMS and tDCS in neurorehabilitation, including in stroke, pediatrics, traumatic brain injury, focal hand dystonia, neuropathic pain, and spinal cord injury. TMS and tDCS are still not widely used and remain poorly understood in neurorehabilitation. Therefore, the present supplement includes articles that highlight ready clinical application of these technologies, including their comparative diagnostic capabilities relative to neuroimaging, their therapeutic benefit, their optimal delivery, the stratification of likely responders, and the variable benefits associated with their clinical use because of interactions between pathophysiology and the innate reorganization of the patient's brain. Overall, the supplement concludes that whether provided in isolation or in combination, noninvasive brain stimulation and neurorehabilitation are synergistic in the potential to transform clinical practice.

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The incidence of many neurologic diseases is rising partly because of an increasingly aged population and improved delivery and timing of acute care for neurologic disorders. As a result, more survivors are emerging from acute care, with most exhibiting life-altering impairments that require neurorehabilitation. One prominent example of this trend is stroke; taking into account both the years of potential life lost from premature death and long-term disability, stroke is also one of the most costly diseases, with 36% of this growing population exhibiting a discernable disability 5 years poststroke,[1] and almost half of survivors remaining dependent on others 6 years poststroke because of the severity of their disability.[2]

The focus of medical teams during hyperacute and acute neurologic care is usually 3-fold: ensure survival/reduce mortality; manage and prevent medical complications; and when possible, salvage existing central nervous system tissue (eg, through the use of thrombolytics in stroke).[3] In contrast, the goal of postacute neurorehabilitation is to maximize patient function, ideally by using surviving brain and central nervous system tissue when possible. However, despite their widely appreciated importance, the efficacy of conventional clinical treatments targeting specific neurologic impairments and sequelae vary widely. Again in the case of stroke, conventional rehabilitative strategies targeting upper extremity hemiparesis in adults offer negligible or no efficacy.[4,5]

Recently developed neurorehabilitative strategies offer slightly more promise but remain limited because of the considerable time and resources that they require to administer. Perhaps the most notable example is constraint-induced movement therapy (CIMT),

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which has been applied to the affected upper extremity after stroke and other neurologic disorders (eg, multiple sclerosis, aphasia, traumatic brain injury [TBI]). One of the hallmarks of CIMT is long-duration training using an affected body part (eg, paretic upper extremity) or capacity (eg, speaking) that lasts up to 6 hours per day and is administered over multiple days (usually 10 consecutive weekdays). Although results have been promising,[6] several studies[7,8] have found that most patients with stroke do not wish to participate in CIMT because of these long-duration treatment parameters, have reported high attrition rates,[9] have reported poor compliance with the CIMT restrictive device wear,[10,11] and have reported on patient inability to participate in the entire 6-hour regimen as a result of fatigue.[12] As a result of the required time, financial resources, and human resources, CIMT has not realized widespread clinical application.[13,14]

Other new neurorehabilitative approaches being taught by training programs and/or adopted by clinics worldwide (eg, partial weight-supported treadmill training, certain automated and splinting approaches) offer negligible efficacy when compared with more conventional strategies[15-17] and/or only work on patients displaying a particular level of impairment. As a result, there remains a gap centering on the need for techniques that extend the efficacy, duration of treatment effect, and/or number of patients who may benefit from promising neurorehabilitative therapies. Noninvasive brain stimulation offers the ability to meet all of these needs and offers efficacy as a stand-alone treatment approach for many neurologic impairments.

What is noninvasive brain stimulation?

After a central nervous system lesion, the target of therapeutic approaches is, ideally, direct stimulation of the central nervous system. However, the structures being incorporated into neurorehabilitative approaches often differ from this target. For example, spasticity is an upper motor neuron disorder causing imbalanced inhibitory signals between the brain and spinal cord and, ultimately, cocontraction in the upper and lower extremities. Because of its origin, brain activity is a logical target of spasticity measurement and treatment. However, conventional spasticity measurement strategies[18,19] estimate brain and spinal cord disinhibition using subjective, behavior-based measures in which the clinician passively ranges the spastic limb. Similarly, most spasticity management strategies provide only a transient effect by affecting the soft tissue of the affected limb (eg, through injection of medications, bracing, stretching the limb). Not surprisingly, the effects of these strategies are transient, equivocal, or negative,[17,20] likely because they do not directly target the brain. The same is true in other forms of neurorehabilitation, where measurement and selection of treatment strategies are frequently based on subjective behavioral evaluations (eg, use and function of a limb, performance on a cognitive test). Although they are of functional relevance, these measurements are, to some extent, surrogates for brain neurophysiology and function; however, the brain constitutes the ultimate target of neurorehabilitative therapies.

Unlike these approaches, noninvasive brain stimulation offers the possibility of directly targeting brain structures to measure neuronal output and interactions, understand the role of networks and their chronometry in behavior, and facilitate or inhibit their activity therapeutically to steer neural plasticity and function remapping in recovery.[21] Unlike surgically based techniques, this stimulation is accomplished noninvasively and therefore with relatively few side effects (eg, with transcranial magnetic stimulation [TMS], transcranial direct current stimulation [tDCS]).[22] Although TMS is a method of neurostimulation that uses electromagnetic induction to generate electrical currents in the brain,[23] tDCS incorporates a small, constant current stimulator and surface electrodes applied directly to the scalp to produce low-level currents (0−2.5mA).[24] TMS offers opportunities for study of physiological motor systems because its single and paired pulses via transsynaptic corticospinal activation can elicit descending volleys and examine local and remote influences.[25] Further, it holds therapeutic potential because its repeated pulses can induce lasting changes in cortical excitability via synaptic associative plasticity and can therefore modify behavior.[22] Stimulation frequencies of $\leq$1Hz are inhibitory for underlying cortical excitability, whereas frequencies $\geq$5Hz are facilitatory.[26] Despite low-level currents, tDCS depolarizes membrane potentials to increase cortical excitability and hyperpolarizes membrane potentials, suppressing cortical excitability.[27] Moreover, the plasticity induced by tDCS has been shown to have therapeutic potential in treatment of a variety of neurologic disorders, including epilepsy,[28] Parkinson disease,[29] and stroke.[30,31]

New advances as stereotactic navigation and electrical field modeling are enabling more precise targeting of patient's residual structures in diagnosis and therapy using noninvasive brain stimulation. For example, navigated TMS is able to integrate a patient's own magnetic resonance imaging (MRI) as basis for his/her stimulation. MRI essentially acts as a map, enabling real-time location of where the magnetic coil is located and its relation in real time to the patient's stereotactic coordinates and those of the targeted area.[32] Use of functional MRI allows even greater functional specificity in diagnosis and delivery, where recovery-associated changes in cortical activation can be tracked longitudinally to closely follow remapped potential.[33] With high-resolution modeling, one is able to predict current flow (eg, that applied via tDCS) as a product of anatomic variability and polarity and orientation of electrodes, advances intended to customize and optimize therapeutic brain stimulation in neurorehabilitation.[34]

Focus of this issue

Noninvasive brain stimulation is being increasingly used with a variety of neurologic diagnoses and can produce comparable levels of plasticity and recovery as conventional rehabilitative strategies. For instance, tDCS offers an affordable, portable alternative or complement to traditional practice strategies and offers the possibility of use as a home-based therapy.[24] Similarly, TMS, while not portable, offers the possibility of targeted, focal, brain stimulation using real-time image guidance to identify and therapeutically affect specific areas for stimulation.[22] Both approaches are safe with few contraindications,[24,35] but they are not widely used and remain poorly understood. Several factors have affected their clinical application both in diagnosis (TMS) and in therapy (repetitive transcranial magnetic stimulation [rTMS],

List of abbreviations:

CIMT	**constraint-induced movement therapy**
MRI	**magnetic resonance imaging**
rTMS	**repetitive transcranial magnetic stimulation**
SCI	**spinal cord injury**
TBI	**traumatic brain injury**
tDCS	**transcranial direct current stimulation**
TMS	**transcranial magnetic stimulation**