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It Takes Two: Non Invasive Brain Stimulation Combined with Neurorehabilitation

Stephen J. Page, Ph.D., M.S., MOT, OTR/L, FAHA[1], **David A Cunningham, M.S.**[2,3], **Ela Plow, P.T., Ph.D.**[2,4], and **Brittani Blazak, B.S.**[1]

[1]The Ohio State University Medical Center, School of Health and Rehabilitation Sciences. Columbus, OH 43210

[2]Dept. of Biomedical Engineering, Lerner Research Inst., Cleveland Clinic, Cleveland, OH

[3]School of Biomedical Sciences, Kent State University, Kent, OH

[4]Dept. of Physical Medicine & Rehab, Neurological Inst., Cleveland Clinic, Cleveland, OH

Abstract

The goal of post-acute neurorehabilitation is to maximize patients' function, ideally by using surviving brain and central nervous system tissue when possible. Yet the structures incorporated into neurorehabilitative approaches often differ from this target, which may explain why efficacy of conventional clinical treatments targeting neurological impairments varies widely. Non-invasive brain stimulation such as with Transcranial Magnetic Stimulation (TMS) and transcranial direct current stimulation (tDCS) offers the possibility of directly targeting brain structures to facilitate or inhibit their activity so as to steer neural plasticity in recovery, and measure neuronal output and interactions for evaluating progress. 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. Thus, 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 due to interactions between pathophysiology and the innate reorganization of the patient's brain. Overall, the supplement concludes that whether provided in isolation or in combination, non-invasive brain stimulation with neuro-rehabilitation are synergistic in the potential to transform clinical practice.

Corresponding author: Stephen J. Page, Ph.D., M.S., MOT, OTR/L, FAHA; The Ohio State University Medical Center; School of Health and Rehabilitation Sciences; 453 West 10th Avenue, Suite 406; Columbus, OH 43210.

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The incidence of many neurological diseases is rising, due in part to an increasingly aged population, as well as improved delivery and timing of acute care for neurological 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 post ictus,[1] and almost half of survivors remaining dependent on others 6 years post stroke due to the severity of their disability.[2]

The focus of medical teams during hyperacute and acute neurological care is usually threefold: (a) ensure survival/reduce mortality; (b) manage and prevent medical complications; and (c) when possible, salvage existing central nervous system tissue (e.g., through the use of thrombolytics in stroke). In contrast, the goal of post-acute neurorehabilitation is to maximize patients' function, ideally by using surviving brain and central nervous system tissue when possible. Yet, despite their widely appreciated importance, the efficacy of conventional clinical treatments targeting specific neurological 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.[3,4]

Recently-developed neurorehabilitative strategies offer slightly more promise, but remain limited due to the considerable time and resources that they require to administer. Perhaps the most notable example is constraint induced movement therapy (CIT), which has been applied to the affected upper extremity (UE) following stroke, as well as in other neurological disorders (e.g., multiple sclerosis; aphasia; traumatic brain injury). One of CIT's hallmarks is high duration training using an affected body part (e.g., the paretic upper extremity) or capacity (e.g., speaking) that lasts up to 6 hours per day, and is administered over multiple days (usually 10 consecutive weekdays). While results have been promising,[5] several studies[6,7] have found that most patients with stroke do not wish to participate in CIT due to these high duration treatment parameters, have reported high attrition rates,[8] poor compliance with the CIT restrictive device wear,[9,10] and patient inability to participate in the entire 6 hour regimen due to fatigue.[11] As a result of the required time, financial, and human resources, CIT has not realized widespread clinical application.[12,13]

Other new neurorehabilitative approaches being taught by training programs and/or adopted by clinics worldwide (e.g., partial weight supported treadmill training, certain automated and splinting approaches) offer negligible efficacy when compared to more conventional strategies,[14,15,16] 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. Non-invasive brain stimulation offers the ability to meet all of these needs, as well as offering efficacy as a stand-alone treatment approach for many neurological impairments.

What is Non-Invasive Brain Stimulation?

Following a central nervous system lesion, the target of therapeutic approaches is, ideally, direct stimulation of the central nervous system. Yet, 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, co-contraction 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[17,18] 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, such as through injection of medications, bracing, or stretching the limb. Not surprisingly, the effects of these strategies are transient, equivocal, or negative,[16,19] 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, such as use and function of a limb, or performance on a cognitive test. While of functional relevance, these measurements are, to some extent, surrogates for brain neurophysiology and function, although the brain constitutes the ultimate target of neurorehabilitative therapies.

Unlike the above approaches, non-invasive brain stimulation offers the possibility of ***directly*** targeting brain structures to both measure neuronal output and interactions, understand role of networks and their chronometry in behavior, and facilitate or inhibit their activity therapeutically so as to steer neural plasticity and function remapping in recovery.[20] Unlike surgically based techniques, this stimulation is accomplished non-invasively and, thus, with relatively few side effects such as with Transcranial Magnetic Stimulation (TMS) and transcranial direct current stimulation (tDCS).[21] While TMS is a method of neurostimulation that uses electromagnetic induction to generate electrical currents in the brain,[22] tDCS incorporates a small, constant current stimulator and surface electrodes applied directly to the scalp to produce low level currents (0-2.5 mA).[23] TMS offers opportunities for study of physiologic motor systems since its single and paired pulses via trans-synaptic corticospinal activation can elicit descending volleys and examine local and remote influences.[24] Further, it holds therapeutic potential since its repeated pulses can induce lasting changes in cortical excitability via synaptic associative plasticity, and thus modify behavior.[21] Stimulation frequencies of ≤ 1Hz are inhibitory for underlying cortical excitability while frequencies ≥5Hz are facilitatory.[25] TDCS, despite low level current, depolarizes membrane potentials to increase cortical excitability, as well as hyperpolarizes membrane potentials suppressing cortical excitability.[26] Moreover, the plasticity induced by tDCS has been shown to have therapeutic potential in treatment of a variety of neurological disorders including epilepsy,[27] Parkinson's disease,[28] and stroke.[29,30]

New advances as stereotactic navigation and electric field modeling are enabling more precise targeting of patient's residual structures in diagnosis and therapy using non-invasive brain stimulation. For example, navigated TMS is able to integrate a patient's own MRI as basis for his/her stimulation. The MRI essentially acts as a “map,” enabling real-time location of where the magnetic coil is located, its relation in real-time to patient's stereotactic coordinates and those of targeted area.[31] 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 re-mapped potential.[32] With high-resolution modeling, one is able to predict current flow, such as that applied via tDCS, as a product of anatomic variability and polarity and orientation of electrodes, advances intended to customize, hence optimize, therapeutic brain stimulation in neuro-rehabilitation.[33]

The Focus of This Issue

Non-invasive brain stimulation is being increasingly used with a variety of neurological diagnoses, and can produce comparable levels of plasticity and recovery as conventional rehabilitative strategies. tDCS, for instance, offers an affordable, portable alternative or complement to traditional practice strategies, and the possibility of use as a home-based therapy.[23] 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.[34] Both approaches are safe with few contraindications,[23,35] but are not widely used and remain poorly understood. Several factors have affected their clinical application both in diagnosis (TMS) and in therapy (rTMS and tDCS). With regards to their diagnostic potential, reliability is a key roadblock,[36] which is even more impairing in neurologic conditions, such as stroke.[37] Validity in measuring what we believe they measure is important to understand as well; for example, inhibition between both hemispheres, which we always believe is a product of transcallosal transmission, may instead be a direct transmission via uncrossed pathways to ipsilateral limb and may be supplementary in recovery of paretic limb such as in stroke. The therapeutic benefits of rTMS and rTMS-like approaches and tDCS are even more controversial. Several studies note positive effects but latest clinical trials acknowledge failure.[38,39] The inconsistency becomes prominent in studies enrolling a more representative sample - patients with more impairment besides those who are mildly impaired. The disconnect is the use of a single approach across this entire spectrum of impairment without systematic investigation of dosing, patient characteristics governing response vs. non-response, type and the location of stimulation that may be most suited etc. Still, to open these lines of discussion so a more strategic investigation of these factors can be conducted in various populations, we present the this supplement which provides data based papers and reviews discussing state of the art clinical and research application and considerations for non-invasive brain stimulation targeting a variety of neurorehabilitative diagnoses and impairments. Featured articles include the following:

- Cunningham et al.[40] discuss the potential utility of neuro-navigated TMS in revealing mechanisms of functional motor recovery in chronic stroke. In comparing its use to state-of-the-art imaging- functional MRI and Diffusion Tensor Imaging (DTI)- they discuss how its neurophysiologic measurements relate to inter-hemispheric balance, and reveal adaptations to damaged output from stroke hemisphere. Overall, in revealing relationships and complementarities, between TMS and imaging, authors present new evidence to potentially accelerate the use of navigated TMS as a more cost-effective clinical diagnostic modality. As a continuation, Chung and Lo[41] review potential diagnostic, as well as therapeutic capabilities of TMS, but this time in pediatric patients with acquired brain injury. They discuss therapeutic uses not only for motor rehabilitation, but also for more common acquired cognitive-behavioral illnesses, such as epilepsy. They identify current gaps in knowledge given the preliminary and proof-of-principle nature of evidence, and highlight how data remains inconclusive regarding which parameters are most effective. Addressing such uncertainties would facilitate therapeutic use of TMS for several disorders affecting children. In the same vein, Gillick et al.[42] demonstrate safety of ‘primed’ rTMS as an adjunct to movement therapy in children with hemiparesis. While Chung and Lo speculate regarding best parameters, Gillick et al. propose a potential novel therapeutic solution- a paradigm that that involves facilitating the unaffected hemisphere which ultimately enables it to be suppressed more robustly for likely greater motor recovery. As the first report of priming in children, Gillick et al. discuss that the nature and occurrence of adverse events are transient and minor, indicating promise for future clinical applications in congenital disorders. Whereas Gillick et al. offer rTMS as an ‘offline’ adjunct, staggered with application of rehabilitation, Straudi et al.[43] discuss the advantage of tandem pairing of its more-portable analogue, tDCS. In a case example of pediatric stroke, they demonstrate tDCS used concurrently with rehabilitation not only improves clinical outcomes, but also optimizes kinematic parameters within a matter of 2 weeks. Although a case example discussing concurrent stimulation makes it difficult to gauge the sole role of tDCS, the combinatorial paradigm nevertheless carries promise for maximizing benefits within *billing-imposed* limits of outpatient therapy. In addition to pediatrics, use of rTMS, constitutes a new application to adults with moderate-to-severe traumatic brain injury (TBI) as well. Nielson et al.[44] ascribe this general reservation to the long-held belief that repeated pulses can cause synchronized neuronal firing to spread from the stimulation site, causing seizure. They contend, by providing example from a case report of a patient with moderate TBI, that risks can be potentially mitigated by taking adequate precautions, including using only low-frequency stimulation, and carefully selecting candidates. By illustrating the potential for safe use of rTMS for the treatment of depression following moderate TBI, they suggest it may be time to test its large-scale safety as a potential viable treatment for post-TBI depression. The next several articles extend the therapeutic utility of rTMS beyond stroke and pediatrics. Kimberley et al.[45] characterize the ability of low-frequency rTMS to modify cortical excitability and improve symptoms in focal hand dystonia (FHD). Adopting a single-subject design, they aim to isolate optimal stimulation parameters for lasting behavioral and physiologic changes. Albeit in a case study design, their methods provide a preliminary model to test on a larger scale how physiologic changes mark behavioral response versus none, offering the ability to stratify likely responders. Along similar lines, Galhardoni et al.[46] enumerate why response to rTMS in chronic pain has been differential. In their review, they identify that only few studies performed repetitive sessions of rTMS for maintenance and even so, the main outcome always focused on reducing pain intensity without treating serious affective-emotional and cognitive-evaluative dimensions that intensify pain experience. In elaborating from their review, a comprehensive investigation of which symptoms of neuropathic pain are preferentially modulated by rTMS would provide a more solid basis for its clinical application in pain. As closing articles for this issue, we present application of rTMS and tDCS in rehabilitation of spinal cord injury (SCI), a condition that presumably 'spares' the brain. Still, Murray et al[47]. and Tazoe and Perez[48] argue that motor cortex and its corticospinal tracts may be promising anatomical substrates following incomplete SCI because muscles below the lesion, albeit weak, may still exhibit viable corticospinal response as sensorimotor cortices exhibit tremendous reorganization. Further, axonal sprouting and changes in intraspinal circuitry can support recovery in areas around the lesion. Murray et al. test the potential by comparing intensities of tDCS that best facilitate corticospinal excitability, which appears to favor use of higher intensity focused stimulation. Finally, Tazoe and Perez review several studies, based on the same original premise as Murray et al., have facilitated motor cortices, via rTMS, to potentially enhance recovery in SCI. They adopt a careful stance; while summarizing how some studies demonstrate positive effect, they maintain others remain negative. In their view, methodological parameters as well as patient's innate neural reorganization at the level the corticospinal tract and the motor cortex influences effects of rTMS, or perhaps even tDCS.

Overall, this supplement illustrates the wide-ranging significance of non-invasive brain stimulation in neurorehabilitation, including stroke, pediatrics, TBI, FHD, neuropathic pain and SCI. These articles also highlight the ready clinical application of these technologies, including their comparative diagnostic capabilities as compared to neuroimaging, their therapeutic benefit, their optimal delivery strategies guided by 'safe' limits and temporal ordering with rehabilitation, the stratification of likely responders based on nature of symptoms and associated physiologic change, and the variable benefits associated with their clinical use due to interactions between pathophysiology and the innate reorganization of the patient's brain.

Neurorehabilitation – and acquired brain injury and spinal cord injury in particular - have been ongoing interest areas to ACRM members and *Archives* readers for decades. Moreover, studies of neurorehabilitative strategies are consistently among the most-cited articles in the *Archives*. It is hoped that this issue illuminates the incredible promise of non-invasive brain stimulation as both a mapping approach to gauge neurorehabilitation efficacy, and as a therapeutic approach. Whether provided in isolation or in combination, non-invasive brain stimulation with neurorehabilitation are synergistic in the potential to transform clinical practice.

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Abbreviations

UE	upper extremity
CIT	constraint induced movement therapy
TMS	transcranial magnetic stimulation
tDCS	transcranial direct current stimulation