ACTA SCIENTIFIC NEUROLOGY

Volume 2 Issue 7 July 2019

Mini Review

Clinical Use and Evidences of Noninvasive Brain Stimulation for Neurorehabilitation

Areerat Suputtitada*

Professor, Physiatrist, Department of Rehabilitation Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

***Corresponding Author:** Areerat Suputtitada, Professor, Physiatrist, Department of Rehabilitation Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand. **E-mail:** prof.areerat@gmail.com

Received: March 23, 2019; **Published:** June 20, 2019

Abstract

Non-invasive brain stimulation methods, especially transcranial Direct Current Stimulation (TDCS) and repetitive Transcranial Magnetic Stimulation (rTMS), are used globally to make the brain plasticity or reorganization after central nervous system (CNS) lesions which essential in sensory and motor recovery. The main physiology of brain plasticity is the long-term potentiation (LTP) and long-term depression (LTD). The neuromodulation means the neurophysiological methods that can facilitate plasticity or modulate cortical excitability or produce interference with normal brain activity and behavior. Transcranial Direct Current Stimulation (tDCS) has increasingly using since it is inexpensive, easy to administer after well trained, portable, and a little side effect. It can either enhance or suppress cortical excitability by a weak and constant direct current applied to the brain according to the 10-20 system of cortical function. TMS works by inducing non-invasively electric currents in localized cortical regions thus modulating their excitability levels and ongoing activity patterns depending on stimulation settings: frequency, intensity, number of pulses, train duration and inter-train intervals. The most update evidences revealed that rTMS and tDCS have the potential to modulate brain cortical excitability with long lasting effects which promising enhance neurorehabilitation for functional recovery and also improving of the cognitive function.

Keywords: Neuromodulation; Transcranial Direct Current Stimulation (tDCS); Repetitive Transcranial Magnetic Stimulation (rTMS); Brain Plasticity; Neurorehabilitation

Transcranial noninvasive brain stimulation (NBS) includes both repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). TMS uses a rapidly changing magnetic field to induce currents and action potentials in underlying brain tissue, whereas tDCS involves the application of weak electrical currents to modulate neuronal membrane potential. Transcranial magnetic stimulation (TMS) uses a high-current pulse generator discharging currents of several thousand amperes that flow through a coil of wire, generating a brief magnetic pulse with field strengths up to several Tesla. When the coil is applied over the brain, the magnetic field undergoes little attenuation by extra cerebral tissues (scalp, cranial bone, meninges and cerebrospinal fluid) and induces an electrical field enough to depolarize superficial axons and to activate cortical neural networks. Several parameters influence the outcome of the stimulation, including the types and orientation of coils; the distance between the coil and the brain; the magnetic pulse waveform; and the intensity, frequency and pattern of stimulation. There are two treatment regimens as the followings; (1) the low-frequency repetitive transcranial magnetic stimulation (rTMS), stimulates at frequencies lower than or equal to 5 Hz, which reduces neuronal excitability; (2) the high-frequency rTMS, stimulates at frequencies higher than or equal to 5 Hz., which increases cortical excitability [1]. A single stimulus of TMS with a specific intensity and orientation causes neuronal depolarization, followed by an action potential which produces an excitatory postsynaptic response of 1 ms, which is in turn followed by an inhibitory postsynaptic potential of 100 ms. TMS has a local effect, interrupting normal neural activity, increasing the refractory period, and regulating the discharge pattern. 1,2 In clinical practice TMS could be used to tell the prognosis by mainly used to explore motor

cortical areas and corticospinal tract conduction and connectivity. The effects of TMS on a specific area extend to other cortical and subcortical areas of both hemispheres; due to brain connectivity, the effects might even reach deep brain areas according to the diaschisis principle [1,2]. Activation or inhibition of a specific area affects distant areas; the effects depend on whether the stimulus is excitatory or inhibitory. rTMS has an effect on neuroplasticity; its neuroprotective effects are beneficial for patients with a wide range of neuropsychiatric disorders as mood disorders (drug-resistant major depression, mania, bipolar disorder, postpartum depression, dysthymia, etc.), schizophrenia, anxiety disorders (obsessive-compulsive disorder, post-traumatic stress disorder, etc.), substance use disorders, autism, attention-deficit/hyperactivity disorder, etc. rTMS effect on neuroplasticity also benefit to patients with neurological disorders as various problems of stroke (improve motor recovery, aphasia and dysphagia), spasticity, drug-resistant epilepsy, Parkinson's disease, essential tremor, Huntington disease, Alzheimer disease, tinnitus, focal dystonia, head trauma, gait disorders, migraine with aura, trigeminal neuralgia, multiple sclerosis, amyotrophic lateral sclerosis, etc. rTMS effect on neuroplasticity also benefit to patients with pain conditions as chronic pain in phantom limb syndrome, neuropathic pain, fibromyalgia, complex regional pain syndrome type I), atypical facial pain, visceral pain, etc [1-3].

Interestingly, rTMS could be used for a wide range of diseases and also had the long-lasting effects. The effects were usually last for more than 6 months [1,2].

There were various potential mechanisms related to the actions of TMS at neural network (mutual excitation and inhibition of cerebral regions), synaptic and/or molecular genetic (changes in gene expression, enzyme activity and neuromediator production) levels. There were recent evidences of changes in neurotransmitter concentrations following rTMS, such as endogenous dopamine and genetic polymorphisms [1,2,5].

The effects of rTMS are greatly dependent on: (1) the stimulus intensity and frequency; (2) the acute and chronic mode of treatment; (3) the total number of pulses; (4) the shape and dimension of coils; and (5) the conscious state. The evidences in rodents indicate that rTMS produces complex neurobiochemical effects such as induction of immediate early genes, changes in modulation of neurotransmitters release, effects on glutamate AMPA receptor/NMDA receptor expression (influencing calcium ion dynamics), action on neuroendocrine systems, neuroprotective effects by reducing oxidative stress and inflammation, and a powerful activation of neurotrophic factors. These molecular effects may modify the intrinsic and extrinsic electrophysiological properties of neurons and reprogram the expression of excitatory and inhibitory neurotransmitters and their cognate receptors, which lead to long-lasting synaptic plasticity-related changes like Long-term potentiation (LTP) and depression (LTD) phenomena [1-5].

The current pieces of evidences recommend Level A (definite efficacy) for the analgesic effect of high-frequency (HF) rTMS of the primary motor cortex (M1) contralateral to the pain area and the antidepressant effect of HF-rTMS of the left dorsolateral prefrontal cortex (DLPFC), recommend Level B (probable efficacy) for the antidepressant effect of low-frequency (LF) rTMS of the right DLPFC, HF-rTMS of the left DLPFC for the negative symptoms of schizophrenia, and LF-rTMS of contralesional M1 in chronic stroke for motor recovery, recommend level C (possible efficacy) for LF-rTMS of the left temporoparietal cortex in tinnitus and auditory hallucinations. The pieces of evidences of rTMS in stroke patients revealed the improvements in motor disorders, aphasia, dysarthria, oropharyngeal dysphagia, depression, and perceptual-cognitive deficits [5,6].

Transcranial Direct Current Stimulation (tDCS) is increasingly used for neurorehabilitation, compared to other noninvasive neuromodulations. It is inexpensive, easy to administer after well trained, portable, and home used design considered as the most cost-effectiveness and good compliance therapy. It can either enhance or suppress cortical excitability by a weak and constant direct current applied to the brain. It has effect for several hours after the stimulation, depending on several factors. The anodal stimulation effects subthreshold depolarization, producing neural excitation. The cathodal stimulation effects subthreshold polarization, suppressing neural activity. In clinical use, two (or more) electrodes are applied over the scalp with the current flowing from the anodal to the cathodal electrode. The strength of electrical currents cannot produce an action potential. The factors influence neural activity including the neuron functions at rest or during stimulation and relearning with a task in the meantime, and also the stimulation time of the day. The positive clinical effects of tDCS in various disorders are caused by the complex interactions between the associated brain network and the area of stimulation [1,7,8].

The current pieces of evidences do not recommend Level A (definite efficacy) for any indication, recommend Level B (probable efficacy) for: (i) anodal tDCS of the left primary motor cortex (M1) (with right orbitofrontal cathode) in fibromyalgia; (ii) anodal tDCS of the left dorsolateral prefrontal cortex (DLPFC) (with right

orbitofrontal cathode) in major depressive episode without drug resistance; (iii) anodal tDCS of anodal tDCS of the left M1 (or contralateral to pain side, with right orbitofrontal cathode) in chronic lower limb neuropathic pain secondary to spinal cord lesion [9].

The evidences revealed combining NIBS, either using rTMS or tDCS, with intensive physical therapy, constraint- induced therapy, robot-therapy, EMG-triggered functional neuromuscular stimulation could enhance adaptive plasticity and limit maladaptive plasticity [6,9].

19 tDCS studies included over 500 participants whose mean ages were in the mid to late 60's showed increasing motor and cognitive. The participants received between 1 and 10 sessions of tDCS, with a duration of 5 to 30 minutes, at an intensity of 1 to 2 mA. There was no serious side effect. 15 studies with over 275 patients that evaluated the effects of tDCS on patients with Alzheimer's disease, Parkinson's Disease, Dementia with Lewy Bodies, Corticobasal degeneration, and Frontotemporal dementia, received between 7 and 30 minutes of stimulation in each of 1 to 10 sessions with an intensity of between 1 and 2.8 mA. There was also no major side effect [10].

Depending on the stimulation parameters, both TMS and tDCS can be used to excite (>5Hz TMS, anodal tDCS) or inhibit (<1Hz TMS, cathodal tDCS) the underlying cortical tissue when applied over the primary motor cortex (M1), but the after effects vary across subjects. Online stimulation refers to the condition in which a person is executing a task (motor, cognitive, etc.) while receiving rTMS/TCS. The off-line approach is when stimulation occurs before a task, but some NIBS-induced after effects may interrelate with the final results. It has been demonstrated that distinct behavioral after effects may outlast the duration of multiple sessions of stimulation by weeks or months and thus may have therapeutic potential. The effect of rTMS decreases with the distance from the stimulating coil, with an immediate effect on underlying brain tissue to a depth of only approximately 2cm beneath the scalp. Moreover, there are the changes in distant interconnected regions.

There was meta-analysis in motor disorders (upper limb functional abilities, gait, balance, and spasticity) of pediatric patients with traumatic brain injury treated with NIBS. 14 RCTs were included (10 studies used tDCS, while 4 studies used rTMS). According to the PEDro scale, 3 studies were excellent, 8 studies were good and 3 studies were fair. The level of evidence of all of the included studies was 1b, except for three studies with grade 2a. There were significant improvements in all upper limb functions, balance and some gait variables [11].

The meta-analysis in 20 studies with a total of 470 PD (Parkinson's disease) patients revealed overall medium effect size favoring active rTMS over sham rTMS in the reduction of motor symptoms (P<.001). Subgroup analysis showed that the effect sizes estimated from high-frequency rTMS targeting the M1 and low-frequency rTMS applied over other frontal regions were significant. Meta-regression revealed that a greater number of pulses per session or across sessions is associated with larger rTMS effects. Using the Grading of Recommendations, Assessment, Development, and Evaluation criteria, we characterized the quality of evidence presented in this meta-analysis as moderate quality [12].

The meta-analysis of six studies with 137 PD patients revealed no effect of tDCS compared to sham tDCS in the proportional change of the Unified Parkinson's Disease Rating Scale (UPDRS, no effect regarding the reduction in off time and on time with dyskinesia, no evidence of an effect for gait speed, health related quality of life and safety/acceptability, measured by dropouts and adverse events (including death) [13].

rTMS at the M1 or DLPFC may increase or decrease the release of monoamines (particularly dopamine) in different cortical and subcortical areas of the brain interconnected with the stimulated area. In addition, high-frequency rTMS applied over the prefrontal cortex may act via the stimulation of the glutamatergic prefrontal neurons and may increase neurotrophic factors in the brain. There are the changes in the effectiveness of synapses between cortical neurons (long-term potentiation (LTP) and long-term depression (LTD)). The high-frequency rTMS protocols seem to produce more significant effects outcomes than low-frequency stimulation protocols. There are evidences of beneficial and long-lasting antidepressant effects in PD populations, particularly when high-frequency stimulation over the left DLPFC and when repeated session protocols are used. The rTMS-induced effect was similar to that of antidepressant medication, with considerably fewer side effects. There is a tendency for enhancement of cognitive speed or time to finish cognitive tasks. The effects of tDCS revealed some benefit on non-motor symptoms of PD such as impaired attention, executive functions, memory, and fatigue and depressive symptoms A potential online combination with either cognitive training or another behavioral activity is possible since patients can move during tDCS [14].

There are evidences that NIBS used in combination with meaningful rehabilitation training will facilitate the reorganization of neuroplasticity. The meaningful rehabilitation program characterized as the followings; (1) the rehabilitation program has to be

meaningful with respect to skill learning. For instance, non-skill and passive training, that is, repeated voluntary and assisted dorsi- and plantarflexion movements, did not increase cortical excitability, while motor skill training had a positive effect. (2) the rehabilitation program has to be task-specific. In the animal study with complete spinal cord transections, those that were trained to stand did not walk well on a treadmill, while those that were trained to walk did not stand well. (3) to reduce the risk of maladaptive reorganization, pathological movement should be avoided in jointly applied rehabilitation training [15].

The meta-analysis of 16 studies in post stroke aphasia revealed medium to large rTMS effect and a small to medium tDCS effect. rTMS was effective for both subacute and chronic aphasia, tDCS was effective only for chronic aphasia. The level of evidence was moderate to high for rTMS and low for tDCS studies as qualified with GRADE (grading of recommendations, assessment, development and evaluations) [16].

In conclusion, Non-invasive stimulation techniques as rTMS and tDCS have the potentials to modulate brain cortical excitability with long lasting effects which promising enhance neurorehabilitation. More researches are upcoming in various indications and stimulation protocols.

Bibliography

1. P M Rossini., *et al.* "Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee". *Clinical Neurophysiology* 126.6 (2015): 1071–1107.

2. Klomjai W., *et al.* "Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS)". *Annals of Physical and Rehabilitation Medicine* 58.4 (2015): 208-213.

3. Di Lazzaro V., *et al.* "The effects of motor cortex rTMS on corticospinal descending activity". *Clinical Neurophysiology* 121.4 (2010): 464-473.

4. Pell GS., *et al.* "Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: influence of timing and geometrical parameters and underlying mechanisms". *Progress in Neurobiology* 93.1 (2011): 59-98.

5. Lefaucheur JP., *et al.* "Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)". *Clinical Neurophysiology* 125.11 (2014): 2150-2206.

6. León Ruiz M., *et al.* "Current evidence on transcranial magnetic stimulation and its potential usefulness in post-stroke neurorehabilitation: Opening new doors to the treatment of cerebrovascular disease". *Neurology* 33.7 (2018): 459-472.

7. Filmer HL., *et al.* "The efficacy of transcranial direct current stimulation to prefrontal areas is related to underlying cortical morphology". *Neuroimage* 196 (2019): 41-48.

8. Cruccu G., *et al.* "EAN guidelines on central neurostimulation therapy in chronic pain conditions". *European Journal of Neurology* 23.10 (2016t): 1489-1499.

9. Lefaucheur JP., *et al.* "Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS)". *Clinical Neurophysiology* 128.1 (2017): 56-92.

10. Bikson M., *et al*. "Safet of transcranial Direct Current Stimulation: Evidence Based Update 2016". *Brain Stimulation* 9.5 (2016): 641–661.

11. Elbanna ST., *et al*. "Noninvasive Brain Stimulation for Rehabilitation of Paediatric Motor Disorders Following Brain Injury: Systematic Review of Randomized Controlled Trials". *Archives of Physical Medicine and Rehabilitation* (2019).

12. Chou YH., *et al.* "Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson disease: a systematic review and meta-analysis". *JAMA Neurology* 72.4 (2015): 432-440.

13. Elsner B., *et al.* "Transcranial direct current stimulation for improving idiopathic Parkinson's syndrome. An abridged version of a Cochrane review". *European Journal of Physical and Rehabilitation Medicine* 52.6 (2016): 902-906.

14. Rektorová I and Anderková Ľ. "Noninvasive Brain Stimulation and Implications for Nonmotor Symptoms in Parkinson's Disease". *International Review of Neurobiology* 134 (2017): 1091-1110.

15. Xu Y., *et al*. "Neuroplasticity in post-stroke gait recovery and noninvasive brain stimulation". *Neural Regeneration Research* 10.12 (2015): 2072-2080.

16. Bucur M and Papagno C. "Are transcranial brain stimulation effects long-lasting in post-stroke aphasia? A comparative systematic review and meta-analysis on naming performance". *Neuroscience & Biobehavioral Reviews* 102 (2019): 264-289.

Volume 2 Issue 7 July 2019