European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2019; 23: 4354-4359

The future of transcranial magnetic stimulation in neuroscience and neurology in the Middle East

F. AL-SULTAN[1], A. AL-ZAHRANI[1], F. AL-KAHTANI[1], A. AL-THAQIB[1], A. AL-MOUSA[1], S. BASHIR[2]

[1]Department of Physiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia
[2]Department of Neurophysiology, Neuroscience Center, King Fahad Specialist Hospital, Dammam, Saudi Arabia

Abstract. – OBJECTIVE: Transcranial magnetic stimulation (TMS) is a noninvasive technique for brain stimulation often used as a diagnostic and therapeutic therapy in neuroscience and psychiatry for different diseases including epilepsy, stroke, multiple sclerosis, and treatment-resistant major depressive disorders, such as autism and schizophrenia.

MATERIALS AND METHODS: Recent studies have shown the enhanced benefits of using TMS for its potential to provoke changes in the physiological processing of the human brain.

RESULTS: In the current review article, emphasis will be placed on both the applications of TMS as well as the different types of TMS used to benefit subjects with epilepsy, stroke, and multiple sclerosis. Furthermore, we aim at discussing the potential of using TMS for the treatment of neurological diseases.

CONCLUSIONS: By paying special consideration to a Middle Eastern context, we aimed at illustrating the possibilities that TMS could bring for clinicians and patients in this nationally prioritized research field.

Key Words:
Transcranial magnetic stimulation, Neuroscience, Saudi Arabia.

Introduction

Transcranial Magnetic Stimulation (TMS) is a non-invasive technique for brain stimulation extensively used in basic research and clinical neurophysiology, including intraoperative monitoring and rehabilitation intraoperative monitoring[1].

The recent integration of TMS with imaging techniques extends the possibilities of TMS even further interesting tool to understand brain physiology. For instance, the combination of TMS with structural and functional Magnetic Resonance Imaging (MRI) allows the orientation and navigation of TMS over the human cortex (neuronavigation) and provides the means for the relatively precise mapping of a given body representation in the motor cortex[1-7]. A paired-pulse TMS (i.e. two consecutively applied TMS pulses) can be used to evaluate excitatory/inhibitory intracortical circuits, thereby providing information on the physiology of the brain as well as the pathophysiology of various neuropsychiatric diseases[2]. Moreover, this technique may also be used to investigate the mechanisms of brain plasticity and the effects of neuroactive drugs on neural excitability[8]. A repetitive TMS (rTMS) uses fast, repeating pulses for a given length of time, which subsequently reveals lasting changes in neural excitability in the target area within a time range of 10-30 minutes. rTMS has made possible to use TMS in the treatment of neuropsychiatric diseases, which are related to brain excitability dysfunctions[9]. A specific rTMS device was approved by the Food and Drug Administration for the treatment of patients with medication-refractory unipolar depression who have failed one substantial (but not more than one) pharmacological trial while rTMS is already approved for use in Canada and Israel for the treatment of medication-refractory depression[10]. There are multiple interesting opportunities for TMS in terms of research, rehabilitation, and treatment options. Unfortunately, there are some limitations of TMS, which require a high level of attention. In this review, we will illustrate the TMS protocols that are currently in use and outline recent TMS studies on rehabilitation and the treatment of neurological disorders. In addition, we shall discuss the current status of TMS research and rehabilitation in the Middle East. The benefits of an increase in TMS research for patients and the public health care system es-

Corresponding Author: Shahid Bashir, Ph.D; email: sbashir10@gmail.com

pecially with reference to Saudi Arabia will also be highlighted.

Applications

Long-lasting influences on the brain depend on changing synaptic strength and cause certain anatomical changes, such as alterations in dendritic spines or sprouting[11]. Since such anatomical changes are a secondary consequence of prolonged changes of synaptic strength, TMS stimulation can be used to change neural processing via changes in synaptic connectivity.

The therapeutic utility of TMS encompasses psychiatric disorders, such as depression, acute mania, bipolar disorders, panic, hallucinations, obsessions/compulsions, schizophrenia, catatonia, post-traumatic stress disorder, and/or drug cravings[12]. Furthermore, certain neurologic diseases have been reported to have benefited from TMS treatment, such as Parkinson's disease, dystonia, tics, stuttering, tinnitus, spasticity, epilepsy, rehabilitation of aphasia, hand functions recovery after stroke, pain syndromes, such as neuropathic pain, visceral pain, or migraine[13].

Stroke

Stroke can be classified into two categories: ischemic stroke and hemorrhagic stroke[14]. Ischemic stroke occurs due to loss of blood supply to part of the brain[15]. After three hours of ischemia, the brain tissues will suffer from irreversible injury[16]. A hemorrhagic stroke, in contrast, results in tissue injury by causing compression of the brain tissue from an expanding hematoma[17]. However, a hemorrhagic stroke can also be due to hypertension, a ruptured aneurysm, AV fistula, and drug-induced bleeding[18].

The incidence of stroke in the Saudi population has been estimated to be 29.9 per 100000[19]. Although the prevalence of stroke is high, pharmacological therapy has still not been properly implemented in areas outside major general hospitals. Given this situation, it seems very unlikely that advanced methods like TMS would be accepted as a therapeutic option.

Functional Mapping In Post Stroke Recovery

The molecular and cellular changes that occur after a stroke are reflected by a significant reorganization of the post-lesion motor cortical map depending on the initial size of the lesion and its precise position in the brain. Consequently, the reorganization of motor cortical maps induced by small M1 lesions is not necessarily easy to detect by custom stimulation/imaging techniques outside the core of the lesion.

TMS mapping enables tracking of the processes arising during/after stroke (i.e. during recovery) and measures the post-stroke brain plasticity resulting from therapeutic interventions. Motor Evoked Potential (MEP) amplitude of arm or hand muscles after a stroke occurs and was shown to predict the degree of behavioral recovery weeks to months later [20]. Moreover, rTMS can determine whether a particular region participates in a recovered function by assessing whether focal stimulation of that region alters behavior[21].

Beyond Cortical Mapping: Modulating Cortical Excitability with Therapeutic Intent

There is now considerable evidence showing that during the occurrence of voluntary movement after stroke, the interhemispheric inhibitory that drives from the unaffected to the affected motor cortex is abnormal[16]. After a stroke, there is acute increased inhibitory input from the healthy to the lesioned hemisphere. This is thought to manifest as a result of the neural attempt to control peri-lesion activity. Following the acute phase, however, a shift of interhemispheric interactions from inhibitory status to excitatory status is expected in order to maximize the capability of the preserved neurons in the injured tissue in order to drive behavioral output[22]. If such a shift should fail to take place, the resulting functional outcome may be unfavorable, with limited behavioral restoration, in part owing to persistent inhibitory inputs from the healthy to the injured hemisphere. In fact, some neuroimaging studies have demonstrated that long-term, persistent activation of the ipsilateral cortex during motor tasks is associated with poor motor outcomes, whereas a good motor recovery is associated with a decrease in activity of the unaffected motor cortex and an increase in the affected primary sensorimotor cortex activity[21-23]. Leveraging this information, it can be conceived that suppression of the ipsilateral motor cortex through low frequency (inhibitory) rTMS may enhance motor performance in patients who are stable following the acute phase of a stroke. Longitudinal studies using larger samples of patients following a stroke and the correlation of interhemispheric interactions with functional measures are needed in order to further explore these avenues.

Much of the spontaneous recovery from stroke after the acute initial phase is based on plastic changes in the brain. One therapeutic approach to increase neural plasticity in the lesioned region is through using TMS. In fact, rTMS administered over the ipsilesional motor cortex for 10 days was shown to significantly improve patients' disability scores[23]. Moreover, in patients with chronic hemiparetic stroke, rTMS applied over the ipsilesional primary motor cortex (M1) resulted in a significantly larger increase in the MEP amplitude[24]. Additionally, neural plastic changes were positively associated with enhanced motor performance accuracy[24].

Another approach to brain stimulation is to target the contralesional M1, which inhibits the ipsilesional M1 via transcallosal inhibition (TCI). A previous study showed that after the neural excitability of the contralesional M1 which was induced by using 1 Hertz rTMS, there was a visible reduction in TCI duration and in the amplitude of MEPs within the contralesional M1[25]. Additionally, rTMS immediately induced an improvement in the pinch acceleration of the affected hand, which significantly correlated with a reduced TCI duration[23,26,27]. It has been observed that in stroke patients with hemiplegia after rTMS of the damaged hemisphere was conducted, MEPs are often absent. Similarly, low amplitude MEPs with increased motor threshold and prolonged Central Motor Conduction Time (CMCT) can be observed in patients with paresis[28]. Taken together then, TMS has been shown to be a good predictor of stroke rehabilitation results.

Multiple Sclerosis

Multiple Sclerosis (MS) is a central nervous system disease that involves the grey and white matter of the brain and spinal cord where demyelinating and inflammatory processes take place. It affects many aspects of a patient's life including their social, personal, and professional life. The underlying cause of multiple sclerosis is unknown[29-31]. However, based on previous studies[32], patients with early stages of MS were shown to activate more brain regions adjacent to the affected brain zones, although they were able to perform the tasks normally before their cognitive functions declined.

TMS is considered to be one of the most sensitive tools that can be used for diagnostic purposes in patients with MS[33,34], specifically when interhemispheric inhibition occurs between the motor cortices. The effect of repetitive transcranial magnetic stimulation (rTMS) was observed in 19 patients with relapsing-remitting multiple sclerosis, who had demonstrated lower limb spasticity. Daily sessions along with two weeks of 5 Hz-rTMS protocols applied to the primary motor cortex, contralateral to the affected limb, resulted in an improvement of lower limb spasticity[35]. Using rTMS can enhance the gait abnormality in MS patients. This was reported in a patient with 4 years history of relapsing remitting multiple sclerosis[36]. Moreover, rTMS can be useful for MS patients who experienced cerebellar dysfunction, a finding observed in a study involving MS patients with dysmetria who showed an improvement in hand dexterity after the application of 5 Hz-rTMS to the hemisphere that was contralateral to the affected hand[37]. The application of 5 Hz-rTMS (applied to the motor cortex) showed an improvement in the voiding phase of the urinary tract. This result could be due to the excitability of the corticospinal tract, which could improve detrusor muscle contraction and/or sphincter relaxation[38]. TMS in combination with MS medications was shown to improve fatigue and depression among MS patients[39]. There are many reasons for considering rTMS in MS patients who suffer from cognitive dysfunction including the absence of pharmacological methods to treat cognitively impaired MS patients, functional reorganization of the patient's brain through changing the functional connectivity that takes place in different brain regions, no major concerns or complications from using rTMS, and the beneficial effects of using rTMS in terms of enhancing the cognitive function among subjects suffering from different neurological diseases[40].

Current and Future Scenario for Using TMS in Saudi Arabia

Compared to other countries, the average age of the Saudi Arabia population is quite younger. However, increasing age could lead to an upsurge in neurological dysfunctions and diseases. The accompanying costs of treatment have to be covered either privately or by the public health care system.

The main challenges of neurological research and rehabilitation in Saudi Arabia are as follows:

1) Lack of a commonly accessible database with precise statistical data for various disease models.
2) Lack of specialized and coordinated centers (such as brain stimulation centers) for the treatment or diagnostics of such diseases.
3) Insufficient knowledge about noninvasive brain stimulation techniques and its applications.

4) Uncoordinated activity between neurosurgeons, psychiatrists, cardiologists, radiologists, physical therapists, anesthesiologists etc. and the lack of knowledge transfer between such medical personnel and researchers.

Given the common interest in solving the aforementioned difficulties between research and medical groups, the investment in research/rehabilitation should prove to be one of the most promising and efficient interventions in Saudi Arabia. Considering the above challenges, the opportunities for TMS research in Saudi Arabia are immense and very promising. Some of these opportunities are as follows: establishment of a database of well recorded data for statistical evaluation, establishment of competence centers for training of TMS researchers in the various fields of neuroscience and improving collaborations between medical and research personnel for the benefit of patients and the public health care system. A collaborative network between different disciplines involved in modern rehabilitation is of utmost importance. Providing active rehabilitation measures and the use of modern rehabilitation techniques (such as TMS), can considerably lower the morbidity and economic burden of neurological treatment for the victims and their families on a social and national level.

Conclusions

Transcranial magnetic stimulation is an excellent and well-established physiological tool, which complements other noninvasive methods for studying human brain physiology. It has proven its effectiveness in diagnostics and carries a high potential for therapeutic use. The main clinical applications of TMS concern testing of the functional integrity of the corticospinal tract in patients with disorders affecting the central nervous system. The applications of standard TMS in neurological disorders provide comprehensive information including – but not limited to – the detection of subclinical upper motor neuron involvement, localization of the anatomical sites of lesions, longitudinal monitoring of motor abnormalities during the course of diseases, and in differential diagnostics. More complex protocols of TMS provide information about the central mechanisms underlying changes in the corticomotor neuronal excitability in various neurological conditions. The repetitive TMS of brain areas opens up a new field of investigation pertaining to cognitive function and mood and of therapeutic possibilities. Moreover, the ability of TMS to measure and modify cortical activity offers multiple possibilities to apply this methodology to clinical neurology, neurorehabilitation, and psychiatry. A longer follow-up in patients that receive treatment with TMS is needed, in order to evaluate the long-term effects. It is also important to individualize the best parameters and targets for each patient in line with their pathologies. The development of new techniques and combinations with other techniques will improve the knowledge of the human brain and the treatment of neurological disorders. The diagnostic and therapeutic potential of TMS, therefore, is evident and holds great promise. With further research and careful considerations, new effective techniques could be developed to further promote the integration of neurostimulation methods into clinical settings. TMS technology is a relatively new tool to be utilized as a reliable treatment modality for neurological patients. Developing countries such as Saudi Arabia, could play a pivotal role in the scientific promotion of TMS and utilize it for the benefit of Saudi patients. TMS, thus, brings new hope in terms of being a cost effective form of intervention that will hopefully improve the quality of life for patients both in Saudi Arabia and across many other countries of the world.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

The authors wish to extend their appreciation to the Deanship of Scientific Research, King Saud University for funding this work through the Undergraduate Students' Research Support Program.

References

1) Rossini PM, Rossi S. Transcranial magnetic stimulation: diagnostic, therapeutic, and research potential. Neurology 2007; 68: 484-488.
2) McClintock SM, Freitas C, Oberman L, Lisanby SH, Pascual-Leone A. Transcranial magnetic stimulation: a neuroscientific probe of cortical function in schizophrenia. Biol Psychiatry 2011; 70: 19-27.
3) Bashir S, Edwards D, Pascual-Leone A. Neuronavigation increases the physiologic and behavioral effects of low-frequency rTMS of primary motor

cortex in healthy subjects. Brain Topogr 2011; 24: 54-64.

4) Bashir S, Perez JM, Horvath JC, Pascual-Leone A. Differentiation of motor cortical representation of hand muscles by navigated mapping of optimal TMS current directions in healthy subjects. J Clin Neurophysiol 2013; 30: 390-395.

5) Bashir S, Yoo WK, Kim HS, Lim HS, Rotenberg A, Abu Jamea A. The number of pulses needed to measure corticospinal excitability by navigated transcranial magnetic stimulation: eyes open vs. close condition. Front Hum Neurosci 2017; 11: 121.

6) Bashir S, Vernet M, Najib U, Perez J, Alonso-Alonso M, Knobel M, Yoo WK, Edwards D, Pascual-Leone A. Enhanced motor function and its neurophysiological correlates after navigated low-frequency repetitive transcranial magnetic stimulation over the contralesional motor cortex in stroke. Restor Neurol Neurosci 2016; 34: 677-689.

7) Bashir S, Vernet M, Yoo WK, Mizrahi I, Theoret H, Pascual-Leone A. Changes in cortical plasticity after mild traumatic brain injury. Restor Neurol Neurosci 2012; 30: 277-282.

8) Cantone M, Bramanti A, Lanza G, Pennisi M, Bramanti P, Pennisi G, Bella R. Cortical plasticity in depression. ASN Neuro 2017; 9: 1759091417711512.

9) Machado S, Arias-Carrión O, Paes F, Vieira RT, Caixeta L, Novaes F, Marinho T, Almada LF, Silva AC, Nardi AE. Repetitive transcranial magnetic stimulation for clinical applications in neurological and psychiatric disorders: an overview. Eurasian J Med 2013; 45: 191-206.

10) Horvath JC, Mathews J, Demitrack MA, Pascual-Leone A. The neuroStar TMS device: conducting the FDA approved protocol for treatment of depression. J Vis Exp 2010; (45). pii: 2345.

11) Markham JA, Greenough WT. Experience-driven brain plasticity: beyond the synapse. Neuron Glia Biol 2004; 1: 351-363.

12) Raymond Lake C. Disorders of thought are severe mood disorders: the selective attention defect in mania challenges the Kraepelinian dichotomy a review. Schizophr Bull 2008; 34: 109-117.

13) Najib U, Bashir S, Edwards D, Rotenberg A, Pascual-Leone A. Transcranial brain stimulation: clinical applications and future directions. Neurosurg Clin N Am 2011; 22: 233-251.

14) National Heart, Lung, and Blood Institute (NHLBI). Stroke. Health Topics, https://www.nhlbi.nih.gov/health-topics/stroke (accessed 5 June 2018).

15) Deb P, Sharma S, Hassan KM. Pathophysiologic mechanisms of acute ischemic stroke: An overview with emphasis on therapeutic significance beyond thrombolysis. Pathophysiology 2010; 17: 197-218.

16) Richard S. Snell. Clinical neuroanatomy. In: clinical neuroanatomy. Philadelphia: Lippincott Williams & Wilkins, 2010 pp. 478-485.

17) National Institute of Neurological Disorders and Stroke (NINDS). Stroke: Hope Through Research. Bethesda, MD: National Institute of Neurological Disorders and Stroke (NINDS), https://catalog.ninds.nih.gov/ninds/product/Stroke-Hope-Through-Research/99-2222 (1999).

18) Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J. Harrison's Principles of Internal Medicine. 18 edition. New York: McGraw-Hill Professional, 2011.

19) Tran J, Mirzaei M, Anderson L, Leeder SR. The epidemiology of stroke in the Middle East and North Africa. J Neurol Sci 2010; 295: 38-40.

20) Eliassen JC, Boespflug EL, Lamy M, Allendorfer J, Chu W-J, Szaflarski JP. Brain-mapping techniques for evaluating poststroke recovery and rehabilitation: a review. Top Stroke Rehabil 2008; 15: 427-450.

21) Kubis N. Non-invasive brain stimulation to enhance post-stroke recovery. Front Neural Circuits 2016; 27: 10: 56.

22) Boddington LJ, Reynolds JNJ. Targeting interhemispheric inhibition with neuromodulation to enhance stroke rehabilitation. Brain Stimulat 2017; 10: 214-222.

23) Khedr EM, Ahmed MA, Fathy N, Rothwell JC. Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. Neurology 2005; 65: 466-468.

24) Kim YH, You SH, Ko MH, Park JW, Lee KH, Jang SH, Yoo WK, Hallett M. Repetitive transcranial magnetic stimulation-induced corticomotor excitability and associated motor skill acquisition in chronic stroke. Stroke 2006; 37: 1471-1476.

25) Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. Stroke 2005; 36: 2681-2686.

26) Hallett M. Transcranial magnetic stimulation: a primer. Neuron 2007; 55: 187-199.

27) Auriat AM, Neva JL, Peters S, Ferris JK, Boyd LA. A review of transcranial magnetic stimulation and multimodal neuroimaging to characterize post-stroke neuroplasticity. Front Neurol 2015; 6: 226.

28) Berardelli A, Inghilleri M, Cruccu G, Mercuri B, Manfredi M. Electrical and magnetic transcranial stimulation in patients with corticospinal damage due to stroke or motor neurone disease. Electroencephalogr Clin Neurophysiol 1991; 81: 389-396.

29) Janardhan V, Bakshi R. Quality of life and its relationship to brain lesions and atrophy on magnetic resonance images in 60 patients with multiple sclerosis. Arch Neurol 2000; 57: 1485-1491.

30) Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. Lancet Neurol 2008; 7: 1139-1151.

31) Lunde HMB, Assmus J, Myhr K-M, Bø L, Grytten N. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. J Neurol Neurosurg Psychiatry 2017; 88: 621-625.

32) Audoin B, Ibarrola D, Ranjeva J-P, Confort-Gouny S, Malikova I, Ali-Chérif A, Pelletier J, Cozzone P. Compensatory cortical activation observed by fMRI during a cognitive task at the earliest stage of MS. Hum Brain Mapp 2003; 20: 51-58.

33) Michels R, Wessel K, Klöhn S, Kömpf D. Long-latency reflexes, somatosensory evoked potentials and

transcranial magnetic stimulation: relation of the three methods in multiple sclerosis. Electroencephalogr Clin Neurophysiol 1993; 89: 235-241.

34) Beer S, Rösler KM, Hess CW. Diagnostic value of paraclinical tests in multiple sclerosis: relative sensitivities and specificities for reclassification according to the Poser committee criteria. J Neurol Neurosurg Psychiatry 1995; 59: 152-159.

35) Centonze D, Koch G, Versace V, Mori F, Rossi S, Brusa L, Grossi K, Torelli F, Prosperetti C, Cervellino A, Marfia GA, Stanzione P, Marciani MG, Boffa L, Bernardi G. Repetitive transcranial magnetic stimulation of the motor cortex ameliorates spasticity in multiple sclerosis. Neurology 2007; 68: 1045-1050.

36) Burhan AM, Subramanian P, Pallaveshi L, Barnes B, Montero-Odasso M. Modulation of the left prefrontal cortex with high frequency repetitive transcranial magnetic stimulation facilitates gait in multiple sclerosis. Case Rep Neurol Med 2015; 2015: 251829.

37) Koch G, Rossi S, Prosperetti C, Codecà C, Monteleone F, Petrosini L, Bernardi G, Centonze D. Improvement of hand dexterity following motor cortex rTMS in multiple sclerosis patients with cerebellar impairment. Mult Scler 2008; 14: 995-998.

38) Centonze D, Petta F, Versace V, Rossi S, Torelli F, Prosperetti C, Rossi S, Marfia GA, Bernardi G, Koch G, Miano R, Boffa L, Finazzi-Agrò E. Effects of motor cortex rTMS on lower urinary tract dysfunction in multiple sclerosis. Mult Scler 2007; 13: 269-271.

39) Palm U, Ayache SS, Padberg F, Lefaucheur JP. Non-invasive brain stimulation therapy in multiple sclerosis: a review of tDCS, rTMS and ECT results. Brain Stimulat 2014; 7: 849-854.

40) Nasios G, Messinis L, Dardiotis E, Papathanasopoulos P. Repetitive transcranial magnetic stimulation, cognition, and multiple sclerosis: an overview. Behav Neurol 2018; 2018: 8584653.

41) Horvath JC, Perez JM, Forrow L, Fregni F, Pascual-Leone A. Transcranial magnetic stimulation: a historical evaluation and future prognosis of therapeutically relevant ethical concerns. J Med Ethics 2011; 37: 137-143.