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The Future of Transcranial Magnetic Stimulation in Epilepsy in Saudi Arabia

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Abstract

Transcranial magnetic stimulation (TMS) is a noninvasive technique for brain stimulation which is often used in neuroscientific research in order to investigate neural excitability and connectivity in the human brain. Recent studies have shown that the application of TMS has the potential to provoke changes in the physiological processing of the human brain. TMS has proven to be a valuable asset, not only in diagnostics, but also for treatment of many neurological disorders, for instance post-stroke motor deficits, depression, epilepsy, autism, and Parkinson's disease. In this review, we focus on the Middle East/ we illustrate the possibilities that TMS could bring for clinicians and patients in this nationally prioritized research field.

Keywords: Transcranial Magnetic Stimulation, Epilepsy, Saudi Arabia.

INTRODUCTION

In 1831, Michael Faraday demonstrated that a rapidly changing magnetic field could induce an electrical current in a nearby conductor [1]. During the following years, scientists explored the great potential of electromagnetic induction and with the beginning of the 20th century, scientists started to apply this principle to nervous tissue and ultimately, the human brain. The development continued constantly and in 1980 scientists Merton and Morton have shown that it was possible to stimulate motor areas of the human brain through the intact skull [2]. However, they used direct current stimulation which was very uncomfortable for the subjects. By using Transcranial Magnetic Stimulation (TMS) over the vertex of the human brain Baker *et al*. (1985) were able to successfully elicit a motor response of hand muscles without negative effects to the subjects. TMS as we know it today was first presented at the London Congress of the International Federation of Clinical Neurophysiology (IFCN) in 1985 by Anthony Barker as a noninvasive technique for brain stimulation [3]. Nowadays, TMS is extensively used in basic research but also in clinical neurophysiology, including rehabilitation and intraoperative monitoring [4]. The recent integration of TMS with imaging techniques extends the possibilities of TMS even further. 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 a relatively precise mapping of a given body representation in the motor cortex [5, 6, 7]. Therefore, TMS and its integrated techniques offer new and inspiring possibilities for rehabilitation and treatment.

Additional TMS protocols enable us to investigate different neurophysiological processes. For instance, paired-pulse TMS (two consecutively applied TMS pulses) can be used to evaluate excitatory/inhibitory intracortical circuits and thus, provide information on brain physiology and pathophysiology of various neuropsychiatric diseases. Further, this method can be used to investigate mechanisms of brain plasticity and the effects of neuroactive drugs on neural excitability.

Besides single-pulse TMS, several other TMS protocols have been established, for instance, repetitive TMS (rTMS) using fast, repeating pulses for a given length of time. As a result, the target area shows lasting changes in neural excitability in the range of 10 – 30 minutes.

Based on the special interest in the research development of Saudi Arabia, this review is extended by the current status of TMS research and rehabilitation in the Saudi Arabia.

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APPLICATION OF TMS IN CLINICAL NEUROLOGY

There is a great deal of evidence depicting the benefits of clinical applications of TMS. In this review we focus on recent developments but also agree that a lot more research needs to be conducted in order to design efficient protocols for treatment. Since the anatomical changes may well be a secondary consequence of prolonged changes of synaptic strength, the basic logic of TMS stimulation is to change neural processing through changes in synaptic connectivity. Such logic has been applied in many disorders which will be outlined in the following paragraphs.

TMS has been shown to have diagnostic and therapeutic use along with its use in research endeavors. Therapeutic utility of TMS has been claimed in the literature for many psychiatric disorders, such as depression, acute mania, bipolar disorders, panic, hallucinations, obsessions/compulsions, schizophrenia, catatonia, post-traumatic stress disorder, or drug craving. Further, neurologic diseases have been described to benefit from TMS such as Parkinson's disease, dystonia, tics, stuttering, tinnitus, spasticity, epilepsy; rehabilitation of aphasia, recovering hand functions after stroke; pain syndromes, such as neuropathic pain, visceral pain or migraine [7]. Other well controlled and sufficiently powered clinical trials of TMS are still under investigation/ongoing.

In a number of clinics worldwide laboratories/programs have been set up offering TMS for treatment of various diseases. Repetitive TMS is already approved by some countries for treatment of medication-refractory depression (i.e., Canada and Israel). In October 2008, a specific rTMS device was approved by the Food and Drug Administration in the United States for the treatment of patients with medication-refractory unipolar depression who have failed one good (but not more than one) pharmacological trial. Given its positive effects during treatment, it is reasonable to expect that the use of rTMS and thus, its expansion in the medical community, will continue to increase across different medical specialties [8, 9].

Epilepsy

Epilepsy patients whose seizure focus lies close to eloquent cortex require accurate preoperative functional mapping of the epileptogenic zone and the surrounding area before resective surgery. Presently, the standard of care for preoperative functional localization is direct current stimulation (DCS) via subdural electrodes. In this setting, preoperative functional mapping using nTMS can non-invasively localize the sensorimotor cortex and can determine its spatial relationship to the seizure focus [6].

In support of this approach, Vitikainen *et al*. showed that nTMS produced spatially more precise mapping of the motor cortical representations than subdural electrode DCS, and proposed that nTMS mapping should be added to the standard preoperative work-up (Vitikainen *et al*., 2009) [10]. Given that some morbidity and substantial financial cost is associated with any length of time that subdural electrodes are implanted, nTMS preoperative mapping may translate to improved efficiency of the epilepsy workup before respective surgery.

The coupling of TMS with real-time EEG (TMS-EEG) suggests its realistic potential as a neurologic stressor to provoke epileptiform activity in a vulnerable cortical region. In some instances where epileptiform abnormalities were triggered by TMS, the interictal scalp EEG was normal (Valentin *et al*. 2008) [11]. However, if sufficiently sensitive and specific, nTMS seizure focus localization, like nTMS presurgical functional mapping, may translate to a reduced number of subdural electrodes and a shorter invasive recording time, and thus reduced morbidity and economic cost.

In epilepsy, it is the inhibitory effect of low (≤1 Hz) rTMS that is most widely-used to suppress seizures with encouraging antiepileptic results in open-label trials [12, 13, 14, 11]. Yet, results from placebo-controlled trials are mixed, with one trial demonstrating a reduction in seizures and improvement of the EEG (Fregni *et al*. 2006), and two others showing insignificant clinical improvement, or improvement of the EEG without a significant reduction of seizures [14, 15]. Similarly, results from open-label rTMS applications in ongoing seizures of epilepsia partialis continua (EPC) are mixed with some instances of seizure termination after rTMS, and other instances of continued seizures despite stimulation. (Rotenberg, *et al*. 2009) [16].

The partial efficacy of rTMS in seizure suppression may relate to suboptimal targetting of the seizure focus. Here, nTMS may be useful in targetting more precicely a adiographically apparent seizure focus such as a tumor or a cortical dysplasia.

Using a paired-pulse TMS protocol, the results indicate an increased excitability of the motor cortex with a reduction of intracortical inhibitory mechanisms [17]. Further, TMS has proved to be useful in testing the mode of action and the responsiveness of neural excitability to antiepileptic drugs [17, 18]. However, there are some inconsistencies between results which probably relate to the multiple types of epilepsy, the presence of drugs through medication/treatment, and different TMS techniques used. Also, motor threshold and MEP amplitudes vary between different forms of epilepsy.

Some investigators have attempted to use low frequency rTMS to treat seizure disorders and other manifestations of cortical hyperexcitability, but effects were transient and controversial [18, 17].

Epilepsy in SA

In Saudi Arabia, the overall prevalence rate is 6.54/1000. This rate for active epilepsy is comparable to the results of other studies from both the developed countries and most developing ones. The average prevalence rate in 32 studies from different parts of the world has been estimated at 5.16/1000 [19].

All studies reported higher prevalence in males (26–29), which was statistically significant in the studies conducted in Saudi Arabia.

Studies conducted in countries of the Eastern Mediterranean region show that the first-line antiepileptic medicines (phenobarbital, phenytoin, carbamazepine and valproic acid) are still the most frequently prescribed [20]. Due to high costs and little experiences, the usage/prescription of the new generation of antiepileptic medicines is increasing but is still low compared to the first-line medicines. Thus, there is a high potential to increase the number of prescriptions for the benefit of the patients by continuing advertisement and education of health care personnel.

CONCLUSION AND PERSPECTIVES

Transcranial magnetic stimulation, introduced 25 years ago, 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 application of TMS concerns testing of the functional integrity of the corticospinal tract in patients with disorders affecting the central nervous system. The application of standard TMS in these neurological disorders provides comprehensive information: Detection of subclinical upper motoneuron involvement, at times localization of anatomical site of lesions, longitudinal monitoring of motor abnormalities during course of diseases, and valuable aid to differential diagnostics. The more complex protocols of TMS applications provide information about the central mechanisms underlying changes in the corticomotoneuronal excitability in various neurological conditions. Repetitive TMS of brain areas opens a new field of investigations of cognitive function and mood, and of therapeutic possibilities. There are interesting results in the short-term treatment of refractory depression by daily sessions of rTMS. By changing the frequency of stimulation, it may be possible either to up or down modulate cortical excitability for therapeutic benefit. The ability of TMS to measure and modify cortical activity offers possibilities to apply this methodology to clinical neurology, neurorehabilitation and psychiatry

A longer follow up most be done of the patients that receive treatment with TMS to evaluate the long-term effects. It is important to individualize the best parameter and target for each patient and pathologies which will be possible based in new articles and meta-analyses. The development of new techniques as new types of coils and sham coils and the combination 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. Although both treatments have their limitations, with further research and careful consideration, new effective techniques could be developed to further promote the integration of neurostimulation methods into clinical settings.

Greater understanding of the mechanisms of action of each approach is necessary in order to optimize their combined use in rehabilitation and realize the promise of a more effective means to promote functional recovery after brain injury. TMS technology is located in their first steps to act as a reliable effective treatment modality for neurological patients; and in this stage, developing countries such as Saudi Arabia, based on their available experiences and understructures could have a fundamental role in scientific promotion of this field and therefore utilize TMS benefits for their patients. In the future, maintaining the life-style of neurologically impaired individuals can be extremely costly and time-consuming. But, TMS brings new hopes for cost effective interventions to improve patient's quality of life in Saudi Arabia and all around the world.

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Conflict of interest

The authors disclose having no conflicts of interest.

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