Special Article

Basic Principle of Transcranial Magnetic Stimulation

Paradee Auvichayapat MD*,
Narong Auvichayapat MD**

** Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*
*** Division of Child Neurology, Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

Background: *Transcranial Magnetic Stimulation (TMS) is a new neurophysiological technique based on the principle of electromagnetic induction. When a pulse of current passes through a coil, it becomes a magnetic field and penetrates the scalp and skull, and reach the brain painlessly.*
Objective: *Review TMS stimulator, types of stimulation, mechanism of action, and its application.*
Material and Method: *There are three types of TMS stimulation: 1) Single pulse; used in studying of motor threshold and phosphene threshold. 2) Paired pulse; used in the study of intracortical inhibitory and facilitatory mechanisms. 3) Repetitive stimulation; changes corticospinal/corticocortical pathway.*
Results: *The mechanisms increases activity of synapse, changes the secretion of neurotransmitter, and causes neuronal plasticity or long-term potentiation. Repetitive stimulation is used in fundamental basic science for brain mapping. It is a new therapeutic method for neuro-psychiatic disorders that does not respond to medications.*
Conclusion: *TMS study is rapidly increasing and accepted as a noninvasive technique. The most favorable treating outcomes are depression and Parkinson disease. Other neuro-psychiatic therapeutic outcomes are ongoing.*

Keywords: *Transcranial Magnetic Stimulation, TMS, Neurophysiologic technique, neuro-psychiatic disorders*

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Transcranial magnetic stimulation (TMS) is a new neurophysiological technique that has an interesting role in scientific and medical researches. TMS was first introduced by Barker A et al in 1985. They provided the information of TMS as a non-invasive, painless method and safe tool[1].

TMS is based on the principle of electro-magnetic induction discovered by Faraday in 1838. When a pulse of current passes through a coil, it becomes a magnetic field and penetrates the scalp and skull into the brain. At the stimulation site, TMS prefers to activate pyramidal cell indirectly by trans-synaptic instead of activating directly at their axon hillock[1]. Motor evoked potentials (MEPs) from first interosseous muscle are detected by electromyography (EMG) (Fig. 1). Nowadays, TMS has been increasingly used for researches, diagnosis, and treatments in neurophysiology, neurology, and psychiatry.

The authors' objective was to review TMS stimulator, types of stimulation, mechanism of action, and its applications.

Correspondence to: Paradee Auvichayapat, Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand. Mobile: 089-6222624. E-mail: aparad@kku.ac.th

TMS stimulator

There are three essential components: storage capacitors, stimulating coil, and timing mechanism. The capacitor produces discharge currents of 5,000 amps or more and is connected to the coil via an electronic switch[1]. Ninety percent of the discharge occurs within the first 100 millisecond then it flows through the coil. The capacitor can generate mono or biphasic TMS waveform depending on each capacitor design[1]. The difference between monophasic and biphasic TMS is increasingly noticed in many researches[2]. The monophasic pulse has one sharp initial quarter cycle whereas the biphasic pulse contributes the induced effect in the second and the third quarter cycle. The

studies on repetitive TMS (rTMS) effects found that biphasic pulse wave might play an important role than monophasic one[2].

The stimulating coil consists of one or more tightly wound and well-insulated copper windings together with temperature sensors and safety switches. The intensity of the stimulation can be controlled by changing the intensity of current flowing in the coil, thus changing the magnitude of the induced magnetic field and of the secondarily induced electrical field. The focus point of the magnetic field depends on the shape of the stimulation coil. The two most commonly used coils are a figure-of-eight shape or butterfly coil and a circular coil. The figure-of-eight coil is two round coils that are placed side by side, so that the currents flow in the same direction at the junction point. The magnetic fields will add together and be maximized at the junction point. This coil allows focal stimulation at a limited and clearly definable location, so that the figure-of-eight coil is more often used than the round coil in researches and clinical applications. The circular coil induces a more widely distributed magnetic field allowing for bihemispheric stimulation, which is particularly desirable in the study of central motor conduction times. In addition to its intensity and focus point, operators can also control the frequency of the delivered stimuli, which will critically determine the effects of TMS on the targeted region of the brain. Anatomically precise localization of stimulation can be achieved by using a frameless stereotactic system (Fig. 2)[3].

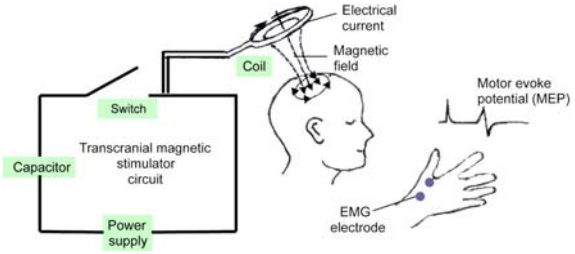

Fig. 1 Principle of transcranial magnetic stimulation, transcranial magnetic stimulator circuit (left) releasing electrical current through the stimulating coil and produces a perpendicular magnetic field to the structures beneath the coil. The detectable muscle contraction or motor evoked potential is quantitatively measured by electromyography (EMG) apparatus

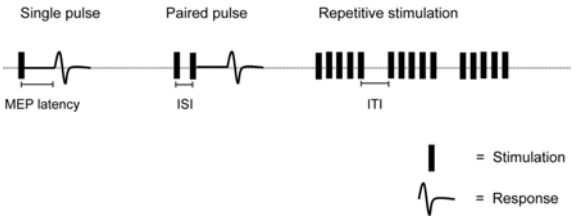

Fig. 2 Types of TMS stimulations, single pulse provides one response. Paired pulse is two pulses stimulation separated by interstimulus interval (ISI). Repetitive stimulation uses trains of pulse separated by intertrain interval (ITI)

Type of TMS stimulation

Single pulse TMS (sTMS)

When stimulating the primary motor cortex of dominant hemisphere by single-pulse. Motor evoked potentials (MEPs) induce small hand muscle and cause motor threshold[4], which are believed to reflect membrane excitability of corticospinal neurons and interneurons projecting onto these neurons in the motor cortex, as well as the excitability of motor neurons in the spinal cord, neuromuscular junctions, and muscle. Motor threshold defined as the lowest intensity required to elicit MEPs of more than 50 μV peak-to-peak amplitude in at least 50% of successive trials, in resting or activated (slightly contracted) target muscles[5].

sTMS applied over the occipital lobe can elicit phosphene in many individuals. Analogous to the motor threshold, a "phosphene threshold" can be determined and used to study the occipital cortex and the visual pathways. Many studies investigated phosphene thresholds in patients with migraine and found that they were significantly lower than control[6,7].

Apart from the motor or phosphene threshold, sTMS is used in studying the amplitude and latency of MEPs and silent period[8].

In many studies, the parameters of sTMS are different. Sommer M, et al found that motor threshold at rest or voluntary contraction of biphasic pulse was significantly lower than monophasic pulse. They also found that the orientation of pulse was important in some parameters. Monophasic pulse had an anteriorly longer silent period than monophasic posteriorly oriented pulses. They concluded that inhibitory interneurons were best activated by posteriorly oriented pulses[9].

Paired pulse TMS (pTMS)

pTMS refers to double stimulation of the same TMS coil at the same region. This method studies

intracortical inhibitory and facilitatory mechanisms by combining a sub-threshold conditioning stimulus with a supra-threshold test stimulus at inter-stimulus through the same coil. The size of a test MEP depends on the stimulus intensity and the inter-stimulus interval. The inhibitory effects are found at short inter-stimulus intervals of 1-4 ms and conditioning stimuli of 60-80% of the resting motor threshold and the inhibition is common, about 20-40% of the test MEPs[10].

The facilitatory effects of the conditioning TMS pulse on the test MEPs can be observed at the intervals of 7-20 ms. The magnitude of the facilitation is varied among individuals, from 120% to 300% of the test MEPs, depending on the amplitude of the test MEPs and the degree of contraction of the target muscle, a critical variable to control in pTMS studies. In many studies, pTMS has been used to investigate the effects of neuropsychological drugs on the human motor cortex. These studies found that it might be useful for selecting the best-suited drug for neuropsychiatric patients such as epilepsy or psychosis[11]. pTMS has been used to study the pathophysiology of various neurological and psychiatric diseases. These results are interesting but seem to be rather non-specific. For example, essentially the same abnormalities in the paired-pulse curve can be seen in dystonia and idiopathic Parkinson's disease. Furthermore, disorders without clear motor-cortex pathology, such as schizophrenia, depression, or obsessive-compulsive disorder have been found to be associated with changes in the TMS paired-pulse curve. However, longitudinal studies of the paired pulse responses may be a prognostic factor for neurological and psychiatric diseases and should be done.

Paired pulse stimulation can also be referred to double stimuli of the different TMS coil at the different region. The applications are to examine inter-hemispheric interactions and transcallosal conduction times by giving a first conditioning supra-threshold stimulus to one motor cortex and after a short interval (4-30 ms) a second, test, TMS pulse is applied to the other motor cortex. Ferbert A, showed that 7-15 ms after suprathreshold TMS of one motor cortex the cortical excitability of the opposite motor cortex is decreased[12]. This inter-hemispheric interaction is influenced by the intensity of the conditioning TMS: the stronger the conditioning TMS, the greater and longer the induced inter-hemispheric inhibition. Patients with cortical myoclonus show no such interactions, which indicate affected transcallosal or cortical inhibitory interneurons.

The stimulation of the different TMS coil can also examine the central motor conduction time (CMCT); calculate by the different of MEP latency of motor cortex and spinal root[13]. This technique was performed by giving a first stimulus to motor cortex and a second stimulus to the spinal root. Many studies found that CMCT was prolonged in multiple sclerosis, amyotrophic lateral sclerosis, stroke, secondary Parkinsonism, secondary dystonia, and brain injury[14].

It seemed to show that pTMS is one of the interesting tools for neurophysiologic diagnosis.

Repetitive TMS (rTMS)

rTMS is a train of TMS pulses of the same intensity applied to a stimulation site at a given frequency. Lower frequencies of rTMS, in 1 Hz range, can suppress excitability of the motor cortex, while high frequencies, 1 Hz or more, stimulation trains seem to temporary increase in cortical excitability[15]. While these effects vary among individuals, the effect of low frequency rTMS is robust and long lasting and can be applied to the motor cortex and to other cortical regions to study brain-behavior relations. The higher the stimulation frequency and intensity, the greater the breaking of cortical function during the train of stimulation. rTMS is a very widespread technique used in fundamental basic science and therapeutic in neuropsychiatric diseases.

Mechanism of action of rTMS

Repetitive transcranial magnetic stimulation could be a therapeutic tool in the specialty of neuronal disorders, in particular by creating long-lasting changes in the excitability of synapses within the brain as a way to modulate symptoms.

There were experiments in animals and in brain slices from animals to investigate the mechanisms of synaptic plasticity by different applications of electrical stimulation delivered through microelectrodes. These studies have identified two main types of post-synaptic, long-term plasticity: long-term potentiation (LTP) and long-term depression (LTD). The types of stimulation that most consistently produce LTP in animal studies are high frequency stimulation (100 pulses at 100 Hz every 10 s for ten trials), which are typically given in an intermittent way, whereas longer periods of lower frequency stimulation (1-5 Hz pulses given continuously for 20-30 min) are applied to produce LTD. Theta burst stimulation is a pattern of stimulation based on the firing arrangement that

occurs in hippocampal neurons. It was an effective way of inducing LTP in animal studies by giving high-frequency (50-100 Hz) bursts of 3-4 pulses repeated at about 4-7 Hz of the theta frequency. The mechanisms of transcranial magnetic stimulation in animals can reproduce the patterns of LTP and LDP in the brains of conscious human beings[16].

TMS for basic neurophysiologic science

Several studies in humans that combined rTMS and functional neuroimaging techniques such as fMRI and PET have detected the suppression after 1 Hz rTMS of the motor cortex stimulation while increased cerebral blood flow and metabolism in the stimulated motor cortex 10-20 Hz[17]. Similar phenomena have been observed after TMS to other cortical areas, such as frontal eye field and dorsolateral prefrontal cortex. Many studies found that the combination of TMS and neuroimaging could be most helpful in the investigation of functional connectivity between regions in the living human brain called brain mapping. Furthermore, the combination of rTMS with tracer PET or magnetic resonance spectroscopy may become a novel tool to investigate neurochemical functional anatomy in health and disease.

TMS for therapeutic application

rTMS is widely used for therapeutic purposes. The lasting modulation of cortical activity by rTMS is not limited to motor cortical areas. There is also evidence that these long-lasting effects of rTMS can be induced in areas outside the motor cortex[18] and be associated with measurable behavioral effects, including visual[19], prefrontal[20], parietal cortex[21], as well as the cerebellum[22].

Treatment of depression is the most thoroughly studied of the potential clinical applications of rTMS. Lasting beneficial effects have been seen in about 40% of patients with medication-resistant depression in the recent studies[23,24]. Both high frequency rTMS of the left dorsolateral prefrontal cortex and low frequency stimulation of the right side can improve depression[25] Lam RW et al performed meta-analysis of published randomized controlled trials rTMS for treatment-resistant depression in 24 studies, involving 1092 patients[26]. The data showed that active rTMS appeared to provide significant benefits in short-term treatment studies. Kimbrell TA et al suggested that decreasing cerebral metabolism might respond better to high frequency and those with hyper metabolism may respond better to low frequency stimulation, which is in line with the frequency-dependent effects of rTMS on the motor cortical excitability[27].

Pascual-Leone A et al first reported that submotor-threshold rTMS at high frequency (5 Hz) to the motor cortex improved contralateral hand function in five patients with Parkinson's disease[28]. There are two rationales for trials of this method in Parkinson's disease: firstly, the increasing cortical excitability to thalamocortical drive, which is believed to lack in this disease; and secondly, modifying catecholamine metabolism subcortically through cortical stimulation. The mild benefits were reproduced by the other groups. Strafella AP et al found that rTMS of the prefrontal cortex could increase dopamine in the caudate nucleus[29]. Fregni F et al performed the systematic review and meta-analysis of rTMS for Parkinson's disease. They evaluated the effects of either 12 studies of TMS on motor function in Parkinson's patients using the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS). They found that rTMS, across applied stimulation sites and parameters, can exert a significant, albeit modest, positive effect on the motor function of patients with Parkinson's disease[30]. Strafella AP et al studied that whether sham rTMS, in patients with Parkinson's disease, induced changes in striatal [11C] raclopride binding potentials as measured with positron emission tomography (PET). They found that the placebo rTMS-induced changes in brain dopaminergic neurotransmission similar to the one activated by other placebo and active dopaminergic drugs it seemed to support the notion of a shared neuronal network[31].

After physiological studies of task-specific dystonia suggested that hyperexcitability of the motor cortex or a failure of intracortical inhibition, rTMS of the motor cortex at 1 Hz has been used to treat the patients with writer's cramp. The improvement of deficient intracortical inhibition and handwriting lasted at the most 3 hours after application of a 30 min train of TMS resulted in clinical benefits in only two of 16 patients studied. In tics disorder, a similarly abnormal increment of cortical excitability is reported[32] and 1 Hz rTMS of the motor cortex can reduce the frequency of tics[33]. These effects are transient, but the data support the concept of impaired inhibitory mechanisms in the motor cortex. Several other studies have tried to use low-frequency rTMS to treat other diseases, for example cortical myoclonus[34] and intractable seizures[35], and showed successful reduction in the frequency of seizures or abnormal movements, but in very few patients. Similar

logic might be applicable to schizophrenia, intractable neurogenic pain, or spasticity, which the suppression of abnormally increased cortical excitability might achieve desirable symptomatic relief.

The outcome after stroke may be favorably influenced by rTMS suppressing maladaptive cortical plasticity and improving adaptive cortical activity to promote neuro- rehabilitation. Functional imaging studies after stroke show the increased activity in undamaged brain areas but the role of these areas is controversial[36,37]. Some activation in the uninjured brain could reflect adaptive cortical reorganization that promotes functional recovery, but some changes may be maladaptive and generate the emergence of behaviors, suppression of which would improve the functional outcome. The symptoms after brain damage are as much due to the damage as to the changes in activity across the undamaged brain.

This finding raises the possibility of therapeutic applications of rTMS to normalize pathologically decreased or increased levels of cortical activity. Several studies of various neurological disorders provide tantalizing results on such uses of rTMS. However, even with such favorable results, there might not be a causal link between improvement and the effect of TMS. More insights into the physiological basis for the behavioral effects of this technique are needed. In addition, to establish a clinical therapeutic indication for rTMS, well-controlled multicenter randomized clinical trials with high numbers of patients are required.

Conclusion

Transcranial magnetic stimulation was introduced 24 years ago. It is an effective and non-invasive tool for studying basic science and therapeutic uses. The main application of transcranial magnetic stimulation concerns testing of the functional integrity of the corticospinal tract. TMS studies are rapidly increasing especially in the year 2008. There was a lot of new knowledge from TMS studies such as for brain mapping as well as good therapeutic outcome for depression and Parkinson disease. The benefit of TMS should be proven in many neuro-psychiatic disorders.

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หลักพื้นฐานของการกระตุ้นด้วยคลื่นแม่เหล็กไฟฟ้าผ่านกะโหลกศีรษะ

ภารดี เอื้อวิชญาแพทย์, ณรงค์ เอื้อวิชญาแพทย์

การกระตุ้นด้วยคลื่นแม่เหล็กไฟฟ้าผ่านกะโหลกศีรษะ เป็นเทคนิคใหม่ทางประสาทสรีรวิทยา หลักการทำงานของเครื่องกระตุ้นแม่เหล็กไฟฟ้าคือการส่งกระแสไฟฟ้าผ่านขดลวด ทำให้เกิดสนามแม่เหล็กคลื่นแม่เหล็กไฟฟ้าที่เกิดขึ้นจะผ่านเข้าสู่เนื้อเยื่อประสาทได้โดยผู้ถูกทดสอบไม่รู้สึกเจ็บปวด

ชนิดของการกระตุ้นด้วยคลื่นแม่เหล็กไฟฟ้าผ่านกะโหลกศีรษะมี 3 ชนิด คือ 1) การกระตุ้นครั้งเดียว มีประโยชน์เพื่อใช้หา threshold ของสมองส่วนต่างๆ ได้แก่ motor cortex และ occipital cortex 2) การกระตุ้นคลื่นคู่ เป็นการตรวจกลไก intracortical inhibition และ facilitation ซึ่งเป็นนวัตกรรมใหม่เพื่อใช้ศึกษาพยาธิสรีรวิทยาของโรคทางระบบประสาทและโรคทางจิตเวชหลายโรค 3) การกระตุ้นซ้ำ ๆ จะสามารถเพิ่มหรือลด corticospinal หรือ corticocortical pathway โดยกลไกที่ยังไม่ทราบแน่ชัดนัก แต่เชื่อกันว่าทำให้มีการเปลี่ยนแปลงผลของจุดประสานประสาท ต่อ long term potentiation (LTP) ทำให้เกิดการปรับเปลี่ยนการทำงานของระบบประสาทในระยะยาว การกระตุ้นซ้ำ ๆ ถูกนำไปใช้ในการศึกษาแผนที่สมอง และเป็นวิธีรักษาโรคทางระบบประสาทและจิตเวชแบบใหม่ที่การรักษาด้วยยาไม่ได้ผล

การกระตุ้นด้วยคลื่นแม่เหล็กไฟฟ้าผ่านกะโหลกศีรษะได้รับความสนใจมากขึ้นเรื่อย ๆ และเป็นที่ยอมรับว่าเป็นเทคนิคใหม่ทางประสาทสรีรวิทยาที่ไม่ก่อให้เกิดอันตราย สามารถรักษาโรคซึมเศร้า และโรคพาร์กินสันได้ผลดีมาก ส่วนการรักษาโรคทางระบบประสาทและจิตเวชอื่น ๆ กำลังอยู่ในระหว่างการศึกษา