Recent Advances in Transcranial Magnetic Stimulation: From First Principles to Medical Applications

Shoogo Ueno[1,2,3]

[1]Department of Biomedical Engineering, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan

[2]Department of Applied Quantum Physics, Graduate School of Engineering, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka, 812-8581 Japan, e-mail: ueno@athena.ap.kyushu-u.ac.jp

[3]Faculty of Medical Technology, Teikyo University, Fukuoka, 4-3-124 Shinkattachi-machi, Omuta, Fukuoka, 836-8505 Japan, e-mail: ueno@fmt.teikyo-u.ac.jp

Abstract

Transcranial magnetic stimulation (TMS) is a technique to stimulate the human brain transcranially by a coil positioned on the surface of the head. Time-varying magnetic fields generated by the coil induce electric fields which stimulate neurons in the brain. By using a figure-eight coil, localized area of the brain can be stimulated, which enables us to study dynamic neuronal connectivity in the human brain non-invasively. The electroencephalographic (EEG) measurements just after TMS reveal the dynamic propagation of exciting fronts in the brain. This paper reviews the principles of magnetic stimulation of nerve tissues and brain, and discusses the usefulness and problems of the TMS for cognitive science and treatments of brain diseases such as depression. To obtain physiological bases for the potential treatments of brain dysfunction by repetitive TMS (rTMS), effects of rTMS on rat hippocampus are studied. The experimental results suggest that the rTMS modulates memory function, and contributes to recovery of injured neurons and acquisition of tolerance against cerebral ischemia.

1. Introduction

When the human body is exposed to time-varying magnetic fields, electric fields or eddy currents are induced in the body due to the Faraday's law on electromagnetic induction. Magnetic stimulation of nerve tissues and brain is realized based on this principle. Transcranial magnetic stimulation (TMS) is a technique to stimulate the human brain trans-cranially by a coil positioned on the surface of the head. The first part of the paper focuses on design and fabrication of a figure-eight coil for TMS, allowing for a local stimulation of the human cortex to produce non-invasive virtual lesions as well as excitatory or inhibitory sites in the specific areas. The combination of TMS and EEG gives us information of dynamic neuronal connectivity in intra- and inter-hemispheric networks. The use of repetitive TMS (rTMS) with figure-eight coil has opened the path for feasible studies on memory and cognitive functions in humans, long-term potentiation in hippocampus, acquisition of tolerance against cerebral ischemia, new forms of treatment for depression and other diseases. The latter part of the paper discusses the potential medical applications of TMS.

2. From Nerve Stimulation to Brain Stimulation

Magnetic nerve stimulation has been studied for more than century. In 1970s, promising methods for nerve stimulation were reported. Maass and Asa [1] proposed a transformer type of nerve stimulation where a nerve bundle was threaded through a magnetic core as the secondary winding. The rapid change of magnetic flux in the core driven by currents through the primary winding was expected to stimulate the nerve bundle. Oberg [2] proposed an air gap type of nerve stimulation where a nerve bundle was positioned in an air gap of magnetic core, and the nerve bundle was exposed to alternating magnetic fields. Induced eddy currents in the membrane tissues could be expected to stimulate nerves. Although these types of magnetic nerve stimulation have been demonstrated using frog nerve-muscle preparations, the underlying mechanisms for nerve excitation processes following magnetic stimulation were not yet well understood. For example, in magnetic stimulation, a possibility of capacitive stimulatory effect was reported [3].

We carried out an experiment to measure action potentials of lobster giant axons under time-varying magnetic fields [4,5]. The nerve axon was excited by galvanic stimulation, and the action potential was recorded intracellularly with micro-electrodes. During the propagation of the action potential along the axon, alternating or pulsed magnetic fields were applied across the middle part of the axon to study whether or not the magnetic fields have any effect on parameters such as conduction velocity, refractory period, amplitude, duration and shape of the action potentials.

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Without galvanic stimulation, the nerve excitation elicited by magnetic stimulation was also observed, changing the shape of nerve chamber exposed to pulsed magnetic fields. The results obtained from the lobster experiments suggest that the nerve excitation by magnetic field influence is mediated via the induction of eddy currents in the tissue surrounding the nerve. The current density induced depends on geometrical factors as well as the conductivity of the tissue in which the current flows. In other words, the macroscopic eddy currents that flow along the nerve axon and in the tissues surrounding the nerve mostly contribute to the depolarization of the membrane. Based on this finding, we proposed a method of magnetic nerve stimulation without inter-linkage between magnetic core and nerve bundle [6]. Assuming that a magnetic core is implanted in the body, targeted nerve tissues are positioned on the hole of the core without inter-linkage between core and nerves. The rapid change of magnetic flux in the core induces eddy currents in the conducting medium. The targeted nerve is excited by the concentrated eddy currents which flow through the well-designed small hole of the core.

3. Localized Stimulation of the Human Brain by TMS with a Figure-Eight Coil

Transcranial magnetic stimulation (TMS) was reported by Barker et al [7]. Their method, however, had the difficulty in targeting stimulation because they used a round coil. We proposed a method to stimulate a localized area in the brain by using a figure-eight coil [8]. The basic idea is to concentrate eddy currents in the targeted area by a pair of oppositely directed time-varying magnetic fields around the target. The pair of time-varying magnetic fields with opposite directions produces two vortices of eddy currents, and the vortices merge at the target beneath the intersection of the figure-eight. Computer simulation shows that the eddy currents concentrate at the target. For TMS of the human brain, transient magnetic fields in the order of 1 T and duration of 0.1-0.2 ms are generally used. Eddy currents induced by these transient magnetic fields contribute to the depolarization of nerve cells in the brain.

The devised method of localized brain stimulation with a figure-eight coil has opened new horizons in studying the human brain [9-11]. Some of important studies on the human brain function are discussed as follows.

3.1 Functional Mapping of the Human Cortex Obtained by TMS

The motor evoked potentials (MEPs), i.e., the electromyographic (EMG) responses to the brain stimulation, were measured from the muscles of hand, arm and foot of the human subjects to obtain functional maps in the motor cortex. The MEP data show that the TMS with a figure-eight coil gives us a high spatial resolution with a 5-mm. Since the induced eddy currents flow in the direction of the tangent of circles of the figure-eight coil, the direction of stimulating currents are controlled by rotating the coil. The so-called vectorial magnetic stimulation is realized by changing the amplitude and direction of stimulating currents. The functional maps in the human motor cortex obtained by this method show the vectorial characteristics exist in the brain function. In other words, optimal directions exist in target areas for brain stimulation. The vectorial characteristics reflect in part the anatomical and functional organization of the brain [9].

3.2 Virtual Lesion and Cortical Activities Related to Associative Memory Task

The localized TMS with a figure-eight coil is a useful method to examine brain function without causing any pain, producing so-called "virtual lesions" for a short period time. The human brain function related to associative memory task involving pairs of Kanji (Chinese) pictographs and unfamiliar abstract patterns was non-invasively examined. Subjects were ten Japanese adults fluent in Kanji, so only the abstract patterns represented novel materials. During memory coding, TMS was applied over the left and right dorsolateral prefrontal cortex (DLPFC). A significant reduction in subsequent recall of new associations was seen only with TMS over the right DLPFC. This result suggests that the right DLPFC contributes to encoding of visual-object associations [12].

3.3 Paired TMS for Study of Cortical Excitatory and Inhibitory Systems

Paired TMS with conditioning stimulus followed by a test pulse is useful for non-invasive investigation of cortical excitatory and inhibitory systems. A conditioning stimulus that has various interstimulus intervals (ISIs) is added prior to the test stimulus. The relationship between the ISI and amplitudes of MEPs responded to the test stimulus gives us the important information of neuronal connections with or without inhibitory neurons. For investigating transcallosal connections between the two sides of the brain, for example, two focal figure-eight coils are used over the lateral part of each hemisphere. Rothwell and Kujirai introduced this important method [13]. One, the conditioning coil, is used to activate, say, the right motor cortex, and the other stimulator is used to test the excitability of the left motor cortex at different times after the conditioning shock. It turns out that a stimulus to the right side of the brain can inhibit responses evoked from stimulating the left motor cortex at the intervals of 6 to 7 ms or longer.

3.4 Combination of TMS and EEG for Study of Dynamic Neuronal Connectivity

The electroencephalographic (EEG) activities just after brain stimulation by TMS with a figure-eight coil give us the spatio-temporal information of dynamic neuronal connectivity in the brain. Ilmoniemi et al [14] measured the EEG activities of human subjects just after TMS. We studied the dynamic neuronal connectivity by combination of TMS and EEG measurements to obtain the EEG mapping and imaging of the exciting front originated from the stimulus site, changing the stimulus points in the cortex [15]. The results show that the stimulation of the motor cortex in the left hemisphere activates the motor cortex in the right hemisphere 20 ms after stimulation, but the stimulation of a area of the posterior parietal cortex does not activate well the right hemisphere. Thus, this method is useful to investigate the functional connectivity in the brain. The functional imaging of dynamic neuronal connectivity in the intra- and inter hemispheric networks will be realized by this technique. The combination of TMS, EEG and fibertractography based on diffusion tensor MRI will be more powerful for study of dynamic neuronal connectivity.

4. rTMS and Hippocampus Functions

The repetitive TMS (rTMS) with repetitive stimulation at rates of several or several 10 Hz has potential therapeutic applications for the treatments of neurological and psychiatric disorders such as depression and Parkinson's disease, as well as for reduction of intractable pain and for rehabilitation or recovery process of injured brain after stroke.

To obtain the basic understanding for the mechanisms for potential treatments of brain diseases, animal experiments on effects of rTMS on neuronal electrical activities in rat hippocampus were studied, focusing on the long-term potentiation (LTP). The LTP is a long-lasting increase in synaptic efficacy resulting from high-frequency stimulation of afferent fibers. The LTP in the hippocampus is a typical model of synaptic plasticity related to learning and memory.

We first investigated the effect of rTMS on the LTP in the rat hippocampus [16]. Rats were magnetically stimulated at a rate of 25 pulses/second for 1,000 pulses /day for 7 days with a coil, in which the peak magnetic fields at the center of the coil were 0.75 T, 1.00 T, and 1.25 T. The TMS with the intensity of 0.75 T gave 85 % of motor threshold, and the 1.00 T gave the motor threshold, and 1.25 T gave 120 % of the motor threshold. The LTP enhancement was observed only in the 0.75-T rTMS group, while no change was observed in the 1.00-T rTMS group. In contrast, the LTP suppression was observed in the 1.25-T rTMS group. These results suggest that the effect of rTMS on LTP depends on the stimulus intensity.

We also studied the effects of rTMS on the LPS in hippocampus of rats in which the brain was in ischemic condition [17]. The condition of cerebral ischemia was realized by changing the flow of artificial cerebrospinal fluid with and without oxygen into the hippocampus slices. The LTP was induced after the hippocampus slices were exposed to the ischemic conditions. The LTP of the stimulated group was enhanced compaired with the LTP of the sham control group in each ischemic condition, suggesting that the rTMS resulted in acquisition of ischemic tolerance in the hippocampus.

The effect of rTMS on injured neurons was also investigated in the rat brain after administration of the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-teyrahydropyridine) [18]. The rats received rTMS (10 trains of 25 pulses/s for 8s) 48 h after MPTP injection. The results showed that the CA3 pyramidal neurons were injured by the injection of MTPT, but the CA3 neurons in the rTMS group were not injured. The measurement of activation of astrocytes by GFAP (glial fibrillary acidic protein) immunoreactivity showed that activation of astrocytes in the CA3 was observed in the rTMS group. Tyrosine hydroxylase (TH) and NeuN expressions were investigated in the substantia nigra. The functional observational battery-hunched posture score for MTPT-rTMS group was significantly lower and the number of rearing events was higher compared with the MPTP-sham group. These results suggest that rTMS reactivates the dopaminergic system in the brain, and contributes to prevention of neurons for injury and recovery of injured neurons.

A series of the animal experiments suggest that the rTMS modulates memory function, and contributes to the learning/memory, neuronal plasticity, and prevention of neurons against injury, recovery of injured neurons and to acquisition of tolerance against cerebral ischemia.

5. Conclusion

Recent advances in transcranial magnetic stimulation were reviewed, and the potential applications of TMS and rTMS for brain science and medical applications were discussed based on the finding mostly obtained in our laboratory in recent years. The TMS has opened new horizons in cognitive brain science and medicine. Further studies on basic experiments are needed to clarify the dynamic neuronal connectivity and the underlying mechanisms for the effects of TMS and rTMS on the brain.

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