Transcranial magnetic stimulation: the method and application

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Summary. *Transcranial magnetic stimulation is a noninvasive method for stimulation of brain that is based on the ability of magnetic field to penetrate skull and brain meninges, subsequently inducing electric current in the brain tissues that produces neuronal depolarization and generation of action potentials. Moreover, transcranial magnetic stimulation has effects on neurochemical and synaptic processes in neurons. Due to its easy use and relatively fair side effects, nowadays, transcranial magnetic stimulation is widely used in neurosciences and medicine. The main areas of transcranial magnetic stimulation application are: 1) the investigation of cortical and spinal excitability, 2) the investigation of neuronal plasticity, 3) the investigation of neuronal connectivity, 4) functional mapping, and 5) the treatment of some neurological and psychiatric disorders. Transcranial magnetic stimulation alone or in combination with other noninvasive neuroimaging (PET – positron emission topography, MRI – magnetic resonance imaging) and neurofunctional (EEG – electroencephalography, ERP – event-related potentials, fMRI – functional magnetic resonance imaging) methods allows conducting research on brain functions. Thus, transcranial magnetic stimulation is suitable as a diagnostic tool in neurologic and neuropsychiatric brain research.*

Introduction

More than 100 years ago, A. D'Arsonval and A. Beer for the first time showed the effects of magnetic field on the human brain (1). However, only from the 1980s, when the powerful capacitors able to generate 1–2 T magnetic field were constructed, it became possible to induce repeatable effects on intact human brain. A. T. Barker *et al.* in 1985 demonstrated that by placing the coil with strong electrical current in it over the human head motor response in some hand muscles could be evoked (2). Since that time transcranial magnetic stimulation (TMS) has become more and more popular because of its relatively easy use, a few side effects, and large potential for application (1, 3). Herein, we will overview the method of TMS – the physical and biological effects it has and current application fields in neurosciences and medicine.

Physical background and technical characteristics of TMS

TMS is a noninvasive *in vivo* method. It is based on the application of magnetic stimuli through the stimulation coil that is attached to the subject's intact head.

There are two main electromagnetic laws in the basis of TMS: Ampere's law – the induction of electric field subsequently induces magnetic field – and Faraday's law – the generation of electric current by changing magnetic field (1, 3, 4).

That is, changing magnetic field easily penetrates the skin, skull, brain meninges and induces secondary electric current in the neurones that are beneath the coil. This leads to the neuronal depolarization and generation of action potentials (Fig.) (1, 5).

The strength of electrical current in the coil is 5–10 kA, the strength of induced magnetic field is 1–2 T, and the cortical area that can be stimulated is about 3 cm^2 and 2 cm in depth (1, 5).

Generally, TMS equipment consists of stimulator that generates brief-pulse electric current, the frequency and intensity of which may be varied, and stimulation coil connected to it.

Mainly, two kinds of coil are used: round coils and figure-eight-shaped coils. The figure-eight-shaped coils are able to stimulate regions of the brain more focally (3, 6).

Two kinds of impulses may be applied in TMS: biphasic and monophasic. The biphasic impulse is

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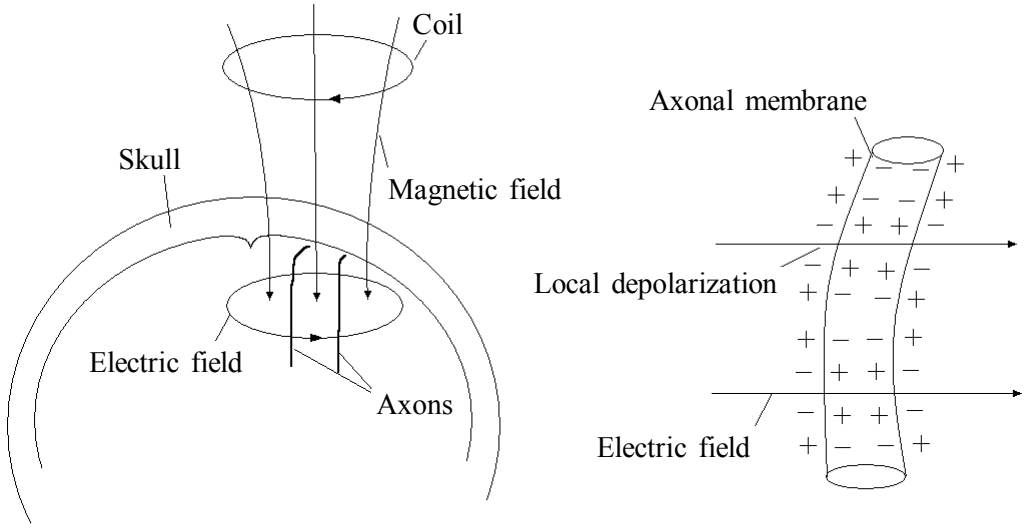

Fig. **Basic principes of transcranial magnetic stimulation**

sinusoidal and it allows producing changing electric field faster and with less energy consumption than monophasic impulse (3). Magnetic impulses can be applied alone (single-pulse TMS), in pairs (paired-pulse TMS), and in series (repetitive TMS, rTMS), which is characterized by the frequency and can be divided into low-frequency or slow rTMS (≤1 Hz) and high-frequency or rapid rTMS (>1 Hz, up to 50 Hz; for magnetic seizure therapy frequencies up to 100 Hz are in use) (5).

TMS procedure description and main definitions

Standard TMS procedure usually implies that the subject remains conscious and is comfortably sitting. The cap is worn during the stimulation that enables marking of the coil position on the surface of the head. During the procedure, surface electrodes that transmit motor-evoked potential (MEP) signals to a digital recording and display device are placed on the target muscle (7).

The first stage of the procedure is called "mapping": the stimulation is performed slightly changing the placement of the coil over the motor cortex and the stimulation intensity until the required response is obtained – the contraction of contralateral target muscle (observed visually and recorded as MEP), usually *abductor pollicis brevis* muscle or *first dorsal interosseus* muscle. This enables identification of "hot spot" for a given muscle (7).

MEP is defined as the electrical potential, registered with the help of surface electrodes from the muscle as the response to the stimulation of motor cortex or motor pathway (5).

After the mapping, the determination of the individual motor threshold (MT) follows. The MT is defined as the lowest stimulation intensity at "hot spot," needed to elicit MEP (5). MT is measured during the muscle relaxation phase – resting motor threshold (RMT). RMT is defined as the minimal stimulator intensity that evokes MEP of 50 μV in at least 5 of 10 consecutive trials when the muscle is relaxed. MT is important for the individual calibration of the stimulus during diagnostic and therapeutic procedures (for example, stimulation at intensity of 110% RMT) (8). Regarding the strength of stimulation, TMS at the intensity of more than about 10% above the RMT is labeled "high-intensity stimulation" (9).

Several methods for the localization of stimulation site can be applied regarding the region of interest. The most widely used and the best-investigated method for the localization of stimulation site is the functional method, when the site of stimulation is determined by the monitoring of TMS-induced response, for example, muscle contraction (when stimulating motor cortex). However, this method is not useful when the function of interest cannot be directly observed (10). The other method is anatomical – coil placement is based on the International 10–20 System for EEG electrode placement. The method is standardized, but not oriented to individual anatomy (10, 11). In clinical practice, the functional-anatomical method is being used. For instance, for application of rTMS as a therapeutic tool in depression, coil should be placed 5 cm anterior from "hot spot" at the motor cortex directed to the prefrontal cortex. However, it is not a precise method either (10). Nowadays, navigated TMS becomes popular. The coil placement is defined with the

help of MRI that allows individual localization. Nevertheless, in this case no functional monitoring is possible (10).

The coil position relatively to the subject's head is also of importance. For clinical studies, it is necessary to divide rTMS into real rTMS and sham rTMS. In the case of sham stimulation, a special sham coil made from special material that prevents the application of magnetic field to the head may be used. The other possibility is to angle the coil away from the head by 45° so that only the outer range is connected to the head (1, 4).

In general, for the treatment and clinical research the following TMS parameters are important: 1) the site of stimulation, 2) the shape of the stimulation coil, 3) the coil position, 4) the stimulation intensity, 5) the stimulation frequency, 6) the interstimulus interval, 7) the number of stimuli in the session, 8) the number of TMS sessions per day, and 9) the total number of TMS sessions during treatment course (*e.g.* treatment course of 10, 15, or more days).

The safety issues

The main advantages of TMS are noninvasiveness and possibility to stimulate small brain areas. However, when applying TMS, specific safety issues need to be taken into account (12). In the review on TMS risk and safety, E. M. Wassermann (1998) reported such known adverse effects of rTMS: seizure induction, effects on cognition, effects on mood, transient effects on hormones and lymphocytes, transient auditory shift, pain and headache, burns from scalp electrodes, and psychological consequences of induced seizure (13). However, nowadays particular attention is paid to the following:

1) Seizures – occasionally, TMS at high stimulation intensities can induce a seizure; the degree of risk varies with the dosing parameters and individual subject's factors; until now, only seven seizures have been reported with high-frequency rTMS (13, 14);
2) Impairment of cognitive functions – results are controversial, suggesting only short-lasting disturbance of working memory after rTMS procedure and no deleterious cognitive effects after the rTMS treatment course (15–17);
3) Pain – TMS application can cause local pain at the site of stimulation, resulting from stimulation of peripheric nerve terminals or local muscle contractions; for some hours after stimulation headache can be experienced (12–14).

Up to now, there is no evidence that TMS has any negative impact on the blood pressure or heart rate and also on the hearing threshold of the subject. It also does not cause neuronal death or mutagenesis (12).

Biological effects of rTMS

Although there are many fields of TMS application, its mechanisms of action are unclear. The data obtained suggest that biological effects of rTMS are related to those of electroconvulsive therapy, which is known to have anticonvulsant properties, effects on neurotransmission and neuronal architecture (18, 19).

There is some evidence that rapid rTMS has anticonvulsant properties in patients with therapeutic refractory epilepsy, but at high stimulation intensities, rTMS can reduce the seizure threshold and even evoke a seizure (4, 14).

TMS may also induce changes in neurotransmitter systems and hormonal axes (Table) (19–24). It can also regulate the expression of some genes, such as c-fos, c-jung, and the synthesis of some peptides (BDNF – brain-derived neurotrophic factor, GFAP – glial fibrillary acidic protein), which are important for neuronal plasticity and synaptic sprouting (4, 12, 21).

The long-lasting effects of rTMS are thought to be to due to long-term depression and long-term potentiation – the long-term forms of synaptic plasticity that are complex and involve coordinated pre- and postsynaptic mechanisms (4, 9, 14).

With the help of positron emission topography (PET) and functional magnetic resonance imaging (fMRI), it has been shown that rTMS also modulates regional cerebral blood flow, but these changes are site specific and depend on the stimulation parameters (12, 25).

Brain functional mapping

In cognitive neurosciences, TMS is used to intervene with the brain activity for short periods, to introduce so-called temporary lesions. This allows investigating the contribution of different brain sites to different aspects of a particular task (applying rTMS) and the time window during which the contribution of an area is essential for the performance of the task (applying single-pulse TMS) (26, 27).

Some of the observable TMS-induced effects can be mentioned. First, TMS over the primary motor cortex induces muscle twitch. The application of TMS over the occipital cortex induces phosphenes. The stimulation of the frontal regions interrupts working memory and speech processes (26). However, TMS can also enhance some processes. For example, single-

Table. **Changes in concentration of neurotransmitters, hormones and density of the neurotransmitters receptors in the brain after transcranial magnetic stimulation**

Substance	Direction of observed changes	Site of changes
Dopamine	Increment Decrement	Nucleus caudatus, putamen, hippocampus, nucleus accumbens, striatum (20–22) Frontal cortex
Serotonin	Increment	Hippocampus (19)
5HT1A receptors	Increment	Frontal cortex, cingulate cortex (4, 23)
5HT2 receptors	Decrement	Frontal cortex (24)
NMDA receptors	Increment	Nuclei hypothalami, corpora amygdaloideum, parietal cortex (23)
Arginine vasopressin	Decrement	Hypothalamus (20, 21)
Taurine	Increment	Hypothalamus (20)
Aspartate	Increment	Hypothalamus (20)
Serine	Increment	Hypothalamus (20)
Thyroid-stimulating hormone	Increment	Blood plasma (24)

NMDA – N-methyl-D-aspartate.

pulse TMS over Wernicke's area shortens reaction time for pictures naming (26). It has also been shown that the use of rTMS can induce mood changes: rTMS over left dorsolateral prefrontal cortex worsens mood and over right dorsolateral prefrontal cortex – improves it (26, 28–30).

Overall, TMS has good temporal resolution that is comparable to that of electroencephalography (EEG), magnetoencephalography (MEG), and event-related potentials (ERPs) and the spatial resolution covering to some extent that of computer tomography (CT), fMRI, magnetic resonance imaging (MRI), and PET (28).

Cortical excitability studies

TMS is extensively used for investigation of the excitability of human brain. Recently, some studies have shown that phosphenes provide a useful measurement of visual cortex excitability. Phosphene threshold is the most commonly used TMS parameter to assess visual cortex excitability (31). In the motor domain, the motor threshold has been established as an objective and standard measure of the corticospinal excitability (5). In contrast to phosphene threshold, MT is based on the electrophysiological measurements – MEP evaluation, whereas phosphene threshold depends on subject's reports (31).

For the motor cortex excitability studies, various stimulation paradigms can be applied. When TMS is applied in single pulses – single-pulse TMS – it allows the investigation of MEP and motor conduction time (important for investigations of the integrity of pyramidal tract) and silent period (both contralateral and ipsilateral) that is a period of suppression in background electromyogram of voluntary contracted muscle following generation of MEP (32, 33). TMS can be also applied in paired pulses – paired-pulse TMS – separated by defined interstimulus interval. This allows investigating intracortical inhibition (also divided into short-interval intracortical inhibition and facilitation (34) and long-interval intracortical inhibition (35), depending on the intensity of stimuli and interstimulus interval (33)). These inhibitory effects are being modulated by neurotransmission (probably, by gamma-aminobutyric acid-ergic system) (5, 36).

In this way, pathophysiological background of some neuropsychiatric disorders with motor dysfunction can be investigated (4, 32, 33). What is more, TMS can be used in clinical practice to monitor the integrity of spinal cord during back surgery, to predict the outcome of comas, and to investigate the development of spinal pathways (37).

Neuronal connectivity studies

Nowadays, it is possible to combine TMS with EEG. It allows monitoring the spread of activation from the site of stimulation. The first study was conducted by R. I. Ilmoniemi *et al.* in 1997. They have

showed that after the stimulation of motor cortex, the activation spreads to the ipsilateral premotor cortex, then to the contralateral premotor cortex, and afterwards to the parietal areas (38).

TMS/EEG combination allows analyzing of local effects and corticocortical connections (both intrahemispheric and interhemispheric), their strength, and changes over the time (39, 40). This also enables monitoring the spread of excitation and epileptic signs during the therapeutic procedures (41).

Neuronal plasticity studies

Neuronal plasticity is the synaptic reorganization induced by the changes in the environment, due to the training or disease (3, 9). TMS can be used to study neuronal plasticity; however, such studies are rare because of the complexity of study paradigms. The most widely applied paradigm for the investigation of neuronal plasticity includes some steps: firstly, TMS-induced movement direction is measured; then the subject is taught to perform simple motor task in its direction opposite to TMS-induced movement. Finally, changes in direction of TMS-induced movement are evaluated over the time (3, 9).

However, different approaches can be adopted to investigate plasticity with TMS. And these approaches are tidily related to already mentioned potentials of TMS. TMS can be used for plasticity studies as a method that allows exploring dynamic changes of functional representation (such as corticospinal excitability or phosphene threshold). As well, it can be helpful in assessing the functional relevance of representational reorganization (by disrupting a distinct brain function or by improving it). Additionally, TMS can be used to promote representational plasticity, subsequently imaging it with any other imaging tool, such as PET, fMRI (9).

rTMS as a treatment tool in psychiatry and neurology

In 1992, rTMS was applied for the first time as a treatment tool for psychiatric disorders in clinical studies. The most of the attention is paid to the treatment of depression (42, 43), but rTMS was also used in studies to treat mania (42), schizophrenia (44), obsessive-compulsive disorder (42), Parkinson's disease (44), and epilepsy (45).

Most of the studies conducted by this day aimed at the evaluation of TMS effectiveness for depression treatment. However, there is still no final conclusion on the antidepressant effects of rTMS. Some of the results suggest that TMS can be effective for treatment of medication therapy-resistant forms of depression (especially as add-on treatment), and that in such cases its effectiveness is similar to that of electroconvulsive therapy (46, 47). However, most of these studies (about 40) showed only moderate antidepressant effect. For confirming or rejecting this, there is an urgent need for thorough, randomized, controlled, multicenter studies involving a large number of patients (48). The results of two such studies (American and German) are expected to be announced in a short time.

For all other psychiatric disorders, the data collected are insufficient to answer the question of efficacy. As well, the sources that bring much inconsistency to the interpretation of the research results are inappropriate control, also differences in stimulation parameters and the use of various medication, different characteristics of patient groups (12).

In summary, rTMS is only known to improve the symptoms of depression.

Transkranijinė magnetinė stimuliacija: metodas ir pritaikymas

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Raktažodžiai: transkranijinė magnetinė stimuliacija, saugumas, biologinis poveikis.

Santrauka. Transkranijinė magnetinė stimuliacija yra neinvazinis galvos smegenų stimuliavimo metodas, pagrįstas tuo, kad kintantis magnetinis laukas be nuostolių pereina per kaukolę bei galvos smegenų dangalus ir indukuoja smegenyse elektros srovę, kuri savo ruožtu sukelia neuronų depoliarizaciją ir veikimo potencialų generaciją. Be to, transkranijinė magnetinė stimuliacija turi įtakos neurocheminiams ir sinapsiniams procesams neuronuose. Dėl naudojimo ir nedidelių pašalinių poveikių transkranijinė magnetinė stimuliacija plačiai naudojama nervų sistemos tyrimuose bei medicinoje. Pagrindinės transkranijinės magnetinės stimuliacijos

panaudojimo kryptys: 1) galvos ir nugaros smegenų sužadinamumo tyrimai, 2) neuroninio plastiškumo tyrimai, 3) atskirų smegenų sričių funkcijų tyrimai, 4) neuroninių ryšių tyrimai, 5) neurologinių ir psichikos sutrikimų gydymas. Transkranijinė magnetinė stimuliacija – viena ir kartu su kitais neurovizualiniais (PET – angl. *positron emission topography*, MRI – angl. *magnetic resonance imaging*) bei neurofunkciniais (EEG – angl. *electroencephalography*, ERP – angl. *event-related potentials*, fMRI – angl. *functional magnetic resonance imaging*) tyrimų metodais įgalina atlikti visapusiškus galvos smegenų funkcijos tyrimus. Taigi transkranijinė magnetinė stimuliacija, kaip diagnostikos metodas, tinka neurologiniams ir neuropsichiatriniams tyrimams atlikti.

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