Review
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Transcranial magnetic stimulation in neurosurgery

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ABSTRACT Transcranial magnetic stimulation (TMS) is a relatively new diagnostic and therapeutic method. Its widespread introduction into neurosurgical practice began in 2009. The method is used for non-invasive detection of eloquent brain areas. The combination with tractography facilitates the projection of pathways. The review summarizes the main results of TMS in the planning of neurosurgical interventions. We described the principle of method, analyzed its benefits and shortcomings, compared it with direct cortical stimulation which is a “gold standart” in detection of eloquent brain centers.

Keywords: transcranial magnetic stimulation, TMS, eloquent brain areas, preoperative planning, neuronavigation
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fMRI — functional magnetic resonance imaging
MEG — magnetoencephalography
MRI — magnetic resonance imaging
PET — positron emission tomography
TMS — transcranial magnetic stimulation

INTRODUCTION

The first description of transcranial magnetic stimulation (TMS) belongs to Barker A. T. (1985) [1]. The subsequent development of frameless stereotaxis expanded its capabilities. By performing magnetic stimulation under the neuronavigation guidance and combining the obtained results («hot spots») with magnetic resonance imaging (MRI), the operator was able to determine the location of functionally significant centers of the brain non-invasively. In 2009 Picht T. et al. were the first to use a new method for planning neurosurgical intervention [2].

TMS is not the only method for locating cortical functional structures performed in neurosurgery before surgery. Functional MRI (fMRI), magnetoencephalography (MEG) and positron emission tomography (PET) are also used for these purposes. To detect brain centers, fMRI evaluates the dynamics of blood flow, MEG records changes in magnetic fields, and in PET glucose consumption increase and hyperperfusion in response to tasks [3]. TMS is based on local activation or inhibition of brain centers when exposed to a magnetic field, which makes this method most similar to intraoperative neurostimulation [3]. Despite this, TMS is rarely used for preoperative planning, due to the high cost of equipment. Most of the works are presented by authors from the same large clinics in Germany, Italy, Japan and the USA. This review summarizes their main results.

METHOD PRINCIPLE

The principle of TMS is similar to the method of cortical stimulation. The study causes stimulation or inhibition of neuronal activity by applying a magnetic field to the scalp. The method of transcranial electrical stimulation was taken as a basis, but when it was used, the currents went randomly in different directions. During TMS, the coil current creates a magnetic field, the change of which induces current only in the right areas of the brain [3].

Stimulation-induced currents in the cortex cause repeated depolarization of axons, leading to stimulation or dysfunction of the desired cortical center. When the primary motor center is located, involuntary muscle contractions or the development of transient paresis are observed. When speech areas are stimulated the speech disturbed [4, 5].

Navigation sensors are attached to the stimulating inductor, tracking its position. The obtained coordinates are overlayed on the MRI anatomical data, forming the location of the functionally significant area [2].

The accuracy of the method is affected by the type of coil, its position, the use of drugs that reduce the excitability of the cerebral cortex, and the age of the patient. In older age data are subject to greater variability, which may be associated with the simultaneous excitation of fewer spinal motor neurons or their less synchronous activation. Despite this, the TMS method has good reproducibility, as the differences in the results between studies do not exceed 5–6 mm. This distance is not significant, given the fact that the area of the functionally significant area in TMS always exceeds its actual size [6].

Before stimulation of the motor area, the motor threshold is determined. To do this, the most excitable area of the cortex is identified, that is, the one with stimulation of which the strongest response is recorded in the short adductor muscle of the first finger of the hand. Further, in this area, the current strength is reduced until the response during myography with the voltage of more than 50 μV is registered in 5 stimulations out of 10 [4].

When performing TMS, the coil of the device is oriented parallel to the course of neurons (the motor center is located perpendicular to the precentral gyrus), since in this case a higher current is given [7].

The data obtained during TMS are combined with anatomical MRI and loaded into the navigation system. When planning tractography, «hot spots» identified during magnetic stimulation are landmarks for constructing pathways. Integration of received data into a single hospital network speeds up the workflow [8].

TMS is usually performed to identify centers of limb movement. But this method can also be used to locate the centers responsible for the movement of the facial muscles. This makes it unique as the center of the facial musculature cannot be detected by fMRI due to the complexity of the models. The location of the centers of innervation of the facial muscles is a more difficult task. Facial muscles are smaller and thus require thinner electrodes. The amplitude of the response from the muscles is lower, and the shape is more complex than from the limbs. To identify such centers, a higher motor threshold is needed, within 105–110%. More often, facial muscles have contralateral innervation, but ipsilateral innervation is possible in 20%. The easiest way is to locate the circular muscle of the mouth, the chin muscle is more difficult to be located (due to the more central position and crossing of muscle fibers), and the muscles of the upper part of the face (frontal, circular muscle of the eye) are even more difficult to be located. The center of voluntary movements of the facial muscles is usually located in the region of the precentral gyrus on the border between the middle and lower thirds. But in 25% cases its anterior or posterior displacement is possible [9].

BENEFITS OF TMS AND ITS CLINICAL USE

Transcranial magnetic stimulation is the only non-invasive way to diagnose functionally significant cortical centers, which mechanism is similar to direct electrical stimulation [10].

The use of TMS allows more accurate planning of the surgical approach and facilitates the detection of the functional center of the brain, which accelerates subsequent neurostimulation [11–13]. In surgery for malignant gliomas, in combination with fluorescence, this leads to a decrease in persistent movement disorders incidence from 29 to 10% and an increase in number of radical resections from 51 to 73% [14].

According to Picht T. et al., when analyzing the results of resection of 70 tumors, TMS in 55% affected the tactics of surgical treatment: the surgical approach was changed in 16%, the volume of tumor resection (both up and down) was changed in 8%, and the tactics of treatment was changed in 3% [15]. The awareness of the exact location of the motor and speech centers identified during TMS, and the absence of«hot spots» in the projection of the surgical approach allows craniotomy to be minimized [10, 16, 17].

Transcranial magnetic stimulation is the most accurate preoperative method for detecting the motor area. In studies, compared with direct cortical stimulation, which is the «gold standard», it turned out to be more accurate than fMRI and MEG [11, 18, 19]. Firstly, this is associated with the identity of the basic principles underlying the methods of TMS and electrical stimulation, based on the inactivation of neurons due to their depolarization [3, 5, 20]. Secondly, the accuracy of TMS is less affected by adjacent tumors and vascular malformations than fMRI [21, 22]. Thirdly, when TMS is performed, there are no artifacts from the combined movement of other muscle groups, which is typical for fMRI (synergistic movements in the limbs, movements of the head) [7].

The method makes it possible to distinguish functionally necessary areas of the brain from non-essential ones, which are involved in the performance of the function, but which resection does not lead to neurological disorders [23].

Unlike fMRI, TMS can be performed in patients with mnestic and intellectual disorders who do not follow commands [20], and in claustrophobia [7]. TMS may be informative for detecting the primary motor center in the presence of deep paresis and plegia, which is not possible with fMRI. When the motor area is compressed, the amplitude of responses decreases, but their registration is possible. Complete disappearance occurs only when the cortical centers or subcortical pathways are destroyed [24].

TMS has a high negative predictive value. This means that if a certain part of the brain is functionally insignificant during TMS, then its resection most likely will not lead to neurological disorders. This is important to take into account when it is impossible to perform neuromonitoring, which allows performing a more radical operation [13].

The use of TMS makes it possible to increase the completeness of tumor resection, improve the functional outcome, and reduce the likelihood of seizures in patients with a history of epilepsy. It is especially necessary to use the method when performing supratotal resection of neoplasms [12, 17].

In surgery of tumors of the motor area using TMS, radical resection can be achieved in 68% of presistent paresis in 8% of patients [25]. The method of cortical and subcortical stimulation is necessary when removing such tumors. But the additional use of TMS and tractography can further improve functional outcomes. Firstly, their use allows more accurate planning of the volume of tumor resection at the preoperative stage. The use of TMS changes the estimated volume of the operation in 14% , and the combination with tractography in 20 [26]. Second, the visual representation of the location of the motor area and the pyramidal tract facilitates subcortical stimulation. A positive response to cortical and subcortical stimulation only tells the surgeon that the cortical center or pathway is at a certain distance from the point of stimulation. This distance depends on the current strength, usually 1 mA corresponds to 1 mm. But the method of neurophysiology does not indicate in which direction the subcortical pathways are located. When combining neuronavigation with the results of TMS, the surgeon sees them. This allows more thorough cortical and subcortical mapping (smaller distance between points) exactly in the direction of the proposed pathway [23, 26]. According to Raffa G. et al. (2018), when isolated neuromonitoring is performed during the removal of tumors of the primary motor area, motor disorders after surgery occur in 57%, and persistent ones occur in 26%. In combination of cortical stimulation with TMS, their incidence decrease to 31% and 17%, and when electrical mapping, TMS, and tractography are combined, it falls to 11% and 3%, respectively [26].

In case of gliomas of the speech areas, the combination of TMS and neurostimulation makes it possible to perform a radical resection of the tumor in 72–73%, while the incidence of persistent speech disorders is only 6–8%. Good results of such operations create prerequisites for surgical treatment of gliomas of the verbal centers under anesthesia based only on TMS and tractography data when surgery is impossible while awake [25, 27]. One of the first such works was done by Hendrix P. et al. (2017). When operating under anesthesia on gliomas of the speech areas using TMS, the authors observed an earlier recovery (in the first 3 months) of speech, and the operation and hospitalization were shorter than without the use of magnetic stimulation. However, the number of persistent verbal disorders could not be reduced. The radicality of resections also did not differ, although it corresponded to that in awake surgery (65%) [28]. According to Shcherbuk A.Yu. et al.

(2015), the use of TMS reduces the number of focal neurological disorders after surgery from 38 to 10% (3.8-fold) [4].

TMS is used to assess higher cortical functions. Ille S. et al. (2018) used it to determine the location of the cortical centers of arithmetic calculations in tumors of the parietal lobe. Despite the lack of comparison with the results of direct electrical stimulation, the authors confirmed the accuracy of preoperative mapping with clinical data: in case of resection of the computational center, violations of the arithmetic count after surgery were more often observed. Sensitivity and negative predictive value of TMS was 1.0, a positive predictive value was 0.8, and specificity was 0.5 [29].

TMS facilitates the construction of brain pathways during tractography [30], makes it possible to distinguish between subcortical tracts for the face, arms and legs [26] and display only functionally significant fibers [31].

TMS is used to predict postoperative functional outcomes in tumors of significant areas. It also helps assess the need for intraoperative neuromonitoring. In gliomas located near the precentral gyrus, risk factors for a poor prognosis are infiltration of the M1 cortex by the tumor, asymmetry of pathological interhemispheric excitability, and a distance from the pyramidal tract to the tumor of 8 mm or less. This distance is calculated using tractography based on TMS data. In the presence of risk factors, postoperative recovery of motor neurological disorders occurs 6 times less often, and persistent dysfunctions develop more often. These parameters are an indication for the use of intraoperative neuromonitoring [32]. In malignant gliomas, the threshold distance between the pyramidal tract and the tumor, which makes it possible to exclude the increase in motor disorders after surgery, is 12 mm [33]. Preservation of motor evoked potentials during postoperative TMS in patients with paresis performed one week after tumor resection is a predictor of early recovery of muscle strength [34].

TMS is used to assess brain plasticity in tumors. The method allows the direction to be to identified and the distance of displacement of significant cortical areas to be calculated. This knowledge makes it possible to assess the exact relative position of the mass formation and the functional centers of the brain, to determine the operability of the tumor, and to clarify the extent of its resection [35]. The awareness of the dislocation of functionally significant centers makes it possible to more accurately assess the volume of tumor resection during its continued growth [20, 36].

In surgery for arteriovenous malformations, TMS, as well as fMRI, makes it possible to assess the true location of a functionally significant area before surgery, which in some patients changes the risk of resection according to the Spitzler –Martin scale and treatment tactics [37]. Germano A. et al. (2019) used this approach to classify and determine indications for surgery in 10 patients with arteriovenous malformation. TMS changed the gradation of malformations according to the Spitzler–Martin scale in 6 cases. The accurateness of the method was assessed by the authors according to the outcomes of the disease, not having received a single deterioration in the condition after the operation [38].

TMS has high individual and group reproducibility, the average error is 5.7 mm [39]. The reproducibility with TMS is higher than with fMRI [7].

Butenschon V. M. et al. (2018) assessed the economic viability of using TMS. Despite the additional costs (842 euros), the total cost of treatment with this method is reduced by reducing the duration of hospitalization. When adding other costs (rehabilitation, psychotherapy, disability and repeated chemotherapy), the differences increase even more. This makes the use of TMS cost-effective and necessary for gliomas of functionally important areas of the brain [40].

DISADVANTAGES

Despite the fundamental similarity between TMS and cortical stimulation, these two methods also have differences. The currents evoked during TMS and cortical stimulation differ in density and direction. During cortical stimulation with bipolar forceps, induced microcurrents flow only between its branches and directly activate cortical neurons. In TMS, the activation of neurons does not occur directly, but through pathways, which makes it possible to activate a larger number of nerve cells [41]. Bypass activation or inhibition of cortical pathways can give a false positive response in TMS in locations that are not directly involved in speech or movement. Resection of such areas of the brain usually does not lead to persistent neurological disorders [5]. But their preservation reduces the radical nature of the operation. Therefore, the combined use of TMS and fMRI, which is more specific in preoperative planning, makes it possible to clarify the location of functionally significant speech areas [13, 42].

Another reason for the differences in data between TMS and cortical stimulation may be differences in the tasks performed by patients, different examination times, and greater attention of the observer during magnetic stimulation. TMS is recorded not in the operating room, but in a calm environment, where the researcher is not limited by time, having the opportunity to perform the procedure more thoroughly [5].

TMS is often limited to the location of only the primary motor cortex. Detection of the supplementary motor area and premotor cortex is difficult. This requires a greater intensity of stimulating impulses. But even in this case, it can be difficult to distinguish them from each other, since these departments are interconnected by synapses. Activation of the non-primary motor cortex often leads to subsequent activation of the primary one, blurring the line between the two [43].

The compression or destruction of the pyramidal cells by the tumor means that TMS stimulation can no longer elicit action potentials from enough neurons to produce a muscle response. The same drawback is also characteristic of direct cortical stimulation, which leads to false negative mapping results [18].

Performing TMS is a long process, it takes 1 hour, and another 30 minutes are required subsequent data processing [7]. Intraoperative brain displacement is the main factor of method inaccuracy [44].

TMS AND CORTICAL STIMULATION

TMS has high accuracy in detecting the primary motor center. When compared with the results of direct cortical stimulation, the average difference is 3.5 –10 mm, which is within the accuracy of the device registration and does not exceed 1 cm. Magnetic stimulation is more accurate than fMRI, in which the average error is 15 mm [2, 7, 10, 11, 16, 18, 44].

The accuracy of TMS depends on the number of points during cortical stimulation: the more is the number of point, the higher is the accuracy. This is associated with the fact that the site of neurostimulation is not a physical point, but an area. In addition, a more thorough study increases the likelihood of finding points closer to the significant zone in TMS. With scrupulous mapping of the cortex and the absence of brain displacement, the difference between the results of TMS and corticostimulation decreases to 2 mm, which is comparable to the registration error of the navigation system [44].

In addition to accuracy, TMS and cortical stimulation have a complete correspondence. TMS reveals the motor area in all cases, if it is detected during corticostimulation. Conversely, if the motor center is not found on TMS, it is not found on electrical mapping either [18].

The accuracy of TMS in detecting the primary motor area is 100%, specificity — 80%, positive predictive value — 90%, negative predictive value — 100% [14]. When identifying speech centers, the sensitivity of the method varies within 63-90%, specificity — 24-67%, positive predictive value — 36-55%, negative predictive value — 74-84% [5, 16].

In isolated detection of Broca's center, the sensitivity of TMS is 100%, the specificity is 13%, its positive predictive value is 57%, and its negative predictive value is 100%. Due to the high accuracy of magnetic stimulation in identifying brain regions not involved in the speech process, this method is sufficient for planning trepanation and corticotomy. However, due to the low specificity of TMS, its data require verification during cortical stimulation [5].

When comparing TMS data with the results of neurostimulation, it should be understood that neuromonitoring methods can also give an error within 10 mm. The inaccuracy of navigation registration of about 2 mm is also important. The displacement of the brain can significantly exceed these figures. Therefore, to minimize cerebral dislocation, methods should be compared immediately after opening the dura mater [7].

CONCLUSION

The high cost of equipment limits widespread use TMS. Only a few works contain more than 100 observations. According to these data, TMS is a highly informative method for detecting functionally significant brain structures. This method makes it possible to locate cortical centers and, in combination with tractography, facilitates the construction of a model of pathways.

The method is most accurate in identifying the primary motor area, exceeding the reliability of fMRI and MEG. But the detection of speech centers with this method is less certain due to the variability in their location.

TMS is an important addition to invasive neurostimulation. With its high sensitivity, it is excellent for craniotomy planning, but due to its low specificity, it requires confirmation by neurophysiological mapping or fMRI.

A wider adoption of TMS among neurosurgeons is a prerequisite for increasing the radical type of operations and improving functional outcomes. Large multicenter studies are needed to confirm these findings.

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