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Significance of diagnostic transcranial magnetic stimulation during radiotherapy

A.V. Kartashev[1,2]*, V.Yu. Chirkin[3], N.V. Ilyin, V.B. Voitenkov[4,5], Yu.N. Vinogradova[1]

[1]Russian Scientific Center of Radiology and Surgical Technologies named after A.M. Granov, St. Petersburg, Russia;
[2]Northwestern State Medical University named after I.I. Mechnikov, St. Petersburg, Russia;
[3]National Medical Research Center named after V.A. Almazov, St. Petersburg, Russia;
[4]Pediatric Research and Clinical Center for Infectious Diseases of the Federal Medical and Biological Agency, St. Petersburg, Russia
[5]Academy of Postgraduate Education of Federal Scientific Research Center of the Federal Medical and Biological Agency, Moscow, Russia

Abstract

Background. Transcranial magnetic stimulation is a non-invasive, painless method that stimulates the cerebral cortex using short magnetic pulses. The information obtained as a result of the research can be further used for an objective assessment of the therapy.
Aim. Evaluation the reliability of transcranial magnetic stimulation technique as a neurophysiological monitoring tool in patients with malignant brain tumors.
Material and methods. There were two groups as a study objects: patients with large-focal solitary lesions of the central nervous system (glioma) who underwent radiotherapy (n=20), median age 49.5±5.3 (39; 60) years, and a comparison group of neurologically healthy individuals (n=16), median age 48.5±6.3 (43.0; 58.8) years. There were no statistically significant age differences between the studied groups. All patients underwent diagnostic transcranial magnetic stimulation before and after therapy. The Mann–Whitney test was used to make comparisons between the two groups. A p value <0.05 was considered statistically significant.
Results. During transcranial magnetic stimulation in patients with malignant brain neoplasms, signs of impaired conduction along the central motor pathways were recorded in 50% of cases, and in total, signs of impaired conduction of all degrees of severity along the central motor pathway were detected in 90% of cases. Carrying out diagnostic transcranial magnetic stimulation according to a single-pulse protocol makes it possible to predict the further course of the recovery period. The use of transcranial magnetic stimulation in dynamics revealed an improvement in conduction along the central motor pathways in patients with malignant brain neoplasms. The obtained statistically significant differences allow us to conclude that transcranial magnetic stimulation can be used for an objective assessment of the state of the motor pathways in patients with neurooncological diseases.
Conclusion. Diagnostic transcranial magnetic stimulation is applicable in large-focal solitary lesions of the central nervous system, since it allows assessing the state of the motor pathways and the functional activity of the brain at different stages of this condition.
Keywords: radiotherapy, transcranial magnetic stimulation, brain tumors, magnetic coil, neurodegenerative diseases, glioma, evoked motor responses.

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*For correspondence: arxiator@mail.ru
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Background

Transcranial magnetic stimulation (TMS) is a neurophysiological research method that is based on the principle of electromagnetic induction. This method consists of neuron stimulation and subsequent response registration using electroneuromyography [1, 2]. TMS was integrated into medical practice as a diagnostic tool in the mid-1980s, and to date, this non-invasive method for studying the conduction motor systems of the brain and spinal cord is widely used in clinical neurology and neurophysiology, to a certain extent because of its painlessness and relative methodological simplicity [3–5]. Additionally, TMS has wide diagnostic and therapeutic capabilities, which has led to its use in a wide range of neurological diseases and pathological conditions in children and adults [6–8].

Aim

The study aimed to determine the reliability of the TMS technique as a neurophysiological monitoring tool in patients with malignant primary brain tumors.

Materials and methods of research

This experimental study was approved by the ethics committee of the A.M. Granov Russian Scientific Center for Radiology and Surgical Technologies, protocol No. 04-19 of 05/22/2019. A total of 20 patients were examined using TMS, including adults with a large-focal solitary lesion of the central nervous system (glioma), who underwent radiation therapy at the A.M. Granov Russian Scientific Center (St. Petersburg, Russia) in 2018–2020.

Infographic characteristics of the base and research methods are presented in Table 1.

The obtained results were compared between the groups. Statistical analysis was performed using the Statistica software package for Windows. Descriptive statistical methods were used to assess the demographic indicators of the groups. The Student's *t*-test was used for normally distributed parameters. The Mann–Whitney test was used for incorrect distributions. A p-value of <0.05 was considered statistically significant. The comparison group consisted of 20 neurologically healthy adults (mean age: 45 ± 4.3 years). The work was performed following the ethical standards and approved by the local ethics committee.

Magnetic stimulation was performed at the cortical and segmental levels to assess the corticospinal tract status [1]. The magnetic coil was placed on the subject's head in such a way that the recorded potential had the highest amplitude, namely in the cerebral motor zone projection to assess the cortical evoked motor response (EMR) and above the cervical and lumbar thickenings of the spinal cord to analyze segmental EMRs.

When examining the upper extremities, the center of a standard ring coil was placed above the *vertex* zone, that is, above the point of intersection of the sagittally drawn line and the line connecting the auditory passages; and the double coil ("figure eight") was placed 5–7 cm lateral to the *vertex* on the contralateral side following the recording electrodes. During segmental magnetic stimulation, the coil was placed at the C_{VII} vertebra level (in this case, the outer diameter of the lower part of the coil was placed at the spinous process level of C_{VII}) or 1 cm laterally on the side of the recording electrodes. The lower extremity examination revealed an annular coil located 2 cm anteriorly and 4 cm contralateral to the registration point above the *vertex* zone and a double coil above the *vertex* zone. The coil was placed at the L_{III} and L_{IV} vertebrae levels with its lateral displacement of 2–3 cm ipsilateral to the recording electrodes to obtain EMR at the segmental level [3].

The activation of neuronal brain structures upon coil stimulation in terms of localization largely coincided with the activation of similar cerebral structures during voluntary movement. TMS-induced activation of neuronal structures located directly in the coil projection, as well as remote cortical areas (ipsi- and contralateral premotor cortex, supplementary motor cortex, ipsilateral somatosensory cortex, cerebellum [predominantly contralateral to the coil], thalamus, and bilateral caudate nuclei and acoustic cortex), coincided to a large extent with the same neuronal structure activation during the voluntary movement but, as a rule, is less in its spatial extent. The long duration of induced activation was probably associated with the excitation circulation through multisynaptic neuronal networks, which gradually attenuated after the end of the TMS procedure. Magnetic induction when using standard coils depends on the distance from their surface.

When performing diagnostic TMS, the recording standard skin electrodes were most frequently placed in *m. abductor pollicis brevis dexter, m. abductor pollicis brevis sinister, m. tibialis anterior dexter, m. tibialis anterior sinister, m. abductor hallucis dexter,* and *m. abductor hallucis sinister.* The "belly-tendon" electrode placement technique is similar to the generally accepted M-response derivation procedure for stimulation electromyography.

In the study of the conductive efferent systems of the upper limbs, the active electrode is placed on the middle belly part of the thumb adductor short muscle (projection of the motor point of *m. ab-*

Table 1. Infographic characteristics of the experimental study

Study sample	A total of 20 patients were examined in the group of gliomas. The mean age of patients was 49.5 (39–60) years. The group was divided into 10 males and 10 females. All patients had a histological diagnosis of glioma of the cerebral hemispheres, of which 8 had anaplastic astrocytoma, 1 had anaplastic oligodendroglioma, and 11 had glioblastoma. The tumors were localized in the right hemisphere in 9 cases and the left hemisphere in 11 patients. Comparison group 1 (neurologically healthy and with transcranial magnetic stimulation as part of a screening study) included 16 patients, with an average age of 48.5 (43.0–58.8) years.
Terms of the study	The period of the study from the presentation of the first complaints ranged from 63 to 164 days, with an average of 110 days. All patients underwent surgical treatment, without complete glioma removal in any case. The average study duration from the surgical treatment was 30 days, and the minimum duration was 22 days. The study on all patients of the glioma group was performed as part of radiation therapy preparation. The therapy consisted of radiation treatment (single focal dose at 3 Gy, total focal dose at 51 Gy).
Technological base of the study	We used a transcranial magnetic stimulator Neuro-MSD (Neurosoft, Russia), with a standard ring coil of 90 mm in diameter. For registration, a Neuro-MVP 4 myograph (Neurosoft, Russia) and cup surface electrodes were used. The evoked motor responses (EMR) from the hands (*m. abductor pollicis brevis*), their threshold, latency, amplitude, and form were recorded, then the time of the central motor conduction was calculated.

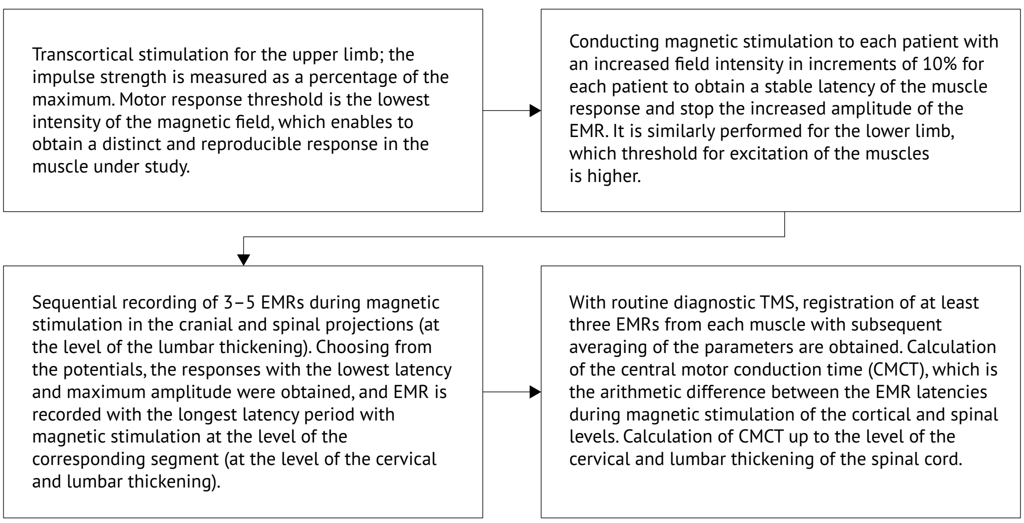

Fig. 1. Algorithm for conducting diagnostic transcranial magnetic stimulation (TMS); EMR: evoked motor response.

ductor pollicis brevis), and the reference electrode is located in the proximal phalanx region of the thumb. During TMS of the conductive lower limb tracts, the active electrode is applied to the middle belly part of the tibial muscle and the reference electrode is placed in the projection of its attachment to the bone (projection of the motor point of *m. tibialis anterior*). Tendons of *m. abductor hallucis* were also used for this purpose. Bone markers were used, namely the head of the capitate bone at the level of the wrist and the anterior surface of the first metacarpophalangeal joint, to apply peripheral recording electrodes. Apply a grounding electrode was obligatory, particularly, when examining the upper limb, which was placed in the middle of the palm. Patients were relaxed during the TMS procedure.

Before installation, the electrodes were treated with cotton wool soaked in 70% ethanol. Afterward, the quality of the electrode placement was checked. This was performed using the available impedance test function for all modern electroneuromyographs manufactured both in Russia and other countries. The recording electrode was additionally soaked with an electrically conductive liquid (isotonic sodium chloride solution) in case of excessive impedance.

The algorithm for performing diagnostic TMS is presented in Fig. 1.

EMRs that are obtained by stimulating the cerebral cortex are called *cortical*, while those obtained by stimulating the spinal cord are called *segmental*, and *peripheral* EMRs are obtained when peripheral structures are stimulated.

Table 2. Indicators of transcranial magnetic stimulation in patients of the main group and the comparison group.

Parameters	Group of gliomas (n = 20)	Comparison group (adults) (n = 16)
Latency of evoked motor responses, ms		
Right hand	23.34±3.3	21.41±1.74
Left hand	21.89±1.43	20.94±2.53
Amplitude of evoked motor responses, mV		
Right hand	1.36±1.12	5.43±2.05
Left hand	1.84±1.62	3.25±2.01
Central motor conduction time, ms		
Right hand	10.13±3.91	7.95±0.7
Left hand	8.75±1.15	7.67±1.01

The value of the central motor conduction time (CMCT) is obtained from the time required for depolarization of cortical motor neurons, synaptic delay and depolarization of corticospinal neurons, impulse conduction along the corticospinal tract, synaptic delay and depolarization at the level of α-motor neurons, and the time required for conduction from the root to the excitation sites at the level of neuronal segmental systems.

The parameters of the motor response, with each variant of magnetic stimulation, can be determined in two states, namely studied muscle at rest and with a slight voluntary tension (facilitation test), at which spinal α-motor neuron activation occurs and the motor response occurrence is facilitated. Spinal motor neurons are believed to play an important role in implementing the facilitation phenomenon. With the development of a voluntary effort of up to 10% of the maximum, the neuronal structures of the spinal cord are mainly activated; however, the cortical and spinal mechanisms begin to identically function with a greater effort.

From a practical point of view, considering that the obtained EMR during facilitation is unstable in amplitude and has a shorter latency and higher amplitude than the induced potential at rest is important. Thus, the recorded EMR at rest on one side of the body cannot be compared with the obtained EMR using facilitation on the other side since these evoked potentials do not reflect the true conduction asymmetry status.

Results and discussion

The indicators obtained during the first study are presented in Table 2.

No significant differences were found between the groups ($p > 0.05$).

The study results in dynamics are presented in Table 3.

The data presented in Figure 4 shows an undoubted tendency in cortical EMR latency shortening, a bilateral increase in their amplitudes, a decrease in CMCT on both sides, and a decrease in the severity of asymmetry of latencies and CMCT between the sides in patients with gliomas after radiation treatment. According to the EMR amplitude parameters on the left in the second series of studies, a significant increase was found in them.

TMS parameter changes that were registered in the group of patients with gliomas (TMS latency shortening and decreased CMCT asymmetry), as well as increased functional activity of cortical motor neurons (increased cortical EMRs amplitudes on both sides), maybe due to the positive effect of chemoradiotherapy, namely a decreased cerebral edema severity, a decreased plus-tissue volume, and the resulting improved conduction along the motor pathways. The only patient who did not have these positive neurophysiological dynamics also did not show clinical improvement.

TMS is used before initiating, during, and after the radiation therapy to assess the motor pathway preservation, map the motor cortex, and study the functional motor neuron status. The use of diagnostic TMS in metastatic brain lesions is known to reduce the hippocampal radiation dose, as well as limit the damage to the motor cortex [9]. This dose reduction reaches 18% [10]. The dose is reduced by 14% when TMS is used in the preoperative period (radiation treatment) for cerebral gliomas [11]. Positive results have also been obtained from a similar combination of treatment methods for brain metastases using a gamma knife [12, 13].

The latencies of the cortical and segmental EMRs, as well as the CMCT, can be for motor pathways preservation. Their changes in the treatment course are considered positive with a decrease in CMCT and shortened latencies. Therefore, the EMR amplitude is assessed, and its increase is considered a sign of positive neurophysiological dynamics.

The EMR threshold is examined to assess the functional activity of motoneurons; the lower the EMR threshold, the higher is its activity [14]. Accordingly, a decreased EMR threshold will be a sign of positive neurophysiological dynamics during radiotherapy.

The resulting EMRs vary according to the stage and volume of the hemispheric process. The size of the focus and the degree of conduction disturbance had no direct dependence due to the large variability in the structure of the pyramidal tracts and neuroplasticity since, at the late convalescence stage, the cortical EMR may have more “normal” parameters (amplitude, latency, threshold, and

Table 3. Indicators of transcranial magnetic stimulation (TMS) in dynamics.

Parameters	TMS parameters (series 1, glioma group) (*n* = 20)	TMS parameters (series 2, glioma group) (*n* = 20)
EMR latency on the right, ms	23.34±3.3	22.9±1.16
EMR latency on the left, ms	21.89±1.43	21.9±1.12
EMR amplitude on the right, mV	1.36±1.12	2.92±1.03
EMR amplitude on the left, mV	1.84±1.62	5.07±1.2*
CMCT on the right, ms	10.13±3.91	10.09±2.41
CMCT on the left, ms	8.75±1.15	9.02±1.03
Asymmetry of latencies, ms	3.3±1.1	1.9±0.9
Amplitude asymmetry, mV	1.85±0.48	2.47±0.93
CMCT asymmetry, ms	3.45±0.9	2.73±0.86

Note: * significant difference compared to the first series of studies ($p = 0.048$); EMR: evoked motor response; CMCT: central motor conduction time.

Table 4. Neurophysiological patterns of conduction along the motor pathways [4, 14]

Neurophysiological patterns	The presence of cortical and segmental EMR is regarded as signs of intact conduction along the motor pathways and incomplete lesions. Movements are subsequently restored in all patients with this pattern.
	The presence of only segmental EMR in the complete absence of cortical EMR is a neurophysiological analog of a complete conduction blockage.
	The absence of both cortical and segmental EMR below the site of the lesion is prognostically unfavorable following the restoration of conduction.

Note: EMR: evoked motor response.

form) than the acute period due to plastic adaptive changes.

With large hemispheric brain neoplasms, a significantly decreased amplitude and lengthened latency of the cortical EMR on the affected side is possible with normal segmental EMR indicators and completely normal cortical and segmental EMR indicators ipsilaterally. First, the obtained data during TMS change depending on the pathological process location and prevalence. In some cases, a large hemispheric tumor almost does not change the EMR and CMCT parameters, while a tumor located in the motor cortex can significantly deform the EMR and reduce its amplitude. In most cases, the period of silence in tumors of hemispheric localization is prolonged in the ipsilateral hemisphere, which reflects an increased central inhibition process [14].

In the analysis of each specific clinical case, pronounced deviations from the norm (cortical EMR polyphasia, CMCT asymmetry of >3 ms, and cortical EMR latency prolongation) are noted in 20% of patients with gliomas. Signs of moderate conduction slowing down along the cortical and motor pathway (cortical EMR dispersion, CMCT asymmetry of 2 ms, and a pronounced difference in the cortical and segmental EMR amplitudes) occur in 30% of cases; and signs of moderate conduction dysfunction in the form of CMCT asymmetry of 1 ms, moderate cortical EMR dispersion, moderate amplitude difference, were registered in 40% of patients. The cortical EMR form in patients with gliomas was changed in 80% of cases.

Thus, during TMS in patients with malignant brain neoplasms, signs of impaired conduction along the central motor pathways are recorded in 50% of cases, while signs of impaired conduction of all degrees of severity along the central motor pathways are detected in 90% of cases.

Parameters of latency and amplitude of cortical EMRs that are close to normal are also recorded and the form often becomes polymorphic when using TMS in the postoperative period in patients with malignant brain neoplasms [14]. The diagnostic TMS according to a single-pulse protocol predicts the further course of the recovery period. Table 4 presents the three key neurophysiological patterns.

All people with intact cortical EMR, even if they are inconsistent and doubtful, subsequently manage to achieve movement improvement. The fact of pattern 2 registration, namely the absence of the cortical EMR with segmental EMR preservation, is similarly not regarded as an unambiguous sign of complete conduction impairment along the motor pathway. Subsequent neuroplasticity activation with motor map restructuring, as well as synaptogenesis and neurogenesis, can restore the conduction [4, 15].

The severity of the registered changes is different. As a rule, the changes in EMR latency and elongation/pronounced asymmetry of the CMCT indicate a more widespread process.

Conclusions

1. Diagnostic transcranial magnetic stimulation is an additional neurophysiological technique in brain damage diagnostics. The technique enables the assessment of the dynamics of conduction along the motor pathways during the radiotherapeutic treatment.
2. Diagnostic transcranial magnetic stimulation can be used for an objective assessment of the motor pathway status in patients with neuro-oncological diseases.

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Conflict of interest. The authors declare no conflict of interest.

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Author details

Artem V. Kartashev, M.D., Cand. Sci. (Med.), Radiotherapist, Senior Researcher, Depart. of Radiation and Combined Methods of Treatment, Russian Scientific Center of Radiology and Surgical Technologies named after Academician A.M. Granova of the Ministry of Health of Russia; Assoc. Prof., Depart. of Radiation Diagnostics and Radiation Therapy, I.I. Mechnikov Northwestern State Medical University of the Ministry of Health of Russia; arxiator@mail.ru; ORCID: http://orcid.org/0000-0002-6714-6413

Vladislav Yu. Chirkin, M.D., Cand. Sci. (Med.), Neurosurgeon, V.A. Almazov National Medical Research Center; 9831766@mail.ru; ORCID: http://orcid.org/ 0000-0002-0610-1131

Nikolaj V. Il'in, M.D., D. Sci. (Med.), Prof., Depart. of Radiation and Combined Methods of Treatment, Russian Scientific Center of Radiology and Surgical Technologies named after Academician A.M. Granova of the Ministry of Health of Russia; ilyin_prof@mail.ru; ORCID: https://orcid.org/0000-0002-8422-0689

Vladislav B. Voitenkov, M.D., Cand. Sci. (Med.), Head, Depart. of Functional Diagnostics, FSBI Children's Scientific and Clinical Center of Infectious Diseases of the FMBA of Russia; Assoc. Prof., Depart. of Nervous Diseases and Neurorehabilitation, Academy of Postgraduate Education of the FMBA; vlad203@inbox.ru; ORCID: http://orcid.org/0000-0003-0448-7402

Yuliya N. Vinogradova, M.D., Doct. Sci. (Med.), Radiotherapist, Head, Depart. of Radiation and Combined Methods of Treatment; Assoc. Prof., Depart. of Radiology, Surgery and Oncology, Federal State Budgetary Institution Russian Scientific Center of Radiology and Surgical Technologies named after academician A.M. Granov; winogradova68@mail.ru; ORCID: http://orcid.org/0000-0002-0938-5213