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Research Article

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The Use of Diagnostic Transcranial Magnetic Stimulation as a Predictor of the Functional Outcome in Ischemic Stroke

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ABSTRACT Determination of rehabilitation potential (RP) is necessary for optimal rehabilitation strategy and the best rehabilitation measures. Navigational transcranial magnetic stimulation (nTMS) has been proposed as a method for PR determination in after-stroke patients.

THE AIM was to study the importance of navigational diagnostic transcranial magnetic stimulation as a neurofunctional predictor of motor function recovery after ischemic stroke.

MATERIAL AND METHODS The study included 28 after-stroke patients, 19 men and 9 women, the mean age was 60.07±5.67 years, who underwent a course of inpatient medical rehabilitation at the Moscow Research and Practice Center for Medical Rehabilitation, Restorative and Sports Medicine named after S.I. Spasokukotsky in 2022–2023. Clinical examination and assessment were conducted before and after the rehabilitation course using validated scales and questionnaires — the Medical Research Committee (MRCs) scale, the Box and Block Test (BBT), the modified Rankin scale (mRS); the rehabilitation routing scale (RRS). The patients were also examined using nTMS at the N.V. Sklifosovsky Research Institute for Emergency Medicine with the determination of motor evoked potential (MEP) parameters from the muscles of the upper and lower extremities.

RESULTS In patients with preserved MEP, there was a significant increase in the strength of the paretic limb on the MRCs scale from 4.00 (2.94–4.06) to 4.22 (3.83–4.89) points (p <0.001) for the upper limb and from 4.00 (3.67–4.00) to 4.44 (3.83–4.61) (p<0.001) for the lower limb. Improvements were revealed according to the mRS scale — the number of patients with an mRS score of 2 points in the group of patients with defined MEP increased by 26.1%, reached values of 1 point — 13.0% of patients, and the number of patients with an assessment of disability and self-care ability of 4 points decreased by 8.7%.

CONCLUSION Navigational transcranial magnetic stimulation is one of the methods for assessing the rehabilitation potential in patients with ischemic stroke. But TMS should not be used as the only method of evaluating rehabilitation potential. The assessment of RP should be comprehensive and based on the complex data obtained.

Keywords: neurorehabilitation, transcranial magnetic stimulation, rehabilitation potential, ischemic stroke

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Ethics Approval The authors declare that all procedures used in this article are in accordance with the ethical standards of the institutions that conducted the study and are consistent with the 2013 Declaration of Helsinki. The study was approved by the Local Ethics Committee of the Moscow Research and Practice Center for Medical Rehabilitation, Restorative and Sports Medicine named after S.I. Spasokukotsky (Protocol No. 2, 19.04.2023)

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APB — abductor pollicis brevis
ARAT — Action Research Arm Test
BBS — Berg Balance Scale
BBT — Box and Block Test
FAT — Frenchay Arm Test
FMA — Fugl–Meyer Assessment
CNS — central nervous system
IS — ischemic stroke
MEP — motor evoked potential
MR — medical rehabilitation
MRCs — Medical Research Council Scale
MRI — magnetic resonance imaging
mRS — modified Rankin scale
NHPT — Nine-Hole Peg Test
nTMS — navigated transcranial magnetic stimulation
PREP2 — Predict Recovery Potential
RMI —Rivermead Mobility Index
RP — rehabilitation potential
RRS — rehabilitation routing scale
SAFE — Shoulder Abduction, Finger Extension
TA — tibialis anterior
TMS — transcranial magnetic stimulation
TUG — Timed Up and Go test

INTRODUCTION

Ischemic stroke (IS) is a disease with high rates of primary disability among surviving individuals of working age. Every year, more than 7.6 million cases of ischemic stroke occur worldwide, of which more than 58% in people under 70 years of age [1]. In most economically developed countries of the world, over the past 10 years, there has been an increase in the incidence and mortality rates of ischemic stroke [2]. In Russia, more than 400 cases of stroke per 100,000 population are registered annually. Among people who have suffered a stroke, every third person has persistent signs of limitation of basic daily activity [3], which determines a high medical and social significance of targeted rehabilitation strategies.

The main goal of medical rehabilitation (MR) in IS is to restore lost functions, return working capacity and improve the patients' quality of life. The possible degree of recovery, i.e. rehabilitation potential (RP), is variable and depends on a set of internal and external factors, among which the localization and extent of brain damage, the volume, intensity and timing of the start of MR, as well as the individual characteristics of the patient are of great importance. Functional outcomes of the disease and the choice of rehabilitation strategies are interrelated with RP, which determines the need for sensitive tools for its assessment.

Over the past decades, several methods have been proposed to assess RP. The use of laboratory biomarkers is proposed, by analogy with cardiospecific enzymes, the most promising of which is considered to be brain-derived neurotrophic factor (BDNF). In addition, such indicators as C-reactive protein, fibrinogen, and interleukin-6 are considered [4–5]. However, the search for biomarkers is limited due to the heterogeneity of IS itself, and the differences in study designs that address this issue.

Another common approach to assessing RP is the separate or combined use of scales, questionnaires or tests. For example, the Fugl–Meyer Assessment (FMA) scale has shown a fairly high predictive ability in the early assessment of post-stroke neurological deficit [6].

To objectify the assessment of RP, it is proposed to use neuroimaging methods, primarily magnetic resonance imaging (MRI) of the brain in various modes. The volume of IS and the degree of damage to the corticospinal tract correlate with the degree of recovery of upper limb functions [7]. Data on the use of tractography to predict walking recovery are contradictory. Thus, Soulard et al. (2020) identified a number of white matter tracts that are part of the subcortical motor connectomes, the state of which can serve as predictors of walking recovery [8]; while in the study by Okamoto Y. et al. (2021) it was shown that the assessment of the state of the pyramidal tract using fractional anisotropy of the right and left internal capsule, evoked motor response in the affected and unaffected hemispheres according to the results of transcranial magnetic stimulation, can be useful for predicting the recovery of function of the upper limbs, but not that of the lower limbs [9].

Another neuroimaging and neurofunctional diagnostic method is navigated transcranial magnetic stimulation (nTMS) which allows one to accurately determine the localization of the cortical representation of various muscles using the motor evoked potential (MEP), as well as its amplitude, response threshold and impulse conduction velocity to the central nervous system (CNS). Since the beginning of the 21st century, attempts have been made to use TMS as a predictor of recovery after stroke [10]. To date, there are a large number of studies describing the use of TMS to predict functional outcomes in relation to hemiparesis, gait and swallowing disorders [11–15]. In 13 of 14 studies included in the systematic review (463 patients with IS, 17 with hemorrhagic stroke and 97 patients in the comparison group with sample sizes from 6 to 84 participants), despite methodological differences in the selection of target muscles of the upper limb, it was shown that the presence of MEP during TMS in the acute period of stroke can be considered as a positive sign for predicting the recovery of post-stroke dysfunction of the upper limb [11].

Currently used methods and programs for determining RP are mainly focused on the acute period of stroke or are insufficiently sensitive and specific [16]. In addition, the heterogeneity of study samples and the definition of the term "stroke", which includes a wide range of nosologies with different mechanisms of occurrence and reparation, remain a problem [17]. There is also no consensus on the choice of neuroimaging method for determining RP [18]. The use of neuroimaging and neurofunctional markers, especially nTMS, appears to be a fairly sensitive method for assessing RP. However, studies conducted to date do not allow a clear assessment of their accuracy, especially in patients at a later stage from the onset of stroke.

The aim of the research was to study the significance of navigated transcranial magnetic stimulation as a neurofunctional predictor of motor function recovery after ischemic stroke.

MATERIALS AND METHODS

The study involved patients who underwent MR in inpatient settings (stage II) at Branch No. 3 of the Moscow Research and Practice Center for Medical Rehabilitation, Restorative and Sports Medicine named after S.I. Spasokukotsky (hereinafter referred to as the Center). All study participants signed informed consent. The study included patients aged 40-70 years with an established diagnosis of primary ischemic stroke in the acute, early and late recovery periods with post-stroke hemiparesis of varying severity.

The MR program comprised physiotherapy procedures and exercise therapy (ET), including the use of high-tech rehabilitation methods; the course duration was 12–14 days.

The criteria for exclusion from the study were as follows: focal brain damage of other etiology; severe cognitive impairment (less than 20 points on the Montreal Cognitive Assessment – MoCA – scale); clinically expressed affective disorders (11 points or more on the Hospital Anxiety and Depression Scale – HADS); sensory and gross motor aphasia; epilepsy and other paroxysmal disorders of consciousness; the presence of electronic stimulators, metal implants in the head area.

All the patients were assessed using standard scales, tests and questionnaires: severity of paresis — according to the Medical Research Council Scale (MRCs); the severity of spasticity was assessed using the Modified Ashworth scale (mAs); gait speed impairment — 10-meter walk test (m/sec); balance, mobility and fall risk — Tinetti Performance Oriented Mobility Assessment (POMA), the Berg Balance Scale (BBS), the Timed Up and Go test (TUG), the Rivermead Mobility Index (RMI); upper limb function – Fugl-Meyer Assessment Upper extremity (FMA-UE) and Action Research Arm Test (ARAT), nine-hole peg test (NHPT), the Frenchay arm test (FAT), Box and Block Test (BBT); basic functional activity was assessed using the Barthel activities of daily living (ADL) Index (BI) and the Rehabilitation Routing Scale (RRS).

Clinical neurological examination and assessment using scales and questionnaires were performed at baseline (T0) and upon completion of the MR course (T1).

All the patients underwent diagnostic nTMS using a NBS eXimia Nexstim complex (Nexstim Ltd., Finland) at the N.V. Sklifosovsky Research Institute for Emergency Medicine. The amplitude, threshold and latency of the MEP from the muscles of the abductor pollicis brevis (APB) and tibialis anterior (TA) of both limbs were assessed.

Mathematical and statistical analysis was performed using the StatTech v. 4.1.2 program (StatTech LLC, Russia). Quantitative indicators were assessed for compliance with normal distribution using the Shapiro–Wilk test. Comparison of three or more groups by the quantitative indicator with a normal distribution was performed using one-way analysis of variance. Comparison of three or more groups by the quantitative indicator which distribution differed from normal was performed using the Kruskal–Wallis test. When comparing quantitative indicators which distribution differed from normal in two related groups, the Wilcoxon test was used. Differences were considered statistically significant at $p<0.05$.

RESULTS

The study included 28 patients, 19 men and 9 women, aged 60.07 ± 5.67 years. The median time from the onset of the disease was 18 (13.75–110.25) days, 16 patients were admitted in the acute period of ischemic stroke, 7 and 5 — in the early and late recovery periods, respectively. The median of the integral strength index of the upper limb was 3.83 (2.75–4.03) points, and of the lower limb, 4.00 (3.47–4.00) points. Based on the results of nTMS performed separately for the upper and lower limbs, 3 groups of patients were identified: 1st — patients without obvious asymmetry of MEP, 2nd — patients with pronounced asymmetry of MEP, 3rd — patients in whom MEP could not be determined (Table 1). The patient groups were comparable in terms of age and gender, as well as severity of the main disorders.

Table 1

Distribution of patients depending on motor evoked potential (MEP)

Indicators	Categories	Abs.	%
MEP from m. APB	Symmetric	12	42.9
	Asymmetric	11	39.3
	Absent	5	17.9
MEP from m. TA	Symmetric	16	57.1
	Asymmetric	7	25.0
	Absent	5	17.9

Notes: MEP — motor-evoked potential; m. APB — m. Abductor pollicis brevis; m. TA — m. Tibialis anterior

The analysis of the dynamics of the severity of post-stroke hemiparesis was performed depending on the presence of MEP from m. Abductor pollicis brevis (APB) and from m. Tibialis anterior (TA). After the MR course in the presence of MEP, we noticed a statistically significant increase in the strength of the paretic limb according to the MRC scale: from 4.00 (2.94–4.06) to 4.22 (3.83–4.89) points ($p<0.001$) for the upper limb, and from 4.00 (3.67–4.00) to 4.44 (3.83–4.61) ($p<0.001$) for the lower limb. In patients without MEP, statistically significant increase in muscle strength was not found. During the intergroup comparison, the dynamics of changes in patients with symmetric MEP and pronounced asymmetry were comparable. However, no difference in strength gains between the upper and lower limbs was noticed. Between-group analysis after the MR course also showed no statistically significant differences, despite the lack of statistically significant strength gains in patients without MEP, which may be due to the small sample size.

A statistically significant improvement was also revealed during the BBT assessment. Patients without MEP from m. APB initially performed worse on the test. During control testing, the improvement did not reach statistically significant differences from the initial values ($p> 0.05$); and in patients with detectable MEP, the dynamics was positive ($p<0.05$) (Fig. 1). The dynamics of the median score in the group with symmetric MEP was 5.5 points (from 26.00 (23.50–31.25) to 31.50 (27.75–39.50), $p=0.003$); in the group with asymmetric responses, the increase was 10.0 points (from 28.00 (18.50–36.50) to 38.00 (26.00–44.50), $p=0.005$). In patients without MEP from the affected hemisphere, statistically significant dynamics were not observed. During intergroup comparison after the MR course, statistically significant differences were found between the groups with detectable MEP and the group without MEP ($p=0.032$). Analysis of the results obtained from testing with other instruments (FMA, ARAT, FAT, NHPT) did not show statistically significant differences between the groups.

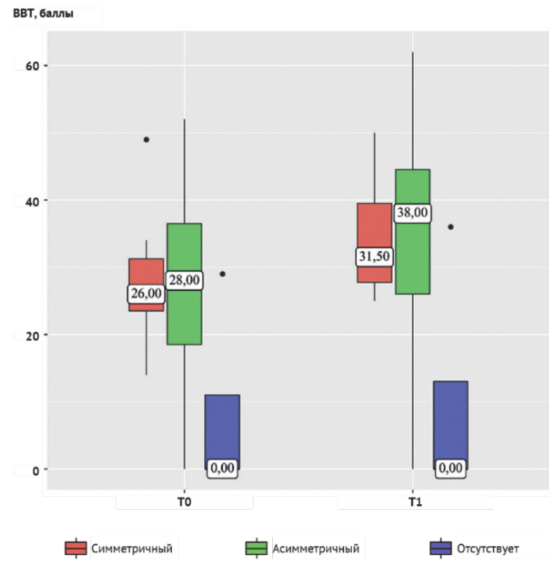

Fig. 1. Analysis of BBT dynamics depending on MEP with m. Abductor pollicis brevis (points)
Notes: MEP — motor evoked potential; m. APB — m. Abductor pollicis brevis; BBT — Box and Block Test; T0 — initial data; T1 — data after the rehabilitation course

Gait analysis was performed, during which in the group of patients with detectable MEP from m. TA, the changes were statistically significant — walking speed increased from 0.59 (0.39–1.07) to 0.67 (0.49–1.21) meters per second ($p=0.007$). In the group without MEP, the increase in walking speed did not reveal statistically significant differences (Fig. 2).

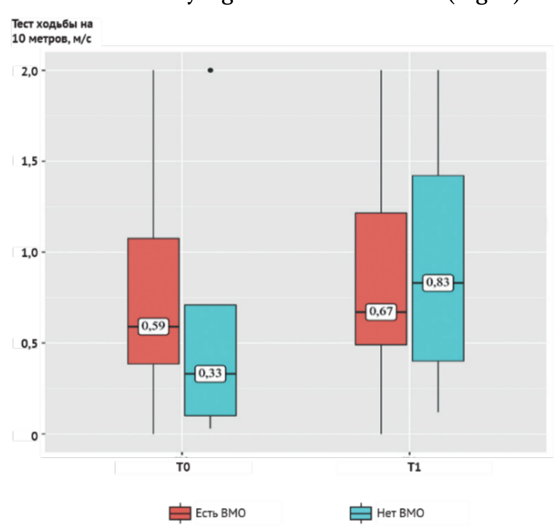

Fig. 2. The dynamics of 10-meter walking test (m/s) analysis
Notes: MEP — motor evoked potential; T0 — initial data; T1 — data after the rehabilitation course

During the intergroup comparison, it was noted that this increase was due to an increase in walking speed in patients with pronounced interhemispheric asymmetry, which is associated with higher initial velocity indicators in patients without asymmetry of MEP from m. TA, despite the fact that patients of the study groups were comparable in this indicator (p=0.537) (Fisher's F-test). No differences were found when analyzing the results obtained from other tests and questionnaires (BBS, Tinetti test, TUG test, and the RMI).

The degree of disability and self-care was also analyzed. During the analysis of the mRS assessment results, statistically significant changes were obtained (p=0.001) in patients with detectable MEP from m. APB; in the group without MEP, no statistically significant changes were found (p=0.317) (Wilcoxon test). The number of patients with an mRS score of 2 points in the group of patients with detectable MEP increased by 26.1%, reaching values of 1 point - 13.0% of patients; while the number of patients with a disability and self-care score of 4 points decreased by 8.7%.

Similar results were obtained when analyzing the distribution of patients by RRS. In the group with detectable MEP, both from m. APB and m. TA, a statistically significantly greater number of patients were transferred to the group with milder functional impairment after the MR course (p<0.001). In case of preserved MEP from m. TA, the number of patients with a RRS score of 4 points decreased by 43.5%, and the number of patients who reached values of 1 point was 8.7%.

There were no statistically significant differences between the groups in the results obtained using other scales and questionnaires used. No adverse events were recorded.

DISCUSSION

Statistical analysis of our data showed a high prognostic value of nTMS of both upper and lower limb muscles in relation to strength in the paretic limb. The main prognostic parameter of TMS is the presence of MEP and its interhemispheric asymmetry. The absence of MEP can be regarded as a predictor of poor recovery of strength in the paretic limb, which is consistent with data obtained by other researchers [19].

Patients with MEP detectable from the paretic muscle showed better recovery after the MR course. There was no significant difference between the increase in muscle strength in patients with symmetric and asymmetric MEP. Similar results were obtained in a 2020 study, where the presence of MEP and their amplitude statistically significantly correlated with a decrease in the severity of upper limb paresis after 3 months, while the motor threshold value did not show prognostic value. Moreover, the concentration of BDNF throughout the observation period did not correlate with the degree of recovery [20]. Similar results were obtained for the lower limb, which is consistent with the data described in the literature [21].

Due to functional reorganization of the brain, TMS parameters in the uninfarcted hemisphere may differ significantly from those in healthy volunteers [22–23]. In a 2014 study, the measurement of MEP during TMS, and MEP in healthy volunteers and in the non-infarct hemisphere in stroke patients with a paretic upper limb varied from good to excellent. In contrast, the MEP measurements in the infarcted hemisphere were less consistent. Considering the lower reproducibility of the results of the TMS measurements in the hemisphere affected by the infarction, the authors recommend repeated application of impulses to increase the reliability of the test [24]. However, later data from McDonnell et al. indicate less significant asymmetry and greater importance of the TMS indicators of the directly affected hemisphere [25]. Due to the peculiarities of the organization of the cerebral cortex, a larger number of impulses are required to evaluate the MEP representation of the lower extremities [26]; moreover, there are objective difficulties in determining MEPs, and they are not always determined even in healthy individuals.

One of the ways to increase the prognostic capabilities of TMS is to study not individual MEPs, but the construction and mapping of neural networks taking into account their interhemispheric interaction, including the use of electroencephalography and MRI. This approach allows us to assess the general ability of the central nervous system to restore damaged functional systems [27–29].

Many experts recommend combining clinical assessment of patients with additional markers, mainly neuroimaging and neurofunctional ones [30]. According to a review of 71 studies on stroke recovery biomarkers, a comprehensive patient assessment was more effective than isolated use of instrumental markers [31–32]. Based on this approach, the ASTRAL (Accurate Species Tree Algorithm) was developed, including 6 indicators, which showed 50% predictive accuracy [33].

The most widely used algorithm for predicting the functional outcome of upper limb movement disorders 3 months after stroke is the PREP2 (The Predict REcovery Potential) algorithm. At the first stage, an assessment is made using the SAFE (Shoulder Abduction, Finger Extension) test. If the SAFE test score is less than 8 points, the next stage involves TMS of the upper limb muscles; and in the absence of MEP, at the third stage, changes in MRI of the brain and (or) the severity of stroke according to the NIHSS are assessed [34]. A number of studies have shown that TMS of ABM does not have prognostic value in relation to the acute period of stroke, compared with the assessment of motor impairments using the SAFE test [35].

The TWIST (Time to Walking Independent after STroke) algorithm, developed to assess walking within 3 months after stroke, includes two main tests: the trunk control test and hip extensor strength assessment using MRC [36]. The PRESS (Predictive Swallowing Score) algorithm, proposed in 2019, is an easy-to-use prognostic tool that reliably predicts swallowing recovery and is a step towards personalized medicine [37]. S. Salvalaggio et al. in their article summarized data on current algorithms for assessing RP for various disorders. The PREP2 algorithm showed the highest accuracy and specificity [38].

When analyzing the dynamics of walking speed, it was determined that in the presence of MEP from m. TA, a statistically significant increase in the indicator according to the 10-meter walking test was noted. According to the literature, no statistically significant differences were found in previous studies [39–40]. The differences obtained may be due to the small number of observations and insufficient sensitivity of the test itself. At the same time, no intergroup differences were recorded in the results of other tests.

When analyzing the functional independence of patients, a statistically significant improvement in the general condition was found according to the modified Rankin Score, which is consistent with the results of previous studies [41]. Similar dynamics were observed when stratifying patients of different groups by RRS: in the presence of MEP, patients were statistically significantly more often transferred to the group with milder functional impairments.

Our findings are consistent with previous studies, confirming the presence of a direct relationship between MEP and the degree of motor function recovery, as well as a decrease in the impairment of basic functional activity. Studies show that nTMS can be considered as one of the methods for assessing RP in patients who have undergone IS. However, it should be noted that its use as the sole source of information for making decisions on MR is not supported by convincing evidence.

CONCLUSION

One of the most common consequences of stroke, limiting the daily activity of patients, are motor disorders in the form of unilateral spastic hemiparesis of varying severity. The search for prognostic markers of recovery from motor disorders is a pressing issue in the personalization of rehabilitation programs.

Recent studies demonstrate the possibility of using navigated transcranial magnetic stimulation as a predictor of functional outcome after stroke, as well as predicting the effectiveness of rehabilitation measures. The results of our study confirm the existence of a direct relationship between the evoked potential and the degree of motor function recovery. However, further study of the correlation between the results of transcranial magnetic stimulation and functional outcome after stroke is necessary. It is important to keep in mind that the effects of transcranial magnetic stimulation may be temporary, and repeated exposure will be required to achieve long-term outcomes.

Overall, the use of diagnostic transcranial magnetic stimulation as a predictor of functional outcome after ischemic stroke represents great potential for the development of new diagnostic and therapeutic methods. This may help improve prognosis and determine an individual approach to patient rehabilitation, which may ultimately significantly improve the effectiveness of medical rehabilitation.

FINDINGS

1. In patients with motor evoked potentials (MEPs), medical rehabilitation demonstrated better functional recovery: the increase in muscle strength of the paretic limb according to the MRC scale was 0.22 points (from 4.00 (2.94–4.06) to 4.22 (3.83–4.89) points, p<0.001) for the upper limb, and 0.44 points (from 4.00 (3.67–4.00) to 4.44 (3.83–4.61) points, p<0.001) for the lower limb; the dynamics of motor coordination as assessed by the BBT in the group of patients with symmetric MEP was 5.5 points (from 26.00 (23.50–31.25) to 31.50 (27.75–39.50), p=0.003), in the group with asymmetric responses – 10.0 points (from 28.00 (18.50–36.50) to 38.00 (26.00–44.50), p=0.005); an increase in walking speed, assessed by the 10-meter walk test – from 0.59 (0.39–1.07) to 0.67 (0.49–1.21) meters per second (p=0.007).

2. A significant improvement in self-care and a decrease in the degree of disability were demonstrated in patients with detectable MEPs after the rehabilitation course. Changes in the mRS scale showed an increase in the number of patients with mild functional impairment, so the number of patients with an mRS score of 2 points increased by 26.1% (p <0.001), reaching values of 1 point - 13.0% of patients (p <0.05); the number of patients with a disability and self-care score of 4 points decreased by 43.5% (p <0.001).

3. In the groups of patients without motor evoked potential from the affected hemisphere, statistically significant dynamics of the functional scale indicators, as well as the degree of disability, were not observed (p> 0.05).

4. The revealed statistically significant differences (p <0.05) in the results of medical rehabilitation between the group of patients with detectable evoked motor response and the group without motor evoked potentials in assessing the indicators of upper limb function, walking speed, and dependence in the daily activities of patients, allow us to conclude that the determination of the evoked motor response using the navigational diagnostic TMS method can be considered as a neurofunctional predictor of the functional outcome of ischemic stroke.

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