NAVIGATED TRANSCRANIAL MAGNETIC STIMULATION: BRIEF REVIEW OF ENGINEERING SOLUTIONS

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Transcranial magnetic stimulation (TMS) stands out among the rapidly developing methods for clinical rehabilitation of patients after cerebral vascular accidents. The method is widely used not only in post-stroke rehabilitation, but also in sports medicine, psychiatry and other fields of medicine. However, there is an unresolved issue related to precise targeting and holding the magnetic field focus on the points of interest in the brain when performing TMS. Unprecise magnetic field focus localization may result in the emergence of side effects during the TMS session. The review provides the existing solutions of these problems, comparison of the commercially available navigation devices for TMS, analysis of their composition and operation algorithms; promising directions of developing hardware for TMS navigation are proposed.

Keywords: transcranial magnetic stimulation, technology overview, medical robots, neuroimaging, positioning

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НАВИГАЦИОННАЯ ТРАНСКРАНИАЛЬНАЯ МАГНИТНАЯ СТИМУЛЯЦИЯ: КРАТКИЙ ОБЗОР ТЕХНИЧЕСКИХ РЕШЕНИЙ

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В числе активно развивающихся методов клинической реабилитации больных после мозговых сосудистых катастроф особо выделяется транскраниальная магнитная стимуляция (ТМС). Метод широко применяют не только для постинсультной реабилитации, но и в спортивной медицине, психиатрии и других областях медицины. При этом существует нерешенная проблема, связанная с четким наведением и удержанием фокуса магнитного поля при ТМС на точках интереса в головном мозге. Из-за нечеткой локализации фокуса магнитного поля возможно возникновение побочных воздействий во время сеанса ТМС. В обзоре представлены существующие варианты решения данных проблем, сопоставлены присутствующие на рынке устройства для навигации ТМС, проанализированы состав и алгоритмы их работы, предложены перспективные направления развития технического обеспечения навигации ТМС.

Ключевые слова: транскраниальная магнитная стимуляция, обзор технологии, медицинские роботы, нейровизуализация, позиционирование

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Transcranial magnetic stimulation (TMS) is an actively developed method for clinical neuromodulation and rehabilitation of ischemic patients. It is based on the brain tissue exposure to short pulses of high-intensity electromagnetic field (up to 4 T or more) generated by the induction effector (inductor or coil) [1, 2]. This results in the neuronal membrane depolarization and excitation [3]. Accumulation and analysis of clinical data on the results of using TMS have resulted in the expanded list of accessible defects, clarified parameters of using TMS in various clinical situations [2, 4]. Furthermore, TMS is used in sports medicine as a motor system stimulation method [5], in psychiatry for diagnosis and treatment of various conditions, and шт other fields of medicine [6]. However, there are still a number of not completely resolved or controversial issues related to localization of the TMS magnetic field focus, desired intensity of exposure, and many other themes [5, 7].

Thus, impossibility to accurately match the stimulation point coordinates to the central nervous system anatomical structures is an important challenge faced when mapping motor areas using TMS [8]. The head and brain size and shape, localization of anatomical structures are unique. This makes the process of inductor positioning relative to the stimulation area challenging.

According to the Talairach coordinate system, individual differences in motor areas are 1.5–2 cm; these can be larger when considered relative to external reference points on the skull. This is also true for Broca's area localization [9], i. e. unique macroanatomy of the brain cannot be adequately defined using an anatomical atlas or a proportional coordinate grid. The navigated TMS (nTMS) method, in which the inductor spatial orientation is set based on the magnetic resonance imaging (MRI) data analysis, has been proposed to address the problem of inductor positioning [8, 10]. The use of this method to a significant extent solves the problem of coil positioning when performing therapeutic and/or diagnostic TMS.

The motor threshold testing for the motor response to the lowest possible stimulation level resulting in contraction of appropriate muscles is considered to be a standard criterion for assessment of the efficiency of the TMS effect on the excitable brain structures. It has been shown that even a slight shift of the inductor relative to the optimal point of exposure can significantly reduce the stimulation efficiency [7, 8, 10, 11–13]. Furthermore, any serial patient's exposure requires high reproducibility. Given its weight and size characteristics, manual holding of the coil in a predetermined position when the session duration is 10 min or more makes these tasks almost impossible, while these require technical execution [8, 10]. However, analysis of information taken from the available databases and catalogues has shown that despite huge number of reports of the nTMS clinical use, the data on engineering solutions for the method and the trends in their development are limited and fragmented. In this review we try to discuss the existing solutions and possible prospects of nTMS development from a technical perspective.

Main principles of navigated TMS functioning

The use of the stereoscopic technical vision system in combination with constructing a 3D model of the brain based on MRI scans turned out to be the most effective solution for matching the point of exposure in the brain to specific tags on the skull, magnetic field focus, and spatial position of the inductor [14]. The study performed by these authors was based on the 3D inductor positioning relative to a solid model of the brain with a stereoscopic video system using a common coordinate grid (Figure).

Two sets of procedures are executed to implement this scheme: initial cycle of nTMS session preparation and the repeating inductor position adjustment cycle. The algorithm for initial cycle shown on the left (Figure) includes the following operations:

1) constructing a 3D model of the brain based on the set of primary T1-weighted (T1W) MRI images;

2) MRI image segmentation and constructing a 3D model of the patient's brain using the BET algorithm [15]. False positive results are automatically deleted, while false negatives are added interactively. The brain surface and structures are reconstructed using flat contours;

3) determining the target area in the brain model relative to the skull considering the features of magnetic field focus and the distance to inductor ensuring the required magnetic field density;

4) recognition and localization of the patient's head using optical tags or any other method. The inductor coil localization and position are recognized the same way;

5) aligning the model of the brain, skull and inductor oriented towards the target area using the coordinate grid;

6) moving the inductor into the estimated baseline position depending on the patient's head position. Preparation for the nTMS session is complete.

In real-world settings it is necessary to consider the change in the patient's posture and his/her head move out of the calculated coordinates. In this case a software module for the repeating cycles of inductor position adjustment is responsible for correction of errors in the nTMS system. This algorithm shown on the right (Figure) includes the following operations:

1) periodic detection of the inductor and patient's head position by the technical vision system and recalculation of current coordinates relative to baseline values. If no discrepancies are found, no action is taken;

2) recalculation of coordinates and the direction of the inductor axis in case of inconsistency between the baseline and current relative position of the inductor and the model of the brain aimed to compensate the error indicated;

3) generation of the message about the need to navigate the inductor to a new position;

4) control recalculation to test whether the new position of inductor is matched to the target area;

5) recalculation and image output in absolute coordinates with the new position of inductor relative to the bias of the brain 3D model .

Efficiency of the described nTMS functioning algorithm has been confirmed by the experiments involving a human skull phantom and head MRI data of the healthy individual. The algorithm showed a trend toward flexibility, safety, accuracy, and time saving [14]. The system included a TMS unit, electromyography system, electroencephalography system, rack with inductor, and a computerized navigation system. The average errors of coordinate selection resulted mainly from the errors of MRI images: the errors on axes X, Y, and Z were 5 mm, 3 mm, and 3 mm, respectively. Later this approach was implemented in other models of nTMS systems [16].

It has been shown, that the TMS-induced electroencephalography (EEG) shows high reproducibility (correlation coefficient r = 0.85) within 200 ms before the stimulus termination given the exposure parameters are constant. Even a 10 mm shift of inductor results in significant EEG changes. The use of nTMS is the only possible way to ensure stability of the evoked effects [7].

However, there are nTMS errors that are yielded by the sources of errors:

1) individual features of magnetic field distribution across the cortex depending on the brain tissue state;

2) errors of brain MRI scan and appropriate distortion of the brain 3D model;

3) shift of focus due to patient's head movement after setting the focus;

4) errors of magnetic field generation by the coil.

The impact of such error on the joint position of the inductor and the head, as well as on the magnetic field, was analyzed based on the simplified and realistic models of the head [11]. Modeling involved the use of the SimNIBS computer subroutine library [12] and the sets of T1-weighted fat-suppressed and

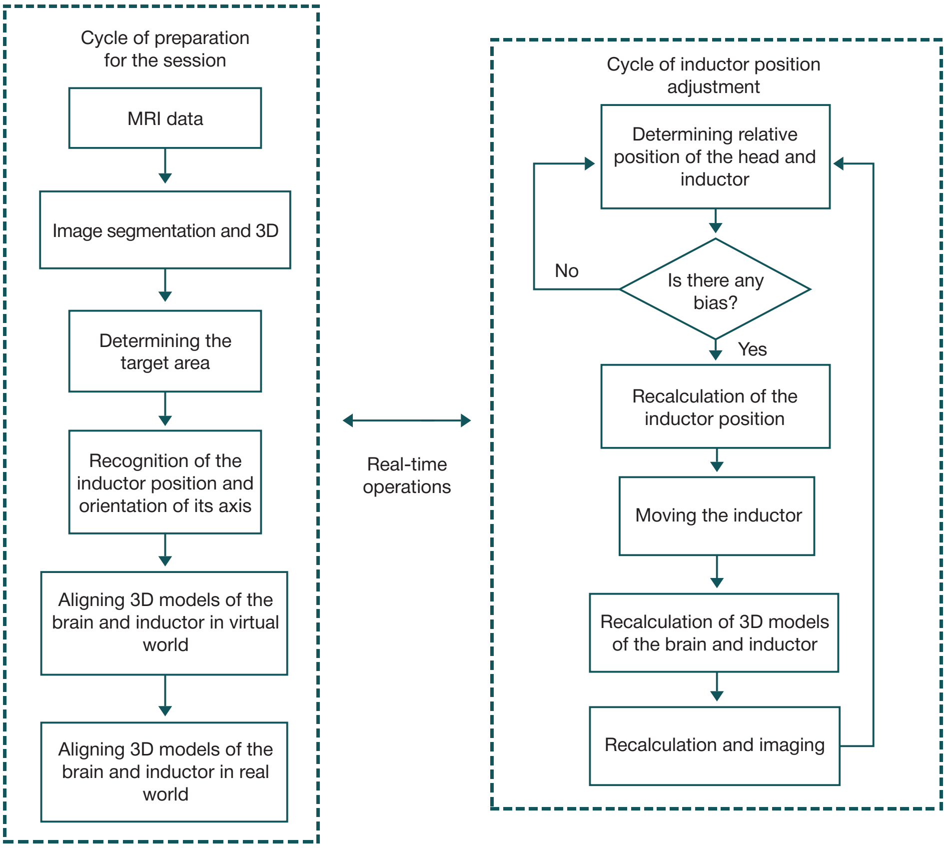

Fig. The nTMS system operation algorithm

T2-weighted MRI images with the 1 mm3/voxel resolution. The average bias of joint spatial position was within 2.2–3.6 mm and 1°. The errors were related to the MRI images with the average bias of 1.5–1.9 mm at the error of 0.2–0.4° and bias of 0.5–0.8 mm at the error of 0.1–0.2° for the models used. When assessing the magnetic field bias, the average accuracy of positioning, assessing the field orientation and peak value was within the ranges of 1.5–5.0 mm, 0.9–4.8°, and 4.4–8.5%. The modeling results showed a significantly reduced inductor positioning error during nTMS relative to standard recommendations, such as “over the projection of the upper third of the cerebral cortex motor area”, and shift of inductor position relative to the external tags on the head measured in centimeters [13].

Commercially available nTMS complexes

Today, the following models of nTMS units implementing standard solutions are mass-produced (Table). The units are built on similar schemes based on the technical vision system (TVS). Optical tags or characteristic areas of face and head are used as orientation elements. The inductor position is changed directly using a robotic manipulator, while indirect changes are made in manual mode by following the signals of the nTMS control system.

The VISOR 2 nTMS system uses a 3D model of the brain constructed based on MRI images [17]. If no such model is available, simplified models are used. TVS tracks optical trackers positioned on the head and inductor. As a result, the 3D model of the brain and the inductor are pinned to the system of external tags in the three-dimensional coordinate grid. The physician follows the commands of the system to position the inductor in space. With a certain skill, the coordinate bias determined is about 2 mm. The VISOR2 system can be operated in combination with compatible TMS complexes, including the domestic Neuro-MC/B complex.

The TMS Navigator navigation system (LOCALITE; Germany) is also based on using technical vision to pin a 3D model of the brain, images of the patient’s head and inductor obtained using video cameras to the three-dimensional navigation grid with optical trackers [18]. The algorithm for accurate matching of these objects to audio indication of the inductor position bias ensures the magnetic flux focus retention. For targeted stimulation, the system allows registration of four inductors of different types. It is possible to calculate the amount of energy that would be delivered to the target point. In the Robotic Edition version of the system, automatic inductor positioning aimed at compensating the patient’s movements is performed using optical feedback.

The TMS Robot robotic system (Axilum Robotics; France) is implemented as a construct that combines a seven-degree-of-freedom manipulator, inductor, control unit, and a chair for the patient [19]. The principles of functioning, determining the coordinates of patient’s head, target area, and inductor are similar to the listed above. After constructing a 3D model of the brain and assessing the head position, a TVS manipulator positions the inductor to ensure a precise focused effect. The patient’s head movements are automatically compensated by moving the inductor. Manipulator and the chair have nine position sensors, which ensure baseline positioning accuracy of at least 1 mm along all axes; when the head moves, the inductor orientation is restored with the accuracy of at least 0.1 mm. This positioning system is used in combination with the Syneika One neuronavigation system.

The Syneika One neuronavigation system (SYNEIKA; France) is an integrated device that ensures coil navigation based on the data of the patient’s brain 3D model [20]. The coil positioning and orientation are accomplished using

Table. Comparison of some existing navigation devices for TMS

System	VISOR2	TMS Navigator	TMS Robot	Syneika One	NBS eXimia Nexstim	Brainsight TMS Navigation	PowerMAG View!
Contractor	ANT Neuro, Netherlands	LOCALITE, Germany	Axium Robotics, France	SYNEIKA, France	Nexstim Ltd., Finland	Brainbox, UK	Jali Medical, USA
Optical navigation (type)	Yes	Yes, trackers	Other sensor type	Other sensor type	Yes, trackers	Yes, trackers	Yes, trackers
Manipulator available	No	Yes	Yes	No	No	No	No
Coil position adjustment	Indirect	Direct	Direct		Indirect	Indirect	Indirect
Chair for the patient	No	Yes	Yes	No	Yes	Yes	Yes
Features					Modeling of magnetic field distribution	Can be assembled of modules	Enables functional brain mapping

options of the described above Axilum Robotics TMS-Robot complex [19]. The TMS-Robot robotic rack guided by Syneika One moves the coil through space, thereby ensuring precise targeting the stimulation area and compensating possible head motion. There are no data on the sensor types used to assess the head and inductor position in the reports available.

TMS-Cobot, manufactured by the same company but implemented as a mobile device, represents a more simple and space-saving solution compared to TMS Robot [21]. The inductor positioning accuracy is 2 mm. The possibility of tracking the head position by optical system is preserved, however, it only supports the patient's head upper hemisphere due to smaller manipulator size. This device is not equipped with its own system for the brain 3D model construction and spatial navigation, it also has to operate under the control of external neuronavigator, such as Syneika One.

The NBS eXimia Nexstim complex (Nexstim Ltd.; Finland) designed in mid 2000s continues to evolve [22, 23]. The complex has advanced software allowing one to construct a high-precision 3D model of the brain consisting of more than 20,000 elements, control its representation and ensure targeted effect using a large touch screen monitor. An option of modeling the magnetic field distribution considering individual brain structure features is a hallmark of the system. Robotic devices are not used for targeting and retaining the coil when the patient moves. The inductor installation on the rack and spatial orientation are done manually following the targeting system instructions. Bias of the effect targeting does not exceed 10 mm.

The Brainsight TMS Navigation neuronavigation series (Brainbox; UK) to be used in combination with the DuoMAG XT series transcranial magnetic stimulator supporting the induced EEG recording [24] has become quite widespread. The market offers the Brainslight TMS Navigator and Brainslight TMS Chair integrated systems. The possibility of assembling specialized complexes of distinct modules is an interesting feature of the company's products.

The PowerMAG View! and ANT Neuro visor2 (Jali Medical; USA) neuronavigation systems, which use optical tags fixed on the patient's head with an elastic band as reference points for stereoscopic system, are used for research and diagnosis [25]. A 3D model of the brain is usually constructed based on MRI data, there is an option for functional brain mapping. The patient is seated in a chair with his head on the headrest. A simple rack is used to attach the inductor.

The NetBrain Neuronavigator 9000 complex (EB Neuro; Italy) is designed to be used in combination with the TMC STM 9000 Magnetic Stimulator manufactured by the same company [26]. The manufacturer positions the complex as a low-end device that nevertheless has advanced characteristics: bias of matching a 3D model of the brain to the coordinates of optical tags on the patient's head using the stereoscopic system can be less than 1 mm. The complex is operated using the Galileo software allowing one to communicate with the TMS unit and construct a 3D model of the brain, as well as to record the procedure and manage the patient's data. The patient reclines in a chair, and the TMS inductor is attached to the rack. The coil positioning and orientation in space are performed based on the prompts generated by the neuronavigation system.

The SimGuide Navigated TMC neuronavigation software package (MagSim Co Ltd; UK) is designed to work with the Horizon 3.0, Horizon Performance, and Horizon Lite units for transcranial therapy manufactured by the same company [27]. In all cases, a high-resolution stereoscopic system and the patient's elastic helmet with optical tags are used for spatial alignment of the head, 3D model of the brain, and the inductor mounted on the rack.

Similar features are offered by the Neuronavigated TMS system for visualization of anatomic and functional features based on the MRI data (SEBERS Medical; USA, Germany) [28]. One software suite enables communication with five types of M-series TMS units manufactured by the same company. The coil installation and orientation are performed using the stereoscopic system. The effect control is ensured by recording evoked EMG potentials using a wireless dual-channel electromyography unit.

It should be noted that the majority of commercially available nTMS systems use magnetic stimulation devices manufactured by third-party companies. The clinical data analysis [4–6] shows that the use of nTMS improves the efficiency of magnetotherapy course, since it ensures proper localization and high reproducibility of the effect, although there are alternative opinions [29]. However, these systems have not yet been widely introduced in domestic practice. Perhaps, this is due to the fact that nTMS systems are expensive, and the use of such systems requires medical personnel to have certain skills and knowledge in the field of computer engineering.

Experimental nTMS systems

The patient's semi-recumbent position with his/her head on the headrest is the simplest solution for nTMS realization [7, 16, 13, 22, 23]. This ensures head motion limitation, and the inductor orientation and retention can be ensured by the rack or by hand. However, this solution prevents exposure of the occipital areas. The alternative is a sitting position (if possible), however, in this case there is a problem of the TMS effect focus retention associated with unrestricted mobility of the head during the session that can be solved by using a robotic coil positioning system [19, 20].

Experimental nTMS systems capable of tracking the patient's movements emerged about 15 years ago [30]. A robotic manipulator moved the inductor to follow the arbitrary trajectory along the axes X and Y within the range of 90 cm at angles of ± 45°, while the Z axis rotation was within the range of 360°. The error of installing the inductor with the weight of 1.5 kg did not exceed 1 mm on all axes. The inductor bias did not exceed 50 μm/min in any plain: it was 1 mm during the 20 min TMS session, which was not critical.

A simplified nTMS system has been described, in which the physician selects the TMS inductor position based on the patient's skull shape only (the output of TVS operation) [31]. The method proposed reduces the amount of data used to construct a 3D model of the brain approximately by an order, however, the risk of effect focusing errors is increased due to individual features of anatomical structure.

The precision nTMS system described by other authors is based on the scheme of the object coordinate recognition that is based on the high-resolution TVS, reflective trackers, and 3D model of the patient's brain constructed using the MRI data [32]. The use of infrared illumination at the wavelength of 850 nm that has partially solved the problem of the impact of hair on the scull model construction is the distinctive feature.

The use of trackers mounted on the patient's head and inductor makes it difficult to prepare for the nTMS session. As an alternative, it is suggested to estimate the head position using the characteristic face areas [33], however, this complicates construction of TVS and related software used to link the data from video cameras, 3D model of the brain, and position of inductor. At the same time, this solution accelerates and simplifies the TMS procedure, eliminates errors associated with the tracker bias.

The more simple nTMS variant involving orientation towards characteristic face areas uses only the skull model constructed based on the TVS data [34]. The inductor orientation is performed based on the scaled anatomical atlas data instead on the brain 3D model constructed using MRI.

When the patient has thick hair, the error of the skull model constructing using TVS and determining the compliance of the brain 3D model constructed can be reduced using the elastic cap that fits tightly on the head or the band with a picture of a chessboard with the elements of known size [35]. However, we believe that this solution represents the variant of using optical trackers with appropriate bias.

The virtual reality systems combining 3D models of the brain, skull, and inductor in a unified coordinate system are used to help the physician during the nTMS session [36]. This makes it possible to control fine-tuning of the inductor position without special skills using the minimalistic graphical and audio interface. The proposed approach turned out to be the least time-consuming in all proposed conditions relative to conventional neuronavigation. However, the latter showed higher targeting accuracy ($p < 0.001$).

When the virtual reality system is supplemented by the image of inductor specifying the magnetic field vector and density [37], the operator has to place the inductor coil in proper position and set the stimulation parameters, other operation will be performed in the automated mode. As a result, clarity of the created exposure scheme, reduction in time required for the session preparation, and simplification of all operations can be observed.

Reduction of the magnetic field side effects on the brain structures adjacent to the exposure focus during the TMS session is an important problem. This problem can be solved by using a figure-eight coil focusing the maximum field strength at the intersection of magnetic flux vectors [38]. As a result, the effect strength range is expanded and the focusing accuracy is increased, thereby reducing the risk of side effects and complications. However, the magnetic field generation system turns out to be rather bulky, requires precision production, and the shape of the target spot turns out to be unpredictable when the source is defocused, like the magnetic field strength in it.

It has been shown that the fixed-position dual centrosymmetric inductors form a dual focus exposure area [39]. This makes it possible to change the focus coordinate within a broad range by controlling the angle of their orientation only before the TMS session.

CONCLUSION

Certainly, it is impossible to provide multiple options and examples of implementation related to the technical background of navigated TMS. However, here we can highlight several areas for development of the method technical background.

First, this is improvement of the software part of constructing 3D models of the patient's brain and skull (head). It seems particularly challenging to increase accuracy of constructing a 3D image of brain tissues based on MRI data: resolution of the high-field MRI scanners enables recognition of objects sized 1–2 mm in increments of 5 mm with an angle error of ± 1° in the images, which is due to the apparatus table motion precision. Therefore, a properly working and adjusted scanner allows one to acquire a series of brain slices with an accuracy of about 1 mm, which is enough for the majority of applications. In rare cases when higher image resolution is required, one of the well-known nonlinear image interpolation methods can be used, however, correctness of such solution is questionable.

Second, it is improvement of the TMS inductor positioning and orientation accuracy. The experience of constructing a 3D model of the brain shows that positioning of the inductor axis with the angle accuracy of ±1º and the coordinates' uncertainty of ± 1 mm on all axes can be enough. It should be noted that the "spot" of magnetic field focus represents a bundle of tension lines (that of figure-eight coil is a circle with a diameter of 5–8 mm and blurry margins) [40]. Adjacent brain structures can be affected, but this can be perceived as the method inevitable cost. The use of the oriented two by two inductors of varying size, magnetic safety screens or magnetic field replicators enables improvement of the focusing accuracy [41].

Third, it is abandoning the handy elements simplifying recognition of the patient's skull position, which include various optical reflectors and probes mounted in pre-defined sites on the patient's head. In addition to the fact that installation of such elements results in inevitable installation accuracy errors, this requires the continuous use of disposables. We believe that aligning 3D models of the patient's brain and head using the clearly distinguishable face elements that are present in both cases (nose, eye sockets, brow ridges, and ears) is the most promising.

Fourth, it is the use of available variants of the control means realization and ensuring safety during the TMS session. This includes preliminary calculation of the field strength in the inductor focus with its indirect control during exposure. In our opinion, the effect strength control circuit is also essential that can be implemented in the form of the automated regulatory link based on the EEG and/or EMG data or in the form of the component of verbal biological feedback via control enabling manual magnetic flux intensity adjustment within certain limits by the patient.

Fifth, it is considerable simplification and acceleration of preparation for the nTMS session due to emerging options and experimental virtual reality systems enabling overlapping of 3D models of the brain, skull, and inductor in the common three-dimensional space considering the magnetic field effect vector.

And finally it is the need for reliable hardware and software implementation of the robotic manipulator used to ensure retention of the inductor focus on the pre-specified brain area regardless of the patient's position. The majority of available nTMS construction variants provide for the patient is in supine or semi-recumbent position, which makes it difficult to place the inductor over the patient's head occipital part. The use of the chair to sit the patient requires installation of the headrest at least for approximate fixation of the head in proper position. However, the headrest inevitably distorts the magnetic field shape, even if made of non-magnetic materials. The only variant is the patient's posture with the head bent to the chest, however, the possibility of the head free motion makes it rather difficult to ensure the inductor focus retention via robotic manipulator control.

In general it should be noted that the nTMS method has evolved considerably in the past 15 years in terms of both methodology and technical background. Despite the fact that the majority of originally existing problems have been solved completely or partially, it is necessary to resume the search for variants of increasing the method efficacy, ensuring its safety, and reducing the cost of hardware.

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