Relevance of Impact of Non-Drug Methods on Neuroplasticity in System of Neurorehabilitation: Multilevel Neuroplastic Effects of Electromagnetic Fields Caused by Transcranial Magnetic Stimulation

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Abstract. Strategic cooperation between clinical research institutions engaged in medical research and pharmaceutical companies focused on identifying and testing targets aimed at creating new innovative, high-quality, safe, effective and affordable medicines to address the therapeutic needs of patients suffering from psychoneurological and related health disorders (multiple sclerosis, neuro-oncology, post-traumatic stress disorder, stroke, drug addiction, alcoholism, etc.) in accordance with the state guarantee program and ICD-11. At the same time, the relevance of the impact of non-drug methods on neuroplasticity in the neurorehabilitation system of patients is beyond doubt. The authors addressed the impact of non-drug methods on neuroplasticity in the neurorehabilitation system. Multilevel neuroplastic effects of electromagnetic fields caused by transcranial magnetic stimulation are presented. The effects of transcranial magnetic stimulation on neurotransmitters and synaptic plasticity, glial cells and the prevention of neuronal death are examined. The neurotrophic effects of transcranial magnetic stimulation on the growth of dendrites, growth and neurotrophic factors are described. The effect of transcranial magnetic stimulation on the genetic apparatus of neurons is traced. It has been demonstrated that transcranial magnetic stimulation has a proven ability to modulate the internal activity of the brain in a frequency-dependent manner, generate contralateral responses, provide, along with the neuromodulatory and neurostimulating effect, influence the brain as a global dynamic system.

Keywords: patient rehabilitation, non-drug methods, electromagnetic fields, neuroplasticity, neurorehabilitation, synaptic plasticity, transcranial magnetic stimulation, multilevel neuroplastic effects.

Introduction. The International Symposium of the Consortium for Advanced Medicines Manufacturing organized meetings for leading scientists, technical experts from industry, academia, and regulatory authorities [1]. The planned tasks were:

- to lay the foundation for the future perception of the medical field, the pharmaceutical

industry, and regulatory policy for optimizing the regulatory system related to the regime of control over the circulation of medicines and the quality of medical care;

- to accelerate the implementation of advanced technologies for the production of small molecules, biologics, and vaccines;
- to create an International Consortium for Advanced Medicines Manufacturing;
- to unite leading scientists and experts from academia, industry, global regulatory authorities, and policymakers to gain access to modern achievements;
- to celebrate successful implementation, assess remaining challenges, and form an opinion on a shared vision for the future that will benefit public health in the system of legal relations "doctor-patient-pharmacist" in countries around the world, during the supply of vital medicines and overcoming problems with technologies and the circulation chain (supply, transportation, etc.).

These measures are aimed at improving the system of legal relations "doctor-patient-pharmacist", preventing medical errors [2], improving qualifications in medical and pharmaceutical law, eliminating criminal and legal risks during the circulation of high-quality, safe and effective medicines, introducing innovative technologies during the diagnosis, treatment and rehabilitation of neurological diseases in wartime conditions, and implementing ICD-11 in the practice of treating mental and behavioral disorders [3-6]. The above issues are discussed and resolved during master classes and multidisciplinary scientific and practical conferences with the participation of foreign specialists [7-9]:

- ✓ Master class "Implementation of ICD-11 in the practice of treating mental and behavioral disorders: problems and solutions". State institution "P.V. Voloshyn Institute of Neurology, Psychiatry and Narcology of the National Medical Academy of Sciences of Ukraine" (Kharkiv - 25.03.2025).
- ✓ Scientific and practical conference with international participation "Innovative technologies for the diagnosis, treatment and rehabilitation of neurological diseases in wartime conditions". State Institution "Petro Vlasovich Voloshyn Institute of Neurology, Psychiatry and Narcology of the National Medical Academy of Sciences of Ukraine" (Kharkiv - 29-30.03.2024, event registration number in the BPR system: No. 3701385).
- ✓ XXI International Multidisciplinary Scientific and Practical Conference "Medical and Pharmaceutical Law of Ukraine: Organization and Economics of Pharmaceutical and Medical Affairs, Drug Circulation, Technology, Safety, Efficiency, Quality Control, General, Forensic, Evidence-Based and Clinical Pharmacy and Medicine, Pharmacotherapy of Health Disorders" (Kyiv-Lviv-Tallinn – 14-15.11.2024, event registration number in the continuous professional development system: No. 1000150).

Therefore, it is the strategic cooperation of scientific and clinical research institutions engaged in medical research and pharmaceutical companies that focus on the problem of identifying and testing targets aimed at creating new innovative, high-quality, safe, effective and affordable medicines to address the therapeutic needs of patients suffering from psychoneurological and related health disorders (multiple sclerosis, neuro-oncology, post-traumatic stress disorder, stroke, drug addiction, alcoholism, etc.) in accordance with the state guarantee program and ICD-11 [10-17].

The relevance of non-drug methods for neuroplasticity in the neurorehabilitation system, multi-level neuroplastic effects of electromagnetic fields require further study to optimize the treatment process of patients [18, 19]:

- excitatory electromagnetic pulses applied to the affected hemisphere of the brain allow optimizing the functional activity of the brain;
- to provide broad and more reliable recommendations on the appropriate use of transcranial magnetic stimulation in patients with multiple sclerosis, more well-designed, randomized, controlled clinical trials with a larger patient population are needed;
- this approach provides adjuvant therapy to the action of other symptomatic treatments and immunomodulatory drugs;

- neuroplasticity, the ability of the brain to reorganize by forming new neural connections, is central to modern neuroscience;
- studies show that plasticity continues throughout life, supporting learning, memory, and recovery from injury or disease;
- significant progress has been made in understanding the mechanisms underlying neuroplasticity, and their therapeutic applications;
- recent strategies for using neuroplasticity (medication, lifestyle interventions, Brain-Computer Interfaces (BCIs), targeted neuromodulation) are evaluated in light of current empirical evidence.

Approaches to the rehabilitation of patients with neurological diseases are increasingly shifting towards stimulating neuroplasticity for better recovery and restoration of function (Fig. 1) [20].

The strategy of physical exercise and non-invasive neuromodulation methods is aimed at neuroplasticity. Includes Transcranial Magnetic Stimulation, nervus vagus stimulation, peripheral nerve stimulation. The use of these interventional strategies is often found in rehabilitation settings: Parkinson's disease, traumatic brain injury, stroke, spinal cord injury. The potential advantage of combining non-invasive neuromodulation with rehabilitation has been established, which has shown an effect in accelerating recovery.

Molecular changes lead to neuroplastic cellular changes: angiogenesis (new blood supply), neurogenesis (growth of new neurons), and synaptogenesis (increase in synaptic connectivity). The result is an increase in the strength of neural pathways.

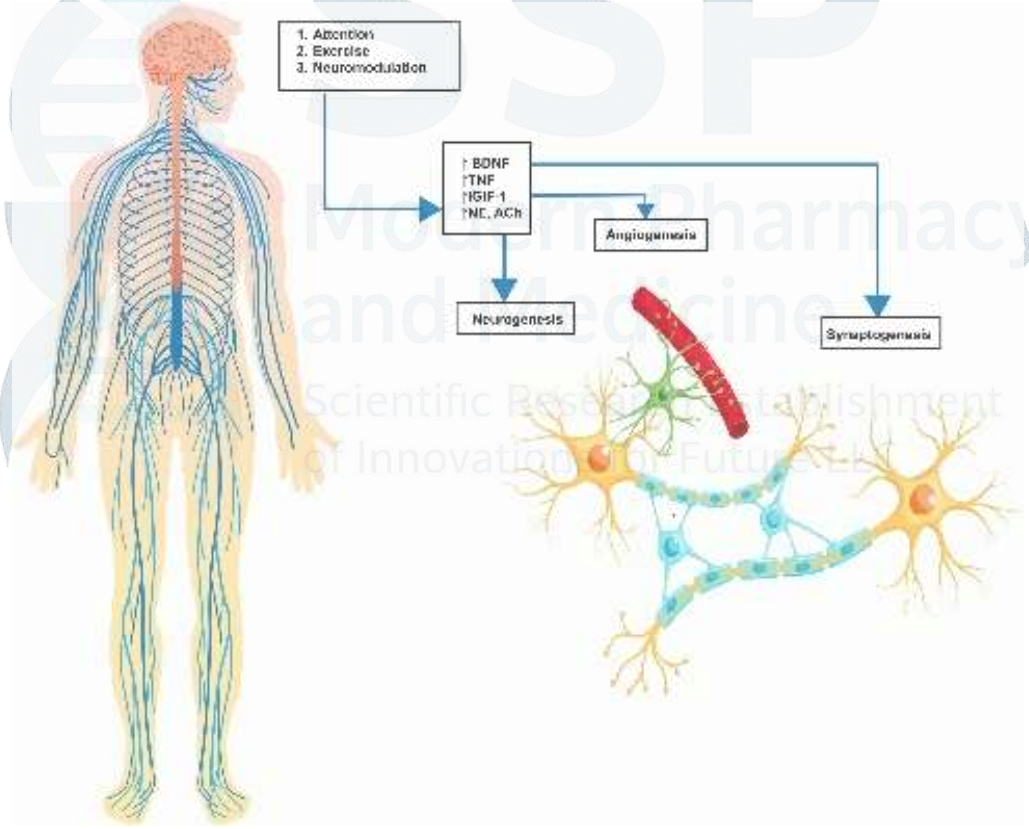

Fig. 1. The neuroplasticity cascade associated with environmental influences through training, exercise, or neuromodulation causes an increase in the number of molecular substrates [20].

The purpose of the study was to research the level of influence of non-drug methods on neuroplasticity in the neurorehabilitation system of patients, as well as the multi-level neuroplastic effects of electromagnetic fields caused by transcranial magnetic stimulation require further study to optimize the treatment process of patients.

Materials and methods. Doctors of the Department of Autoimmune and Degenerative Diseases of the Nervous System (2nd Neurological Department) of the State Institution P.V. Voloshin Institute of Neurology, Psychiatry and Narcology of the National Academy of Sciences of Ukraine specialize in the diagnosis of diseases of the central, peripheral, nervous system in the context of multidisciplinary research [22-26].

The research of the article is a fragment of research works of P.V. Voloshyn Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine on the following topics:

- "Study mechanisms of inheritance of multiple sclerosis in persons born from parents with this disease" (state registration number 0121U111900, implementation period 2022-2024);
- "Development of rehabilitation programs for the mobilization of compensatory-adaptive neuroplasticity processes in Parkinson's disease" (code NAMN.KhP.2P.20, implementation period 01.01.2020-31.12.2022);
- Resolution of the Cabinet of Ministers of Ukraine dated 13.03.2024 No. 296 "On approval of the Procedure for conducting rehabilitation (post-isolation, reintegration) measures, adaptation, support (support) measures for persons in respect of whom the fact of deprivation of personal liberty as a result of armed aggression against Ukraine has been established, after their release" [21].

Results and discussion. Studies show that the insufficiently studied effectiveness of existing therapeutic approaches in neurorehabilitation of patients determines the search for new, optimization of old and modification of known non-drug methods of inducing neuroplasticity. Thus, the phenomena of multidirectional action of functional neuroplasticity are described when using the method of transtympanic chemical vestibular dereception, transcranial micropolarization, intracerebral neurotransplantation [27-30].

An important place among such methods is occupied by transcranial stimulation. The practice of transcranial stimulation is based on the fact that brain activity is based on the electrical activity of neurons [31]. By the action of an electric current, a magnetic field, or another physical agent, it is possible to modulate electrical activity and have a directional influence on the process of forming temporary or permanent changes in electrical activity.

The transcranial stimulation group consists of [32-41]:

- Transcranial Magnetic Stimulation;
- Transcranial Electrical Stimulation (tES);
- Transcranial Random Noise Stimulation (tRNS);
- Transcranial Ultrasound Stimulation (tUS)

In this review, the neuroplastic effects arising under the action of transcranial magnetic stimulation are considered. Note that transcranial magnetic stimulation uses variable magnetic fields for non-invasive stimulation of neurons in the patient's brain [42]:

- ❖ transcranial magnetic stimulation is the most actively developing direction, which is based on the modulation of neuroplasticity mechanisms;
- ❖ activation or inhibition of certain areas of the cerebral cortex is carried out due to Heterosynaptic Potentiation;
- ❖ transcranial magnetic stimulation allows to reorganize neuronal networks by means of modulation of their connections [43, 44];
- ❖ in clinical neurology, the method of Transcranial Magnetic Stimulation, known as repetitive Repetitive Transcranial Magnetic Stimulation, is widely used.

There are two main modes of Repetitive Transcranial Magnetic Stimulation:

1) low-frequency, which is determined by stimulation at frequencies below 1 Hz;

2) high-frequency, which is determined by stimulation at frequencies above 5 Hz.

Low-frequency Repetitive Transcranial Magnetic Stimulation reduces the excitability of neurons. High-frequency Repetitive Transcranial Magnetic Stimulation increases cortical excitability [45].

Navigational Transcranial Magnetic Stimulation (nTMS) is also widely used. Systems of

Navigational Transcranial Magnetic Stimulation (nTMS) take into account the individual anatomy of a specific person and allow to apply the stimulus purposefully and locally, based on MRI data [42].

The methods of transcranial magnetic stimulation became the methods of Sharbafshaaer M., Cirillo G., Esposito F. et al. The data indicate changes in human brain activity and improvement in synaptic plasticity.

Repetitive transcranial magnetic stimulation and theta burst stimulation have been recognized as valuable non-pharmacological treatments for a wide range of patient neurological disorders [46]. Among these modalities, Repetitive Transcranial Magnetic Stimulation and Theta Burst Stimulation (TBS) show significant promise in improving outcomes for adults with complex neurological and neurodegenerative diseases (Alzheimer's disease, stroke, Parkinson's disease). Optimizing their effects remains challenging due to variability in patient response and limited understanding of how these modalities interact with critical neurotransmitter systems.

The mechanisms of repetitive transcranial magnetic stimulation and theta burst stimulation that enhance neuroplasticity and functional improvement have been studied.

How repetitive transcranial magnetic stimulation and theta burst stimulation affect neuroplasticity and functional connectivity, particularly in relation to Brain-Derived Neurotrophic Factor (BDNF) and Tropomyosin Receptor Kinase B (TrkB), has been investigated; significant potential of this research to advance understanding of neuroplasticity and improve patient outcomes.

The neurobiological mechanisms of Repetitive Transcranial Magnetic Stimulation and Theta Burst Stimulation, using neuroimaging findings, help to develop more effective, personalized treatment plans; effectively address issues related to neurological disorders; improve the quality of neurorehabilitation services; provide future directions for patient care [46].

Figure 2 explains depicted is the signaling pathway where neurotransmitters bind to membrane receptors, activating G proteins and effector proteins to produce the second messengers $Ca2^{+}$ and Cyclic Adenosine Monophosphate (cAMP). These messengers activate protein kinases, which leads to protein phosphorylation and activation of transcription factors (e.g., Cyclic Adenosine Monophosphate (cAMP) response Cyclic Element-binding Protein, JunD proto-oncogene, AP-1 transcription factor subunit (JunD) in the nucleus. This triggers transcription of immediate early genes, which leads to RNA synthesis and changes in gene expression [46].

Figure 3 demonstrated neural processes in synaptic mechanisms and plasticity, highlighting the role of brain-derived neurotrophic factor (BDNF). The brain is depicted with highlighted neuronal activity and a brain stimulation device, indicating methods such as long-term potentiation (LTP) and long-term depression (LTD). Figure 3 depicts an axon, myelin sheaths, oligodendrocyte, presynaptic terminals with proteins, neurotransmitters (e.g., glutamate), N-methyl-D-aspartate receptor (NMDAr), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor AMPar, Gamma-Aminobutyric Acid Type A receptor (GABA_A) and postsynaptic terminals with Tropomyosin Receptor Kinase B (TrkB) receptors binding Brain-Derived Neurotrophic Factor (BDNF), calcium ions and protein synthesis machinery. Arrows point to neurotransmitter release and signaling directions, highlighting interactions required for synaptic function and neural plasticity [46].

It is important to note that the effect of repetitive transcranial magnetic stimulation on neurotransmitters and synaptic plasticity is reflected in the studies of Strafella A.P., Cho S.S., Strafella A.P., Ko J.H., Huang Y.Z., Lisanby S.H., Belmaker R.H., Cho S., Kuwabara S., Hoogendam J.M., Duffau H., Cooke S.F., Bliss T.V., Teo J.T. et al. [47-57].

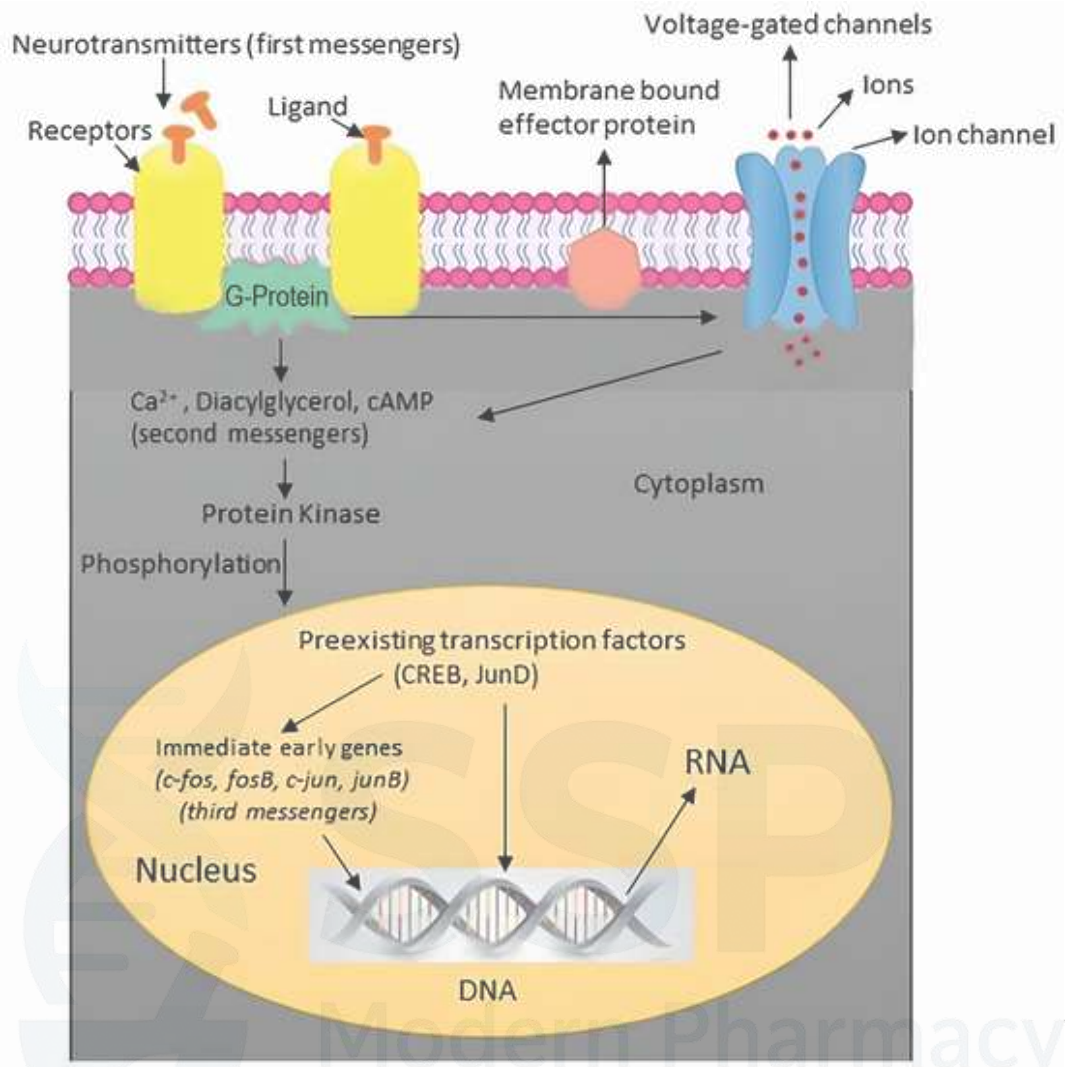

Fig. 2. Mechanisms of communication of neurotransmitters with membrane receptors [46].

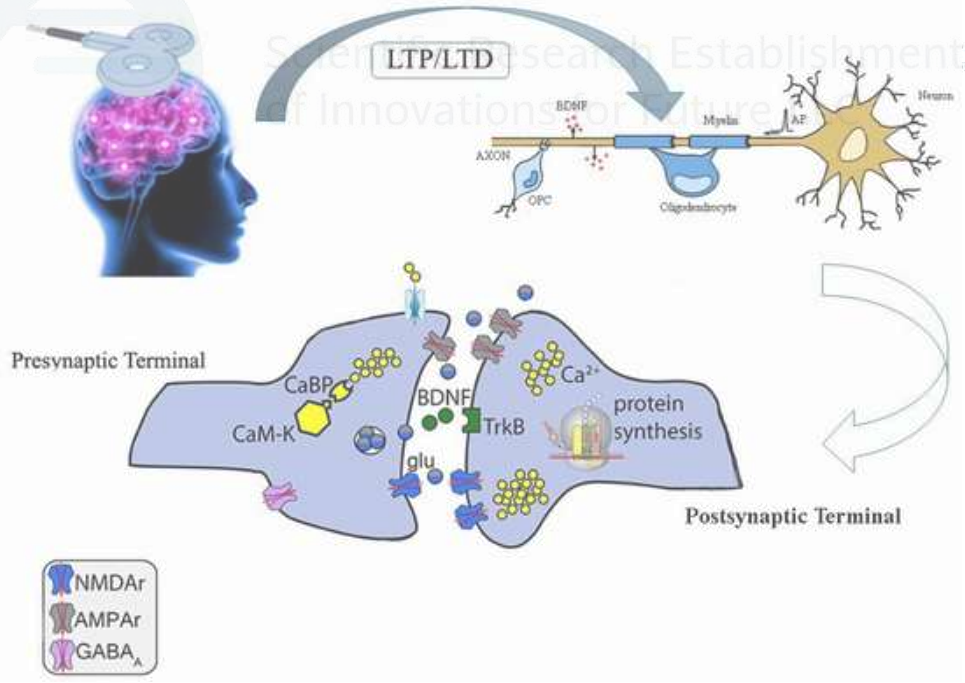

Fig. 3. Neural processes in the synapses of Brain-Derived Neurotrophic Factor (BDNF) [46].

A functional neuroimaging study in patients with Parkinson's disease showed that [58]:

- Repetitive Transcranial Magnetic Stimulation increased endogenous dopamine concentrations in the ipsilateral striatum [47];
- High-frequency (10 Hz) Repetitive Transcranial Magnetic Stimulation left Dorsolateral Prefrontal Cortex (DLPFC) increased ipsilateral dopamine release in Brodmann areas 25/12 and 32, as well as in Brodmann area 11, which is located in the medial orbitofrontal cortex [48];
- Changes in dopamine production result in a decrease in the ligand binding potential [41] FLB 457 (Carbon-11 labeled fluorolobenzamide) FLB 457 during positron emission tomography (PET) scanning;
- No significant changes were observed in the right Dorsolateral Prefrontal Cortex (DLPFC) using Repetitive Transcranial Magnetic Stimulation;
- Similar data were obtained regarding transcranial magnetic stimulation-induced changes in dopamine production;
- Theta-burst (high frequency) stimulation applied to the left Dorsolateral Prefrontal Cortex (DLPFC) in healthy volunteers worsened motor performance and reduced bilateral striatal dopamine production [49];
- The ipsilateral caudate nucleus and ipsilateral putamen showed the most significant reduction in dopaminergic activity;
- The effects of the stimulation regimen are related to its long-term inhibition (up to 60 minutes) of the underlying brain segments through neuroplastic changes in synaptic structure, which likely occur through activation of N-methyl-D-aspartate (NMDA) receptors [50];
- Repetitive transcranial magnetic stimulation also affects the expression levels of various receptors and other neurotransmitters. After exposure to repetitive transcranial magnetic stimulation, a decrease in the number of β-adrenergic receptors is observed in the frontal and cingulate cortex, but an increase in the number of NMDA receptors in the ventromedial thalamus, amygdala and parietal cortex [51];
- Rats exposed to 5 days of electromagnetic radiation (frequency 60 Hz, amplitude 20 Gs) show high levels of nitric oxide and Cyclic Guanosine Monophosphate (cGMP) in the cerebral cortex, convolutions and hippocampus;
- However, the number and morphology of neurons remain unchanged. Based on the presented data, it was suggested that increased expression of genes responsible for the synthesis of neuronal NO synthase may underlie the effects of transcranial magnetic stimulation [52];
- The effects of repetitive transcranial magnetic stimulation are primarily determined by specific combinations of stimulation frequency and intensity due to a shift in the ionic balance around the population of stimulated neurons [53]; this shift manifests itself as altered synaptic plasticity [42].

At the same time, Hoogendam J. M., Ramakers G. M., Di Lazzaro V. believe that the long-term therapeutic effects of Repetitive Transcranial Magnetic Stimulation and the influence of magnetic stimulation on the processes described above are associated with 2 phenomena [54]:

- ✓ Long-Term Potentiation (LTP);
- ✓ Long-Term Depression (LTD).

As Duffau H. believes, Long-Term Potentiation (LTP) and Long-Term Depression (LTD) are key mechanisms that support long-term changes in synaptic strength after exposure to Transcranial Magnetic Stimulation [55].

At the same time, Long-Term Potentiation (LTP) increases synaptic strength and can persist for several days, weeks or months, while Long-Term Depression (LTD) leads to a long-term decrease in synaptic strength [54, 55]. The molecular mechanisms associated with Transcranial Magnetic Stimulation–Induced Changes likely involve N-methyl-D-aspartate receptors located on

the postsynaptic membrane [42]. They contain a cation channel that is blocked by magnesium ions in the resting state [56]. Depolarization of the cell membrane removes this channel block and allows calcium ions to enter the postsynaptic neuron [56], which ultimately leads to the induction of Long-Term Potentiation (LTP).

Clinical studies have shown that combinations of transcranial magnetic stimulation treatment and pharmacotherapy also have interesting results [50-57]:

- small doses of memantine, a non-competitive antagonist of N-methyl-D-aspartate receptors, can block the facilitatory effect during Long-Term Potentiation (LTP);
- small doses using D-cycloserine can block the facilitating effect during Long-Term Potentiation (LTP).

In the publications of Arias-Carrión O., May A., Meng D.P., Hajak G., Ueyama E., Ke S., Ogawa A., Xu T., Guo F.J., Vlachos A., Fujiki M., Ogiue-Ikeda M., Feng H.L., Gao F., Yoon K.J., Ukai S. et al. the effect of Repetitive Transcranial Magnetic Stimulation on glial cells and prevention of neuronal death was shown [59-70].

An important aspect associated with the action of transcranial magnetic stimulation is its effect on neuroprotective mechanisms and this was morphometrically demonstrated in the studies of May A., Hajak G. and Gänssbauer S. [59]. Repetitive transcranial magnetic stimulation with a frequency of 1 Hz was applied to the left superior temporal gyrus (Brodmann areas 41 and 42) for 5 days at an intensity of 110% of the transcranial magnetic stimulation threshold. It significantly increased the volume of gray matter at the stimulation site. No changes in the volume of gray matter were recorded in patients who underwent sham Transcranial Magnetic Stimulation. At the same time, May A. suggested that the above-described macroscopic changes depended on synaptogenesis, angiogenesis, gliogenesis, neurogenesis, an increase in cell size and an increase in cerebral blood flow [60].

In turn, Ueyama E., Ukai S., Ogawa A. reported that Repetitive Transcranial Magnetic Stimulation with a frequency of 25 Hz for 14 days enhances neurogenesis in the dentate gyrus of mice [61]. Meng D.P., Xu T., Guo F.J. found that high-intensity alternating magnetic fields (0.1-10 T (tesla)) have a positive effect on the differentiation and growth of neural stem cells in neonatal rats in vitro [62].

Maximum effects were achieved in a 40,000 gauss (4 tesla) magnetic field). After inducing unilateral damage in the substantia nigra using 6-hydroxydopamine, mice subjected to a 60-day period of treatment with Repetitive Transcranial Magnetic Stimulation showed in situ differentiation of neurons in the subventricular zone into dopamine-producing neurons [63].

The number of new dopamine-producing cells correlated with increased locomotor activity. Vlachos A. et al. [64] studied the effects of high-frequency (10 Hz) stimulation in cultured mature CA1 (cornu ammonis) hippocampal neurons of mice. They found that magnetic stimulation induced remodeling of dendritic spines. These effects were associated with the influence of transcranial magnetic stimulation N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors.

Studies using transient ischemic attack and prolonged ischemia models showed that Repetitive Transcranial Magnetic Stimulation [65-67]:

- protects neurons from death and changes blood flow and metabolism in the brain;
- promotes the restoration of neuronal function after cerebral ischemia-reperfusion injury in rats.

At the same time, in order to clarify the mechanisms underlying these effects, Feng H.L. investigated the effect of Repetitive Transcranial Magnetic Stimulation on striatal Adenosine Triphosphate (ATP) levels and microtubule-associated protein 2 expression using an ischemia-reperfusion injury model [67].

Repetitive Transcranial Magnetic Stimulation was found to significantly increase the content of adenosine triphosphate in the striatum of the ischemic hemisphere. Different stimulation modes caused different effects. High-intensity and low-intensity (200 and 120%) high-frequency stimulation (20 Hz) significantly increased the content of adenosine triphosphate. A significant

increase in the expression of Microtubule-Associated Protein 2 was observed in the left ischemic hemisphere. Similar to the content of adenosine triphosphate, the highest number of Microtubule-Associated Protein 2-positive areas was observed after high-frequency stimulation.

A study was conducted by Gao F. et al. on the neuroprotective effects of high-frequency repetitive transcranial magnetic stimulation in a mouse model of transient ischemic attack using Positron Emission Tomography (PET) imaging [68]. The infarction area was significantly smaller in the affected hemispheres of mice exposed to repetitive transcranial magnetic stimulation. Glucose metabolism was higher. The number of caspase-3-positive cells was significantly lower in the Repetitive Transcranial Magnetic Stimulation group compared to the control group, indicating that Repetitive Transcranial Magnetic Stimulation inhibited apoptosis in the ischemic area.

As shown in the scientific work of Yoon K.J., the effects of transcranial magnetic stimulation were revealed in the areas surrounding the infarction area in mice [69]. These experimental data contributed to the development of clinical protocols. They use magnetic stimulation during the acute phase of stroke. The application of low-frequency stimulation to mice before the introduction of a lithium-pilocarpine mixture (a lithium-pilocarpine model for epileptogenesis) was studied by Ke S., Zhao H., Wang X. They found an increase in B-Cell Leukemia/Lymphoma 2 (Bcl-2) expression, a decrease in Fas-associated protein with death domain expression in Fas in the hippocampus [70, 71]. It was assumed that this transcranial magnetic stimulation induced antiepileptic effect antiepileptic effect occurs through the activation of anti-apoptotic mechanisms.

The latter study is of particular interest, since the number of clinical studies studying the effect of transcranial magnetic stimulation on patients with refractory epilepsy is increasing [72]. The neuroprotective effects of transcranial magnetic stimulation are evident in another model using the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The CA3 (cornu ammonis) hippocampal neurons of mice not exposed to transcranial magnetic stimulation were affected 48 h after treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The CA1 (cornu ammonis) hippocampal neurons of mice exposed to Repetitive Transcranial Magnetic Stimulation were not affected. Measurement of glial fibrillary acidic protein (GFAP) levels in astrocytes from mice exposed to Transcranial Magnetic Stimulation (TMS) revealed that these cells were activated after stimulation [73]. In addition, astrocytes exhibit an increased ability to migrate to the central nervous system after magnetic stimulation in an animal model of spinal cord injury. It has been suggested that this may be due to the activation of specific mitotic pathways (Mitogen-activated Protein Kinase/Extracellular-Regulated Kinase) and increased expression of several genes [74].

Clinical studies conducted by Belmaker R.H., Ma J., Baquet Z., Yukimasa T., Zanardini R., Lang C., Schüler D., Gedge L., Wang H.Y., Angelucci F., Lisanby S.H., Müller M.B. indicate the establishment, identification, and study using evidence-based medicine that [51, 75-83]:

- neurotrophic effects of repetitive transcranial magnetic stimulation affect the growth of dendrites and are associated with growth and neurotrophic factors;
- magnetic stimulation does not always give a positive result and that these effects largely depend on the stimulation mode;
- in hippocampal cell cultures, low-intensity stimulation (1.14 T, 1 Hz) leads to the sprouting of dendrites (axon growth) and increases the density of synaptic contacts;
- high-intensity stimulation (1.55 T, 1 Hz) has destructive effects that lead to a decrease in the number of dendrites and axons, the presence of neuronal damage and a decrease in the number of synapses;
- these results are associated with the Brain-Derived Neurotrophic Factor (BDNF) - Tyrosine Kinase B (TrkB) signaling system;
- Brain-Derived Neurotrophic Factor - (BDNF) has a wide range of functions, including increasing the survival of neurons after damage to the central nervous system, influencing neurogenesis, migration and differentiation of neurons, the growth of dendrites and axons and the formation of synapses.

A number of studies have shown that:

- ❖ an external magnetic field, which is a consequence of transcranial magnetic stimulation, can affect the content of Brain-Derived Neurotrophic Factor (BDNF) in serum and cerebrospinal fluid [42];
- ❖ an increase in serum levels of Brain-Derived Neurotrophic Factor (BDNF) after repetitive transcranial magnetic stimulation was noted in publications by Yukimasa T. [77], Zanardini R. [78];
- ❖ other researchers do not confirm such a clear effect of Transcranial Magnetic Stimulation (TMS) [79, 80];
- ❖ high-frequency transcranial magnetic stimulation increases the levels of Brain-Derived Neurotrophic Factor (BDNF) in serum and the affinity of Brain-Derived Neurotrophic Factor (BDNF) for tyrosine kinase B (TrkB) receptors
- ❖ low-frequency Transcranial Magnetic Stimulation (TMS) reduces the levels of Brain-Derived Neurotrophic Factor (BDNF) [81];
- ❖ patients with amyotrophic lateral sclerosis Amyotrophic Lateral Sclerosis (ALS) showed a decrease in the level of Brain-Derived Neurotrophic Factor (BDNF) in the serum after applying low-frequency Repetitive Transcranial Magnetic Stimulation to the motor cortex [82]; high-frequency stimulation was shown to increase the level of Brain-Derived Neurotrophic Factor (BDNF) in the blood plasma of patients with depression [77].

Long-term repetitive transcranial magnetic stimulation (5 days with a 2-day break - 11 weeks) increases the expression of brain-derived neurotrophic factor and cholecystokinin Matrix Ribonucleic Acid (mRNA) in specific areas of the rat brain [83]. These RTMS-induced effects on neurotrophic factor production may explain previously reported neuroplastic inductions by RTMS. For example, increased hippocampal mossy fiber sprouting [51].

It has been proposed that RTMS directly influences the production of Brain-Derived Neurotrophic Factor (BDNF). Brain-Derived Neurotrophic Factor (BDNF) proteins synthesized in the magnetic field induced by RTMS exhibit all typical properties [66].

Repetitive transcranial magnetic stimulation has been shown to influence the production of Brain-Derived Neurotrophic Factor (BDNF) in stimulated as well as remote brain regions [42]. These results offer many new possibilities regarding therapeutic options for patients with central nervous system disorders [84].

The results of published studies by Aydin-Abidin S., Ji R.R., Funamizu H., Cheeran B., Komssi S., Zanardi R., Simis M., Hausmann A., Zhi W., Luber B. et al. showed the effect of repetitive transcranial magnetic stimulation on the genetic apparatus of neurons [73, 84-95]:

- ✓ one session of repetitive transcranial magnetic stimulation increased the expression of Matrix Ribonucleic Acid (mRNA) in the paraventricular nuclei of the thalamus and, to a lesser extent, in the frontal and cingulate gyri, but not in the parietal cortex;
- ✓ magnetic stimulation had a stronger effect than electrical stimulation;
- ✓ a 14-day series of repetitive transcranial magnetic stimulation sessions increased the expression of Matrix Ribonucleic Acid (mRNA) in the parietal cortex of the brain;
- ✓ study of the effect of low- and high-frequency transcranial magnetic stimulation on the genetic expression of Cellular-Fos (c-Fos) and Zinc finger protein 268 (zif268);
- ✓ low- and high-frequency stimulation increased the expression of the c-Fos gene in all studied cortical areas;
- ✓ theta-burst stimulation had similar effects, but only in the limbs.
- ✓ theta-burst stimulation also increased the expression of Zinc finger protein 268 (zif268) in all cortical areas;
- ✓ stimulation at 10 Hz produced this effect only in the motor and sensory cortex areas;
- ✓ stimulation at 1 Hz and sham stimulation did not affect the expression of Zinc finger protein 268 (zif268);
- ✓ fictive stimulation increased the expression of Cellular-Fos (c-Fos) in the limbic area;
- ✓ repetitive transcranial magnetic stimulation affects the expression of tyrosine hydroxylase and Neuronal Nuclei antibody (NeuN) in the substantia nigra;

- ✓ polymorphism in the genes that encode serotonin (5-HT) carriers, 5-hydroxytryptamine and Brain-Derived Neurotrophic Factor (BDNF) receptors affect the sensitivity of patients to repetitive transcranial magnetic stimulation [78];
- ✓ a study of polymorphism in the 5-HT 1A receptor gene showed that patients with C/C are more susceptible to repetitive transcranial magnetic stimulation therapy than patients with cytosine/guanine and guanine/guanine (C/G and G/G) [88];
- ✓ another clear illustration of the relationship between genetic polymorphisms and transcranial magnetic stimulation is the difference between subjects with the Valine 66 (sixty-six) Methionine (Val66Met) and 66 Valine (sixty-six) Valine (Val66Val) alleles of the Brain-Derived Neurotrophic Factor (BDNF) gene [87].

Thus, the relevance of conducting studies on the impact of non-drug methods on neuroplasticity in neurorehabilitation is considered. Multilevel neuroplastic effects of electromagnetic fields under the influence of transcranial magnetic stimulation were studied. Further studies are ongoing.

Conclusions. The development of scientifically advanced clinical institutions and pharmaceutical companies has been continued to improve the therapeutic needs of patients who suffer from neuropsychiatric and related health disorders of up to programs of medical guarantees and MKH-11. The effects of transcranial magnetic stimulation on many factors (neuron morphology; neurogenesis; cell differentiation and proliferation; concentration of neurotransmitters, etc.) have been identified. Transcranial magnetic stimulation has a proven ability to modulate intrinsic brain activity in a frequency-dependent manner, provide neuromodulatory and neurostimulatory effects, and influence the brain as a global dynamic system. It has been shown that a promising direction is the induction of neuroplasticity in neurorehabilitation, a combination of transcranial magnetic stimulation and pharmacotherapy, which requires further pharmacoeconomic justification. 5. The study of scientific and theoretical publications shows that transcranial magnetic stimulation stimulates and induces gene expression and enhances the production of a number of enzymes. It has also been established that the effects of repetitive transcranial magnetic stimulation are often stronger than the effects of direct electrical stimulation, and some changes are observed only after repetitive transcranial magnetic stimulation. Multidisciplinary studies by the authors of the article indicate that the insufficient effectiveness of existing therapeutic approaches in the neurorehabilitation of patients determines the search for new, optimization of old and modification of known non-drug methods of inducing neuroplasticity.

Declaration of conflict interest. The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The authors confirm that they are the authors of this work and have approved it for publication. The author salso certify that the obtained clinical data and research were conducted in compliance with the requirements of moral and ethical principles based on medical and pharmaceutical law, and in the absence of any commercial or financial relationships that could be interpreted as potential conflict of interest.

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Data availability statement. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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