Cellular and Molecular Mechanisms Underlying Transcranial Magnetic Stimulation: Experimental Data for Evaluating Changes in Nervous Tissue

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Abstract

Transcranial magnetic stimulation (TMS) is a non-invasive method for targeted modulation of the electrical activity of brain neurons with a magnetic field. Although TMS efficacy was demonstrated in the treatment of several neurological and mental disorders, changes in nervous tissue at the cellular and molecular levels with different duration and intensity of stimulation have been relatively understudied by cellular neurobiology methods. Aim. The aim of this review was to evaluate and summarize new experimental data on the fundamental mechanisms underlying the action of TMS and its potential in modulating structural and functional changes in nervous tissue. This article summarizes recent data on the effects of different TMS protocols on the mechanisms underlying synaptic plasticity, neurogenesis, and neuronal differentiation. Separate sections summarize the neuroprotective effects of this method and glial microenvironment response. Studies to investigate the mechanisms of TMS will contribute to the development of more effective and reliable treatment protocols.

Keywords: *transcranial magnetic stimulation; neuroplasticity; glia; neurogenesis; neuroprotection; synaptogenesis*

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Клеточные и молекулярные механизмы транскраниальной магнитной стимуляции: экспериментальные данные в оценке изменений нервной ткани

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Аннотация

Транскраниальная магнитная стимуляция (ТМС) – неинвазивный метод направленного воздействия на электрическую активность нейронов головного мозга магнитным полем. Несмотря на доказанную эффективность в лечении ряда неврологических и психических заболеваний, изменения в нервной ткани на клеточном и молекулярном уровнях при разной длительности и интенсивности стимуляции мало изучены методами клеточной нейробиологии. Целью работы явился анализ и обобщение новых экспериментальных данных о фундаментальных механизмах действия ТМС и потенциальных возможностях данного метода в модуляции структурно-функциональных изменений в нервной ткани. В работе систематизированы современные сведения о влиянии разных протоколов ТМС на механизмы синаптической пластичности, нейрогенез и дифференцировку нейронов. Отдельные разделы посвящены нейропротективным эффектам данного метода, а также ответной реакции глиального микроокружения. Исследования механизмов ТМС будут способствовать разработке более результативных и надёжных протоколов лечения.

Ключевые слова: *транскраниальная магнитная стимуляция; нейропластичность; глия; нейрогенез; нейропротекция; синаптогенез*

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Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive method for targeting the electrical activity of neurons. It is used to stimulate nerve cells with short magnetic pulses that cause depolarization of the pre- and postsynaptic membrane. In the brain, a magnetic field induces an electric current that affects the electrophysiological parameters of neurons in the stimulated area [1–3].

TMS is widely used in current clinical practice for diagnosis, treatment, and rehabilitation of patients with various neurological and mental disorders. According to the European guidelines [4], this method was shown to be effective in the management of treatment-resistant depression [5–7], neuropathic pain [8–10] (level of evidence A) and in rehabilitation of patients with post-stroke motor deficit [11, 12] (level of evidence B). Statistically significant improvement was observed in Parkinson's disease [13, 14], spasticity in multiple sclerosis [15], migraine [16], etc.

In research practice, TMS is used to assess the excitability of the motor cortex, changes in cognitive processes over time, and functional brain mapping [3].

The method is usually well tolerated by patients. Compliance with safety recommendations minimizes the occurrence of such serious adverse effects as epileptic seizures (incidence rate less than 1 per 60,000 sessions) [17, 18]. Other side effects, such as pain at the stimulation site, are more

common but in most cases they do not affect the tolerability of the procedure [19].

Studying TMS effects on brain structures is challenging because the type of the effect is difficult to be assessed in non-motor areas of the cortex. Therefore, it is difficult to predict and interpret the results obtained by activating a set of neural networks. Simultaneous electroencephalography [20], functional magnetic resonance imaging, cognitive testing, and other methods [21] can only partially address detection issues.

While clinical effects of TMS are recognized, changes in neural tissue at the cellular and molecular levels with different duration and intensity of stimulation have been poorly studied by cellular neurobiology. Experiments in laboratory animals are complicated due to a mismatch between the size of the coil and a stimulated area of the brain. Targeted exposure and correlating experimental data with clinical results are difficult.

Fundamental studies to evaluate neural morphology, functional activity, and cellular environment in response to a magnetic field with different parameters would significantly improve the efficacy of this method.

Aim. The aim of this review was to evaluate and summarize new experimental data on the fundamental mechanisms underlying the action of TMS and its potential in modulating structural and functional changes in nervous tissue.

This review included experimental studies mainly from the last 5–7 years that assessed structural and functional TMS-induced changes in the cellular elements of the nervous tissue using neuromorphology and neuroimaging methods. The search was carried out in the PubMed and Google Scholar databases.

General aspects of TMS

Most studies investigating the cellular mechanisms of TMS in laboratory animals involved stimulation of a hemisphere or the whole brain of rats and mice. Due to their small size, focal stimulation in rodents is difficult; however, it can be achieved by using mini-coils of different design (including ferromagnetic cores) or shielding materials [22, 23]. Early studies showed that local stimulation was achievable in rats using clinically used figure-eight coils. Such coils for rats allowed generating unilateral motor evoked potentials of a single limb, thus indicating the possibility of fairly local effects without significant changes in coil design [22]. Another approach to achieve a local effect is to reduce magnetic field intensity [24], which, however, is criticized due to difficulties in translating experimental results to humans.

Differences in brain size, magnetic induction intensity, and electrical field interaction with nerve tissue make translation of preclinical results difficult, although computer modeling can facilitate the selection of similar stimulation conditions [25] and analysis of electric fields generated in cell cultures [26]. Additional limitations of TMS in animal studies include the use of anesthesia in some cases.

However, the advantages of studying the effects of TMS in experimental animal models are also obvious: controlled experimental conditions, homogeneity of the study sample, use of genetic models of diseases, use of the entire arsenal of modern neuroimaging methods, including *in vivo* microscopy, and neuromorphological studies to assess off-line effect (Table 1).

TMS can be classified into single-pulse, paired-pulse, and repetitive TMS (rTMS). In the latter case, a series of pulses with different frequency and intensity is generated. rTMS can be roughly classified into low-frequency stimulation (0.2–1.0 Hz), which reduces neuronal excitability, and high-frequency stimulation (5 Hz or more), which has an excitatory effect [2].

Low-frequency rTMS most often uses continuous delivery of single pulses, while high-frequency rTMS typically uses a train of stimuli lasting 2–10 s separated by pauses of 20–50 s.

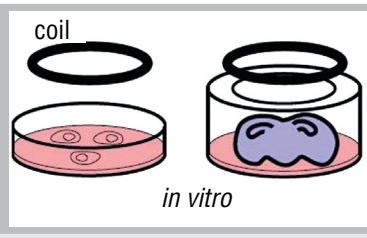
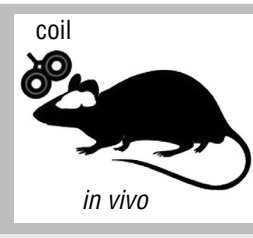
In addition to these conventional rTMS types, there are several other approaches, one of which uses θ-pattern, i.e. intermittent theta-burst stimulation (iTBS) or continuous theta-burst stimulation (cTBS) [3]. iTBS was shown to increase cortical excitability within 1 h of exposure while cTBS decreased it [27, 28].

Two groups of effects can be seen with TMS: online (during stimulation) and offline (after its completion).

A burst of action potentials is the most common online effect of single-pulse TMS at the neuronal level. The alternating magnetic field from the stimulator coil generates an induced electric field in the brain followed by an electrical current [29], with some neurons exhibiting combined activity. In this case, after the initial excitation, a long phase is observed, which combines periods of inhibition and excitation [30]. This phenomenon is likely to be caused by delayed activation of neighboring inhibitory interneurons. Not all neurons, even in the center of stimulation, respond to TMS. This heterogeneity in susceptibility to magnetic pulses may be due to differences in the local orientation of nerve cells relative to the TMS-induced electric field. The effect at the organism level also varies depending on coil orientation, with neural populations being recruited differently [31, 32].

According to modern concepts, the effects of TMS are most often associated with a neuroprotective effect, stimulation of neuro- and synaptogenesis, and optimization of synaptic transmission processes in the structures of the central nervous system [33, 34]. Pattern stimulation protocols and rTMS are used to induce an offline effect [35, 36].

Table 1. Summary of experimental methods to assess TMS effects

				
Object, assessed effects, level of organization	Cell cultures; online, offline effects; cell, intercellular interactions	Acute slices, online; cell, individual brain structures	Animal, online, offline; structures and systems	Mathematical model, online; structures and systems
Key study methods	Electrophysiology, fluorescence imaging, immunomorphology, biochemistry, molecular and biochemical methods	Electrophysiology, fluorescence imaging of fast processes	Electrophysiology, behavior (motor and cognitive tests), *in vivo* microscopy, immunomorphology, molecular and biochemical methods	
Excitation and synaptic transmission	+	+	+/–	Simulation of conditions and analysis of magnetic and electric fields in an object during stimulation
Proliferation, differentiation, and migration	+	–	+	
Intercellular, glioneuronal interactions	+	+/–	+	
Synaptogenesis	+	–	+	
Development of new clinical stimulation protocols	–	–	+/–	+

In response to rTMS, neuronal excitability changed due to a shift in the ionic balance around the population of stimulated cells. Depolarization dominates in the mechanism of excitability modulation, which resembles the induction of synaptic plasticity. However, hyperpolarization also plays an important role by influencing the membrane potential [37, 38].

Effects of TMS on synaptogenesis and synaptic transmission mechanisms

The functional effects caused by rTMS continue for a certain time after stimulation [39]. In addition to its effects on the metabolic cell profile and synaptic transmission, rTMS

causes changes in synaptic architecture. The most common theory suggests that this phenomenon is similar to synaptic plasticity mechanisms, such as long-term depression or potentiation, which are induced by stimulation of neuronal activity at different frequencies [40, 41]. According to modern concepts, the molecular mechanisms underlying structural and functional rearrangements of neural networks under the influence of TMS are associated with NMDA receptors on the postsynaptic membrane. For example, rTMS induced phenomena similar to long-term potentiation, thus triggering rearrangement of the actin cytoskeleton, which finally led to structural dendrite remodeling [42]. During long-term potentiation, dendritic spines first rapidly enlarge and deform due to increased actin polymerization and branching, and at following stages, proteins responsible for the functioning of postsynaptic densities and receptor clustering are attracted to the synapse area [43].

The effects of TMS on synaptogenesis and synaptic transmission processes were best studied in the motor areas of the cerebral cortex and hippocampus.

A.D. Tang et al. used two-photon imaging to track the plasticity of dendritic spines in the fifth layer of the motor cortex in mice of different ages. The study showed that a single train of subthreshold iTBS on the motor cortex increased the rate of dendritic spine loss 21 h after the session regardless of mice age and resulted in a significant decrease in the density of these structures 45 h after the session [44].

Meanwhile, a recent study showed that 5-day high-frequency rTMS (15 Hz) treatment increased total spine density in M1 L2/3 apical and basal dendrites 24 h post-stimulation in juvenile mice [45].

rTMS of hippocampal cell cultures was reported to induce clustering of postsynaptic AMPA receptors [42]. Data by M. Lenz et al. showed that high-frequency rTMS (10 Hz) *in vitro* affected synaptic transmission of predominantly excitatory synapses located on the proximal dendrites of cultured CA1 pyramidal neurons. AMPA receptor stimulation and retrograde membrane depolarization activated voltage-gated sodium and calcium channels and removed a reversible magnesium block from NMDA receptors [46]. This led to a local increase in calcium levels, rapid dendrite depolarization, generation of so-called "proximal area of dendritic plasticity" and a calcium-dependent increase in AMPA levels on the postsynaptic membrane of the dendritic spine. Moreover, selective pharmacological inhibition of NMDA receptors or α-1 subunit of calcium channels (L-VGCC) inhibited the rTMS effect on the proximal dendrites [47].

Dysfunction of neural networks may be explained by an imbalance of excitation and inhibition, so TMS effects on inhibitory synapses of neuronal circuits should be also considered. A study by M. Lenz et al. showed that 10 Hz magnetic stimulation affected Ca^{2+}/calcineurin-dependent oligomerization of gephyrin [48], a postsynaptic scaffold protein that mediates stabilization and clustering of ionotropic glycine and γ-aminobutyric acid (GABA-A) receptors. The main cluster of GABA-A receptors is located on the soma and axonal hillocks of hippocampal neurons [49]. Long-term potentiation of excitatory synapses (described above) was associated with gephyrin-mediated Ca^{2+}/calcineurin-dependent restructurization of inhibitory synapses. These structural and functional changes require activation of voltage-gated L-type sodium and calcium channels and NMDA receptors, and they were not observed when calcineurin protein phosphatases were pharmacologically blocked [50]. Accordingly, 10 Hz stimulation was associated with destabilization of gephyrin, GABA-A, and glycine receptor clusters and a decrease in the activity of inhibitory synapses.

A. Thomson et al. illustrated the excitatory effect of iTBS using SH-SY5Y cells (a human neuroblastoma cell line) pre-incubated with Fluo-4 AM, a fluorescent calcium indicator, as a synaptic plasticity model. A protocol similar to iTBS was associated with increased fluorescent response to the addition of KCl (depolarization-induced neuronal activation), while a protocol similar to cTBS was associated with decreased fluorescent response compared with control [51].

Phosphorylation of ribosomal S6 in neurons is known to be a marker of NMDA-dependent signaling pathway activation and induce synaptic and cellular changes that underlie plasticity. High-frequency TMS (400 Hz) was associated with activation of mTORC1 signaling pathway, which phosphorylates threonine at position 389 of S6 protein, thus activating rpS6 kinase. There was a more than 3-fold increase in rpS6 phosphorylation 15 min, 2 h, and 4 h after completion of high-frequency TMS. These effects were eliminated by treatment with rapamycin, which blocks the activation of this signaling pathway [52].

In a study with high-frequency (400 Hz) TMS in mice, there was an increase in the content of phosphorylated ribosomal protein S6 in the islands of Calleja and the paraventricular nucleus of the hypothalamus, ventromedial-lateral posterior nuclei of the thalamus, piriform cortex, and central nucleus of the amygdala [53]. A group of rpS6 phospho-mutant mice did not show any long-term potentiation and excitatory post-synaptic currents after high-frequency TMS (100 Hz) [54].

In hippocampal cell cultures, low-intensity TMS (1.14 T, 1 Hz) caused dendritic sprouting and an increase in synaptic contact density, while high-intensity TMS (1.55 T, 1 Hz) had a destructive effect, leading to a decrease in the number of processes and synapses. The authors showed that low-intensity low-frequency TMS (1.14 T, 1 Hz) could induce dendritic and axonal growth in cultured hippocampal neurons by activating brain-derived neurotrophic factor (BDNF)/extracel-

lular signal-regulated kinase (ERK) signaling pathway, which resulted in increased expression of postsynaptic density protein (PSD95) and synaptophysin [55], as well as postsynaptic membrane thickening [56].

According to other data, a protocol similar to iTBS (2-second trains of stimuli every 10 s, total exposure time 180 s) stimulated PSD95 and synaptophysin transcription, while low-frequency TMS did not have any similar effect [57].

Low-intensity TMS is associated with remodelling of abnormal neural connections into a topographically more appropriate position. Ephrin-A2/A5 double knockout mice lack key signals for axonogenesis and, therefore, have impaired topography of the visual pathways. Two-week low-intensity rTMS (10 mT; 10 min/day) reduced the number of abnormal projections in subcortical [58] and cortical visual circuits [59].

The metabolic profile of neurons pre-treated with TMS showed depleted pools of aspartate, phenylalanine and isoleucine, which was explained by the authors by the need to replenish the tricarboxylic acid cycle. Low-frequency TMS was associated with an increase in GABA synthesis and spontaneous release (which may be associated with decreased levels of pyroglutamate and alanine). The content of serine and glycine also decreased significantly after 1 Hz and 10 Hz stimulation, which is likely to be due to increased synthesis of proteins such as BDNF, c-fos, and various neurotransmitter receptors [60].

The cellular and molecular changes that are associated with synaptic plasticity and develop after TMS were illustrated by very few studies in animals and cell cultures with inconsistent results (Table 2). The most significant improvement in synaptic plasticity was found when high-frequency TMS (10 Hz) was used in cell cultures; however, there is no commonly accepted position regarding the intensity of the effect. Low-intensity TMS using various protocols led to positive effects in neuronal cultures but did not improve synaptogenesis at the organism level. Additional studies are needed to clarify the effects of TMS protocols, especially regarding the intensity of magnetic stimulation. An analysis of recent literature showed that fundamental experimental studies overall confirmed that some TMS protocols induced processes similar to long-term depression, while others induced long-term potentiation. However, delayed effects of TMS are often variable and depend not only on exposure parameters but also on previous neuronal activity and several other factors. The long-term effects of TMS may be mediated by a combination of different types of plasticity, including metaplasticity [61].

Table 2. Effects of TMS on synaptogenesis and synaptic transmission mechanisms

Effects of TMS	TMS type	Frequency, Hz	Effect	Reference
Positive	Low intensity	15	Density of dendritic spines on pyramidal neurons increased	[45]
		1	Dendritic sprouting and synaptic contact density increased through activation of BDNF/ERK pathway	[55, 56]
		10	Synaptic potentiation of predominantly excitatory synapses on proximal dendrites of cultured CA1 pyramidal neurons induced	[46]
		10	Structural and functional plasticity of inhibitory synapses induced	[48]
		400	NMDA-dependent pathways upregulated via mTORC1 pathway	[52]
		400	NMDA-dependent pathways upregulated through S6 increased	[53]
		6,67/10	Neuron connections remodelled	[58, 59]
Negative	Low intensity	50	Density of dendritic spines decreased after 45 h; loss rate increased after 21 h	[44]
	High intensity	1	Number of processes and synapses decreased	[56]

Neuroprotective and regenerative effects of TMS

Studies in experimental neurological disease models showed anti-apoptotic and restorative effects of low-intensity TMS, which were mediated by profound changes in regulatory cascades in neurons. In one study, rTMS treatment was applied at a frequency of 10 Hz, 10 min per day during 14 days to mice with spinal cord transection at the T9–T11 level; proteomic analyses showed a decrease in the levels of several pro-apoptotic proteins, such as annexin A2, thus contributing to neuron survival and remyelination. This study also demonstrated that TMS with these parameters was associated with increased proliferation of progenitor nerve cells of the spinal cord and increased levels of NEUM, CDC42, and RHOG proteins, which are known to cause increased axon growth and branching [62].

Another study showed that in middle cerebral artery occlusion TMS reduced neuronal death in the blood supply area by affecting apoptosis regulator proteins, enhancing anti-apoptotic Bcl-2 expression, and inhibiting pro-apoptotic Bax expression [63]. A study in a genetic Alzheimer's disease model showed that high-frequency TMS (25 Hz) reduced neuronal loss and apoptosis of hippocampal cells due to activation of PI3K/Akt/GLT-1 pathway, which is associated with decreased excitotoxicity [64].

However, TMS can also have detrimental effects on cells. Experiments on primary neuron cultures showed that 10 and 100 Hz modes with continuous stimulation were associated with an increase in the number of apoptotic cells [65].

In a study in a culture of primary hippocampal neurons, rTMS (40% and 60% of the maximum power of the stimulator) increased the expression of catalase and aconitase (i.e. iron-containing proteins that are involved in antioxidant protection) and increased neuron survival. It is interesting that high-intensity TMS accelerated their damage [66].

Therefore, different experimental models demonstrated that several TMS modes suppressed molecular mechanisms that underlie neuronal damage and death such as apoptosis, excitotoxicity, and oxidative stress. Continuous and high-intensity TMS exacerbated cell damage (Table 3).

Effects of TMS on neurogenesis and neuron differentiation

E. Ueyama et al. assessed BrdU incorporation into proliferating cells and showed that 14-day 25 Hz rTMS enhanced neurogenesis in the hippocampus of intact mice [67]. Studies in models of spinal cord damage showed that neural stem cells resting near the central canal of the spinal cord differentiated into astrocytes [68, 69] and oligodendroglia under the influence of TMS [62]. TMS effects on the proliferation, differentiation, and migration of neuronal precursors in neurogenic niches was best studied *in vivo* in stroke models in order to justify its use in patient rehabilitation.

In an ischemic brain injury model, 10 Hz rTMS promoted the proliferation of neuronal precursors in the subgranular zone of the hippocampus of experimental rodents. In TMS-treated animals, expression of BDNF, TrkB, p-AKT, and anti-apoptotic Bcl-2 was increased while expression of pro-apoptotic Bax was significantly decreased [63]. BDNF plays a critical role in promoting neuronal survival by specifically binding to tropomyosin receptor kinase B (TrkB). This binding results in auto-phosphorylation and dimeriza-

Table 3. Effects of TMS on mechanisms underlying neuroprotection and regeneration

Effects of TMS	TMS type	Frequency, Hz	Effect	Reference
Positive	Low intensity	10	Levels of several pro-apoptotic proteins decreased, those of proteins affecting axonogenesis and antioxidant enzymes increased	[62]
		10	Expression of anti-apoptotic Bcl-2 increased and expression of pro-apoptotic Bax suppressed	[63]
		25	Neuronal loss and apoptosis of hippocampal cells reduced	[64]
		Not specified	Expression of aconitase and catalase, which are involved in antioxidant defense, increased	[66]
Negative	High intensity	10/100	Number of apoptotic cells increased	[65]

tion of the TrkB receptor, thus triggering the activation of phosphatidylinositol 3-kinase PI3K. The PI3K/Akt signaling pathway is the main TrkB-mediated survival pathway that protects against apoptosis [70]. In a similar experiment with a similar frequency of stimulation, a significant increase in the expression of miR-25 (i.e. microRNAs that are involved in the differentiation and proliferation of neural stem cells) was shown in the subventricular zone [71]. High-frequency rTMS (20 Hz) also stimulated BDNF and pERK1/2 expression, which confirmed the influence of the BDNF/ERK signaling pathway on increased proliferation of neural stem cells in the hippocampus [72, 73]. The authors highlighted the similarity of the changes with the effects of antidepressants and electroconvulsive therapy.

Therefore, one of the mechanisms underlying the effects of TMS includes the enhancement of neurogenesis and repair processes due to stimulation of BDNF production, which promotes the survival of stem cells and neuronal differentiation, as well as the formation of new synapses. The neuroprotective effect of BDNF was shown in animal models of Alzheimer's disease [74, 75].

However, besides BDNF effects, other mechanisms were investigated. For example, N. Liu et al. found that the proliferation of neural stem cells *in vitro* after high-frequency rTMS was associated with a dose-dependent increase in expression of microRNAs of miR-106b~25 cluster (miR-106b, miR-93, miR-25), which are involved in cell cycle regulation [76].

In addition to enhancing neurogenesis in neurogenic niches, TMS was shown to have an effect on the migration of neurons to the damage area. For example, rTMS (10 Hz every 24 hours for 5 days) was associated with an increase in the levels DCX-positive neuronal precursors in the cortex in a hemorrhagic stroke model. In an *in vitro* experiment with neurospheres, the same authors showed an increase in the percentage of Sox2 and $Ki67^+$ cells, which suggested increased proliferation of neural stem cells associated with TMS (10 Hz every 24 hours for 72 hours) [77].

The study showed an increase in proliferation and a role of chemokine receptors in 10 Hz rTMS effects on the migration of neural stem cells from the subventricular area to the perifocal area of ischemic infarction. TMS was also associated with improved behavioral parameters of rats in this experiment [78].

Similar conclusions were made after staining with Nestin/SOX2 and Nestin/beta3-tubulin: rTMS increased the pool of neuronal progenitors in the peri-infarction area of the cerebral cortex in post-stroke setting. The number of immature neurons in the peri-infarction area was higher in animals exposed to rTMS; the authors concluded that cells migrated to the peri-infarction area due to the direction of $\beta3\text{-tubulin}^+$ processes [79].

Although most studies showed that TMS was associated with a improvement in neurological deficit in stroke models, it is still unclear whether TMS promotes the integration of newly formed nerve cells in the perifocal area of the infarction or recovery occurs due to other TMS-stimulated mechanisms such as the prevention of neuronal death, or the reorganization or restoration of neuronal connections.

There is little data on TMS effects on human neuron differentiation, although they are of particular interest in the context of the development of cell therapy methods. For example, a study in human neurons derived from induced pluripotent stem cells *in vitro* showed effects of different TMS protocols on neuron differentiation and maturation: high-frequency TMS promoted the differentiation of neuronal precursors into glutamatergic neurons, while iTBS enhanced synaptogenesis, suggesting its effect on neuron maturation [57].

The influence of TMS on differentiation of transplanted neural stem cells remains almost not studied. J.J. Peng et al. showed that animals with transplanted human neural stem cells who received TMS (10 Hz) demonstrated better functional recovery after ischemic infarction compared with animals with no TMS exposure; this was associated by the authors with the activation of the BDNF/TrkB signaling pathway that we discussed previously [80].

In these studies, the effect of TMS on neurogenesis both in the dentate gyrus of the hippocampus and the subventricular area was repeatedly demonstrated using immunohistochemical markers of neuronal precursor proliferation and neuronal differentiation. The vast majority of studies used high-frequency TMS protocols, most commonly 10 and 20 Hz. The stimulating effect of high-frequency TMS on the migration of progenitor cells to peri-infarction areas was consistently demonstrated. We can assume that TMS influences neurogenesis mainly through activation of the BDNF/TrkB pathway and effects on transcripts of genes that regulate the cell cycle.

Effects of TMS on glial cells

Although several studies did not reveal any direct effects of rTMS on glial cell cultures, changes in all types of neuroglia were repeatedly shown when pathological conditions were simulated. There is growing evidence that glial cells may actively participate in the neuroprotective effect of TMS [81].

Besides the direct response of gliocytes to TMS, which remains controversial, glia changes in mixed cultures or tissue can be also explained by increasing electrical activity of neurons, which cause a response in glial cells.

Closely interacting with neurons, astrocytes participate in the regulation of synaptogenesis. Addition of astrocyte-conditioned medium or their co-culturing with nerve cells in-

creased the number of functional excitatory synapses formed in the culture, while removal of astrocytes had the opposite effect [82]. Thrombospondins (TSPs) are factors that are secreted by astrocytic glia and associated with the regulation of synaptogenesis [83]. For example, TSP1/β-integrin signaling pathway controls the excitation/inhibition ratio in the spinal cord by upregulating glycinergic receptors and downregulating surface expression of AMPA receptors. Astrocyte-mediated TSP1/α2δ-1 signaling in the striatum was shown to modulate the activity of excitatory synapses [84].

Astroglia also controls the number of synapses through phagocytosis. Synaptic elimination is mediated by the transmembrane protein Megf10, which is expressed by astrocytes [85]. Astrocytes were shown to phagocytize synapses via the Megf10 and Mertk pathways in both developing and adult brains [86]. J. Lee et al. also confirmed that astrocytic Megf10 mediated the elimination of excitatory synapses in the CA1 region of the adult hippocampus [87].

Clustering of AMPA receptors at postsynaptic terminals of excitatory synapses, which may be astrocyte-dependent, is one of the mechanisms underlying synaptic plasticity, which is also seen with TMS. One of the mechanisms regulating the clustering process is mediated by ephrin A3 of astrocytic processes and its receptor EPHA4, which is expressed by dendritic spines [88, 89]. To support the connection between neuroplasticity and astrocyte response, we can mention a study by N. Monai et al. They showed that direct current-stimulated astrocyte response affected long-term potentiation of neurotransmission, was associated with fluctuations in Ca^{2+} levels, and depended on adrenergic receptors [90].

TMS (1 Hz for 10 min) increased STIM1 and ORAI3 protein expression in astrocytes; STIM1 protein acts as a sensor for Ca^{2+} stores depletion in the endoplasmic reticulum, while ORAI3 is a Ca^{2+} influx channel. This study demonstrated decreased expression of several inflammatory response genes in astrocytes associated with frequencies of 1 and 10 Hz [91].

A recent study in a mixed culture exposed to high-frequency TMS showed that astrocytes released a neurotrophic factor that induced the neuronal expression of ERK1/2 gene, associated with synaptic plasticity and neuronal activation, and immediate-early *c-fos* gene, thus confirming the bidirectional interaction of astroglia and neurons after stimulation [92].

High-frequency TMS and a very low-intensity magnetic field (0.5 mT) induced a transient increase in the expression of the astrocytic marker GFAP *in vivo* in mice after ischemic injury and reperfusion, which may indirectly indicate the recruitment of astrocytes to the damaged area (continuous 50 Hz exposure for 7 days) [93]. Similar data were obtained in a murine model of spinal cord injury. 1 Hz magnetic stimulation with 5-min sessions on 14 consecutive days induced GFAP expression by astrocytes and ERK1/2-dependent migration into the lesion areas [94].

A number of articles highlighted the role of microglia in the response of nervous tissue to TMS. In microglia-depleted tissue cultures, CA1 pyramidal neurons did not show any local depolarization of the postsynaptic membrane associated with 10 Hz TMS. Depletion of microglia *in vivo* had no significant effect on baseline synaptic transmission. In experiments with TMS, control mice with intact microglia showed spontaneous depolarizations of post-synaptic membranes (mEPSCs) in excitatory synapses in the medial prefrontal cortex vs. no such potentials in mice with depleted microglia [95].

S. Chen et al. showed that high-frequency TMS (20 Hz) was associated with an improvement in the cognitive functions of mice on day 28 after temporary occlusion of the middle cerebral artery. The volume of white matter lesions reduced, levels of pro-inflammatory cytokines decreased, and microglia switched to the M2 phenotype [96].

Oligodendrocyte proliferation was evaluated in several studies. Their results were inconsistent. G. Liu et al. reported stimulation of oligodendrocyte proliferative capacity [57] and induction of progenitor cell differentiation into oligodendrocytes in a study with high-frequency rTMS. A study by C.L. Cullen et al. did not confirm these effects [97]. Effects of iTBS and cTBS on oligodendrocytes were evaluated in Plp-CreER:Tau-mGFP and Pdgfra-CreERT2 transgenic mice. iTBS was shown to increase the number of newly formed oligodendrocytes [98].

Information about the effects of TMS on glia is currently insufficient, and this aspect requires further investigation. The neuroprotective effect of glial cells on ischemic and damaged tissues was shown indirectly. TMS modulates glia to create anti-inflammatory environment by switching microglia and astrocytes to a pro-inflammatory phenotype. A special role is played by TMS-induced release of glial cell neurotrophic factor from astrocytes, which leads to an increase in ERK1/2 expression in neurons. ERK1/2 activation is required for the BDNF cascade, which results in increased dendritic density and proliferation of neuronal progenitors. However, studies to investigate the effects of rTMS on glial cells are extremely scarce, so additional research is needed in this topic.

Conclusion

The effects of TMS discussed in the review, which are associated with the regeneration and restoration of nervous system functions, cell differentiation, and stimulation of synaptic plasticity, can substantiate the use of this method in cell therapy of neuropsychiatric disorders. However, many questions remain unresolved. The effect of TMS on

the differentiation and maturation of neuronal precursors is little studied. Isolated effects of TMS on glial cells remain a controversial issue.

Many studies in cell cultures were conducted using frequencies that are not relevant for clinical practice. Special attention should be paid to standardizing the intensity of stimulation, since in affects glial and neuronal responses. It should be remembered that results obtained in cell cultures do not always correlate with the response at the organism level.

Further studies to evaluate the mechanisms of TMS would contribute to the development of more effective treatment protocols with this method.

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