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TRANSCRANIAL MAGNETIC STIMULATION IN THE TREATMENT OF OBSESSIVE-COMPULSION DISORDER

Abstract. Relevance of the research. Transcranial magnetic stimulation is one of the non-invasive, widely used methods, used for the treatment of mental disorders for the last two decades in many countries of Europe and the USA. This method has also successfully proven itself and is used in the practice of Ukrainian psychiatrists and neurophysiologists. The advantage of this method is not only the painlessness of application but also the practical absence of side effects, in comparison with prolonged use of antidepressants. The effectiveness of eliminating intrusive thoughts, anxiety, and restlessness by using localized electrical stimulation, compared with pharmacotherapy and psychotherapeutic methods, shows significantly better treatment results in patients with a different course of the disease, regardless of the somatic state of health, the presence of concomitant diseases, age of the patient.

The aim of the research. To review the advantages, side-effects, and contraindications for the use of nonmedical and non-invasive transcranial magnetic stimulation in the treatment of the obsessive-compulsive disorder.

Research method. The theoretical basis for this study is the review of the application of the rTMS method in patients with obsessive-compulsive disorder, based on the experience and earlier scientific researches in Ukraine and abroad.

Results. The basic types of transcranial magnetic neurostimulation as one of the non-invasive treatment methods in psychiatry have been analyzed, studied based on many randomized studies, and practically applied for obsessive-compulsive disorder treatment. Based on these studies, the therapeutic efficacy and safety of rTMS for obsessive-compulsive disorder have been evaluated. The strategy of using both repetitive transcranial magnetic stimulation (rTMS) and deep transcranial magnetic stimulation (dTMS) in psychotherapeutic practice goes beyond the pharmacological and psychological treatment of patients with obsessive-compulsive disorder and is often used to treat persistent forms of this disorder. Prolonged and repeated use of

both methods results in changes in the excitability of the person's cortex who experiences a period of stimulation. Recent research in psychoneurophysiology proves that application of both repetitive and deep electrostimulation methods induces functional changes in nervous activity, modulates the brain at the cortical level.

Keywords: non-invasive magnetic electrostimulation, obsessive-compulsive disorder, neuromodulation, repetitive transcranial neurostimulation, psychiatric disorder, deep transcranial neurostimulation.

Introduction. According to scientists, about 3% of Ukrainians suffer from obsessive-compulsive disorder (OCD). The peak of this pathological condition, as a rule, develops in childhood or teenage years. For adults - till the age of twenty-five. The presence of this type of mental condition of chronic character is accompanied by significant material costs [1]. For example, according to Fineberg et al. (2020), a program from the Epidemiologic Catchment Area (ECA) special study, the cost of treating OCD in the United States is more than \$8 billion per year [2].

OCD as a pathological condition occurs quite often. According to surveys of citizens, this pathology ranks fourth in prevalence after depression, alcohol abuse, drug abuse, and social phobia. A person in a state of anxiety, fear, and worry can often hide their condition even from their own family. This type of disorder leads to problems in relationships, interferes with studies, work, and becomes a serious problem of the patient's interaction in society. Often when OCD develops, the consequences are unfortunate for the patient's health. For example, fear of infection, constant hand-washing, and washing can lead to the development of dermatitis, and "oversharing" behavior causes distraction and lack of attention to other, more important aspects of assessing one's health status. According to the WHO, OCD's presence is one of the biggest problems, reduces a person's standard of living, and becomes the cause of her loss of income [3].

As evidenced by epidemiological studies, most patients do not often receive specialized treatment. There is a problem with the early diagnosis of OCD at the beginning of the disease. Studies in the United States have shown that more than half of patients do not receive adequate treatment due to the lack of medical professionals with the necessary qualifications and competence to detect this type of pathology in its early manifestations [3].

In the last decade, TMS has become a new treatment option for OCD. It has evolved from a purely experimental treatment to a widely available therapy, confirmed by studies that demonstrate its effectiveness. Because TMS does not require surgery and is an increasingly affordable treatment option, it is in substantial demand among practicing neuropsychologists and patients alike.

To treat OCD quickly and effectively, the safest treatment needs to be introduced, as young and working-age populations are often ill, which can lead to

significant social and material consequences in the future.

Literature review. The separate aspects of the application of the transcranial magnetic stimulation method in the treatment of obsessive-compulsive disorder and its obvious advantages are covered by Ukrainian scientist Oros M. (2018) [4]. Practical application of the non-medical method of treatment of anxiety disorders, depression by transcranial magnetic stimulation is carried out based on the state institution "Institute of neurology, psychiatry, and narcology of the Academy of Medical Sciences of Ukraine" [5]. Advantages of transcranial magnetic stimulation method application for treatment of many neurological diseases are actively covered and have practical application in Educational Scientific Medical Center "University Clinic" of Zaporozhe State Medical University [6].

According to Young et al. (2017), which is the use of rTMS as an alternative treatment technique for OCD, proves that in this analysis, symptoms in treatment-resistant patients with obsessive-compulsive disorder decreased after 20 sessions, without cognitive decline or serious adverse reactions [7]. A pilot study by Mantovan et al. (2021) conducted jointly by American and Italian neurophysiologists, shows that a daily double session of rTMS is safe and effective and has a positive effect on obsessive-compulsive behavior [8]. In a scientific study conducted by Cocchi et al. (2018), TMS is described as a non-invasive therapy used to normalize brain activity and relieve some psychiatric symptoms [9].

New research shows that non-invasive electrical stimulation, personalized according to the activity pattern of the brain departments that control reward, can reduce compulsive behavior. One new study shows that transcranial electrical stimulation is associated with reductions in compulsive and compulsive behavior. Even in some participants with severe symptoms, the study showed good and effective results from the effects of TMS. Reinhart R., Ph.D., and lead researcher at the Center for Systems Neuroscience at Boston University (Boston, Massachusetts) rated this result as "promising because it suggests that neuromodulation may be beneficial in severe clinical situations such as obsessive-compulsive disorder and substance use".

LeMonda W., Ph.D., senior neuropsychologist at Lenox Hill Hospital (New York, USA), commented on the use of TMS: "the results are very promising because we have limited treatment for severe OCD, we can add to our scheme, help patients relieve symptoms - this is great," what struck me is that patients had symptom relief within about 3 months, and those with severe symptoms also had positive effects from treatment, really remarkable because many of these patients as right

The study conducted by Pallanti et al. (2016) indicated that rTMS over an additional motor area was effective in about 2/3 of patients with OCD refractory to SSRIs (selective serotonin reuptake inhibitors). The additional motor area may be a new target area that should be further investigated with neuromodulation for the treatment of OCD [11].

A scientific paper by Euser et al. (2017) involving 502 patients, analyzed the effect and duration of rTMS compared to the placebo effect in the treatment of resistant OCD. A consistent treatment effect was found for rTMS compared to placebo stimulation, which lasted from several weeks to three months [12].

Freire et al. (2020) describe in their study the effectiveness of rTMS not only in treating persistent OCD but also in treating other anxiety disorders and posttraumatic stress disorder. Also, this study compares rTMS treatment with electroconvulsive therapy, transcranial direct current stimulation, vagus nerve stimulation, and trigeminal nerve stimulation, where not only are these treatments less effective for OCD but also in comparison their invasiveness is higher [13].

That rTMS is an alternative treatment option with proven efficacy, especially for OCD, depression, schizophrenia, Alzheimer's disease, resistance to drugs is also described in a study by Pastuszak et al. (2016) [14].

Resistance to medication and psychotherapy in about 30-40% of patients with OCD is described in a study that reviews the state of the art on the causes, diagnosis, clinical data, and treatment strategies of patients with resistant OCD [15].

The negative effects on the lives of patients and their relatives are described in the study Dell'Osso B. et al. (2018), which indicates that with OCD frequent suicide attempts, significantly worsen the lives of patients and their caregivers [16].

The use of TMS is a safe method, as one of the studies described by Ugur D. et al (2020) describes how this method of treatment was used in a patient with epilepsy in the 3rd trimester of pregnancy, ended in the birth of a healthy, full-term baby [17].

The safety of rTMS is described in a study by Laura et al. (2019), which highlights that the technique is becoming safe, has good tolerability, and is a potentially effective therapeutic strategy for several childhood psychiatric and neurological disorders [18].

The TMS method is an alternative treatment option for OCD in many patients and is effective and safe in the studies described above. However, there are many unresolved issues in this method, which require further research, especially, concerns TMS application schemes in children and adolescents. Therefore, high-quality randomized controlled trials in this direction should be conducted in the future.

The aim is to analyze the benefits, contraindications, and side effects of transcranial magnetic stimulation in the treatment of obsessive-compulsive disorder as one of the components of non-medicinal therapy. An important task of this work is to review randomized controlled trials of rTMS and dTMS stimulation over different brain regions in OCD, using different stimulation parameters.

Materials and Methods. The theoretical basis for this research, is a review of the use of rTMS in patients with obsessive-compulsive disorder, based on experience and previous scientific studies in Ukraine and abroad. Participants of the study were patients with obsessive-compulsive disorder diagnosed according to any criteria, regardless of sex, age, or nationality.

Results. Electrical activity of the brain has sparked interest for more than two centuries, with electrophysiology becoming the "prominent" method of visualizing brain function. In recent years, the field of affective neuroscience has become richer. The availability of sophisticated neuroimaging techniques and new neurostimulation techniques that can detect, monitor, and correlate neural changes with affective, cognitive, and behavioral processes has stimulated the development of neurophysiology. The recognition that neural networks are interconnected and "communicate" at different levels has contributed to a better understanding of neurobiological concepts related to mental disorders. However, consistent treatment outcomes for complex mental disorders, such as OCD, have not been fully understood.

The basic principles of OCD treatment worldwide indicate the effectiveness of both medication and psychological treatments. The first-line drugs of primary treatment recommendations include serotonin reuptake inhibitors, including SSRIs or clomipramine drugs. Also among the mainstream treatments is a strategy of cognitive behavioral therapy to prevent exposure/response. About half of patients do not notice a clinically significant effect from the use of (SSRIs); about 1/3 of patients have a positive effect from the use of another active ingredient in this group of drugs. Second-line treatments for OCD include treatment with antipsychotics and the use of complementary therapies such as motivational interviewing, exercise, cognitive therapy, and acceptance and attachment therapy. However, most patients find these therapies to be symptomatic and unsustainable in achieving a meaningful clinical effect. For this reason, new therapies that directly affect OCD, have the fewest side effects and can be used with minimal contraindications, such as compared to pharmacotherapy (Table 1), have long been of interest to psychiatric and neuroscientific scientists in many countries around the world.

Table 1

Correlation of medication and TMS eligibility criteria in the treatment of obsessive-compulsive disorder

Name	TMS	Pharmacotherapy
The need for in-treatment	No matter if applied in outpatient treatment	Intake, both outpatient and inpatient
Development of addiction	Not formed	Formed
Existence of concomitant pathology	Not important, only in extreme cases	Important
Patient's age	Not important	Important
Presence of implanted pace-makers, stent systems	Contraindicated	Applied

The neurobiology of OCD is well known; understanding neurocirculation can help inform treatment, particularly approaches to brain stimulation and brain lesions. Neurobiological models of OCD describe changes in the cortico-striate-thalamocortical circuits responsible for emotional, cognitive, and motor functions. Other areas of the brain, such as the limbic and parietal regions, have also recently been studied in this aspect.

Historically, neurosurgery has been considered the last treatment for OCD after pharmacological and psychotherapeutic strategies for the disorder have been exhausted. The primary target is the cingulate gyrus and the anterior limb of the internal capsule connecting the cortex to the thalamic nuclei. Such interventions have demonstrated varying levels of efficacy with variable long-term success. During the last two decades, interest in non-invasive neuromodulation has emerged, including rTMS and dTMS, the latter method is the newest. rTMS uses a low-intensity magnetic field applied to the surface of the scalp using specially designed coils to induce neurophysiological changes in the cerebral cortex and subcortical area. Neurostimulation protocols include low-frequency waves that cause decreased neuronal activity in the cortex and high-frequency waves that increase cortical activity by promoting synaptic neuronal activity. The dTMS uses specially designed coils to reach deeper subcortical structures while generating a localized magnetic field.

Principle of Action: TMS is a non-invasive way to "stimulate" or change activity in the brain using magnetic fields. During treatment, patients sit in a chair while the TMS device is pressed against the outside of the head. There is a wire coil inside it. When an electric current is passed through this coil, it generates a magnetic field. The magnetic field passes through the hair, scalp, muscles, and skull and reaches the brain, where the magnetic field changes brain activity. This magnetic field can be targeted to reach and stimulate certain areas of the brain, including those that have a place for OCD development. The patient may feel tapping on the head during the treatment, but people who receive TMS do not experience painful sensations. Patients do not receive sedation during the procedure; discomfort is usually mild. TMS treatment is usually done as an outpatient. Treatment sessions last on average 5 days a week for 4-6 weeks. The advantage of this method is that the person who has undergone a TMS session may immediately return to habitual activity, not exclude it from his/her usual way of life, disconnection from the family and work.

TMS is impossible without a combination of the three components of the process, namely the coil, the protocol that determines at what frequency the coil must be implemented, and the areas of the brain where the generating impulses must be directed. rTMS devices generate magnetic waves to a specific area of the brain in a series of repetitive pulses. dTMS also provides a repetitive series of pulses, but the coil design allows these pulses to reach deeper brain structures and target areas inaccessible to standard rTMS devices. The stimulation protocol determines at what

frequency the pulses are repeated: high frequency, low frequency, intermittent burst (iTBS), continuous burst (cTBS). The iTBS and cTBS protocols can shorten treatment sessions by as little as 5 minutes, compared to 40 minutes for other protocols, but all of these protocols are still being studied and are not as widely used. The magnetic pulses generated by the coil can be directed at different parts of the brain, including those that can be affected by OCD. Several studies have analyzed that using rTMS to target the dorsomedial prefrontal cortex, anterior supplemental motor area, and bilateral, right dorsolateral prefrontal cortex has positive therapeutic effects on OCD patients.

In examining published systematic reviews and meta-analyses in recent years that focus on the overall effectiveness of neurostimulation for OCD, the results are mixed. Such examinations have not investigated the neurobiological rationale for modulation of different brain areas, subordinating the neurobiological mechanisms that cause obsessive, compulsive, and anxiety disorders in OCD. Existing systematic reviews and meta-analyses of neuromodulation in OCD have not fully explored the heterogeneity of treatment parameters [19].

In a study of the results of rTMS treatment of OCD, the appearance of a favorable clinical effect after 14 days, lasting up to 14 weeks, has been noted. The use of rTMS offers a treatment approach with a mechanism of action that can directly affect the pattern of obsessive and compulsive symptoms [20].

Non-invasive neurostimulation interventions targeting cortico-striate-thalamocortical circuits hold promise as an enhancing intervention in treatment-resistant OCD. rTMS is a better studied non-invasive modulatory intervention in OCD. This technique is thought to be delivered with low-frequency waves (≤ 1 Hz) that suppress subcortical brain activity, whereas high-frequency waves (≥ 5 Hz) enhance cortical activity. Conventional rTMS presented through a simple coil is relatively focal while modulating only superficial cortical areas at a depth of about 2 cm. LF-rTMS protocols targeting the supplementary motor area (SMA) are useful for the treatment of OCD established on meta-analyses. In the process, it was investigated that this effect can last up to three months.

In contrast, the use of techniques targeting the dorsolateral prefrontal cortex, compared to major depressive disorder, has been found to have very negative results with OCD. A multicenter randomized trial has shown that high-frequency deep rTMS when acting over the dorsomedial prefrontal cortex is effective and well-tolerated in treatment-resistant OCD populations. But, given the cost of this device, there is a need for repeated studies that can confirm the efficacy of the above protocol [21].

According to individually randomized trials, conventional TMS only allows stimulation of focal targets, without navigation rTMS misses the target in 27-32% of patients. In an attempt to eliminate these limitations, a new method of dTMS was introduced, which includes all the advantages of rTMS (no need for hospitalization or anesthesia, minor side effects) with a predominance of stimulation of deep brain

targets with a smaller focal distribution of the electric field. Similar to the traditional rTMS technique, dTMS uses short magnetic pulses to induce targeted depolarization of neurons in the brain using Faraday's law of electromagnetic induction. Usually, sequences of pulses delivered by high-frequency stimulation result in a facilitation effect, causing increased neuronal excitability. In this way, it is possible to modulate hypo- or hyperactivity of specific brain regions. With conventional TMS coils that directly stimulate targets up to 1 cm below the skull surface, dTMS can simulate up to 4 cm below the skull surface, depending on the coil that is used. This increased depth of stimulation is achieved by multiple windings in multiple planes within the helmet coil. The magnetic fields of these windings summarize and improve the depth penetration of the electromagnetic field without the need to increase the electrical intensity [22].

The application of the dTMS method in OCD treatment appeared after the effectiveness of deep brain stimulation on subcortical structures was observed. This method develops as the application to the study of non-invasive methods of stimulation of deep structures of a brain. Dual-cone and H coils have been developed to reach and stimulate deep subcortical structures of interest in OCD, which have been consistently involved in neurostimulation through neuroimaging results and observations of improvement in OCD symptoms after preliminary cingulotomy.

Several studies have been conducted on the side effects and harmfulness of the TMS method, one of which states that the method is well tolerated, with an adverse event rate of 4.5% among 300 patients. The side effects are mild, mostly limited to temporary discomfort or pain in the scalp, spasms, or short-term twitching of the facial muscles. Seizures, hypomania, or mania (mostly in patients with the bipolar psychiatric disorder) were among the rare side effects that were common in patients with concomitant neuropsychiatric pathology.

Contraindications to the use of this OCD treatment include the presence of a stent in the neck or brain, the presence of metal implants in the ears or eyes, the presence of bullet fragments in the head, facial tattoos with magnetic ink, implanted stimulators similar to those used in deep brain stimulation. Patients with co-occurring mental health disorders, such as depression, should be sure to report their symptoms to their physician before beginning TMS treatment.

Discussion. TMS is a new research technique used to investigate various neural processes and treat various neuropsychiatric diseases, with few, if any, side effects. The most moderate advantage of TMS is its ability to directly stimulate the cerebral cortex with little effect on the surrounding tissues. A new neurostimulation technique, rTMS shows promise as an integral part of the OCD treatment toolkit [23]. Its non-invasiveness, good tolerability, and the small spectrum of side effects make it attractive for treatment and wide practical use. The basic neurobiological mechanisms associated with TMS are still being evaluated, but the effectiveness of this method in patients with a long-term course has already been proven [24].

In the future, in addition to addressing methodological issues that have arisen in earlier studies, it will be interesting to consider rTMS as a strategy used at the beginning of the treatment process and to consider the possibility of parallel stimulation of multiple cortical brain regions [25]. Also, rTMS can be evaluated as an option in patients who have not received medication and have limited benefit from psychotherapy techniques. Advances in targeted brain stimulation through the development of novel coils combined with functional neuroimaging offer a step further in understanding and treating OCD [26].

The interpretation and generalization of periodic TMS findings in OCD are beset by a certain number of methodological differences across studies. For example, there is great variability among studies in terms of characteristics such as the age of onset of OCD, severity, subtype of OCD, duration of disease, treatment plan, and stimulation protocols [27]. Age of onset and duration of disease may affect the degree of response to recurrent TMS, as both may be associated with comorbidities and treatment resistance [28]. The severity of OCD may additionally affect the degree of therapeutic effect. For example, in depression, where the severity of the disease has demonstrated a rate of remission with repetitive TMS [29]. Therefore, patients with mild to moderate disease respond better to treatment.

Another challenge for the study of this issue is to determine how different brain regions are responsible for mediating different degrees of OCD symptom manifestation [30]. Understanding this may allow an assessment of which brain regions will respond to rTMS separately in each patient. Larger studies may provide more statistical power to identify meaningful treatment effects.

Conclusion. In a summary, TMS is a new and progressive area of development for the treatment of resistant cases of OCD. The main advantage of using this method is that there are virtually no contraindications, adverse reactions are rare, mostly manifested by minor discomfort, which are temporary in nature. A characteristic difference from other methods of treatment, such as pharmacotherapy or psychotherapy is that TMS is a safe method that can be used in patients of any age, the therapeutic effect is more durable and stable. Given that OCD most often affects young, able-bodied individuals, the use of TMS is justified to preserve social well-being and prevent the development of economic losses in the population. This study and previous observations indicate favorable effects of the practical use of non-invasive brain stimulation, which is the basis for further research in this direction.

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