EXPERIENCE OF STANFORD NEUROMODULATION THERAPY IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

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Stanford neuromodulation therapy (SNT) is the state-of-the-art magnetic stimulation protocol that has been developed for management of treatment-resistant depression (TRD). The study was aimed to assess the possibility of SNT implementation in clinical practice and to define the protocol safety and efficacy in patients with TRD being an episode of the recurrent depressive disorder or bipolar disorder at the independent center. The study involved six patients (among them three women aged 21–66) with TRD associated with recurrent depression and type 1 or 2 bipolar disorder. The patients received intermittent theta-burst stimulation in accordance with the SNT protocol for five days: applying 10 triple blocks of stimulation daily at intervals of 1 hr between the blocks to the selected stimulation site showing maximum negative functional connectivity with subgenual cingulate cortex within the left dorsolateral prefrontal cortex. The Montgomery–Asberg Depression Rating Scale (MADRS) was used for clinical assessment of the effects, the follow-up period was three months. The improvement of depressive symptoms to the levels characteristic of remission immediately after the SNT completion was observed in five patients (MADRS score ≤10). After three months, two patients still had remission, the condition of three patients met the criteria of mild depressive episode, and one female patient withdrew from the study due to logistical difficulties. No serious adverse events were reported. The findings confirm safety and potentially high efficacy of SNT, including in patients with type 1 and 2 bipolar disorders.

Keywords: treatment-resistant depression, bipolar disorder, transcranial magnetic stimulation, theta-burst stimulation

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Compliance with ethical standards: the research protocol was approved by the Ethics Committee at the Research Center of Neurology (protocol № 11-1/21 of 22 December 2021); the study was conducted in accordance with the principles of the Declaration of Helsinki; the informed consent was submitted by all study participants.

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ОПЫТ ПРИМЕНЕНИЯ СТЭНФОРДСКОЙ НЕЙРОМОДУЛИРУЮЩЕЙ ТЕРАПИИ У ПАЦИЕНТОВ С ТЕРАПЕВТИЧЕСКИ РЕЗИСТЕНТНОЙ ДЕПРЕССИЕЙ

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Стэнфордская нейромодулирующая терапия (SNT) — новейший протокол магнитной стимуляции, разработанный для лечения терапевтически резистентных депрессий (ТРД). Целью исследования было оценить возможности реализации SNT в клинической практике, определить безопасность и эффективность протокола в независимом центре у пациентов с ТРД в рамках рекуррентного депрессивного и биполярного расстройств. В исследование вошли шесть пациентов (из них три женщины в возрасте 21–66 лет) с ТРД в рамках рекуррентной депрессии и биполярного расстройства 1-го и 2-го типов. В течение пяти дней пациентам проводили стимуляцию интермиттирующими тета-вспышками по протоколу SNT: ежедневно по 10 тройных блоков стимуляции с интервалом 1 ч между соседними блоками и выбором зоны стимуляции с максимальной негативной функциональной коннективностью с субгенуальной поясной корой в пределах левой дорсолатеральной префронтальной коры. Для клинической оценки эффекта применяли шкалу Монтгомери–Асберг, длительность периода наблюдения составила три месяца. У пяти пациентов сразу после окончания SNT отмечено снижение выраженности депрессии до уровня ремиссии (≤10 баллов по MADRS). Через три месяца два пациента оставались в ремиссии, у троих состояние соответствовало легкому депрессивному эпизоду, одна пациентка выбыла из исследования из-за логистических трудностей. Серьезных нежелательных явлений не зарегистрировано. Полученные результаты подтверждают безопасность и потенциально высокую эффективность SNT в том числе при биполярных расстройствах 1-го и 2-го типов.

Ключевые слова: терапевтически резистентная депрессия, биполярное аффективное расстройство, транскраниальная магнитная стимуляция, стимуляция тета-вспышками

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High prevalence of treatment-resistant depressive (TRD) determines the relevance of developing new effective non-drug approaches to treatment of this condition [1–3]. The noninvasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), can be considered the non-pharmacological methods most widely used in clinical practice. According to the existing concepts, the long-term effects of stimulation result from induction of processes similar to the processes underlying synaptic plasticity, and are mediated by NMDA and AMPA receptors [4]. Along with modulation of synaptic plasticity, the impact of rTMS on neurogenesis and neurotransmitter secretion, together with physical effects of electromagnetic fields, continue to be discussed [4, 5].

Large double-blind controlled trials provided strong evidence of the efficiency of using non-invasive stimulation methods in treatment of depression [6, 7]. According to current guidelines, high levels of evidence for the effects of using rTMS and theta-burst stimulation (TBS) in treatment of TRD were reached [8]. The U. S. Food and Drug Administration (FDA) approved two protocols for management of TRD: high-frequency (10 Hz) rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) in 2008, and intermittent theta-burst stimulation (iTBS) of the left DLPFC in 2018 [9]. However, despite a rather strong evidence to support the use of the listed above stimulation protocols in patients with TRD, pronounced variability of the effects is the main constraint on greater use of the protocols. Thus, according to two largest meta-analyses, the patients who respond to therapy with rTMS constitute 25–55%, and clinical remission can be achieved only in 16–30% of cases [10, 11]. Increasing the efficiency of stimulation and reducing the effect variability are the major challenges faced by researchers.

Several approaches to increasing the efficiency are currently being developed. Personalized target selection and the use of so-called accelerated protocols could be considered the most promising and well understood in the context of TRD. A personalized approach to the stimulation target selection was proposed in 2012 that was based on the analysis of functional connectivity (FC) between the subgenual cingulate (Sg) and left DLPFC [12]. The approach is based on the data on the altered functional connectivity of Sg in patients with depression [13], as well as on the relationship between the clinical effects of rTMS and FC between the stimulated site and Sg [12]. However, when comparing the effectiveness of rTMS using personalized and standard approaches, heterogenous results were obtained [14, 15]. Protocols, that include several sessions of stimulation per day aimed at achieving the total numbers of pulses significantly above the standard values, are called accelerated protocols. According to recent meta-analysis that includes studies involving accelerated protocols, the use of such protocols has a moderate effect and still does not solve the problem of high variability [16].

Finally, the protocol combining target selection based on the analysis of FC and extremely large number of pulses (18,000 pulses per day vs. 3000 and 600 pulses per day in standard rTMS and TBS protocols) was developed in 2019, called Stanford neuromodulation therapy (SNT) [17]. According to the pilot data of the open-label trial, 90% of patients, who received SNT, achieved remission (defined as the Montgomery–Asberg Depression Rating Scale score below 11), which was well above the effectiveness of the previously used protocols [17]. In 2022, the same group published the results of the double-blind controlled trial that showed significant effects of SNT compared to sham stimulation, confirmed safety and a very high proportion of responders and remitters [18].

But so far the findings have not been confirmed by other research groups. Furthermore, the patients diagnosed with major depressive disorder (major depression) were included in the original study, while no studies of safety and efficacy of SNT in patients with depressive episode associated with bipolar disorder were performed.

Thus, the pilot study was aimed to assess the possibility of the SNT protocol implementation in clinical practice and to acquire data on the protocol safety and efficacy at the independent center, particularly in the new cohort of patients with bipolar disorder.

METHODS

Patients

The patients were recruited at the Moscow Research Institute of Psychiatry, the branch of V.P. Serbsky Federal Medical Research Center for Psychiatry and Narcology, and SNT was performed at the Institute of Neurorehabilitation, Research Center of Neurology, in 2022.

Inclusion criteria: ongoing mild-to-moderate drug-resistant depressive episode associated with recurrent depressive disorder or bipolar disorder; age 18–70 years; no contraindications to MRI and TMS; no severe general medical condition that requires maintenance of vital functions using the life-support devices; no severe cognitive impairment or other nervous system disease. Drug resistance was defined based on the absence of clinical effects after two or more courses of treatment with antidepressants of various groups used in adequate doses for at least 4 weeks [19, 20]. Some patients continued to receive the unchanged doses of antidepressant, antipsychotic, and anxiolytic medications. Exclusion criteria: serious adverse events (SAEs) during TBS, such as epileptic seizure, syncope, intense headache; onset of severe general medical condition or mental disorder, nervous system disease after the study enrollment, as well as pacemaker insertion, cardiac catheterization, brain surgery that requires metal objects retained in the cranial cavity, getting pregnant, or refusal to participate further in the study.

Prior to stimulation with the use of the Neuron-Spectrum-4/P (Neurosoft; Russia) and actiCHamp Plus 64 (BP-100-2511) (Brain Products GmbH; Germany) systems the patients underwent screening EEG aimed at detecting epileptiform discharges. The patients, who showed epileptiform discharges, were excluded from the study.

Identification of stimulation target

To perform target localization for stimulation, all patients underwent neuroimaging on the Magnetom Prisma 3T system (SIEMENS; Germany) that included two sequences: T1-weighted images were acquired at isotropic resolution for further multiplanar reconstruction (MPR) aimed at obtaining structural data (TR 2200 ms, 1 mm slice thickness, number of slices 176), and multiplanar gradient echo mode (ep2d_bold_moco: TR 2200 ms, 36 slices in the axial plane) was used for assessment of functional connectivity. The targets for stimulation were determined for each patients based on assessment of the resting-state functional MRI data. Neuroimaging data were preprocessed in the CONN functional connectivity toolbox (Functional Connectivity SPM Toolbox 2017, McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, USA; http://ww.nitrc.org/projects/conn), ver. 17f, and SPM12 (Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/

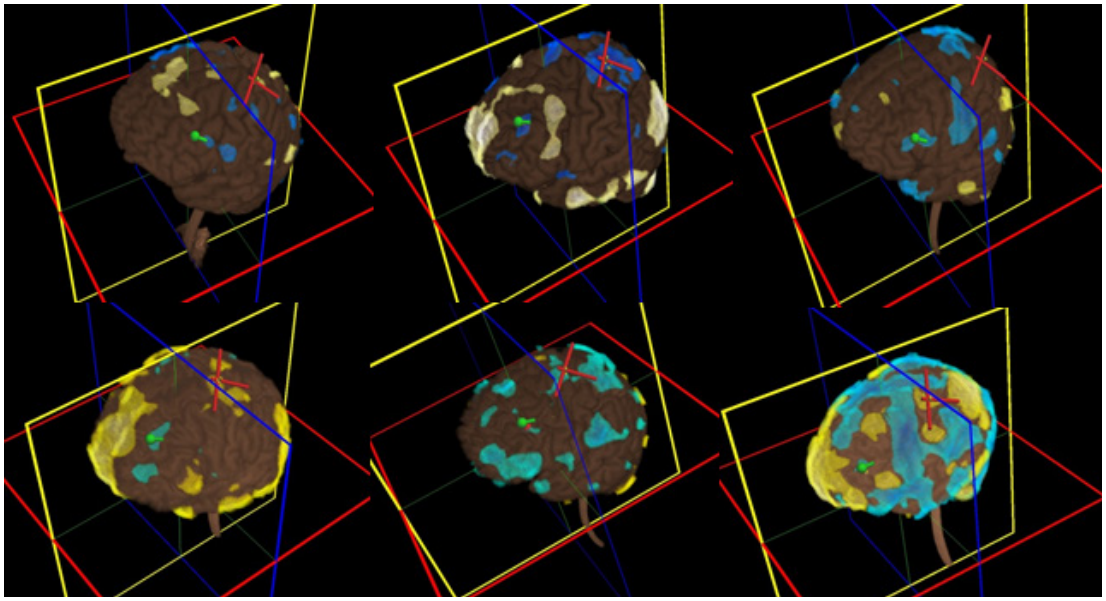

Fig. 1. Visualization of the functional connectivity (FC) analysis data and target selection in patients. Color shows FC values between the subgenual cingulate and the visualized cortical areas. The target is marked with a *green tag*

spm/software). Preprocessing consisted of the earlier reported standard steps [15]. After preprocessing, the maps showing FC of subgenual cingulate with all other brain regions were created individually for each patient using the same software package, the region was selected within anatomical limits of left DLPFC that showed maximum negative FC (Fig. 1). A 10-mm diameter sphere generated around the subgenual part of the cingulate gyrus (Sg) (a point with MNI coordinates (6, 16, –10)) was used as a seed region.

Stimulation protocol

Intermittent theta-burst stimulation was performed with the MagPro X100 MagOption system (Tonica Elektronik A/S; Denmark), equipped with the liquid-cooled figure-eight coil, in combination with the Localite TMS Navigator navigation system (Localite GmbH; Germany) and Axilum Robotics TMS-Cobot robotic device (Axilum Robotics; France). The stimulus intensity was 120% resting motor threshold defined by recording motor evoked potentials (MEPs) of the right first dorsal interosseous muscle in accordance with the Rossini–Rothwell algorithm. Stimulation was performed for five consecutive weekdays. Every day, the patients were through 10 sessions of intermittent theta-burst stimulation with a 1-hr interval between sessions. Each session included tree standard blocks of theta-burst stimulation (600 pulses/block). Thus, the patient received a total of 18,000 pulses during the day, and 90,000 pulses during the entire course (Fig. 2).

Clinical assessment

The Montgomery-Asberg Depression Rating Scale (MADRS) was used to assess the clinical effects of SNT [21]. Assessment was performed at five different time points: prior to stimulation, immediately after stimulation, 1, 2 and 3 months after stimulation. The MADRS scores reduced by more than 50% from baseline were considered a clinically significant response, while the scores of 10 points and lower were considered a remission [22]. Furthermore, TRD was staged by Maudsley Staging Method (MSM) in all patients prior to the study [23]. The original questionnaires were used to assess safety, tolerability and adverse events (AEs): AEs reported during stimulation and

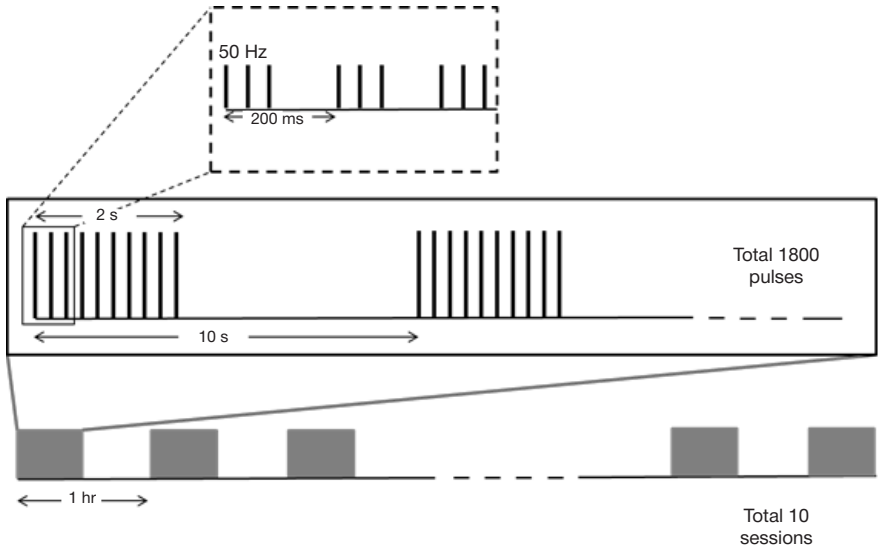

Fig. 2. Scheme of the Stanford Neuromodulation Therapy (SNT) protocol

Table. Clinical and demographic data of the patients enrolled

№	Sex	Age	Diagnosis (ICD-10 code)	MADRS score	MSM score	Disease duration, years	Number of episodes
1	м	36	F33.1	19	10	13	8
2	м	29	F33.1	14	7	13	7
3	м	66	F31.8	19	10	47	10
4	f	31	F31.3	19	6	15	10
5	f	21	F31.8	21	7	5	4
6	f	58	F31.3	27	6	34	12

Note: MADRS — Montgomery–Asberg Depression Rating Scale; MSM — Maudsley Staging Method.

AEs reported within 24 hrs after stimulation were analyzed separately.

RESULTS

The study involved six patients (three women and three men) aged 21–66 with the ongoing mild-to-moderate drug-resistant depression associated with recurrent depressive disorder (two patients), bipolar disorder type 1 (two patients) and 2 (two patients) (Table). The disease duration was 5–47 years, and the number of episodes per patient was at least four.

The improvement of depressive symptoms to the levels characteristic of remission (MADRS score 10 or lower) immediately after the end of therapy (day 6) was observed in five patients out of six (Fig. 3). The MADRS score of the sixth patient remained unchanged immediately after the end of the course. One of the female patients withdrew from the study at the assessment stage immediately after the stimulation completion. Thus, the data acquired from five patients were available for investigation of the clinical effect stability. Assessment performed within a month showed that one patient still had remission (diagnosis code F31.8), while the scores of other four patients met the criteria of mild depressive episode (diagnosis code F33.1 in two patients, and F31.3 in two female patients). Two months later the condition of three patients met the criteria of remission (diagnosis codes F31.8, F33.1, F31.3), and the condition of two patients was considered a mild depressive episode (diagnosis codes F33.1, F31.3). Assessment of scores, that were compared to baselines, in four patients out of five met the criteria of the clinically significant response to therapy (reduction by more than 50% from baseline). After three months, two patients still had remission (diagnosis codes F33.1, F31.3), and the condition of three patients met the criteria of mild depressive episode (diagnosis codes F31.8, F33.1, F31.3). Two patients met the criteria of the clinically significant response to therapy compared to baselines. It is interesting to note that no long-term effects were observed in the only patient who showed no response to therapy immediately after the end of stimulation (diagnosis code F33.1).

No serious AEs were reported, such as epileptic seizure, syncope, or intense headache. Two patients reported mild headache (pain intensity with the Numerical Pain Rating Scale score below 3 points), that resolved spontaneously within 2–3 hrs without supplementary medication, after the end of the first block of stimulation (in the evening of the first day). These patients had no headache on other days. Furthermore, one female patient complained of the increase in anxiety, mood change, and sleeping disorder after the first block of stimulation. However, agitation resolved by the next morning. Later, mood changes and insomnia did not bother this patient. Phase inversion was reported in none of the patients with bipolar disorder.

DISCUSSION

The pilot study showed safety and good tolerability of the new SNT protocol in patients with depressive episodes associated with both recurrent depression and bipolar disorder. Inclusion of patients with bipolar disorder distinguishes our study from other research. The identified AEs were mild, never required prescribing supplementary medication and never resulted in rejection of procedures or refusal to participate in the study.

The findings showed that the proportion of patients, whose symptoms of depression met the criteria of remission immediately after the end of stimulation, was 83%. Heterogeneous data

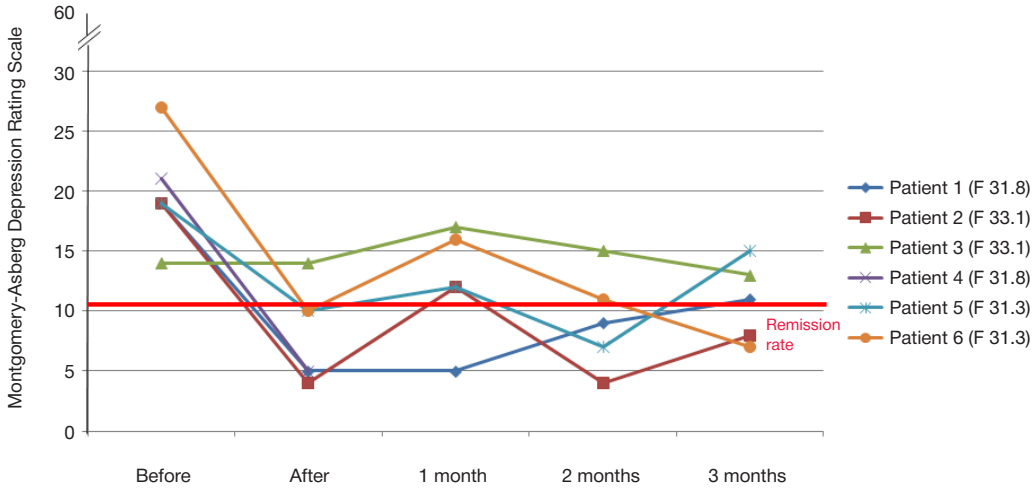

Fig. 3. Dynamics of depressive symptoms: individual data

were obtained when assessing durability of response: in 75% of patients, who showed clinically significant effects of SNT immediately after the end of stimulation, the effects persisted for two months, and in a third of patients the effects persisted for at least three months. The pilot data obtained suggest that SNT efficacy in patients with recurrent depression is high, it is well above the efficacy of the FDA-approved protocols, which is in line with the data provided by the designers of SNT. Furthermore, reduced depressive symptom severity is reported in patients with bipolar disorder, which brings up to date conducting the double-blind controlled trials of SNT efficacy in this cohort of patients as well.

To date, there is no clear concept whether higher efficacy of SNT compared to FDA-approved protocols results from more precise target selection, larger number of pulses per session or course, the combination of these factors, or other mechanisms. Despite the fact that some researchers have shown the effectiveness of the target selection algorithm based on the analysis of FC with Sg compared to sham stimulation [24], no increase in the efficacy of stimulation has been found when using the algorithm involving standard target selection [15]. Thus, it seems unlikely that precise target selection is the only contributor to the increased efficacy. Talking about accelerated protocols, it is important to note heterogeneity of the currently available results: the early studies showed encouraging results [25], however, further larger trials, that involved the use of both high-frequency rTMS and theta-burst stimulation, generated negative results [26, 27]. However, direct comparison of the protocols, used in the two latter studies, with SNT is not quite correct since the total number of pulses used in SNT is several times larger than the number of those used in the studied accelerated protocols. Moreover, not only the total number of pulses, but also, for instance, the duration of single block of stimulation or the time between blocks can contribute significantly to the effect size. These issues are particularly relevant in the context of metaplasticity concept, which has been actively developed in recent years [28]. According to the concept of metaplasticity, prior activity determines the threshold for induction of the activity-dependent plasticity, not only the values and duration of the neuroplastic changes induced, but also the direction of neuroplasticity. Thus, in the context of SNT, each preceding block of stimulation can promote changes induced by subsequent block through the mechanism of additive metaplasticity. It is important to note that the discussed potential mechanisms of increasing the efficacy of SNT compared to approved protocols are hypothetical and require testing in the studies that involve controlling each of the mentioned factors separately.

When performing clinical testing of the SNT protocol, we have identified a number of factors that restrict widespread introduction of the method into practice. First, these factors include high labor costs of the protocol: each patient needs 10 sessions of stimulation provided at intervals of 1 hr daily for five days. This requires special organisation of both the employee work mode and the patient mode. The total working hours of both staff and patients are 11 hrs per day. Moreover, when used for SNT, the transcranial magnetic stimulation device throughput is significantly limited: only three patients can be treated with the same device at the same time. Implementation of the protocol requires high-tech equipment (TMS device equipped with the neuronavigation system and high-field MRI scanner) and staff members involved in analysis of neuroimaging data and working with the neuronavigation system. These factors negate affordability of the technique in general. It seems promising to study the efficacy of protocols that are partially compliant with SNT (for example, with respect of multiplicity and number of pulses, but without precise target selection), the use of which given their efficacy would significantly increase the method affordability.

The study limitations are as follows: small number of patients enrolled, no controls, and moderate severity of the patients' affective disorders. However, it is important to note that the study was aimed to assess the possibility of the SNT protocol implementation in clinical practice, as well as to provide independent confirmation of its safety and efficacy, particularly in the new cohort of patients with bipolar disorder. The findings show SNT feasibility and the perspective for further investigation of the method efficacy and safety, including the potential of blind controlled trials within the larger cohorts of patients.

CONCLUSIONS

The results of clinical testing performed in a small sample of patients show that Stanford neuromodulation therapy is a safe and potentially highly efficient method for management of treatment-resistant depression. However, the labor costs of the method are high. Further research, that would potentially allow to expand the spectrum of indications for SNT and increase affordability of the method, seems to be a promising area in the field of non-invasive brain stimulation in patients with affective disorders resistant to psychopharmacotherapy.

References

1. Maksimova NM, Rusyaev VYu, Uzbekov MG. Nejrobiologicheskie mexanizmy razvitiya rezistentnyx depressij. Social'naya i klinicheskaya psixiatriya. 2021; 31 (4): 71–79. Russian.
2. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of Treatment-Resistant Depression: Challenges and Strategies. Neuropsychiatr Dis Treat. 2020; 16: 221–34.
3. Mosolov SN, Alfimov PV, Kostyukova EG. Sovremennye metody preodoleniya terapevticheskoj rezistentnosti pri rekurrentnoj depressii. V knige: S. N. Mosolov, redaktor. Biologicheskie metody terapii psixicheskix rasstrojstv. M., 2012; s. 438–73. Russian.
4. Miron JP, Jodoin VD, Lespérance P, Blumberger DM. Repetitive transcranial magnetic stimulation for major depressive disorder: basic principles and future directions. Ther Adv Psychopharmacol. 2021; 11: 20451253211042696.
5. Chervyakov AV, Chernyavsky AY, Sinitsyn DO, Piradov MA. Possible Mechanisms Underlying the Therapeutic Effects of Transcranial Magnetic Stimulation. Front Hum Neurosci. 2015; 9: 303.
6. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry. 2007; 62 (11): 1208–16.
7. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet. 2018; 391 (10131): 1683–92.
8. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An

update (2014–2018). Clin Neurophysiol. 2020; 131 (2): 474–528.
9. Boes AD, Kelly MS, Trapp NT, Stern AP, Press DZ, Pascual-Leone A. Noninvasive Brain Stimulation: Challenges and Opportunities for a New Clinical Specialty. J Neuropsychiatry Clin Neurosci. 2018; 30 (3): 173–79.
10. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med. 2014; 44 (2): 225–39.
11. Sehatzadeh S, Daskalakis ZJ, Yap B, Tu HA, Palimaka S, Bowen JM, et al. Unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression: a meta-analysis of randomized controlled trials over 2 decades. J Psychiatry Neurosci. 2019; 44 (3): 151–63.
12. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry. 2012; 72 (7): 595–603.
13. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct. 2008; 213 (1–2): 93–118.
14. Antonovich BA, Maĭorova LA, Cukarzi EhEh, Mosolov SN. Neĭronnye seti sostoyaniya pokoya pri depressiyax i perspektivy primeneniya personificirovannoj TMS. Sovremennaya terapiya psixicheskix rasstrojstv. 2019; 3: 2–11. Russian.
15. Poydasheva AG, Sinitsyn DO, Bakulin IS, Suponeva NA, Maslenikov NV, Tsukarzi EE. i dr. Opredelenie misheni dlya transkranial'noj magnitnoj stimulyacii u pacientov s rezistentnym k farmakoterapii depressivnym ehpizodom na osnove individual'nyx parametrov funkcional'noj magnitno-rezonansnoj tomografii pokoya (pilotnoe slepoe kontroliruemoe issledovanie. Nevrologiya, nejropsixiatriya, psixosomatika. 2019; 11 (4): 44–50. Russian.
16. Sonmez AI, Camsari DD, Nandakumar AL, Voort JLV, Kung S, Lewis CP, et al. Accelerated TMS for Depression: A systematic review and meta-analysis. Psychiatry Res. 2019; 273: 770–81.
17. Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, et al. Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression. Am J Psychiatry. 2020; 177 (8): 716–26.
18. Cole EJ, Phillips AL, Bentzley BS, Stimpson KH, Nejad R, Barmak F, et al. Stanford Neuromodulation Therapy (SNT): A Double-Blind Randomized Controlled Trial. Am J Psychiatry. 2022; 179 (2): 132–41.
19. Axapkin RV, Bukreeva ND, Vazagaeva TI, Kostyukova EG, Mazo GEh, Mosolov SN. Depressivnyj ehpizod, rekurrentnoe depressivnoe rasstrojstvo. Klinicheskie rekomendacii. Vzroslye. Ehlektronnoe izdanie. 2021. Dostupno po ssylke: https://cr.minzdrav.gov.ru/recomend/301_2. Russian.
20. Mosolov SN, Kostyukova EG, Ladyzhenskij MYa. Algoritm biologicheskoj terapii ostrogo ehpizoda rekurrentnogo depressivnogo rasstrojstva. Sovremennaya terapiya psixicheskix rasstrojstv. 2016; 3: 27–40. Russian.
21. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979; 134: 382–9.
22. Hawley CJ, Gale TM, Sivakumaran T; Hertfordshire Neuroscience Research group. Defining remission by cut off score on the MADRS: selecting the optimal value. J Affect Disord. 2002; 72 (2): 177–84.
23. Fekadu A, Wooderson SC, Markopoulou K, Cleare AJ. The Maudsley Staging Method for treatment-resistant depression: prediction of longer-term outcome and persistence of symptoms. J Clin Psychiatry. 2009; 70 (7): 952–7.
24. Siddiqi SH, Taylor SF, Cooke D, Pascual-Leone A, George MS, Fox MD. Distinct Symptom-Specific Treatment Targets for Circuit-Based Neuromodulation. Am J Psychiatry. 2020; 177 (5): 435–46.
25. Loo CK, Mitchell PB, McFarquhar TF, Malhi GS, Sachdev PS. A sham-controlled trial of the efficacy and safety of twice-daily rTMS in major depression. Psychol Med. 2007; 37 (3): 341–9.
26. Blumberger DM, Vila-Rodriguez F, Wang W, Knyahnytska Y, Butterfield M, Noda Y, et al. A randomized sham controlled comparison of once vs twice-daily intermittent theta burst stimulation in depression: A Canadian rTMS treatment and biomarker network in depression (CARTBIND) study. Brain Stimul. 2021; 14 (6): 1447–55.
27. Fitzgerald PB, Hoy KE, Elliot D, Susan McQueen RN, Wambeek LE, Daskalakis ZJ. Accelerated repetitive transcranial magnetic stimulation in the treatment of depression. Neuropsychopharmacology. 2018; 43 (7): 1565–72.
28. Abraham WC, Bear MF. Metaplasticity: the plasticity of synaptic plasticity. Trends Neurosci. 1996; 19 (4): 126–30.

Литература

1. Максимова Н. М., Русяев В. Ю., Узбеков М. Г. Нейробиологические механизмы развития резистентных депрессий. Социальная и клиническая психиатрия. 2021; 31 (4): 71–79.
2. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of Treatment-Resistant Depression: Challenges and Strategies. Neuropsychiatr Dis Treat. 2020; 16: 221–34.
3. Мосолов С. Н., Алфимов П. В., Костюкова Е. Г. Современные методы преодоления терапевтической резистентности при рекуррентной депрессии. В книге: С. Н. Мосолов, редактор. Биологические методы терапии психических расстройств. М., 2012; с. 438–73.
4. Miron JP, Jodoin VD, Lespérance P, Blumberger DM. Repetitive transcranial magnetic stimulation for major depressive disorder: basic principles and future directions. Ther Adv Psychopharmacol. 2021; 11: 20451253211042696.
5. Chervyakov AV, Chernyavsky AY, Sinitsyn DO, Piradov MA. Possible Mechanisms Underlying the Therapeutic Effects of Transcranial Magnetic Stimulation. Front Hum Neurosci. 2015; 9: 303.
6. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry. 2007; 62 (11): 1208–16.
7. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet. 2018; 391 (10131): 1683–92.
8. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). Clin Neurophysiol. 2020; 131 (2): 474–528.
9. Boes AD, Kelly MS, Trapp NT, Stern AP, Press DZ, Pascual-Leone A. Noninvasive Brain Stimulation: Challenges and Opportunities for a New Clinical Specialty. J Neuropsychiatry Clin Neurosci. 2018; 30 (3): 173–79.
10. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med. 2014; 44 (2): 225–39.
11. Sehatzadeh S, Daskalakis ZJ, Yap B, Tu HA, Palimaka S, Bowen JM, et al. Unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression: a meta-analysis of randomized controlled trials over 2 decades. J Psychiatry Neurosci. 2019; 44 (3): 151–63.
12. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry. 2012; 72 (7): 595–603.
13. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry

models of depression. Brain Struct Funct. 2008; 213 (1–2): 93–118.
14. Антонович Б. А., Майорова Л. А., Цукарзи Э. Э., Мосолов С. Н. Нейронные сети состояния покоя при депрессиях и перспективы применения персонифицированной ТМС. Современная терапия психических расстройств. 2019; 3: 2–11.
15. Пойдашева А. Г., Синицын Д. О., Бакулин И. С., Супонева Н. А., Масленников Н. В., Цукарзи Э. Э. и др. Определение мишени для транскраниальной магнитной стимуляции у пациентов с резистентным к фармакотерапии депрессивным эпизодом на основе индивидуальных параметров функциональной магнитно-резонансной томографии покоя (пилотное слепое контролируемое исследование. Неврология, нейропсихиатрия, психосоматика. 2019; 11 (4): 44–50.
16. Sonmez AI, Camsari DD, Nandakumar AL, Voort JLV, Kung S, Lewis CP, et al. Accelerated TMS for Depression: A systematic review and meta-analysis. Psychiatry Res. 2019; 273: 770–81.
17. Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, et al. Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression. Am J Psychiatry. 2020; 177 (8): 716–26.
18. Cole EJ, Phillips AL, Bentzley BS, Stimpson KH, Nejad R, Barmak F, et al. Stanford Neuromodulation Therapy (SNT): A Double-Blind Randomized Controlled Trial. Am J Psychiatry. 2022; 179 (2): 132–41.
19. Ахапкин Р. В., Букреева Н. Д., Вазагаева Т. И., Костюкова Е. Г., Мазо Г. Э., Мосолов С. Н. Депрессивный эпизод, рекуррентное депрессивное расстройство. Клинические рекомендации. Взрослые. Электронное издание. 2021. Доступно по ссылке: https://cr.minzdrav.gov.ru/recomend/301_2.
20. Мосолов С. Н., Костюкова Е. Г., Ладыженский М. Я. Алгоритм биологической терапии острого эпизода рекуррентного депрессивного расстройства. Современная терапия психических расстройств. 2016; 3: 27–40.
21. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979; 134: 382–9.
22. Hawley CJ, Gale TM, Sivakumaran T; Hertfordshire Neuroscience Research group. Defining remission by cut off score on the MADRS: selecting the optimal value. J Affect Disord. 2002; 72 (2): 177–84.
23. Fekadu A, Wooderson SC, Markopoulou K, Cleare AJ. The Maudsley Staging Method for treatment-resistant depression: prediction of longer-term outcome and persistence of symptoms. J Clin Psychiatry. 2009; 70 (7): 952–7.
24. Siddiqi SH, Taylor SF, Cooke D, Pascual-Leone A, George MS, Fox MD. Distinct Symptom-Specific Treatment Targets for Circuit-Based Neuromodulation. Am J Psychiatry. 2020; 177 (5): 435–46.
25. Loo CK, Mitchell PB, McFarquhar TF, Malhi GS, Sachdev PS. A sham-controlled trial of the efficacy and safety of twice-daily rTMS in major depression. Psychol Med. 2007; 37 (3): 341–9.
26. Blumberger DM, Vila-Rodriguez F, Wang W, Knyahnytska Y, Butterfield M, Noda Y, et al. A randomized sham controlled comparison of once vs twice-daily intermittent theta burst stimulation in depression: A Canadian rTMS treatment and biomarker network in depression (CARTBIND) study. Brain Stimul. 2021; 14 (6): 1447–55.
27. Fitzgerald PB, Hoy KE, Elliot D, Susan McQueen RN, Wambeek LE, Daskalakis ZJ. Accelerated repetitive transcranial magnetic stimulation in the treatment of depression. Neuropsychopharmacology. 2018; 43 (7): 1565–72.
28. Abraham WC, Bear MF. Metaplasticity: the plasticity of synaptic plasticity. Trends Neurosci. 1996; 19 (4): 126–30.