Psychiatria Danubina, 2022; Vol. 34, Suppl. 8, pp 179-188 *Conference paper*

THE EFFECTS OF TRANSCRANIAL MAGNETIC STIMULATION ON COGNITIVE FUNCTIONING IN BIPOLAR DEPRESSION: A SYSTEMATIC REVIEW

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SUMMARY

Background: *The features of bipolar affective disorder (BAD) include mood swings, recurring episodes of mania, depression, and mixed states. Numerous studies of people living with BAD have found the presence of cognitive impairments that affect patients' daily social functioning and quality of life. Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique recommended for the treatment of bipolar depression (BD). The effect of TMS on cognitive function in BD patients remains mostly unclear.*

Subjects and methods: *We carried out a systematic search in the databases of PubMed and Scopus for the whole publication period until March 30th, 2022. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) was used to identify all data published in English language and related to the use of TMS in the treatment of depression in BAD and its impact on cognitive function. Articles related to TMS, cognition, and BD were identified using predefined term search algorithms. Articles on clinical trials and case reports were included, but reviews were excluded. The PICOS (Population Intervention Comparison Outputs Study) formula in our review included: P - patients with bipolar depression, I - TMS treatment, C - patients without TMS treatment / placebo TMS, O - changes in cognitive functions, S - all types of original studies.*

Results: *Within the primary screening for assessment of full texts, 25 documents met our selection criteria to test the effect of TMS on cognitive functioning in BD. Based on a secondary screening of the full-text analysis, 10 articles (N=259 patients) were included into the current review. Among these, the majority of articles were based on the randomized controlled trials (RCTs, N=6), whereas the remaining four presented a case report, an open unblinded study, an open-label study, and a pilot study, respectively. Most of the studies produced mixed result. However, the limited data strongly suggested that TMS is without detriment to cognition in BD patients and is indeed beneficial in specific domains of cognitive function, namely (i) verbal fluency, (ii) verbal memory, and (iii) executive functioning. Small sample sizes, heterogeneity across the study designs, lack of the control groups data in some of the trials, different TMS protocols parameters and outcome measures represent significant limitations for comparing and analyzing the available results.*

Conclusions: *Thus, present data on the effects of TMS in improving cognition in BD patients remains limited. To our mind, in order to evaluate properly the effectiveness of TMS in cognitive functioning improvement in BD, there is need for further randomized controlled trials and the corresponding development of the clinical standards for research recommendations. Such studies could define the appropriate methods for valid assessments of cognitive functions, and guide the selection of optimal TMS protocols when planning RCTs. We suggest that efforts should be expended to organize centralized large-scale clinical trials to determine the optimal parameters of TMS procedures and the range of effects of this treatment on various indicators of cognitive functioning in BD. This applies equally to other socially significant mental disorders marked by perturbations in cognitive functioning.*

Key words: *bipolar depression - bipolar disorder - cognitive impairment - functional recovery -neurocognitive assessment - rTMS - transcranial magnetic stimulation - verbal fluency*

Abbreviations: *BAD / BD - bipolar affective disorder / bipolar depression; DLPFC - dorsolateral prefrontal cortex; RCTs - randomized clinical trials; dTMS / rTMS / TMS - deep / repetitive (rhythmic) / transcranial magnetic stimulation*

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INTRODUCTION

Bipolar depression (BD) is one of the most common mental disorders, which frequently presents with pronounced cognitive deficits that persists even during the euthymic phase of the disease (Myczkowski et al. 2018a). Moreover, bipolar disorder (BAD) patients demonstrated higher risks in developing clinical depression and suicidality in response to the major social changes, such as the COVID-19 pandemic and related lockdown conditions (Fountoulakis et al. 2022a,b, Syunyakov et al. 2022). It is important to focus on the cognitive deficits emerged in BD patients over the course of the disorder (e.g. in processing speed, attention, working memory, verbal memory, problem solving, and etc.) (Depp et al. 2012). Meta-analytic data have shown that cognitive deficits in conjunction with a factor of the disease progression have a greater negative impact on the unemployment rate in BD, than primary disease symptoms or sociodemographic factors (Tse et

al. 2014). In this regard, there is an undoubted need to find methods to restore the cognitive impairments that accompany the course of BAD in order to improve the functional recovery of individual patients, and to reduce the associated socio-economic costs of patients' management (Miskowiak et al. 2016). Pharmacological agents used in BD treatment can significantly aggravate existing cognitive impairment, which highlights the importance of developing new interventions that provide "cognitive safety" (Myczkowski et al. 2018b). Key BD medications, including anticonvulsants and antipsychotics, provoke cognitive exacerbations (e.g. psychomotor retardation, memory loss) (Gualtieri & Johnson 2006). The mainstay treatment for BAD is lithium, which likely has significant effects on the core components of neurocognition (e.g. psychomotor speed, verbal memory, verbal fluency). Indeed, studies show that lithium has a complex profile of neurocognitive effects (Malhi et al. 2016). Cognitive impairment has also been reported with sodium valproate in BAD patients (Xu et al. 2019). At the same time, efforts to restore neurocognitive functions of patients are met with great difficulties. However, there is limited research data in this area, and proposed medical treatment options for cognitive deficits are few in number. On the other hand, there is an emerging evidence of cognitive improvement with selected pharmacological therapies, electroconvulsive therapy and rTMS, while research on psychotherapeutic interventions remains inconclusive (Fountoulakis 2020).

Currently, we are experiencing a re-emergence of non-pharmacological somatic therapies and new methods of non-invasive brain stimulation for BD, possibly due to the limited efficacy of drug treatments for a significant percentage of patients (Rush et al. 2006). Since the inception of TMS, there has been a high interest in this approach as a treatment for depression, and the numerous TMS trials have been carried out around the world. In general, there is little industrial sponsorship of rTMS specifically as an "antidepressant" (or therapy for other targets of socially significant mental disorders), and funding for these trials has until recently mostly come from foundations and governments, as well as being sponsored by the patients themselves (Reti 2015).

Rhythmic transcranial magnetic stimulation (rTMS) is a non-pharmacological approach to modulate brain activity using electromagnetic pulses discharged through a coil placed over the patient's head (Rosa & Lisanby 2012). TMS creates magnetic fields with flux lines perpendicular to the plane of the coil. The figure-of-eight coil, which is commonly used for therapeutic purposes, produces a relatively focal field, with the sum of the field lines induced by each of the eight loops producing a stronger magnetic field at the center. The width of the induced magnetic field corresponds to the size of the coil, while its depth of penetration to brain is usually limited to 2 cm or less, as the magnetic flux density decreases with the square of the distance from the stimulating coil (Rosa & Lisanby 2012). Along with the rTMS technique, deep TMS (dTMS) has been used to treat BD. Deep TMS has a unique coil design, the H-Coil, that allows practitioners to stimulate deeper and larger areas of the brain than are accessible to standard TMS coils. The dTMS method has been approved by the US Food and Drug Administration since 2013 for treatment-resistant depression (Rapinesi et al. 2018). TMS is a relatively safe and effective treatment for BD (Tee & Au 2020). However, its effect on cognitive functioning in this group of patients remains unclear.

In our review, we focused on the evidence-based findings for the effectiveness of the TMS method and a qualitative assessment of its potential benefits in the improvement of cognitive functioning in BD. However, we did not conduct a broader quantitative meta-analysis of the available evidence for the cognitive effects of TMS in BD due to significant methodological differences between the available studies. These notably include differences in TMS course protocols and treatment schedules (duration and frequency of procedures), study designs (for example, single or double blind, with or without placebo control), and with respect to the instruments used to study cognitive functioning.

SUBJECTS AND METHODS

This systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines and has been conducted for the articles (i) on BD (excluding data on unipolar depression), (ii) published in English language, (iii) presented in the PubMed and Scopus databases across the whole time period until March 30th, 2022 (Figure 1). The keywords search algorithm and review protocol are presented in Figure 1. The PICOS in our review was as follows: P - patients with bipolar depression, I – treatment with TMS, C - patients without TMS treatment/ placebo TMS, O - cognitive function change, S - all types of original research.

RESULTS

Our systematic search, including additional manual searches, yielded (i) 281 results related to the topic of this study. After the removal of duplicates, (ii) 247 articles were included in the processing of titles/ abstracts (primary screening). Of these, (iii) 25 articles met eligibility criteria for the secondary screening. Full-text analysis resulted in the selection of (iv) ten articles that matched the PICOS criteria and were therefore reviewed in detail (Table 1).

Table 1. Original research articles related to the findings on the effects of transcranial magnetic stimulation on cognitive functioning in bipolar depression

Reference	Research design/ Article type	Sample size	Period of treatment	rTMS, dTMS (intervention)	Cognitive tests	Main findings
Yang L et al. (2019)	Single-blind randomized controlled trials	N = 52	10 sessions; two weeks	High-frequency rTMS over the left DLPFC at 110% of the motor threshold.	MATRICS Consensus Cognitive Battery (MCCB)	rTMS improved cognitive function in BD participants in the WMS-III Spatial Span (F1,50=6.484, p=0.014), and MCCB Category Fluency subtest (F1,50= 4.853, p=0.032). Working memory and processing speed significantly improved in BD participants, suggesting rTMS to have a positive effect on cognitive function in BD participants.
Bersani F et al. (2013)	Case Report	1	20 daily sessions, three months follow-up including one session per two weeks	dTMS over the prefrontal cortex at 120% of the motor threshold.	Mini Mental State Evaluation (MMSE)	Cognitive performances improved. MMSE scores progressively increased (showing improvement) from 27 at the baseline to 30 at the 20th session, mainly due to the improved orientation.
Thomas-Ollivier V et al. (2017)	Open unblinded study	N = 7	daily sessions, four weeks	High-frequency rTMS on the left DLPFC 10 Hz, 110% of the motor threshold; low-frequency rTMS on the right DLPFC 1 Hz 110% of the motor threshold.	1. ERD score 2. MoCA (Montreal Cognitive Assessment)	ERD: before (23.7 ± 10); after (14.3 ± 8.1).; MoCA: before (26 ± 2.6); after (26.1 ± 2.4). Significant effects of rTMS treatment on depression, PMR, and speech fluency.
Myczkowski M et al. (2018)	Randomized double-blind, sham-controlled trial	N = 43	8 weeks, encompassing 4 weeks of 20 daily TMS sessions (excluding weekends); a follow-up of four weeks without TMS sessions	dTMS using an H1-coil over left DLPFC at 18 Hz and 120% motor threshold.	1. Trail making test-A 2. Stroop color 3. Digit symbol-coding (Wechsler Adult Intelligence Scale, WAIS-III) 4. Digit span forward (WAIS-III) 5. Stroop word 6. Stroop interference 7. Wisconsin card Sorting Test 8. Iowa gambling task 9. Rey-Osterrieth Complex Figure 10. Cubes (WAIS-III) 11. Wisconsin card sorting test – hits 12. Trail making test-B 13. Digit Span Backward (WAIS-III) 14. Sequence of number and Letters (WAIS-III) 15. FAS verbal fluency 16. Animal verbal fluency 17. Wechsler memory scale (Immediate verbal memory) 18. RAVLT (Rey Auditory Verbal Learning Test, Immediate verbal memory) 19. Wechsler memory scale (Long-term verbal memory) 20. RAVLT (Long-term verbal memory)	The results of this exploratory study provide evidence on the cognitive safety of H1-coil TMS for BD patients. Putative pro-cognitive effects of rTMS in BD were not observed and thus should be further investigated.

Table 1. Continues

Reference	Research design/ Article type	Sample size	Period of treatment	rTMS, dTMS (intervention)	Cognitive tests	Main findings
Hu S et al. (2016)	Prospective randomized and controlled study	N = 38	5 days a week, four weeks, 20 sessions in total	High-frequency rTMS over left DLPFC 10 Hz and 80% motor threshold; low-frequency rTMS over right DLPFC 1 Hz and 80% motor treshold.	1. Wisconsin Card Sorting Test (WCST) 2. Stroop Word-Color Interference Test (Stroop) 3. Trail Making Test (TMT)	No statistically significant treatment differences were found in terms of cognitive measures (WCST, Stroop or TMT) across the three groups in response to the rTMS treatment ($p>0.05$).
Kazemi R et al. (2018)	Open-label study	N = 20	10 sessions of sequential bilateral rTMS, 6 days a week	1 Hz rTMS over right DLPFC with subsequent 10 Hz rTMS over left DLPFC	1. Verbal Fluency Test (VFT) 2. RAVLT 3. Stroop Test 4. WCST	Bilateral rTMS resulted in significant changes in the executive functions, verbal memory. No significant changes were observed in relation tot he selective attention and verbal fluency measures.
Matsuda Y et al. (2020)	Randomized, double-blind, sham-controlled trial	N = 25	5 days a week, 4–6 weeks	dTMS 18 Hz over the left DLPFC at 120% motor threshold	1. Stroop test 2. Trail making test	No between-group significant differences have been registered.
McIntyre R et al. (2021)	Triple-blinded, randomized, placebo-control trial	N = 36	20 sessions; up to six weeks	10 Hz rTMS over left *DLPFC* with 110% motor threshold	1. Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) 2. Consensus Cognitive Battery (MCCB)	Herein, we observed that when compared to sham, rTMS did not improve most measures of cognitive function. We did, however, find a significant effect in favour of verbal learning within the active rTMS group.
Speer A et al. (2001)	Randomized double-blind cross-over study	N = 18	10 daily sessions; two weeks	Sham design, 1 Hz, or 20 Hz rTMS administered over left DLPFC at 100% of motor threshold	1. The Buschke Selective Reminding Test of episodic memory 2. Memory Cards from the Colorado Neuropsychologic Battery visual spatial memory test 3. Word Fluency and Category Fluency, assessing semantic memory and language 4. The Continuous Performance Task, assessing attention, concentration, and motor performance 5. The Shipley Institute of Living Scale (SILS), used to calculate an estimated Full Scale IQ score based on the WAIS	No major changes in cognitive test scores as a result of 10 days of either 1 Hz or 20 Hz rTMS have been registered. Moreover, any minor attenuation in cognition was not related to the degree of clinical improvement. Cognitive functioning was not disrupted.
Harel E et al (2011)	Open pilot study	N = 19	5 days a week; four consecutive weeks	H1-Coil rTMS Left Prefrontal cortex (rTMS: 20 Hz, 2 s on, 20 s off, 1680 stimuli in total); 120% of the measured motor treshold	The Cambridge Neuropsychological Test Automated Battery (CANTAB)	No deterioration in the cognitive functioning in biploar depression was observed. Reaction time and spatial working memory improved, no correlations with a decrease in the severity of depression registered.

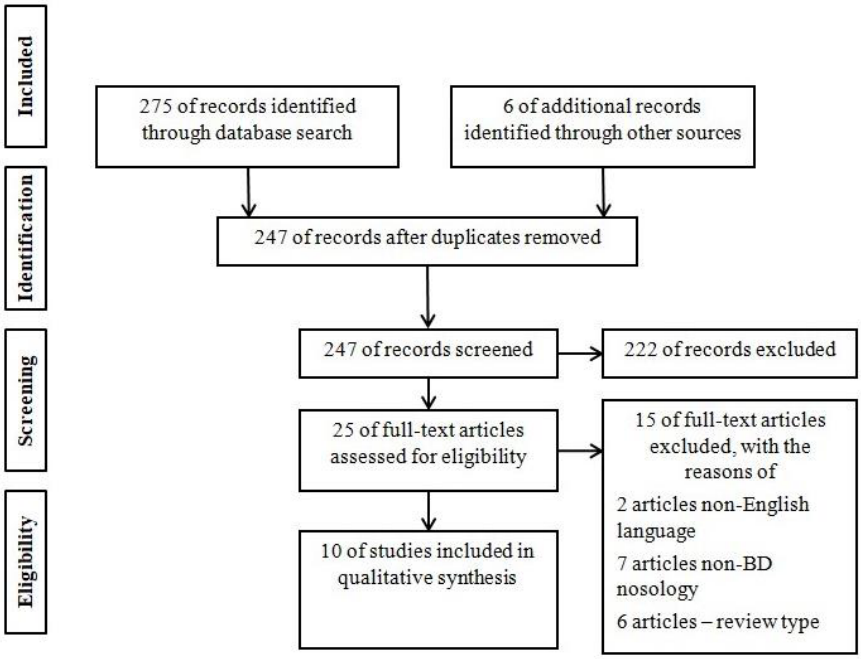

Figure 1. PRISMA flow diagram of the literature search algorithm of studies related to the TMS effects on cognitive functioning in bipolar depression

Research design

Most of the studies were RCTs (N=6), including one single-blind randomized controlled trial (Yang et al. 2019), two double-blind randomized sham-controlled trials (Matsuda et al. 2020, Myczkowski et al. 2018c), one prospective, randomized and controlled study (Hu et al. 2016), one triple-blinded, randomized, placebo-control trial (McIntyre et al. 2021) and one randomized double-blind cross-over study (Speer et al. 2001). One article was a case report (Bersani et al. 2013), two were open-label studies (Kazemi et al. 2018, Thomas-Ollivier et al. 2017), and there was one open pilot study (Harel et al. 2011).

Patients selection

The selection size of the studies was heterogeneous, with a total of N=259 patients included. The overall age range in eight studies was 16 to 78 years, one study reported only a mean age of 45±7 years, and one did not report the age of the patients. Patients diagnosed as having BAD (type I or II) and currently experiencing an episode of depression established by psychiatrists, and the diagnosis was verified by formal diagnostic interviews using the Mini-International Neuropsychiatric Interview (MINI), the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), with the add-on scales assessments (e.g. HDRS-17, BDI-II).

Parameters of TMS procedures

Most of the studies presented in the active group used rTMS stimulation (N=7), while the case report, open pilot study, and randomized, double-blind, placebo-controlled study used dTMS (N=3). Stimulation was delivered over the left prefrontal dorsolateral cortex (left DLPFC) in six of the ten studies. In three studies, TMS treatment target the bilateral DLPFC, with one study describing stimulation over the prefrontal cortex, without specification of side. The stimulation parameters varied by the factor of motor response threshold from 80, 100, 110, and up to 120%, in particular. The duration of TMS therapy differed significantly, ranging from two weeks to three months. In the case report (Bersani et al. 2013), therapy consisted of 20 daily consecutive dTMS sessions and one dTMS session once every two weeks for the following three months; this was the longest reported intervention. In the other studies, the duration of therapy was two, four, or six weeks. In all patients, TMS was performed against the background of ongoing pharmacotherapy, including mood stabilizers and antipsychotics.

Cognitive tests in the context of research objectives

Dynamics of cognitive functioning during the ongoing BD treatment with add-on TMS was one of the main objectives in all ten studies. Therefore, each study entailed a baseline assessment of cognitive indicators before the start of TMS treatment, with follow-up assessment at the end of the course. However, the context in which this task was posed could differ between studies. In five studies, the analysis of changes in cognitive functioning in response to TMS was the central subject of the study, whereas this was a secondary

outcome measure in the remaining five studies. All ten studies discussed the safety of TMS in BD in terms of preservation of cognitive functioning. In four studies, this aspect was the sole purpose for assessing cognitive parameters (Bersani et al. 2013, Harel et al. 2011, Matsuda et al. 2020, Speer et al. 2001). Four studies assessed cognitive functioning primarily in terms of clinical dynamics versus depressive symptoms (Hu et al. 2016, McIntyre et al. 2021, Myczkowski et al. 2018c, Yang et al. 2019). Only two studies considered cognition as a marker of treatment effectiveness, along with other clinical and neurobiological markers (Kazemi et al. 2018, Thomas-Ollivier et al. 2017).

In terms of the scales design used to assess changes in cognitive functioning ranged from 1 to 20. The focus of researchers' attention was either on the integrative assessment of cognitive functioning (in three studies), or from 1 to 8 distinct domains or processes of cognitive functioning (in seven studies). In descending order of the frequency of being mentioned, the following cognitive domains were reported: executive functions, problem solving and IQ score (seven), attention/vigilance (six), working memory (six), visuospatial memory and visual learning (four), verbal memory and learning (four), psychomotor speed (reaction time) (four), language and fluency (three), social cognition (two), other types of memory (long-term) (one), and inhibitory control (one). The frequency of use of neurocognitive techniques in the studies, in descending order were (i) the Stroop Word-Color Interference Test (Stroop) and Wisconsin Card Sorting Test (WCST) (four), (ii) MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB) and Trail making test (TMT) (three), (iii) Rey Auditory Verbal Learning Test (RAVLT) and Wechsler Adult Intelligence Scale (WAIS-III) subtests (two). The Cambridge Neuropsychological Test Automated Battery (CANTAB), specifically three screening clinical scales aimed at an integrative assessment of cognitive functioning without division into cognitive areas, was used in one study, as well as the remaining ten cognitive tests to assess individual domains of functioning (Table 1). We note that results of some of the test batteries used are correlated with each other. For example, all ten subtests and the assessment of cognitive spheres in MCCB scores are significantly correlated with the WCST, Raven's standard progressive matrices, and Stroop scores (Yang et al. 2019), which allows us to consider them to some extent interchangeable.

Cognitive functions change as a result of the use of TMS

The data obtained on changes in cognitive functioning should properly be ranked depending on the main objective of the researchers. Studies that focused on the safety of TMS exposure in BD (Bersani et al. 2013, Harel et al. 2011, Matsuda et al. 2020, Speer et al. 2001) reported that the use of TMS in BD is safe with respect to cognitive functioning. Expanding on that consistent finding in a case report by Bersani et al. (2013), which confirmed the safety of dTMS in terms of cognitive functioning, and even note a slight improvement in the MMSE score from 27 to 30 after four weeks of therapy. A study by Harel et al. (2011) reported no deterioration in cognitive function (as measured by CANTAB) in BD patients treated with TMS. Moreover, an improvement in reaction time and spatial working memory was found in that study, although this improvement did not correlate with a decrease in the severity of depression scores. Matsuda et al. (2020) concluded that the dTMS was safe, finding no difference in cognitive functioning changes from baseline to following, either in treatment or control groups. Speer et al. (2001) reported no impairment of cognitive functioning during rTMS therapy.

Four studies assessed cognitive functioning in terms of clinical dynamics and in relation to the assessment of depressive symptoms (Hu et al. 2016, McIntyre et al. 2021, Myczkowski et al. 2018c, Yang et al. 2019); these studies had heterogeneous results without significant correlations between cognitive and other clinical parameters. Hu et al. (2016) found no statistically significant effect of rTMS treatment on cognitive measures (WCST, Stroop or TMT) ($p>0.05$) in three treatment groups: (i) left high frequency rTMS, (ii) right low frequency rTMS, and (iii) placebo stimulation. McIntyre et al. (2021) noted that, compared with placebo treatment, rTMS does not improve most of the measures of cognitive functioning. However, they did find a significant improvement in auditory learning functions in the active rTMS group. The study by Myczkowski et al. (2018) reported cognitive safety of H1-coil TMS for BD patients, but found no correlations with the changes in depression scores and the concomitantly observed cognitive improvement. At the same time, the authors of that study noted an absence of the supposed procognitive effects of rTMS in BD, and therefore should be further studied. At the same time, the results of Yang et al. (2019) showed that measures of working memory and processing speed improved significantly in BD participants after rTMS, suggesting that rTMS indeed had a positive effect on cognitive function in BD participants. Moreover, two studies that looked at cognitive parameters as a marker of treatment effectiveness along with other clinical and neurobiological markers (Kazemi et al. 2018, Thomas-Ollivier et al. 2017) and memory and fluency after TMS. Kazemi et al. (2018) state that bilateral stimulation of the DLPFC region led to significant changes in executive functions and verbal memory, as the main node of the central executive network (CEN), leading to changes in the activity of the sensorimotor network. At the same time, they noted no significant changes in the indicators of

selective attention and verbal fluency. However, a study by Thomas-Ollivier et al. (2017) again pointed to a significant positive effect of rTMS treatment on depression, psychomotor retardation, and fluency in BAD patients. They described a correlation between the deceleration scale for depression and measures of verbal fluency after treatment, which also importantly clarified the role of psychomotor function in cognition in depression. Further investigation is needed to understand better these complex relationships, including other cognitive measures as part of an objective psychomotor retardation assessment.

Adverse reactions when using the TMS method in BD therapy

The studies we reviewed described some adverse reactions from TMS treatment, although most were rated by investigators as mild in their severity. The most common mild side effects were headaches, insomnia, dizziness (Yang et al. 2019), which are recorded in the treatment not only of BD, but also other disorders. In one study, a BD patient experienced transient hypomania after three weeks of left-sided, high-frequency rTMS (Hu et al. 2016). A single generalized seizure has also been described, which was not causally linked with the direct effects of a TMS session (Harel et al. 2011). According to the authors' report, a possible factor contributing to the onset of seizures was the concomitant use of lithium, which, in turn, could have increased the risk of seizures by lowering the motor threshold. Relationships between the cognitive effects of TMS and adverse reactions have not been investigated.

DISCUSSION

In this review, we carried out a systematic search and analysis of currently available data on the effect of TMS at cognitive functions in BD patients. Our search query initially yielded in 275 articles, that were reduced to ten after further stages of screening according to the PRISMA guidelines and the PICOS formula (Figure 1). Most of the studies evaluating the effects of TMS in BD have focused on rTMS, which involves repeated magnetic pulses at a given intensity level in a specific area of the brain. In all of the studies we reviewed, stimulation with TMS was performed over the DLPFC region, either on one side or bilaterally. Previous research data indicates that the DLPFC is mainly involved in cognitive control and emotional regulation (Miller & Cohen 2001, Ochsner & Gross 2005). Our main hypothesis is that stimulating the DLPFC with rTMS can improve the cognitive function in BD patients. There are several reasons why this might be the case of rTMS. First, rTMS can prolong neuronal depolarization, enhance neurotransmission between cells, and alter neural loop activity (Gerschlager et al. 2002). Second, rTMS appears to increase brain-derived neurotrophic factor mRNA expression and protein levels, which may have a neuroprotective effect (Müller et al. 2000). Also rTMS can regulate cortical brain function by altering cortical excitability and enhancing synaptic plasticity (Machii et al. 2006). The published studies included various TMS protocols (bilateral and unilateral) and types of TMS treatment (standard rTMS, and less often deep dTMS). Consequently, the available results do not conclusively compare specific (potentially more effective) TMS protocols with certain cognitive changes, as has been previously noted in a review of the topic (Gold et al. 2019).

The available studies entailed markedly differing durations of TMS therapy, which ranged from two weeks to three months. This may reflect the present difficulty in choosing the optimal time frame for rTMS treatment, and the expectation of increased effectiveness of the treatment with increasing the duration of therapy. Some clinical parameters may be related to the need for longer rTMS treatment in BD. Thus, older patients with long-term, refractory, and severe bipolar depression may require more rTMS sessions than younger patients with briefer episodes of BD (Cohen et al. 2010). For future studies of TMS, it shall be important to clarify the optimal number of treatment sessions and to establish whether an additional phase of maintenance treatment can improve outcomes in relation to certain targeted clinical parameters, including cognition (Tavares et al. 2017).

We consider it notable that in all studies, patients had received TMS in addition to standard pharmacotherapy. From this perspective, the results of studies cannot be fully generalized, since patients with BD often receive varied and complex treatment regimens (Lin et al. 2006). However, this is not so much of a limitation as it reflects the real clinical situation for patients with bipolar disorder who may be the candidates for TMS treatment.

When analyzing the methods of neurocognitive assessment used in the various studies, we found no general methodological approach for studying cognitive functions in BD. We contend that such a framework should include uniform and comparable approaches to the identification of specific cognitive areas that are impaired and require correction, constituting a specific profile of cognitive impairment in BD as defined by specific neurocognitive markers. In this regard, appropriate research tools should be identified, namely standard psychometric methods for assessing cognitive functions through neurocognitive test batteries. The studies in the analyzed articles addressed these issues on varying measures, but, overall, this has not been sufficiently identified as a research focus. The tasks themselves and the context in which cognitive parameters were studied had considerable heterogeneity between studies. Neurocognitive testing has been

conduction either (i) in the context of the safety of TMS, or (ii) as a component of general improvement in patients with depression, or (iii) as a pathogenic marker of TMS efficacy, along with neurophysiological and clinical markers. The set of studied cognitive domains and the battery of cognitive tests differed significantly between studies. The theoretical and methodological motivation for such divergent approaches in assessing cognitive functions cannot be fully explained by the different expressed research goals. In this regard, it is also difficult to compare the choice of cognitive tests for research, their reliability and validity relative to the goals.

The studies reviewed have shown the fundamental safety and potential benefits of TMS for cognitive functioning in the treatment of patients with BD. TMS seems to improve a number of cognitive functions, such as verbal fluency (Thomas-Ollivier et al. 2017), executive function, and verbal memory (Kazemi et al. 2018), which is consistent with the findings of a previously published review (Gold et al. 2019). It is notable that the review by Gold et al. describes an improvement in working memory reported in the study by Myczkowski et al. (2018), while the authors of that study themselves noted an improvement in all studied cognitive functions (attention, inhibitory control, working memory, speech, verbal memory) regardless of the intervention group, i.e. active, sham and placebo stimulation. This does not allow us to attribute these cognitive improvements to direct effectiveness of TMS. Reports of improvement in some cognitive functions are also consistent with the available evidence of a positive effect of rTMS not only on depressive symptoms, but also on the cognitive functions in major depressive disorder, in particular, improved attention function and a tendency to improve the verbal learning score (Nadeau et al. 2014). In future studies, it shall be important to assess whether the cognitive improvement is associated with improvements in patients' daily functioning (Gold et al. 2019).

The reviewed studies confirmed high cognitive safety in BD patients, despite findings of certain mild adverse reactions to TMS treatment, namely transient headaches, insomnia, and dizziness (Yang et al. 2019). In addition, one study reported a case of transient hypomania after three weeks of left-sided, high-frequency rTMS (Hu et al. 2016), and another reported a single generalized seizure, as noted above (Harel et al. 2011). A number of studies have reported a phase reversal effect, with switching from BD to a manic episode either during or shortly after TMS treatment (Dell'Osso et al. 2015). Within the framework of the clinical problem we are studying, the presence of adverse effects during TMS treatment requires additional evaluation in terms of their relationship with the results of cognitive tests, and the potential for interaction with psychopharmacotherapy.

CONCLUSIONS

The results of our study show that (i) despite the great interest in the TMS method, the number of studies on the effects of TMS on cognition in BD remains limited. The studies we analyzed indicated (ii) fundamental safety of the TMS method in relation to cognitive functioning in BD and its potential benefits for cognitive functioning upon treatment of BD patients. In particular, TMS therapy improved indicators of cognitive functions in BD such as verbal/speech fluency, verbal memory, and the patterns of executive functioning. Finally, give that researchers have used different methodological approaches to assess cognitive functions in bipolar depression, it is evidently (iii) important to undertake centralized large-scale studies to identify optimal markers of cognition, and to structure future studies according to international standards and research recommendations for conducting clinical trials. This would enable a robust assessment of the evidence-based value of TMS protocols targeting specific cognitive functions in BD, and likewise in other socially significant mental disorders marked by perturbations in cognitive functioning.

Limitations of the study

The number of suitable primary studies meeting our criteria is small. Patients sample size, heterogeneity of study designs, lack of control groups in some studies, and differing outcome measures are some of the most significant limitations for comparing and analyzing the results obtained. In particular, the studies used differing rTMS protocols and assessed various cognitive functions.

Acknowledgements:

We express our sincere gratitude to Professor Paul Cumming of Bern University, Bern, Switzerland, for language review of the manuscript and valuable commentaries given to improve the text of this paper.

Contribution of individual authors:

Anna Strelnik & Daria Smirnova formulated the working hypothesis, inclusion criteria and search algorithm for the systematic review based on the prerequisites of relevance, and in connection with an ongoing project to study the effect of the TMS method on cognition in bipolar depression.

Anna Strelnik, Sergey Strelnik & Daria Smirnova were responsible for the literature search and wrote the first draft of the manuscript.

Ekaterina Markina, Alexander Zakharov, Aleksandr Kolsanov & Daria Smirnova contributed to the supervision in the data analysis, writing and editing of the manuscript.

Alexandr Kolsanov & Daria Smirnova share senior authorship in this paper.

All authors approved the final version of the article before its submission.

Conflict of interest:

Research project “Innovative Neuropsychiatry Research Bank: Priority-2030” is managed by the International Centre for Education and Research in Neuropsychiatry (ICERN), and supported by the strategic academic leadership program “Priority-2030” for Samara State Medical University.

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