Title: fMRI findings in cortical brain networks interactions in migraine following repetitive transcranial magnetic stimulation

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Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) is one of high-potential non-pharmacological methods for migraine treatment. The purpose of this study is to objectively evaluate the efficacy of rTMS in patients with migraine based on data from functional magnetic resonance imaging (fMRI).

Methods: 19 patients with migraine without aura underwent a 5-day course of rTMS of the ventrolateral prefrontal cortex bilaterally, at 10Hz frequency and 60% of motor threshold response of 900 pulses. Resting-state functional MRI (1.5 T) and battery of tests were carried out for each patient to clarify their diagnosis, qualitative and quantitative characteristics of pain, and associated affective symptoms. Changes in functional connectivity (FC) in the brain's neural networks before and after the treatment were identified through independent components analysis.

Results: Over the course of therapy, we observed an increase in FC of the default mode network within it, with pain system components and with structures of the visual network. We also noted a decrease in FC of the salience network with sensorimotor and visual networks, as well as an increase in FC of the visual network. Besides, we identified 5 patients who did not have a positive response to one rTMS course, presumably because of an increased trend to depressive symptoms and neuroimaging criteria for depressive disorder.

Conclusions: Our findings provide evidence of a 70% efficacy of rTMS judging by neuroimaging changes and a decrease in clinical symptoms. Moreover, we identified neuroimaging criteria for the therapy efficacy as well as possible predictors of successful/unsuccessful response to the therapy.

Keywords: migraine, headache, neurostimulation, neuroimaging, functional connectivity

Introduction:

The fact that every seventh human in the world suffers from migraine, which remains second among the causes of disability of young people, determines the importance of the subject under study [1, 2]. A low efficacy of existing symptomatic therapies and high costs in view of unknown consequences after the cessation of targeted medications force us to look for new methods for treating this disease [3].

One of high-potential alternative approaches to treatment of migraine is neurostimulation [4] and particularly repetitive transcranial magnetic stimulation (rTMS) [5]. The efficacy of this method has been confirmed for acute and preventive migraine treatment [6, 7]. Another significant advantage of TMS is the absence of side effects [8]. The most frequently used regions for TMS are the prefrontal dorsolateral cortex and primary motor cortex, the stimulation of which resulted in a lower number of migraine attacks and increased quality of life among patients [9, 10]. Yet there still are no objective criteria for treatment efficacy, nor have its pathophysiological mechanisms been thoroughly studied.

The existing paradigms of TMS efficacy in depression [11] and secondary headaches [12] are based on the application of neuroimaging methods, particularly functional magnetic resonance imaging (fMRI) which is a promising tool for

assessing interactions of the brain's neural networks in migraine patients as well [13–15]. As we know, migraine is characterized by various changes in functional connectivity (FC) in the brain's neural networks, which mostly result in pain perception disorder and the inadequate response to pain [16]. Therefore, combined rTMS/fMRI studies can help us better understand the mechanisms underlying this method of migraine treatment and set up objective criteria to assess the efficacy of therapy [17]. To assess changes in FC during TMS treatment, we have applied independent component analysis (ICA) which is based on registration of spontaneous low-frequency oscillations that occur in spatially separated, functionally connected, continuously communicating anatomical regions representing neural networks of the brain.

To select regions for TMS, we relied on the mechanisms underlying migraine and effects of TMS application as reflected in fMRI studies [18]. A headache in migraine, which arises through sensibilization of neurons in the trigeminal thalamocortical pathway, is characterized by imbalance between attention to external and internal stimuli in favor of the latter [13]. The network that is largely involved in these processes is salience network, which is responsible for perceiving, processing and switching attention between stimuli [19, 20]. Its primary structure is the insular cortex, which is a portion of the cerebral cortex folded deep within the lateral sulcus. At the same time, the activity of the inferior frontal gyrus, which is a part of the frontal temporal neural network, is closely associated with cognitive and emotional components of pain [21], and stimulating of this region by TMS can cause changes in FC of other neural networks as well [22, 23], including the default mode network, for which FC changes in migraine were described earlier [24]. In view of this, for stimulation we selected the region of the fronto-temporo-parietal junction to ensure the maximum coverage of described structures.

Methods:

Aim

We presume that fMRI and subsequent analysis of changes in FC will allow to assess the efficacy of TMS treatment in patients with migraine. To achieve this goal, we compared FC data before and after a 5-day course of rTMS by using independent component analysis for the brain's core neural networks.

Sample

During one-year screening at the Clinic of Nervous Diseases, Military Medical Academy, we selected 56 patients with diagnosed migraine without aura according to the criteria of the International Classification of Headache Disorders, 3rd edition [25]. The following criteria were applied for the inclusion in the study group: voluntary informed consent for research participation, diagnosed migraine without aura, aged 18 to 65, absence of headache at the moment of screening. The criteria for non-inclusion: contraindications to MRI and/or TMS, major psychiatric or neurological disorders, pregnancy, antidepressant medication treatment. The criteria for exclusion: interruption of the 5-day TMS therapy course, invalid/unreadable MRI scans, refusal to continue participation in the study. There were 27 patients

included in the study, but 8 patients were excluded in the course of research under the above criteria.

Thus, this study is based on the results obtained from 19 patients (16 women, average age 39.8 ± 11.1) who underwent a complete TMS course and fMRI scanning before and after the course.

All participants received a complete description of research and gave their informed consent in writing. The protocol was approved by the local ethic committee of the Military Medical Academy, St. Petersburg, Russia, and conformed to ethical standards and principles described in the Helsinki Declaration.

Test battery

A test battery was filled out by the patients twice – immediately prior to conducting fMRI before and after the TMS course. The numerical rating scale (NRS) for pain allowed to evaluate the pain intensity during the last attack before scanning, where “0” meant the absence of pain, and “10” referred to the most acute pain. The respondents filled out a standardized questionnaire in which they assessed the duration of migraine, migraine family history, number of days with headache per month; the Migraine Disability Assessment Questionnaire (MIDAS); the drug overuse anamnesis was assessed by the Leeds Dependence Questionnaire (LDQ). In addition, the patients filled out the hospital anxiety and depression scale (HADS) for screening of associated affective disorders.

Statistical analysis of demographic data and headache characteristics

Data statistical processing was performed with the software suite SPSS-25 (SPSS Inc., USA). Data distribution normality was validated by using Kolmogorov–Smirnov and Shapiro-Wilk tests. Ordinal scale data were analyzed by using the Mann-Whitney U test, matched samples with normal distribution – by using Student's t-test, and non-parametric matched samples – by using the Wilcoxon signed-ranks test, differences between which had the significance levels $p \leq 0,05$ and $p \leq 0,01$. The results were represented with Mean and Standard Deviation ($M \pm S.D.$) as well as the median and the interquartile range for ordinal scales. Pearson and Spearman analysis was used to assess correlations of test battery data.

TMS procedures

The procedures were carried out at the TMS laboratory of the Clinic of Nervous Diseases, Military Medical Academy. The patients did not receive antianginal therapy during the procedures. Each patient received five rTMS sessions during five days outside migraine attacks. Stimulations were performed with a circular coil. The stimulation field covered the lower frontal region at the temporal lobe junctions and the projection region of trigeminal nerve sensory branches. TMS was performed using a Neuro-MS/D transcranial magnetic stimulator (Neurosoft, Ivanovo, Russia). Motor thresholds were determined by independent measurements on the primary motor cortex on both sides before the first treatment session. The motor response threshold was determined by the percentage intensity of a stimulus that generated 50 μ V in the contralateral muscle abducting the thumb in 5 of 10 trials. A TMS

session consisted of bilateral stimulation at 10Hz and 60% of the motor threshold response of 900 pulses. The 10Hz protocol was introduced as a series of 60 pulses during 6.0 seconds, followed by 20 second rest (15 trains 6.5 minutes for one side).

fMRI scanning

Patients underwent fMRI scanning not earlier than a week before and not later than a week after the 5-day TMS course on a Philips Ingenia 1.5T magnetic resonance imaging scanner in attack-free intervals. The protocols – T1-weighted (301 axial sections, planar resolution of 1x1mm ; repetition time / echo time 8.0 / 3.7ms; flip angle = 8) and EPI (echo-planar imaging scan) (35 axial sections; planar resolution of 3.03x3.03mm; section depth of 4.0mm; repetition time / echo time 3000/50ms; flip angle = 90) – were obtained for each patient with preceding instructions: “Remain lying and relaxed, with closed eyes, but do not sleep.”

MRI data processing

Data were preprocessed using MATLAB R2019b software (MathWorks, Natick, MA) and the CONN 19c toolbox for functional connectivity analysis [26]. The data processing included the functional realignment and unwarp, slice-timing correction, outlier identification, direct segmentation, and normalization into standard MNI space. Functional smoothing was performed using spatial convolution with a Gaussian kernel of 8mm full width half maximum. The default denoising pipeline combines two general steps: linear regression of potential confounding effects in the blood-oxygen-level-dependent imaging signal (BOLD) based on an anatomical component-based noise correction procedure – "aCompCor" and temporal band-pass filtering. Temporal frequencies below 0.008 Hz or above 0.09 Hz are removed from the BOLD signal to focus on low-frequency fluctuations while minimizing the influence of physiological, head- motion, and other noise sources. All data were processed on a single MacBook (OS Catalina 10.15.5 software).

Statistical analysis of MRI data

Group dimensional independent component analysis was performed using the methodology of group analysis according to Calhoun [27]. All obtained data regarding functional connectivity before and after treatment were distributed into 10 components. After the spatial correlation analysis, the following components corresponding to the primary neural networks were selected: ICA_3 – salience neural network, ICA_5 – default mode network, ICA_7 – visual neural network, and ICA_10 – sensory motor network.

The subsequent comparison of FC of these networks was carried out on the basis of parametric statistics using the random field theory [Worsley, 1996] with the clusterization threshold: $p < 0.05$, the cluster size with the Benjamini–Hochberg correction (p-FDR-corrected), and the voxel threshold: $p < 0.001$ p-uncorrected. We compared 1) FC of four obtained neural networks in all the patients before and after the therapy; 2) FC of obtained neural networks in responders to the therapy and FC in non-responders to the therapy; 3) possible dependence of test results and FC changes.

Results:

Demography and clinical data

All demographical and clinical data are presented in Table 1. Statistically valid differences were observed between the results of the numerical rating scale for pain, the Leeds dependence questionnaire, the scale for evaluation of migraine impact on daily activities and fitness for work, and hospital anxiety scale for responders before and after the course of treatment.

Table 1. Demographical and clinical data of patients before and after a 5-day course of rTMS and two months after the treatment (5 of 19 patients undergo more than one TMS therapy course)

	Before TMS (n=19) [M±S.D.]	After TMS (n=19) [M±S.D.]	A month after TMS (n=19) [M±S.D.]
Gender (male/female)	3/16		
Age	39.84±7.09		
Illness duration	15.71±5.24		
The numerical rating scale for pain (last episode)**	7.74±1.45	2.42±1.57	1.75±1.71
The scale for evaluation of migraine impact on daily activities and fitness for work*	18.30±2.52	12.64±1.94	8.79±1.88
The Leeds dependency questionnaire**	13.31±5.08	7.05±4.50	7.50±3.52
Hospital anxiety scale*	7.21±2.84	5.58±2.87	5.31±2.49
Hospital depression scale*	4.89±2.40	4.11±2.34	4.25±2.98

* – $p < 0.05$ (significant differences between the states before and after one course of therapy); ** – $p < 0.01$ (significant differences between the state before and after one course of therapy); HADS = Hospital Anxiety and Depression Scale.

Results of fMRI – independent component analysis

According to ICA, the TMS course was followed by increased FC in the default mode network, decreased FC in the salience network, and both increase and decrease in FC in the visual network (Fig. 1, Table 2).

Increased FC was observed in the region between the default mode network and lateral occipital cortex + fusiform gyros / precuneus / precentral gyrus / lingual gyrus / intracalcarine cortex. On the other hand, decreased FC was observed in the regions between the salience network and postcentral gyrus / lateral occipital cortex. FC between elements of the visual network and lateral occipital cortex was increased, while in the anterior cingulate cortex the visual network FC decreased after the TMS therapy.

Fig. 1. Changes in functional connectivity in the default mode network, salience and visual networks after a 5-day TMS course. Column 3 shows ROI with changed FC (blue – before TMS; orange – after TMS). The pictures represent neural network models from *Chabran et al.* [28].

Table 2. Changes in functional connectivity in three networks with cluster names, sizes, locations according to MNI (Montreal Neurological Institute) coordinates, and validity of resulting changes with the Benjamini–Hochberg correction.

Network	MNI-space			Structure name	Cluster size (voxels)	P-FDR
	x	y	z			
Default mode network (ICA_05)	-26	-70	-18	Lateral Occipital Cortex + Fusiform gyros	125	0.000036
	+10	-54	+66	Precuneus	84	0.026138
	-30	-06	+60	Precentral gyrus	71	0.026138
	-14	-74	-02	Lingual gyrus + Fusiform gyros	70	0.033545
	+04	-74	+00	Intracalcrine Cortex	55	0.033545
Salience network (ICA_03)	+56	-14	+50	Postcentral gyrus	138	0.007110
	+18	-84	+28	Lateral Occipital Cortex + Occipital pole	81	0.022571
Visual network (ICA_07)	-22	-70	+34	Lateral Occipital Cortex	223	0.000116
	+00	+20	+34	Anterior Cingulate gyrus	124	0.003183

Results of fMRI – response to therapy

We compared the selected groups of responders and non-responders to the course of therapy in order to find out a reason for failure in the first week of stimulation. As a result, we revealed a significant difference in FC in the default

mode network (ICA_5). In nonresponders to one course of therapy, much higher dissociation of FC was observed between the medial prefrontal cortex and other regions of default mode network, that associated with affective alterations (Fig. 2). It should be noted that there was a statistically valid difference in the dynamics of decreasing scores on the scale for evaluation of migraine impact on daily activities and fitness for work and on the depression scale for responders to the therapy in comparison with non-responders (Table 3).

Fig. 2. Changed functional connectivity of the medial prefrontal cortex in the default mode network (ICA_5) in responders in comparison with the non-responders.

Table 3. Test battery data of responders and non-responders to one course of TMS therapy.

	Responders (n=14) [M±S.D.]	Non-responders (n=5) [M±S.D.]
The numerical rating scale for pain (last episode)		
Before	8.14±1.41	6.60±0.89
After	2.36±1.44	4.25±0.96
The scale for evaluation of migraine impact on daily activities and fitness for work*		
Before	18.30±2.52	21.66±3.12
After	12.64±1.94	18.82±2.73
The Leeds dependency questionnaire		
Before	13.31±5.08	13.36±3.61
After	7.05±4.50	10.5±4.80
Hospital anxiety scale		
Before	7.20±2.84	9.60±2.88
After	5.40±2.87	7.00±3.31
Hospital depression scale*		
Before	4.89±2.40	5.20±1.93
After	3.64±1.90	5.40±3.29

* – p<0.05 (significant differences between the state before and after one course of therapy).

Discussion:

The presented pilot study of efficacy of stimulating the ventrolateral prefrontal cortex by repetitive TMS in patients with migraine has demonstrated certain evidence of the therapy success based on correlations of clinical and neuroimaging data. The statistically significant differences based on the results of testing the patients before and after the applied therapy point to positive effects of TMS on patients' quality of life and amount of medication treatment. Furthermore, it should be noted that the effect of the applied TMS therapy remained evident for a month. We obtained the results of independent component analysis which revealed FC changes in three primary neural networks of the brain.

Default Mode network is a neural network which activity is registered (as evident from its name) in a relaxed state of rest and which is extremely important for self-referential cognitive processes, interoception, and self-control [24, 29]. Most authors have reported a decrease in FC both inside the default mode network and between it and other neural networks in patients with migraine, which could point to functional disorders in that network, yet there are data to the contrary as well [24].

In the structure of the default mode network, the connectivity of the posterior cingulate gyrus with the precuneus plays a key role in antinociceptive and multisensory integration, and a decrease in FC between these structures might be a reason for the described functional disorders. Such contradictory findings point to a slight increase in FC between the posterior cingulate gyrus and the precuneus in patients with migraine in comparison with healthy volunteers [31]. Our study has shown an increase in FC between the default mode network structure and the precuneus, which could be explained by activation of the antinociceptive system of that network and normalization of the multisensory integration function, presumably as a result of the course of therapy [32].

Reduced FC between the default mode network and precentral gyrus could reflect difficulties of multisensory information integration [33]. The restoration of this connections after a TMS therapy course also allows to presume an increase in antinociceptive activity of the so-called brain's pain system and a decrease in pain rumination [34].

Finally, increased FC with the lateral occipital cortex, lingual gyrus, and fusiform gyros could be evidence of interaction between the default mode network and the visual network whose activity changes have been observed in patients with migraine [35]. Reduced FC between these two networks was a characteristic feature that distinguished patients with migraine without aura from healthy volunteers [36]. Our findings provide evidence of normalized connectivity between the default mode network and the visual network after a course of TMS therapy.

Visual network – FC changes in the visual network are the most indicative differences of patients with migraine from healthy volunteers, presumably due to hyperexcitability of the visual cortex in migraine patients both with and without aura [32]. In addition to the increase in FC with the default mode network, there was observed a decrease in connectivity between both the visual (lateral occipital cortex) and salience (anterior cingulate gyrus) networks. This observation could explain a decrease in inner attention to external and internal stimuli, which, in turn, reduces

headache severity [37]. Often observed photophobia in patients could also be a reason for changed FC, and therefore its absence would lead to normalization of neural network activity [35].

Salience network is a neural network that is presumably involved in pain stimulus integration and subsequent switching between resting-state and active networks in migraine [19, 20]. Increased FC with the postcentral gyrus and the right insular cortex was observed in migraine patients in previous studies [38]. The change of FC between those regions may play an important role not only in decreasing inner attention to pain impulses, including due to an actual decrease in the number of pain stimuli, but also in decreased pain rumination [34]. It might also be supposed that the TMS effect results in normalizing the mechanisms of multisensory processing which are damaged in migraine patients [32].

Fig. 3. Overall scheme of 5-day rTMS course effects on changes in FC between main resting-state neural networks. FC – functional connectivity; VN – visual network; DMN – default mode network; SN – salience network; SMN – sensorimotor network.

Finally, we found possible predictors of positive response to TMS therapy according to the described protocol. We presume that patients' predisposition to comorbid depressive symptoms, as well as their identifiable neuroimaging criteria (Fig. 3, Table 3), could be a reason for negative response to therapy. In this case, attention should be paid to their early recognition and the use of the simulation protocol for the dorsolateral prefrontal cortex or other treatment options [39].

Our study has some substantial limitations, such as the absence of placebo control in the form of sham TMS, a relatively small sample of patients, no control over medication intake, and no analysis of FC changes in subcortical structures

which could be associated with the pain system. Questions also arise regarding the absence of correlation between FC changes and applied test scales.

Conclusion:

The results of this study to a certain extent prove the efficacy of the protocol of repetitive transcranial magnetic stimulation in migraine patients as a preventive therapeutic method. Moreover, we identified neuroimaging criteria for determining the efficacy of therapy as well as possible predictors of successful/unsuccessful response to the therapy. However, further research is required, with an extended sample and placebo control, which we intend to conduct in near future.

List of abbreviations:

rTMS – repetitive transcranial magnetic stimulation
fMRI – functional magnetic resonance imaging
FC – functional connectivity
ICA – independent component analysis
MIDAS – Migraine Disability Assessment Questionnaire
LDQ – Leeds Dependence Questionnaire
HADS – hospital anxiety and depression scale
BOLD – blood-oxygen-level-dependent

Declarations:

Ethics approval and consent to participate

All participants received a complete description of research and gave their informed consent in writing. The protocol was approved by the local ethic committee of the Military Medical Academy, St. Petersburg, Russia, and conformed to ethical standards and principles described in the Helsinki Declaration.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

AT performed the neurological examination of patients, analyzed and interpreted the patient data, and was contributor in writing the manuscript. KM analyzed and

interpreted the patient data, performed the neuroimage data analysis, and was a major contributor in writing the manuscript. DF performed the TMS procedures. IL was contributor in writing the manuscript. DT performed the fMRI scanning procedures. AK performed the statistical analysis of patient data. VP performed the neurological examination of patients. AE performed the fMRI scanning procedures. DM made the translation of the manuscript. All authors read and approved the final manuscript.

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