STRUCTURAL AND FUNCTIONAL BIOMARKERS OF EFFICACY OF NAVIGATED REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN THERAPY FOR TRIGEMINAL NEURALGIA

Poydasheva AG ✉, Sinitsyn DO, Bakulin IS, Suponeva NA, Piradov MA

Research Center of Neurology, Moscow, Russia

Repetitive transcranial magnetic stimulation (rTMS) is an alternative treatment option for patients with drug-resistant trigeminal neuralgia (TN). However, the effect of rTMS is variable. The aim of this study was to find neuroimaging biomarkers of clinical efficacy of navigated rTMS. Seventeen patients with TN (14 women and 3 men, median age 56 years) received 10 sessions of high-frequency rTMS of the motor cortex contralateral to pain side. The data were analyzed for correlations between functional connectivity (FC), the grey matter (GM) volume and the reduction in pain intensity. Positive correlations were established between the reduction in average pain intensity and GM volume in caudate nuclei in both hemispheres (p(unc) = 0.03), both cerebellar hemispheres (p(unc) = 0.002) and the postcentral gyrus contralateral to pain side (p(unc) = 0.005); between the reduction in peak pain intensity and GM volume in the caudate nucleus contralateral to pain side (p(unc) = 0.04) and the cerebellar hemisphere ipsilateral to pain (p(unc) = 0.03). Significant positive correlations were discovered between the reduction in average pain intensity and FC between the thalamus contralateral to pain side, the postcentral gyrus and the insular operculum (both ipsilateral to pain side; (p(FWE) = 0.018), as well as between the cingulate cortex and the anterior cingulate cortex ipsilateral to pain (p(FWE) = 0.017), between the contralateral subcallosal gyrus and the cerebellar hemisphere ipsilateral to pain (p(FWE) = 0.018). A negative correlation was established for FC between the contralateral putamen and the occipital lobes in both hemispheres (p(FWE) = 0.001). Our findings may spur the development of individual predictors of rTMS efficacy in patients with chronic pain.

Keywords: neuralgia, trigeminal nerve, voxel-based morphometry, functional connectivity, biomarker, transcranial magnetic stimulation

Author contribution: Poydasheva AG, Bakulin IS, Suponeva NA designed and planned the study; Poydasheva AG analyzed the literature; Poydasheva AG, Sinitsyn DO collected and analyzed the obtained data, wrote the draft version of the manuscript; All authors participated in editing the manuscript.

Compliance with ethical standards: the study was approved by the local Ethics Committee of the Research Center of Neurology (Protocol № 9–4/16 dated October 5, 2016) and complied with the Declaration Helsinki; informed consent was obtained from all study participants.

✉ **Correspondence should be addressed:** Alexandra G. Poydasheva
Volokolamsckoe shosse, 80, Moscow, 125367; poydasheva@neurology.ru

Received: 18.05.2021 **Accepted:** 02.06.2021 **Published online:** 12.06.2021

DOI: 10.24075/brsmu.2021.027

СТРУКТУРНО-ФУНКЦИОНАЛЬНЫЕ БИОМАРКЕРЫ ЭФФЕКТИВНОСТИ НАВИГАЦИОННОЙ РИТМИЧЕСКОЙ ТРАНСКРАНИАЛЬНОЙ МАГНИТНОЙ СТИМУЛЯЦИИ В ЛЕЧЕНИИ НЕВРАЛГИИ ТРОЙНИЧНОГО НЕРВА

А. Г. Пойдашева ✉, Д. О. Синицын, И. С. Бакулин, Н. А. Супонева, М. А. Пирадов

Научный центр неврологии, Москва, Россия

У пациентов с невралгией тройничного нерва (НТН), не отвечающих на фармакотерапию, в качестве альтернативы можно применять ритмическую транскраниальную магнитную стимуляцию (рТМС). Однако эффект рТМС вариабелен. Целью исследования был поиск нейровизуализационных биомаркеров клинической эффективности навигационной рТМС. Семнадцати пациентам с НТН (14 женщин; медиана возраста — 56 лет) проведено 10 сессий высокочастотной рТМС моторной коры полушария, контрлатерального локализации боли. Проводили анализ корреляций функциональной коннективности (ФК) и объема серого вещества головного мозга (СВГМ) со снижением интенсивности боли. Показана положительная корреляция между снижением средней интенсивности боли и объемом СВГМ в области хвостатых ядер (p(unc) = 0,03), мозжечка билатерально (p(unc) = 0,002) и контрлатеральной постцентральной извилине (p(unc) = 0,005); между снижением максимальной интенсивности боли и объемом СВГМ в области хвостатого ядра контрлатерально боли (p(unc) = 0,04) и мозжечка ипсилатерально (p(unc) = 0,03). Продемонстрирована положительная связь снижения средней интенсивности боли с ФК между таламусом (контрлатерально локализации боли) и ипсилатеральной постцентральной извилиной и покрышкой островка (p(FWE) = 0,018), между поясной корой и передними отделами поясной коры ипсилатерально боли (p(FWE) = 0,017), между контрлатеральной паратерминальной извилиной и мозжечком ипсилатерально (p(FWE) = 0,018); отрицательная корреляция для ФК между контрлатеральной скорлупой и затылочными долями обоих полушарий (p(FWE) = 0,001). Полученные результаты могут стать предпосылкой к разработке индивидуальных предикторов эффективности рТМС у пациентов с хроническими болевыми синдромами.

Ключевые слова: невралгия, тройничный нерв, воксель-ориентированная морфометрия, функциональная коннективность, биомаркеры, транскраниальная магнитная стимуляция

Вклад авторов: А. Г. Пойдашева, И. С. Бакулин, Н. А. Супонева — планирование и дизайн исследования; А. Г. Пойдашева — анализ литературы; А. Г. Пойдашева, Д. О. Синицын — сбор и анализ данных, подготовка черновика рукописи статьи; все авторы — интерпретация данных; все авторы — редактирование рукописи.

Соблюдение этических стандартов: проведение исследования одобрено локальным этическим комитетом ФГБНУ НЦН (протокол № 9–4/16 от 05 октября 2016 г.) и соответствовало принципам Хельсинкской декларации; все пациенты подписали добровольное информированное согласие.

✉ **Для корреспонденции:** Александра Георгиевна Пойдашева
Волоколамское шоссе, 80, г. Москва, 125367; poydasheva@neurology.ru

Статья получена: 18.05.2021 **Статья принята к печати:** 02.06.2021 **Опубликована онлайн:** 12.06.2021

DOI: 10.24075/vrgmu.2021.027

Trigeminal neuralgia (TN) is characterized by short-lived paroxysms of acute severe facial pain in the cutaneous trigeminal distribution. The prevalence of TN in the general population is estimated at 0.03–0.3% [1]. Although therapy with sodium channel blockers is highly effective against TN, as many as half of the affected patients develop resistance to it over time [2]. Invasive procedures (e.g. microvascular decompression) and transcranial magnetic stimulation (TMS) offer an alternative to conventional pharmacotherapy for TN [3–5].

TMS is a non-invasive technique for brain stimulation that uses a high-density alternating magnetic field to modulate the excitability of a target (stimulated) brain area. During

repetitive (rhythmic) transcranial magnetic stimulation (rTMS), multiple magnetic pulses (usually over 1,000) are applied in succession; the directionality of their effect on the target depends on stimulation frequency. It is widely hypothesized that the underlying mechanisms of rTMS share similarity with long-term potentiation (LTP) and long-term depression (LTD) or may affect neurotransmitter synthesis and the genetic apparatus of the cell [6]. Regarding the analgesic effect of rTMS, studies show that rTMS can modulate endogenous opioid neurotransmission in the antinociceptive structures of the brain, restore cortical excitability and impaired intracortical interactions [7]. The panel of European experts has concluded that rTMS has the highest level of evidence-based efficacy for chronic neuropathic pain (level A, or "definitely effective") [4]. According to the systematic review of 11 studies investigating the efficacy of rTMS against chronic neuropathic orofacial pain, including trigeminal neuralgia, rTMS is an effective and safe modality [8]. At the same time, in another study the protocol recommended for chronic pain relief (high-frequency stimulation of the primary motor cortex contralateral to pain side) had no significant analgesic effect in patients with TN and atypical facial pain [9]. The reason for such inconsistency and one of the factors impeding wide use of rTMS in clinical practice is the variability in the rTMS-induced effect [10]. Conducting a search for predictors of response to rTMS may hold promise for finding the right solution [11]. Here, one of the approaches is to identify brain regions in which structural or functional changes are correlated with rTMS efficacy. This approach was best elaborated for depressive disorders. For example, 4 biotypes were identified from patient resting-state fMRI data based on patient response to rTMS [12]. Other studies demonstrated that functional connectivity (FC) between various brain regions can serve as a predictor of response to rTMS, but the results of those studies were very heterogenous and no clear concept was proposed for identifying patients with a potentially good response to stimulation from specific connections [11, 13]. It is reported that structural data can be used to predict response to rTMS among patients with depressive disorders, tinnitus and schizophrenia [14, 15]. But no similar studies have been conducted in patients with trigeminal neuralgia so far.

The aim of this study was to find neuroimaging markers of clinical efficacy of navigated rTMS in patients with trigeminal neuralgia.

METHODS

Methodology of the study

The study included patients aged 18-80 years with classical TN according to the International Classification of Headache Disorders 3rd edition, 2013 (ICHD-3). The following inclusion criteria were applied: primary trigeminal neuralgia; mean pain intensity ≥ 4 points on the Pain Numeric Rating Scale (NRS); insufficient efficacy or intolerance of standard medication therapy for TN. Exclusion criteria: contraindications for MRI or rTMS; refusal to participate in the study; severe adverse effects; pregnancy. Prior to the study, all the participants underwent at least a one-month long fixed-dose therapy with sodium channel blockers. The patients did not receive other drugs that could have affected their central nervous system.

Neuroimaging

Every patient underwent a neuroimaging examination, which was conducted using a Siemens 3T Magnetom Verio scanner (Erlangen, Siemens; Germany).

Anatomical T1-weighted scans were acquired at isotropic resolution for further multiplanar reconstruction (MPR) (TR 1900 ms, TE 2.47 ms, slice thickness 1 mm, number of slices 176, scan time 4 min 18 s). The obtained structural data were analyzed by means of voxel-based morphometry (VBM) and used for neuronavigation and coil orienting during rTMS. Before the VBM analysis, the obtained structural MR images of the brain were preprocessed in SPM 12 using the Dartel method for VBM [16]. Briefly, the images were segmented into different tissue types; then, a common (TN-group specific) template was created and nonlinear transformations were computed to normalize the images to this template using the Dartel algorithm. After that, the data were normalized to MNI space using the option of preserving the amount of tissue and smoothed with a Gaussian kernel (FWHM = 10 mm). Statistical analysis of the resulting images was done in SPM 12. Specifically, the relative volumes of the grey matter (GM) were analyzed; for that, the images were normalized by the brain volume for each study participant.

Resting-state fMRI images for the subsequent FC analysis were acquired in the multiplanar gradient echo mode (ep2d_bold_moco: TR 2400 ms, TE 30 ms; flip angle 90°, matrix 64 × 64; FoV 192 × 192 mm^2, 36 slices in the axial plane). The obtained functional images were preprocessed in the CONN functional connectivity toolbox, ver. 17f (Alfonso Nieto-Castanon; USA) and SPM12 (The Wellcome Centre for Human Neuroimaging; UK). Preprocessing included realignment (head motion correction), slice-timing correction, structural/functional co-registration, segmentation of structural images, normalization to a standard MNI (Montreal Neurological Institute) space, identification and rejection of outlier scans using the ART tool, and spatial smoothing with an 8 mm Gaussian kernel. For each patient, the total number of outlier scans had to be less than a half. To denoise the images, a 0.008–0.09 Hz band-pass filter was applied.

Navigated rTMS

Navigated rTMS was performed using a Magstim Rapid2 stimulator (The Magstim Company Ltd; US) calibrated for NBS (Navigated Brain System) Eximia Nexstim (Nexstim Plc.; Finland). Each patient received a total of 10 rTMS session (5 daily sessions a week, except weekends) of high-frequency rTMS of the primary motor cortex contralateral to pain localization (stimulation frequency 10 Hz, intensity 90% of the resting motor threshold, train duration 4 s, intertrain interval 26 s, a total of 1,600 pulses per session). The hotspot of the abductor pollicis brevis muscle on the body side ipsilateral to pain side was used as a target. The resting motor threshold was determined once, before the beginning of the first rTMS session, by means of the Rossini–Rothwell method. The stability of coil position was monitored during each session using the neuronavigation system. The analgesic effect of rTMS was measured on NRS. Peak and average pain intensity was assessed before and immediately after 10 rTMS sessions. Statistical analysis was carried out in MATLAB R2017a (Mathworks, Inc.; USA) using the Wilcoxon signed rank test. Differences were considered significant at $p = 0.05$.

Study of clinical and neuroimaging correlations

To identify neuroimaging biomarkers of clinical efficacy of rTMS, we analyzed how changes in average and peak (for VBM analysis only) pain intensity measured on NRS were correlated

Table 1. Areas of interest (Henssen et al., 2019) selected for the analysis of clinical and neuroimaging correlations between the strength of response evoked by rTMS and structural/functional features of the brain

Cluster	Gyrus/region	Brodmann areas	R/L	Cluster volume, mm^3	Cluster coordinates (MNI) *x, y, z*, mm		
1	Pulvinar		L	880	–11.1	–27.2	7.1
2	Superior Temporal Gyrus	22	L	736	–49.8	–17.8	4.7
3	Subcallosal Gyrus	47	L	592	–13.7	22.2	–10
4	Insula	13	R	552	29.3	–21.9	16.2
5	Thalamus		R	520	5.2	–8.7	5.4
6	Cingulate Gyrus	31	R	520	4.9	–42.7	28.3
7	Middle Temporal Gyrus	21	R	496	39	–6.8	–12.8
8	Caudate Head		R	360	7.6	8.2	–5.1
9	Putamen		L	296	–23.3	–7.8	7.7
10	Transverse Temporal Gyrus	41	R	216	35.8	–32.3	11
11	Caudate Head		L	136	–8.5	7.8	1.9
12	Precentral Gyrus	6	L	136	–55.9	0.7	27.5
13	Anterior Cingulate Cortex	24	L	128	–1.7	33.7	8
14	Putamen		L	120	–20.6	7.7	3.7
15	Anterior Cerebellar Lobe		L	112	–3.6	–43.9	–7.3
16	Medial Frontal Gyrus	10	R	112	17.8	60.6	2.1
17	Middle Frontal Gyrus	9	R	112	48.7	12	33.3
18	Postcentral Gyrus	1	L	112	–53.5	–18.7	45.8
19	Insula	13	R	104	34.3	12.7	–8.3
20	Culmen		R	104	6.3	–48	–5.4
21	Precuneus	31	R	104	9.7	–62.3	27.2
22	Medial Frontal Gyrus	9	R	104	10	27.4	32.3

Note: R — right hemisphere; L — left hemisphere.

with FC and GM volume (measured before rTMS) in those brain regions that, according to [17], are characterized by a significantly lower amount of grey matter in patients with TN than in healthy volunteers (Table 1).

The neuroimaging data of patients who had pain on the left side (n = 4) were intentionally flipped so that pain was localized to the right side for all study participants. For the analysis of functional biomarkers, the average signal in each area of interest was correlated with the signals from all voxels in the brain (seed-based analysis). The significance of rTMS effects was assessed from the resultant statistical parametric maps using Gaussian random field theory. The voxel-wise significance threshold was assumed to be 0.001 (uncorrected); significant clusters were selected, using a two-sided test with FWER control at 0.05. The results were not corrected for the number of areas of interest. For the analysis of structural biomarkers, we also employed the regression analysis of associations between GM volume in the areas of interest and changes in average and peak pain intensity. The analysis was carried out in MarsBaR (Matthew Brett; UK) for SPM, with a significance threshold of 0.05, without correction for multiple comparisons.

RESULTS

Voluntary informed consent to participate in the study was given by 20 patients. Two patients decided to drop out after sessions 4 and 7, respectively, due to commuting problems; one more patient was excluded from the analysis due to the presence of strong motion artifacts on his MRI scans. Thus, the final dataset subjected to the analysis included data of 17 patients (median age: 56 years [38; 65]).

While analyzing the effects of navigated rTMS, we discovered a statistically significant reduction in peak (p = 0.01) and average (p < 0.01) pain intensity on NRS. For half of the patients, the analgesic effect was significant: peak pain intensity had dropped by more than 30% relative to its initial level.

The analysis of correlations between the reduction in peak and average pain intensity on the numeric rating scale and

Table 2. Correlations between grey matter volume and rTMS effect

Clinical parameter	Areas in which grey matter volume positively correlates with rTMS effect	ROI (coordinates), *x, y, z* (Henssen et al., 2019)	*p* (unc)
Reduction of average pain intensity	Caudate Head (I)	7.6 8.2 –5.1	0.033
	Caudate Head (C)	–8.5 7.8 1.9	0.034
	Anterior Cerebellar Lobe (C)	–3.6 –43.9 –7.3	0.002
	Postcentral Gyrus (C)	–53.5 –18.7 45.8	0.005
	Culmen (I)	6.3 –48 –5.4	0.003
Reduction of peak pain intensity	Caudate Head (C)	–8.5 7.8 1.9	0.04
	Culmen (I)	6.3 –48 –5.4	0.033

Note: C — the area of interest is localized to the hemisphere contralateral to pain side; I — the area of interest is localized to the hemisphere ipsilateral to pain side.

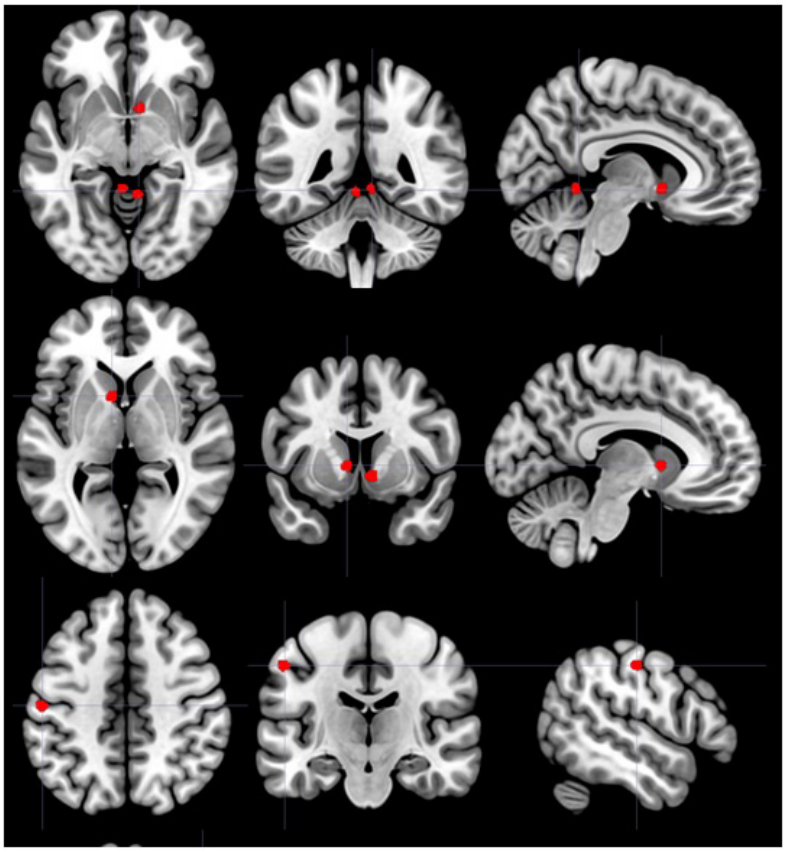

Fig. 1. Brain areas in which grey matter volume is positively correlated with the reduction in peak or average pain intensity (p(unc) < 0.05)

GM volume in the areas of interest identified in [17] showed that the reduction in average pain intensity was positively correlated with GM volume in the caudate head (bilaterally), in the postcentral gyrus contralateral to pain side and in both cerebellar hemispheres (Table 2).

In turn, the reduction in peak pain intensity was positively correlated with GM volume in the caudate head contralateral to pain and in the cerebellar region ipsilateral to pain (Table 2; Fig. 1).

The analysis of correlations between the clinical effect of rTMS and functional connectivity in the areas of interest identified in [17] revealed a positive correlation between the reduction in average pain intensity on NRS and the functional connectivity between the thalamus (contralateral to pain), the postcentral gyrus ipsilateral to pain side and the insular operculum ipsilateral to pain side (Table 3).

In addition, a positive correlation was established between the reduction in average pain intensity and FC between 1) the cingulate cortex ipsilateral to pain side and the anterior cingulate cortex ipsilateral to pain side, and 2) the subcallosal gyrus contralateral to pain localization and the cerebellar hemisphere and peduncle contralateral to pain. A negative correlation was established between the reduction in average pain intensity and FC between the putamen contralateral to pain side and the occipital lobes in both hemispheres (Fig. 2).

DISCUSSION

After a series of navigated repetitive transcranial magnetic stimulation sessions, a significant reduction in peak and average pain intensity was observed among patients with TN. The response to magnetic stimulation was correlated with some anatomical and functional changes in central nervous system structures detected prior to the beginning of rTMS therapy. Specifically, we found correlations between the effect of rTMS and the functional connectivity of brain areas involved in the primary processing of pain inputs (the thalamus and

Table 3. Correlations between the functional connectivity of brain regions and rTMS effect on average pain intensity. The table features cluster-wise FWE-corrected p values for the areas of interest on each connectivity map, uncorrected for the number of such zones (clusters with p(FWE) < 0.05)

Areas of interest	Anatomical regions	Cluster coordinates (MNI) *x, y, z*, mm	Cluster volume, mm^3	p (FWE)	Direction of correlation
Thalamus (C)	Postcentral Gyrus (I) Insular Operculum (I)	+60 –16 +18	133	0,018	+
Subcallosal Gyrus (C)	Cerebellar Hemisphere and Cerebellar Peduncle (I)	+32 –62 –38	126	0,018	+
Cingulate Cortex (I)	Anterior Cingulate Cortex (I)	+26 +34 +06	151	0,017	+
Putamen (C)	Occipital Pole (I) Fusiform Gyrus (I)	+20 –100 +00	211	0,001	–
	Occipital Pole (C) Lateral Occipital Cortex (C)	–18 –100 –08	195	0,002	–

Note: C — the area of interest is localized to the hemisphere contralateral to pain side; I — the area of interest is localized to the hemisphere ipsilateral to pain side.

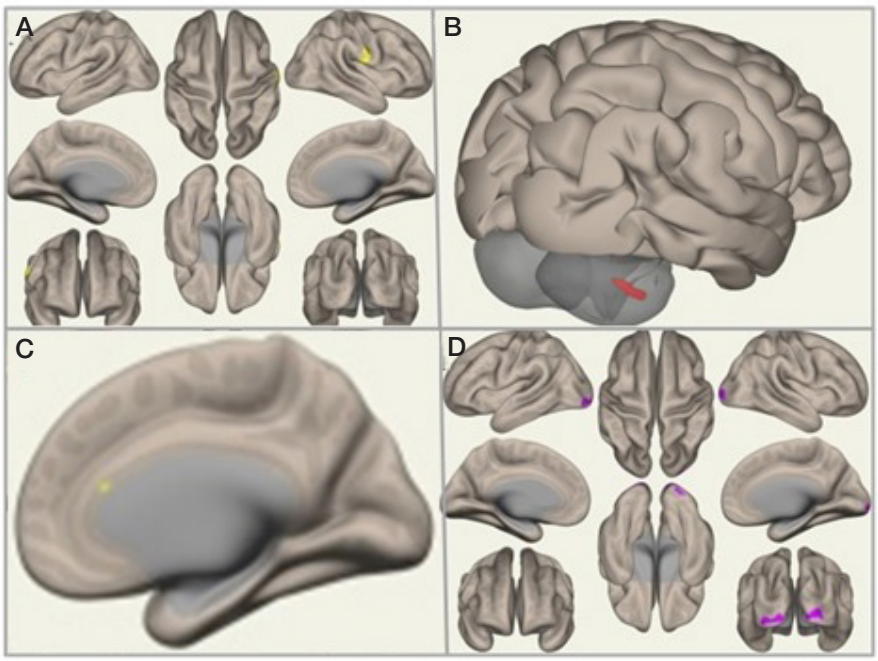

Fig. 2. Brain areas for which FC is correlated with the reduction in average pain intensity (p(FWE) < 0.05). **A**. Thalamus contralateral to pain side. **B**. Subcallosal gyrus contralateral to pain side. **C**. Cingulate gyrus ipsilateral to pain side. **D**. Putamen ipsilateral to pain side

the postcentral gyrus), the affective component of pain and behavioral response to it (the insula and the cingulate cortex). While investigating the structural biomarkers of response to rTMS, we found that the strength of the rTMS effect was positively correlated with GM volume in the caudate nuclei, the postcentral gyrus and the cerebellum.

Before embarking on a more detailed discussion of specific zones, their role and function in the development of TN, we would like to highlight the use of intentional dataset flipping as part of the methodology employed for this study: patient data was flipped left to right for group analysis so that the left hemisphere was contralateral to pain side for all study participants. Our intention was to obtain more homogeneous data in the areas associated with pain transmission and primary processing (the thalamus, primary somatosensory regions, the insula of the contralateral hemisphere, etc.). At the same time, this manipulation resulted in the increase in the heterogeneity of the signal from structures which had been previously shown to have structural and functional left-right asymmetries. For example, large-sample VBM-based studies reported an asymmetry in the frontal, temporal, occipital poles, Heschl gyrus, hippocampus, regions involved in speech and language, etc. [18]. Similar findings were reported in a study of functional connectivity; the greatest asymmetry was observed in the associative areas of the frontal, temporal and occipital lobes and language-related regions [19]. In a study [20], GM volumes were compared between patients with TN and healthy volunteers; the same areas were identified using flipped and non-flipped datasets, but the strength of the effect was less for the non-flipped data. So, having analyzed the literature, we decided to flip our dataset. However, this may have been the reason why no expected correlations for the rTMS effect were observed in the dorsolateral prefrontal cortex and the superior and middle temporal gyri, which were structurally and functionally changed in patients with TN in comparison with healthy volunteers.

The thalamus in the hemisphere contralateral to pain side stands out among the areas whose functional connectivity was correlated with the effect of rTMS in our study. The nuclei of the thalamus are the central relay that forwards nociceptive pulses from the sensory nuclei of the trigeminal nerve to the primary somatosensory cortex; i.e., the thalamus is the key player involved in the processing of pain signals. Destruction of the specific complex of thalamic nuclei by means of gamma knife surgery in patients with drug-resistant TN effectively reduces pain intensity without causing a sensory deficit [21]. Importantly, the thalamus might be immediately involved in producing the analgesic effect in response to rTMS. In the experiment on rats, the neuronal activity of some thalamic nuclei was inhibited by invasive direct current stimulation of the motor cortex [22]. Thus, the established correlations between FC of the thalamus and the response to rTMS may be associated with the diverse roles of thalamic nuclei in the processing of pain inputs, the development of chronic pain and the response to the stimulation of the motor cortex.

Our study established a correlation between the rTMS-induced effect and the functional connectivity of the anterior cingulate cortex. It is traditionally held that the anterior cingulate cortex plays an essential role in the development and maintenance of neuropathic pain; specifically, it participates in the modulation and processing of pain affect [23]. Moreover, the inhibition of the cingulate cortex in rats with optogenetically induced trigeminal neuropathy attenuates pain-associated behaviors and inhibits the pathologic activity of thalamic sensory neurons [24]. However, experiments involving deafferentation pain models demonstrate that the analgesic effect of direct current stimulation of the motor cortex is associated with the activation of the anterior cingulate cortex [25]. Despite controversial data on the possible association between the activity of the anterior cingulate cortex and pain, it is clear that modulation of this brain region may be associated with a change in the intensity of pain, primarily due to its involvement in the affective processing of pain inputs.

Another correlation discovered in this study is between GM volume and the functional connectivity of striatum structures, including the putamen and the caudate nucleus, and the rTMS effect. This finding is supported by the results of other experimental works, including a PET-based study in macaques in which rTMS of the primary motor cortex led to an increase in extracellular dopamine concentrations in the ventral striatum

and a decline in dopamine levels in the putamen [26]. In turn, the effect of rTMS on dopaminergic neurotransmission is hypothesized to underly the analgesic effect of this modality [7].

Interestingly, we established an association between GM volume in cerebellar structures and the response to rTMS. A PET-based experimental study revealed reduced functional connectivity between the cerebellum and some prefrontal brain regions in animals with neuropathic pain [27]. The role of the cerebellum in the processing of pain inputs and development of chronic pain was confirmed by a number of studies. Specifically, it was reported that signals from primary nociceptive afferent nociceptors are transmitted to cerebellar structures [28], cerebellar structures were activated following modeling of acute and chronic pain [29], and the current stimulation of the cerebellum modulated the processing of pain inputs [30]. Besides, GM volume was reduced in the cerebellar structures of patients with TN [17, 20].

Brain areas identified in our study coincide with brain areas where changes had been previously associated not only with TN, but also with other types of chronic pain [31]. This may indicate that imaging biomarkers of rTMS response bear connection to perception, integration and processing of pain inputs, as well as mechanisms implicated in the development of chronic pain, but are not associate with a particular disease, which is confirmed by the efficacy of rTMS against a variety of chronic pains [32].

The optimization of treatment choice for expediting recovery, minimizing adverse effects and reducing therapy-associated costs is one of priority tasks facing the research community. Methods of patient selection based on neuroimaging data are being intensively developed in psychiatry: there are ongoing studies of biomarkers of response to pharmacotherapy, psychotherapy, rTMS [12; 33]. This approach holds promise for other nosologies. Our findings may create a premise for developing neuroimaging predictors of response to rTMS in patients with chronic pain and confirm the feasibility of this approach in the context of noninvasive brain stimulation.

Study limitations

The first limitation is the absence of multiple comparisons correction for the number of areas of interest. Because of that, the established correlations indicate the areas of the brain with the highest probability of finding the effects and require verification in further studies. Second, our sample size was quite small and thus was a constraint for the generalization of the obtained results. Finally, we had no control group and therefore cannot assert that the identified biomarkers are absolutely specific for active, non-placebo rTMS. However, previous controlled studies provided compelling evidence on the advantage of active rTMS effects over placebo in patients with TN [8], and the proportion of responsive individuals in our study was consistent with previously reported data [4].

CONCLUSIONS

Our study was the first to identify structural and functional biomarkers that are the most likely predictors of the analgesic effect of navigated transcranial magnetic stimulation therapy in patients with TN. We have established a few positive and negative correlations between the response to rTMS and the functional connectivity of the thalamus, the postcentral gyrus, the insular operculum, the anterior cingulate cortex and other regions, as well as between the response to rTMS and GM volume in caudate nuclei, the postcentral gyrus and the cerebellum. Our findings may create a premise for developing individual predictors of rTMS effect and tailoring noninvasive brain stimulation methods to individual patients with chronic pain.

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