Journal of Pain Research

Dovepress
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ORIGINAL RESEARCH

The Neural Mechanisms of rTMS and Placebo Effects in Trigeminal Neuralgia: Evidence From fMRI Network Dynamics

Ying Liu[1,*], Hao Chen[1], Suhui Chen[2], Liangjiecheng Huang[3], Zhiying Jin[3], Xuanqi Guo[3], Xiaofeng Jiang[4], Ying Wang[4–6,*]

[1]Department of Radiology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, 230001, People's Republic of China; [2]Department of Rehabilitation, The First Affiliated Hospital of USTC, Hefei, Anhui, 230001, People's Republic of China; [3]School of Humanities and Social Sciences, University of Science and Technology of China, Hefei, Anhui, People's Republic of China; [4]Department of Neurosurgery, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, 230001, People's Republic of China; [5]Anhui Provincial Stereotactic Neurosurgical Institute, Hefei, Anhui, 230001, People's Republic of China; [6]Anhui Province Key Laboratory of Brain Function and Brain Disease, Hefei, Anhui, 230001, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiaofeng Jiang; Ying Wang, Email xfjiang110@126.com; wy1987@ustc.edu.cn

Objective: Repetitive transcranial magnetic stimulation (rTMS) has been suggested to possess analgesic properties, yet its efficacy in treating trigeminal neuralgia (TN) remains uncertain.

Methods: In this randomized, double-blind trial, thirty-four patients were randomly allocated to one of three groups: active M1-targeted rTMS, sham stimulation, or active stimulation of the dorsolateral prefrontal cortex (dlPFC) as a control. The treatment protocol spanned two weeks, consisting of two 5-day stimulation sessions separated by a 2-day interval. MRI and clinical outcomes (VAS, Hamilton Anxiety/Depression Scales) were assessed pre-/post-intervention and at one-month follow-up.

Results: Significant reductions in pain, anxiety, and depression occurred across all groups. Neuroimaging revealed decreased insular cortex activation universally, while increased frontal lobe activity emerged specifically in sham and control groups. Notably, no intergroup differences in clinical outcomes were observed despite distinct neural pathways, specifically involving the insula rather than the prefrontal cortex.

Conclusion: In the active rTMS group, clinical improvements were associated with modulation of the insula, reflecting targeted neurophysiological effects. In contrast, improvements in the sham group were linked to increased prefrontal and orbitofrontal cortex activation, consistent with placebo-related mechanisms.

Significance: This study unveils the critical role of cognitive-emotional pathways in rTMS efficacy, urging integration of neurobiological and psychological strategies for TN therapies.

Plain Language Summary:

1. All groups showed pain reduction in TN, revealing strong placebo effects in rTMS treatment.
2. rTMS decreased insula (pain) but increased prefrontal activity (anticipation), showing dual pain control.
3. Highlights rTMS's dual action on brain pain networks and cognitive modulation.

Keywords: placebo effect, rTMS, TN, pain perception and expectation

Introduction

Trigeminal neuralgia (TN), characterized by recurrent, excruciating facial pain along the sensory distribution of the trigeminal nerve, is widely recognized as one of the most debilitating neurological disorders globally.[1] Epidemiological studies report a prevalence of 12–29 cases per 100,000 individuals worldwide, with regional variations as high as 56 per 100,000 in certain

Received: 16 June 2025
Accepted: 21 November 2025
Published: 2 December 2025

Chinese urban populations.[2,3] Beyond its physical toll, TN severely impairs quality of life and is frequently comorbid with anxiety and depression.[4–6] While pharmacological agents such as carbamazepine remain first-line treatments, their long-term use is limited by adverse effects ranging from drowsiness to life-threatening cutaneous reactions.[7] Surgical interventions like microvascular decompression (MVD) show efficacy in classic TN with vascular compression, yet outcomes remain unpredictable in idiopathic cases, and invasive procedures inherently carry risks of complications and recurrence.[8] These challenges underscore the urgent need for safer, non-invasive therapeutic alternatives.

Non-invasive brain stimulation (NIBS), particularly repetitive transcranial magnetic stimulation (rTMS), has emerged as a promising neuromodulatory tool for chronic pain management. By targeting cortical regions involved in pain processing, rTMS modulates neural excitability and has demonstrated analgesic effects in conditions such as fibromyalgia.[9] However, existing rTMS studies on TN are constrained by critical limitations: small sample sizes (typically <20 participants), inconsistent sham-controlled designs, and inadequate exploration of neurophysiological mechanisms.[10–12] Crucially, the placebo effect—a potent modulator of subjective pain perception—has been insufficiently addressed, potentially inflating estimates of rTMS-specific efficacy.

To address these gaps, this randomized, double-blind, controlled trial rigorously evaluates the clinical and neurobiological effects of rTMS in early-stage TN. In this study, "early-stage TN" refers to patients who have received a formal diagnosis of TN but have had symptoms for less than 1 year and have not yet undergone any surgical interventions for their condition. Methodological innovations include: (1) a three-arm design comparing active M1-targeted rTMS, sham stimulation, and dorsolateral prefrontal cortex (dlPFC) stimulation; (2) multimodal assessment integrating resting-state functional MRI (fMRI) to characterize dynamic brain network reorganization; and (3) longitudinal follow-up at one month to evaluate sustained outcomes. By elucidating both physiological (insula-mediated pain processing) and psychological (prefrontal placebo-related modulation) mechanisms, this study advances a neuropsychobiological framework for optimizing TN therapies.

Materials and Methods

Participants and Procedure

Thirty-four patients with early-stage trigeminal neuralgia (TN) were recruited from the First Affiliated Hospital of the University of Science and Technology of China and randomly assigned to one of three groups: All patients were diagnosed by two experienced chief neurosurgeons based on the clinical characteristics of TN. The inclusion criteria for patients were as follows: (1) have received a formal diagnosis of TN but have had symptoms for less than 1 year and have not yet undergone any surgical interventions for their condition, and (2) exclusion of other potential causes of facial pain. Additionally, all participants underwent TMS safety screening, which included the absence of scalp implants, pacemakers, or other medical implants; no history of cortical stroke, brain tumors, or other forms of brain injury; no history of seizures; no prior neurosurgery; and no metallic, mechanical, or magnetic implants in the body. Exclusion criteria included: (1) patients who did not meet the typical clinical presentation of TN, (2) those who responded well to medication, (3) individuals with serious systemic diseases or coagulation disorders, (4) those lacking imaging evidence, and (5) patients unwilling to cooperate with the treatment protocol.

All patients were right-handed, with no major medical, psychiatric, or neurological illnesses, and no gross structural abnormalities were observed in their T1-weighted MRI scans. None of the participants had a history of drug dependence (current or past). Informed consent was obtained from all participants, and the study was approved by the Research Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China, in accordance with the principles of the Declaration of Helsinki.

Prior to the intervention, all participants underwent morphological 3D-T1 magnetic resonance imaging (MRI) and resting-state functional MRI scans. On the day before the first stimulation session, patients completed the Visual Analog Scale (VAS), Hamilton Depression Scale (HAMD), and Hamilton Anxiety Scale (HAMA) to evaluate their baseline levels of pain, depression, and anxiety.

The treatment protocol spanned two weeks, consisting of two 5-day stimulation sessions separated by a 2-day interval. In each session, active repetitive transcranial magnetic stimulation (rTMS) was administered once daily at the

same time for five consecutive days, with a two-day interval between the two sessions. For the sham control group, sham rTMS was delivered using the same setup as the M1-rTMS group, but with only rotating the stimulation coil by 90 degrees to remain perpendicular to the stimulation target. For the PFC-rTMS control group, the stimulation targeted the contralateral prefrontal cortex (PFC) relative to the side of pain.

Following the completion of the treatment, all participants underwent the same MRI scans and repeated assessments of pain, depression, and anxiety levels using the Visual Analog Scale (VAS), Hamilton Depression Scale (HAMD), and Hamilton Anxiety Scale (HAMA). Additionally, all participants completed the same assessments of pain, depression, and anxiety levels using the VAS, HAMD, and HAMA scales during a one-month follow-up.

This is a randomized, double-blind, controlled trial. In this study, the random grouping was performed by the TMS treatment operator using a random number table, while the personnel responsible for scale assessments, MRI data collection, and data analysis were blinded to the group assignments. The blinding was maintained until the final intergroup statistical comparisons were conducted, at which point the data analysts performed the statistical analysis.

Navigated rTMS Treatment

The navigated rTMS treatment was carried out at the Department of Neurology, the First Affiliated Hospital of USTC, with a stimulator (The magstim company limited, UK) using a figure 8 coil, following the safety guidelines and protocols for rTMS. Navigation was performed using a neuronavigational system (ant-neuro visor2, GmbH, Germany) to guide the magnetic stimulation as previously described. Briefly, before the first rTMS session, T1-weighted magnetic resonance imaging of the patient was integrated into the navigation system and a three-dimensional reconstruction of the patients' brain was generated accordingly. A 3D-printed mask with ball-like tracking points (NDI, Canada) was attached to the patient's head. The position of the tracking points and the location and orientation of the coil were co-registered and visualized by an infrared camera system, which allowed the operator to place the coil over the target region precisely. The targeted region was M1 corresponding to facial and cervical muscles. During the treatment, patient was asked to lie comfortably on an examine chair in a quiet room. Active rTMS was delivered in a frequency of 10 Hz, 100 pulses per train, a stimulation duration of 10 seconds, an inter-train interval of 50 seconds, repeated 25 times, with a total session duration of 25 minutes. The intensity of stimulation was set at 80% of the resting motor threshold (RMT) of the hand area. The RMT was determined before the first rTMS session as follows: After skin preparation, an electromyography (EMG) recording electrode (approximately $1cm^2$) was placed over the muscle belly of musculi abductor pollicis brevis. The hand area of contralateral primary motor cortex (M1) was stimulated and the RMT was defined as the lowest stimulation intensity which could elicit motor evoked potential 50 mV in at least 5 of 10 consecutive stimulations.

Pain, Depression and Anxiety Estimate

The Visual Analogue Scale (VAS), Hamilton Anxiety Scale (HAMA, 14 items),[13] and Hamilton Depression Scale (HAMD, 24 items)[14] are widely utilized in clinical practice to assess patients' pain levels and emotional states. Evaluations were conducted by two experienced assessors through a combination of structured interviews and behavioral observations. Following the assessment, each assessor independently assigned scores. The total scores derived from these scales serve as reliable indicators of disease severity, with lower scores reflecting milder symptoms and higher scores indicating more severe conditions.

MRI Data Acquisition

Gradient echo-planar magnetic resonance imaging data were obtained during the whole task procedure on the 3.0 T GE MR750 (United States) in the First Affiliated Hospital of the University of Science and Technology of China. Before entering the MRI scanner, all participants were told to keep their heads steady during all scans. A circularly polarized head coil was used, with foam padding to restrict head motion. Resting-state MRI data with 242 frames were acquired with a T2*-weighted echo-planar imaging sequence (TE = 30 ms, TR = 2000 ms, FOV = 240 mm, matrix = 64 × 64, flip angle = 85°) with 33 axial slices (no gaps, voxel size: 3.6 × 3.6×3.6 mm3) covering the whole brain. Corresponding high-resolution T1-weighted three-dimensional gradient-echo (for stereotaxic transformation) images were also collected (TR = 1900 ms; TE = 2.26 ms; TI = 900 ms; 1 mm isotropic voxel; 250 mm field of view (FOV)).

fMRI Data Analysis

The results included in this manuscript were generated from preprocessing performed using fMRIPrep 23.0.0. We first used preprocessed fMRI data to quantify head movements and other confounding factors and then used these estimates in the Xcp-d to denoise the fMRI signal and estimate functional connectivity.

Network Construction and Community Detection

After preprocessing, we extracted the time series of resting-state fMRI data from 100 brain regions of interest (ROIs) of the Schaefer Atlas. Next, we calculated the Pearson correlation coefficient between the time series of each pair of brain regions. Afterwards, FDR correction was performed and significant correlations were maintained and others were corrected to 0. For each participant, resting state network was partitioned using a community detection algorithm to extract groups of brain regions (ie communities).

Network Statistics

For each community structure, we estimated the following network statistics to characterize the functional interactions among functionally-defined regions of interest.

Module Allegiance and Recruitment

We used this measure to summarize the consistency with which functionally-defined regions of interest are assigned to communities.[15,16] According to the Schaefer Atlas, 100 brain regions of interest (ROIs) were categorized into seven subsystems (or 14 subsystems considering bilateral partitioning). We were able to quantify for each functionally-defined region of interest the probability with which it is assigned to the same community with functionally-defined regions of interest from the same subsystem (recruitment) (full details are provided in the Supplementary Materials and Methods 1)[15,17].

Statistical Analysis

A two-way analysis of variance (ANOVA) was conducted on the VAS scores, HAMA scores, and HAMD scores of the three groups of participants before and after rTMS treatment, as well as during the one-month follow-up. This analysis was performed using the anovan function in Matlab R2018b. In this model, the two factors were the different groups and the time points (before and after treatment), while the subject was treated as a random factor. Since the subjects were nested within fixed groups, the subject factor was nested within the group factor. After obtaining the overall significance results from the variance analysis, post-hoc t-tests were further conducted to clarify the significance of differences in scores between groups or at different time points within the same group.

Considering that the baseline scores of participants in different groups before treatment were not entirely consistent, we standardized the pre-treatment baseline scores to the same level for easier comparison. Subsequently, scores at other time points were proportionally adjusted to facilitate a more intuitive observation of the similarities and differences in trends between groups.

Resting-state functional MRI scans were performed for each group both before and after the treatment. For these scans, we analyzed the resting-state recruitment metrics of 100 brain regions for each individual. Subsequently, a paired *t*-test was conducted for each of the 100 brain regions (Schaefer Atlas) within each group, comparing pre- vs post-treatment recruitment values. The resulting p-values from all 100 tests were then corrected for multiple comparisons using the Benjamini-Hochberg False Discovery Rate (FDR) procedure, with a significance threshold set at $q < 0.05$.

Results

Demographical, Behavioral, and Clinical Comparisons

No significant differences were observed in age, gender, or other demographic variables among the three groups (all ps > 0.05). The groups were composed as follows: the M1-rTMS group included 13 patients (6 females; mean age 59.5 ± 10.3 years), the sham group consisted of 11 patients (5 females; mean age 66.6 ± 9.2 years), and the PFC-rTMS control group contained 10 patients (5 females; mean age 61.0 ± 3.8 years).

For VAS scores (shown in Figure 1a–c), there was a significant difference in the group factor (F = 7.19, p = 0.0014), as well as a significant difference in the time factor (before and after treatment) (F = 9.25, p = 0.0002). However, the interaction between time and group was not significant (F = 0.13, p = 0.972).

For depression scores (shown in Figure 1d–f), there was no significant difference in the group factor (F = 2.76, p = 0.07), but a significant difference was found in the time factor (F = 3.57, p = 0.03). The interaction between time and group was not significant (F = 0.15, p = 0.96).

For anxiety scores (shown in Figure 1g–i), there was no significant difference in the group factor (F = 2.18, p = 0.12), but a significant difference was observed in the time factor (F = 2.96, p = 0.05). The interaction between time and group was not significant (F = 0.59, p = 0.67).

The significant differences of the post-hoc *t* test were also shown in the Figure 1 marked with asterisks.

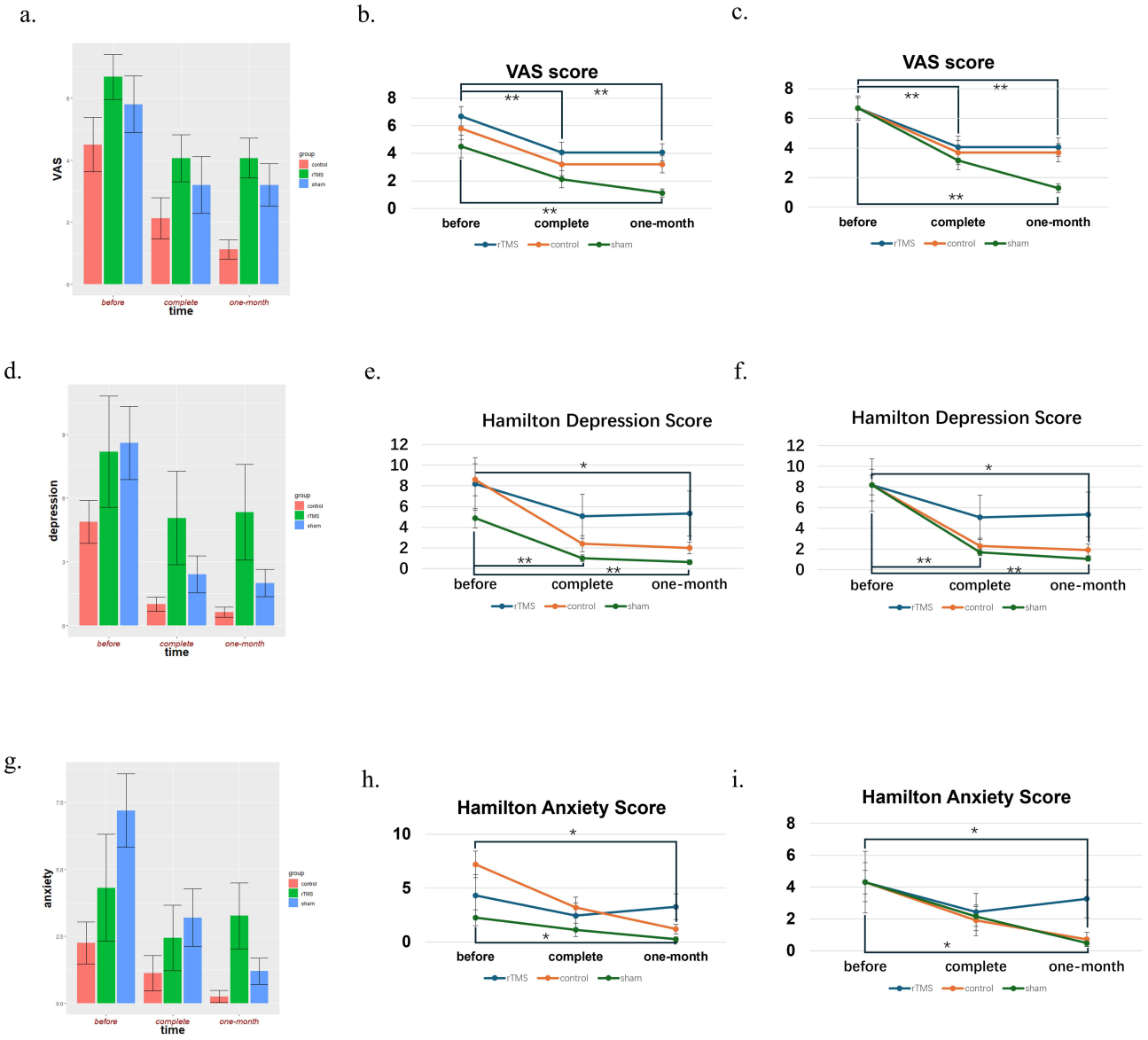

Figure 1 Bar plot and line chart illustrating the changes and group differences in VAS, HAMA, and HAMD scores throughout the rTMS treatment process. (**a–c**): VAS Scores. A significant difference was observed in the group factor (F = 7.19, p = 0.0014), as well as in the time factor (before vs after treatment) (F = 9.25, p = 0.0002). However, the interaction between time and group was not significant (F = 0.13, p = 0.972). (**d–f**): Depression Scores. No significant difference was found in the group factor (F = 2.76, p = 0.07), but a significant difference was detected in the time factor (F = 3.57, p = 0.03). The interaction between time and group was not significant (F = 0.15, p = 0.96).(**g–i**): Anxiety Scores. No significant difference was observed in the group factor (F = 2.18, p = 0.12), but a significant difference was noted in the time factor (F = 2.96, p = 0.05). The interaction between time and group was not significant (F = 0.59, p = 0.67). The error bars indicate the standard error. *, p < 0.05; **, p < 0.01.

https://doi.org/10.2147/JPR.S547405

The results of fMRI Analysis

By analyzing the resting-state data before and after treatment in each group, we found that for the treatment group, the recruitment value of the right insula (r-insula) significantly decreased after rTMS treatment (pFDR < 0.05), with no significant changes observed in other brain regions (Figure 2a). In contrast, for the control brain region treatment group (Figure 2b and c) and the sham stimulation group (Figure 2d and e), in addition to a significant decrease in the recruitment value of the insula, there was also a notable increase in the recruitment values of the prefrontal cortex (PFC) and orbitofrontal cortex (OFC) (pFDR < 0.05) following rTMS treatment.

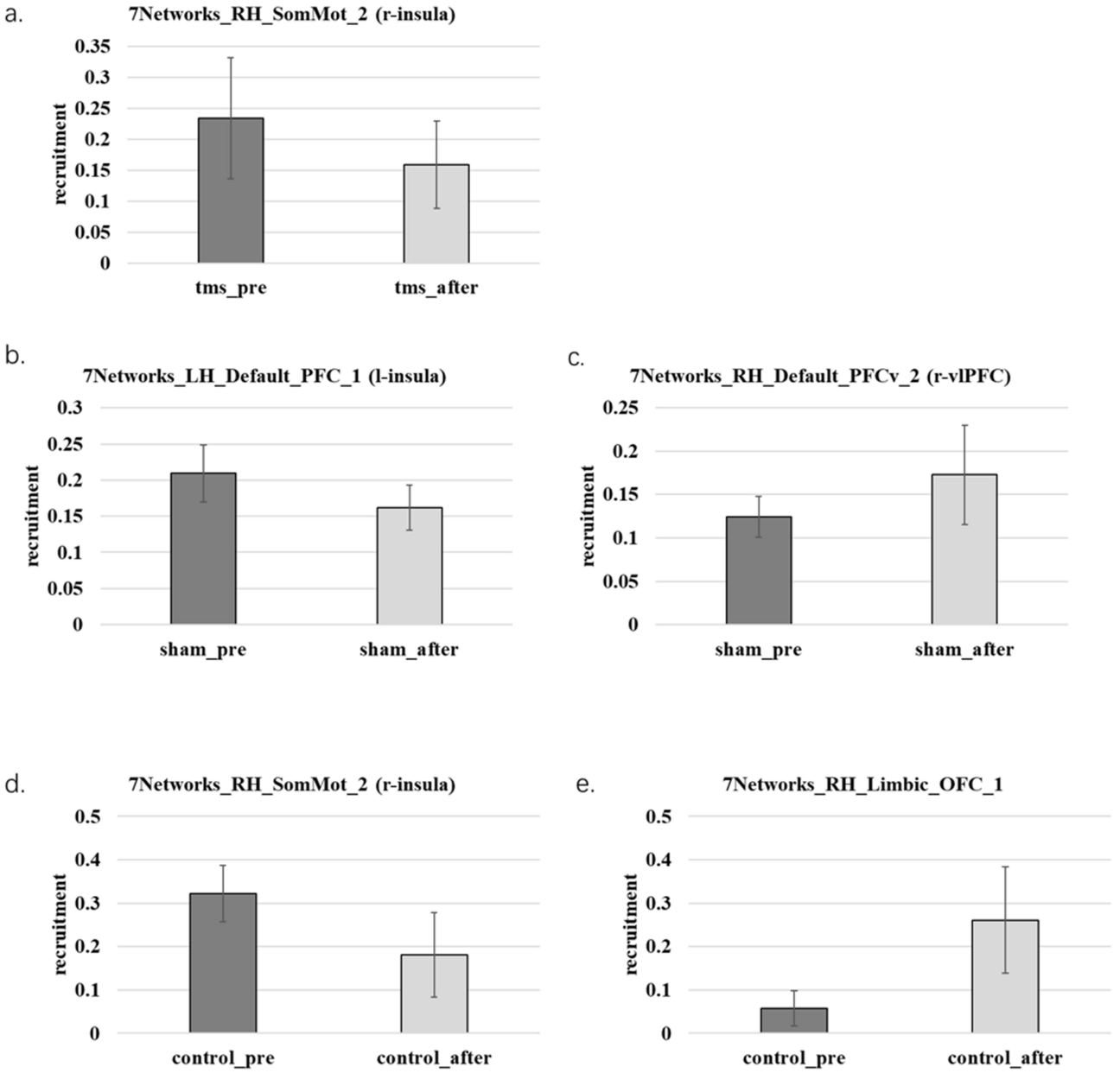

Figure 2 The results of fMRI analysis. (**a**), for the treatment group, the recruitment value of the right insula (r-insula) significantly decreased after rTMS treatment, with no significant changes observed in other brain regions (Figure 2a). (**b** and **c**), for the PFC-rTMS control group and the sham stimulation group (**d** and **e**), in addition to a significant decrease in the recruitment value of the insular, there was also a notable increase in the recruitment values of the prefrontal cortex (PFC) and orbitofrontal cortex (OFC) following rTMS treatment.

Discussion

This randomized, double-blind, controlled trial investigated the efficacy of repetitive transcranial magnetic stimulation (rTMS) in treating early-stage trigeminal neuralgia (TN) and explored the associated changes in brain functional networks using fMRI. The study revealed several key findings that contribute to our understanding of the mechanisms underlying rTMS-induced pain relief and the role of placebo effects in TN treatment.

To help interpret our neuroimaging findings, it is important to understand what "recruitment value" represents. In simple terms, it measures how consistently a specific brain region "teams up" or communicates with other regions that belong to the same functional network. A higher recruitment value indicates that a region is more strongly and reliably integrated into its "home team" network, suggesting it plays a more influential or coordinated role in the brain's overall communication. A lower recruitment value suggests that a region is becoming less locked into its usual network patterns, potentially reflecting a reduction in its influence or a shift in its functional role.

In our study, the decrease in the insula's recruitment value following treatment suggests that this key pain-processing region became less dominant within the brain's network activity. This is consistent with a reduction in the intensity of pain signals being generated and processed. Conversely, the increase in recruitment values within the prefrontal cortex (PFC) and orbitofrontal cortex (OFC)—observed in the control and sham groups—indicates that these higher-order cognitive regions became more strongly integrated and influential. This likely reflects their increased role in top-down processes, such as regulating emotional responses to pain, reevaluating the pain experience, and generating placebo effects through expectation and belief. Therefore, these changes in recruitment values provide a network-level explanation for how both direct stimulation (via insula modulation) and psychological factors (via prefrontal modulation) can lead to pain relief.

Pain, Anxiety, and Depression Outcomes

The results demonstrate comparable reductions in pain, anxiety, and depression across all three groups. The universal VAS decline reveals potent analgesia irrespective of intervention type, aligning with studies highlighting placebo effects in pain conditions where psychological factors modulate perception.[18,19] Critically, the absence of intergroup differences in clinical outcomes underscores that placebo mechanisms may dominate rTMS efficacy.

The reduction in anxiety and depression scores, as measured by the Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD), also suggests that rTMS may have a broader impact on emotional well-being, independent of its direct effects on pain. This is consistent with prior research indicating that rTMS can modulate emotional states, potentially through its influence on brain regions involved in mood regulation, such as the prefrontal cortex (PFC).[20,21]

Neuroimaging Findings

The fMRI analysis revealed significant changes in brain network recruitment following rTMS treatment. In the treatment group, a significant decrease in the recruitment value of the right insula (r-insula) was observed, which is consistent with the insula's well-established role in pain processing and perception.[22] The insula is known to integrate sensory and emotional aspects of pain, and its decreased activation may reflect a reduction in the overall pain experience following rTMS.

In contrast, both the sham and PFC-rTMS control groups exhibited not only a decrease in insula recruitment but also an increase in recruitment values in the prefrontal cortex (PFC) and orbitofrontal cortex (OFC). These regions are associated with higher-order cognitive functions, including pain modulation, emotional regulation, and expectation processing.[23,24] The increased activation in these areas may reflect the brain's attempt to modulate pain perception through cognitive and emotional pathways, particularly in the absence of direct neural stimulation. This finding further supports the idea that placebo effects may involve changes in pain expectancy and cognitive reappraisal of pain.[25,26]

Implications for rTMS in TN Treatment

Our data establish that placebo-driven prefrontal modulation is a primary contributor to rTMS efficacy. While active stimulation may directly alter pain processing, sham interventions achieve similar relief through cognitive reappraisal. This mandates strategic enhancement of placebo effects (eg, optimizing patient expectations) in future rTMS protocols.

Beyond its mechanistic insights, our study raises the important question of how placebo-related effects might be ethically harnessed to improve clinical outcomes in neuromodulation for pain. Rather than seeking to eliminate these

effects, future protocols could proactively and transparently incorporate elements known to enhance positive expectations (eg, optimized patient-clinician communication, contextual factors that boost treatment credibility) as adjuncts to active treatment. This aligns with a biopsychosocial model of care that aims to maximize therapeutic efficacy through combined biological and psychological pathways.

Regarding long-term applicability, while our study demonstrated sustained effects at one month, the durability of this response remains a critical area for future investigation. We recommend that subsequent trials implement longer follow-up periods (eg, 3–6 months) to determine the persistence of both the neurophysiological and placebo-mediated benefits. Furthermore, studies exploring periodic "booster" sessions of rTMS or complementary psychological interventions could help clarify strategies for maintaining the initial clinical gains.

Limitations and Future Directions

The interpretations of our findings should be tempered by several methodological considerations. First, the relatively small sample size, although adequate for a pilot investigation, limits the statistical power of the study, particularly in detecting small to moderate intergroup effects. This may explain the lack of significant differences in clinical outcomes between the active and control groups despite the observed neurobiological disparities. The low statistical power increases the risk of a Type II error (failing to detect a true effect that exists). Therefore, we cannot definitively rule out the possibility that a larger, sufficiently powered trial might indeed find a significant difference in efficacy between active M1-rTMS and control interventions.

Second, the one-month follow-up period is relatively short. This is particularly relevant in the context of TN, where placebo responses and spontaneous fluctuations are known to be most pronounced in the early phases. Therefore, our results primarily reflect short-term efficacy, and the long-term sustainability of the observed effects—both physiological and placebo-mediated—remains an open question. Future studies with extended follow-up durations (eg, 3, 6, and 12 months) are warranted.

Third, while we used a validated sham control, the strong placebo effect observed underscores the challenge of completely blinding NIBS trials. Future research could employ active controls targeting other brain regions or more sophisticated sham techniques. Our choice of dlPFC stimulation as a control group introduces a unique interpretive challenge. As the reviewer astutely notes, the dlPFC is itself a target for neuromodulation therapies in pain and depression, making it an "active control" rather than an "inert" or sham control. This design means that the improvements seen in the PFC-rTMS group could be due to either a specific therapeutic effect of PFC stimulation or the non-specific placebo effect. Consequently, our three-arm design does not perfectly isolate the placebo effect but rather compares active M1 stimulation to another potentially active intervention (PFC-rTMS) and a sham. This limitation tempers our ability to attribute the entirety of the improvement in the control groups to placebo effects alone. However, the similar outcomes across all three groups still strongly suggest that the non-specific effects of context and expectation are powerful contributors to the observed clinical benefits, likely overshadowing any specific target effects in this cohort and timeframe.

Finally, our primary clinical outcome was the VAS. Although significant, a reduction in VAS does not necessarily equate to a clinically meaningful response for all patients. Future trials should incorporate a broader range of outcome measures, such as the proportion of patients achieving a 30% or 50% reduction in pain intensity, patient global impression of change (PGIC), and quality-of-life metrics, to provide a more comprehensive assessment of efficacy. Regarding the generalizability of our findings, an important consideration arises from our exclusion criteria. By excluding patients who responded well to medication, our study cohort likely represents a subpopulation of early-stage TN patients with a degree of treatment resistance. While this was a necessary design to investigate the efficacy of rTMS in a population with a clear unmet clinical need, it also means that our results may not be fully generalizable to all early-stage TN patients, particularly those who experience satisfactory relief from first-line pharmacological therapies. Future studies including a broader spectrum of early-stage TN patients are needed to confirm the wider applicability of our conclusions.

Conclusion

This pilot trial provides preliminary evidence that rTMS may alleviate TN symptoms via dual pathways. The prominent placebo effects revealed here call for integrated biopsychosocial approaches to maximize rTMS therapeutic potential in

future, larger-scale confirmatory studies. Building on our findings, future clinical trials could operationalize a biopsychosocial approach by integrating targeted rTMS with psychological interventions such as cognitive-behavioral therapy (CBT) or structured expectancy enhancement protocols. This combined strategy would simultaneously modulate the neurophysiological substrates of pain and amplify the placebo-related mechanisms identified in this study, potentially leading to greater and more sustained therapeutic outcomes.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

Informed consent was obtained from all participants, and the study was approved by the Research Ethics Committee of the First Affiliated Hospital of the USTC and conformed to the tenets of the Declaration of Helsinki.

Acknowledgments

We thank all the study participants for their support of our research.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Talent Introduction Plan Project (RC2021004).

Disclosure

The authors declare that they have no competing interests in this work.

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