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REVIEW

Abnormal Regional Brain Functional Activity and Brain Network Connectivity in Primary Trigeminal Neuralgia Patients: An Activation Likelihood Estimation Meta-Analysis Based on Resting-State fMRI

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Objective: This study integrates resting-state functional magnetic resonance imaging (rs-fMRI) studies to systematically identify core regions of altered regional brain activity and abnormal functional connectivity within cerebral networks in patients with primary trigeminal neuralgia (PTN).

Methods: We systematically searched PubMed, Web of Science, and EMBASE for rs-fMRI studies (between January 2010 and June 2025) comparing PTN patients with healthy controls (HCs). Through a standardized data extraction protocol, coordinates of divergent brain functional metrics and network connectivity parameters were collected. Ultimately, we included 16 studies, of which 14 were related to functional specific indices (375 patients) and 5 to functional connectivity (204 patients). Separate modality-specific Activation Likelihood Estimation (ALE) meta-analyses were conducted for studies employing Amplitude of Low-Frequency Fluctuation (ALFF/fALFF), Regional Homogeneity (ReHo), and Degree Centrality (DC), to reflect their unique neurophysiological meanings.

Results: ALE analysis revealed index-specific alteration patterns with limited spatial overlap. The ALFF/fALFF analysis identified consistent hypoactivity in the left medial prefrontal cortex. In contrast, ReHo and DC analyses converged to show hyperactivity in the posterior cerebellar lobe and temporal pole. Notably, Seed-based functional connectivity analyses yielded no convergent findings, and limbic system activation was highly heterogeneous.

Conclusion: Our meta-analysis demonstrates that PTN involves complex, multidimensional brain remodeling, not a dysfunction of a single "pain center." The distinct spatial patterns identified by different rs-fMRI metrics underscore their complementary value in uncovering PTN pathophysiology. These findings advance the understanding of PTN's central mechanisms, support the development of targeted interventions, and highlight the need to differentiate neurophysiological metrics and clinical subtypes in future research.

Keywords: primary trigeminal neuralgia, resting-state functional magnetic resonance imaging, meta-analysis, regional brain activity, functional connectivity

Introduction

Primary trigeminal neuralgia (PTN) is a chronic neuropathic facial pain disorder characterized by paroxysmal, electric shock-like or stabbing pain attacks in the distribution of one or more branches of the trigeminal nerve.[1–3] Approximately

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one-third of patients with chronic TN experience moderate to severe depression, and about half of these patients also exhibit anxiety symptoms directly related to TN.[4–6]

In clinical practice, PTN patients often encounter challenges such as diminished drug efficacy, severe side effects, or pain recurrence and inadequate pain relief after surgical intervention, posing significant hurdles to pain management and patients' quality of life. This heterogeneity in treatment response implies potential interindividual variations in the underlying central mechanisms. Although PTN has traditionally been considered to be primarily associated with peripheral lesions of the trigeminal nerve root, the experience of chronic pain extends far beyond peripheral signal afference. Long-term chronic pain stimulation drives secondary adaptive remodeling in the brain, and these central adaptive changes may represent the key to the transition of pain from acute to chronic, the emergence of emotional comorbidities (such as anxiety and depression), and heterogeneity in treatment response. Multiple rs-fMRI studies have reported abnormal changes in regional brain functional activity, functional network connectivity, and related clinical behavioral aspects in TN patients from different perspectives.[7] For example, some studies used low-frequency amplitude (ALFF), fractional low-frequency amplitude (fALFF), regional homogeneity (ReHo), and other methods to analyze spontaneous brain activity in TN patients, identifying abnormal ALFF or ReHo values in specific brain regions.[8,9] Ge et al conducted a more comprehensive study on ALFF, ReHo, and dynamic frequency. Other studies focusing on brain network connectivity changes have found disorders in resting-state network modular organization,[10] dynamic characteristics of functional networks,[11] and structural and functional connectivity of the salience network[12] in TN patients. These findings indicate that the central nervous system of trigeminal neuralgia patients has undergone changes at multiple levels, which may play a key role in the process of pain perception, transmission, and regulation.

However, discrepancies exist across studies in terms of methodology, sample characteristics, and analytical metrics, leading to inconsistent findings regarding specific regional brain abnormalities and altered connectivity patterns. Notably, some results even demonstrate contradictory conclusions. Therefore, a systematic meta-analytical integration of available brain functional imaging data is essential to identify stable central functional remodeling patterns in patient populations, localize consistent abnormal brain regions and network connectivity alterations, and provide evidence for defining core neural circuits of pain chronicity and target interventions. The activation likelihood estimation (ALE) is a well-established coordinate-based meta-analysis method that assesses statistical convergence of reported brain coordinates across studies, serving as an ideal method to synthesize heterogeneous study findings and identify consistently affected brain regions.[13] Based on this, this study uses the ALE meta-analysis method to systematically integrate the brain functional imaging data of patients with PTN. This study aims to use ALE meta-analysis to independently analyze studies using different indices (eg, ALFF/fALFF, ReHo, DC), with the objective of uncovering multidimensional features of brain functional abnormalities in PTN patients and exploring the specificity of each index in revealing pathological changes. Specifically, we hypothesized that these different fMRI indices, which capture distinct aspects of neural function, would reveal complementary and largely non-overlapping patterns of brain alterations, thereby reflecting the multifaceted pathophysiology of PTN.

Materials and Methods

This study has been prospectively registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/home) with registration number: CRD42025641261.

Literature Inclusion and Exclusion Criteria

The literature inclusion criteria were as follows: (1) Studies were required to be peer-reviewed investigations utilizing rs-fMRI to compare cerebral functional alterations between PTN patients and HCs; (2) Participants must have been formally diagnosed with PTN according to internationally recognized criteria (ICHD-3);[14] (3) Studies must utilize analytical approaches including amplitude of ALFF, fALFF, ReHo, degree centrality (DC), or seed-based functional connectivity; additionally, reported brain regions showing significant differences must be presented with Montreal Neurological Institute (MNI)[15] or Talairach stereotactic coordinates.

The literature exclusion criteria were as follows: (1) Studies published in languages other than English were excluded; (2) Studies were excluded if they represented duplicate publications or contained overlapping data with previously

included studies; (3) Studies were excluded if they failed to report stereotactic coordinates (MNI/Talairach); (4) Studies were excluded if they were reviews, meta-analyses, or case reports; (5) Studies with low methodological quality, as determined by predefined criteria, were excluded due to insufficient evidence for inclusion in subsequent analyses.

Literature Search Strategy

A systematic search was conducted for rs-fMRI studies published between January 2010 and June 2025 in PubMed, Web of Science, and EMBASE databases. Search terms included: "trigeminal neuralgia", "primary trigeminal neuralgia", "classic trigeminal neuralgia", "idiopathic trigeminal neuralgia", "fMRI", "functional connectivity", "FC", "functional MRI", "Resting-State Functional MRI", "rs-fMRI", "ALFF", "fALFF", "amplitude of low-frequency fluctuation", "fractional amplitude of low-frequency fluctuation", "ReHo", "regional homogeneity". To avoid omissions, we also manually searched reference lists of relevant reviews. All retrieved records were imported into EndNote (a reference management tool) for screening.

Literature Screening and Data Extraction

Literature screening and data extraction were independently performed by two reviewers, followed by cross-verification. Discrepancies were resolved through discussion. The data extraction included: (1) Study information: first author, publication year, sample size, age, VAS score, disease duration, analysis method, correction method, peak center coordinate presentation format, and peak center coordinates of differential brain regions; (2) Further analysis of extracted MNI coordinates using MRIcroGL, adhering to ALE analysis criteria.

Quality Assessment

Study quality was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates three domains: (1) Selection of Study Participants, including representativeness of the case group, appropriateness of control group selection, reliability of exposure determination methods, and response rate; (2) Comparability of Groups, assessing control of confounding factors during design (eg, age, gender) and statistical adjustments during analysis (eg, multivariate regression); and (3) Exposure/Outcome Assessment, evaluating objectivity of outcome measurement (eg, blinding or laboratory testing), adequacy of follow-up duration (covering disease latency), and completeness of outcome data. Studies scoring>6 points (maximum 9) were included for subsequent analysis.

Meta-Analysis Strategy

Considering that different resting-state fMRI indices reflect distinct physiological dimensions of neural activity, pooled analysis without discrimination may obscure significant changes specific to individual indices, leading to ambiguous results. Therefore, we adopted a modality-specific meta-analysis strategy, conducting independent ALE meta-analyses for studies using three types of indices: (1) Amplitude metrics (ALFF/fALFF): Reflecting the energy consumption level of spontaneous neuronal activity at rest;[16] (2) ReHo index: Reflecting the temporal consistency of neuronal activity within local brain regions;[17] (3) DC index: Reflecting the importance of brain region nodes in the whole-brain functional network. Studies have suggested that regions with reduced ReHo often coincide with those showing decreased nodal efficiency, implying an inherent association between local synchrony and global connectivity.[11,12,17] Given that both ReHo and DC measure the local information integration capacity of brain regions to some extent,[17,18] we conducted an exploratory joint analysis to test whether these two indices showed synergistic alterations and to enhance the robustness of the results. Each analysis was performed independently, and their outcomes were regarded as reflections of different aspects of TN pathophysiology.

Data Processing

This study integrated neuroimaging data in standard MNI space using GingerALE 3.0.2 (https://www.brainmap.org/ale/) to quantify PTN-related activation consistency and identify differential patterns vs controls.

MNI coordinates and participant numbers were compiled into focus files per GingerALE best practices. ALE analysis involved iterative Gaussian smoothing to generate MA maps, followed by voxel-wise weighted overlay; higher ALE

values indicated stronger cross-study consistency.[19] Monte Carlo simulations (1000 iterations) with cluster-level FWE correction controlled error rates, using uncorrected $p < 0.001$ for cluster formation and FWE-corrected $p < 0.05$ for significance.[20,21]

For seed-based functional connectivity studies, we employed an adapted Meta-Analytic Connectivity Modeling (MACM) approach to integrate findings across different seed regions.[22,23] Specifically, we used Sleuth 3.0.4 software to perform a "dual screening" of the seed-based studies: first, we identified all brain regions that were reported as showing altered connectivity in PTN patients (regardless of seed), and then we treated these regions as if they were activation foci in a conventional ALE. In this way, we could use GingerALE to conduct a convergence analysis on the reported connectivity foci, analogous to how ALE is applied to activation peaks[nature.com]. This allowed us to detect brain regions that were consistently reported as part of abnormal connectivity networks in PTN across multiple seed-based studies.

Finally, MRIcroGL (https://www.nitrc.org/mricrogl) overlaid ALE maps onto standard templates, generating 3D volume renderings of activated regions.

Result

Results of Systematic Literature Search and Data Extraction

A total of 251 relevant articles were initially retrieved. After stepwise screening, 16 eligible studies were finally included.[8–10,16,17,24–34] The literature screening process is detailed in Figure 1. Specifically, 9 studies adopted ALFF/fALFF analysis,[8,16,24,26,28,30,31,34] 6 used ReHo analysis,[9,17,24,26,27,31] 3 applied DC analysis,[24,29,32] and 5 focused on seed-based functional connectivity.[10,28,30,33,34] Detailed literature data are presented in Tables 1 and 2.

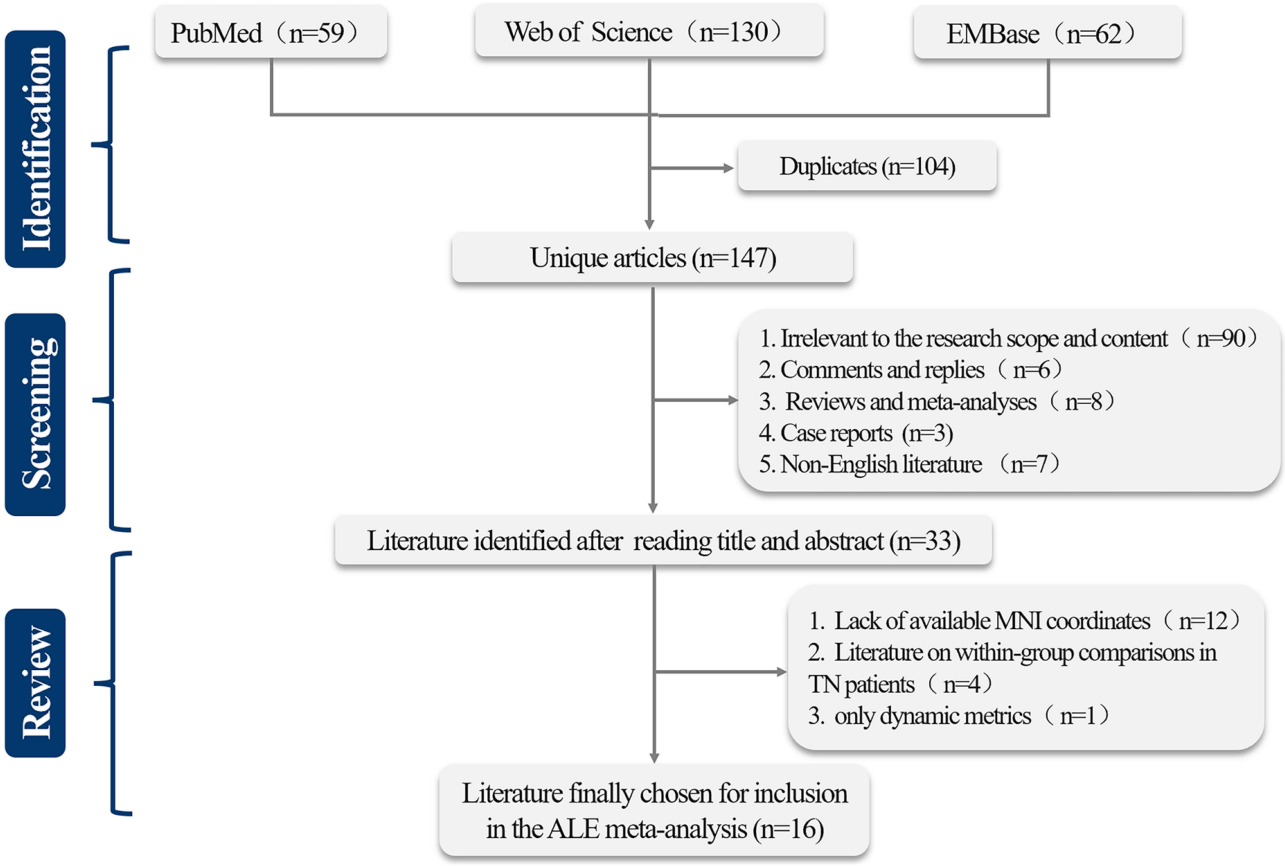

Figure 1 Flowchart of literature selection for TN ALE meta-analysis.

Table 1 The Literature Data Included in the ALE Analysis

First Author	Sample Size (Case)		Age (y)		VAS	Duration	Analysis Method	Correction	Coordinates	NQS
	PTN	HCs	PTN	HCs						
(Wang et al, 2015)[9]	17	19	63.41 ± 7.25	62.53 ± 7.41	6.29 ± 1.46	6.98 ± 5.64	ReHo	AlphaSim	MNI	4/1/2
(Wang et al, 2017)[25]							ALFF	GRF	MNI	4/1/2
(Yuan et al, 2018)[26]	23	23	59.6 ± 12.5	63.1 ± 9.8	8.1 ± 1.6	5.69 ± 3.33	fALFF, ReHo	AlphaSim	MNI	4/1/2
(Chen et al, 2019)[8]	28	28	51.39 ± 9.37	51.36 ± 9.30	6.32 ± 1.44	3.73 ± 4.10	ALFF	GRF	MNI	4/1/2
(Xiang et al, 2019)[27]							ReHo	AlphaSim	MNI	4/1/2
(Zhu et al, 2020)[29]							DC	GRF	MNI	4/1/2
(Zhang et al, 2019)[28]	29	34	48.1 ± 11.9	43.3 ± 10.1	6.31 ± 1.15	6.02 ± 4.35	ALFF/fALFF	FWE	MNI	4/2/2
(Liu et al, 2022)[30]	34	29	53.06 ± 10.9	54.21 ± 6.33	7.97 ± 1.42	4.63 ± 3.53	ALFF	FDR	MNI	4/2/2
(Liu et al, 2023)[32]							DC	FDR	MNI	4/2/2
(Ge et al, 2024)[24]	77	73	54.08 ± 10.8	52.11 ± 8.8	8.16 ± 1.84	4.96 ± 4.9	ALFF, ReHo, DC	GRF	MNI	4/2/2
(Wang et al, 2024a)[17]	33	21	—	—	—	—	ReHo	FWE	MNI	4/2/1
(Wang et al, 2024b)[31]	38	20	62.2 ± 10.3	56.8 ± 9.4	8.32 ± 1.00	5.23 ± 6.18	ALFF, ReHo	FWE	MNI	4/2/2
(Zhang et al, 2025)[16]	46	35	57.61±10.18	54.23±8.53	—	4.21±4.96	ALFF	AlphaSim	MNI	4/2/1
(Wu et al, 2025)[34]	50	43	53.12±5.39	51.23±6.11	7.24±0.85	5.70±4.14	fALFF	FDR	MNI	4/2/2

Notes: Data are basic information of screened literature.

Abbreviations: PTN, classic trigeminal neuralgia; HCs, healthy controls; VAS, visual analog scale; Duration, refers to the duration of pain; ReHo, regional homogeneity; ALFF, amplitude of low frequency fluctuation; fALFF, fractional amplitude of low frequency fluctuation; ReHo, Regional Homogeneity; DC, degree centrality; AlphaSim, alpha simulation; GRF, gaussian random field; FWE, family wise error; FDR, false discovery rate; MNI, Montreal neurological institute; NQS, Newcastle-Ottawa scale.

Table 2 The Literature Data Related to Seed-Based Functional Connectivity

Basic Information		Seed Region	Sample Size (case)		Age (y)		VAS	Duration	Correction	Coordinates	NQS
			PTN	HCs	PTN	HCs					
Higher	(Tsai et al, 2018)[10]	THA(R)	26(L)	19	59.0 ± 6.6	55.6 ± 8.2	9.4 ± 0.9	63.2 ± 59.0	FWE	MNI	4/1/2
	(Zhang et al, 2018)[33]	AMY(R)	29	34	48.1 ± 11.9	43.3 ± 10.1	6.31 ± 1.15	6.02 ± 4.35	FWE	MNI	4/2/2
	(Wu et al, 2025)[34]	mPFC, ACC	50	43	53.12±5.39	51.23±6.11	7.24±0.85	5.70±4.14	FDR	MNI	4/2/2
Lower	(Tsai et al, 2018)[10]	SFG(R)	36(R)	19	58.0 ± 7.7	55.6 ± 8.2	9.3 ± 0.7	63.2 ± 59.0	FWE	MNI	4/1/2
		PreCG(L)	26(L)	19	59.0 ± 6.6	55.6 ± 8.2	9.4 ± 0.9	63.2 ± 59.0	FWE	MNI	4/1/2
	(Zhang et al, 2018)[33]	AMY(L)	29	34	48.1 ± 11.9	43.3 ± 10.1	6.31 ± 1.15	6.02 ± 4.35	FWE	MNI	4/2/2
	(Zhang et al, 2019)[28]	PCC(L), DLPFC(L)	29	34	48.1 ± 11.9	43.3 ± 10.1	6.31 ± 1.15	6.02 ± 4.35	FWE	MNI	4/2/2
	(Liu et al, 2023)[32]	LG(R), MCC(L)	34	29	53.06 ± 10.9	54.21 ± 6.33	7.97 ± 1.42	4.63 ± 3.5	FDR	MNI	4/2/2
	(Wu et al, 2025)[34]	mPFC, AMY(R)	50	43	53.12±5.39	51.23±6.11	7.24±0.85	5.70±4.14	FDR	MNI	4/2/2

Abbreviations: R, right; L, left; THA, thalamus; AMY, amygdala; mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; SFG, superior frontal gyrus; PreCG, precentral gyrus; PCC, posterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; LG, lingual gyrus; MCC, middle cingulate cortex; PTN, classic trigeminal neuralgia; HCs, healthy controls; VAS, visual analog scale; FWE, family wise error; FDR, false discovery rate; MNI, Montreal neurological institute; NQS, Newcastle-Ottawa scale.

Results of Data Analysis

In the independent analysis of ALFF/fALFF, patients with PTN exhibited reduced co-activation in the left medial frontal gyrus (Figure 2 and Table 3). The independent ReHo analysis revealed increased co-activation in the left temporal pole and right posterior cerebellar lobe in PTN patients (Figure 3 and Table 4). In the DC-based independent analysis, PTN patients showed reduced co-activation in the right lingual gyrus–cuneus region (Figure 4 and Table 5). Combined ReHo and DC analyses demonstrated synergistic enhancement of co-activation in the left temporal pole and bilateral posterior cerebellar lobes, alongside synergistic reduction in the right cuneus (Figure 5 and Table 6).

Regarding seed-based functional connectivity, no significant co-activation clusters were identified in the cross-seed core regions through ALE analysis.

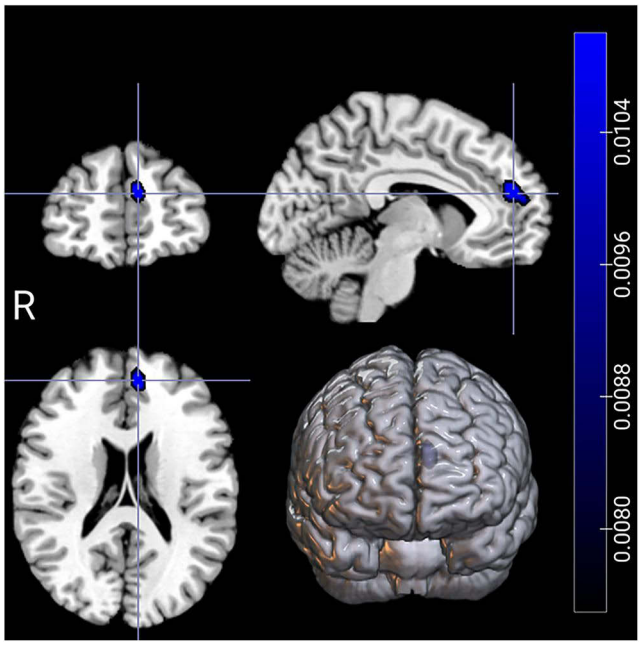

Figure 2 Convergent regions of reduced activation in PTN patients in the exclusive ALFF/fALFF analysis. The analysis identified a significant cluster in the left medial frontal gyrus. Results are displayed on a standard MNI template. The color bar indicates the ALE value. Statistical significance was determined using a cluster-forming threshold of $p < 0.001$ with a cluster-level FWE correction at $p < 0.05$.

Discussion

Modality-specific meta-analyses based on different fMRI indices depicted a multidimensional profile of brain functional remodeling in PTN patients. Results showed minimal spatial overlap among abnormal brain regions identified by independent analyses. We argue that this finding does not diminish the biological significance of the results, but rather profoundly reveals the complexity and multidimensionality of central mechanisms in PTN. Additionally, although studies by Nardoni et al[35] and Zhu et al[36] both identified consistent structural and functional changes in TN patients, neither strictly distinguished between different functional indices or imaging modalities in their respective meta-analyses, but instead combined multiple results for analysis. This approach may mask significant changes under specific indices, and due to the lack of index differentiation, there is a certain ambiguity in interpreting the meta-analytic results. Below, we contextualize major findings to explore their potential neurobiological implications and associations with PTN pathophysiology. Thus, the following section will interpret the key findings in conjunction with relevant specific indices and conduct an in-depth discussion on the causes of PTN heterogeneity, aiming to provide certain references for future research.

Prefrontal Cortex

The medial prefrontal cortex (mPFC), a key subregion of the PFC, serves as a critical node for emotional and cognitive processing in chronic pain. It integrates nociceptive information with emotional responses and forms a "pain-emotion-cognition" interactive network through extensive neural circuits connecting to the hippocampus, amygdala, thalamus, and

Table 3 Convergent Regions of Reduced Activation in PTN Patients in Exclusive ALFF/fALFF Analysis

Location	Brain Region	BA	Cluster Size (mm^3)	The Coordinates of the Peak Point of MNI			Max Value of ALE
				X	Y	Z	
Left	Medial Frontal Gyrus	9	1000	−6	48	20	0.014

Abbreviations: PTN, primary trigeminal neuralgia; ALFF, amplitude of low frequency fluctuation; fALFF, fractional amplitude of low frequency fluctuation; BA, Brodmann area; MNI, Montreal neurological institute.

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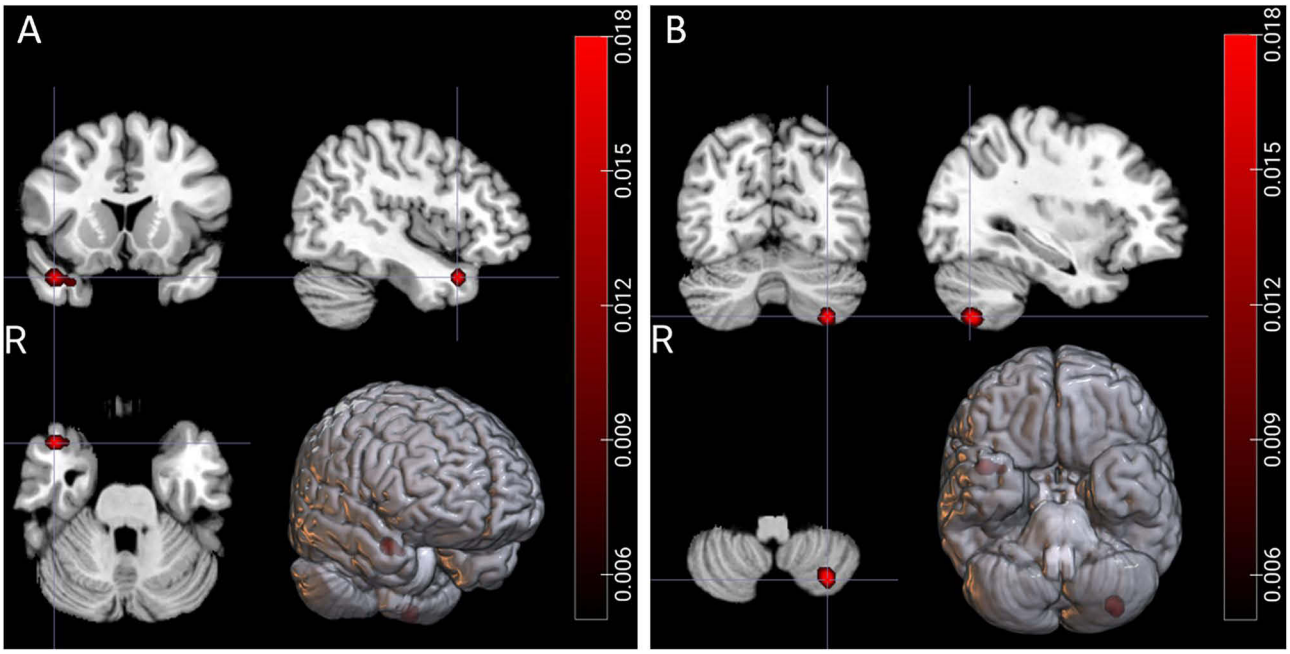

Figure 3 Convergent regions of increased activation in PTN patients in the exclusive ReHo analysis. The analysis identified significant clusters in (**A**) the right temporal pole and (**B**) the left cerebellum posterior lobe. Results are displayed on a standard MNI template. The color bar indicates the ALE value. Statistical significance was determined using a cluster-forming threshold of $p < 0.001$ with a cluster-level FWE correction at $p < 0.05$.

other regions.[37–39] Furthermore, the mPFC plays a key role in the endogenous pain modulation network by projecting to the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM), thereby activating descending pain inhibitory systems to effectively suppress spinal nociceptive transmission.

The meta-analysis based on ALFF/fALFF indicates that, when compared to HCs, PTN patients have areas of reduced co-activation in the left mPFC. We tentatively hypothesize that under the long-term chronic pain stimulation, the decreased intensity of spontaneous activity in the mPFC of PTN patients may suggest a certain functional deficiency in this area. This functional deficiency can lead to impairments in the related descending pain inhibitory pathways, which in turn worsen pain sensitization. Moreover, it may be linked to the impaired regulation of negative emotions such as anxiety, depression, and catastrophic thinking in TN patients.

In related functional studies, latest study observed decreased ALFF in the left superior/medial frontal gyrus of TN patients, which inversely correlated with pain severity and negative emotional indices.[40] Sliding window functional connectivity analysis revealed that PFC-PAG connectivity negatively correlated with perceived pain intensity during spontaneous TN fluctuations.[41] In seed-based functional connectivity analyses, studies found that amygdala-DLPFC and amygdala-mPFC circuits correlate with clinical pain duration and emotional state ratings, respectively; Zhang et al reported that posterior cingulate-mPFC functional connectivity strength inversely correlates with pain intensity.[28] A recent study by Lv et al identified the ventral hippocampus-mPFC circuit and CRH-CRHR1 signaling as mediators of chronic TN-related anxiety and depression, with pathway/signal inhibition effectively alleviating anxiety- and

Table 4 Convergent Regions of Increased Activation in PTN Patients in Exclusive ReHo Analysis

Location	Brain Region	BA	Cluster Size (mm^3)	The Coordinates of the Peak Point of MNI			Max Value of ALE
				X	Y	Z	
Right	Temporal Pole	38	688	44	15	−30	0.018
Left	Cerebellum Posterior Lobe	—	848	−32	−66	−54	0.021

Abbreviations: PTN, primary trigeminal neuralgia; ReHo, Regional Homogeneity; BA, Brodmann area; MNI, Montreal neurological institute.

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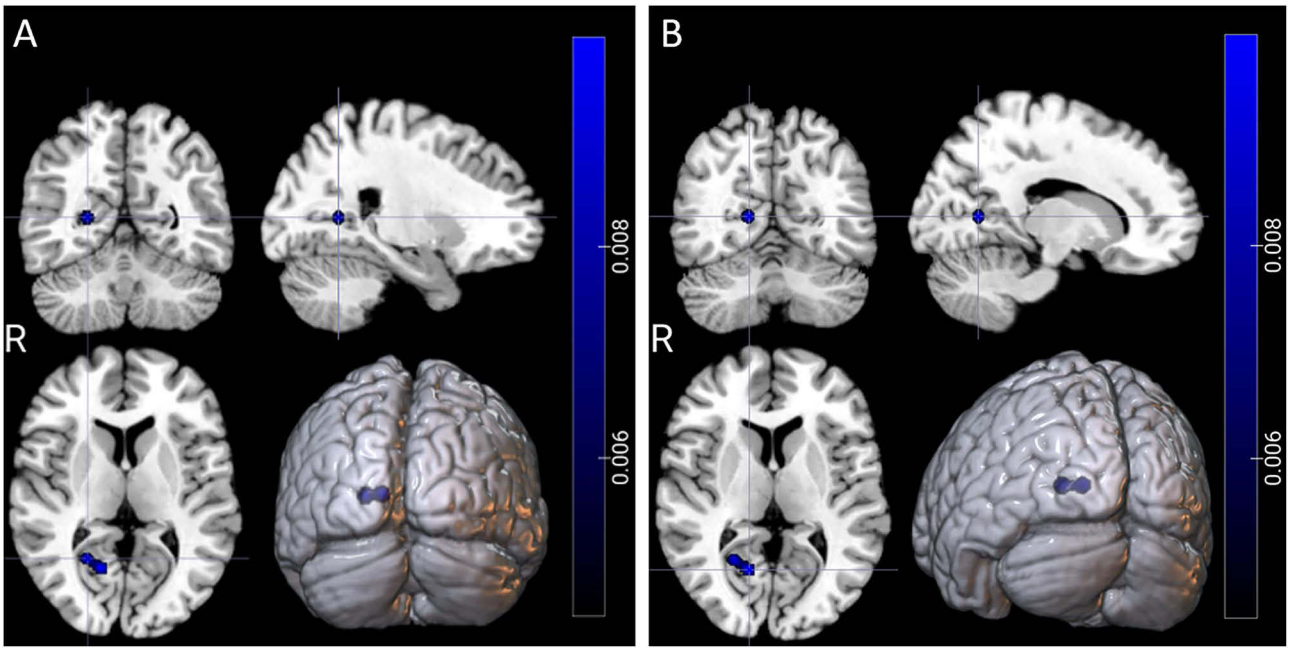

Figure 4 Convergent regions of reduced activation in PTN patients in the exclusive DC analysis. The analysis identified a significant cluster spanning (**A**) the right cuneus and (**B**) the right lingual gyrus. Results are displayed on a standard MNI template. The color bar indicates the ALE value. Statistical significance was determined using a cluster-forming threshold of $p < 0.001$ with a cluster-level FWE correction at $p < 0.05$.

depression-like behaviors. These findings align closely with our results, suggesting that prefrontal dysfunction may drive the chronification of pain through weakened descending pain inhibition and limbic system regulation, forming a "pain-emotion-cognition" vicious cycle.

Occipital Lobe

The medial occipital lobe (lingual gyrus-cuneus complex) integrates visual processing and pain perception.[42] Our rs-fMRI analysis revealed consistent hypoactivation in the right cuneus-lingual gyrus via ReHo/ReHo-DC metrics, suggesting adaptive chronic pain responses involving visual-nociceptive integration dysfunction and pain-modulatory circuit suppression.

Previous studies suggest that increased temporal lobe activity in TN patients may induce dysfunction in brain regions, potentially heightening sensitivity to action recognition related to TN pain attacks,[43,44] while structural MRI reports reduced cuneus cortical thickness correlated with carbamazepine dosage, indirectly supporting functional suppression in this region.[45]

Cerebellum

While traditionally linked to motor coordination, the cerebellum modulates pain via interactions with sensory-motor, executive, and limbic systems.[46–49] A meta-analysis conducted by Moulton et al demonstrated consistent activation of vermal lobules IV/V and hemispheric lobules V/VI during pain processing in chronic pain patients.[47] Subsequent meta-

Table 5 Convergent Regions of Reduced Activation in PTN Patients in Exclusive DC Analysis

Location	Brain Region	BA	Cluster Size (mm^3)	The Coordinates of the Peak Point of MNI			Max Value of ALE
				X	Y	Z	
Right	Cuneus—Lingual Gyrus	19	1040	24 16	−58 −62	6 6	0.009

Abbreviations: PTN, primary trigeminal neuralgia; DC, degree centrality; BA, Brodmann area; MNI, Montreal neurological institute.

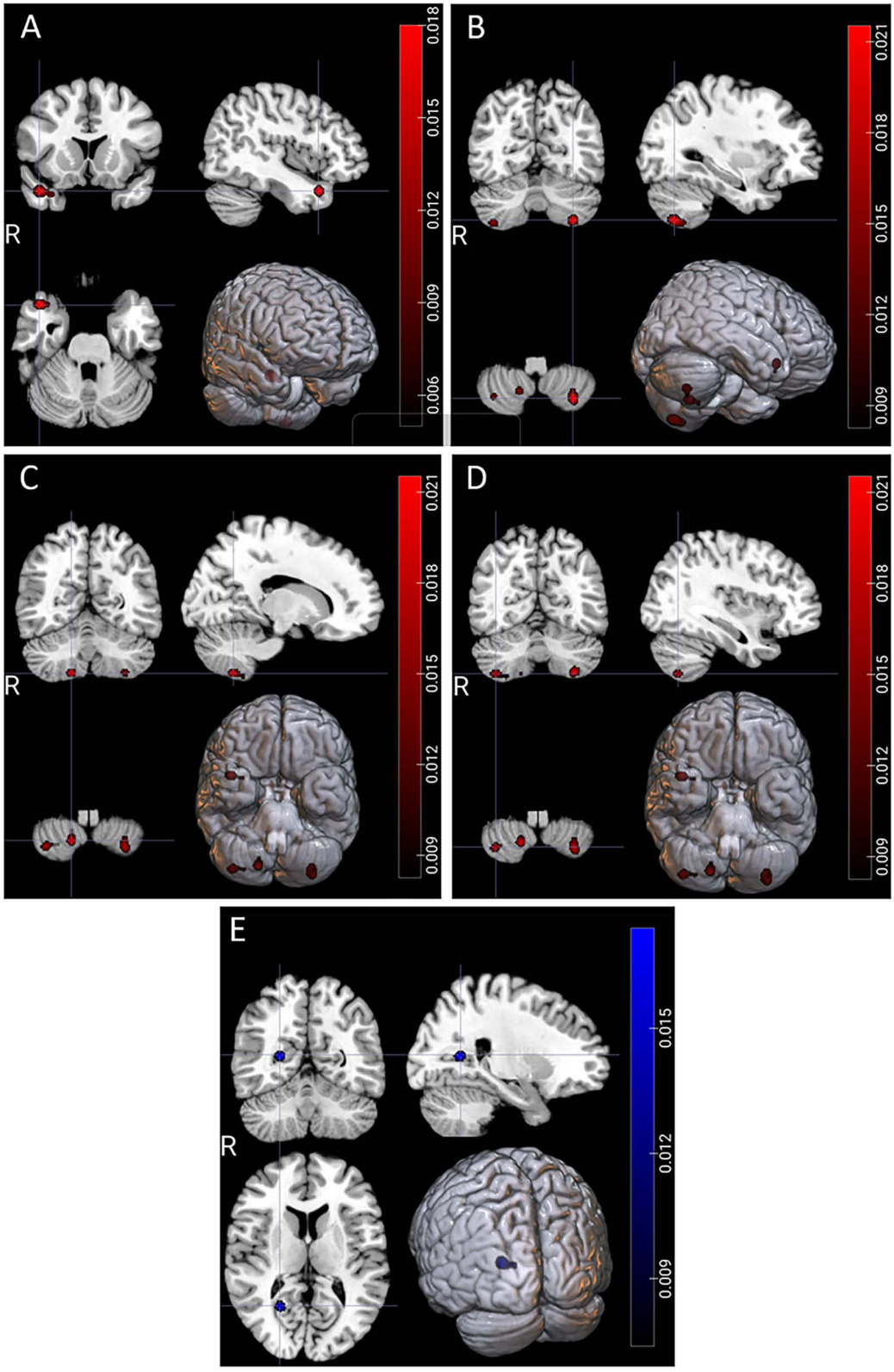

Figure 5 Convergent regions of synergistic alteration in PTN patients in the combined ReHo & DC analysis. The analysis revealed regions of increased activation in (**A**) the right temporal pole, (**B**) the left cerebellum posterior lobe, and (**C** and **D**) the right cerebellum posterior lobe. A region of decreased activation was identified in (**E**) the right cuneus. Results are displayed on a standard MNI template. The color bars indicate the ALE values. Statistical significance was determined using a cluster-forming threshold of $p < 0.001$ with a cluster-level FWE correction at $p < 0.05$.

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Table 6 Convergent Regions of Reduced Activation in PTN Patients in Combined ReHo&DC Analysis

Contrast	Location	Brain Region	BA	Cluster Size (mm^3)	The Coordinates of the Peak Point of MNI			Max Value of ALE
					X	Y	Z	
Increase	Right	Temporal Pole	38	672	44	15	−30	0.018
	Left	Cerebellum Posterior Lobe	—	1136	−32	−66	−54	0.022
	Right			704	16	−60	−58	0.019
	Right			640	38	−64	−58	0.017
Decrease	Right	Cuneus	18	864	23	−58	8	0.017

Abbreviations: PTN, primary trigeminal neuralgia; ReHo, Regional Homogeneity; DC, degree centrality; BA, Brodmann area; MNI, Montreal neurological institute.

analyses by Lanz et al.,[50] Jensen et al[51] and Xu et al[52] further linked chronic pain to altered activation intensity in lobules V/VI and Crus I.

In this study, consistent co-activation synergistic enhancement in the posterior cerebellar lobe of PTN patients was identified in both independent ReHo analysis and combined ReHo-DC analysis. We hypothesize that this reflects functional network remodeling of the cerebellum under chronic pain conditions, suggesting that this region not only exhibits increased local neuronal synchronization but also serves as a critical "hub" within the pain network, mediating functional connectivity with pain-related regions across the whole brain.

Studies have demonstrated altered persistent activity patterns in the cerebellum of chronic pain patients. For instance, patients with chronic orofacial neuropathic pain exhibit increased oscillation intensity in the low-frequency range within lobule VI and Crus I of the cerebellum.[53] Furthermore, functional connectivity (FC) between the cerebellum and other cortical/subcortical regions is aberrant in chronic pain populations. For example, enhanced FC between the left Crus I and bilateral insular regions has been observed in patients with persistent headache.[54] Mehnert et al further reported that noxious trigeminal input induces activation in multiple cerebellar regions (lobule VI, VIIIa, Crus I), which show enhanced connectivity with classical "pain matrix" regions and bilateral precentral gyrus facial areas.[55]

Temporal Lobe

The temporal lobe plays a role in numerous intricate functions, such as language processing, auditory perception, memory handling, and emotional control.[56–58] In recent years, it has been regarded as one of the brain regions for central pain integration.[59]

Our ALE analysis revealed enhanced left temporal pole co-activation in PTN via ReHo/ReHo-DC metrics, linking temporal lobe dysfunction to chronic pain modulation and disease severity. Structural MRI studies demonstrate negative correlations between superior temporal gyrus (STG) gray matter volume and pain duration/anxiety scores,[60] while aberrant STG-posterior cingulate gyrus(PCG)/default mode network(DMN) connectivity exacerbates pain persistence.[61] Temporal lobe volume loss further correlates with TN progression,[62] highlighting its role in pain chronification and potential as a neuromodulatory target.

Others

The limbic system (including the amygdala, hippocampus, cingulate gyrus, etc.) serves as the central hub for emotional and memory processing, playing a pivotal role in the development and maintenance of chronic pain.[63] The chronification of pain is often accompanied by spatiotemporal reorganization of brain activity, shifting from sensory to emotional and limbic regions.[64]

Although numerous studies have reported abnormalities in the extensive limbic system and its related structures (such as the thalamus) in TN patients,[10–12,17,28,31,33,65–67] this meta-analysis failed to identify cross-study consistent activation clusters in these regions. We argue that this is not a methodological failure but an important signal reflecting clinical reality. Specifically, the heterogeneity of the limbic system may be associated with the following factors: (1) Pain subtypes and severity: differences in pain frequency, intensity, and the presence of persistent pain among patients may

lead to varying limbic system responses. For example, Wang et al found significantly increased ALFF values in the right anterior cingulate gyrus of TN patients with high neurovascular compression (NVC) scores,[31] while Zhang et al reported decreased ALFF values in the bilateral anterior cingulate gyrus;[28] (2) Clinical subtypes and lateralization effects in PTN: recent studies have revealed that there are potential differences in functional connectivity and spontaneous brain activity between classical trigeminal neuralgia (CTN), idiopathic trigeminal neuralgia (ITN), and trigeminal neuralgia on different sides;[34,68] (3) Emotional comorbidities: Limbic system activity and connectivity may differ between TN patients with emotional disorders and those without. For instance, some studies have found abnormally increased functional connectivity of the amygdala in TN patients,[33] whereas others have reported reduced functional connectivity and nodal efficiency in the hippocampus;[17] (3) Disease duration and stage: Neuroplasticity during TN progression exhibits dynamic changes, and functional reorganization of the limbic system may have time-dependent characteristics and complex topological properties. For example, using dynamic functional network connectivity analysis, Zhang et al found reduced nodal efficiency in the anterior cingulate cortex (within the salience network) and thalamus/caudate nucleus (within the subcortical network), with changes in topological properties negatively correlated with TN duration and attack frequency.[11] This suggests that the involvement of the limbic system may differ across different disease stages.

Additionally, in seed-based functional connectivity analyses, our study observed no significant cluster formation. Potential contributing factors include: 1) spatial dispersion of coordinate data due to varying anatomical seed point selections across PTN-related connectivity studies, which may reduce the ALE algorithm's ability to detect consistent activation; 2) disparities in experimental paradigms, insufficient study inclusion, and small sample sizes across studies, leading to increased spatial fuzziness in MA maps and reduced ALE value convergence. Therefore, larger sample sizes, refined seed-based analysis protocols, stricter data filtering, stratified analysis, and multi-method cross-validation may improve detection of PTN-specific dysfunctional couplings.

Clinical Value and Futural Prospection

In our study, the final results highlight the central role of prefrontal dysfunction in descending pain inhibition failure, the potential compensatory value of cerebellar and temporal networks in chronic pain adaptation, and the marked heterogeneity of activation patterns in traditional limbic structures and thalamus. These findings provide important neuroimaging clues for the future development of more targeted individualized treatment strategies.

Current studies indicate that while pharmacological therapies and invasive surgical interventions can alleviate pain symptoms in TN patients to varying degrees, a subset of individuals still experience inadequate pain control or pain recurrence.[2,69–75] Based on the preceding discussion, we hypothesize that there may be subgroup differences in central neuroimaging signatures among PTN patients with varying treatment responses. Danyluk et al found that limbic system functional changes correlate with surgical treatment resistance in TN, enabling partial differentiation between responders and non-responders.[76] Prof. Karen D. Davis' team identified structural differences in brain regions between treatment-effective and treatment-ineffective TN patient groups, proposing that neuroimaging-based brain signatures could identify patients likely to benefit from therapy, thereby highlighting the potential of neuroimaging analysis for treatment efficacy evaluation and patient stratification in TN.[77–79] Liu et al analyzed rs-fMRI data from migraine patients and demonstrated that functional connectivity strength within the limbic system, prefrontal cortex, and other brain regions effectively distinguished patient subgroups with varying headache frequencies.[80] However, current research predominantly focuses on cross-sectional resting-state fMRI studies, with notable gaps in neuroimaging-based PTN subgroup classification, longitudinal dynamic mechanism investigations, and explorations of whole-brain dynamic functional connectivity patterns. Limited sample sizes further restrict the comprehensive capture of dynamic functional alterations during TN progression. Future studies should prioritize large-scale longitudinal cohorts, multimodal technical integration, and individualized modeling to elucidate dynamic brain network characteristics in PTN patients, thereby providing scientific foundations for personalized treatment strategies and prognostic prediction.

Furthermore, long-term pharmacotherapy or repeated surgical interventions may lead to more severe side effects and complications in patients with refractory or recurrent TN.[81–83] Consequently, there is an urgent clinical and patient-driven demand for non-invasive, safe, and effective therapeutic alternatives to conventional drugs and surgeries. Brain stimulation, a non-invasive technology capable of guiding neuroplasticity, aims to alleviate chronic pain by directly altering

brain activity through induced electrical stimulation.[84] Retrospective studies in chronic pain have demonstrated promising analgesic effects of non-invasive brain stimulation techniques, particularly repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS).[84,85] A recent review by Babakhani et al evaluated tDCS efficacy in refractory TN patients, finding significant pain reduction with differing polarities potentially acting through distinct neural pathways. Neuroimaging methods were shown to identify imaging biomarkers of tDCS treatment response in TN.[86] rTMS studies further indicate that targeting the primary motor cortex (M1) effectively alleviates pain in refractory TN.[87,88] Despite promising analgesic outcomes of transcranial electrical stimulation in chronic TN management, the underlying mechanisms of non-invasive neuromodulation remain unclear, stimulation protocols lack standardization, and interventions typically rely on fixed anatomical targets (eg, M1 or DLPFC). Future research is warranted to elucidate optimal individualized treatment strategies and target selection. Additionally, the complexity of chronic TN pain necessitates longitudinal investigations using multimodal fMRI techniques to characterize baseline and post-intervention features of the brain's nociceptive-perceptive and inhibitory pathways, thereby comprehensively analyzing pain-related neural networks across sensory, cognitive, and emotional dimensions.

Limitations

First, a major limitation of this study is that due to most original studies failing to provide subgroup coordinate data for stratified meta-analysis, we did not separately analyze different subtypes of primary trigeminal neuralgia (ie, classic trigeminal neuralgia and idiopathic trigeminal neuralgia). Secondly, several of our ALE analyses, particularly the DC analysis, were based on a relatively small number of studies (n=3), which may limit the statistical power and the stability of the identified convergence patterns. Thirdly, the combined ReHo and DC analysis was exploratory in nature, designed to test for synergistic alterations. While the results are theoretically grounded, they should be interpreted with caution pending further validation in future studies. Additionally, we did not differentiate clinical heterogeneities such as persistent pain and pain laterality effects in patients. We speculate that clinical heterogeneity may be one of the key reasons leading to the highly discrete activation patterns of the limbic system and the failure to form consistent results. Future original studies should strive to report detailed data of different clinical subtypes to reveal neuroimaging markers of specific subgroups. Finally, the ALE method only models based on activation coordinates reported in the literature, which is essentially a spatial convergence analysis and cannot obtain activation intensity, range, and temporal dynamic information of neural activity in the original images.

Conclusion

This study systematically revealed the complex landscape of brain functional remodeling in PTN patients through modality-specific meta-analysis. Our core contribution lies in demonstrating that different fMRI indices uncover complementary rather than overlapping abnormal patterns. Collectively, these findings challenge the traditional approach of seeking a single "pain center" and emphasize the necessity of understanding PTN central mechanisms from a multi-dimensional and multi-metric perspective. However, due to study limitations, further research is required to validate and refine these findings, promoting clinical progress in PTN diagnosis and treatment.

Abbreviations

PTN, Primary Trigeminal Neuralgia; fMRI, functional Magnetic Resonance Imaging; ALE, Activation Likelihood Estimation; rs-fMRI, Resting-State Functional Magnetic Resonance Imaging; HC(s), Healthy Control (s); ALFF, Amplitude of Low-Frequency Fluctuation; fALFF, Fractional Amplitude of Low-Frequency Fluctuation; ReHo, Regional Homogeneity; DC, Degree Centrality; MNI, Montreal Neurological Institute; NOS, Newcastle-Ottawa Scale; FC, Functional Connectivity; VAS, Visual Analogue Scale; NVC, Neuro Vascular Compression; STG, Superior Temporal Gyrus; PCG, Posterior Cingulate Gyrus; DMN, Default Mode Network; PFC, Prefrontal Cortex; mPFC, medial Prefrontal Cortex; PAG, Periaqueductal Gray; RVM, Rostral Ventromedial Medulla; DLPFC, Dorsolateral Prefrontal Cortex; CRH, Corticotropin-Releasing Hormone; CRHR1, Corticotropin-Releasing Hormone Receptor 1; MACM, Meta-Analytic Connectivity Modeling; FWE, Family-Wise Error; BOLD, Blood Oxygen Level-Dependent; rTMS, repetitive

Transcranial Magnetic Stimulation; tDCS, transcranial Direct Current Stimulation; ICHD-3, International Classification of Headache Disorders, 3rd edition; EEG, Electroencephalogram.

Data Sharing Statement

All supporting documentation related to this meta-analysis, comprising data collection templates, research datasets, coding frameworks, and methodological records, are available upon request to verified academic professionals. Researchers seeking to replicate or extend the work may initiate access procedures by emailing the study's principal investigator, Dr. Hongan Yang, through his official university Email (Email: 460879635@qq.com).

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Disclosure

Hongan Yang, Chuan Zhang and Baijintao Sun contributed equally to this work and share first authorship. All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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