Structural and Functional Brain Abnormalities in Trigeminal Neuralgia: A Systematic Review

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Aims: To evaluate the available literature on structural and functional brain abnormalities in trigeminal neuralgia (TN) using several brain magnetic resonance imaging (MRI) techniques to further understand the central mechanisms of TN. **Methods:** PubMed and Web of Science databases and the reference lists of identified studies were searched to identify potentially eligible studies through January 2019. Eligible articles were assessed for risk of bias and reviewed by two independent researchers. **Results:** A total of 17 articles meeting the inclusion criteria were included in this study. The methodologic quality of the included studies was moderate. A total of 10 studies evaluated structural gray matter (GM) changes, and there was reasonable evidence that the GM of some specific brain regions changed in TN patients. In addition, there was a significant change in the root entry zone of the trigeminal nerve and in several regions of white matter. Functional changes in resting state were assessed in 9 studies. TN patients showed increased activation of resting state, and this activation was reduced in specific brain regions. There were several studies that focused on the correlation between functional parameters or strength of functional connectivity and clinical features (eg, visual analog score and pain duration), but each study focused on different brain areas or different functional connectivities within the brain. **Conclusion:** There is moderate evidence that TN patients show structural brain differences in specific cortical and subcortical regions. In addition, TN patients show changes in pain-related functional connections in the resting state. Future research should focus on longitudinal designs and integration of different brain-imaging techniques. *J Oral Facial Pain Headache 2020;34:222–235. doi: 10.11607/ofph.2626*

Keywords: *functional connectivity, gray matter, trigeminal neuralgia, white matter*

Trigeminal neuralgia (TN) is one of the most prevalent facial pain conditions and is characterized by excruciating shooting pain in regions dominated by the trigeminal nerve.[1] TN is not just a matter of physical pain, since it can also induce emotional stress that sometimes culminates in clinical depression and may even result in suicide.[2] According to current scientific opinion, the primary pathophysiology of TN is the demyelination of the trigeminal nerve root, which is caused by neurovascular compression.[3] While there is ample evidence that neurovascular compression may be a risk factor for the development of TN, there are other causes that may also induce TN.[4,5] Jannetta[6] found that 12% of patients with TN did not have neurovascular compression, whereas Kakizawa et al[7] found that, based on magnetic resonance imaging (MRI), up to 49% of people exhibited a nerve vessel contact but did not develop TN. Moreover, a large number of MRI studies have shown abnormalities in the structure and function of the central nervous system (CNS) in patients with TN.[8–10] The CNS factors of TN have increasingly become the focus of attention in recent research. The schematic pathway of TN and its neuromodulation pathway are shown in Fig 1, but the specific underlying mechanisms remain unclear.[4] Some noninvasive MRI techniques for brain structure and function can be used to gain a deeper understanding of the location and characteristics of brain responses to TN.

In terms of brain structural characteristics, gray matter (GM) and white matter (WM) volumes can be quantified. Commonly used measurement methods are voxel-based morphometry (VBM)[4] and FreeSurfer software.[11] In addition, WM tracts can be visualized using diffusion tensor imaging (DTI).[12] The main parameters of DTI include fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD).[13,14] FA, which ranges from 0 to 1, is a measure of the degree of directionality of water diffusion. It represents the degree of tissue anisotropy and thus indicates the integrity of the WM fiber. The MD of a region reflects the overall diffusion of water molecules in that particular region. FA and MD give information about any alterations in the barriers to diffusion. Lower MD values have been reported to be associated with higher WM integrity. AD measures the rate of water diffusion along the longitudinal axis, while RD measures it along the perpendicular axis. An increase in axial AD is associated with axonal degeneration, while an increase in RD is related to demyelination.[12] As an extension of DTI, diffusion kurtosis imaging (DKI) has also been used to assess changes in WM. Unlike DTI, which assumes the diffusion of water is Gaussian and is thus unable to completely characterize tissue microstructure, DKI measures non-Gaussian behavior of water diffusion and may provide more information about the heterogeneity of nerve structures.[16] DKI-derived parameters include axial kurtosis (AK), mean kurtosis (MK), and radial kurtosis (RK).[15,16] MK represents the average of the diffusion kurtosis along all diffusion directions. AK represents the measure of the kurtosis along the principal diffusion tensor eigenvector, while RK represents the measure of the kurtosis perpendicular to the principal eigenvector. The principal diffusion tensor eigenvector is the direction that maximizes the diffusivity.[16] Parameters derived from DKI have been reported to be more sensitive than conventional DTI parameters, preferably because DKI is highly sensitive to any changes in tissue microstructural organization.

In addition to structural characteristics of the brain, functional changes in the brain can be detected using functional MRI (fMRI). With fMRI, brain activity can be measured indirectly by monitoring changes in the brain blood-oxygen level dependent response.[17] The main analytic methods of fMRI include regional homogeneity (ReHo), amplitude of low-frequency fluctuation (ALFF), and functional connectivity (FC). The ReHo measures the consistency of the spontaneous neuronal activity of a given voxel compared to that of its adjacent voxel at rest, thereby providing information about differences in local brain activity.[18] Intrinsic fluctuations of bold signals, which display the local spontaneous static-state brain activity, can be measured by the ALFF. ALFF has been demonstrated to be a valuable parameter in reflecting the intensity of spontaneous nerve activity.[19] FC can reflect the effects of pain on the central nervous system at the level of the brain's functional network.

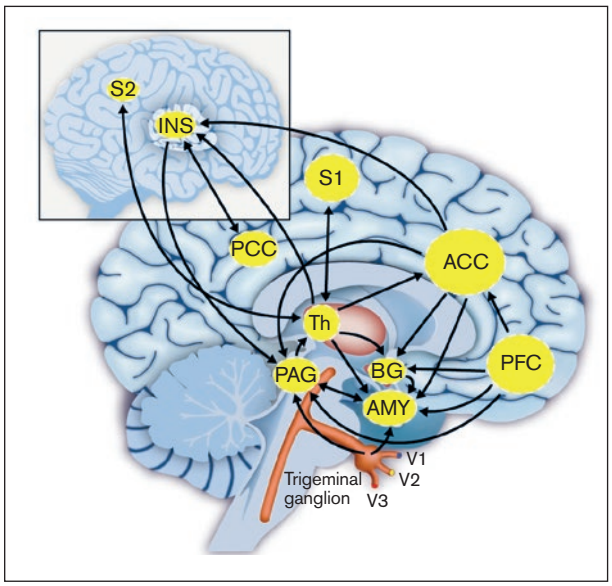

Fig 1 Schematic pathway of trigeminal neuralgia and its possible neuromodulation pathway. The arrows represent ascending and descending modulatory pathways for pain for a simplified overview of the brain targets. The brain regions involved in pain and emotional regulation of TN include the thalamus (TH), anterior cingulate cortex (ACC), insula (INS), primary and secondary somatosensory cortices (S1 and S2, respectively), periaqueductal gray (PAG), prefrontal cortices (PFC), basal ganglia (BG), amygdala (AMY), and posterior cingulate cortex (PCC).

There is increasing knowledge of structural and functional neuroplastic changes in TN. However, due to the differences in techniques and regions of interest in the brain, the results are often difficult to interpret. The present systematic review summarizes the existing evidence on structural and functional brain differences in TN.

Materials and Methods

Registration of Systematic Review

The protocol details of the systematic review were registered prospectively with PROSPERO (international prospective register of systematic reviews; registration number: CRD42018107954) on August 24, 2018, and are available at the following link: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=107954.

Information Sources and Search Strategy

Searches were conducted in the online databases PubMed and Web of Science. The keywords included

"trigeminal neuralgia," "brain imaging," "fMRI," "rs-fMRI," "voxel-based morphometry," "VBM," "diffusion tensor imaging," and "DTI."

Study Selection

In the first phase of study selection, the initial screening of retrieved articles was carried out by one author (H.H.). In the second phase, full texts for all of the eligible studies were retrieved and reviewed by the second author (C.Z.) to ensure that the selection criteria were maintained. Any uncertainties or disagreements were discussed and resolved at a consensus meeting with a third reviewer (S.K.D.). Furthermore, the reference lists of relevant primary articles were reviewed to identify studies that may have been missed in the initial search.

Inclusion and Exclusion Criteria

The retrieved articles needed to meet the following inclusion criteria: *(1)* human subjects; *(2)* all patients met the criteria of the International Headache Society for classical TN and were not diagnosed with systemic diseases; *(3)* at least one structural or fMRI technique was used; *(4)* the study recruited patients with classical TN and compared them to healthy controls; *(5)* articles were published in English prior to December 2018; and *(6)* articles were a full text of original research and not case reports, reviews, systematic reviews, or meta-analyses. Studies of patients with symptomatic (or secondary) TN (eg, that associated with MS or tumor) were excluded.

Outcomes

The following information was extracted from each included article: *(1)* publication details, such as author(s) and year of publication; *(2)* imaging equipment used; *(3)* characteristics of the trial (eg, sample sizes, duration, and pain scores); *(4)* gender and age of the TN/control groups; and *(5)* main findings.

Risk of Bias in Individual Studies

To assess the methodologic quality of each individual study, the Newcastle-Ottawa Scale (NOS) for case-control studies was utilized. The Cochrane Collaboration group recommends the NOS as a quality assessment tool for observational studies. The NOS is divided into three subcategories (selection, comparability, and exposure/outcome) and consists of eight questions with a maximum possible total score of 9 points. Higher scores are indicative of greater methodologic quality.

Two authors (C.Z. and H.H.) independently applied the NOS to each individual study. Afterwards, the results were compared, and differences were determined at a consensus meeting with the third reviewer (S.K.D.).

Levels of Evidence

The level of evidence for each study was determined based on study design and methodologic quality according to the Dutch Institute for Healthcare Improvement (CBO).[20] The CBO classification reflects the level of evidence: A1 is a systematic review of at least two independent randomized double-blinded studies of sufficient quality and size; A2 is a randomized double-blinded study of sufficient quality and size; B is a comparative study that does not meet all of the criteria of an A2 study; C is a non-comparative study; and D is expert opinion.[21]

Finally, a strength of conclusion was calculated for each outcome parameter. A strength of conclusion 1 represents that there are at least two independently conducted studies of evidence level A2; a strength of conclusion 2 represents that there are at least two independently conducted studies of level B or one study of level A2; and a strength of conclusion 3 represents that there is one study of level B.[22]

Results

Study Selection

The search yielded 240 results in total from all of the databases. After excluding duplicate studies, 95 unique articles were selected. A total of 75 articles were further excluded for not meeting the inclusion criteria. Finally, after both screening phases and the additional manual search, 17 articles were included for evaluation in the present study.[4,10,15,18,19,23–34] The flowchart of the screening process can be found in Fig 2.

Risk of Bias and Level of Evidence

The results of the evaluation of methodologic quality are shown in Table 1. A total score of nine was possible, with one point awarded for fulfillment of each criterion, except for criteria five, for which two points were awarded if the study fulfilled more than one factor. For the majority of items, an equal score was given by both raters (141/152; 92.7%). Any differences were discussed to reach a definitive score. All of the included studies were given a B level of evidence.

Study Characteristics

The characteristics and results of both groups from each study are listed in Table 2. All of the studies recruited patients with classical TN and compared them to healthy controls.

Structural Organization

Gray Matter. The changes in brain GM structure were assessed in 10 studies. Global GM was reported in only 1 study,[23] which found a decrease in global

Table 1 Quality Assessment of Individual Studies

Study	Scoring criteria for quality assessment									
	1. Case definition adequacy	2. Representativeness of cases	3. Selection of controls	4. Definitions of controls	5. Comparability of cases and controls based on design and analysis	6. Ascertainment of exposure	7. Same method of ascertainment for cases and controls	8. Same nonresponse rate for both groups	Total score (/9)	Level of evidence
Obermann et al[4] (2013)	1	1	1	1	2	1	1	1	9	B
DeSouza et al[10] (2015)	1	1	1	1	2	1	1	1	9	B
Tian et al[15] (2016)	1	1	1	1	1	1	1	1	8	B
Yuan et al[18] (2018)	1	1	1	1	2	1	1	1	9	B
Wang et al[19] (2017)	1	1	1	1	2	1	1	1	9	B
Wang et al[23] (2017)	1	1	1	1	2	1	1	1	9	B
Parise et al[24] (2014)	1	1	1	1	2	1	1	1	9	B
Tsai et al[25] (2018)	1	1	1	1	2	1	1	1	9	B
Zhang et al[26] (2018)	1	1	1	1	2	1	1	1	9	B
Li et al[27] (2017)	1	1	1	1	2	1	1	1	9	B
Moon et al[28] (2018)	1	1	1	1	2	1	1	1	9	B
DeSouza et al[29] (2013)	1	1	1	1	1	1	1	1	8	B
Wang et al[30] (2018)	1	1	1	1	2	1	1	1	9	B
Liu et al[31] (2018)	1	1	1	1	2	1	1	1	9	B
DeSouza et al[32] (2014)	1	1	1	1	1	1	1	1	8	B
Wang et al[33] (2015)	1	1	1	1	1	1	1	1	8	B
Xiang et al[34] (2019)	1	1	1	1	1	1	1	1	8	B

One point was given for the fulfillment of each criterion, with the exception of criteria 5, for which 2 points were given if the study fulfilled more than 1 factor.

GM volume in TN patients compared to healthy controls. Nine studies reported regional GM differences in TN patients.[4,10,24–30]

Multiple studies found that TN patients had reduced GM in the anterior cingulate cortex (ACC),[4,23,27–29] posterior cingulate cortex (PCC),[10,28,29] insula,[4,10,23,29,30] secondary somatosensory cortex (S2),[4,23] cerebellum,[4,25,27] caudate nucleus,[4,27] fusiform gyrus,[24,26] and left cuneus.[4,24] In contrast, the frontal pole (FP)[10,29] showed increased GM in two studies by DeSouza et al.[10,29] Additionally, two studies found an increase in GM in the primary somatosensory cortex (S1), primary motor cortex (M1), putamen, and periaqueductal gray (PAG).[10,29] However, Obermann et al[4] found reduced GM in the S1 and putamen. Moreover, Zhang et al[26] found reduced GM in the PAG, and Wang et al[23] found decreased GM in the M1. Inconsistent results were also found for several other brain regions. For the thalamus, DeSouza et al[10] found an increase in GM, while Obermann et al[4] found a decrease. In the frontal cortex[4,10,25,29] and the temporal gyrus,[23,27] a decrease of GM was found in four studies,[4,10,25,29] but this decrease was located in different subregions for each study. The amygdala, a key structure in the limbic system, showed a GM decrease in the study by Zhang et al[26] and a GM increase in the study by DeSouza et al.[29]

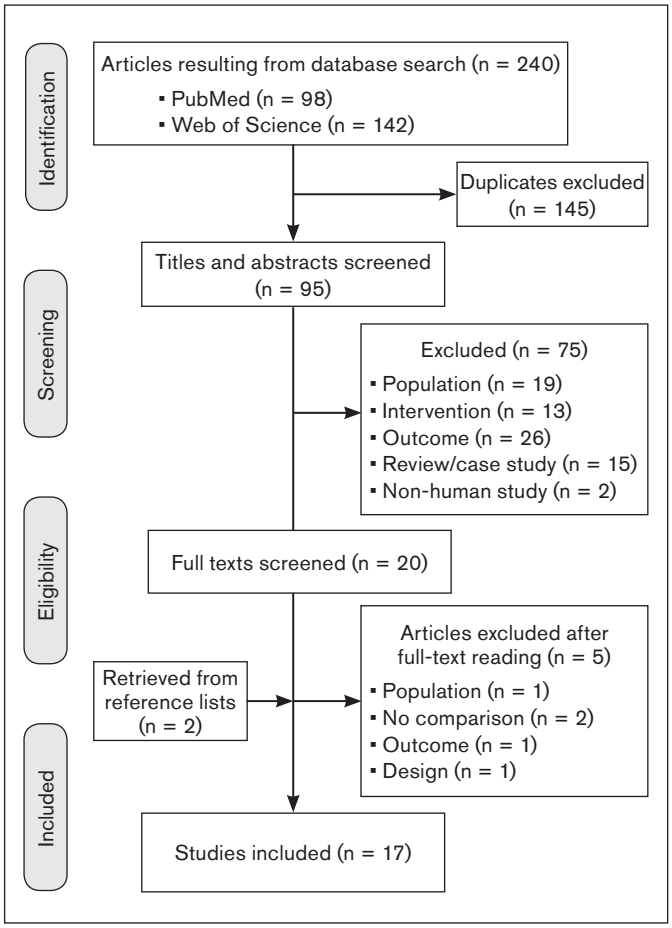

Fig 2 Flowchart of study selection.

Table 2 Evidence Table of Structural and Functional Brain Magnetic Resonance Imaging (MRI) in

Study (country, y)	MRI scan	Subjects (no., mean ± SD age, left/right)	Disease duration, mean ± SD	Pain intensity (VAS), mean ± SD
Obermann et al[4] (Germany, 2013)	1.5T	Patients = 60 (36 F/24 M), 62 ± 13.2 y HC = 49 (28 F/21 M), 61.8 ± 9 y	8.3 ± 6.7 y	7.7 ± 1.8
DeSouza et al[10] (Canada, 2015)	3.0T	Patients = 25 (15 F/10 M), 57.6 ± 11.5 y HC = 14 (9 F/5 M), 51.7 ± 10.9 y	7.96 ± 6.37 y	9.44 ± 1.29
Tian et al[15] (China, 2016)	3.0T	Patients = 20 (12 F/8 M), 52.6 ± 8.9 y HC = 22 (16 F/6 M), 52.2 ± 6.1 y	21.1 ± 16.2 mo	7.7 ± 1.6
Yuan et al[18] (China, 2018)	3.0T	Patients = 23 (9 F/14 M), 59.6 ± 12.5 y HC = 23 (11 F/12 M), 63.1 ± 9.8 y	5.69 ± 3.33 y	8.1 ± 1.6
Wang et al[19] (China, 2017)	1.5T	Patients = 17 (10 F/7 M), 62.53 ± 7.14 y HC = 19 (11 F/8 M), 61.75 ± 6.02 y	6.98 ± 5.64 y	6.11 ± 1.50
Wang et al[23] (China, 2017)	3.0T	Patients = 38 (22 F/16 M), 55.87 ± 8.38 y HC = 38 (22 F/16 M), 55.89 ± 8.06 y	7.05 ± 5.32 y	5.79 ± 1.70

ACC = anterior cingulate cortex; AD = axial diffusivity; AK = axial kurtosis; ALFF = amplitude of low-frequency fluctuation; BNI = Barrow Neurologic Institute; BOLD = blood oxygen level dependent; CC = corpus callosum; CR = corona radiata; CTN = classic trigeminal neuralgia; DLPFC = dorsolateral prefrontal cortex; dPI = dorsal posterior insula; EC = external capsule; FA = fractional anisotropy; FC = frontal cortex; FCD = functional connectivity density; FP = frontal pole; GM = gray matter; HAMA = Hamilton Anxiety Rating Scale; HAMD = Hamilton Depression Rating Scale; HC = healthy control; IC = internal capsule; ITG = inferior temporal gyrus; LF = longitudinal fasciculus; LGI = local gyrification index; MD = medial dorsal; mPFC = middle prefrontal cortex; MTG = middle temporal gyrus; M1 = primary motor cortex; NPRS = numeric pain rating scale; OFC = orbitofrontal cortex; PAG = periaqueductal gray; PCC = posterior cingulate cortex; PFC = prefrontal cortex; PMA = premotor area; RD = radial diffusivity; ReHo = regional homogeneity; REZ = root entry zone; ROI = region of interest; rsFC = resting state functional connectivity; SPL = superior parietal lobule; STG = superior temporal gyrus; S1 = primary somatosensory cortex; S2 = second somatosensory cortex; TH = thalamus; vAI = ventral anterior insula; VAS = visual analog scale; VL = ventral lateral; VPM = ventral posteromedial; WM = white matter.

Trigeminal Neuralgia (TN)

Main findings	Results
GM: Decrease of GM volume in S1, OFC, ACC, insula, S2, TH, putamen, caudate nucleus, DLPFC, precuneus, and cerebellum.	Negative correlation between GM volume decrease within the ACC, parahippocampus, and temporal lobe and increasing disease duration.
GM: Decrease of cortical thickness in the right vAI , posterior insula bilaterally, left OFC, and right PCC; increase of cortical thickness in the left M1, left S1, and FP bilaterally, putamen bilaterally, PAG, and TH; decrease of cortical thickness in the right vAI, bilateral posterior insula, OFC, ACC, and right PCC in the effective treatment group; increase of cortical thickness in the M1 bilaterally, left S1, and the FP cortex bilaterally in the effective treatment group. WM differences: Decrease of FA and increase in MD, RD, and AD in the REZ of TN patients; Decrease of FA in the affected REZ compared to unaffected side and to HC; increase of MD, RD, and AD in patients bilaterally. FA and the bilateral MD, RD, and AD abnormalities in the affected trigeminal REZ resolved after effective treatment.	Negative correlation between the percent pain relief after treatment and the pre- to posttreatment differences in MD, RD, and AD.
WM: Increase of AD in the right CC, bilateral superior LF, bilateral anterior thalamic radiation, forceps major, bilateral inferior LF, bilateral inferior fronto-occipital fasciculus, and bilateral uncinate fasciculus. Decrease of AK in the right corticospinal tract, right superior LF, bilateral anterior thalamic radiation, bilateral inferior LF, and bilateral inferior fronto-occipital fasciculus. FC: Increase of long-range FCDs in the left hippocampus and bilateral striatum. Decrease of long-range FCDs in the bilateral precuneus, bilateral PFC, right angular gyrus, and right supramarginal gyrus. Increase of local FCDs in the right thalamus and left precentral gyrus. Decrease of local FCDs in the bilateral medial PFC and left angular gyrus.	The total decreased long-range FCDs/local FCDs were significantly correlated with AD and AK changes, respectively.
Functional differences: Increase of ReHo in posterior lobe of cerebellum, ACC, MTG, precuneus, and medial and superior frontal gyrus. Increase in cerebellum and insula.	Positive correlation between the ReHo value of the posterior lobe of the cerebellum and the MTG and VAS score. Negative correlation between the ReHo value of the ACC, precuneus, medial frontal gyrus, superior frontal gyrus, insula, and VAS score.
Functional differences: Increase of ALFF in left middle occipital gyrus, left middle frontal gyrus, right middle cingulate gyrus, right cerebellum, and bilateral temporal cortices.	Positive correlation between subjective pain ratings and amplitudes of higher frequency BOLD signals in pain localization brain regions. Negative correlation between subjective pain ratings and amplitudes of lower frequencies in pain signaling/modulating brain regions. Negative correlation between ALFF decrease in medial/orbital prefrontal regions and pain duration.
Global GM: Lower total GM volume in CTN. Regional of GM: Decrease of GM volume in ACC, MCC, insula, S2, M1, PMA, and several portions of temporal lobe. Increase of GM volume in a small part of the SPL. Global WM skeleton: Decrease of FA and increase of MD. Regional of WM skeleton: Decrease of FA and increase of MD in the CC. Decrease of FA and increase of MD in the anterior, posterior, and superior CR. Increase of MD in the bilateral inferior/superior cerebellar peduncle, corticospinal tract, TH, anterior/posterior limb of IC, EC, and superior LF. FC: Increase of functional connectivity between the right insula/S2 and the ACC, mPFC, PCC, and bilateral DLPFC.	Negative correlation between GM volume in left ITG and disease duration, pain intensity. Negative correlation between the connectivity strength of right insula/S2 to ACC and pain intensity, anxiety, and depression indices.

Table 2 Evidence Table of Structural and Functional Brain Magnetic Resonance Imaging (MRI) in

Study (country, y)	MRI scan	Subjects (no., mean ± SD age, left/right)	Disease duration, mean ± SD	Pain intensity (VAS), mean ± SD
Parise et al[24] (Brazil, 2014)	1.5T	Patients = 24 (18 F/6 M), 55.8 ± 8.5 y, 13 left/11 right HC = 24 (12 F/6 M), 56.3 ± 7.8 y	7.1 ± 3.94 y	10
Tsai et al[25] (Taiwan, 2018)	3.0T	Patients = 62 (38 F/24 M); Right = 8.0 ± 7.7 y, left = 59.0 ± 6.6 y HC = 19 (15 F/4 M), 55.6 ± 8.2 y	Right = 69.6 ± 75.4 mo, left = 63.2 ± 59.0 mo	R = 9.3 ± 0.7 L = 9.4 ± 0.9
Zhang et al[26] (China, 2018)	3.0T	Patients = 29 (19 F/10 M), 48.14 ± 11.89 y HC = 34 (21 F/13 M), 43.32 ± 10.07 y	6.02 ± 4.35 y	6.31 ± 1.15
Li et al[27] (China, 2017)	1.5T	Patients = 28 (13 F/15 M), 45.86 ± 11.17 y HC = 28 (13 F/15 M, 44.89 ± 7.67 y	8.43 ± 3.65 y	8.7 ± 1.2
Moon et al[28] (Korea, 2018)	7T	Patients = 15 (11 F/4 M), 48.4 ± 2.75 y HC = 16 (12 F/4 M), 42.88 ± 3.99 y	5.4 ± 1.72 y	3.6 ± 0.21 (BNI pain score)
DeSouza et al[29] (Canada, 2013)	3.0T	Patients = 24 (15 F/9 M), 48.5 ± 12.7 y HC = 24 (15 F/9 M), 47.6 ± 12.3 y	6.3 ± 3.0 y	–
Wang et al[30] (China, 2018)	3.0T	Patients = 20 (15 F/5 M), 56 ± 11.75 y HC = 21 (16 F/5 M), 55 ± 9.69 y	6.25 ± 5.89 y	2.30 ± 1.41 (NPRS)
Liu et al[31] (China, 2018)	3.0T	Patients = 29 (20 F/9 M), range 35–77 y HC = 35 (27 F/8 M), range 41–74 y	10.2 ± 9.6 y	5.9 ± 3.1
DeSouza et al[32] (Canada, 2014)	3.0T	Patients = 18 (11 F/7 M), 54.1 ± 17.0 y HC = 18 (11 F/7 M), 49.6 ± 12.7 y	–	–
Wang et al[33] (China, 2015)	1.5T	Patients = 17 (10 F/7 M), 63.41 ± 7.25 y HC = 19 (10 F/9 M), 62.53 ± 7.41 y	6.98 ± 5.64 y	6.12 ± 1.50
Xiang et al[34] (China, 2019)	3.0T	Patients = 28 (16 F/12 M), 51.392 ± 9.372 y HC = 28 (16 F/12 M), 51.357 ± 9.302 y	3.73 ± 4.10 y	6.32 ± 1.44

ACC = anterior cingulate cortex; AD = axial diffusivity; AK = axial kurtosis; ALFF = amplitude of low-frequency fluctuation; BNI = Barrow Neurologic Institute; BOLD = blood oxygen level dependent; CC = corpus callosum; CR = corona radiata; CTN = classic trigeminal neuralgia; DLPFC = dorsolateral prefrontal cortex; dPI = dorsal posterior insula; EC = external capsule; FA = fractional anisotropy; FC = frontal cortex; FCD = functional connectivity density; FP = frontal pole; GM = gray matter; HAMA = Hamilton Anxiety Rating Scale; HAMD = Hamilton Depression Rating Scale; HC = healthy control; IC = internal capsule; ITG = inferior temporal gyrus; LF = longitudinal fasciculus; LGI = local gyrification index; MD = medial dorsal; mPFC = middle prefrontal cortex; MTG = middle temporal gyrus; M1 = primary motor cortex; NPRS = numeric pain rating scale; OFC = orbitofrontal cortex; PAG = periaqueductal gray; PCC = posterior cingulate cortex; PFC = prefrontal cortex; PMA = premotor area; RD = radial diffusivity; ReHo = regional homogeneity; REZ = root entry zone; ROI = region of interest; rsFC = resting state functional connectivity; SPL = superior parietal lobule; STG = superior temporal gyrus; S1 = primary somatosensory cortex; S2 = second somatosensory cortex; TH = thalamus; vAI = ventral anterior insula; VAS = visual analog scale; VL = ventral lateral; VPM = ventral posteromedial; WM = white matter.

Trigeminal Neuralgia (TN)

Main findings	Results
Global WM: No differences. Regional WM: Decrease in mid-anterior portion of C. Regional GM: Decrease of cortical thickness in left fusiform cortex and cuneus/pre-cuneus.	Negative correlation between thickness reduction of fusiform cortex and carbamazepine.
GM: Increase of GM volume (right) in the superior and inferior frontal gyrus, precentral gyrus, cerebellar tonsil; decrease (left) in inferior frontal gyrus, precentral gyrus, and cerebellum. Functional differences: Right TN compared to HC: Decrease in connection of right superior frontal gyrus with right middle frontal gyrus. Left TN compared to HC: Decrease in connection of left precentral gyrus with left superior frontal gyrus; increase in connection between the pulvinar of bilateral TH.	Moderate correlations between GM volume in the left ventral striatum and pain duration in the right TN group. Moderate correlations of GM volume of the ventral nucleus, right TH, medial dorsal nucleus, and left TH and pain duration in the left TN group.
GM: Decrease of GM volume in bilateral amygdala, PAG, and right insula. Functional differences: Decrease of connectivity strengths of left amygdala, left TH, and putamen; decrease between left amygdala and left DLPFC	Negative correlation between the rsFC strengths (left amygdala and left DLPFC) and pain duration. Positive correlation between rsFC strength (right amygdala and right PFC) and HAMD, and HAMA.
GM: Decrease of GM volume in bilateral STG/MTG, bilateral parahippocampus, left ACC, caudate nucleus, right fusiform gyrus, and right cerebellum.	Negative correlation between mean GM volume of bilateral STG/MTG and pain duration.
GM: Decrease of cortical thickness in left PCC, right PCC, and left caudal ACC in TN patients.	Negative correlation between pain duration and cortical volume and thickness (temporal region).
GM: Increase of cortical thickness in the left S1, FP, and M1 bilaterally. Decrease of cortical thickness in the pregenual ACC and the ventral OFC bilaterally, right dPI, vAI, and PCC. Increase of GM bilaterally in the MD nucleus, the VPM nucleus, the pulvinar, and the VL nucleus. Increase of GM in the right amygdala, nucleus accumbens, caudate, anterior putamen and posterior putamen, and PAG bilaterally.	No correlation between GM abnormalities and pain duration.
GM: Decrease of cortical thickness in the insula. WM: Decrease of FA in the left EC, superior CR, and posterior limb of IC. FC: Increase of functional connectivity between insula and left posterior cingulate cortex and PCC/TH.	Positive correlations between the mean FA of EC, CR, IC and mean LGI of the insular ROI.
WM: Right TN patients: Decrease of FA and increase of RD in most left WM.	Negative correlations between disease duration/VAS and the FA of left anterior corona radiata, left external capsule, and left cerebral peduncle. Positive correlations between disease duration/VAS and the RD of left anterior corona radiata and left external capsule.
WM: Increase of FA and RD, AD, MD at the REZ of affected trigeminal nerves in patients. Decrease of FA and increase of RD/MD in the CC of patients. Increase of AD in the CC (splenium) of patients. Decrease of FA and increase of RD/MD in the cingulum and posterior CR bilaterally in patients. Decrease of FA and increase of RD in the left superior longitudinal fasciculus in patients.	–
Functional differences: Decrease of ReHo in left amygdala, right parahippocampal gyrus, and left cerebellum; increase in right inferior temporal gyrus, right TH, right inferior parietal lobule, left pre- and postcentral gyrus.	Positive correlation between ReHo increase in the left precentral gyrus and VAS score.
Functional differences: Increase of ReHo values in the inferior cerebellum bilaterally, right inferior temporal, right fusiform, right middle occipital, right superior frontal, and right precentral gyrus.	–

Furthermore, multiple studies investigated the correlation between changes in GM volume and clinical parameters. Obermann et al,[4] Tsai et al,[25] Li et al,[27] and Moon et al[28] found negative correlations between disease duration and thickness reduction of GM. However, DeSouza et al[29] reported no correlation between GM changes and pain duration. Additionally, Parise et al[24] found a negative correlation between a reduction of thickness in the fusiform cortex and carbamazepine.

In conclusion, there is reasonable evidence that the GM of some specific brain regions changes in TN patients, including in the frontal cortex, ACC, PCC, insula, S1, S2, caudate nucleus, and cerebellum (strength of conclusion 2). In addition, there was a negative correlation between GM abnormalities and pain duration (strength of conclusion 2).

White Matter. Seven studies reporting WM abnormalities in TN were investigated.[10,15,23,24,30–32] Global WM volumes were analyzed in two studies, for which one study reported global WM volume decreases in TN[23] while the other reported no difference between TN and control groups.[24]

Multiple studies found that FA was reduced[10,30,32] and that MD,[10,32] RD,[10,31,32] and AD were increased[10,32] at the root entry zone (REZ) of the trigeminal nerve in TN patients. Three studies reported WM structural changes in the corpus callosum (CC),[23,24,32] corona radiata,[23,30,32] and longitudinal fasciculus (LF).[15,23,32] Lower FA and higher MD in the CC were observed in the studies of DeSouza et al[32] and Wang et al.[23] Higher RD and AD in the CC were reported by DeSouza et al.[32] However, Parise et al[24] found only lower FA in the CC of TN patients when compared to healthy controls. Additionally, DeSouza et al[32] and Wang et al[23] also found lower FA and higher MD in the CR in TN patients. Similar changes in FA of the CR were also reported by Wang et al.[23] In the LF, lower FA and higher MD/RD/AD/AK were found in three studies,[15,23,32] but were located in different subregions. For example, Tian et al[15] observed these changes in the bilateral inferior and superior LF. In contrast, Wang et al[23] discovered higher MD in the anterior and posterior limbs of the internal capsule and the external capsule, whereas lower FA was found in the left external capsule and posterior limb of the internal capsule. DeSouza et al[32] found lower FA and higher MD/RD in the WM of the cingulum. This result is consistent with the study of Tian et al,[15] in which a higher AD was found in the right cingulate gyrus.

Furthermore, two studies investigated the correlations between changes in WM and clinical parameters. Liu et al[31] found negative correlations between the FA of the left anterior CR/left external capsule/left cerebral peduncle and VAS/disease duration. In their study, they also found positive correlations between the RD of the left anterior CR/left external capsule and VAS/disease duration. DeSouza et al[10] found that FA/MD/RD/AD changes in the affected trigeminal REZ recovered after effective treatment, and the percentage of pain relief after treatment was significantly correlated with the pre- to posttreatment differences in MD/RD/AD.

In conclusion, there is reasonable evidence that FA is reduced and MD is increased in the REZ of the trigeminal nerve, CC, CR, and LF (strength of conclusion 2).

fMRI During Rest. Functional changes in resting state were assessed in nine studies.[15,18,19,23,25,26,30,31,34] The results of these studies were partially consistent, reporting ReHo/ALFF changes in several regions in TN patients. Overall, patients showed increased activation in the precentral gyrus,[33,34] ACC,[18] fusiform gyrus,[34] and superior frontal gyrus,[18,34] as well as decreased activation in the insula.[18] Both increased activation and decreased activation were found in the cerebellum,[33,34] left postcentral gyrus (PoCG),[33] temporal gyrus,[18,19,34] occipital lobe,[18,19,34] and inferior parietal lobule.[33] In addition, Wang et al[33] observed decreased activation in the left amygdala and right parahippocampal gyrus and increased activation in the right thalamus. Yuan et al[18] found increased activation in the putamen and precuneus.

Furthermore, some studies found that the functional parameters in several areas were correlated with VAS and pain duration. Wang et al[33] found a positive correlation between the increase of ReHo value in the left precentral gyrus and VAS scores. Yuan et al[18] observed a positive correlation between the ReHo value of the posterior lobe of the cerebellum and the middle temporal gyrus (MTG) and VAS score. However, there were negative correlations between VAS scores and the ReHo values of the ACC, precuneus, medial/superior frontal gyrus, and insula. Wang et al[19] found a negative correlation between pain duration and ALFF decrease in medial/orbital prefrontal regions. In a case-cohort study by Dou et al,[1] a positive correlation was observed between the ReHo of the left PoCG and VAS scores. Additionally, they found a negative correlation between disease duration and postsurgical ReHo in the left inferior parietal lobule.

Functional connectivity between different brain regions was also investigated. Wang et al[23] found enhanced FC between the right insula/S2 and ACC, middle prefrontal cortex, PCC, and bilateral dorsolateral prefrontal cortex (DLPFC) in TN patients. In addition, negative correlations were found between the FC of the right insula/S2/ACC and pain intensity, depression, and anxiety ratings. Wang et al[30] found that TN patients exhibited increased insular FC to the left PCC and thalamus, which was positively correlated

with pain duration. In contrast, both weaker connectivity (left amygdala and thalamus, putamen, and left DLPFC) and enhanced connectivity (right amygdala and PFC) were observed in a study by Zhang et al.[26] This study also found a negative correlation between resting-state FC strength (left amygdala and DLPFC) and pain duration and a positive correlation between resting-state FC strength (right amygdala and PFC) and the Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale. Tsai et al[25] found that the connectivity between the right and left thalamus was moderately correlated with pain duration in left TN patients.

In conclusion, there is sufficient evidence to show that TN patients exhibit functional changes in the precentral gyrus, ACC, temporal gyrus, and cerebellum (strength of conclusion 2). However, the correlation between FC and clinical parameters (VAS and pain duration) is inconclusive. Furthermore, some studies found that the functional parameters in several areas were correlated with VAS and pain duration. Wang et al[33] found a positive correlation between the increase of ReHo value in the left precentral gyrus and VAS scores. Yuan et al[18] observed positive correlations between the ReHo value of the posterior lobe of the cerebellum and middle temporal gyrus (MTG) and VAS score. However, there were negative correlations between VAS scores and the ReHo values of the ACC, precuneus, medial/superior frontal gyrus, and insula. Wang et al[19] found a negative correlation between pain duration and ALFF decrease in the medial/orbital prefrontal regions. In a case-cohort study by Dou et al,[1] a positive correlation was observed between the ReHo of the left PoCG and VAS scores. Additionally, they found a negative correlation between disease duration and postsurgical ReHo in the left inferior parietal lobule.

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Discussion

The primary objective of this study was to systematically review the literature regarding the structural and functional neuroplastic changes of TN to identify its central underlying mechanisms. Although there were large differences in brain imaging techniques and research designs, several important results were identified and are discussed below.

Gray Matter

Neuropathic pain can cause changes in the plasticity of brain structure, such as variation in the GM density of the cortex in the brain region. A GM volume reduction was the most consistent finding among all of the studies. Most of these brain areas are multiintegrative secondary processing regions that assess, integrate, and predict pain and are closely related to mood and anxiety. However, not all implicated brain regions were detected in the above studies, and the authors often interpreted such discrepancies as arising from small differences in image acquisition and other methodologic factors.[12]

The CC is part of the limbic system, which has many functions, including emotional behavior, motivation, and memory.[35] The ACC is associated with pain, cognitive control, and negative affect.[36] Pain-related cortical volume decreases occur in the ACC.[4,23,27–29] In addition, Obermann et al[4] found that GM volume decreased in the ACC and was correlated with increased pain duration in TN patients, indicating that the ACC is an important region in the development of TN. Similar results were found in a study by Schmidt-Wilcke et al,[37] in which they suggested that the ACC is involved in pain modulation through its connection with the PFC and amygdala. The ACC plays an important role in the assessment and integration of pain perception, cognition, and emotion.[38,39] Thus, the observed GM reduction in this region may reflect the high degree of pain-related emotional responses induced by TN. Similarly, the PCC exhibits structural abnormalities in TN.[10,28,29] The PCC is associated with pain and memory and may play a significant role in brain FC by modulating global brain dynamics.[40] A study using a positron emission tomography (PET) scan reported that an increase in the regional cere-

bral blood flow in the ACC region was associated with the unpleasantness of noxious thermal stimulation. Moreover, this study reported an increase in endogenous opioid binding in a similar cingulate region, which was correlated with the unpleasantness rating of induced masseter pain. These findings support the role of the ACC and PCC in TN pain modulation.[28]

The insular cortex has been extensively implicated in pain processing, and there were five studies[4,10,23,29,30] reporting a reduction of GM volume in the insular cortices of TN patients. The insular cortex is associated with pain intensity and expectation, as well as negative emotions such as anxiety and depression.[41] In fact, the insular cortex is anatomically connected to a wide range of cortical, limbic, and paralimbic structures and has been considered to be a multidimensional integration site of pain.[42] Moreover, there is an assumption proposing that, aside from integrating the dimensions of pain perception, the insular cortex also serves as a central multimodal and nociceptive-specific magnitude estimator.[43,44] Consistent with this assumption, Wang et al[30] observed a trend toward a negative correlation between pain intensity and GM change of the insular cortex in TN patients, indicating that the insular cortex may have a role in the encoding of pain intensity.

Two studies found GM reductions in the fusiform gyrus of TN patients and indicated that the fusiform gyrus plays an important role in the expectation and perception of pain regulation.[27] In addition, two other studies found GM reductions in the left cuneus of TN patients. Some researchers speculate that one of the functions of the cuneus may be to integrate somatosensory information with other sensory stimuli and cognitive processes, which include attention, learning, and memory.[45,46] The GM volume decrease of the cuneus may indicate that the above functions are affected in TN patients.

In addition, three studies have also found abnormal changes in the GM volume of the S1. One of the studies found a GM reduction,[4] and two other studies found GM increases, in the S1.[10,29] The increase of GM in the S1 indicates that the cortex of the S1 thickens as the disease progresses chronically, especially in the contralateral putative facial area, which may reflect enhanced intensity and location of noxious stimulation information from the facial pain areas. This theory is supported by research on migraine and temporomandibular disorders.[47,48] However, there are also other explanations for the GM volume reduction of S1 in TN patients.

In addition, three studies have also found GM changes in PAG. The PAG region of the brainstem is considered to be a modulator of somatic pain transmission. The PAG acts as a hub for the descending pain-modulatory network. It receives inputs arising in multiple areas, including the hypothalamus, the amygdala, and the rostral ACC, and communicates with medullary nuclei, which then send descending projections to the spinal cord.[24] Therefore, the GM volume changes in the PAG in these studies verified that TN pathogenesis might be due to impairment in this anatomical region.

Overall, even though many regional GM volume changes have been found in many studies, there is no consistent and definitive conclusion. However, there is valuable evidence of changes in GM volume in TN, including an increase or decrease in GM and the specific areas in which these changes have occurred.

White Matter

WM fiber bundle is the material basis for connecting the various nodes of the network for information transmission. Similar to the GM volume investigation of TN, many studies have focused on WM abnormalities in TN. Four studies agreed that there was a lower FA and a higher RD in the REZ of the trigeminal nerve in TN patients, and half of these studies also found higher MD and AD in the REZ. Currently, the most common theory is that alterations in the trigeminal nerve are usually caused by vascular compression. Structurally, these alterations may include neurovascular compression (NVC) causing focal demyelination of WM fibers in the REZ,[49] resulting in the decrease of FA in the REZ of affected nerves. Additionally, DeSouza et al[32] pointed out that the increased MD and RD may be related to neurovascular compression–induced focal demyelination of the trigeminal REZ, neuroinflammatory processes, and/or edema.[50] FA, MD, RD, and AD changes in the affected trigeminal REZ following recovery were seen after effective treatment.[50] Therefore, some DTI parameters may be used to evaluate the efficacy of TN.

In addition to the abnormalities found in the REZ of the trigeminal nerve, abnormal changes of WM in other regions were also found in the brain. Several studies reported lower FA[23,24,32] and higher MD[23,32] in the CC, and lower FA[23,30,32] and higher MD[23,32] in the CR, suggesting possible deficits in the inter- and intra-hemispheric transmission of information. Furthermore, abnormal DTI metrics in the CR may be related to attention and reaction to noxious threats in the surrounding environment. In contrast, Tian et al[15] found higher AD and lower AK in the LF, suggesting that the superior LF may play an important role in higher-order cognitive function and that the inferior LF may be correlated with pain intensity.[15]

The lower FA and higher MD of the REZ in TN patients provides more accurate evidence for the underlying pathophysiology of TN. In addition, several regions with certain specificities were discovered in WM, including the CC, CR, and LF.

Resting-State fMRI

Resting-state fMRI is a research method for targeting baseline brain activity at rest. The resting-state fMRI signal displays spontaneous fluctuations associated with the temporal patterns of neural activity. The precentral gyrus could reflect sensory pain responses to repeated TN, motor inhibition of the maxilla, and facial muscle tension.[51] In addition to the aforementioned GM volume changes in the ACC, it has been found that ACC function also changes in TN patients. There are hypotheses that ACC is critical for the development of chronic pain[52,53] because the ACC has integrated functions for pain processing, cognition, mood, and negative affect, all of which are associated with chronic pain or are risk factors for its development.[54] In addition, a PET study of TN found an increase in regional cerebral blood flow in the ACC, indicating that the ACC is crucial for suffering in chronic pain.[55] Wang et al[33] observed a reduction of activation in the left amygdala. The amygdala is an important structure in emotional processing.[56] Fear regulation is the most noted emotional process associated with the amygdala. In addition, the function of the amygdala has been extended to other aspects, including reward learning and motivation, as well as some psychiatric disorders, such as anxiety and depression.[57,58] In addition, four studies have reported abnormalities of function in the temporal lobe, which is involved in the processing of auditory perception, speech, language comprehension, and emotion.[59] Therefore, it is speculated that the major function of the temporal lobe that is compromised in TN is its regulation of the emotional response to pain. Moreover, there were four studies reporting functional abnormalities of the cerebellum in TN patients. Recently, it has been reported that the cerebellum controls and regulates pain through extensive functional connections with the cortex and subcortical structures.[60] Although neuroimaging has shown that noxious stimuli can activate the cerebellar cortex, the specific relationship between the cerebellum and pain remains poorly understood.[61] In addition, other studies have found that the cerebellum is also involved in the emotional regulation of mental disorders.[34]

There were several studies focusing on the correlation between functional parameters—or the strength of FC—and clinical features (eg, VAS and pain duration), although each study focused on different brain areas or different FCs within the brain. Thus, the present authors suggest that future research should focus on further elucidating these relationships.

Limitations and Suggestions for Further Research

It should be noted that the quality of the research methodologies included in the analyzed studies was moderate, and the studies were considered to have a B level of evidence. In addition, some of the study sample sizes were small. Moreover, only a small number of studies examined the relationship between GM and WM changes and these changes in relation to changes in FC. Given these relationships, a combination of more structural and functional brain-imaging studies could provide more information to understand the underlying mechanisms of TN. In addition, for better understanding of the temporal relationship regarding pain and neuroplastic changes in TN, more longitudinal research is warranted. Moreover, further research is needed to investigate the effects of treatment on brain structural and functional properties in TN patients.

There is also a point that cannot be ignored: It is necessary to pay more attention to differential diagnosis for the inclusion and exclusion of subjects in future research. Previous studies have shown that there are different functional changes in the central nervous system between classical TN and atypical TN. While neuropathic pain was correlated with a decrease in blood flow in several regions, including the thalamus, primary somatosensory, and cerebellar cortices, chronic nonneuropathic pain was correlated with an increase in blood flow in regions commonly associated with higher-order cognitive and emotional functions.[62] This may be used as a method for clinical classification and diagnosis. Furthermore, with the emergence of new technical methods such as the seven tesla (7T) MRI and PET-MRI, the display of brain structure, function, and nerves will be better optimized,[28,63] which may provide a new perspective for the neuropathologic mechanisms of TN.

Conclusions

There is moderate evidence that TN patients show structural brain differences in specific cortical and subcortical regions. In addition, TN patients show changes in pain-related functional connections in the resting state. Future research should focus on longitudinal designs and integration of different brain-imaging techniques.

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