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ORIGINAL ARTICLE

Alterations of brain structural MRI are associated with outcome of surgical treatment in trigeminal neuralgia

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Abstract

Background and purpose: To assess magnetic resonance imaging (MRI) alterations occurring in patients with trigeminal neuralgia (TN) and to explore the predictive ability of MRI for initial surgical outcome and long-term pain relief/recurrence after Gamma Knife radiosurgery (GKS).

Methods: Thirty patients with idiopathic or classic TN, who underwent GKS and were followed for at least 24 months, were retrospectively included. Pre-treatment structural MRI and pre- and serial, postoperative clinical features were investigated. Fifteen age- and sex-matched healthy controls were also enrolled. Cortical thickness and gray matter (GM) volumes were assessed in TN patients relative to controls, as well as between patient subgroups according to treatment outcomes (initial responders/non-responders, patients with pain recurrence/long-lasting pain relief at the last follow-up). Clinical and MRI predictors of treatment outcomes were explored.

Results: Cortical thinning of temporal, prefrontal, cingulate, somatosensory and occipital areas bilaterally was found in TN patients relative to controls. No cortical thickness and GM volume differences were observed when TN initial responders and non-responders were compared. Patients who experienced TN recurrence after initial pain relief were characterized by thicker parahippocampal and temporal cortices bilaterally and greater volume of right amygdala and hippocampus compared to patients with long-lasting pain relief. In TN patients, disease duration and baseline cortical thinning of right parahippocampal, left fusiform and middle temporal cortices were associated with poor outcome after GKS at the last follow-up (R^2=0.57, p<0.001).

Conclusion: The study provides novel insights into structural brain alterations of TN patients, which might contribute to disease development and pain maintenance.

KEYWORDS
atrophy, cortical thickness, magnetic resonance imaging, radiosurgery, trigeminal neuralgia

INTRODUCTION

Trigeminal neuralgia (TN) is a neuropathic disorder characterized by recurrent paroxysms of facial pain in the area of distribution of the fifth cranial nerve, typically triggered by innocuous stimuli.[1,2] The annual incidence of TN varies between 4.3 and 28.9 cases per 100,000 person-years worldwide, and it is more common in women and in people aged 50 years and older.[3,4] According to the International Classification of Headache Disorders, third edition,[5] TN is classified as: idiopathic, approximately 10% of affected individuals; classic, associated with neurovascular compression in the trigeminal root entry zone; or secondary, caused by an underlying disease.

Medical treatment is the first therapeutic choice in TN, whereas surgery, including radiosurgery, microvascular decompression and trigeminal rhizotomy, is indicated in cases of pharmacological therapy failure or in presence of medication-related side effects.[1,2] It is well known that, in TN unresponsive to pain relief medications, surgical treatments result in a high initial success rate, with 80%–90% pain relief at 90 days.[1] However, the merit of surgery should be long-lasting pain relief, whereas this is probably one of the main unresolved issues, and is greater after radiosurgical treatment than microvascular decompression.[1] Why the rate of pain recurrence is so high and exactly how surgical treatments work in resolving and maintaining pain relief is still unclear.

In patients with TN, several magnetic resonance imaging (MRI) studies were conducted, concentrating on the trigeminal nerve, based on the assumption that the disease is caused by the hyperexcitability of the nerve itself (both compressed and not compressed).[6-8] More recently, the focus has been shifted onto brain gray matter (GM) changes.[9-11] Patterns of atrophy involving the somatosensory, prefrontal, temporal and fusiform regions, parahippocampus, cingulate cortex, insula and thalamus were observed in TN patients compared to healthy controls,[9,10] suggesting possible involvement of central nervous system (CNS) mechanisms in TN. These findings raise the question of whether structural brain changes are the cause or consequence of TN development and evolution, and support the hypothesis that clinical outcomes after surgical treatment of the trigeminal nerve may, at least partially, derive from a different effect of neuromodulation on the cerebral regions involved in the development and/or maintenance of pain.[12] To our knowledge, however, no studies have investigated GM abnormalities in patients with TN recurrence or durable pain relief after surgical treatment, probably due to the lack of long-term follow-up.

Against this background, we analyzed pre-treatment structural MRI of patients with TN who underwent Gamma Knife radiosurgery (GKS) and followed them for at least 24 months. The aims of our study were to investigate abnormalities of brain GM in TN patients and to determine whether cortical thinning and subcortical atrophy are involved in initial and long-term pain maintenance and prediction of treatment outcomes.

METHODS

Study design

For this retrospective observational study, patients with TN who underwent GKS between January 2009 and December 2018 at the Neurosurgery Unit, IRCCS Ospedale San Raffaele (Milan, Italy) were recruited. All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration, approval was received from the local Ethical Committee on Human Experimentation, and written informed consent was obtained from all patients participating in the study.

Participants

A total of 244 patients with TN underwent GKS because of medication-resistant TN, medication intolerance or patient's preference when other surgery was proposed. Patients had to meet all the following inclusion criteria to be eligible for the present study: diagnosis of idiopathic or classic TN[5]; GKS performed as first surgical treatment for unilateral TN; available MRI-based GKS planning; and at least 24 months of clinical follow-up. Patients who underwent prior surgical procedures for facial pain, and patients with painful trigeminal neuropathies or secondary TN (e.g., skull base tumors or multiple sclerosis) were excluded. Furthermore, patients were excluded if they had: any significant other neurological disorder, psychiatric conditions or further pain syndrome; history of illicit drug use; brain MRI showing severe cerebrovascular disorders or intracranial masses; incomplete MRI or movement during scanning. Based on the inclusion and exclusion criteria, 30 TN patients were enrolled in the study (Figure 1). Fifteen age- and sex-matched healthy controls without any neurological disorder, psychiatric disorder and/or other pain condition were also included.

Clinical Evaluation

On the day of treatment, which includes pre-treatment MRI and subsequent GKS, and at each follow-up visit (3 and 6 months after GKS and thereafter yearly or if required for clinical issues), an experienced neurosurgeon performed the clinical assessment. Demographic, general clinical and family data (sex, age, handedness, age at onset, side of onset, TN duration, medications, family history) were obtained using a semi-structured interview. Disease duration was defined as the time from TN diagnosis to GKS treatment. A neurological examination was performed. Furthermore, patients were asked to assess the average pain level of their attacks using both a numeric rating scale (NRS) of pain from 0 to 10 (with 10 as the worst pain imaginable)[13] and the Barrow National Institute (BNI) pain intensity scale (I, complete pain relief without medication; II, occasional pain not requiring medication; IIIa, no pain, continued medications; IIIb, some pain but controlled with medications; IV, some pain inadequately controlled with medication; V, continued severe pain or no pain relief).[14] The presence of hypoesthesia was investigated using the BNI hypoesthesia scale.[14]

Initial pain outcome was evaluated at 6 months after GKS treatment. According to the BNI pain intensity scale, patients were classified as initial "responders" and "non-responders" if they fell under BNI scores I–IIIb and IV–V at 6 months after radiosurgery, respectively.[14-16] In responders, any change from the best class after GKS

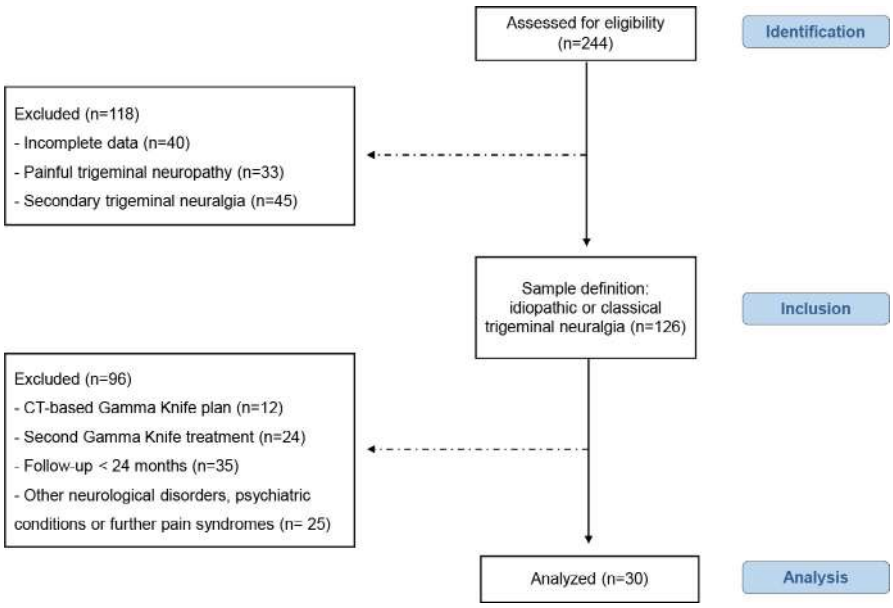

FIGURE 1 Flowchart illustrating the inclusion/exclusion criteria of individuals in the study. Chart data for 244 patients who underwent Gamma Knife radiosurgery for trigeminal neuralgia at the Neurosurgery and Radiosurgery Department, IRCCS Ospedale San Raffaele, Milan, Italy. According to the inclusion and exclusion criteria, 30 patients affected by idiopathic or classic trigeminal neuralgia were included in the study. Patients were assessed by clinical evaluation and brain magnetic resonance imaging before treatment. They were then clinically evaluated 3 and 6 months after radiosurgery and thereafter yearly. Abbreviations: CT, computed tomography

to a lower outcome class over time was considered as a "recurrence". A "long-lasting pain relief" was defined by the absence of any recurrence at last follow-up.[14-16]

The GKS Procedure and MRI Acquisition

The GKS procedure has been previously described in detail.[15] First, the Leksell stereotactic head frame (model-G; Elekta Instruments AB, Stockholm, Sweden) was positioned. Then (before treatment), a brain MRI scan was performed on a 1.5-T Achieva Magnetic Resonance scanner (Philips Healthcare, Best, the Netherlands) at the Neuroradiology Unit, including the following sequences: three-dimensional axial T2-weighted turbo-spin-echo (repetition time [TR]=1500 ms, echo time [TE]=250 ms, flip angle=90°, slice thickness=1.0 mm, voxel size 1.0×1.0×1.0 mm, matrix size=256×256); three-dimensional axial T1-weighted turbo-field-echo (TR=30 ms, TE=4605 ms, flip angle=25°, slice thickness=1.0 mm, voxel size 1.0×1.0×1.0 mm, matrix size=256×256). Finally, using the Leksell Gamma Knife Perfexion model (Elekta Instruments AB), the treatment plan was carried out via 4-mm collimator single shot. The retrogasserian portion of the symptomatic trigeminal nerve was irradiated in each patient with a maximal dose that ranged from 70 to 90 Gy (100% of isodose) according to the brainstem proximity[15]; specifically, six of 30 patients received 90 Gy as maximal dose (20%) and 24 of 30 patients received 80 Gy (80%). The mean (range) integral dose[17] was 1.82±0.72 (0.40–3.40) mJ. Healthy controls underwent the same MRI protocol on the same MRI machine as TN patients.

MRI Analysis

The MRI analysis was performed at the Neuroimaging Research Unit by two experienced observers, blinded to patient identity. Cortical reconstruction and estimation of cortical thickness and regional GM volume analysis of the caudate, pallidum, putamen, thalamus, amygdala and hippocampus bilaterally were performed on the pre-treatment T1-weighted images using, respectively, FreeSurfer image analysis suite[18] and the Oxford Centre for Functional MRI of the Brain (FMRIB)'s Integrated Registration and Segmentation Tool (FIRST) in the FMRIB Software Library, as previously described.[19]

Statistical analysis

Demographic and clinical data

Demographic data were compared between TN patients and controls using analysis of variance (ANOVA) models, followed by pairwise Bonferroni-corrected post hoc comparisons. The chi-square test was used to determine differences in the distribution of categorical variables. A p value <0.05 was taken to indicate statistical significance. Analyses were performed using IBM SPSS Statistics

package (SPSS Statistics version 25.0; IBM Corporation, Armonk, NY, USA).

MRI data

A cross-sectional vertex-by-vertex analysis was performed to assess differences in cortical thickness between overall TN patients and controls, left-sided TN patients and controls, right-sided TN patients and controls, and left- and right-sided TN patients using a general linear model in FreeSurfer, adjusting for age and sex. The same analysis was carried out to compare TN initial responder and non-responder patients, as well as TN patients with pain recurrence versus those with long-lasting pain relief at the last follow-up, adjusting for age, sex and TN side. Maps showing contrasts were obtained by thresholding the *t*-statistic at $p<0.05$, false discovery rate-corrected for multiple comparisons.

The mean regional cortical thickness of 34 regions of interest (ROIs) per hemisphere[20] and the mean GM volumes were compared between different TN subgroups and healthy controls using ANOVA models, Bonferroni-corrected for multiple comparisons at level of 0.05 adjusting for age and sex. Analyses between TN subgroups were also adjusted for TN side.

Clinical–MRI correlation analysis

In order to evaluate pain change over time, we created a score named the Trigeminal Neuralgia Outcome (TNO) as a numeric indicator of pain prognosis, accounting for the two pain scales: NRS and BNI score (the latter converted from 1 to 6, where 3, 4, 5 and 6 were equivalent to IIIa, IIIb, IV and V, respectively). The BNI scale, in contrast to the NRS, also considers the assumption of drug therapies. For TNO, the z-scores of each scale were averaged. For calculating the change (follow-up-treatment), we used the mean/standard deviation (SD) from treatment as the reference. Assuming that k scores (i.e z1, z2, z3, ...,z_k) are needed to calculate TNO, the following formula was used:

$$\mathrm{TNO} = \mathrm{mean}\left[\left(\frac{z_{1,FU} - z_{1,Bas}}{SD(z_{1,Bas})}\right), \left(\frac{z_{2,FU} - z_{2,Bas}}{SD(z_{2,Bas})}\right), \cdots, \left(\frac{z_{k,FU} - z_{k,Bas}}{SD(z_{k,Bas})}\right)\right]$$

Higher TNO scores indicate a worsening of pain, whereas lower TNO scores suggest an improvement in pain. The TNO was calculated at 6 months and at the last follow-up in each patient.

To assess the relationship between baseline GM results (mean regional cortical thickness and GM volumes) and pain outcome, a correlation analysis was performed. More specifically, partial correlations among baseline MRI metrics and TNO scores (at 6 months and at the last follow-up) were estimated using the Pearson correlation coefficient (R) at the level of significance $p<0.05$ (SPSS). Correlation analyses were Bonferroni-corrected for multiple comparisons adjusting for sex, age, TN side and individual follow-up duration.

MRI prediction models of clinical evolution

In all TN patients, linear regression models assessed the associations of baseline MRI metrics (showing significant correlations with TNO scores) and TNO scores. A stepwise model selection procedure was applied to candidate baseline MRI metrics chosen a priori on the basis of MRI variables that presented significant correlations with TNO score. TNO scores at 6 months and at the last follow-up were considered as the dependent variables into each model, which also included age, sex, TN side, disease duration, individual follow-up duration and baseline MRI metrics (independent variables). The R^2 goodness-of-fit statistic was estimated for each model at issue, for all TN patients at 6 months (accounting for initial responders and non-responders) and at the last follow-up (accounting for initial non-responders, responders who experienced pain recurrence over time, and responders with long-lasting pain relief at the last follow-up), separately.

RESULTS

Demographics and clinical features

Table 1 shows the sociodemographic and clinical features of TN patients and healthy controls. Pain affected the left side of the face in 60% of cases and the V2-V3 branches of trigeminal nerve were the most frequently involved (36.6%). The NRS score ranged from 8 to 10 before treatment (mean 9.18±0.78), and 17 of 30 cases (56.7%) and 13 of 30 cases (43.3%) were categorized in the BNI intensity pain class IV and class V, respectively.

Outcomes after GKS are summarized in Table 1. A total of 25 out of 30 patients (83.3%) were initial responders to GKS (6 months after treatment). The overall mean pain intensity decreased from 9.18±0.78 to 2.82±3.31 ($p<0.001$) according to the NRS at 6 months. Pain recurrence at last follow-up occurred in nine out of 25 initial responders (36.0%) and the average time to TN recurrence was 33.20±27.26 months. New onset of facial hypoesthesia during follow-up occurred in two of 30 patients (6.7%); both patients were classified as BNI hypoesthesia score II (mild facial numbness, not bothersome). The mean disease duration was longer in TN patients who experienced pain recurrence compared to those with long-lasting pain relief at the last follow-up (102.11±81.80 vs. 52.93±49.56 months; $p=0.02$). The TNO score at the last follow-up correlated with disease duration ($r=0.38$, $p=0.04$).

MRI findings

Cortical thickness

Patients with TN versus controls. In the vertex-by-vertex analysis, a pattern of bilateral cortical thinning involving the temporal (banks of superior temporal sulcus and superior temporal gyrus), prefrontal

TABLE 1 Demographic and clinical characteristics of healthy controls and trigeminal neuralgia patients

Variables	Healthy controls	TN patients	*p*
N	15	30	-
Demographic and clinical features			
Age at MRI, years	62.14 ± 10.61 (42–77)	66.24 ± 10.57 (38–78)	0.16
Men/women, *n* (%)	5 (33.3)/10 (66.7)	9 (30.0)/21 (70.0)	0.74
Disease duration, months	-	82.10 ± 81.77 (10–360)	-
Age at onset, years	-	59.33 ± 10.99 (31–74)	-
Handedness, *n* (%) Right Left Both	14 (93.3) 1 (6.7) 0 (0)	27 (90.0) 3 (10.0) 0 (0)	0.63
Side of onset, *n* (%) Right Left Both	-	12 (40.0) 18 (60.0) 0 (0)	-
Branches involved, *n* (%) V1 V1-V2 V1-V2-V3 V2 V2-V3 V3	-	2 (6.7) 3 (10.0) 2 (6.7) 6 (20.0) 11 (36.6) 6 (20.0)	-
Vascular compression, *n* (%) Yes No	-	18 (60.0) 12 (40.0)	-
Preoperative NRS pain score	-	9.18 ± 0.78 (8–10)	-
Preoperative BNI pain intensity scale, *n* (%) IV V	-	17 (56.7) 13 (43.3)	-
Medication, *n* (%) Carbamazepine Pregabalin Gabapentin	-	19 (63.3) 5 (16.6) 9 (30.0)	-
Outcomes of TN patients treated by radiosurgery			
BNI score at 6 months, *n* (%) I–IIIb IV–V	-	25 (83.3) 5 (16.7)	-
NRS score at 6 months	-	2.82 ± 3.31 (0–10)	-
TNO score at 6 months	-	−8.16 ± 4.48 (−13.67 to 0)	-
Follow-up duration, months	-	43.48 ± 34.82 (24–144)	-
Pain recurrence at last follow-up, *n* (%)	-	9/25 (36.0)	-
Time to recurrence, months	-	33.20 ± 27.26 (7–84)	-
BNI at last follow-up, *n* (%) I-IIIb IV-V	-	16 (53.3) 14 (46.7)	
NRS at last follow-up	-	5.10 ± 4.01 (0 – 10)	
TNO score at the last follow-up	-	−5.72 ± 5.45 (−13.67 to 0.87)	
Preoperative NRS vs NRS at 6 months, % of change	-	−69.28	<0.001
Preoperative NRS vs NRS at last follow-up, % of change	-	−44.44	<0.001

Note: Values are reported as mean ± standard deviation (range) or absolute and percentage frequency (%) for continuous and categorical variables, respectively. Differences between TN patients and healthy controls were assessed using analysis of variance models (for continuous demographic and clinical variables) and chi-square tests (for all categorical variables).

Abbreviations: BNI, Barrow National Institute; MRI, magnetic resonance imaging; NRS, numeric rating scale; TN, trigeminal neuralgia; TNO, Trigeminal Neuralgia Outcome.

(rostral middle frontal gyrus, pars triangularis and pars orbitalis), cingulate (isthmus cingulate), somatosensory/parietal (postcentral gyrus, supramarginal gyrus, precuneus and superior parietal lobule) and lateral occipital cortices was observed in all TN patients compared to controls (Figure 2A; Table S1). In addition, thinner middle temporal gyrus, lingual gyrus and cingulate cortex (posterior cingulate and caudal anterior cingulate) were observed in the left hemisphere in TN patients compared with controls, and thinner caudal middle frontal gyrus, pars opercularis, superior frontal gyrus, lateral orbito-frontal cortex, inferior parietal lobule, fusiform gyrus and insula cortex in the right hemisphere (Figure 2A; Table S1). The analysis of the mean cortical thickness values of the 34 ROIs per hemisphere showed similar results (Table 2).

Left- and right-sided TN patients. In the vertex-by-vertex analysis, when left- and right-sided TN patients were compared to controls separately, a bilateral cortical thinning involving the temporal cortex, prefrontal cortex, cingulate cortex, somatosensory/parietal cortex and occipital cortex was found with similar distribution regardless of the side of TN (Figure 2B and 2c; Table S2 and S3). In line with these results, no differences in cortical thickness were found when left- and right-sided TN patients were compared, in either vertex-by-vertex or regional analyses (Table 2).

Initial responder and non-responder TN patients. Results between controls and TN responders and non-responders are shown in Figure 3A and summarized in Table S4 and S5. In the vertex-by-vertex and regional analyses, no differences were found when responders and non-responders were compared (Figure 3A; Table S9).

Trigeminal neuralgia patients with pain recurrence and patients with long-lasting pain relief. In the vertex-by-vertex analysis, TN patients who experienced pain recurrence showed an increased cortical thickness in the temporal cortex bilaterally (parahippocampal, fusiform, superior temporal gyri), left frontal cortex (frontal pole, superior frontal and medial orbito-frontal gyri), left transverse temporal gyrus, right middle temporal gyrus, right insula and right lateral occipital cortex compared to those with long-lasting pain relief at the last follow-up (Figure 3B; Table S6). Thicker bilateral mean parahippocampal and temporal cortices were confirmed when TN patients with pain recurrence and those with long-lasting pain relief were compared in regional analysis (Table 3). Comparisons between these two groups of patients and controls are shown in Figure 3B and summarized in Tables S7 and S8. Notably, in the vertex-by-vertex analysis, non-responders and patients with pain recurrence showed a similar cortical atrophy pattern when compared to controls (Figure 3A and 3B); in an analogous way, responders and long-lasting pain relief patients were alike (Figure 3A and 3B).

Gray matter volumes

Gray matter volume analysis revealed no differences between TN patients and controls, nor between left- and right-sided TN patients, and responders and non-responders. However, an increased volume of the right amygdala (p=0.03) and right hippocampus (p=0.048) was found in TN patients who experienced pain recurrence compared to those with long-lasting pain relief (Table 3).

Correlation analysis and stepwise prediction model

No significant correlation between baseline MRI metrics and TNO score at 6 months was found. By contrast, the TNO score at last follow-up was related to right amygdala volume (r=0.36, p=0.04), and

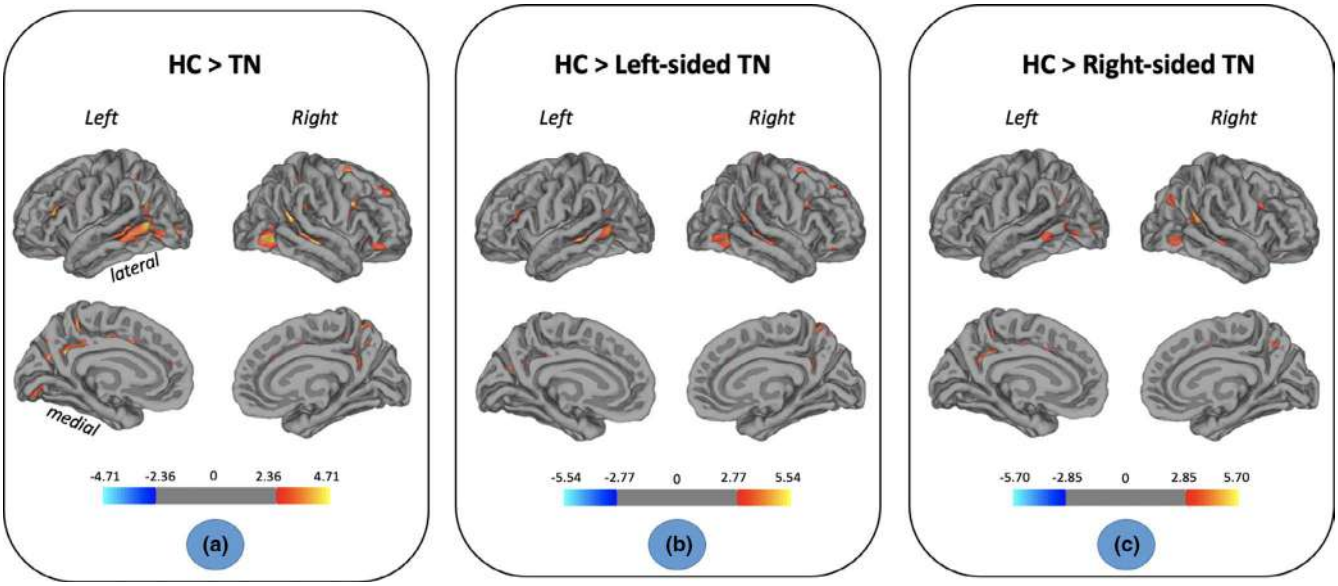

FIGURE 2 Cortical thickness patterns in trigeminal neuralgia (TN) patients relative to healthy controls. Cortical thickness findings in overall TN patients relative to controls (a), in left-sided TN patients relative to controls (b) and in right-sided TN patients relative to controls (c). *p* values are corrected for multiple comparisons using false discovery rate (FDR), adjusting for age and sex. Color bars represent *t*-values. Abbreviations: HC, healthy controls; L, left; R, right

TABLE 2 Cortical thickness values and gray matter volumes in healthy controls and trigeminal neuralgia patients

Region	Healthy controls	TN patients	L-TN patients	R-TN patients	*p* value, healthy controls vs. TN	*p* value, healthy controls vs. L-TN	*p* value, healthy controls vs. R-TN	*p* value, L-TN vs. R-TN
L Banks of Superior Temporal Sulcus	2.41±0.29 (1.87–2.92)	2.19±0.27 (1.72–2.61)	2.16±0.27 (1.72–2.61)	2.22±0.27 (1.76–2.54)	0.04	0.048	0.16	0.57
L Inferior Parietal	2.28±0.14 (2.07–2.47)	2.14±0.20 (1.80–2.57)	2.13±0.21 (1.80–2.57)	2.15±0.20 (1.91–2.55)	0.10	0.05	0.02	0.81
L Isthmus Cingulate	2.25±0.17 (1.97–2.57)	2.11±0.19 (1.61–2.55)	2.09±0.22 (1.61–2.56)	2.13±0.14 (1.90–2.35)	0.02	0.02	0.04	0.36
L Lateral Occipital	2.03±0.17 (1.75–2.35)	1.87±0.20 (1.63–2.47)	1.86±0.22 (1.63–2.47)	1.89±0.16 (1.69–2.15)	0.03	0.03	0.04	0.72
L Lateral Orbitofrontal	2.49±0.18 (2.11–2.84)	2.32±0.22 (1.83–2.81)	2.31±0.25 (1.83–2.81)	2.35±0.17 (2.12–2.72)	0.06	0.08	0.10	0.65
L Lingual	2.01±0.20 (1.73–2.44)	1.78±0.21 (1.36–2.28)	1.76±0.22 (1.36–2.28)	1.81±0.20 (1.52–2.18)	0.01	0.01	0.04	0.53
L Middle Temporal	2.63±0.18 (2.31–2.90)	2.36±0.20 (1.91–2.65)	2.35±0.22 (1.91–2.65)	2.37±0.19 (2.05–2.64)	<0.001	0.002	0.004	0.75
L Posterior Cingulate	2.37±0.10 (2.15–2.54)	2.22±0.19 (1.81–2.55)	2.19±0.20 (1.81–2.55)	2.28±0.17 (1.96–2.51)	0.02	0.01	0.05	0.76
L Precuneus	2.28±0.16 (1.93–2.50)	2.11±0.18 (1.81–2.52)	2.13±0.20 (1.81–2.52)	2.07±0.15 (1.82–2.35)	0.02	0.07	0.004	0.43
L Superior Temporal	2.41±0.18 (2.07–2.80)	2.28±0.19 (1.92–2.66)	2.27±0.21 (1.93–2.66)	2.30±0.13 (1.92–2.44)	0.11	0.17	0.08	0.71
R Banks of Superior Temporal Sulcus	2.39±0.24 (1.86–2.63)	2.17±0.24 (1.69–2.65)	2.15±0.23 (1.72–2.43)	2.18±0.26 (1.69–2.65)	0.02	0.01	0.04	0.64
R Inferior Parietal	2.26±0.17 (1.96–2.51)	2.09±0.21 (1.55–2.44)	2.10±0.20 (1.76–2.44)	2.05±0.23 (1.55–2.32)	0.04	0.048	0.01	0.43
R Isthmus Cingulate	2.27±0.13 (2.07–2.46)	2.14±0.19 (1.80–2.53)	2.13±0.19 (1.80–2.49)	2.16±0.20 (1.93–2.53)	0.03	0.03	0.09	0.64
R Lateral Occipital	2.02±0.19 (1.59–2.30)	1.88±0.17 (1.57–2.23)	1.87±0.19 (1.57–2.23)	1.90±0.16 (1.66–2.12)	0.03	0.02	0.07	0.70
R Pars Opercularis	2.47±0.20 (2.12–2.96)	2.26±0.19 (1.86–2.65)	2.24±0.21 (1.86–2.65)	2.30±0.11 (2.16–2.54)	0.005	0.01	0.03	0.38
R Pars Orbitalis	2.45±0.18 (2.11–2.68)	2.24±0.27 (1.76–2.84)	2.25±0.27 (1.87–2.84)	2.23±0.28 (1.76–2.82)	0.03	0.06	0.01	0.82
R Pars Triangularis	2.27±0.17 (1.93–2.54)	2.12±0.20 (1.86–2.78)	2.13±0.24 (1.86–2.78)	2.11±0.12 (1.93–2.35)	0.09	0.16	0.03	0.76

(Continues)

TABLE 2 (Continued)

Region	Healthy controls	TN patients	L-TN patients	R-TN patients	*p* value, healthy controls vs. TN	*p* value, healthy controls vs. L-TN	*p* value, healthy controls vs. R-TN	*p* value, L-TN vs. R-TN
R Precuneus	2.25±0.16 (1.96–2.48)	2.09±0.19 (1.76–2.56)	2.10±0.21 (1.79–2.56)	2.06±0.14 (1.76–2.28)	0.02	0.04	0.005	0.53
R Superior Parietal	2.04±0.14 (1.77–2.21)	1.90±0.20 (1.48–2.30)	1.91±0.19 (1.58–2.29)	1.89±0.22 (1.48–2.16)	0.03	0.02	0.01	0.71

Note: Values are reported as mean ± standard deviation (range). Cortical thickness values are in mm. Differences between TN patients and healthy controls, and between TN subtypes were assessed using age- and sex-adjusted analysis of variance models. *p* values were adjusted for multiple comparisons controlling at level 0.05. Only regions with at least one significant contrast are reported.

Abbreviations: L-TN, left-sided trigeminal neuralgia; R-TN, right-sided trigeminal neuralgia; TN, trigeminal neuralgia.

cortical thickness values of the right middle temporal gyrus (r=0.36, p=0.04), parahippocampal cortex (r=0.47, p=0.01), superior temporal gyrus (r=0.50, p=0.01), left fusiform gyrus (r=0.42, p=0.02), middle temporal gyrus (r=0.37, p=0.04), parahippocampal cortex (r=0.49, p=0.01) and superior temporal gyrus (r=0.39, p=0.03). Linear regression and stepwise prediction model results are shown in Table 4 and Figure 4. The model including disease duration and left fusiform gyrus, left middle temporal gyrus, and right parahippocampal gyrus cortical thickness values was the best predictor of poor TNO score at the last follow up (R^2=0.57, p<0.001).

DISCUSSION

Growing evidence supports the role of the CNS in the modulation of pain in TN patients.[9,10,21-24] In line with this observation, we obtained the following main findings: thinner temporal, prefrontal, cingulate, somatosensory and occipital cortices in TN patients compared to healthy controls; thicker temporal, parahippocampal and insula cortex, and greater amygdala and hippocampus volume in TN patients who experienced pain recurrence than those with long-lasting pain relief at the last follow-up after GKS; greater thickness values of the temporal cortex and limbic regions as predictors of poor pain outcome at the last follow-up after treatment.

The pattern of GM changes that we observed in TN patients compared to controls is similar to that which was previously described in patients with other diseases involving the trigeminal nociceptive system such as migraine,[25,26] chronic facial pain,[27] and painful trigeminal neuropathy.[28,29] Furthermore, the bilateral pattern of cortical thinning observed with similar distribution regardless of the side of TN, in line with a previous MRI study on TN,[30] is probably not specific to TN paroxysmal pain and its side of onset, but seems to reflect the involvement of a system that receives chronic nociceptive stimuli. More specifically, the primary somatosensory cortex has been suggested to be involved in sensory and discriminative aspects of pain,[31] whereas the secondary somatosensory cortex seems to be implicated in pain learning and memory.[32] The cingulate cortex is involved in the affective aspects of pain[33] and the insula and temporal cortex has been suggested to be a site of integration between the sensory and affective aspects of pain.[34,35] The prefrontal cortex, although not implicated in the direct pain pathway, plays a role in higher executive functions, attention, and placebo, all of which can affect the perception of pain and the detection of noxious stimuli.[36] Whether these changes are a consequence of pain or whether pre-existent alterations of these regions make patients more susceptible to the development of TN remains uncertain.

Another major issue is whether the development of brain changes in TN patients influences the clinical outcome after treatment. The GM modifications observed in the present study could suggest the existence of a self-sustaining mechanism of pain that could potentially confer treatment resistance. In particular, we found greater thickness of the frontal and temporal cortex, and greater amygdala and hippocampus volume in cases of pain recurrence at the last

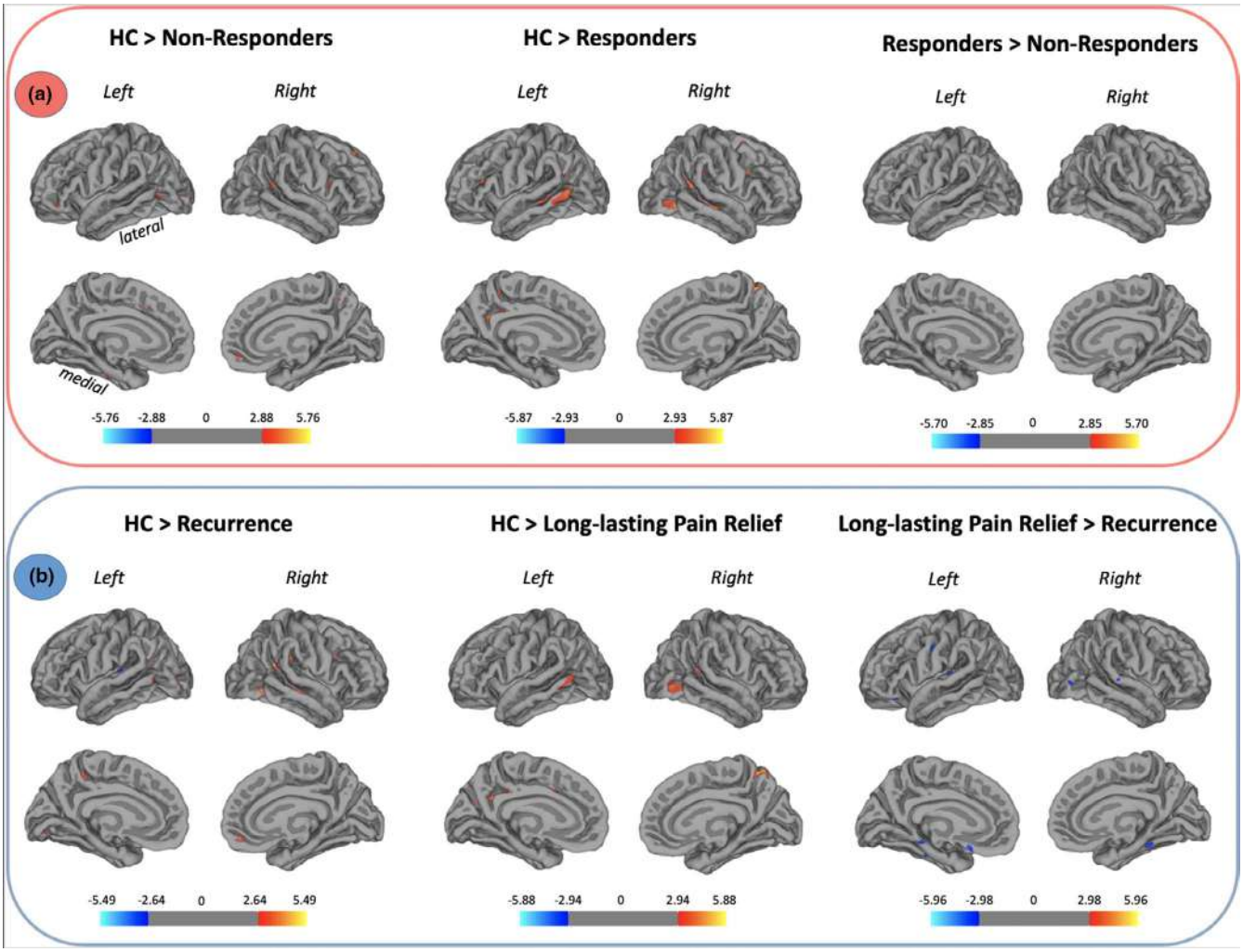

FIGURE 3 Cortical thickness patterns in trigeminal neuralgia (TN) patients, stratified according to their clinical outcomes relative to healthy controls and each other. (a) From left to right, cortical thickness findings in TN non-responder patients to radiosurgery relative to controls, in TN initial responder patients to radiosurgery relative to controls and between responders and non-responders. (b) From left to right, cortical thickness findings in TN patients who experienced pain recurrence relative to controls, in TN patients with long-lasting pain relief relative to controls and between patients who experienced pain recurrence and long-lasting pain relief. *p* values are corrected for multiple comparisons using false discovery rate, adjusting for age, sex and TN side (in case of between patient comparison). Color bars represent *t*-values. Abbreviations: HC, healthy controls; L, left; R, right

follow-up compared to those without. Furthermore, using TNO score to estimate pain changes over time, along with the stepwise approach, we demonstrated that a greater thickness value of some temporal cortical and limbic areas, together with longer disease durations, are the best predictors of poor long-term response (which includes both non-responders and TN recurrences) to GKS. While the trigeminal sensory system is certainly crucial to the development of acute pain in TN, affective temporal and limbic contributions have also been shown to be important in chronic pain experience/memory.[37-39] These findings are consistent with our observation that treatment-resistant TN patients have increased temporal and limbic thickness/volumes, potentially due to increased activity related to the recollection and then integration of emotionally significant stimuli with the experience of chronic pain.[37,38] Furthermore, our results are in line with a previous study,[39] showing an increased hippocampal volume in TN non-responders relative to responders after microvascular decompression. Taken together, these findings support our idea of the existence of a central self-sustaining mechanism of pain, not driven by a single brain structure and probably related to the pain experience, which confers treatment resistance regardless of the kind of surgical treatment.

In patients with chronic facial pain, refractory to medical and standard surgical treatments, central neuromodulation therapies, including stimulating (e.g., deep brain stimulation) and ablating techniques (e.g., CNS radiosurgery, high-intensity focused ultrasonography) might be considered.[40] To date, the thalamic nuclei, periventricular or periaqueductal gray and the anterior cingulate cortex are the most frequently used targets.[40] Our findings pave the way to a potential therapeutic role of direct or indirect stimulation of hippocampal-parahippocampal circuitry for chronic and intractable

TABLE 3 Cortical thickness values and gray matter volumes in controls and trigeminal neuralgia patients who experienced recurrence and long-lasting pain relief

Region	Healthy controls	Recurrence	Long-lasting pain relief	*p* value, healthy controls vs. recurrence	*p* value, healthy controls vs. long-lasting pain relief	*p* value, recurrence vs. long-lasting pain relief
L Entorhinal	2.32±0.37 (1.85–3.09)	2.70±0.45 (1.99–3.16)	2.26±0.46 (1.44–3.09)	0.049	0.97	0.04
L Fusiform	2.39±0.19 (2.03–2.62)	2.41±0.70 (2.28–2.49)	2.24±0.30 (1.66–2.66)	0.75	0.34	0.04
L Inferior Temporal	2.63±0.17 (2.38–2.89)	2.59±0.22 (2.30–2.99)	2.41±0.23 (2.01–2.78)	0.79	0.04	0.10
L Lingual	2.01±0.20 (1.73–2.44)	1.79±0.16 (1.57–2.14)	1.77±0.25 (1.36–2.29)	0.03	0.059	0.90
L Middle Temporal	2.63±0.19 (2.31–2.90)	2.42±0.19 (2.14–2.66)	2.31±0.20 (1.91–2.63)	0.02	0.001	0.35
L Parahippocampal	2.00±0.30 (1.39–2.42)	2.29±0.22 (2.02–2.72)	1.98±0.34 (1.51–2.57)	0.03	0.86	0.03
L Posterior Cingulate	2.37±0.10 (2.15–2.54)	2.25±0.21 (1.97–2.55)	2.19±0.22 (1.81–2.52)	0.056	0.048	0.49
L Precuneus	2.28±0.16 (1.93–2.50)	2.14±0.22 (1.83–2.52)	2.11±0.18 (1.87–2.46)	0.18	0.04	0.95
L Superior Temporal	2.42±0.16 (2.08–2.80)	2.41±0.11 (2.30–2.66)	2.21±0.19 (1.93–2.56)	0.94	0.049	0.003
L Frontal Pole	2.34±0.19 (2.07–2.76)	2.45±0.10 (2.31–2.60)	2.22±0.28 (1.68–2.60)	0.09	0.48	0.047
L Transverse Temporal	1.87±0.17 (1.63–2.18)	2.12±0.23 (1.85–2.55)	1.86±0.19 (1.33–2.07)	0.003	0.19	0.002
R Amygdala	958.25±231.31 (595.74–1342,00)	1238.00±359.32 (870.32–1717.99)	878.00±343.37 (334.76–1464.99)	0.06	0.33	0.03
R Hippocampus	3200.03±758.39 (1952,00–4755,02)	3565.34±769.91 (2671–4809.98)	2802.10±958.17 (482.01–3859.23)	0.23	0.37	0.048
R Inferior Temporal	2.53±0.24 (2.20–2.87)	2.59±0.20 (2.26–2.90)	2.33±0.27 (1.94–2.83)	0.56	0.10	0.04
R Parahippocampal	2.07±0.33 (1.59–2.53)	2.37±0.20 (2.07–2.76)	1.97±0.33 (1.46–2.52)	0.04	0.56	0.01
R Superior Temporal	2.36±0.18 (2.01–2.69)	2.40±0.16 (2.18–2.60)	2.16±0.20 (1.80–2.47)	0.50	0.055	0.005
R Inferior Parietal	2.27±0.18 (1.97–2.51)	2.18±0.19 (1.88–2.41)	2.07±0.19 (1.77–2.44)	0.38	0.04	0.26
R Middle Temporal	2.55±0.21 (2.25–2.89)	2.48±0.30 (2.03–2.87)	2.29±0.22 (1.84–2.64)	0.66	0.03	0.13
R Pars Opercularis	2.48±0.20 (2.12–2.96)	2.35±0.10 (2.17–2.51)	2.21±0.21 (1.87–2.66)	0.15	0.01	0.09
R Pars Triangularis	2.46±0.18 (2.11–2.68)	2.33±0.33 (1.76–2.84)	2.19±0.25 (1.88–2.72)	0.25	0.02	0.43
R Precuneus	2.25±0.17 (1.96–2.49)	2.17±0.19 (1.93–2.56)	2.06±0.17 (1.84–2.49)	0.57	0.04	0.24

Note: Values are reported as mean ± standard deviation (range). Cortical thickness values are in mm. Differences between healthy controls and TN recurrent patients and long-lasting pain relief patients, and between TN subtypes were assessed using sex-, age- and TN side-adjusted analysis of variance models. *p* values were adjusted for multiple comparisons controlling at level 0.05. Only regions with at least one significant contrast are reported.

Abbreviations: L, left; R, right; TN, trigeminal neuralgia.

TABLE 4 Linear regression model and stepwise prediction model results of TNO score at the last follow-up and MRI metrics in all TN patients

Independent variables	Regression slope (β coefficient)	R^2	*p* values
R Amygdala volume	0.19	0.22	0.02
L Fusiform thickness	136.52	0.48	0.001
L Middle Temporal gyrus thickness	71.12	0.44	0.001
L Parahippocampal gyrus thickness	10.97	0.46	0.001
L Superior Temporal gyrus thickness	11.17	0.30	0.01
R Middle Temporal gyrus thickness	9.47	0.32	0.004
R Parahippocampal	6.18	0.41	0.002
R Superior Temporal gyrus thickness	11.92	0.29	0.002
L Fusiform gyrus thickness + L Middle Temporal gyrus thickness + R Parahippocampal gyrus thickness + Disease Duration	22.21	0.57	< 0.001

Note:: Linear regression and stepwise regression models were built to assess the association between baseline clinical and MRI measures models and TNO score at the last follow-up. TNO was considered as the dependent variable in each model, which also included age, sex, TN side, individual follow-up duration, and baseline MRI metrics (independent variables). Both regression slope (also called β coefficient) of each statistically significant metric (i.e., $p<0.05$) and overall R^2 goodness-of-fit statistic were estimated for each model at issue, separately.

Abbreviations: L, left; R, right; TN, trigeminal neuralgia; TNO, Trigeminal Neuralgia Outcome.

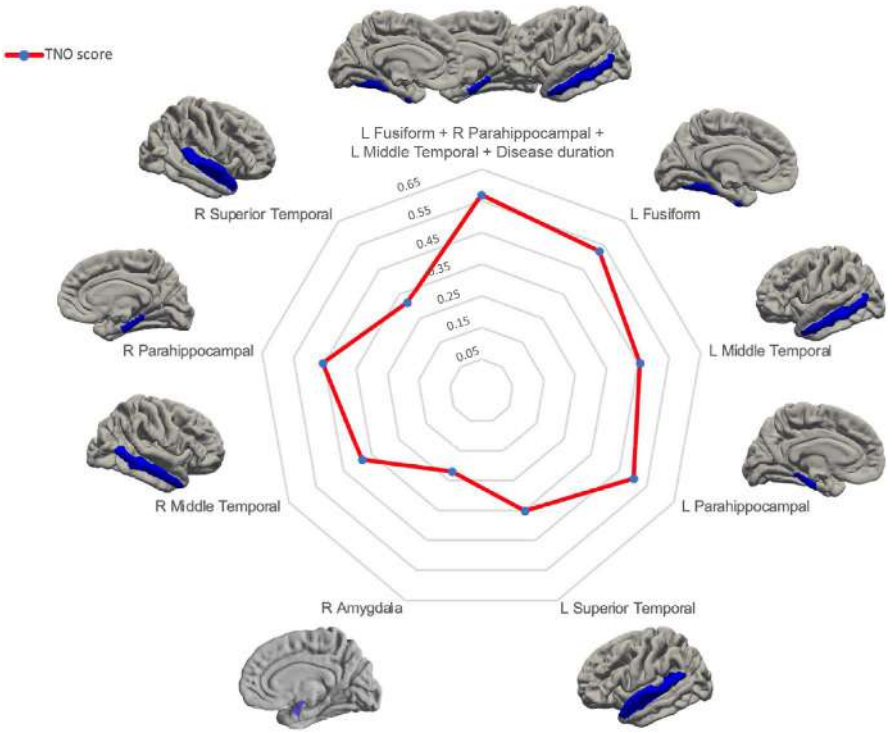

FIGURE 4 Radar chart of Trigeminal Neuralgia Outcome (TNO) score at last follow-up using linear regression and stepwise prediction model. Radar chart showing the relationship (R^2) between TNO score at last follow-up and magnetic resonance imaging metrics (both regional mean cortical thickness and mean deep gray matter [GM] volumes). Table 4 reports R^2 values between each GM region and TNO score with its statistical significance value. Abbreviations: L, left; R, right

TN, as already studied in patients with Alzheimer's disease and epilepsy.[41]

The present study has some limitations. First, it had a small sample size; further studies with a larger patient population are needed to confirm and support our results. Second, all patients were taking medication for TN, with the most common being anticonvulsants (carbamazepine), although the precise impact of these medications on brain morphology is not known. Third, both right- and left-sided TN patients were included. However, no differences were observed when the two groups of patients were compared and our bilateral cortical findings are in line with previous functional MRI studies. Fourth, we were unable to include postoperative MRI scans due to the retrospective nature of this study; it would be interesting to have postoperative MRI data for a better understanding of what happens to the late recurrence. Finally, TN patients who received both 80 or 90 Gy of maximal dose were included; however, to date, no

significant differences between 80 and 90 Gy in terms of pain relief have been suggested.[16,42-44]

In conclusion, the present study supports the role of the CNS as a strong modulator of chronic pain in TN. Our findings suggest that the TN pain could be associated with alterations in brain GM that contribute not only to the development of TN pain but also to its maintenance.

CONFLICT OF INTEREST

L. Albano, S. Basaia, A. Castellano, V. Parisi, L. R. Barzaghi, A. Falini and P. Mortini report no disclosures. F. Agosta is Section Editor of *NeuroImage*: *Clinical*, received compensation for consulting services and/or speaking activities from Philips, Novartis, Biogen Idec and Roche, and receives or has received research support from the Italian Ministry of Health, AriSLA (Fondazione Italiana di Ricerca per la SLA), and the European Research Council. R. Messina declares compensation for speaking activities from Novartis, Eli Lilly and Teva Pharmaceutical Industries. M. Filippi is Editor-in-Chief of the *Journal of Neurology*, Associate Editor of *Human Brain Mapping*, Associate Editor of *Neurological Sciences*, and Associate Editor of *Radiology*, received compensation for consulting services and/or speaking activities from Almiral, Alexion, Bayer, Biogen, Celgene, Eli Lilly, Genzyme, Merck-Serono, Novartis, Roche, Sanofi, Takeda and Teva Pharmaceutical Industries, and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Teva Pharmaceutical Industries, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

AUTHOR CONTRIBUTIONS

Luigi Albano: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Writing – original draft (equal); Writing – review and editing (equal). **Federica Agosta:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Supervision (equal); Validation (equal); Writing – original draft (equal); Writing – review and editing (equal). **Silvia Basaia:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Writing – original draft (equal); Writing – review and editing (equal). **Antonella Castellano:** Resources (equal); Validation (equal); Writing – review and editing (equal). **Roberta Messina:** Conceptualization (equal); Methodology (equal); Writing – review and editing (equal). **Veronica Parisi:** Data curation (equal); Investigation (equal); Writing – review and editing (equal). **Lina Raffaella Barzaghi:** Conceptualization (equal); Data curation (equal); Investigation (equal); Validation (equal); Writing – review and editing (equal). **Andrea Falini:** Resources (equal); Validation (equal); Visualization (equal); Writing – review and editing (equal). **Pietro Mortini:** Conceptualization (equal); Data curation (equal); Investigation (equal); Supervision (equal); Validation (equal); Writing – review and editing (equal). **Massimo Filippi:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Supervision (equal); Validation (equal); Writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

The dataset used and analyzed during the present study will be made available by the corresponding author upon request to qualified researchers (i.e., affiliated to a university or research institution/hospital).

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SUPPORTING INFORMATION

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Table S1-S9

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