Structural and functional brain changes in patients with classic trigeminal neuralgia: A combination of voxel-based morphometry and resting-state functional MRI study

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Research Article

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Abstract

Background

Brain structural and functional abnormalities have been separately reported in patients with classic trigeminal neuralgia (CTN). However, whether and how the functional deficits are related to the structural alterations remains unclear. This study aimed to investigate the anatomical and functional deficits in CTN patients and explore their association.

Methods

Thirty-four CTN patients and twenty-nine age-, gender-matched healthy controls (HCs) were recruited. All subjects underwent structural and resting-state functional magnetic resonance imaging scanning and neuropsychological assessments. Voxel-based morphometry (VBM) was applied to characterize the alterations of gray matter volume (GMV). The amplitude of low-frequency fluctuation (ALFF) method was used to evaluate regional intrinsic spontaneous neural activity. Further correlation analyses were performed between the structural and functional changes and neuropsychological assessments.

Results

Compared to the HCs, significantly reduced GMV was revealed in the right hippocampus, right fusiform gyrus (FFG), temporal-parietal regions (the left superior/middle temporal gyrus, left operculo-insular gyrus, left inferior parietal lobule, right inferior temporal gyrus) in CTN patients. Increased functional activity measured by ALFF were observed mainly in the limbic system (the bilateral hippocampus and bilateral parahippocampal gyrus), bilateral fusiform gyrus, basal ganglia system (the bilateral putamen, bilateral caudate, and right pallidum), left thalamus, left cerebellum, midbrain, and pons. Moreover, the right hippocampus and FFG were the overlapped regions with both functional and anatomical deficits. Furthermore, GMV in the right hippocampus was negatively correlated with pain intensity, anxiety, and depression. GMV in the right FFG was negatively correlated with illness duration. The ALFF value in the right FFG was positively correlated with anxiety.

Conclusion

Our results revealed concurrent structural and functional changes in CTN patients, indicating that the CTN is a brain disorder with structural and functional abnormalities. Moreover, the overlapping structural and functional changes in the right hippocampus and FFG suggested that anatomical and functional changes might alter dependently in CTN patients. These findings highlight the vital role of hippocampus and FFG in the pathophysiology of CTN.

Background

Classic trigeminal neuralgia (CTN) is a chronic neuropathic pain that is limited to one or more branches of the trigeminal nerve branches [1]. It usually presents as abrupt paroxysmal electric shock-like or stabbing pain and can be provoked by normally innocuous mechanical stimuli or occur spontaneously. Unlike other neuropathic pain conditions, pain attacks become more frequent with disease progression and may become sustained subsequently [2], which would seriously affect the patient's physical and mental health [3]. The prevailing theory of CTN etiology is neurovascular compression at the entry zone of nerve root [4, 5]. However, till now, the pathophysiology of CTN is still unclear. Recently, many neuroimaging studies have found brain structural and functional abnormalities in patients with CTN [3, 6–9].

Several brain structural studies have revealed gray matter volume (GMV) changes in CTN patients, and it mainly involved primary somatosensory cortex, insula, thalamus, anterior cingulate cortex, basal ganglia, hippocampus, temporal cortex, and cerebellum, mostly notably in pain matrix [6–10]. Meanwhile, brain functional abnormalities revealed by functional magnetic resonance imaging (fMRI) studies in CTN patients have been detected and mainly localized in the prefrontal, temporal, and parietal regions, posterior cingulate cortex, insula, and cerebellum, particularly in the salient network and default-mode network [11–17]. It can be observed that there were different and overlapped brain regions, where structural and functional abnormalities were identified in the above previous studies. It is well known that brain structure and function are intimately related to each other. Thereby, altered brain function would probably result in altered gray matter changes or vice versa. However, most of these studies have only investigated functional or anatomical changes alone. Few studies have focused on structural and functional changes in the same sample, thereby it is not clear whether concurrent structural and functional abnormalities could exist or not. More important issue that remains unclear is whether and how the functional deficits are related to the anatomical alterations. If overlapping regions with structural and functional alterations were observed, it may indicate that the structure and function of those regions alter simultaneously in patients with CTN. The significance of defining concurrent structural and functional deficits may provide specific insights to unravel adaptive or maladaptive changes occurring in brain regions in patients with CTN.

Therefore, we used a multimodal neuroimaging approach to investigate the anatomical and functional alterations in CTN. Voxel-based morphometry (VBM) was used to analyze gray matter volume (GMV) changes and the amplitude of low-frequency fluctuation (ALFF) method was applied to evaluate the regional spontaneous brain activities alterations. The aim of this study was to characterize changes of GMV and ALFF in CTN patients, the relationship between the functional alterations and anatomical deficits, as well as their association with clinical variables in CTN patients. According to the current understandings of CTN, we hypothesized that concurrent structural and functional changes would be present in CTN patients, and there would be overlapped regions with both functional and anatomical alterations.

Methods

Participants

Thirty-four patients with CTN were recruited prospectively from the First Affiliated Hospital of Zhengzhou University. The diagnostic criteria of CTN are based on the International Classification of Headache Disorders (ICHD-3) [18]. Two neurologists confirmed the diagnosis according the ICHD-3. The inclusion criteria for the patients were as follows: (i) age > 18 years; (ii) right-hand dominance; (iii) unilateral pain restricted to one or more branches of the trigeminal nerve branches; (iv) intense, shooting or stabbing, abrupt pain paroxysms, with or without the trigger of normally innocuous mechanical stimuli or orofacial movements; (v) no other neurological or sensory deficit; (vi) no evident abnormal lesions on conventional T2-weighted image. Exclusion criteria were: (i) any other causes of facial pain; (ii) other primary headache disorders; (iii) neural-associated or psychiatric disorders; (iv) history of brain surgery; (v) contraindications to MRI scan.

Twenty-nine healthy controls (HCs) with age- and gender-matched were also recruited for this study. Inclusion criteria for HC were as follows: (i) age > 18 years; (ii) right-hand dominance; (iii) no neuropsychiatric disorders; (iv) no contraindications to MRI scan.

This study was approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University. According to the Declaration of Helsinki, written consent was obtained from each participant.

Questionnaires and ratings

The visual analogue scale (VAS) ranging from 0 (no pain) to 10 (the worst pain) was used to grade the pain intensity of CTN patients. Patients were required to rate their pain intensity in the last 7 days using the VAS, then the average score were calculated. The Hamilton Depression Rating Scale (HAMD) and the Hamilton Anxiety Rating Scale (HAMA) were applied to evaluate the anxious and depressive symptoms. All questionnaire assessment was performed under the supervision of experimenters.

MRI data acquisition

MRI data were collected on a 3.0-T scanner (Discovery 750 System, Milwaukee, WI, USA), equipped with a 16-channel phased-array head coil. All participants were instructed to stay awake and relaxed but to keep their eyes closed without falling asleep during scanning. In order to reduce the noise and avoid head motion, the earplugs and foam pad were used. First, T2-weighted imaging sequence was acquired in all participants to rule out the possibility of asymptomatic lesions. Then a high-resolution structural image was acquired using the following parameters: field of view (FOV) = 256 × 256 mm^2, matrix = 256 × 256, time of repetition (TR) = 8.15ms, Time of inversion = 450ms, time of echo (TE) = 3.17ms, spatial resolution = 1.00 × 1.00 mm2, flip angle = 12.0˚. The rs-fMRI data were obtained using the following parameters: 32 contiguous slices, FOV = 220 × 220 mm^2, in-plane matrix = 64 × 64, spatial resolution = 3.44 × 3.44 × 4 mm^3, TR = 2000ms, TE = 30ms, flip angle = 90˚, and a total of 180 volumes and lasted 360 s for each subject.

VBM analysis

VBM analysis was performed following the standard pipeline of CAT 12 toolbox (http://dbm.neuro.uni-jena.de/cat12/) to obtain GMVs. The details could be referred to Ashburner et al.'s study [19]. The main steps were as follows: bias-field correction, segmentation (gray matter, white matter, and cerebrospinal fluid), adjustment for partial volume effects, normalization into Montreal Neurological Institute space, resampled to 1.5 mm× 1.5 mm × 1.5 mm and nonlinear modulation [19, 20]. Finally, the gray matter maps were smoothed using 6 mm full width at half maximum (FWHM) Gaussian kernel. The total intracranial volume for each participant was calculated for the next produces [21, 22].

Resting-fMRI Data Preprocessing and Calculation of zALFF

The resting-fMRI data were preprocessed using Data Processing Assistant for Resting-State fMRI package (DPARSFA, http://www.restfmri.net). The first 10 volumes were deleted and then the remaining functional images were corrected for slice timing and realignment. The mean frame-wise displacement (FD) was calculated for each subject according to a previously published formula [23, 24]. Subjects were excluded if the translational and rotational displacement exceeded 3.0 mm or 3.0° from subsequent analyses. The functional images were spatially normalized to the standard EPI template and resampled to 3 × 3 ×3mm^3. Subsequently, the functional images were further smoothed with 6 × 6 × 6 mm^3 FWHM Gaussian kernel and detrended to reduce low-frequency drift. Next, several nuisance covariates, including white matter signals, cerebrospinal fluid signals, and Friston-24 head motion parameters [25], were regressed out. Then temporal band-pass filter (0.01-0.08Hz) was conducted. Scrubbing with cubic spline interpolation was used to exclude the influence of head motion and ensure the contiguous time points.

The ALFF maps were calculated using resting-state fMRI data processing toolbox (REST) [26] and zALFF maps (subtracting the global mean value and dividing it by the standard deviation) were chosen for the following analysis.

Statistical Analysis

SPSS software version 23.0 (IBM Corporation, Armonk, NY) was used for the demographic and clinical data analyses. Two-sample t-tests (for age, HAMA and HAMD scores) and chi-square tests (for gender) were used to analyze the differences between CTN patients and HCs subjects. To further investigate the changes of GMV and ALFF, a two-sample t-test was performed between the CTN patients and HCs, with age, gender and mean FD as covariates using SPM12. Multiple comparisons were corrected false discovery rate (FDR) approach ($p < 0.05$).

To verify the overlapped brain regions between functional and anatomical alterations in the CTN, the regions with significant abnormalities in GMV and ALFF were overlaid on the same template as described in the previous studies [27, 28].

Correlation Analysis with clinical variables

Once the overlapped regions with significant differences in GMV and ALFF were found, the GMV and ALFF values from those brain regions were extracted, respectively. Pearson correlation was performed to examine the relationship between the mean GMV values and the mean ALFF values in the overlapped regions. Then, a two-tailed partial correlation analysis was performed to further evaluate the relationship between the values (GMV and ALFF) and clinical variables (VAS scores, disease duration, HAMD and HAMA scores) in the CTN group, controlling for age, gender. A statistically significant threshold of $p < 0.05$ was set for all correlation analyses.

Results

Demographic and clinical characteristics

The demographics and clinical features of the two groups are summarized in Table 1. No significant differences were found between CTN patents and HC subjects in terms of demographic characteristics, such as age, gender. Compared with HCs, CTN patients had significantly higher scores of the HAMA and HAMD.

Grey matter volume changes

Compared with HCs, CTN patients exhibited significant reduced GMV in the right hippocampus, right fusiform gyrus (FFG), right inferior temporal gyrus (ITG), left superior temporal gyrus (STG), left operculo-insular gyrus, left middle temporal gyrus (MTG) (Fig. 1, Table 2). ($P < 0.05$, FDR corrected).

ALFF changes

Brain regions with significant ALFF differences are shown in Fig. 2 and Table 3. Compared with HCs, CTN patients showed significantly increased ALFF in the bilateral hippocampus, bilateral FFG, bilateral caudate, left thalamus, bilateral putamen, right pallidum, bilateral parahippocampal gyrus (PHG), left cerebellum, midbrain, and pons.

Association between functional and anatomical findings

The right hippocampus and right FFG were overlapped regions with both functional and anatomical abnormalities in the CTN patients (Fig. 3). No significantly correlation between the GMV and ALFF values in those overlapped regions was found. Furthermore, GMV in the right hippocampus was negatively correlated with pain intensity ($r = -0.370$, $P = 0.031$), anxiety ($r = -0.489$, $P = 0.001$), and depression scores ($r = -0.356$, $P = 0.039$) of the CTN patients. GMV in the right FFG was negatively associated with the illness duration ($r = -0.369$, $P = 0.032$). There was a positive correlation of the ALFF value in the right FFG with anxiety ($r = 0.361$, $P = 0.036$) scores of the CTN patients. (Fig. 4)

Discussion

This study revealed concurrent brain anatomical and functional abnormalities in CTN patients using the VBM and ALFF methods. Reductions in GMV were found mainly in the temporal-parietal regions (the left superior/middle temporal gyrus, left operculo-insular gyrus, left inferior parietal lobule, right ITG, right FFG) and limbic system (the right hippocampus). The increased regional spontaneous functional activities were observed in the basal ganglia system (the bilateral putamen, bilateral caudate, and right pallidum), limbic system (the bilateral hippocampus and bilateral PHG), left thalamus, bilateral FFG, left cerebellum, midbrain, and pons. More importantly, the right hippocampus and right FFG were the overlapped regions with both functional and anatomical alterations, suggesting the structure and function of brain might alter synchronously in CTN. GMV reduction in the right hippocampus was negatively related to the pain intensity and negative emotions. GMV reduction in the right FFG was negatively related to the illness duration. Increased activity in the right FFG was positively correlated with anxiety.

Our study identified reduced GMV in multiple brain regions, including ITG, STG, MTG, left operculo-insular cortex, and inferior parietal lobule. The GMV atrophy in these brain regions may indicated neural damage and loss during the recurrent attack of pain in CTN patients. This may represent the cortical maladaptive response to the long-term and repeated nociceptive input, and pain modulation. It is notably that most of the brain regions with reduced GMV located in the temporal gyrus, which is consisted with previous studies [7, 10, 29, 30], indicating that the temporal lobe was particularly vulnerable in CTN. A possible explanation is that multiple temporal regions involved in the modulation of the emotional and motivational aspects of pain. The STG has been reported involved in the perception of emotions, and MTG is the component of default mode network and served as the key part of the dynamic pain connectome [31–34]. The ITG has the projection to the amygdala and hippocampus, which are related to the process of emotion and cognition [35–37]. The potential mechanism is that the STG, MTG, ITG, and hippocampus were recruited to regulate aversive memory recognition and maintain the emotions in the modulation and anticipation of severe pain [36, 38, 39]. After prolonged pain attack, these responses would probably become maladaptive, lead to allostatic load over time, and cause negative emotional disorders. Therefore, we speculate that the GMV atrophy of temporal regions result in impairment of emotional processing aspect of pain and contribute to the negative moods observed in CTN patients.

Meanwhile, compared to HCs, increased spontaneous brain activity was identified mainly in subcortical nuclei and limbic system in the CTN group. Several previous studies have also reported increased spontaneous functional activity, but the involved brain regions varied among the studies, including temporal gyrus, occipital gyrus, precentral gyrus, and cerebellum [17, 40]. The putamen, caudate, pallidum, thalamus, and midbrain are the main nodes of the cortex-basal ganglia-thalamus loops, which involved in motor control. This loop has been reported that could regulate the motor and behavioral response to pain [41, 42]. Thereby, the hyperactivity in the cortex-basal ganglia-thalamus loops and limbic system revealed in our study may be a compensatory response to pain attack. It is reasonable to assume that abnormal hyperactivity of this loop could prompt patients to limit their orofacial movements, such as chewing, in order to avoid triggering of pain[43, 44]. Besides, central sensitization, which has been reported in patients with chronic daily headache [45, 46], may be another possible explanation for the

increased spontaneous functional activity in our study. Central sensitization would cause the subcortical nuclei and limbic system to be easily activated and present as increased spontaneous functional activity. Furthermore, in previous studies, the altered GMV of basal ganglia and thalamus in CTN patients has been reported [8, 9, 29, 15, 47–49], which proved that basal ganglia and thalamus were involved in pathogenesis of CTN. However, we did not observe GMV alterations in basal ganglia and thalamus in CTN patients, which were considered caused by the different disease durations of CTN in our study. This is supported by Shen et al.'s study, which used VBM to investigate the changes of brain structure in patients with CTN grouped according to disease duration and they found GMV alterations in different brain regions at different stages of CTN [50]. Tsai et al. found reduced volume in the thalamus, but along with the duration of the disease, the volume of thalamus gradually increased[8]. Those findings suggest that the GMV alterations are highly dynamic. Longitudinal neuroimaging investigations in CTN patients with analysis of both structure and function would provide further evidence for the dynamic changes in pain disorders.

More importantly, our findings revealed that the right hippocampus and FFG were the overlapped regions with both reduced GMV and increased ALFF, suggesting that the functional and anatomical alterations might alter simultaneously and dependently. Consistent with our study, reduced GMV in hippocampus has also been reported in other studies of CTN[30, 51], but they did not investigate the functional change of the hippocampus. In the correlation analysis, we found that the volume of right FFG was negatively associated with the duration of CTN. Vaculik el al. has reported similar finding that hippocampal volume was negatively correlated with the illness duration in CTN patients[52]. These findings indicated that the volume of hippocampus and FFG would gradually decrease along with the duration of the disease. The anatomical alterations revealed by VBM may reflect more stable and long-standing abnormalities. The reduced GMV of hippocampus and FFG in CTN patients may represent maladaptive plasticity caused by the prolonged pain attack in CTN patients. It is unexpected that the regional spontaneous activities in those GMV-reduced regions were found increased concurrently in our study. Functional alterations measured by the ALFF method may represent physiological compensatory changes during the recurrent acute pain attacks. Although the volume of right hippocampus and FFG was found reduced, we considered that the degree of reduction in these regions may be not sufficient yet to cause decreased functional activity, and these regions were still capable of exhibiting compensatory response to the recurring pain attacks in CTN patients. Therefore, we speculate that the increased functional activity detected in our study probably was an adaptive and compensatory response of the brain to meet the increased demand for pain processing during the recurring attacks of CTN. The other possible explanation of this functional-structural alterations is that GMV loss may be a result of increased functional activity. Malenka et al. has found that alterations in neuronal activity can elicit long-lasting changes in the synaptic function and dendritic spine density [53], which may consequently lead to gray matter changes [54–56]. Similar to our findings, Drevets et al. has reported decreased volume and increased activity in subgenual prefrontal cortex in the patient with major depression [57]. Taken together, our findings suggested that the functional changes are accompanied by anatomical alterations in CTN patients.

The hippocampus, an important component of the limbic system, has widespread anatomical connections to cortical and subcortical regions, and has key roles in learning, memory, cognition and emotion formation[58–60]. Accumulating evidence demonstrated that the hippocampus participates in pain processing, especially for affective and motivational component of pain [61–66]. It has been speculated that the hippocampal formation amplifies aversive effects as a protective mechanism to define appropriate behavioral responses [67]. Longitudinal imaging studies suggest the representation of pain gradually shifts from sensory to emotional circuits and limbic structures as the pain disorders progress and become chronic [68, 69]. Previous studies have reported that CTN patients have an increased risk of developing psychiatric comorbidities, including anxiety and depression [70]. Meanwhile, the GMV in the right hippocampus was found negatively related to the severity of pain, anxiety, and depression scores in our study. This suggested that the degree of GMV abnormalities in the right hippocampus may reflect pain severity and related to the negative emotions in CTN patients. In patients with migraine, morphological and functional alterations in hippocampus have also been reported and these changes were associated with headache frequency, accumulative number of migraine attacks, and severity of anxiety and depression [71]. Combined with our findings, it is strongly suggested that hippocampus participated in the pathophysiological process of neuropathic pain disorders, especially in the affective and cognitive dimension of pain, which mainly contribute to the pain chronification.

It is interesting that the right FFG have similar anatomical and functional changes with the right hippocampus. Several studies confirmed cortical atrophy in the FFG in CTN patients [72, 29]. Chen et al. reported increased ALFF in bilateral fusiform cortex [17]. Painful electrical shock has been found to activate the fusiform cortex [73]. Thus, it is speculated that pain in CTN could also activate FFG, as the feature of pain in CTN is electrical-shock-like. The potential mechanism may be that the fusiform cortex relates to the retrieval of similar sensation in CTN patients during recurrent electrical-shock-like pain. Besides, the fusiform cortex was found related to the retrieval of similar sensation in CTN patients during recurrent electrical-shock-like pain. Moreover, the regional spontaneous activity of the right FFG was positively correlated with anxiety in our study, indicating that the FFG was related to the modulation of affective aspect of pain. Therefore, the present findings added robust evidence that FFG involved in the pain perception and modulation in CTN.

There were several limitations in the current study that should be addressed. First, we cannot exclude the potential effect of anti-epileptic agents on brain structure and function. Thus, this would be an important confounder of the study. Second, the present study was a cross-sectional study with a relatively small sample size, so the structural and functional findings here were exploratory and preliminary. Future longitudinal studies with large number of CTN patients should be recruited to further clarify the relationships between the structural and functional alterations. Additionally, the current analysis focused on regional intrinsic neuronal activity, the effects of the interactions between different brain areas in CTN patients need to be analyzed.

Conclusions

Our results present evidence that concurrent anatomical and functional alterations occurred in the patients with CTN, indicating that the CTN is a brain disorder with structural and functional abnormalities. The overlapping structural and functional changes in the right hippocampus and FFG of CTN suggested that anatomical and functional changes might alter dependently in CTN patients, and suggested the vital role of hippocampus and FFG in the pathophysiology of CTN. Therefore, this study highlights the importance of combining structural and functional MRI methods, which could offer complementary information for the understanding of the pathophysiology and chronification of CTN. Future studies should illustrate the causes of functional and anatomical changes and clarify whether the structural and functional alterations can be reversed after effective treatment of CTN.

Abbreviations

CTN, Classic trigeminal neuralgia; GMV, Gray matter volume; fMRI, Functional magnetic resonance imaging; VBM, Voxel-based morphometry; ALFF, Amplitude of low-frequency fluctuation; VAS, Visual analogue scale; HAMD, Hamilton Depression Rating Scale, HAMA, Hamilton Anxiety Rating Scale; FWHM, Full width at half maximum; FFG, Fusiform gyrus; ITG, Inferior temporal gyrus; STG superior temporal gyrus; MTG, Middle temporal gyrus; PHG, Parahippocampal gyrus.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. Written informed consents were obtained from all participants before experiment.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

HL, JC, and SH conceived and designed the study. HL and FL supervised the conduct of the study. HL, RZ, and YZ contributed to the MR data acquisition. FL, HH contributed to the clinical data acquisition. HL, HH analyzed the data and drafted original manuscript writing. HL, SH contributed to the methodology and software and data curation. HH, YZ, and SH reviewed and revised the manuscript. All authors read and approved the final manuscript.

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References

1. Scholz J, Finnerup NB, Attal N et al. (2019) The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain 160 (1):53–59. doi:10.1097/j.pain.0000000000001365
2. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition (2018). Cephalalgia: an international journal of headache 38 (1):1-211. doi:10.1177/0333102417738202
3. DeSouza DD, Hodaie M, Davis KD (2016) Structural Magnetic Resonance Imaging Can Identify Trigeminal System Abnormalities in Classical Trigeminal Neuralgia. Frontiers in neuroanatomy 10:95. doi:10.3389/fnana.2016.00095
4. Nurmikko TJ, Eldridge PR (2001) Trigeminal neuralgia–pathophysiology, diagnosis and current treatment. British journal of anaesthesia 87 (1):117–132. doi:10.1093/bja/87.1.117
5. Maarbjerg S, Wolfram F, Gozalov A et al. (2015) Significance of neurovascular contact in classical trigeminal neuralgia. Brain: a journal of neurology 138 (Pt 2):311–319. doi:10.1093/brain/awu349
6. Obermann M, Rodriguez-Raecke R, Naegel S et al. (2013) Gray matter volume reduction reflects chronic pain in trigeminal neuralgia. NeuroImage 74:352–358. doi:10.1016/j.neuroimage.2013.02.029
7. Wang Y, Cao DY, Remeniuk B et al. (2017) Altered brain structure and function associated with sensory and affective components of classic trigeminal neuralgia. Pain 158 (8):1561–1570. doi:10.1097/j.pain.0000000000000951
8. Tsai YH, Yuan R, Patel D et al. (2018) Altered structure and functional connection in patients with classical trigeminal neuralgia. Human brain mapping 39 (2):609–621. doi:10.1002/hbm.23696
9. Tang Y, Wang M, Zheng T et al. (2020) Grey matter volume alterations in trigeminal neuralgia: A systematic review and meta-analysis of voxel-based morphometry studies. Progress in neuro-psychopharmacology & biological psychiatry 98:109821. doi:10.1016/j.pnpbp.2019.109821
10. Wu M, Jiang X, Qiu J et al. (2020) Gray and white matter abnormalities in primary trigeminal neuralgia with and without neurovascular compression. The journal of headache and pain 21 (1):136. doi:10.1186/s10194-020-01205-3

11. Alshelh Z, Di Pietro F, Youssef AM et al. (2016) Chronic Neuropathic Pain: It's about the Rhythm. The Journal of neuroscience: the official journal of the Society for Neuroscience 36 (3):1008–1018. doi:10.1523/jneurosci.2768-15.2016
12. Tian T, Guo L, Xu J et al. (2016) Brain white matter plasticity and functional reorganization underlying the central pathogenesis of trigeminal neuralgia. Scientific reports 6:36030. doi:10.1038/srep36030
13. Tsai YH, Liang X, Yang JT et al. (2019) Modular organization of brain resting state networks in patients with classical trigeminal neuralgia. NeuroImage Clinical 24:102027. doi:10.1016/j.nicl.2019.102027
14. Zhang P, Jiang Y, Liu G et al. (2021) Altered brain functional network dynamics in classic trigeminal neuralgia: a resting-state functional magnetic resonance imaging study. The journal of headache and pain 22 (1):147. doi:10.1186/s10194-021-01354-z
15. Zhong J, Chen DQ, Hung PS et al. (2018) Multivariate pattern classification of brain white matter connectivity predicts classic trigeminal neuralgia. Pain 159 (10):2076–2087. doi:10.1097/j.pain.0000000000001312
16. Wang Y, Xu C, Zhai L et al. (2017) Spatial-temporal signature of resting-state BOLD signals in classic trigeminal neuralgia. Journal of pain research 10:2741–2750. doi:10.2147/jpr.S143734
17. Chen Y, Xiang CQ, Liu WF et al. (2019) Application of amplitude of low–frequency fluctuation to altered spontaneous neuronal activity in classical trigeminal neuralgia patients: A resting–state functional MRI study. Molecular medicine reports 20 (2):1707–1715. doi:10.3892/mmr.2019.10404
18. The International Classification of Headache Disorders, 3rd edition (beta version) (2013). Cephalalgia: an international journal of headache 33 (9):629–808. doi:10.1177/0333102413485658
19. Ashburner J (2009) Computational anatomy with the SPM software. Magnetic resonance imaging 27 (8):1163–1174. doi:10.1016/j.mri.2009.01.006
20. Han S, Xu Y, Guo HR et al. (2022) Two distinct subtypes of obsessive compulsive disorder revealed by heterogeneity through discriminative analysis. Human brain mapping. doi:10.1002/hbm.25833
21. Han S, Zheng R, Li S et al. (2021) Progressive brain structural abnormality in depression assessed with MR imaging by using causal network analysis. Psychological medicine:1–10. doi:10.1017/s0033291721003986
22. Han S, Chen Y, Zheng R et al. (2021) The stage-specifically accelerated brain aging in never-treated first-episode patients with depression. Human brain mapping 42 (11):3656–3666. doi:10.1002/hbm.25460
23. Power JD, Barnes KA, Snyder AZ et al. (2012) Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage 59 (3):2142–2154. doi:10.1016/j.neuroimage.2011.10.018
24. Han S, Cui Q, Wang X et al. (2020) Resting state functional network switching rate is differently altered in bipolar disorder and major depressive disorder. Human brain mapping 41 (12):3295–3304. doi:10.1002/hbm.25017

25. Satterthwaite TD, Wolf DH, Loughead J et al. (2012) Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. NeuroImage 60 (1):623–632. doi:10.1016/j.neuroimage.2011.12.063
26. Song XW, Dong ZY, Long XY et al. (2011) REST: a toolkit for resting-state functional magnetic resonance imaging data processing. PloS one 6 (9):e25031. doi:10.1371/journal.pone.0025031
27. Ren W, Lui S, Deng W et al. (2013) Anatomical and functional brain abnormalities in drug-naive first-episode schizophrenia. The American journal of psychiatry 170 (11):1308–1316. doi:10.1176/appi.ajp.2013.12091148
28. Guo W, Song Y, Liu F et al. (2015) Dissociation of functional and anatomical brain abnormalities in unaffected siblings of schizophrenia patients. Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology 126 (5):927–932. doi:10.1016/j.clinph.2014.08.016
29. Li M, Yan J, Li S et al. (2017) Reduced volume of gray matter in patients with trigeminal neuralgia. Brain imaging and behavior 11 (2):486–492. doi:10.1007/s11682-016-9529-2
30. Wang Y, Yang Q, Cao D et al. (2019) Correlation between nerve atrophy, brain grey matter volume and pain severity in patients with primary trigeminal neuralgia. Cephalalgia: an international journal of headache 39 (4):515–525. doi:10.1177/0333102418793643
31. Humphries C, Willard K, Buchsbaum B et al. (2001) Role of anterior temporal cortex in auditory sentence comprehension: an fMRI study. Neuroreport 12 (8):1749–1752. doi:10.1097/00001756-200106130-00046
32. Liotti M, Mayberg HS, Brannan SK et al. (2000) Differential limbic–cortical correlates of sadness and anxiety in healthy subjects: implications for affective disorders. Biological psychiatry 48 (1):30–42. doi:10.1016/s0006-3223(00)00874-x
33. Smallwood J, Gorgolewski KJ, Golchert J et al. (2013) The default modes of reading: modulation of posterior cingulate and medial prefrontal cortex connectivity associated with comprehension and task focus while reading. Frontiers in human neuroscience 7:734. doi:10.3389/fnhum.2013.00734
34. Kucyi A, Moayedi M, Weissman-Fogel I et al. (2014) Enhanced medial prefrontal-default mode network functional connectivity in chronic pain and its association with pain rumination. The Journal of neuroscience: the official journal of the Society for Neuroscience 34 (11):3969–3975. doi:10.1523/jneurosci.5055-13.2014
35. Webster MJ, Ungerleider LG, Bachevalier J (1991) Connections of inferior temporal areas TE and TEO with medial temporal-lobe structures in infant and adult monkeys. The Journal of neuroscience: the official journal of the Society for Neuroscience 11 (4):1095–1116. doi:10.1523/jneurosci.11-04-01095.1991
36. Price DD (2000) Psychological and neural mechanisms of the affective dimension of pain. Science (New York, NY) 288 (5472):1769–1772. doi:10.1126/science.288.5472.1769
37. Vincent MB, Hadjikhani N (2007) Migraine aura and related phenomena: beyond scotomata and scintillations. Cephalalgia: an international journal of headache 27 (12):1368–1377.

doi:10.1111/j.1468-2982.2007.01388.x

38. Bauch EM, Rausch VH, Bunzeck N (2014) Pain anticipation recruits the mesolimbic system and differentially modulates subsequent recognition memory. Human brain mapping 35 (9):4594–4606. doi:10.1002/hbm.22497
39. Tillfors M, Furmark T, Marteinsdottir I et al. (2002) Cerebral blood flow during anticipation of public speaking in social phobia: a PET study. Biological psychiatry 52 (11):1113–1119. doi:10.1016/s0006-3223(02)01396-3
40. Xiang CQ, Liu WF, Xu QH et al. (2019) Altered Spontaneous Brain Activity in Patients with Classical Trigeminal Neuralgia Using Regional Homogeneity: A Resting-State Functional MRI Study. Pain practice: the official journal of World Institute of Pain 19 (4):397–406. doi:10.1111/papr.12753
41. Bingel U, Gläscher J, Weiller C et al. (2004) Somatotopic representation of nociceptive information in the putamen: an event-related fMRI study. Cerebral cortex (New York, NY: 1991) 14 (12):1340–1345. doi:10.1093/cercor/bhh094
42. Starr CJ, Sawaki L, Wittenberg GF et al. (2011) The contribution of the putamen to sensory aspects of pain: insights from structural connectivity and brain lesions. Brain: a journal of neurology 134 (Pt 7):1987–2004. doi:10.1093/brain/awr117
43. Zhang Y, Mao Z, Pan L et al. (2018) Dysregulation of Pain- and Emotion-Related Networks in Trigeminal Neuralgia. Frontiers in human neuroscience 12:107. doi:10.3389/fnhum.2018.00107
44. Bennetto L, Patel NK, Fuller G (2007) Trigeminal neuralgia and its management. BMJ (Clinical research ed) 334 (7586):201–205. doi:10.1136/bmj.39085.614792.BE
45. Chen WT, Lin YY, Fuh JL et al. (2011) Sustained visual cortex hyperexcitability in migraine with persistent visual aura. Brain: a journal of neurology 134 (Pt 8):2387–2395. doi:10.1093/brain/awr157
46. Maleki N, Becerra L, Brawn J et al. (2012) Concurrent functional and structural cortical alterations in migraine. Cephalalgia: an international journal of headache 32 (8):607–620. doi:10.1177/0333102412445622
47. Desouza DD, Moayedi M, Chen DQ et al. (2013) Sensorimotor and Pain Modulation Brain Abnormalities in Trigeminal Neuralgia: A Paroxysmal, Sensory-Triggered Neuropathic Pain. PloS one 8 (6):e66340. doi:10.1371/journal.pone.0066340
48. Gustin SM, Peck CC, Wilcox SL et al. (2011) Different pain, different brain: thalamic anatomy in neuropathic and non-neuropathic chronic pain syndromes. The Journal of neuroscience: the official journal of the Society for Neuroscience 31 (16):5956–5964. doi:10.1523/jneurosci.5980-10.2011
49. Henssen D, Dijk J, Knepflé R et al. (2019) Alterations in grey matter density and functional connectivity in trigeminal neuropathic pain and trigeminal neuralgia: A systematic review and meta-analysis. NeuroImage Clinical 24:102039. doi:10.1016/j.nicl.2019.102039
50. Shen S, Zheng H, Wang J et al. (2022) Gray matter volume reduction with different disease duration in trigeminal neuralgia. Neuroradiology 64 (2):301–311. doi:10.1007/s00234-021-02783-y

51. Hayes DJ, Chen DQ, Zhong J et al. (2017) Affective Circuitry Alterations in Patients with Trigeminal Neuralgia. Frontiers in neuroanatomy 11:73. doi:10.3389/fnana.2017.00073
52. Vaculik MF, Noorani A, Hung PS et al. (2019) Selective hippocampal subfield volume reductions in classic trigeminal neuralgia. NeuroImage Clinical 23:101911. doi:10.1016/j.nicl.2019.101911
53. Malenka RC (2003) Synaptic plasticity and AMPA receptor trafficking. Annals of the New York Academy of Sciences 1003:1–11. doi:10.1196/annals.1300.001
54. Metz AE, Yau HJ, Centeno MV et al. (2009) Morphological and functional reorganization of rat medial prefrontal cortex in neuropathic pain. Proceedings of the National Academy of Sciences of the United States of America 106 (7):2423–2428. doi:10.1073/pnas.0809897106
55. Klausberger T (2009) GABAergic interneurons targeting dendrites of pyramidal cells in the CA1 area of the hippocampus. The European journal of neuroscience 30 (6):947–957. doi:10.1111/j.1460-9568.2009.06913.x
56. McEwen BS (1999) Stress and hippocampal plasticity. Annual review of neuroscience 22:105–122. doi:10.1146/annurev.neuro.22.1.105
57. Drevets WC, Price JL, Simpson JR, Jr. et al. (1997) Subgenual prefrontal cortex abnormalities in mood disorders. Nature 386 (6627):824–827. doi:10.1038/386824a0
58. Fortin NJ, Agster KL, Eichenbaum HB (2002) Critical role of the hippocampus in memory for sequences of events. Nature neuroscience 5 (5):458–462. doi:10.1038/nn834
59. Nestler EJ, Barrot M, DiLeone RJ et al. (2002) Neurobiology of depression. Neuron 34 (1):13–25. doi:10.1016/s0896-6273(02)00653-0
60. Kim S, Dede AJ, Hopkins RO et al. (2015) Memory, scene construction, and the human hippocampus. Proceedings of the National Academy of Sciences of the United States of America 112 (15):4767–4772. doi:10.1073/pnas.1503863112
61. Mutso AA, Petre B, Huang L et al. (2014) Reorganization of hippocampal functional connectivity with transition to chronic back pain. Journal of neurophysiology 111 (5):1065–1076. doi:10.1152/jn.00611.2013
62. Mutso AA, Radzicki D, Baliki MN et al. (2012) Abnormalities in hippocampal functioning with persistent pain. The Journal of neuroscience: the official journal of the Society for Neuroscience 32 (17):5747–5756. doi:10.1523/jneurosci.0587-12.2012
63. Liu MG, Chen J (2009) Roles of the hippocampal formation in pain information processing. Neuroscience bulletin 25 (5):237–266. doi:10.1007/s12264-009-0905-4
64. Gerrits MM, van Marwijk HW, van Oppen P et al. (2015) Longitudinal association between pain, and depression and anxiety over four years. Journal of psychosomatic research 78 (1):64–70. doi:10.1016/j.jpsychores.2014.10.011
65. Simons LE, Elman I, Borsook D (2014) Psychological processing in chronic pain: a neural systems approach. Neuroscience and biobehavioral reviews 39:61–78. doi:10.1016/j.neubiorev.2013.12.006

66. Apkarian AV, Mutso AA, Centeno MV et al. (2016) Role of adult hippocampal neurogenesis in persistent pain. Pain 157 (2):418–428. doi:10.1097/j.pain.0000000000000332
67. Maleki N, Becerra L, Brawn J et al. (2013) Common hippocampal structural and functional changes in migraine. Brain structure & function 218 (4):903–912. doi:10.1007/s00429-012-0437-y
68. McCarberg B, Peppin J (2019) Pain Pathways and Nervous System Plasticity: Learning and Memory in Pain. Pain medicine (Malden, Mass) 20 (12):2421–2437. doi:10.1093/pm/pnz017
69. Hashmi JA, Baliki MN, Huang L et al. (2013) Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. Brain: a journal of neurology 136 (Pt 9):2751–2768. doi:10.1093/brain/awt211
70. Wu TH, Hu LY, Lu T et al. (2015) Risk of psychiatric disorders following trigeminal neuralgia: a nationwide population-based retrospective cohort study. The journal of headache and pain 16:64. doi:10.1186/s10194-015-0548-y
71. Liu HY, Chou KH, Chen WT (2018) Migraine and the Hippocampus. Current pain and headache reports 22 (2):13. doi:10.1007/s11916-018-0668-6
72. Parise M, Kubo TT, Doring TM et al. (2014) Cuneus and fusiform cortices thickness is reduced in trigeminal neuralgia. The journal of headache and pain 15 (1):17. doi:10.1186/1129-2377-15-17
73. Ter Minassian A, Ricalens E, Humbert S et al. (2013) Dissociating anticipation from perception: Acute pain activates default mode network. Human brain mapping 34 (9):2228–2243. doi:10.1002/hbm.22062

Tables

Table 1. Demographic and clinical characteristics

Variables	CTN (n = 34)	HC (n = 29)	t/χ^2	*P* value
Age (years)	53.06 ± 10.91	54.21 ± 6.33	-0.520	0.606
Gender (male/female)	16/18	15/14	0.136	0.712
Duration of CTN (years)	4.63 ±3.53	NA		
VAS	7.97±1.42	NA		
Side affected (L/R), n	14/20	NA		
Score of HAMA	8.56±6.01	3.93±2.92	3.98	0.001
Score of HAMD	10.62±6.73	4.6±2.27	4.88	0.001

Abbreviations: CTN, classic trigeminal neuralgia; HC, healthy control; VAS, Visual Analogue Scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; NA, not applicable

Table 2. Brain regions displaying significant differences in GMV between CTN patients and HC subjects

Anatomical region	MNI coordinates			Cluster size	*T* value
	x	*y*	*z*		
Fusiform_R	41	-18	-26	315	4.67
Hippocampus_R	41	-30	-12	273	4.78
Inferior temporal gyrus_R	43	-19	-19	150	3.69
Superior temporal gyrus_L	-48	-35	15	1457	4.60
Operculo-insular_L	-37	-30	12	163	3.99

Abbreviations: GMV, gray matter volume; CTN, classic trigeminal neuralgia; HC, healthy control; MNI, Montreal Neurological Institute; L, left; R, right.

Table 3. Brain regions with altered ALFF in CTN patients

Regions	MNI coordinates			Voxels	*T* value
	x	*y*	*z*		
Hippocampus_R	33	-15	-21	50	5.09
Fusiform_R	34	-10	-32	41	3.27
Caudate_R	10	7	1	64	3.01
Pallidum_R	17	-2	0	44	3.48
Fusiform_L	-33	-21	-22	117	4.19
Hippocampus_L	-33	-18	-18	100	5.20
Putamen_L	-24	3	3	49	3.32
Thalamus_L	-17	-28	10	79	3.24
Caudate_L	-6	5	10	101	3.17
Cerebellum Anterior Lobe	-18	-51	-33	85	4.14
ParaHippocampal_R	33	-18	-24	41	4.66
ParaHippocampal_L	-30	-30	-15	32	5.38

Abbreviations: ALFF, amplitude of low frequency fluctuation; CTN, classic trigeminal neuralgia; HC, healthy control; MNI, Montreal Neurological Institute; L, left; R, right.

Figures

Figure 1

GMV alterations in CTN patients. Differences between the CTN patients and HCs were analyzed using a two-sample t-test. The statistical significance level was set at $p < 0.05$, FDR corrected. Patients with CTN showed significantly increased GMV in the right hippocampus, right FFG, right ITG, left STG, left operculo-insular gyrus, and left MTG. The color bar displayed t-values. GMV, gray matter volume; CTN, classic trigeminal neuralgia; HC, healthy control; FFG, fusiform gyrus; ITG, inferior temporal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus.

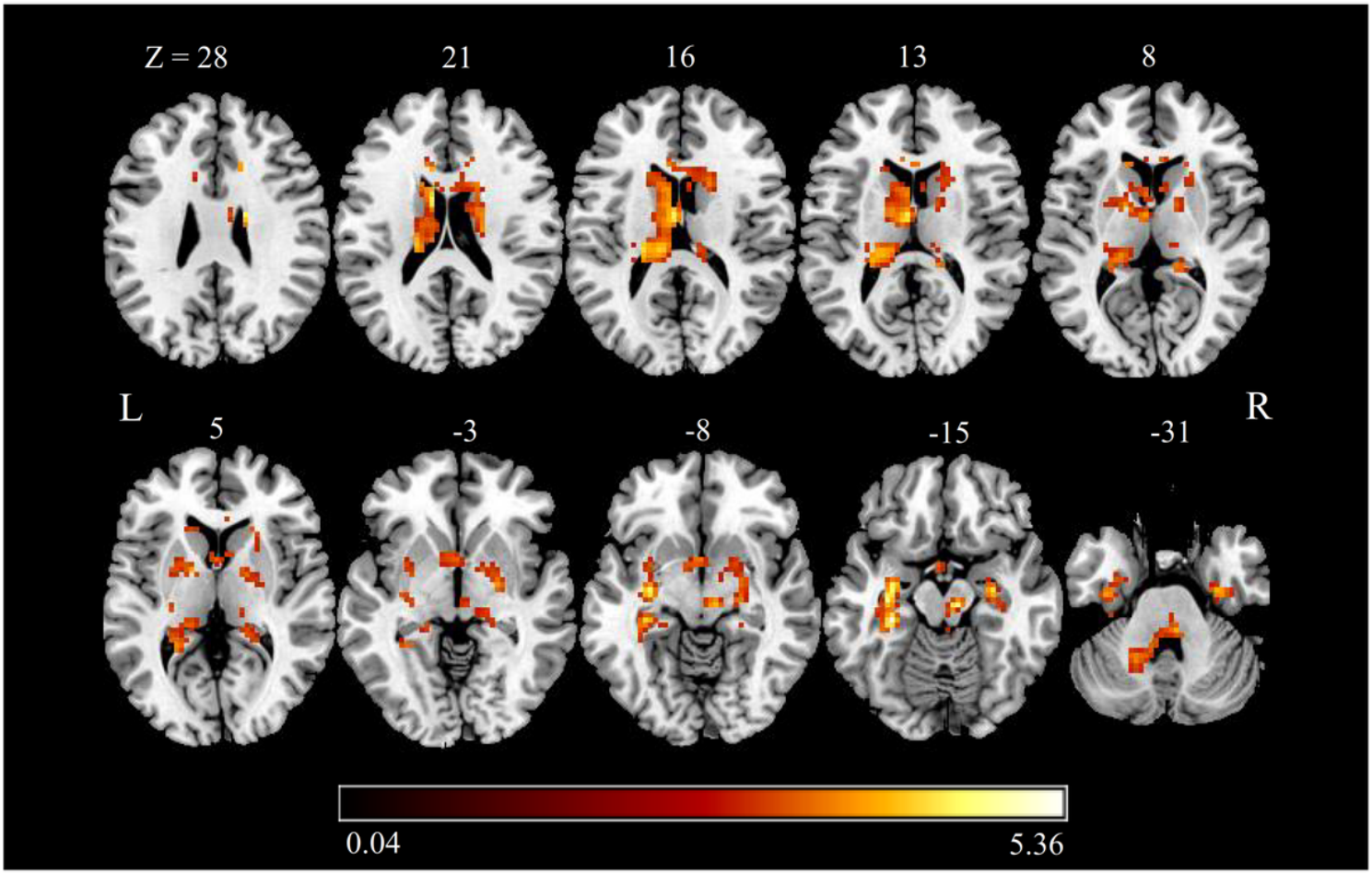

Figure 2

ALFF alterations in CTN patients. The differences between the CTN patients and HCs were analyzed using a two-sample t-test. The statistical significance level was set at $p < 0.05$, FDR corrected. Patients with CTN showed significantly decreased ALFF in the bilateral hippocampus, bilateral fusiform FFG, bilateral caudate, left thalamus, bilateral putamen, right pallidum, bilateral PHG, and left cerebellum. The color bar displayed t-values. ALFF, amplitude of low frequency fluctuation; CTN, classic trigeminal neuralgia; HC, healthy control; FFG, fusiform gyrus; PHG, parahippocampal gyrus.

Figure 3

Overlapped brain region with structural and functional changes. The right hippocampus (first row) and right fusiform gyrus (second row) within the red circle represent the overlapped areas with both increased ALFF (hot colored regions) and decreased GMV (cold colored regions) in patients with CTN. GMV, gray matter volume; ALFF, amplitude of low frequency fluctuation; CTN, classic trigeminal neuralgia.

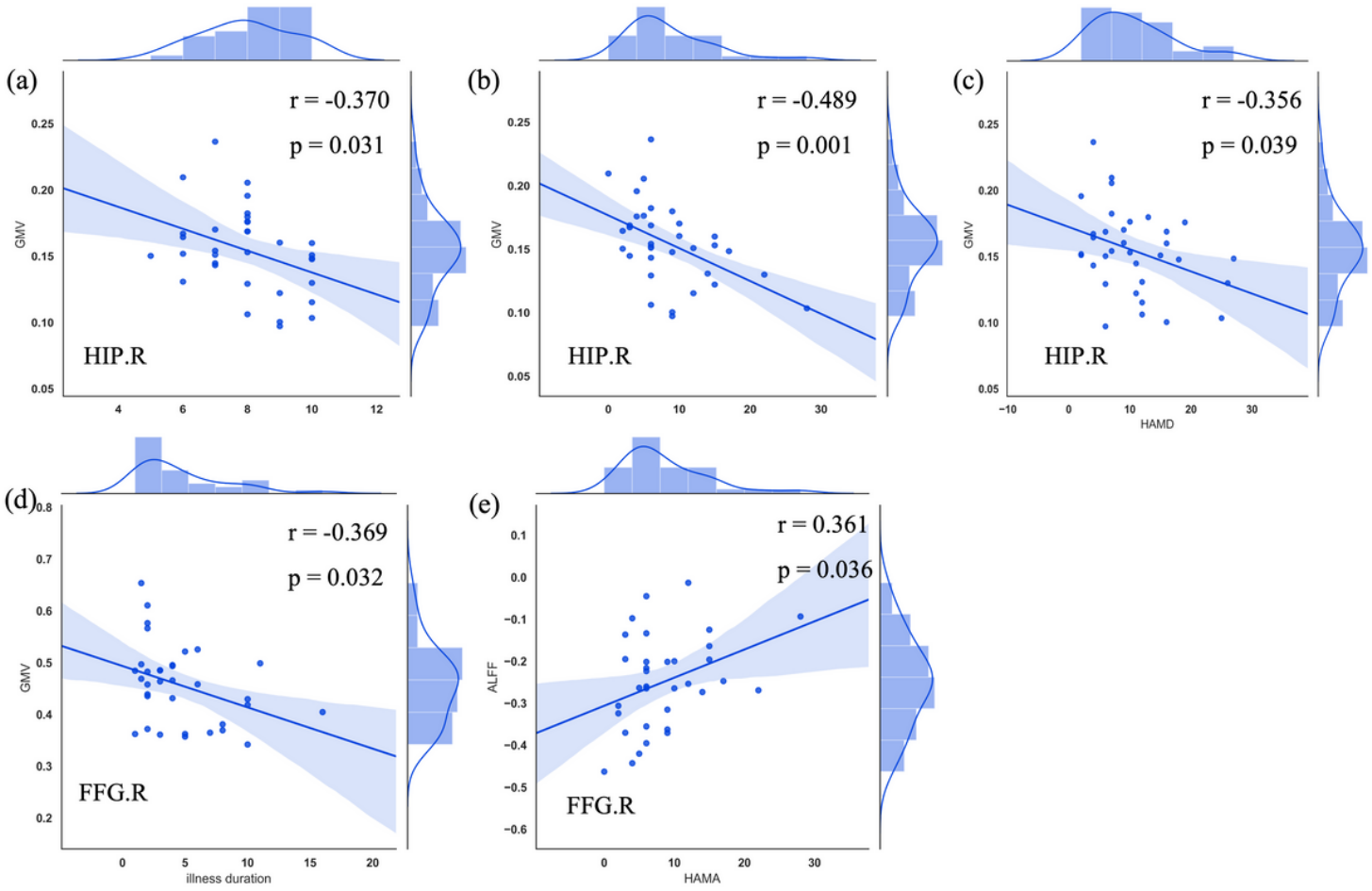

Figure 4

Correlation between GMV, ALFF alterations and clinical variables in CTN patients. GMV in the right hippocampus was negatively associated with VAS (a), HAMA (b), and HAMD (c) scores of CTN patients. GMV in the right FFG was negatively correlated with illness duration (d). Increased ALFF in the right FFG was positively correlated with HAMA score of the CTN patients(e). GMV, gray matter volume; ALFF, amplitude of low frequency fluctuation; CTN, classic trigeminal neuralgia; HIP, hippocampus; VAS, visual analogue scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; FFG, fusiform gyrus.