Study of normal-tension glaucoma based on OCTA and VBM-DARTEL analysis

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Abstract. The aim of the present study was to investigate the detection value of optical coherence tomography angiography (OCTA) and voxel-based morphometry with diffeomorphic anatomical registration through exponentiated lie algebra (VBM-DARTEL) in normal-tension glaucoma (NTG), as well as the correlation between the two functional indicators. A total of 30 patients (15 males, 15 females) with NTG and 30 (15 males, 15 females) age-, sex- and education-matched healthy controls underwent OCTA and 3.0 T MRI scanning. The OCTA technique was used to scan the optic disc area of all subjects and measure the density of blood vessels around the optic disc; 3.0 T MRI scanning was used to obtain MRI images of the brain structure and the VBM-DARTEL method was applied for image processing using Matlab7.11R2010b (MathWorks). Imaging data were compared between the groups using two-samples t-tests to identify differences in the density of blood vessels around the optic disc and the change in brain parenchyma. Correlation analysis was used to explore associations between the density of blood vessels around the optic disc and the change in brain parenchyma in NTG. The results indicated that the vascular density around the optic disc in the NTG group was significantly decreased compared with that in the control group; the vascular density was decreased with disease progression. The difference between the two groups was statistically significant (P<0.05). The VBM-DARTEL analysis indicated that the volume of the left middle frontal gyrus, right superior frontal gyrus, right precuneus, right angular gyrus and right middle occipital gyrus was decreased, whereas the volume of the right anterior central gyrus was increased. The area under the receiver operating characteristic curve for the local volume difference in brain parenchyma to predict the diagnosis of NTG was >0.7. The area of brain parenchyma reduction was positively correlated with the density of blood vessels around the optic disc (P<0.05), whereas the right anterior central gyrus was negatively correlated with vascular density. In conclusion, OCTA and VBM-DARTEL technology may facilitate non-invasive monitoring of changes in NTG structure and function, and provide non-invasive diagnostic imaging support in the early stage of the disease. These advantages are of great importance in the diagnosis and follow-up of NTG.

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Introduction

Normal-tension glaucoma (NTG) is associated with high rates of blindness is and characterized by chronic and progressive damage to the optic nerve. The intraocular pressure in patients with this type of glaucoma is within the normal range. Therefore, symptoms (e.g., eye distension and pain) are frequently absent and the disease onset is insidious, potentially leading to delayed diagnosis and treatment. Symptoms become obvious to patients only when the damage to the visual field is extensive. In recent years, the incidence of NTG in China has been increasing (1) and the prevalence is relatively high in middle-aged and elderly individuals (2-4). There are currently no effective indicators for the early diagnosis of NTG; hence, misdiagnosis is common (5). With the in-depth study of the pathogenesis of glaucoma and the development of imaging technologies, optical coherence tomography angiography (OCTA) and voxel-based morphometry with diffeomorphic anatomical registration through exponentiated lie algebra (VBM-DARTEL) have been widely used in measurement studies of a variety of diseases, and may accurately display small changes in tissue morphology (6-8). In the present study, OCTA technology was used for the quantitative and accurate detection of optic disc blood vessels in patients with NTG, while VBM-DARTEL technology was used for the study of brain structural changes in patients with NTG. In the present

study, the correlation between the two functional indices was analyzed. Furthermore, the possible pathological changes and damage mechanisms associated with NTG are discussed, providing novel ideas for the early diagnosis of NTG.

Materials and methods

Participants. A total of 30 patients with NTG (60 eyes in total; 15 males and 15 females; all with bilateral NTG; average age, 52.6±9.4 years; mean duration of NTG, 8.3±2.6 years) were recruited from the First Affiliated Hospital of Nanchang University (Nanchang, China). Furthermore, 30 healthy controls (HCs; 60 eyes in total; 15 males and 15 females) with comparable characteristics (sex, age and educational status) to those of the patients with NTG were enrolled. The methods and protocols of the present study were approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University (Nanchang, China), and were in accordance with the principles of the Declaration of Helsinki. All subjects were informed regarding the objectives and content of the study and latent risks, and provided written informed consent prior to their participation. Detailed review of the medical history and data collection was performed for all subjects. Furthermore, all subjects underwent a routine ophthalmological examination, anterior chamber angle microscopy, central corneal thickness and ocular axis assessments, ultrasound biological microscopy, OCTA, fundus photography and computer-assisted visual field examination. The criteria for inclusion in the NTG group were as follows (9): Intraocular pressure <21 mmHg in both eyes for 24 h without the administration of anti-glaucoma drugs; open anterior chamber angle; presence of characteristic optic papillary damage for glaucoma; typical visual field loss for glaucoma; and absence of other eye diseases and systemic diseases that may cause changes to the optic disc and visual field, including previous traumatic increase of intra-ocular pressure, long-term use of corticosteroids and history of uveitis.

OCTA scans of the disc area. All subjects of the present study underwent scanning of the optic disc area using the Angio Vue OCTA angiography system (Optovue, Inc.) with the Angio Disc (4.5x4.5 mm) standard quantization program. All examinations were performed by a single operator. The subject maintained their position, placed their jaw on the mandible bracket, placed their forehead on the forehead band and stared at the fixed light. The examiner adjusted the subject's gaze and scanning situation through the monitoring screen. The image acquisition for each scan was completed within 3 sec. The scanner used the optic disc as the center and scanned an area 4.5x4.5 mm to reveal the distribution of blood vessels in the optic disc region. The quality of the blood flow images was determined according to the signal intensity. When the signal intensity value was <50, the subjects were re-scanned or excluded from further analysis. Only high-quality images without any motion artifacts and vitreous floats were selected for analysis. Owing to the lack of a unified analysis system for vascular parameters in the optic disc region, the contour map was drawn using the method of local fractal dimension and the acquired images were quantitatively analyzed (10). Areas with a standard pixel ratio of 0.9-1.0 represented the large vessels of the optic disc (i.e., retinal arteries and veins), while the small vessels (i.e., retinal capillaries) had ratios of 0.7-0.9, the non-vascular areas had ratios of 0-0.3 and the other areas corresponded to capillary gaps (11). In the present study, the ratio of the area of blood vessels in the scanned area (4.5x4.5 mm) denoted the blood vessel density in the optic disc area, including the large-vessel density (%), capillary density (%), capillary gap density (%) and avascular zone density (%). All of these analyses were performed using Matlab7.11R2010b (MathWorks) to observe and evaluate the vascular density and structural damage in the NTG optic disc area. When calculating blood vessel density, there was no requirement to take retinal image amplification into account. There was no refractive error and the eye axis was in the normal range in all patients, so no correction was required when calculating vascular density with OCTA (11).

VBM-DARTEL data acquisition and processing. Data were acquired using a Siemens 3.0 T superconducting MRI scanner (Siemens AG). A sagittal image was used as the reference, with the thalamus as the center of the stratum and the scan baseline parallel to the anterior and posterior joint lines. The sagittal three-dimensional T1-weighted image high-resolution magnetization was used to prepare a fast gradient back. The wave sequence was a full brain scan. The specific scanning sequence and parameters were as follows: Repetition time, 2,300 msec; echo time, 2.98 msec; field of view, 256x256 mm; matrix, 256x256 pixels; number of layers, 192; layer thickness, 2 mm; layer spacing, 0 mm; flip angle, 150˚; and voxel size, 1x1x1 mm. The raw data were imported into the computer during pre-processing, and the VBM-DARTEL software package equipped with SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London) was used for image processing on the Matlab7.11R2010b (MathWorks). After spatial pre-processing, smoothing and modulation, the images of the gray and white matter and cerebrospinal fluid were segmented and adopted. The DARTEL registration generated the optimal template to normalize the image map. Subsequently, parametric statistical tests were used to individually compare the components of the segmented brain tissue, and the density and volume of the gray and white matter were quantitatively measured to determine any abnormalities in brain morphology.

Statistical analysis. Values are expressed as the mean ± standard deviation and were analyzed using the SPSS version 19.0 statistical software (IBM Corp.). Analysis of variance was used to evaluate differences in general data and the visual field detection indices between the two groups. A paired-samples t-test was used to compare the differences in blood vessel density and brain parenchyma between the two groups. The Pearson parametric correlation test was used to analyze the correlations between blood vessel density around the optic disc and changes in brain parenchyma. $P<0.05$ was considered to indicate statistical significance. The area under ROC (receiver operating characteristic curve) was used to evaluate the diagnostic rate.

Results

Comparative analysis of general data and visual field detection indicators between the two groups. Regarding the clinical data, there were no statistically significant differences in terms of age, sex, weight, blood pressure, educational level

Table I. Comparison of general data and visual field detection indexes between NTG group and HCs.

Characteristic	NTG (n=30)	HCs (n=30)	t	P-value
Age (years)	52.62±9.44	56.92±10.87	-0.437	0.835
Males/females	15/15	15/15	N/A	>0.99
Body weight (kg)	67.87±7.62	66.12±6.14	0.132	0.874
Systolic blood pressure (mmHg)	127.73±17.32	128.85±17.57	-0.164	0.802
Diastolic blood pressure (mmHg)	83.89±10.74	84.76±11.58	-0.217	0.797
Education level (years)	11.63±3.44	10.68±2.72	0.563	0.523
Best-corrected visual acuity	0.62±0.24	1.0±0.13	-8.378	<0.001
Intraocular pressure (mmHg)	15.75±1.74	16.02±1.69	-0.164	0.703
Average visual field defect (dB)	-9.86±6.65	0.23±0.12	-9.824	<0.001

Values are expressed as the mean ± standard deviation. NTG, normal tension glaucoma; HC, healthy control; N/A, not applicable.

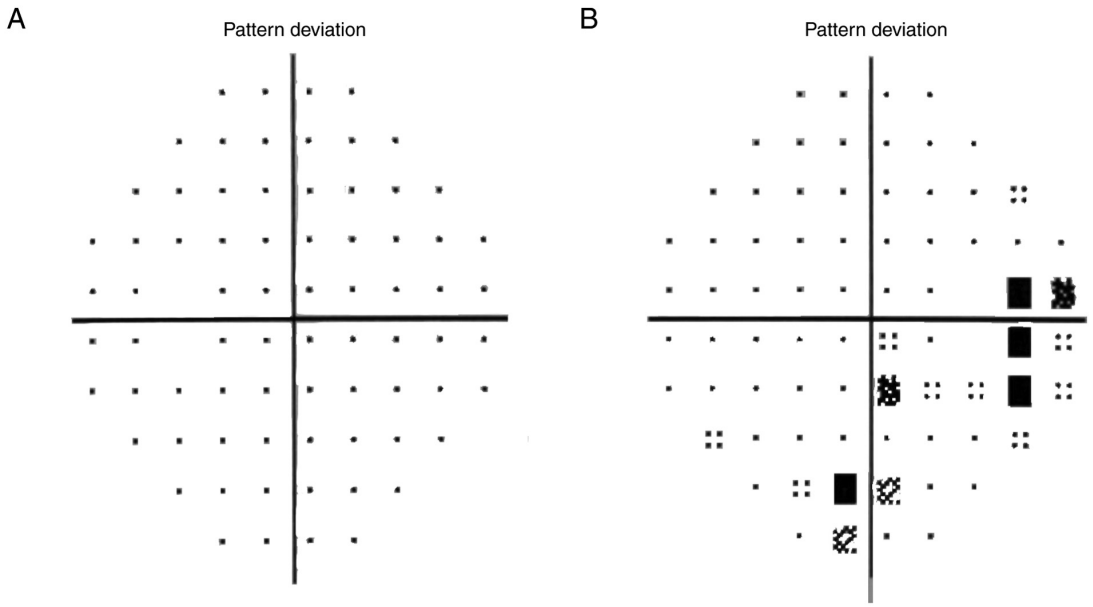

Figure 1. Representative images of the visual field in (A) healthy controls and (B) patients with normal tension glaucoma; black squares denote the locations of visual field defect in patients with normal intraocular pressure glaucoma.

or intraocular pressure between the two groups. By contrast, the best-corrected visual acuity and visual field mean defect were significantly different (P<0.001; Table I, Fig. 1).

Contrastive analysis of vascular density parameters in the optic disc area from OCTA scanning. The density of large vessels, capillaries and whole-area vessels in the patients with NTG was significantly lower than that in the HCs (P<0.001). However, the density of the capillary gap and avascular zone in the patients with NTG was significantly higher than that in the HCs (P<0.01; Table II, Fig. 2).

Comparison of whole-brain gray matter, white matter and brain parenchymal volume through VBM-DARTEL. The results of the VBM-DARTEL analysis indicated that the volume percentages of whole-brain gray matter, white matter and brain parenchyma were not significantly different between the NTG and HC groups (P>0.05). The volume of local gray matter areas [i.e., the left middle frontal gyrus (LMFG), right superior frontal gyrus (RSFG), right precuneus (RP) and right angular gyrus (RAG)] decreased; however, there was no increase observed in the gray matter area (P<0.05). The volume of the white matter decreased in the RMOG, whereas it increased in the RPG (P<0.001; Tables III and IV, Fig. 3).

Comparison of the diagnostic efficacy of brain regions with local volume differences in the NTG group. ROC curves for the diagnosis of NTG were drawn for the LMFG, RPG, RMOG, RP, RAG and RSFG (Fig. 4). Each index exhibited high diagnostic efficacy. Larger areas under the curve (AUC) denoted higher diagnostic rates. The right middle occipital region exhibited the highest diagnostic efficacy (AUC=0.918, P<0.001).

Correlation between the local volume difference and vascular density of the optic disc area in the NTG group. In the NTG group, the brain regions with local volume differences in gray

Table II. Comparative analysis of optical coherence tomography angiography vascular parameters between NTG group and HCs.

Indicators	NTG (n=30)	HCs (n=30)	t	P-value
Macrovascular density	21.32±5.97	30.52±7.31	-4.318	<0.001
Capillary density	17.72±6.12	30.37±6.98	-4.742	<0.001
Capillary gap density	35.40±8.39	28.02±4.63	3.975	<0.001
Density of avascular zone	25.56±5.28	10.09±2.35	6.448	<0.001
Regional vascular density	39.04±5.97	60.89±8.86	-4.471	<0.001

Values are expressed as the mean ± standard deviation. NTG, normal tension glaucoma; HCs, healthy controls.

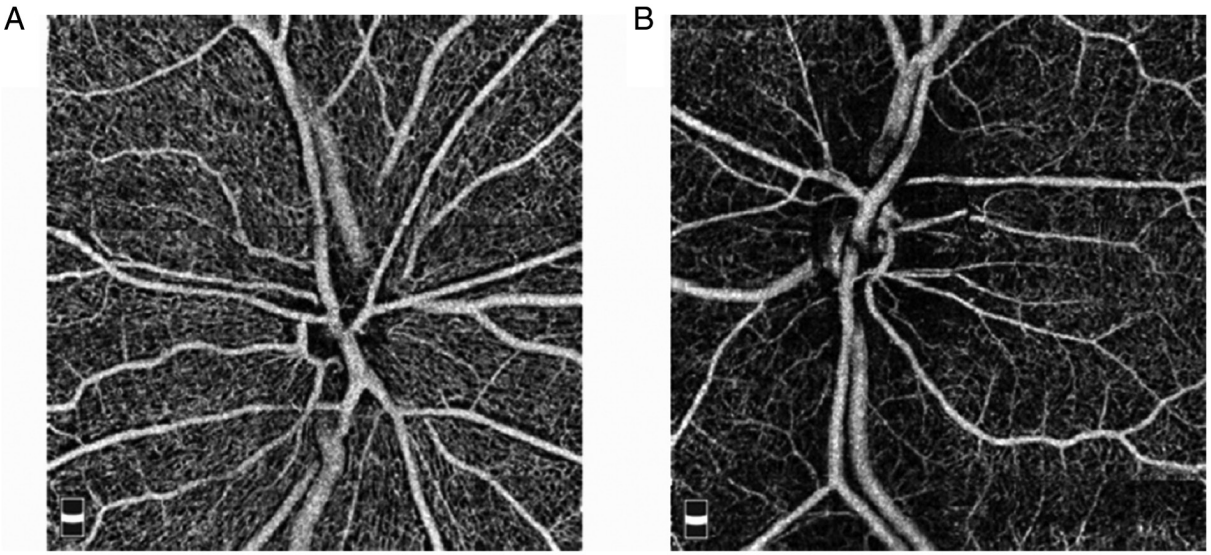

Figure 2. Representative images of distribution of blood vessels in the optic disc region of (A) healthy controls and (B) patients with normal tension glaucoma.

and white matter were correlated with the vascular density of the optic disc region. The vascular density of the optic disc region was positively correlated with the voxel value of the LMFG (r=0.748, P≤0.001), RSFG (r=0.451, P≤0.001), the RP (r=0.894, P≤0.001), the RP (r=0.367, P≤0.001) and the right occipital middle (r=0.846, P≤0.001). Furthermore, the vascular density of the optic disc region was negatively correlated with the voxel value of the right central anterior gyrus (r=-0.513, P≤0.001). Therefore, the voxel value of the RP exhibited the strongest correlation with the vascular density of the optic disc region (r=0.894, P≤0.001), whereas that of the RAG exhibited the weakest correlation (r=0.367, P≤0.001; Fig. 5).

Discussion

NTG is a condition associated with chronic and progressive damage to the optic nerve and is associated with high rates of blindness. The etiology and pathogenesis of this specific type of glaucoma remain to be fully elucidated. In the clinical setting, it is not obvious in the early stage and is often missed or misdiagnosed. The disease is not confirmed until the patient presents with typical glaucoma fundus changes and visual field defects. Due to the particularity and complexity of the clinical manifestations, diagnosis and prognosis of NTG, effective diagnostic methods for NTG have been frequently debated worldwide, and there is currently no unified standard. In recent years, an increasing number of scholars have suggested that glaucoma is not simply an eye disease but also a central nervous system disease (12-14). NTG and other brain diseases may exhibit similar or partially similar pathogeneses in the central nervous system. These similarities are of great importance for studying the etiology and pathogenesis of NTG. Morphological imaging using novel technologies (i.e., OCTA and VBM-DARTEL) has attracted considerable attention from clinicians. These technologies are used in research on glaucoma owing to their non-invasiveness, sensitivity, objectiveness, accuracy and reproducibility (11). Therefore, OCTA and VBM-DARTEL technologies may be used to accurately display the subtle changes in the morphology and structure of the eye and brain tissues, study the characteristic structural changes of the eye and brain in NTG, discover differences between patients with NTG and healthy individuals and identify anatomical changes in patients with early NTG. From these data, the correlation between the vascular density in the optic disc region of patients with NTG and brain changes may be examined. The local volume of gray matter and white matter and the voxel value of each brain region were detected by using VBM-DARTEL analysis and the vascular density of the optic disc region was detected by OCTA. The correlation analysis

Table III. Comparison of volume results of cerebral gray matter, white matter and cerebral parenchyma between NTG group and HCs.

Indicators	NTG	HCs	t	P-value
Ectocinerea	715.3±62.7	706.9±59.3	0.581	0.543
White matter	332.8±45.3	344.5±48.6	-0.941	0.325
Brain substance	1,061.3±102.4	1,052.6±100.8	0.366	0.366

Values are expressed as the mean ± standard deviation. NTG, normal tension glaucoma; HCs, healthy controls.

Table IV. Comparison of different brain regions in local volume of brain essence between normal tension glaucoma group and healthy controls.

Brain region	Brodmann division	MNI coordinates (x, y, z)	Voxels (units)	t	P-value
Decreased volume of gray matter in brain					
Left middle frontal gyrus	9	-35, 1,37	56	2.923	<0.001
Right superior frontal gyrus	32	10, 32, 46	76	3.561	<0.001
Right precuneus	7	9, -59, 30	141	4.833	<0.001
Right angular gyrus	39	45, -55, 33	37	3.764	<0.001
White matter volume reduction area					
Right middle occipital gyrus	18	37, -74, 21	89	2.431	<0.001
White matter volume enlargement area					
Right precentral gyrus	4	32, -17, 56	117	4.982	<0.001

MNI, Montreal Institute of Neurology.

indicated an association between the measurements obtained with the two technologies. These analyses are conducive to better understanding the nature of the disease and may be used as an effective tool for exploring means of early diagnosis, the disease process and internal pathological changes of NTG. In the present study, OCTA was used to measure the vascular density in the optic disc area of patients with NTG as well as HC volunteers. The brain structure was analyzed using VBM-DARTEL with a 3.0 T MRI instrument. OCTA is a newly developed non-invasive fundus blood flow imaging technology. It is able to rapidly obtain vascular images of the optic disc and retina. Compared with traditional optical coherence tomography, OCTA has a higher resolution and faster scanning speed, and offers the advantages of real-time and non-invasive examination. It is able to quantitatively measure the vascular density of the optic disc and the surrounding retina using designated measurement software. It is a novel method currently used to detect the local microcirculation in the optic disc, allowing for early identification of glaucoma (15-18). The present study indicated that the vascular density in the optic disc region of the patients with NTG was significantly decreased compared with that in the HCs, and it increased with disease progression. These results suggested that the vascular density around the optic disc and in the entire region gradually decreases with disease progression. Other studies have also suggested that the vascular density in the deep retina decreases with disease progression (19-23). Therefore, the vascular density in the optic disc region has a higher diagnostic value for NTG and provides a novel method for the evaluation of this disease.

Processing of images with the VBM-DARTEL method indicated that the NTG group did not exhibit any significant differences in whole-brain gray matter, white matter or volume of brain parenchyma compared with those of the HCs. The volume of local gray matter areas (i.e., in the LMFG, RSFG, RP and RAG) decreased; however, there was no increase in the gray matter area. The volume of white matter in the RMOG decreased, whereas that in the right anterior central gyrus increased. The AUC values of the ROC curves for the diagnosis of NTG in these regions based on a local volume difference were all >0.5, indicating high diagnostic efficacy. In the NTG group, a good linear correlation between the regional volume change in brain structure and the vascular density of the optic disc was determined. The brain structure and the vascular density of the optic disc were able to provide a variety of non-invasive, reliable and reproducible indicators for the diagnosis of NTG. It was determined that NTG may not cause any changes in gray matter, white matter or brain parenchymal volume of the entire brain. This result may be due to the small number of samples included in the present study. Therefore, multicenter research studies with larger sample sizes are warranted.

The present study indicated that NTG is characterized by volume changes in the local gray and white matter in the brain, and these changes mainly involve a volume reduction. The changes in brain structure are mainly concentrated in

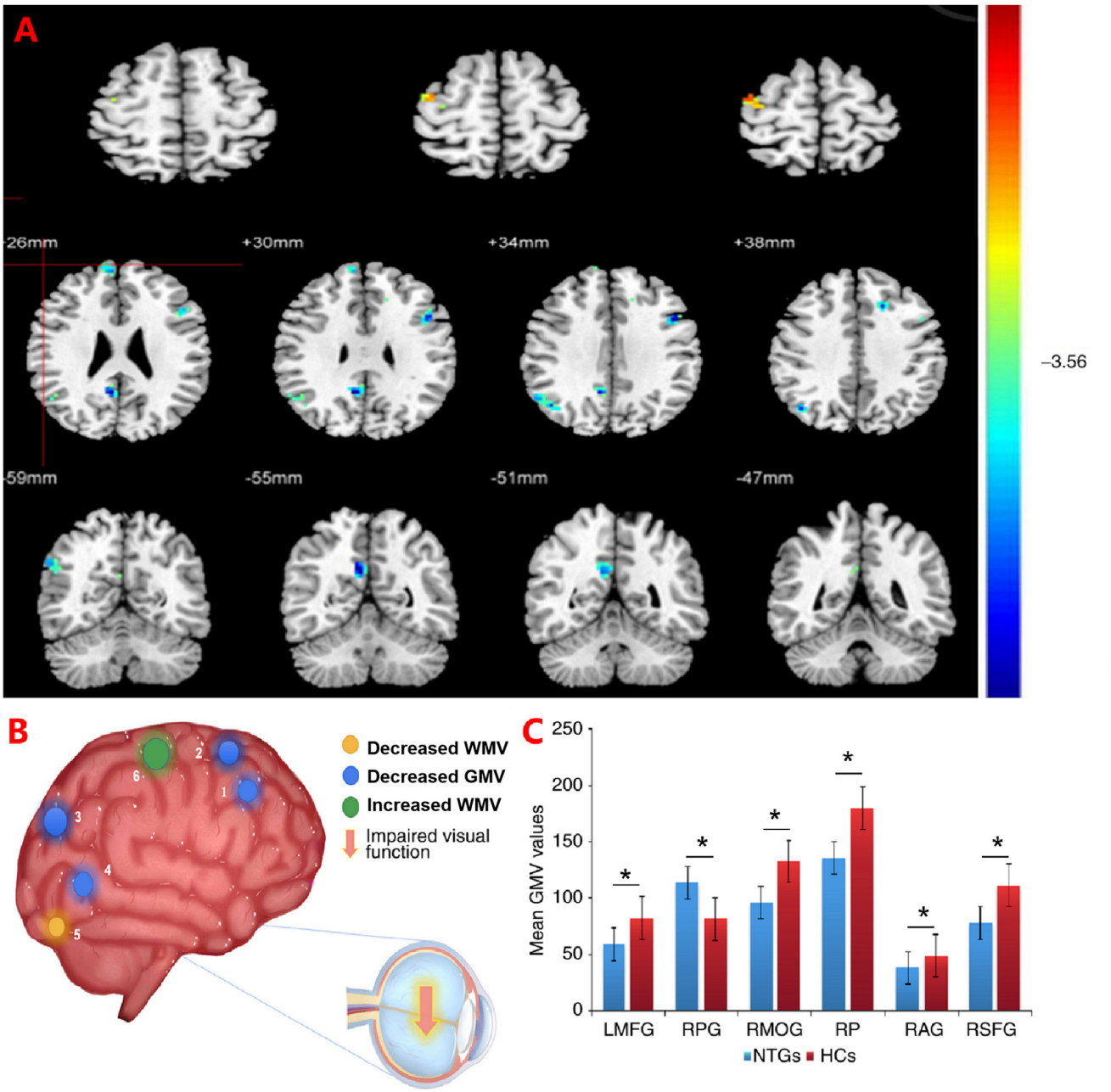

Figure 3. Significant differences in local brain volume between patients with NTG and HCs. (A) Brain regions with significant differences. The sizes of the spots denote the degree of quantitative changes. Differences were observed in the LMFG, RSFG, RP, RAG, RMOG and RPG. The yellow areas denote brain areas with a lower WMV and the green areas denote brain areas with a higher WMV in brain areas, while the blue areas denote brain regions with lower GMV in patients with NTG vs. HCs (P<0.001 for multiple comparisons using Gaussian random-field theory (z.2.3; P<0.001; cluster: >13 voxels; Alphasim-corrected). (B) 1-6 denote RSFG, LMFG, RAG, RP, RMOG and RPG, respectively. (C) Mean values of GMV were compared between the NTG group and HC group. The statistical threshold was set as voxels with P<0.01 for multiple comparisons using family-wise error correction (z>2.3; P<0.01; cluster: >40 voxels). *P<0.05. NTG, normal tension glaucoma; HCs, healthy controls; GMV, gray matter volume; WMV, white matter volume; LMFG, left middle frontal gyrus; RPG, right precentral gyrus; RMOG, right middle occipital gyrus; RP, right precuneus; RAG, right angular gyrus; RSFG, right superior frontal gyrus.

the frontal lobe (LMFG, RSFG, right anterior central gyrus), occipital lobe (RP and RMOG) and parietal lobe (RAG). The frontal lobe has a specific role in emotional decision-making, emotional self-regulation and inhibition of reaction. A study demonstrated that patients with glaucoma exhibit various degrees of functional deficits in emotional regulation, which may be closely linked to structural damage and dysfunction of this region in the frontal lobe (24). Similar to the results obtained in the present study, other studies have indicated that glaucoma is closely linked to various degenerative diseases of the central nervous system, mainly manifested by extensive atrophy of the brain (8,24). However, the observed increase in volume in the right anterior central gyrus is not in accordance with the results of the present study, and the specific mechanism underlying this difference remains elusive.

As the visual center, the occipital lobe is mainly involved in the functional activities of visual formation and perception. In the present study, the reduction in the volume of the right middle occipital gyrus in the occipital lobe region of

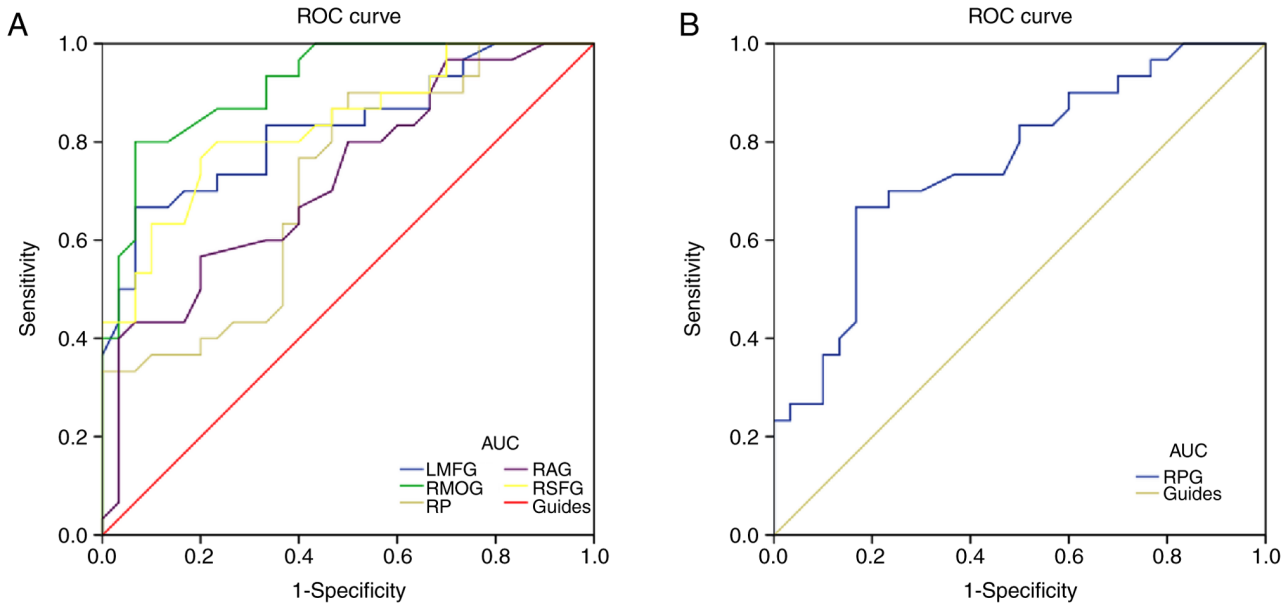

Figure 4. ROC curve analysis of the normal tension glaucoma mean gray matter volume values for altered brain regions. (A) AUC in brain areas with significant differences: LMFG, 0.827 (P<0.001; 95% CI: 0.722-0.932); RMOG, 0.918 (P<0.001; 95% CI: 0.851-0.985); RP, 0.718 (P=0.004; 95% CI: 0.588-0.847); RAG, 0.726 (P=0.003; 95% CI: 0.598-0.853); and RSFG, 0.834 (P<0.001; 95% CI: 0.733-0.935). (B) The area under the ROC curve for RPG was 0.757 (P=0.001; 95% CI: 0.635-0.879). ROC, receiver operating characteristic; AUC, area under the ROC curve; LMFG, left middle frontal gyrus; RMOG, right middle occipital gyrus; RP, right precuneus; RAG, right angular gyrus; RSFG, right superior frontal gyrus; RPG, right precentral gyrus.

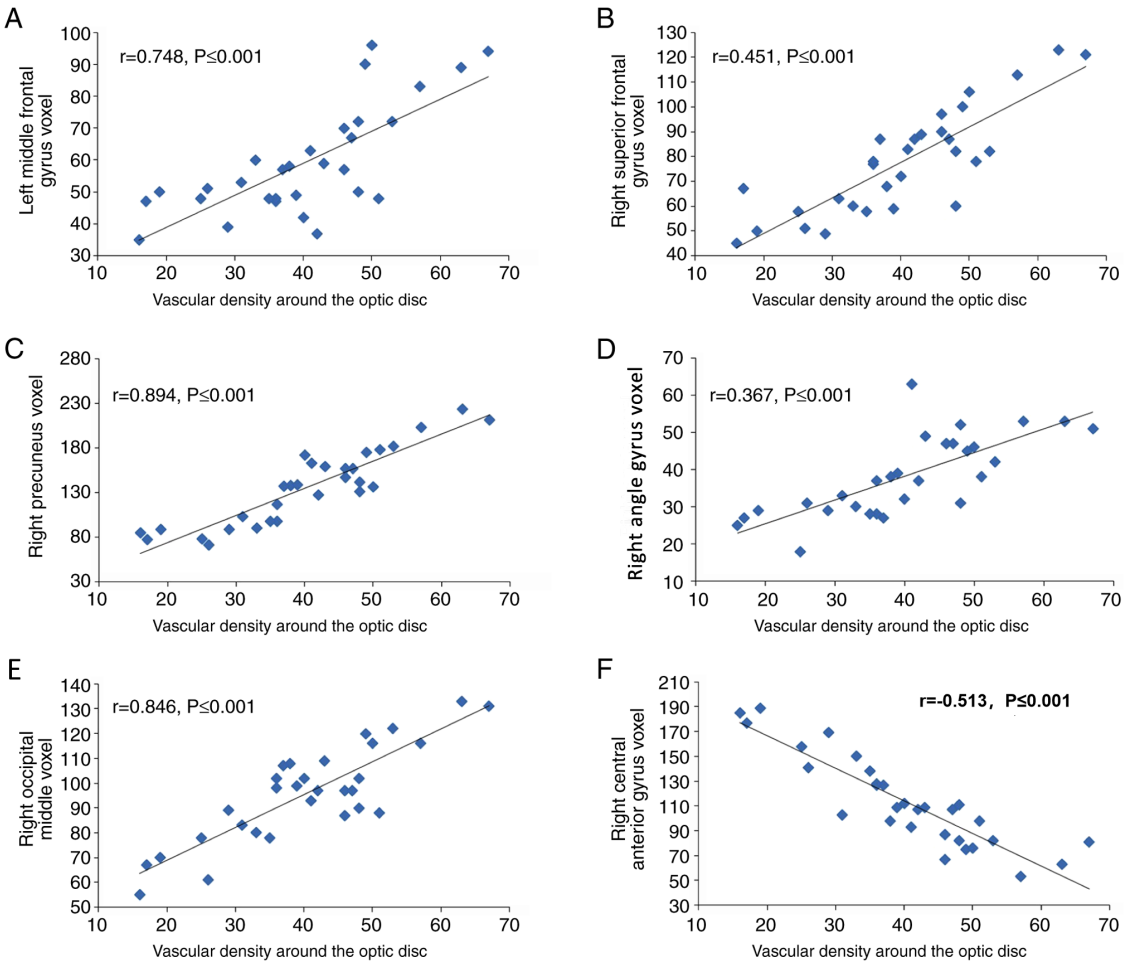

Figure 5. Correlations between the local volume difference and the vascular density of the optic disc area in the normal tension glaucoma group. The vascular density of the optic disc region was positively correlated with the voxel value of the (A) left middle frontal gyrus voxel (r=0.748, P≤0.001), (B) left middle frontal gyrus voxel (r=0.451, P≤0.001), (C) right precuneus (r=0.894, P≤0.001), (D) right angle (r=0.367, P≤0.001), (E) right occipital middle (r=0.846, P≤0.001). (F) The vascular density of the optic disc region was negatively correlated with the voxel value of the right central anterior gyrus (r=0.513, P≤0.001).

patients with NTG was also supported by the fact that the occipital lobe exhibited local atrophy in such patients. The parietal lobe is an important region that connects the somatosensory, visual and auditory systems of the brain (24). The specific mechanism underlying the changes in the parietal lobe caused by damage to the angular gyrus in NTG remains elusive. However, the present evidence confirms, to a certain extent, the close association between glaucoma and central neuropathy. Chen *et al* (8), Li *et al* (24), Williams *et al* (25) and Wang *et al* (26) used magnetic resonance technology to study the pathogenesis of glaucoma from multiple perspectives, demonstrating changes in the total visual pathway from the retina to the visual cortex. They identified lesions in numerous associated brain regions that correlated with disease severity. In different studies, the abnormal brain areas are not exactly the same, but they all go beyond the visual cortex, suggesting that glaucoma may have a wide impact on the nervous system. Hence, damage associated with glaucoma is complex and extensive (27,28).

In conclusion, OCTA and VBM-DARTEL technologies were used to detect a wide range of ocular and cerebral parenchymal structural abnormalities in patients with NTG, identifying a significant correlation between the two. These technologies are expected to provide non-invasive diagnostic imaging support to improve the clinical diagnosis of early NTG, therapies and prediction of prognosis, as well as facilitate the exploration of the pathophysiology of NTG. However, additional multicenter studies with larger sample sizes are warranted to verify the value of these technologies in assessing the anatomical structure and function in patients with NTG.

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Availability of data and materials

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

Authors' contributions

HLL and YS designed the study. QZ and CGP recruited healthy controls. JJ performed MRI scanning. TP, BL and XMC collected and analyzed the data. HLL wrote the manuscript. HLL and YS confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The methods and protocols of the study were approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University (Nanchang, China) and followed the principles of the Declaration of Helsinki. All subjects were informed of the objectives and content of the study and latent risks, and then provided written informed consent to participate.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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