# Altered Static and Dynamic Voxel-mirrored Homotopic Connectivity in Patients With Frontal Glioma

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# Abstract

Contralateral regions play critical role in functional compensation in glioma patients. Voxel-mirrored homotopic connectivity (VMHC) characterizes the internal functional connectivity of the brain, which is considered to have a regional functional basis. This study aims to investigate the alterations of brain regional function and VMHC in patients with frontal glioma, and further investigate physiological significance of these alterations.

We enrolled 22 patients with frontal glioma and 22 demography matched healthy controls (HC). We determined degree centrality (DC), regional homogeneity (ReHo), and VMHC to investigate the alterations of regional function and internal functional connectivity in patients. Furthermore, partial correlation analysis was conducted to explore the relationship between these indicators and cognitive functions.

Compared with HC, patients showed decrease in static VMHC, DC, ReHo and dynamic ReHo (dReHo) within right middle frontal gyrus (MFG.R), left middle frontal gyrus (MFG.L), right precuneus(PCUN.R), left precuneus(PCUN.L), left limbic lobe (LIMB.L), right superior frontal gyrus (SFG.R), right postcentral gyrus (POCG.R), right inferior parietal lobule (IPL.R), but increase in dynamic VMHC (dVMHC) within PCUN.R and PCUN.L. Meanwhile, MFG.R with decreased VMHC, LIMB.L with decreased DC, LIMB.L with decreased ReHo, and PCUN.R with increased dVMHC were significantly positively correlated with cognitive function, but the SFG.R with decreased DC was significantly negatively correlated with memory.

This study preliminarily confirmed glioma not only cause regional dysfunction, but also disturb long-distance functional connectivity, and the long-distance functional connectivity showed strong instability in patients with frontal glioma. Meanwhile, the altered functional indicators may compensate cognitive function in patients with frontal glioma.


# 1. Introduction

Glioma, which is the most common primary malignant brain tumor in adults, can occur anywhere in the central nervous system (CNS), but mainly in the brain and glial tissue(Ostrom et al., 2014). With the progressive development of glioma in the brain, it often causes alterations in the cerebrum structure of patients, and even causes shifting of the midline in the cerebrum. In addition to the alterations of physiological structure, the infiltration of glioma often causes the alterations of brain function and the functional connectivity (FC) and has corresponding effects on cognitive function. These effects of glioma are not localized frequently and may cause alterations structurally and functionally in distant brain regions in patients with glioma. For instance, it has been found in some studies that patients with unilateral temporal glioma existed homotopic compensatory increase in gray matter (GM) volume and amplitude of low-frequency fluctuation (ALFF) in the contralateral temporal lobe(Hu et al., 2020; D. Liu et al., 2020). Almairac et al. also came to the similar foundings in their studies that there is not only an increase in contralateral GM volume but also an alteration in FC in patients with insular glioma(F. Almairac et al., 2021; Fabien Almairac, Duffau, & Herbet, 2018), which reminded us that the undamaged

contralateral brain region played a crucial role in functional compensation in patients with glioma. It may help us better understand the potential compensatory patterns and protect cognitive function in patients with glioma by exploring homotopic alterations in brain.

Voxel-mirrored homotopic connectivity (VMHC) characterizes the internal functional structure of the brain by quantifying the FC between each voxel in one hemisphere and the mirror voxel in the opposite hemisphere(Zhang et al., 2017). Therefore, we could explore the FC between the voxels of the two brain hemispheres in patients with glioma by applying VMHC. VMHC is altered in many psychiatric and neurological disorders(Anderson et al., 2011; Hermesdorf et al., 2016; Kelly et al., 2011), such as the major depressive disorder, early-onset schizophrenia, amyotrophic lateral sclerosis, and stroke(J. Chen et al., 2021; W. Guo et al., 2013; H. J. Li, Xu, Zhang, Hoptman, & Zuo, 2015; Y. Wang et al., 2015; Zhang et al., 2017). These previous studies consistently suggested that the alterations of VMHC were strongly correlated with cognitive function, which suggested that VMHC could be well used to explore the alterations of homotopic function and its physiological significance in many brain diseases. From many previous studies, we are aware of that it clearly show homotopic functional and structural alterations in patients with glioma(F. Almairac et al., 2021; Fabien Almairac et al., 2018; Dongming Liu, 2019; Hu et al., 2020; Y. Liu et al., 2020), suggesting that the healthy contralateral brain regions play a crucial role in compensating for disease progression. Therefore, we can speculate that VMHC can be well used to explore the homotopic functional alterations in patients with glioma.

Functional magnetic resonance (fMRI) has been widely used in the prospective study of glioma and has made great contributions to the investigation of the potential mechanism of glioma. Some brain regions with certain correlation between FCs form some networks with specific functions, such as motor, language, visuo-spatial, and executive functions(Duffau, 2015; Park & Friston, 2013). As stated previously, the large number of data using fMRI to compare glioma patients with HCs indicated that tumor-induced brain FC alterations were not only localized, but also support the effect of tumors across a broad network(Duffau, 2020). For instance, Lang et al. showed that glioma patients have increased FC of the superior parietal cortex (SPC) within the tumor-affected hemisphere. However, some researchers found different alteration of FC in executive control network (ECN)(Y. Liu et al., 2020; Maesawa et al., 2015). Meanwhile, Liu et al. found there existed cross-network functional reorganization of the salience network (SN), default mode network (DMN), and ECN) in patients with frontal glioma. Although many studies have explored the changes of FC within specific, between networks or between distant brain regions, few studies have systematically studied the effect of VMHC in patients with glioma.

Both degree centrality (DC) and regional homogeneity (ReHo) represented the regional functional features within the brain based on voxels. DC represented the number of direct connections between certain given voxels(Di Martino et al., 2013; Zuo et al., 2012), while ReHo represented the consistency in regional spontaneous neural activity(Zang, Jiang, Lu, He, & Tian, 2004). There exists not only abnormal FC, but also abnormal alterations in regional functional parameter (ReHo and DC) in many diseases, such as the parkinson's diseases, early psychosis, major depressive disorder, and migraineurs(X. Chen et al., 2019; M. Guo et al., 2020; Sun et al., 2018; Tang et al., 2019; Zhang et al., 2016). Actually, there are also regional

functional alterations in patients with glioma(Agarwal, Sair, & Pillai, 2017; Y. Liu et al., 2020). However, the alterations of regional indicators in patients with frontal glioma and their clinical significance are still remaining unclear. Meanwhile, the regional functional basis of altered homotopic connectivity also remain unclear.

Therefore, in the present study, we aim to investigate the alterations of VMHC in patients with frontal glioma. Moreover, we attempt to invetigate not only the hemispheric variations of VMHC, but also the variations of regional function, such as DC and ReHo. In addition, we also explored the dynamic variability of VMHC, DC, and Reho to further measure the static and dynamic functional alterations in patients with frontal glioma. Finally, we attempt to explain the physiological significance of the changes in these indicators by analyzing the correlation between these indicators and scale scores. We hypothesized that alterations of static and dynamic VMHC, DC, and ReHo may be compensations of cognitive function in patients with frontal glioma.

# 2. Methods

## 2.1 Participants enrollment

We enrolled 22 patients with frontal glioma (mean age 45.55 ± 11.64) and 22 demographically matched HCs (mean age 54.82 ± 8.51) with no brain disorders or diseases in this study. Data used in this study were obtained from the Nanjing Brain Hospital-Brain Tumor Neuroimaging Project (NBH-BTnp) database, which is summarized in Supplemental Data Methods S.1. All of the participants in this study were right-handed Chinese descent. Patients must meet the following criteria for inclusion: (1) All patients underwent surgery, and postoperatively histopathologic examination showed frontal glioma; (2) There was no history of drug or alcohol addiction or abuse and no history of head trauma in the patients; (3) The patients had no contraindications to Magnetic Resonance Imaging (MRI) and there were no metal implants in vivo that were not suitable for MRI; (4) The patients had no prior neuropsychiatric disease and had not used psychoactive substances in the past month. HCs must meet the last three criteria above and have no history of brain disease or traumatic brain injury. To ensure that these individuals did not have a history of systemic disease, head trauma, or psychological disorders, we evaluated HC using unstructured clinical interviews. This study was approved by the Institutional Ethical Committee for Clinical Research of the Affiliated Brain Hospital of Nanjing Medical University. Written informed consent was obtained from all participants. However, the data of subjects are not publicly available due to privacy or ethical restrictions.

## 2.2 MRI data acquisition

We acquired all MRI images from 3.0 Tesla Verio Siemens scanner, which equipped with an 8-channel head radiofrequency coil in the Department of Radiology in the Affiliated Brain Hospital of Nanjing Medical University. Notably, the MRI images of all patients were obtained preoperatively from 2013 to 2019.

The 3-dimensional (3D) T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) scans were axially acquired using the following acquisition parameters: repetition time (TR) = 1.9 seconds, echo time (TE) = 2.49 ms, time inversion (TI) = 900 ms, matrix = 256 x256, flip angle (FA) = 90°, slice thickness = 1 mm, and gap = 0.5 mm, and slice number = 176 slices covering the whole brain.

Two sets of scanning parameters were used to obtain the resting-state functional images of subjects in the same scanner, including 140/240 volumes. We detailed the image acquisition parameters in the Supplemental Data Methods S.2 according to our previously published study(Y. Liu et al., 2020). In this study, different parameters have nothing to do with the purpose of the study, only optimizing imaging protocol. Although the data in this study had different parameters, different parameters were also considered as non-interest covariates in subsequent studies.

## 2.3 Neurocognitive assessments

All participants included in the present study were evaluated during a standardized clinical interview and neurocognitive tests which were performed by two experienced neuropsychologists to ensure the reliability of the results. Subjects were conducted the following neurocognitive tests: digit span test (DST), memory test, visuospatial test, math exam test, digital symbol substitution test (DSST), mapping test, and similarity test.

## 2.4 Image preprocessing

All images were reviewed by a neuroradiologist to insure there were no artifact or midline shift. The MRI images were preprocessed using the Data Processing and Analysis of Brain Imaging (DPABI)(Yan, Wang, Zuo, & Zang, 2016) based on Statistical Parametric Mapping (SPM) program, version 8 (http://www.fifil.ion.ucl.ac.uk/spm) running on MATLAB2014a (http://www.mathworks.com/products/matlab/) environment. We detailed the preprocessing steps in Supplemental Data Methods S.3.

## 2.5 Static VMHC, DC, and ReHo calculation

By using our defined gray matter mask, we calculated DC (threshould 0.25) and ReHo (performed on unsmoothed images). A symmetric brain mask was applied. VMHC maps were computed for each participant by calculating Fisher z-transformed Pearson correlations between each voxel and its mirrored counterpart in the opposite hemisphere.

## 2.6 Dynamic VMHC, DC, and ReHo calculation

We calculated the dynamic parameter using the temporal dynamic analysis tool box of DPABI(Yang et al., 2020). By using our defined gray matter mask, we set the window size of 10, window step of 1, window type of harmming to calculate the dynamic VMHC (dVMHC), dynamic DC (dDC, threshould 0.25), and dynamic ReHo (dReHo, cluster 27) to further analysis.

## 2.7 Statistical analysis

## 2.7.1 Demographic and neurocognitive characteristics

Two-sample t-test was performed among patients and HCs on age and education for the statistical analysis of the patients' demographics. We performed a $\chi 2$ test for sex ratio among aubjects. Comparation of neurocognitive scores between HCs and glioma patients was conducted using two-sample t-test with Bonferroni corrected p-value of $p < 0.05/7$.

## 2.7.2 Static and dynamic difference of VMHC, DC, and ReHo

Analyses were performed using age, education, gender, and scanning parameters as covariates. Two-sample t-test was used to compare the VMHC, DC, and ReHo values between patients and controls by using the DPABI toolkit. The TFCE-FWE–corrected p-value of $p < 0.05$ was considered statistically significant in DC, and ReHo, but $p < 0.01$ in VMHC. The times of permutation were set to 1000 times and the cluster size was set at 50. The Fisher z-transformed CV matrices of dVMHC, dDC, and dReHo were compared between patients and HCs by two-sample t-test by DPABI toolkit. Gaussian random field (GRF) correction was conducted in dynamic analyses with voxel-level $p < 0.01$, cluster-level $p < 0.001$, and cluster size of 50.

## 2.7.3 The clinical significance of altered static and dynamic of VMHC, DC, and ReHo in patients

Correlation analysis was performed between neurocognitive scores and the altered VMHC to investigate the relationship between cognitive function and altered VMHC in patients with frontal glioma,. Meanwhile, we controlled the effect of age, education, gender, and scanning parameters in correlation analyses. However, due to data loss or incomplete cognitive scale assessment, we conducted correlation analyses with scale data for about half of the patients. Bonferroni correction of $p < 0.05/7$ was considered as statistically significant. Dynamic VMHC, static and dynamic DC and ReHo were conducted the same correlation analysis described above.

We used the Statistical Package for the Social Sciences (SPSS) for Windows, version 22 (SPSS, Chicago, IL, USA) as the statistical tool in all the statistical analysis.

# 3. Results

## 3.1 Demographic and clinical information of the subjects

We summarized the demographic and clinical information of the subjects in the Table 1 and Table 2. There were no significant difference in education and sex ratio. However, age between patients and controls existed significant difference ($p = 0.004$). Cognitive scores showed that there existed significant difference between patients and HCs in visuospatial test, math exam, DSST, mapping, and similarity.

Table
1

## 3.2 Comparisions of static VMHC, DC, and ReHo between patients and the HCs

When we compared the VMHC between patients and HCs, we found there were several reduced clusters in the right middle frontal gyrus (MFG.R), left middle frontal gyrus (MFG.L), right precuneus (PCUN.R), left precuneus (PCUN.L) (Table 3 and Fig. 1). Compared with HCs, patients with frontal glioma showed reduced DC in left limbic lobe (LIMB.L), right superior frontal gyrus (SFG.R), and right postcentral gyrus (POCG.R) (Table 3 and Fig. 2). Interestingly, when compared ReHo between patients and the HCs, we found similar reduction in the LIMB.L of patients with frontal glioma (Table 3 and Fig. 3).

## 3.3 Comparisions of dynamic VMHC, DC, and ReHo between patients and the HCs

When we compared the dVMHC between patients and HCs, we found there were two incresed clusters in the PCUN.R and PCUN.L (Table 3 and Fig. 4). Compared with HCs, patients with frontal glioma showed no significant difference when we compared dDC among groups. There was reduced dReHo in the right inferior parietal lobule (IPL.R) in patients with frontal glioma compared with controls(Table 3 and Fig. 4).

## 3.4 Correlation between the altered intrinsic functional parameter and clinical characteristic

In the correlation analysis of VMHC, Pearson's partial correlation analysis revealed that the reduced VMHC value in MFG.R was significantly positively correlated with visuospatial scores ($r = 0.8820$, $p = 0.0017$, Fig. 1). When we conducted correlation analyses, there existed significantly positive correlation between reduced DC value in LIMB.L and mapping scores($r = 0.9864$, $p = 0.0000$, Fig. 2), but significantly negative correlation reduced DC value in SFG.R and memory scores($r=-0.7998$, $p = 0.0097$, Fig. 2). Analogously, the reduced ReHo value in LIMB.L was significantly positively correlated with mapping scores($r = 0.8561$, $p = 0.0032$, Fig. 3). After statistical analysis of dynamic parameters and cognitive scores, we only found increased dVMHC value in PCUN.R was significantly positively correlated with similarity scores($r = 0.8948$, $p = 0.0011$, Fig. 4).

# 4. Discussion

In this study, patients with frontal glioma showed decreased homotopic connectivity and decreased regional function in resting state, which indicated that tumors can not only cause regional dysfunction but also disturb long-distance functional connectivity in patients with frontal glioma. The increased dVMHC revealed an upward tendency in the fluctuation of long-distance homotopic connectivity,but the reduced dReHo indicated a reduced fluctuation of regional function in patients with frontal glioma, which indicated that long-distance functional connectivity showed stronger instability in patients with frontal

glioma. The correlation between the alterations of these indicators and cognitive function on the one hand revealed the decline of cognitive function with the progression of glioma, and on the other hand, it also reflected that there may be some brain regions with abnormally increased activities in glioma patients that compensate for some cognitive functions.

VMHC changed vary according to the types of disease and the different progression of the disease in many neurological and psychiatric diseases(Mancuso et al., 2019; Q. Wang et al., 2018; Zhu et al., 2016). Some researchers have found decreased homotopic connectivity, called VMHC, in some brain regions in patients with medial temporal lobe epilepsy and schizophrenic patients(W. Guo et al., 2018; Xu et al., 2014). In fact, alterations of VMHC not only exist in benign diseases, but also in glioma patients. Some researchers have found that preoperative homotopic connectivity of glioma patients was significantly reduced(Coget et al., 2018), which is consistent with the foundings of our study. We found that VMHC was reduced in both left and right frontal lobes (MFG.R, MFG.L) and left and right precuneus (PCUN.R, PCUN.L) in patients with frontal glioma. The frontal lobe is an important functional brain region of ECN(J. Chen et al., 2016; Dosenbach et al., 2007; Seeley, Crawford, Zhou, Miller, & Greicius, 2009), and the medial prefrontal lobe is an important component of the human brain DMN(Raichle, 2015), while the precuneus is a relatively core functional region in the DMN(Cunningham, Tomasi, & Volkow, 2017; R. Li et al., 2019). In this study, patients with frontal glioma showed not only functional alterations in the frontal lobe but also alterations in the precuneus. Such VMHC changes may be caused by alterations within the DMN of glioma patients, or the functional changes between the ECN and DMN caused by the tumor. This also confirmed that the impact of regional tumors was not localized, but existed a wide range of effects. This study provided a new perspective for the functional change pattern of frontal glioma, revealed that there may exist functional compensation within or between networks caused by neurologic deficits by the effects of regional tumors.

Both DC and ReHo reflected the regional function within the brain based on voxels(Di Martino et al., 2013; Zang et al., 2004; Zuo et al., 2012). In this study, frontal glioma patients showed decreased DC in LIMB.L, SFG.R and POCG.R. Interestingly, patients also showed reduced ReHo in LIMB.L. The limbic lobes are located in the medial side of the cerebral hemisphere, which is close to the corpus callosum. The analysis of ReHo and DC both revealed that the limbic lobes showed decreased local function, which may be the regional functional basis for the decreased homotopic connectivity. The regional functional decline of DC in the frontal lobe and posterior central gyrus may be caused by the localized influence of frontal glioma itself.

In various brain disorders, multiple functional indicators also fluctuate over time(Y. Li et al., 2020; Schumacher et al., 2019; Zarghami & Friston, 2020), thus we also explored the changes of dynamic VMHC, DC and REHO in patients with frontal glioma. In the present study, we found that patients with frontal glioma showed increased dVMHC in PCUN.R and PCUN.L and decreased dReHo in IPL.R. VMHC was decreased in precuneus, while dVMHC was increased in precuneus, suggesting that patients with frontal glioma may have decreased symmetrical homotopic connectivity due to tumor infiltration, but long-distance brain functional connectivity showed a more unstable pattern than normal subjects. Indeed,

dDC in the inferior parietal lobule of patients in this study showed a downward trend, indicating that the local functional fluctuation of glioma was decreased.

The frontal lobe played a crucial role in cognitive control(Badre & Nee, 2018; Wiggins et al., 2019). Therefore, by using correlation analysis, we also explored the relationship between various cognition and functional indicators to find the clinical significance of alterations in functional indicators. The VMHC value of MFG.R region was significantly positively correlated with the visuospatial score, the DC value of LIMB.L region was significantly positively correlated with the mapping score, and the ReHo value of LIMB.L region was significantly positively correlated with the mapping score, while the reduced DC value of SFG.R region was significantly negatively correlated with the memory score. All the above positive correlations indicated that the higher the functional indicators, the higher the cognitive score, indicating a strong correlation between functional indicators and clinical practice. Meanwhile, the negative correlation between DC and memory also indicated that there must be some brain regions compensate DC. Indeed, these results reflected the progression of the disease, the more the compensatory increase, the more serious progression of the disease, which is highly consistent with the results of previous studies(Hu et al., 2020; D. Liu et al., 2020). Besides, the increased dVMHC in the PCUN.R region was positively correlated with the similarity test scores, suggesting that the increased fluctuation of symmetrical homotopic connectivity in glioma patients may be a potential biological model of cognitive compensation.

# 5. Conclusion

In summary, it is preliminarily confirmed that glioma not only cause regional dysfunction, but also disturb long-distance functional connectivity, and the long-distance functional connectivity showed strong instability in patients with frontal glioma. Meanwhile, the correlation analyses indicated that the altered functional indicators may compensate cognitive function in patients with frontal glioma. Long-distance functional protection may be more conducive to recovery of glioma patients.

# 6. Limitation

The limitations of this study are as follows: first, the sample size is relatively insufficient, and we believe that the study with a larger sample size may be more conducive to the general applicability of the research results. Our research team will also continue to collect subjects to conduct a larger study to determine the generality of the results. Second, in this study, there was a statistical difference in age between groups. However, in the statistical analysis, age was included as a covariable to eliminate the impact of age difference on results.

# Declarations

### Ethical Approval

his study was approved by the Institutional Ethical Committee for Clinical Research of the Affiliated Brain Hospital of Nanjing Medical University.

### Consent to Participate

Written informed consent was obtained from the participants for the publication of any potentially identifiable images or data included in this article.

### Consent to Publish

All authors read, revised and approved the final version of the manuscript.

### Authors Contributions

Conceived and designed the experiments: Jiu Chen, Guanjie Hu, Xinhua Hu. Preprocessed and analyzed MRI data: Guanjie Hu, Jiu Chen. Contributed materials/analysis tools: Xinhua Hu, Kun Yang, Chaoyong Xiao, Xiao Hu, Hongyi Liu. Preparation of the article, figures, and tables: Guanjie Hu, Honglin Ge, Dongming Liu, Jiu Chen, Xinhua Hu, Yong Liu, Yuanjie Zou, Zijuan Jiang.

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### Competing Interests

The authors declare that they have no conflict of interest.

### Availability of data and materials

Due to privacy or ethical restrictions, the data and materials were not publicly available.

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# Tables

***Table1*** **Demographic characteristics of patients with gliomas and healthy control**

| **Variable** | Patients | HC | $T/\chi^2$ | ***p*** **values** |
|---|---|---|---|---|
| No. | 22 | 22 | NA | NA |
| Age, year | 45.55±11.64 | 54.82±8.51 | 3.016 | 0.004* |
| Education, year | 9.23±2.81 | 10.14±4.49 | 0.806 | 0.425 |
| Sex ratio, F/M, n | 13/9 | 11/11 | 0.367 | 0.545 |
| Handedness | R | R | NA | NA |

Abbreviation: R, right-handed; HCs, healthy controls; NA, not applicable. Data were expressed as the mean ± standard deviation. * significant differences were found between groups. The *p*-values were determined using two-sample *t*-test for age and education; however a $\chi^2$ test was used for sex ratio.

*Table2* **Cognitive scores of patients with gliomas and healthy controls**

| Cognitive domain | Patients | HCs | *p* values |
|---|---|---|---|
| DST | 7.89±5.84 | 11.00±2.67 | 0.179 |
| Memory test | 6.44±5.00 | 11.88±1.55 | 0.010 |
| Visuospatial test | 4.33±3.97 | 10.63±1.60 | 0.001* |
| Math exam | 5.67±4.03 | 10.63±2.00 | 0.007* |
| DSST | 4.56±5.70 | 11.88±1.64 | 0.003* |
| Mapping | 4.00±2.01 | 9.88±0.64 | 0.000* |
| Similarity | 5.33±3.32 | 10.00±1.07 | 0.002* |

Abbreviation: HCs, healthy controls; DST, Digit Span Test; DDST, Digital Symbol Substitution Test. Each cognition scores of patients with gliomas and HCs were expressed as the mean ± standard deviation. The significant cognitive scores were obtained by two-sample *t*-tests and *p*-values of less than 0.007 (Bonferroni corrected p-value of <0.05/7) was considered statistically significant, symbolized with *.

*Table3* **Peak locations of regions after comparisons between healthy controls and glioma patients**

| Variables | Regions | Peak location (MNI Coordinates) | | | Cluster size (voxels) | T |
|---|---|---|---|---|---|---|
| | | X | Y | Z | | |
| **VMHC** | MFG.R | 42 | 24 | 30 | 89 | 4.8987 |
| | MFG.R | 27 | 15 | 57 | 289 | 5.1429 |
| | MFG.L | -6 | 21 | 63 | 66 | 4.5675 |
| | PCUN.R | 12 | -54 | 60 | 391 | 6.3283 |
| | PCUN.L | -12 | -54 | 60 | 364 | 6.3283 |
| | MFG.L | -27 | 15 | 57 | 102 | 5.1429 |
| **DC** | LIMB.L | 0 | 15 | 36 | 180 | 4.3145 |
| | SFG.R | 18 | -6 | 72 | 201 | 5.3008 |
| | POCG.R | 18 | -30 | 60 | 65 | 6.3043 |
| **ReHo** | LIMB.L | 0 | -3 | 39 | 196 | 5.1773 |
| **dVMHC** | PCUN.R | 3 | -54 | 51 | 79 | -4.1179 |
| | PCUN.L | -3 | -54 | 51 | 79 | -4.1179 |
| **dReHo** | IPL.R | 69 | -45 | 24 | 102 | 5.2161 |

Abbreviation: HCs, healthy controls; VMHC, voxel-mirrored homotopic connectivity; DC, degree centrality; ReHo, regional homogeneity; dVMHC, dynamic voxel-mirrored homotopic connectivity; dReHo, dynamic regional homogeneity; MFG.R, right middle frontal gyrus; MFG.L, left middle frontal gyrus; PCUN.R, right precuneus; PCUN.L, left precuneus; LIMB.L, left limbic lobe; SFG.R, right superior frontal gyrus; POCG.R, right postcentral gyrus; IPL.R, right inferior parietal lobule. All results were obtained after controlling effects of age, gender, education. The results of VMHC were tfce fwep corrected with $p$ 0.01 and voxel 50. The results of DC were tfce fwep corrected with $p$ 0.05 and voxel 50. The results of ReHo were tfce fwep corrected with $p$ 0.05 and voxel 50. The results of dVMHC were grf corrected with voxel $p$ 0.01 cluster $p$ 0.001 (two tailed) and voxel 50. The results of dReHo were grf corrected with voxel $p$ 0.01 cluster $p$ 0.001 (two tailed) and voxel 50.

# Figures

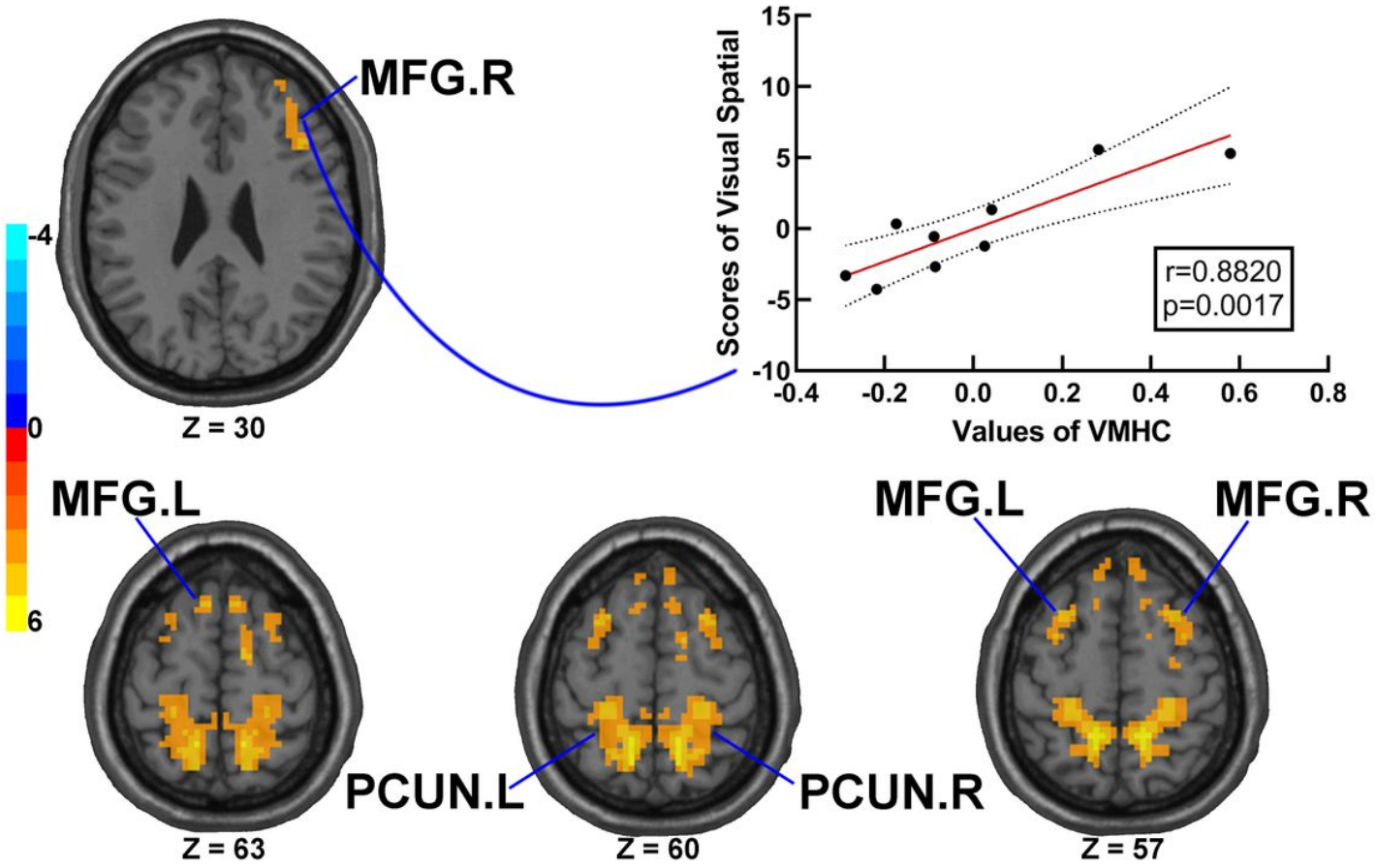
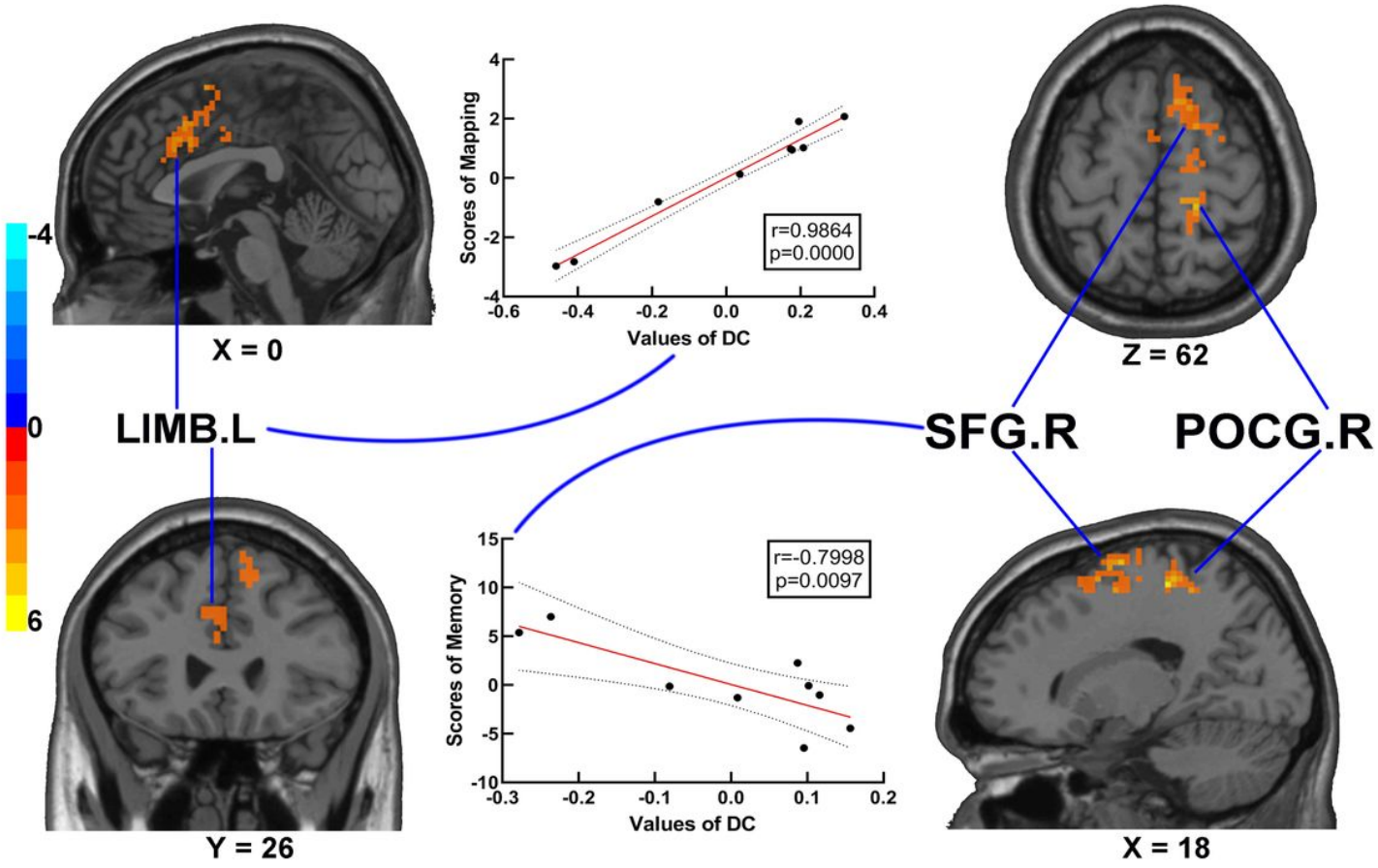



**Figure 1**

Alterations of VMHC and its relationship with cognitive functiopn in patients with frontal glioma Abbreviation: MFG.R = right middle frontal gyrus, MFG.R = left middle frontal gyrus, PCUN.L = left precuneus, PCUN.R = right precuneus. Patients with frontal glioma showed dereased VMHC in the above brain regions. Indeed, the VMHC value of MFG.R is significantly positively correlated with the visuospatial scores




## Figure 2

Alterations of DC and its relationship with cognitive functiopn in patients with frontal glioma
Abbreviation: LIMB.L = left limbic lobe; SFG.R = right superior frontal gyrus; POCG.R = right postcentral gyrus. Patients with frontal glioma showed dereased DC in the above brain regions. Indeed, the DC value of LIMB.L is significantly positively correlated with the mapping scores. However, the DC value of SFG.R is significantly negatively correlated with the memory scores.

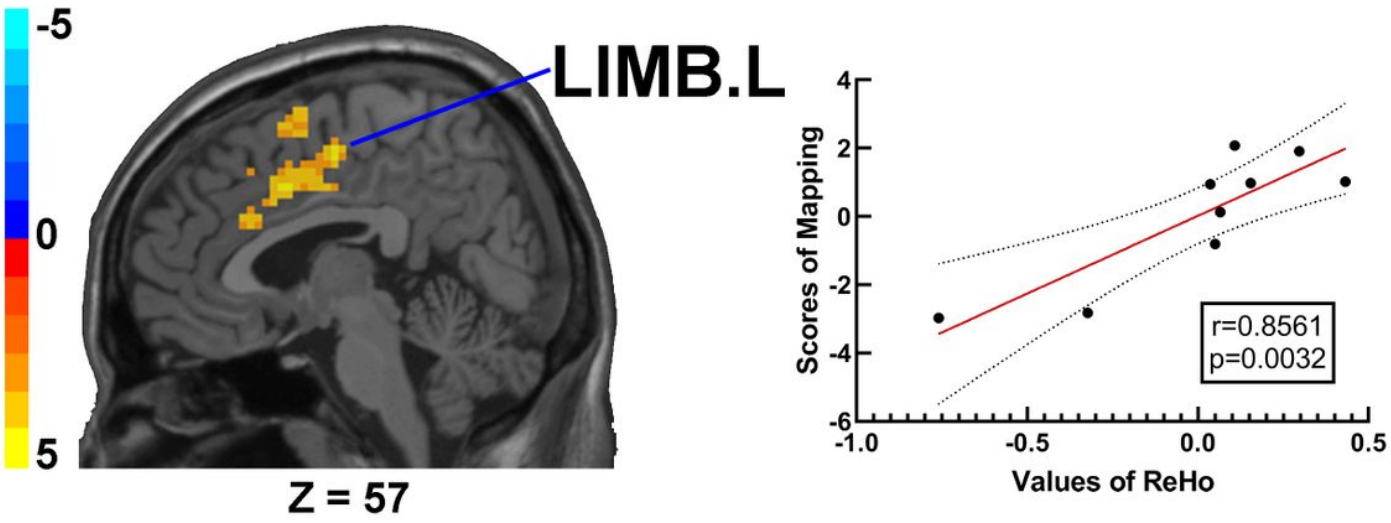


**Figure 3**

Alterations of ReHo and its relationship with cognitive functiopn in patients with frontal glioma Abbreviation: LIMB.L = left limbic lobe. Patients with frontal glioma showed dereased ReHo in LIMB.L. Indeed, the ReHo value of LIMB.L is significantly positively correlated with the mapping scores.

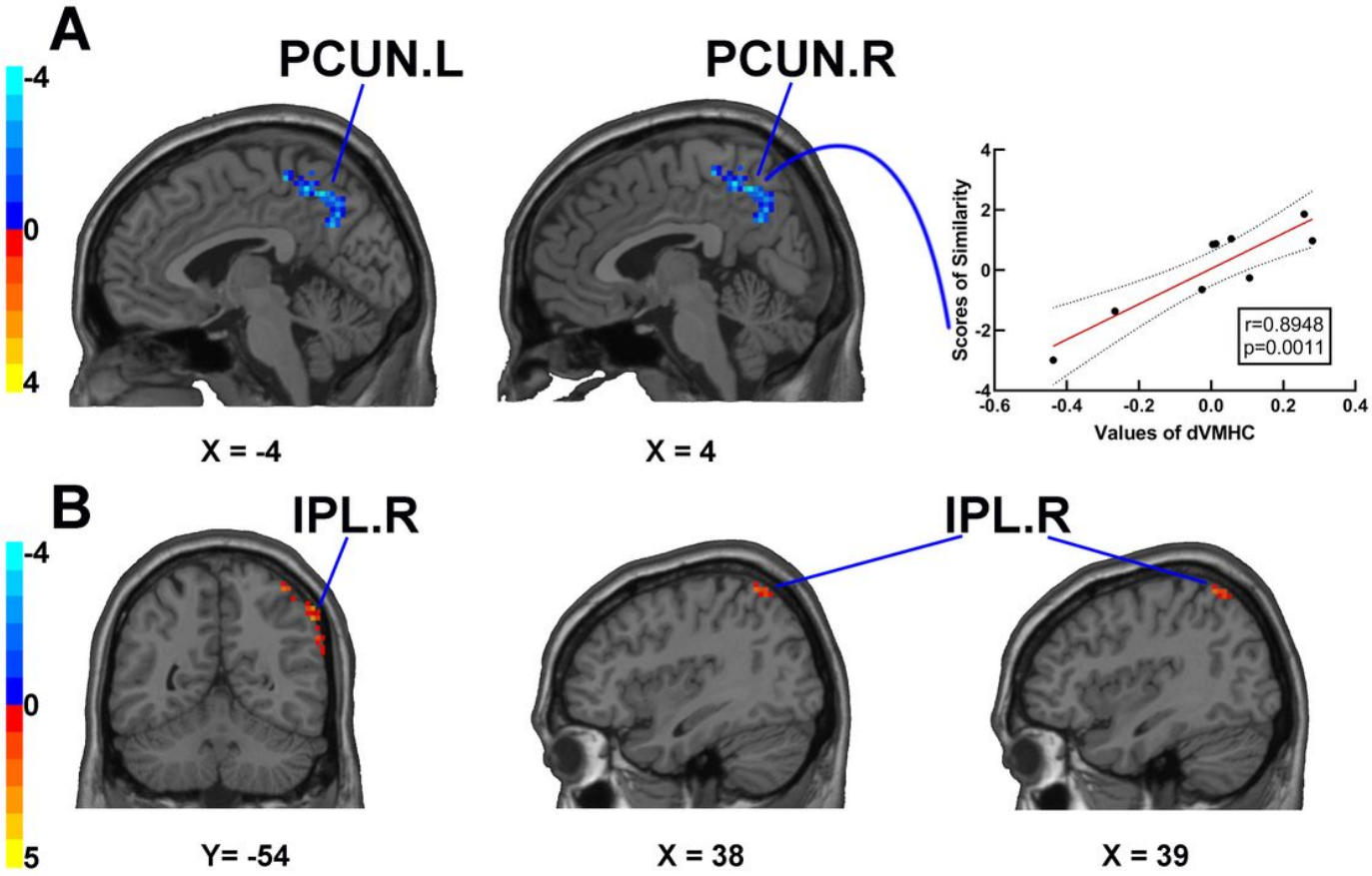



**Figure 4**

Alterations of dVMHC and dReHo and its relationship with cognitive functiopn in patients with frontal glioma Abbreviation: PCUN.L = left precuneus, PCUN.R = right precuneus, IPL.R = right inferior parietal lobule. The figure A indicated that patients with frontal glioma showed increased dVMHC in PCUN.L and PCUN.R. Indeed, the dVMHC value of PCUN.R is significantly positively correlated with the similarity scores. The figure B indicated that patients with frontal glioma showed decreased dVMHC in IPL.R.

# Supplementary Files

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- supplementarymaterialv3.doc