# Individual structural MRI abnormality indexes are associated with molecular, histological and cognitive indicators for frontal glioma patients

**Guo-Bin Zhang**
Beijing Tiantan Hospital
**Hua-Wei Huang**
Beijing Tiantan Hospital
**Yong-Gang Wang**
Beijing Tiantan Hospital
**Xiao-Kang Zhang**
Beijing Tiantan Hospital
**Hao-Yi Li**
Beijing Tiantan Hospital
**Yun-Yun Duan**
Beijing Tiantan Hospital
**Hong-Yan Chen**
Beijing Tiantan Hospital
**Ya-Ou Liu**
Beijing Tiantan Hospital
**Bin Jing**
Capital Medical University
**Song Lin** ( linsong_ttyy@sina.com )
Beijing Tiantan Hospital https://orcid.org/0000-0002-1760-1887

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# Abstract

**Purpose**: The conventional examination of molecular characteristics for glioma requires surgical removal and could not be used in the surgery planning. The aim is to develop a method previewing glioma malignancy with regular structural MRI images.

**Methods:** 52 glioma patients in frontal lobe (mean age 43.2±9.3 years, 34 male) and 117 healthy controls (mean age 32.6±9.8 years, 83 male) participated in the study. All patients underwent neurocognitive test and molecular examinations, including 1p/19q co-deletion, isocitrate dehydrogenase (IDH) mutation, telomerase reverse transcriptase (TERT) promoter mutation and $O^6$-methylguanine-DNA methyltransferase (MGMT) promotor methylation. A series of individual structural abnormality indexes based on preoperative structural MRI were proposed and explored the associations with these clinical indicators.

**Results:** Individual structural abnormality maps displayed that bilateral hippocampus, parahippocampus, insula, putamen and thalamus were constantly affected by glioma regardless of the histological grade, tumor hemisphere and molecular status. Higher grade glioma patients suffered more structural abnormalities, especially in the contralateral hemisphere and non-tumor regions. The molecular indicators, including IDH1 mutation, 1p/19q co-deletion, TERT promoter mutations and MGMT promoter methylation, as well as neurocognitive performance were all significantly correlated to individual structural abnormality indexes.

**Conclusion:** Our proposed individual structural abnormality indexes show great potentials to access the glioma pathological, neurocognitive and molecular indicators, which is very helpful for neurosurgeons to determine the personalized treatment strategies.


# Introduction

Gliomas represent the majority of primary central nervous system (CNS) malignant tumors, and the surgical outcomes are dependent on the precise and comprehensive acquirement of various diagnostic information, which includes histological grades, molecular biomarkers and cognitive function. Since 2016, World Health Organization (WHO) updates the classification criteria for CNS tumors, and specific molecular biomarkers are included for gliomas beyond histological characteristics[1]. For example, the incidence of isocitrate dehydrogenase (IDH) mutations, 1p/19q co-deletions, and telomerase reverse transcriptase (TERT) promoter mutations in glioma were predictors for better treatment outcome regardless of histological results[2-4]. In light of the crucial roles of theses molecular parameters in glioma management, examinations of IDH mutations,1p/19q co-deletions, and TERT promoter mutations have become the routine diagnostic items in many neuropathology centers. However, the conventional determination of these molecular characteristics requires surgical removal of tumor tissues. Therefore, a noninvasive method that could access IDH-mutants, 1p/19q-co-deletions and TERT promoter mutations

before surgery would be more helpful in the treatment strategy selection and the prognostic prediction, especially for initially diagnosed patients and patients who do not prefer surgery as the treatment.

Medical imaging technologies such as magnetic resonance imaging (MRI) and computed tomography (CT) are routine ways to obtain macroscopic information about glioma for the advantages of low cost, low or no damage and convenience[5,6]. Besides, the microscopic characteristics concealed in medical images have also been discovered, such as Radiomics, which has been widely used to predict histological and molecular biomarkers for glioma patients[7-9]. However, these studies have several intrinsic disadvantages: 1. extract group-level but not individual-level (patient-specific) features for classification or prediction; 2. only pay attention to the tumor regions, but the tumor related alterations in non-tumor regions are ignored. In this context, individualized imaging indexes that could delineate whole-brain alterations are highly desired for glioma patients before surgery.

Recently, Stoecklein et al. proposed a novel individual index based on the functional connectivity of resting state functional MRI (rs-fMRI), and found this individual index was positively correlated with WHO tumor grade and the IDH mutation status[10]. However, rs-fMRI is still not a clinical routine MRI scan, and its spatial resolution is commonly not very high. Moreover, rs-fMRI analysis is usually limited to gray matter (GM) but rarely within white matter (WM). In contrast, T1 sequence is a basic structural MRI scan, and plenty of analyzing tools have been developed for T1 images to extract morphological features such as cortical volume and thickness. If T1 could offer individualized diagnostic information about genotype, histological grade, and neurocognitive score, it will be largely helpful to personalized presurgical planning and prognosis prediction. Inspired by the previous study[11] in measuring individual structural abnormality, we extend to quantify both GM and WM abnormality at individual level, and propose series of individual structural abnormality indexes based on extracted individual GM/WM abnormality map. The associations between these individual structural indexes and histological, molecular, and neurocognitive indicators are explored respectively, and these indexes were additionally combined together through canonical correlation analysis to improve the associations.

# Materials And Methods

### Patients

The study was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University, Beijing, China (KY2020-048-01). The study was also registered at Chinese ClinicalTrial Registry (ChiCTR2000031805). All study procedures were in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. Fifty-two glioma patients and one hundred seventeen healthy controls participated this study, which were listed in Table 1. All gliomas in the cohort were diagnosed according to the criteria of the WHO classification system in the revised version of 2016. Inclusion criteria were suspected, newly diagnosed glioma with only one cancer region in the brain and age over 18 years. Exclusion criteria were previous cranial surgery, neuropsychiatric comorbidities, and any contraindications to MR scanning such as metal implants. Neuropsychological testing was

conducted prior to the first MRI scan using the *Montreal Cognitive Assessment* (MOCA) test. Histological confirmation of the diagnosis was obtained by surgical resection. Molecular markers, including 1p/19q codeletion, IDH1/2 mutation, TERT promoter mutation and $O^6$-methylguanine-DNA methyltransferase (MGMT) promotor methylation were all collected. Chromosomes 1 and 19 were analyzed by the fluorescence in situ hybridization method, and the IDH1/2 mutation and TERT promoter mutation were detected by sequence analysis, both following a previously described protocol[12]. MGMT promoter methylation was assessed by methylation-specific PCR as described previously by our team[13]. Patients were followed with routine clinical visits after initiation of therapy. All healthy controls were recruited from the local community and university students.

### Structural MRI acquirement

All subjects were scanned with a Philips Ingenia 3.0T MRI scanner at Beijing Tiantan Hospital. For both glioma patients and healthy controls, T1 sequence was collected with the following parameters: TR: 6.5 ms, TE: 3.0 ms, Flip angle: 8°, voxel size: 1×1×1 $mm^3$, image dimension: 256×256×196. In addition, T2-flair was also scanned for glioma patients with the listed parameters: TR: 4.8 s, TE: 0.34 s, Flip angle: 90°, voxel size: 0.625×0.625×0.55 $mm^3$, image dimension: 400×400×300.

### Image processing

The tumor region of every patient was extracted from T2-flair images with two sequential steps: 1. launch an automatic segmentation by ITK-SNAP software; 2. manually correct the segmentation by experienced neurosurgeons. After the segmentation, individual T2-flair image was co-registered to its corresponding T1 image by SPM software, and the transformation matrix was used on the segmented tumor to obtain the matched tumor region in T1 image space.

Individual T1 images were processed with CAT12 software to calculate the brain tissue volume. The skull stripping and correction for bias-field inhomogeneities were subsequently conducted. After that, the whole brain was segmented into different tissue types, e.g. gray matter and white matter. Then, the segmented GM and WM images were normalized to the MNI standard space with a modulation manner by DARTEL algorithm. Finally, the normalized GM and WM images were smoothed with 4-mm FWHM Gaussian kernel.

### Individual structural abnormality index

Figure 1 illustrated the flowchart of the proposed individual structural abnormality map. In order to calculate individual structural abnormality maps for each glioma patient, all healthy controls were firstly used to construct the normative brain volume model. In this model, general linear model (GLM) was adopted to discover the relationship between voxel-wise volume and variables including age, sex, and total intracranial volume (TIV) as the following equation.

$$volume = \beta_1 \times age + \beta_2 \times sex + \beta_3 \times TIV + residual \qquad (1)$$

Here, $\beta_1$, $\beta_2$, $\beta_3$ were weights for age, sex and TIV on the voxel-wise volume, and GM and WM volume models were respectively constructed.

Once the models had been created, the individual structural abnormality map for each glioma patient was calculated based on W score, which was calculated as following:

$$W\ score = \frac{volume_{patient} - \beta_1 \times age_{patient} - \beta_2 \times sex_{patient} - \beta_3 \times TIV_{patient}}{standard\ deviation\ of\ residuals\ in\ normative\ model} \qquad (2)$$

After the calculation of W score for each patient, a cutoff threshold (|W|>3) was set to the individual W score map to generate the individual structural abnormality map. Notably, an individualized explicit mask was generated for every patient which combined the corresponding tissue (GM/WM) prior probability template (threshold: 0.2) with individual tumor mask. Through the individual structural abnormality map, we proposed a series of abnormality indexes (8 GM indexes and 8 WM indexes, 16 in total) to reflect the characteristics of structural damages induced by glioma, which were listed in detail in Table 2. For GM/WM, there are respectively 8 individual structural abnormality indexes: GM atrophy ratio in tumor hemisphere (*GM-ART*), WM atrophy ratio in tumor hemisphere (*WM-ART*), GM atrophy ratio in contralateral hemisphere (GM-ARC), WM atrophy ratio in contralateral hemisphere (WM-ARC), GM enlargement ratio in tumor hemisphere (*GM-ERT*), WM enlargement ratio in tumor hemisphere (*WM-ERT*), GM enlargement ratio in contralateral hemisphere (GM-ERC), WM enlargement ratio in contralateral hemisphere (WM-ERC), GM abnormality ratio in tumor hemisphere (*GM-ABRT*), WM abnormality ratio in tumor hemisphere (*WM-ABRT*), GM abnormality ratio in contralateral hemisphere (*GM-ABRC*), WM abnormality ratio in contralateral hemisphere (*WM-ABRC*), GM abnormality in non-cancer region in comparison to cancer region (*GM-ABNC*), WM abnormality in non-cancer region in comparison to cancer region (*WM-ABNC*), GM abnormality in non-cancer region in comparison to whole brain (*GM-ABNW*) and WM abnormality in non-cancer region in comparison to whole brain (*WM-ABNW*).

### Associations with molecular, histological, and cognitive indicators

To explore the relationship between each of 16 abnormality indexes and IDH1, TERT mutation, 1p/19q deletion, MGMT methylation, histological grade and MOCA score, Spearman correlation was used and a $P < 0.05$ was thought as significance. Moreover, concerning the combinations of the proposed 16 individual structural abnormal indexes may further boost the correlation with these clinically concerned indicators, Canonical Correlation Analysis (CCA) was used to merge all indexes into a new canonical variable for each clinical indicator. CCA is in fact to seek the optimal linear combinations of these indexes that display the largest correlational relationship with these clinical indicators. Clearly, the weights (coefficients) of 16 abnormal indexes were different for each clinical indicator.

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

# Results

### Histology, molecular markers, and clinical course

There were 52 glioma patients (mean age 43.2±9.3 years, 34 male) and 117 healthy controls (mean age 32.6±9.8 years, 83 male) that participated in the study. All patients were prospectively included between May 2019 and July 2020. The WHO histological grade, IDH1, TERT mutation, 1p/19q deletion, MGMT methylation were acquired for every patient, and Montreal Cognitive Assessment (MOCA) score was also recorded. Table 1 summarized the demographic and clinical information for all subjects.

### Individual structural abnormality map could discover structural alterations not only within the tumor but also outside the tumor.

It is no doubt that glioma could induce whole brain alterations. Figure 2 illustrated several patients' T1 images and corresponding personalized GM/WM abnormality maps (mapping back into T1 space). Obviously, the cerebral structural abnormalities not only lay in tumors but also in non-tumor regions, and all patients displayed both atrophies and enlargements in GM and WM. Although the patients varied in tumor sizes and tumor grades, the personalized GM abnormality maps could more precisely detect the tumor region than WM abnormality maps. In addition, high grade glioma patients were found with larger abnormalities in non-tumor regions. Figure 3 respectively displayed the overlapping regions for individual structural abnormality map, and it is clear that no matter the tumor is located at the left hemisphere or right hemisphere, several regions outside the tumor were consistently found abnormality, including bilateral hippocampus, insula, putamen, parahippocampus, thalamus.

### Individual structural abnormality indexes were associated with clinical indicators, and combinations of these indexes would promote the correlation.

Table 3 listed the correlation relationships between clinical indicators and proposed individual structural abnormality indexes. For WHO histological grade, 7 individual structural abnormality indexes correlated with it, and WM-ABRT achieved the highest correlation value (r=0.457). For IDH1 mutation, 3 indexes were significantly related with it, including GM-ART (r= -0.335), GM-ABRT (r= -0.326) and GM-ABNC (r= 0.330). For 1p19q deletion, 7 indexes displayed correlational relationship with it, and WM-ABNW obtained the highest correlational value (r=0.468). For TERT mutation, 6 indexes were found correlation with it, and GM-ABNW showed the highest correlational value (r=0.440). For MOCA score, WM-ARC (r=0.290) and WM-ERT (r=-0.284) were related with it. There was no single index that correlated with MGMT (all $p>0.05$).

Figure 4 summarized the scatter plots between corresponding canonical variable (linear combinations of 16 individual structural abnormality indexes) and these clinical indicators. It is obvious that combining

the individual structural indexes together could achieve better correlations with these indicators, and the detected canonical variable displayed the highest correlational value (r=0.786) for histological grade and high correlations for IDH1 type (r=0.654), 1p/19q deletion status (r=0.619) and TERT promoter type (r=0.615), while relatively lower correlational values were found for MOCA (r=-0.553) and MGMT (r=0.480). These results indicated individual structural abnormality indexes could serve as a promising way to access molecular, histological and cognitive indicators for preoperative glioma patients.

# Discussion

In this study, we firstly depicted the structural abnormality characteristics for glioma patients through an individual level method, and proposed several quantitative indexes to reflect the individual abnormality severity, which were also found with high correlations with histological, molecular, and cognitive indicators. These findings demonstrated their enormous potentials in providing multiview information for the preoperative assessment of glioma patients, which may be finally used for individualized precision treatment and prognosis evaluation for glioma patients.

The non-invasiveness and convenience of imaging technologies make them act as indispensable tools for presurgical assessment of glioma patients. Among them, contrast-enhanced MRI is currently served as the diagnostic golden standard for patients with suspected brain neoplasms, which is often supplemented with spectroscopy, PET, or diffusion imaging. In contrast, T1 image is a basic structural imaging sequence that has been widely collected in various populations. Specially, it could be easily gained for healthy controls while contrast-enhanced MRI or PET is usually not applicable for healthy controls. Therefore, these imaging modalities are usually used in a manner of visual inspection by experienced neurosurgeons. In addition, there are commonly two ways to analyze T1 images for glioma patients: 1. Use voxel/tensor/surface/deformation based morphometry methods to study the structural alterations, but these methods could be only conducted through statistical comparisons at the group level; 2. Use Radiomics methods to predict tumor phenotypes and clinical indicators, however, these methods only focus on the tumor region, hence couldn’t provide information about non-tumor regions. Our method in the study solved the above-mentioned shortcomings, and further proposed a series of abnormality metrics at individual level to quantitatively delineate the structural alterations caused by glioma. Therefore, our method could offer comprehensive information about every glioma patient and may assist neurosurgeons to decide the most appropriate therapeutic strategy for every glioma patient.

Recently, Stoecklein et al. firstly demonstrated the feasibility of rs-fMRI to characterize individual glioma patient[10]. More importantly, this study manifested the tumor related changes in functional connectivity was unique for glioma patients with different histological grades, emphasizing the essentials of individual imaging biomarkers[10]. However, rs-fMRI is a type of technology with relatively low signal to noise ratio, and its test-retest reliability is also not high and dependent on the scanning durations, which makes it still challengeable for widespread applications for glioma patients. By contrast, structural MRI (sMRI) is with high image quality and test-retest reliability as well as appropriate scanning time. Besides, fMRI is usually limited to the gray matter while sMRI could detect the morphological changes in both gray

matter and white matter. Moreover, our results discovered white matter indexes are as informative as gray matter indexes, and combining them together could improve the associations with clinical indicators of glioma patients. Finally, our study actually demonstrated the structural alterations in the brain were also unique among glioma patients. Taken together, glioma may lead to patient specific alterations in both brain function and structure.

Although glioma patients display distinct structural abnormalities at the individual level, it is interesting to find they also share common structural abnormalities in regions such as bilateral hippocampus, insula, putamen, thalamus and parahippocampus. Specially, these abnormal regions are not dependent on the hemisphere of tumor, histological grade and molecular indicators. On the one hand, it implies tumor related structural abnormalities are not only limited in the tumor hemisphere but also in the contralateral hemisphere no matter whether the tumor hemisphere is the dominant hemisphere. On the other hand, why these regions rather than other regions show abnormalities needs additional consideration. We speculate one possible reason is that all glioma patients in the study are with tumor in the frontal lobe, which participates in some key function networks (e.g. default mode network, attention network, salience network, affective network) together with these abnormal regions. Once the frontal lobe suffers from the glioma, these abnormal regions have to undergo some compensatory alterations to maintain these functions. Previous literatures have reported that as many as 90% of brain tumor patients would show tumor-related cognitive deficits (e.g., memory, attention, information processing, executive functioning impairments)[14,15], we infer this may be caused by the broken compensatory balance after the glioma surgery. At last, our findings show that the combination of all structural indexes achieved a high correlation (r=-0.553) with MOCA score, indicating the cognitive ability is actually related to the structural abnormalities in glioma patients.

For the prognosis of glioma patients, the histological grade and IDH mutation are two vital known factors. For example, lower grade gliomas with wild-type IDH were reported to show similar prognosis with glioblastomas, and IDH mutated glioblastomas were found with better prognosis than IDH wild-type glioblastomas[16,17]. In addition, anaplastic gliomas with IDH wild-type have worse prognosis than glioblastomas with IDH mutation[16]. However, it is still difficult to timely know genetic examination results during the surgery, therefore the analysis of preoperative images has become the most possible way to predict these indicators. Several studies[18-20,7] using different modality images have been adopted for IDH prediction with high accuracy, but these models (e.g. deep learning) are hard to interpret intuitionally. Our individual structural abnormality indexes provide new perspective to access both histological grade and IDH mutation, and several single indexes show high correlations with histological grade and IDH mutation. When all these indexes are combined together, the correlational values are further improved (r=0.786 and 0.654 respectively). Our results indicate the potential of these individual structural abnormality indexes in the IDH prediction, and could be integrated with other imaging biomarkers together to construct an interpretable model for IDH prediction.

Several molecular biomarkers (e.g. TERT, 1p/19q co-deletion, MGMT) are also found to be related with the treatment selection and prognosis prediction. Lower grade glioma with TERT mutation is reported to have

better prognosis, and TERT mutation is also a promising indicator for the treatment response of radiotherapy and temozolomide in primary glioblastoma multiforme (GBM)[21-25]. 1p/19q co-deletion is a strong predictor of better prognosis for patients with oligodendroglioma after radiotherapy or alkylating chemotherapy[26,27]. GBM patients with methylated MGMT are more sensitive to temozolomide and radiotherapy, resulting in better prognosis[28-30]. For predictions of these molecular markers, Radiomics models are usual ways with acceptable results, however, Radiomics features are also not intuitional and dependent on many factors (e.g. scanning image parameter, scanning machine type). In our study, several abnormal indexes were found with direct correlational relationship with these molecular markers, and combination of all indexes could display high correlations with them (r=0.619,0.615 and 0.480 respectively). The results indicate that the intrinsic molecular characteristics of tumor could be reflected by the structural abnormal pattern in glioma patients.

Finally, one limitation should not be ignored: the study is with limited data from single-center. Future studies should include more patients from multicenter to verify the usefulness of the novel structural indexes.

# Conclusion

We propose a series of structural indexes for glioma patients to quantify the individual structural abnormal characteristics, which are found to correlate with tumor-specific features such as WHO grade and molecular status as well as neurocognitive performance. The proposed indexes enhance the diagnostic information from conventional structural MRI, perhaps allowing for a more holistic assessment of disease severity for individual glioma patients and helping neurosurgeons to determine the personalized treatment strategies.

# Declarations

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Hao-Yi Li, Yun-Yun Duan and Hong-Yan Chen; Supervision: Song Lin, Guo-Bin Zhang and Yong-Gang Wang; Funding acquisition: Guo-Bin Zhang and Hua-Wei Huang

**Ethics approval:** Approval was obtained from the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University (KY2020-048-01). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

**Consent to participate:** Informed consent was obtained from all individual participants included in the study.

**Data availability:** The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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# Tables

**Table 1** The demographic and clinical information of all subjects.

| | Glioma patients | Healthy controls |
|---|---|---|
| Number | 52 | 117 |
| Sex (M/F) | 34/18 | 83/34 |
| Age | 43.2±9.3 | 32.6±9.8 |
| TIV | 1484.1±116.2 | 1459.5±145.2 |
| Tumor volume | 59.6±66.1 | - |
| Histological grade (□/□/□) | 35/11/6 | - |
| IDH1 mutation (mutated/wild) | 42/10 | - |
| TERT promoter mutation (mutated/wild) | 33/19 | - |
| 1p/19q deletion (both 1p/19q /only 19q/only 1p/none) | 24/5/4/19 | - |
| MGMT promoter methylation | 0.25±0.16 | - |
| MOCA | 22.2±5.0 | - |

Abbreviation: IDH, isocitrate dehydrogenase; MGMT, $O^6$-methylguanine-DNA methyltransferase; MOCA, Montreal Cognitive Assessment; TERT, telomerase reverse transcriptase; TIV, total intracranial volume.

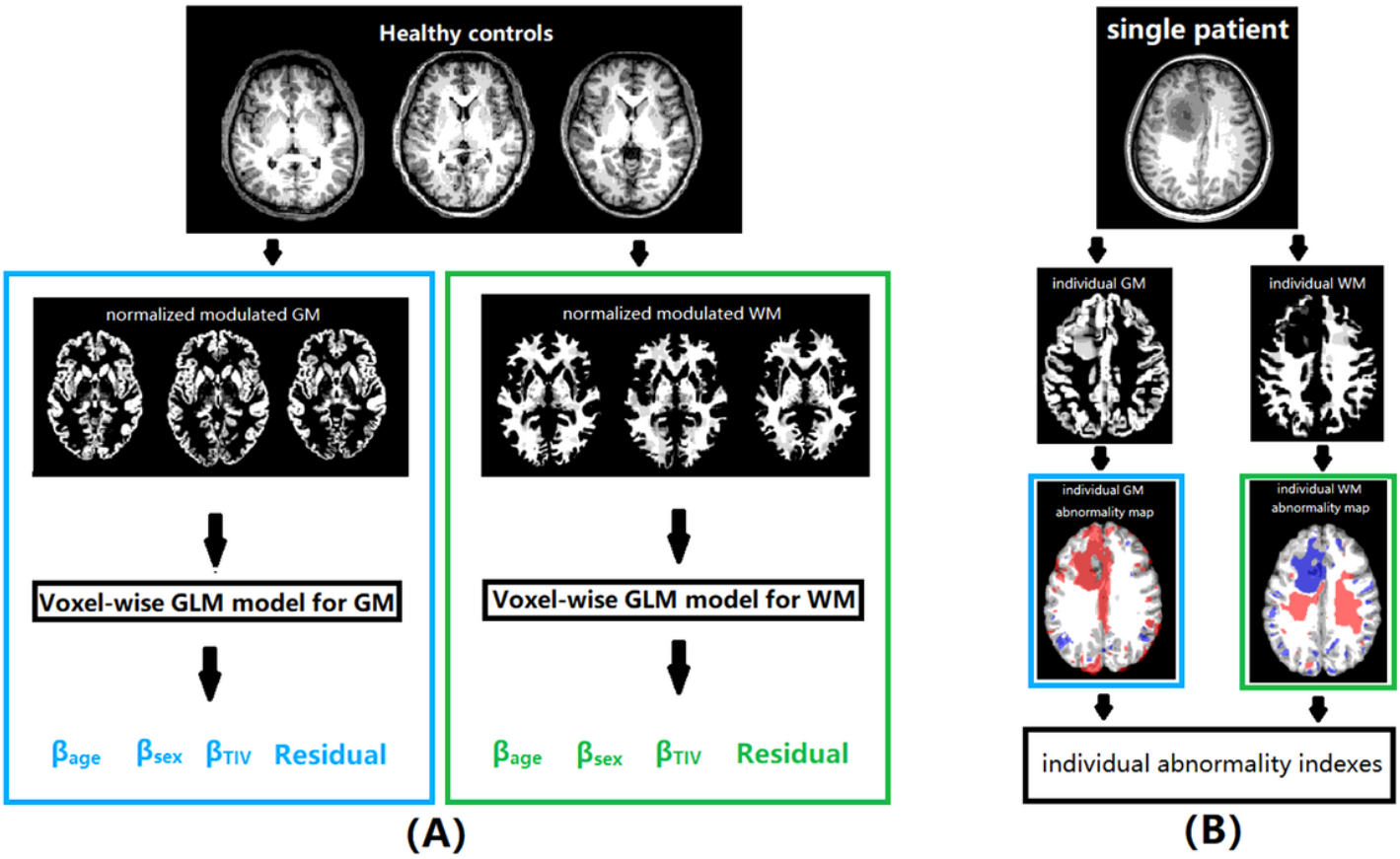
Due to technical limitations, Table 2 is only available as a download in the supplementary files section.

**Table 3** The correlation value between individual structural abnormality index and molecular indicators.

| Molecular indicators | Individual structural abnormality index | Correlation value (Spearman) |
|---|---|---|
| *WHO histological grade* | GM-ART | 0.304 |
| | GM-ABRT | 0.408 |
| | WM-ART | 0.375 |
| | WM-ERT | 0.322 |
| | **WM-ABRT** | **0.457** |
| | GM-ABNW | -0.323 |
| | GM-ABNC | -0.357 |
| *IDH1 mutation* | GM-ART | -0.335 |
| | GM-ABRT | -0.326 |
| | **GM-ABNC** | **0.330** |
| *1p/19q deletion* | GM-ART | -0.396 |
| | GM-ABRT | -0.422 |
| | WM-ERT | -0.291 |
| | GM-ABNW | 0.465 |
| | GM-ABNC | 0.433 |
| | **WM-ABNW** | **0.468** |
| | WM-ABNC | 0.397 |
| *TERT mutation* | GM-ART | -0.331 |
| | GM-ABRT | -0.334 |
| | **GM-ABNW** | **0.440** |
| | GM-ABNC | 0.382 |
| | WM-ABNW | 0.435 |
| | WM-ABNC | 0.355 |
| MOCA | **WM-ARC** | **0.290** |
| | WM-ERT | -0.284 |

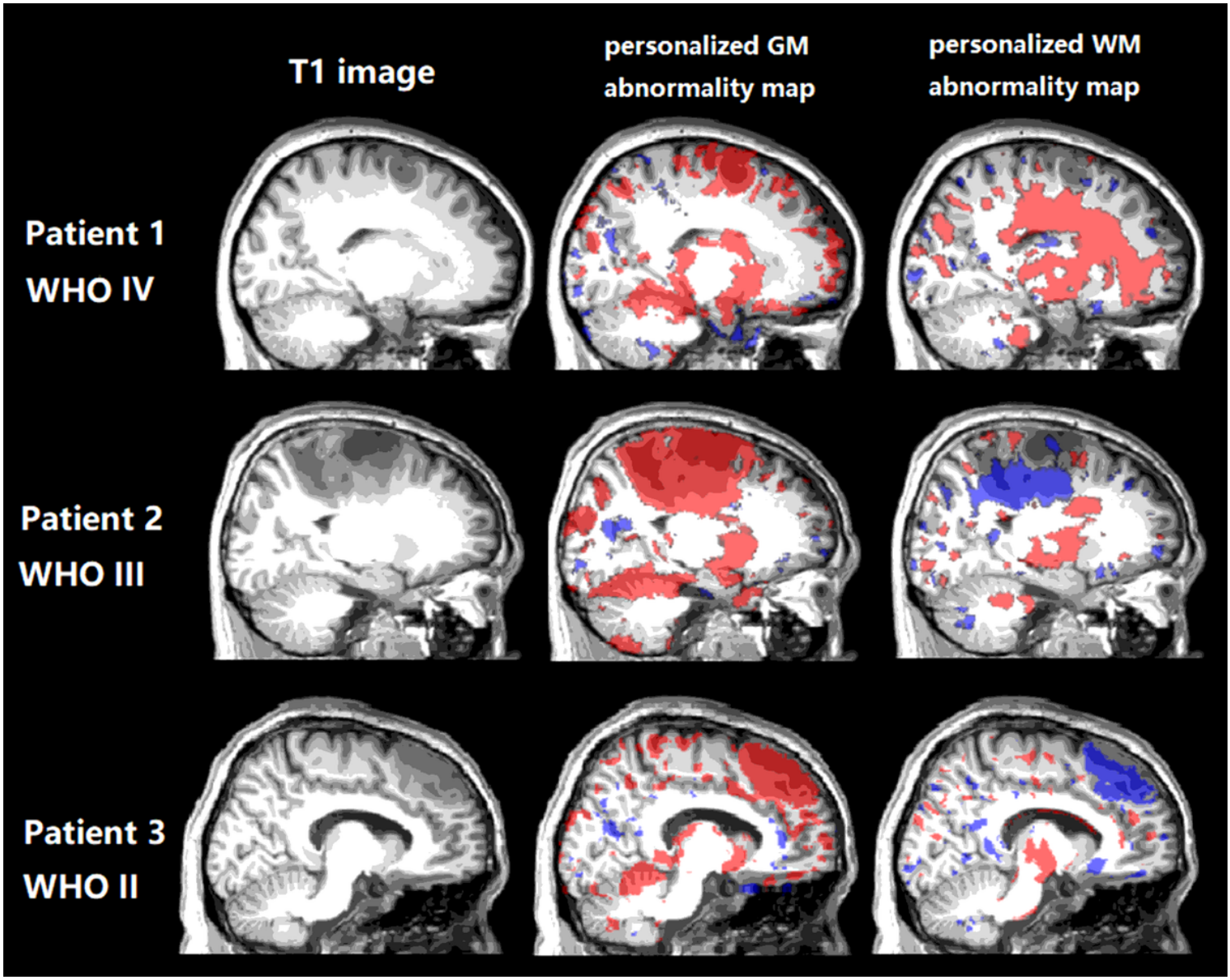
Abbreviation: ABNC, abnormality in non-cancer region in comparison to cancer region; ABNW, abnormality in non-cancer region in comparison to whole brain; ABRT, abnormality ratio in tumor hemisphere; ARC, atrophy ratio in contralateral hemisphere; ART, atrophy ratio in tumor hemisphere; ERT, enlargement ratio in tumor hemisphere; GM, gray matter; IDH, isocitrate dehydrogenase; MOCA, Montreal Cognitive Assessment; TERT, telomerase reverse transcriptase; WHO, World Health Organization; WM, white matter.

# Figures



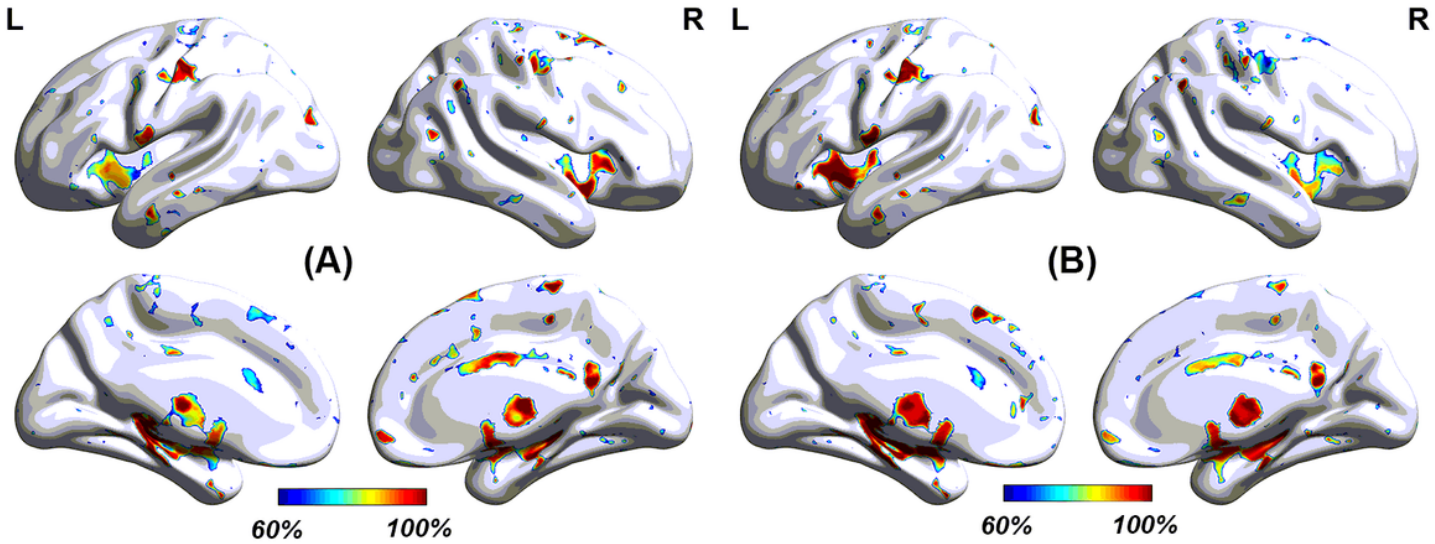

## Figure 1

The flowchart of the proposed structural abnormality indexes: (A). the construction of normative brain volume model; (B). the calculation of the proposed individual abnormality indexes.



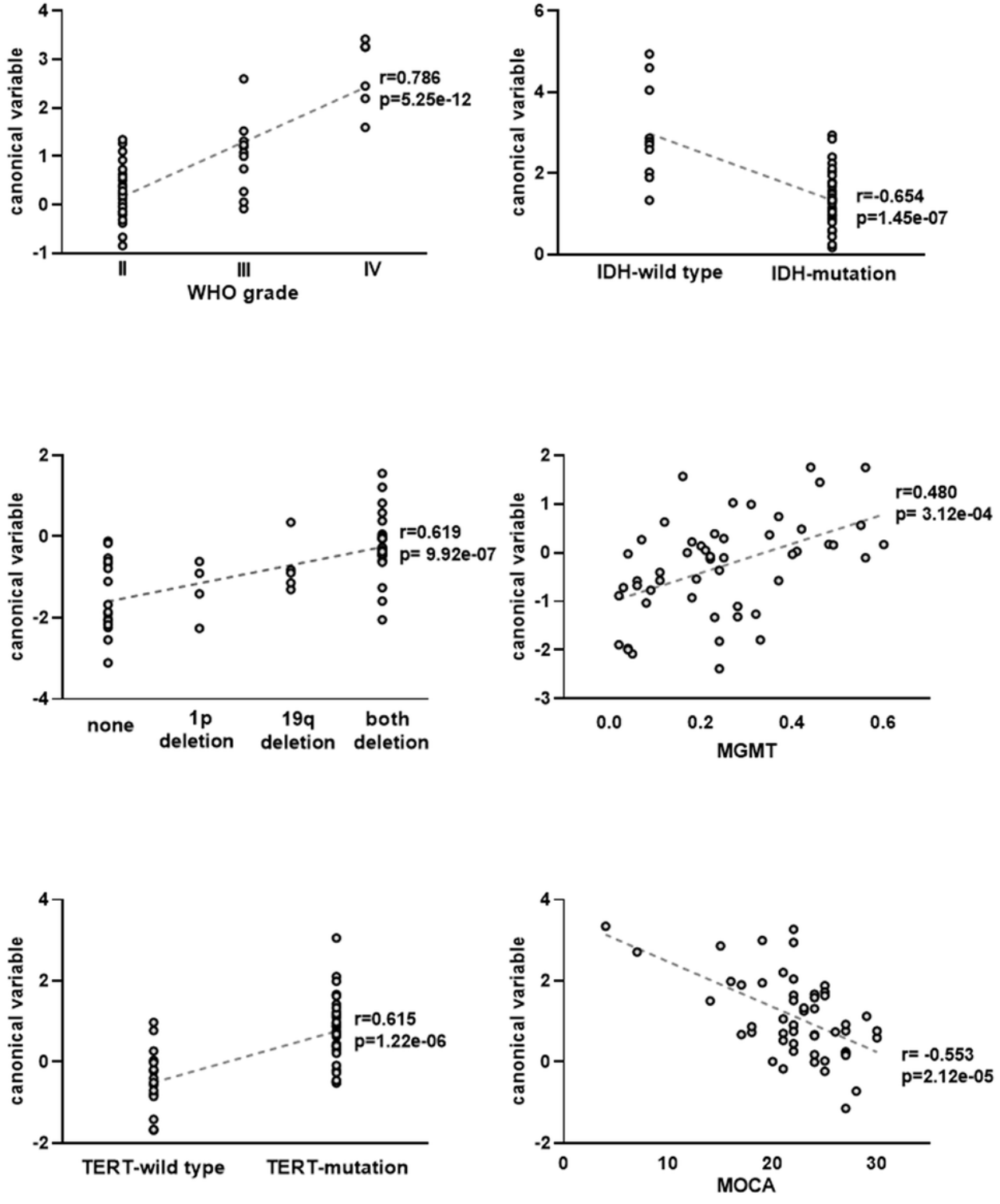

## Figure 2

Several examples of personalized GM/WM abnormality maps.



## Figure 3

Overlapping gray matter abnormalities in non-tumor regions for all patients with tumor on (A) left hemisphere and (B) right hemisphere. Notably, 60% in the color-bar means 60% of all patients displayed abnormality in corresponding position.




## Figure 4

The scatter plot between the generated canonical variable (linear combination of individual structural abnormality indexes) and molecular, histological, and cognitive indicators

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table2.pdf