1 **Probing individual-level structural atrophy in frontal glioma patients**

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44

45 **Abstract**

46 Although every glioma patient varies in tumor size, location, histological grade and molecular
 47 biomarkers, structural abnormalities are commonly conducted in a group-level, leading to the miss of
 48 individual structural atrophy. In this study, we introduced an individual-level structural abnormality
 49 detection method for glioma patients and proposed several novel abnormality indexes to depict the
 50 individual atrophy pattern. Forty-five glioma patients in frontal lobe and fifty-two age-matched healthy
 51 controls participated in the study. All patients underwent neurocognitive test and molecular
 52 examinations, including 1p/19q co-deletion, isocitrate dehydrogenase (IDH) mutation, telomerase
 53 reverse transcriptase (TERT) promoter mutation and O6-methylguanine-DNA methyltransferase
 54 (MGMT) promoter methylation. Individual structural abnormality maps for every glioma patient were
 55 calculated from the preoperative T1 images, and the individual abnormality index were further
 56 computed and explored the associations with clinical indicators. The results manifested that: 1. Every
 57 glioma patient show unique atrophy pattern; 2. Glioma patients also share consistent atrophy regions; 3.
 58 The atrophy pattern is influenced by some molecular biomarkers. Our study provides an effective way
 59 to access the individual structural abnormalities in glioma patients, and displays great potentials in
 60 individualized precision medicine for glioma patients.

61 **Keywords:** frontal glioma, structural MRI, individual structural atrophy, abnormality index, molecular
 62 indicators

63

64 **Introduction**

65 Gliomas represent the majority of primary central nervous system (CNS) malignant
 66 tumors, and the surgical outcomes are dependent on the comprehensive acquirement
 67 of various diagnostic information including histological grades and molecular
 68 biomarkers. However, these golden standard indicators are hard to acquire before
 69 neurosurgery, and neuroimaging has consequently served as a key way to perceive the
 70 glioma status. There are many imaging modalities collected for glioma patients, such
 71 as diffusion weighted/tensor imaging (DWI/DTI), resting-state functional MRI
 72 (rs-fMRI), positron emission tomography (PET) and structural magnetic resonance
 73 imaging (sMRI). Among them, sMRI (e.g. T1, T2) is an easy-to-collect and
 74 economical modality with high spatial resolution and test-retest reliability, which is
 75 thus widely collected in most neurosurgical centers. Usually, neurosurgeons only take
 76 qualitative evaluations for the tumor regions on structural images through visual
 77 inspection, and an individual-level quantitative analysis for tumor-related alterations
 78 is still lacking in clinical presurgical evaluation.

79

80 With the appearance of Radiomics, the quantitative analysis for the tumor region on
 81 structural images has been demonstrated to provide useful information about the
 82 histological/molecular biomarkers(Lohmann et al., 2018; Lu et al., 2018; Soike et al.,
 83 2018; Takahashi et al., 2019). However, the alterations in non-tumor regions are rarely
 84 to access in Radiomics studies, which may be also important to the postsurgical
 85 prognosis. Although the conventional morphological analysis such as voxel-based

86 morphometry could detect structural changes (e.g. contralateral hemisphere) for
 87 glioma patients, the results are based on the group-level statistical analysis and the
 88 structural changes at individual level are still not clear. Specifically, every glioma
 89 patient may suffer unique structural alterations in non-tumor regions, and detecting
 90 and quantifying individual-level structural alterations may further deepen the
 91 understanding of the influences of tumor regions.

92

93 In recent years, individualized neuroimaging has appeared and displayed great
 94 potentials in precision diagnosis and treatment(Liu, Liu, Wang, & Dahmani, 2020;
 95 Wang et al., 2015). Stoecklein et al. found individual functional connectivity
 96 characteristics of glioma patients were significantly related with WHO tumor grade
 97 and the IDH mutation status(Stoecklein et al., 2020). However, rs-fMRI is not a
 98 clinical routine scan sequence, and to collect a high quality rs-fMRI dataset is also
 99 challenging for glioma patients. In this condition, sMRI becomes an alternative choice
 100 to model the individual alterations in the brain. Previous studies(Perry et al., 2017)
 101 have manifested W-score could successfully measure individual gray matter changes
 102 in neurological diseases, which is firstly introduced into glioma patients in the study.
 103 Furthermore, we extend the W-score method to both gray matter and white matter,
 104 and propose several novel structural abnormality indexes to depict the individual
 105 structural alteration patterns. The main purposes of the study are to ascertain: 1.
 106 Whether frontal glioma patients display unique structural alterations for every subject?
 107 2. Whether frontal glioma patients display consensus structural alterations and where

108 are they located? 3. Whether individual atrophy patterns vary with clinical and
109 molecular indicators?

110

111 **Materials and Methods**

112 **Patients**

113 The study was approved by the Institutional Review Board of Beijing Tiantan
114 Hospital, Capital Medical University, Beijing, China (KY2020-048-01). The study
115 was also registered at Chinese Clinical Trial Registry (ChiCTR2000031805). All study
116 procedures were in accordance with the Declaration of Helsinki. Written informed
117 consent was obtained from all patients. Fifty-two glioma patients and one hundred
118 seventeen healthy controls participated this study, which were listed in Table 1. All
119 gliomas in the cohort were diagnosed according to the criteria of the WHO
120 classification system in the revised version of 2016. Inclusion criteria were suspected,
121 newly diagnosed glioma with only one cancer region in the brain and age over 18
122 years. Exclusion criteria were previous cranial surgery, neuropsychiatric
123 comorbidities, and any contraindications to MR scanning such as metal implants.
124 Neuropsychological testing was conducted prior to the first MRI scan using the
125 *Montreal Cognitive Assessment* (MOCA) test. Histological confirmation of the
126 diagnosis was obtained by surgical resection. Molecular markers, including 1p/19q
127 codeletion, IDH1/2 mutation, TERT promoter mutation and O⁶-methylguanine-DNA
128 methyltransferase (MGMT) promoter methylation were all collected. Chromosomes 1
129 and 19 were analyzed by the fluorescence in situ hybridization method, and the

130 IDH1/2 mutation and TERT promoter mutation were detected by sequence analysis,
131 both following a previously described protocol(Suh, Kim, Jung, Choi, & Kim, 2019).
132 MGMT promoter methylation was assessed by methylation-specific PCR as described
133 previously by our team(Zhang et al., 2013). Patients were followed with routine
134 clinical visits after initiation of therapy. All age-matched healthy controls were
135 recruited from the local community and university students.

136

137 **Structural MRI acquirement**

138 All subjects were scanned with a Philips Ingenia 3.0T MRI scanner at Beijing Tiantan
139 Hospital. For both glioma patients and healthy controls, T1 sequence was collected
140 with the following parameters: TR: 6.5 ms, TE: 3.0 ms, Flip angle: 8°, voxel size:
141 1×1×1 mm³, image dimension: 256×256×196. In addition, T2-flair was also scanned
142 for glioma patients with the listed parameters: TR: 4.8 s, TE: 0.34 s, Flip angle: 90°,
143 voxel size: 0.625×0.625×0.55 mm³, image dimension: 400×400×300.

144

145 **Image processing**

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

152

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

160

161 Individual structural atrophy map

162 Figure 1 illustrated the flowchart to generate individual structural atrophy map. First
163 of all, all healthy controls were used to construct the normative brain volume model.
164 In this model, general linear model (GLM) was adopted to discover the relationship
165 between voxel-wise volume and variables including age, sex, and total intracranial
166 volume (TIV) as the following equation.

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

167 Here, β_1 , β_2 , β_3 were weights for age, sex and TIV on the voxel-wise volume, and GM
168 and WM volume models were respectively constructed.

169

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

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

173

174 After the calculation of W score for each patient, a cutoff threshold ($|W| > 6$) and a
175 cluster size ($K > 100$) were set to generate the individual structural abnormality map.
176 Notably, an individualized explicit non-tumor mask was produced for every patient in
177 which individual tumor mask was deleted from the tissue (GM/WM) prior probability
178 template (threshold: 0.2). Based on the individual structural abnormality map, we
179 further proposed 4 novel abnormality indexes on GM/WM to reflect the
180 characteristics of structural damages induced by glioma: Ipsilateral atrophy ratio,
181 Contralateral atrophy ratio, Non-cancer atrophy ratio, Relative atrophy ratio, which
182 were listed in details in Table 2.

183

184 **Associations with various glioma indicators**

185 To explore the associations between each of 8 abnormality indexes and various
186 glioma indicators, for continuous variables like tumor volume, MGMT methylation,
187 and MOCA score, Spearman correlation was used to ascertain the linear relationship
188 with these atrophy indexes; for categorical variables such as TERT mutation, 1p/19q
189 deletion, histological grade and IDH1, two-sample T test was used to determine
190 whether the atrophy indexes varied with these indicators. An FDR corrected $P < 0.05$
191 was thought as the significance level for both analyses.

192

193 **Results**

194 **The clinical characteristics for glioma patients**

195 There were 45 glioma patients (mean age 43.2 ± 9.7 years, 29 male) and 51 healthy
196 controls (mean age 42.6 ± 9.7 years, 24 male) that participated in the study. All patients
197 were prospectively included between May 2019 and July 2020. The WHO
198 histological grade, IDH1, TERT mutation, 1p/19q deletion, MGMT methylation were
199 acquired for every patient, and Montreal Cognitive Assessment (MOCA) score was
200 also recorded. Table 1 summarized the demographic and clinical information for all
201 subjects.

202

203 **Every glioma patient displayed distinct atrophy pattern**

204 All patients only displayed atrophies in GM and WM. Figure 2 illustrated three
205 selected patients' T1 images and corresponding individualized GM/WM atrophy maps
206 (mapping back into T1 space). Obviously, the structural atrophies not only lay in
207 regions close to tumors but also in regions far away from tumors. Although the
208 patients vary in tumor sizes and tumor grades, it is clear that every subject displayed
209 unique atrophy pattern.

210

211 **Every glioma patient also showed common atrophy regions**

212 Figure 3 displayed the overlapping GM regions in individual structural atrophy map.
213 No matter the tumor is located at the left hemisphere or right hemisphere, the
214 atrophies in right temporal lobe are more obvious than the left one, mainly including
215 hippocampus, amygdala, parahippocampus and thalamus. Moreover, the contralateral
216 frontal regions also displayed some degree of atrophy. Figure 4 exemplified the

217 consistent WM regions in individual structural atrophy map. The main atrophy
218 regions are located at bilateral thalamus and pallidum, and the contralateral part is
219 more severely atrophied than the ipsilateral part.

220

221 **Individual brain atrophy indexes were associated with some clinical indicators**

222 Fig 5 illustrated all possible relations between the proposed individual abnormality
223 indexes and clinical indicators, and all of them had passed an FDR correction with
224 $P < 0.05$. GM/WM relative atrophy ratio were found to significantly correlate with the
225 tumor size, however, with the increasement of the tumor volume, the relative atrophy
226 ratio was decreased (power law distribution), and no other individual structural
227 indexes were related with tumor size. WM contralateral atrophy ratio was found with
228 significant differences between IDH wild type and mutation type, while WM relative
229 atrophy ratio were obviously different between 1p/19q wild type and mutation type.
230 Moreover, both GM/WM relative atrophy ratio displayed between-group differences
231 in TERT wild type and mutation type. No other relationships were detected with
232 MOCA and MGMT.

233

234 **Discussion**

235 In this study, we firstly depicted individual non-tumor structural atrophy
236 characteristics for glioma patients, and proposed several quantitative indexes to
237 ascertain the relationship between individual atrophy patterns and clinical indicators.
238 The results demonstrated every glioma patient displays distinct atrophy pattern but

239 also shared overlapping atrophy regions. In addition, several atrophy indexes were
240 related with tumor size and molecular indicators.

241

242 Neuroimaging has acted as indispensable tool for presurgical assessment of glioma
243 patients. However, most imaging studies only focus on the tumor region in order to
244 judge the status of tumor, and the non-tumor alterations are rarely to access. Moreover,
245 neuroimaging is usually used by two conventional manner: 1. visual inspection by
246 experienced neurosurgeons; 2. group-level statistical comparison between glioma
247 patients and healthy controls. Both manners may miss the individual unique changes
248 in non-tumor regions. Our study firstly offers an individual-level manner to describe
249 individual atrophy in every glioma patient, and manifested that every glioma patient
250 displays unique structural atrophy in non-tumor regions, which was consistent with
251 previous individual fMRI study(Stoecklein et al., 2020). Taken together, glioma may
252 lead to patient-specific alterations in both brain function and structure, and
253 individualized neuroimaging methods show great potentials in the pre-surgical
254 evaluation and post-surgical prognosis estimation.

255

256 Although glioma patients display distinct structural atrophy at the individual level, it
257 is interesting to find they also share overlapping GM atrophies in regions like bilateral
258 hippocampus, amygdala, thalamus and parahippocampus. Specially, these atrophies
259 are not dependent on the hemisphere of tumor, tumor size, histological grade or
260 molecular indicators, indicating that frontal glioma could introduce systematic

261 atrophy in brain structure. In addition, GM atrophy were more obvious in right
 262 temporal lobe than the left one regardless the tumor hemisphere, implying right
 263 temporal lobe is more vulnerable to the frontal tumor, and there is lateralization in the
 264 structural damages induced by the frontal tumor. Previous literatures have reported
 265 that as many as 90% of brain tumor patients would show tumor-related cognitive
 266 deficits (e.g., memory, attention, information processing, executive function)(Gehring,
 267 Roukema, & Sitskoorn, 2012; Gehring, Sitskoorn, Aaronson, & Taphoorn, 2008),
 268 which may be explained by the current findings that limbic system including
 269 hippocampus, amygdala, parahippocampus and thalamus are damaged in glioma
 270 patients.

271
 272 The consistent WM atrophies were mainly located at bilateral thalamus and pallidum,
 273 and the contralateral hemisphere was more severely atrophied than the ipsilateral one.
 274 These regions are involved in two fiber bundles linking fronto-temporal regions:
 275 superior longitudinal fasciculus (SLF) and uncinate fasciculus (UF). SLF has been
 276 reported to correlate with the spatial working memory deficit(Kinoshita et al., 2016),
 277 visuospatial dysfunction(Nakajima et al., 2017) and transmission of speech and
 278 language(Henderson, Abdullah, Verma, & Brem, 2020) in glioma patients. UF has
 279 been demonstrated to relate with the language(Duffau, Gatignol, Moritz-Gasser, &
 280 Mandonnet, 2009) and cognitive deficits(Incekara, Satoer, Visch-Brink, Vincent, &
 281 Smits, 2018) in glioma patients. The common WM atrophies also prompt the possible
 282 cognitive damages in frontal glioma patients, and may provide a possible pathway

283 that link the remote GM atrophy covariation.

284

285 GM/WM relative atrophy ratio but not other individual indexes were negatively

286 related (in fact power law distribution) with tumor volume, and two conclusions may

287 thereby be generated: 1. the volume of atrophy in the brain was in fact not dependent

288 on the tumor volume; 2. the relative atrophy volume becomes smaller when the tumor

289 volume enlarges. Moreover, WM contralateral/relative atrophy ratio were found with

290 significant differences in IDH and 1p/19q mutation. IDH and 1p/19q are both known

291 indicators for the prognosis of glioma patients. For example, lower grade gliomas

292 with wild-type IDH were reported to show similar prognosis with glioblastomas, and

293 IDH mutated glioblastomas were found with better prognosis than IDH wild-type

294 glioblastomas(Darvishi et al., 2020; Hartmann et al., 2010). In addition, anaplastic

295 gliomas with IDH wild-type have worse prognosis than glioblastomas with IDH

296 mutation(Hartmann et al., 2010). 1p/19q co-deletion is found with better prognosis for

297 patients with oligodendroglioma after radiotherapy or alkylating

298 chemotherapy(Jenkins et al., 2006; van der Voort et al., 2019). Additionally, GM/WM

299 relative atrophy ratio were found differences in TERT mutation, which is also a

300 promising indicator for the treatment response of radiotherapy and temozolomide in

301 primary glioblastoma multiforme (GBM)(Eckel-Passow et al., 2015; Peng et al., 2020;

302 Vuong et al., 2017; Yang et al., 2016; Yuan et al., 2016). In summary, individual

303 structural atrophy patterns are influenced by the genetic type.

304

305 Finally, several limitations should be mentioned: 1. The optimal threshold for W is not
 306 clear, and we chose $|W| > 6$ in order to reduce the false positive rate in atrophy
 307 detection. 2. The gender and TIV are not well matched between glioma patients and
 308 healthy controls, and future studies could involve more patients from multicenter to
 309 verify the robustness of the current findings.

310

311 **Conclusion**

312 Our study firstly depicted the individual atrophy pattern for glioma patients, and
 313 found individual structural atrophy was unique and driven by genetic information.
 314 Our findings could provide valuable information for the individualized presurgical
 315 evaluation and postsurgical prognosis.

316

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

	Glioma patients	Healthy controls
Number	45	51
Gender (M/F)	29/16	24/27
Age	43.2±9.7	42.6±9.7
TIV	1475.1±114.0	1425.9±144.9
Tumor volume	37.6±38.0	-
Histological grade (□/□/□)	33/10/2	-
IDH1 mutation (mutated/wild)	39/6	-
TERT promoter mutation (mutated/wild)	33/19	-
1p/19q deletion (both 1p/19q /only 19q/only 1p/none)	24/2/4/15	-
MGMT promoter methylation	0.25±0.16	-
MOCA	22.6±4.6	-

406 Abbreviation: IDH, isocitrate dehydrogenase; MGMT, O⁶-methylguanine-DNA methyltransferase;

407 MOCA, Montreal Cognitive Assessment; TERT, telomerase reverse transcriptase; TIV, total

408 intracranial volume.

409

410 **Table 2** The proposed 8 structural abnormality indexes.

Abnormality index	Description
Ipsilateral atrophy ratio	$= \frac{\text{number of GM/WM atrophy voxels in hemisphere with tumor}}{\text{number of all voxels in hemisphere with tumor}}$
Contralateral atrophy ratio	$= \frac{\text{number of GM/WM atrophy voxels in contralateral hemisphere}}{\text{number of all voxels in contralateral hemisphere}}$
Non-cancer atrophy ratio	$= \frac{\text{number of abnormal GM/WM voxels in non – cancer region}}{\text{number of all voxels in whole brain}}$
Relative atrophy ratio	$= \frac{\text{number of abnormal GM/WM voxels in non – cancer region}}{\text{number of all voxels in cancer region}}$

411 Abbreviation: GM, gray matter; WM, white matter.

412 **Figure legends**

413 **Figure 1** The flowchart of the proposed structural abnormality indexes: (A). the construction of
414 normative brain volume model; (B). the calculation of the proposed individual abnormality indexes.

415

416 **Figure 2** Three examples of individualized GM/WM abnormality maps.

417

418 **Figure 3** Overlapping gray matter atrophy in non-tumor regions for all patients with tumor on (A) left
419 hemisphere and (B) right hemisphere.

420

421 **Figure 4** Overlapping white matter atrophy in non-tumor regions for all patients with tumor on left
422 hemisphere and right hemisphere.

423

424 **Figure 5** The relationship between abnormality indexes and clinical/molecular indicators.

425

426

Voxel-wise GLM model for GM

β_{age} β_{sex} β_{TIV} Residual

Voxel-wise GLM model for WM

β_{age} β_{sex} β_{TIV} Residual

(A)

individual abnormality indexes

(B)

T1 image

**individualized GM
atrophy map**

**individualized WM
atrophy map**

**Patient 1
WHO IV**

**Patient 2
WHO III**

**Patient 3
WHO II**

The shared GM atrophy regions among patients

The shared WM atrophy regions among patients

Z=58

Z=74

Z=90

Left glioma patients

Z=58

Z=74

Z=90

Right glioma patients