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Review

Brain MRI morphometry for structural alterations in patients with glioma – A systematic review

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ABSTRACT

Background: It is already known that patients with glioma develop functional plasticity, including recruiting regions of contralateral hemisphere. However, it is still unclear, if and what kind of structural changes in contralateral hemisphere are present, and there is lack of comprehensive comparison of studies on this issue.
Objectives: First aim of this review was to summarize methodology and findings of morphometric studies of contralateral hemisphere of patients with glioma before treatment. Second aim was to discuss the possible neurobiological background of changes, methodological difficulties and possibilities, and to identify challenges for future studies.
Material and methods: Neuroimaging studies were searched in four electronic databases. Found studies were compared and discussed regarding their methodology and outcomes, and undergone thorough quality assessment.
Results: In this systematic review, we eventually included 16 studies from 2080 initially found articles. Analyzed groups of patients suffered from different types and grades of gliomas. For brain scan analyses, authors used voxel-based or surface-based morphometry. Results differed across studies, reporting both increase and atrophy of contralateral grey matter. We identified some methodological issues in papers, which were further discussed.
Conclusions: Contralateral hemisphere in glioma patients undergoes complicated structural changes, including grey matter volume increase and atrophy, which both could be signs of compensation. These are dependent on tumor location, grade of glioma, individual attributes of a given patient, and should be interpreted carefully. There is still need for further research, and we present challenges and issues which should be overcome.

1. Introduction

Gliomas are primary CNS tumors which constitute a broad and highly heterogenous group. A common feature of all gliomas is widespread infiltration of surrounding CNS tissue [1]. This infiltrative pattern of growth damages not only an area where tumor is located, but also impairs overall functioning of the brain [2]. On the other hand, it has been widely acknowledged that patients with gliomas, especially with slowly growing, "low grade" tumors, can preserve many CNS functions even when they are associated with the most affected part of brain [3]. This is due to the ability of this organ to compensate the damage, namely its plasticity.

Plasticity is the ability of CNS to adapt in response to both physiological and pathological changes. It is among others associated with recruiting different parts of brain into the function of the impaired one. Functional studies have shown that such process is gradual and ranges from perilesional recruitment to, finally, recruitment of areas from contralateral hemisphere. Neuroplasticity may alter also the structure of the brain, leading to changes in thickness of the cortex or in whole volume of involved brain regions [4].

To this day, a lot has been studied about the functional plasticity in patient with gliomas, indicating the important role of homotopic contralateral areas. However, contralateral structural plasticity remains poorly explored.

The topic of contralateral structural plasticity is important from many points of view. First of all, studying it enables us to better understand mechanisms of brain adaptation in slowly (as in low grade gliomas) and quickly (as in high grade gliomas) occurring brain injury.

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Moreover, it is interesting, if the structural changes occur only in homotopic contralateral areas or in other regions of contralateral hemisphere and if only grey matter is involved.

Clinically, analysis of this process may allow us to better understand the process of glioma progression, and perhaps, in the future, to identify patients with better prognosed post-surgery outcome. Indeed, plasticity is the outcome of both structural and functional changes, which frequently occur together. Analyzing and understanding of brain structure may therefore help to identify patients more amenable to functional compensation, facilitating recruitment for the surgery, and development of rehabilitation strategies [5]. It may also provide information about brain reorganization without performing functional studies, which are technically more demanding than non-contrast brain T1 MPRAGE studies.

Such research is also important from technical point of view. The structure of brain is most frequently analyzed using automated methods of morphometry, such as VBM or SBM, in which the brain MRI scans are processed adequately. However, in the presence of lesion the workflow of morphometry is complicated [6]. There are different approaches to overcome this, ranging from simply excluding changed hemisphere from analysis, to replacing lesioned part of brain with "virtual graft" of healthy brain tissue [7].

We have a feeling that, due to the importance of the topic on the one hand, and difficulty of the research on the other, there is a strong need for organizing already gathered knowledge. Therefore, we conducted a comprehensive, systematic review of the topic.

Our goals were: to give an overview of already published studies on the contralateral structural plasticity in patients with glioma, including their methodology and limitations, and to identify challenges which should be addressed in further studies.

2. Material and methods

2.1. Search strategy

This is a systematic review carried out according to PRISMA for systematic reviews [8]. The search strategy was registered in International prospective register for systematic reviews (PROSPERO) under the ID CRD42023477070. Search was conducted in four databases (Medline via PubMed, Scopus, Embase, Web of Science). We used following search term: 'glioma' AND ('morphometry' OR 'volumetry' OR 'neuroplasticity' OR 'structural') AND ('magnetic resonance imaging' OR 'MRI'). We included studies published since 1990 onwards. Two independent researchers (MS and JW) performed the literature search. The search was conducted on 20.02.2024 and reconducted on 11.11.2024, with no new studies found. In case of inconsistency, the decision was made by the third independent researcher, KK.

2.2. Inclusion and exclusion criteria

The observational studies were deemed appropriate for the analysis. The inclusion criteria were: a) the studied population consisted of adults over 18 years old, with diagnosis of glioma, with no previous treatment, b) control group, i.e. healthy controls, normative population data, or matched controls from different dataset were included, c) brain MRI and an analysis using brain morphometry were performed, d) the analysis of the structures contralateral to glioma was performed. The exclusion criteria were: a) studies not published in English, b) narrative or systematic reviews and meta-analyses, b) animal studies, c) case reports, errata, comments, letters to editors and editorials, d) no controls were included.

2.3. Data extraction

The extraction of the following data was performed: the first author's name, year of publication, country and institution in which study was conducted, sample size, age and sex of the study population, inclusion and exclusion criteria, studied parameters and regions of interest, technical parameters (type of MRI scanner and used sequences, type of morphometry and software used, full width at half maximum used at smoothing, thresholds, type of family wise error or false discovery rate correction). If applicable, significant alterations and voxel peaks in MNI coordinates were collected.

2.4. Quality assessment

We did not find any standardized quality assessment tools composed for morphometry studies. We used MINORS [9] and, in addition, a checklist proposed by Xin et al. specifically for neuroimaging reviews [10]. The second scale was primarly implemented in a morphometric study of patients with fibromyalgia, and we chose it after careful literature search, based on its comprehensivity. It includes diagnostic procedures, clinical and demographic characteristics, sample size, scanning parameters, analysis methods, and the caliber of the given outcomes. The detailed description with precise scoring is available elsewhere [10].The quality assessment was performed by one researcher (MS).

3. Results

3.1. Literature search

The PRISMA flow chart of study selection was demonstrated in Fig. 1. 2080 results were identified from electronic databases. After removing duplicates, 1603 studies remained and underwent title and abstract screening. 18 papers underwent full assessment for eligibility. Finally, 16 studies were included in the review.

3.2. Study quality assessment

The summaries of study quality assessments were demonstrated in Fig. 2 and Fig. 3. Briefly, we used two scales to comprehensively assess included papers. The first one, widely known and standardized, is dedicated to observational studies; the second one which we found in the literature is devoted specifically to brain morphometry studies. We found some drawbacks in methodology of included papers. None of included studies reported sample size calculation. Data about patients were collected retrospectively in 12 studies, whereas 8 of them gathered data on healthy controls prospectively. Obviously, in these studies groups were not contemporary. In 4 papers there were no baseline equivalence of patients and healthy controls groups (they differed in age or education level). Two studies calculated only VOIs and they did not report standard space coordinates (we marked them as not applicable in this category). One study reported GMV alterations in specific brain regions without mentioning coordinates and as such failed this criterion.

3.3. Studies characteristics

Sixteen studies were included in the review. Sample size ranged from 13 to 153 patients. Studies mostly considered mixed groups of patients with low- and high- grade gliomas (6 – all WHO grades; 2 – grades 1, 2, 3; 1 – grades 2 and 3; 1 – did not mention). Three studies considered only low-grade gliomas (WHO 1 and 2) and 3 studies included only high-grade gliomas (WHO 4).

Two studies included patients with insular gliomas, 6 studies - frontal gliomas, 2 studies - middle temporal gliomas, 1 study considered gliomas involving thalamus and basal ganglia, 1 study - gliomas with hippocampal involvement. Four studies considered gliomas in various localizations. The locations of gliomas included in the studies were presented in Fig. 4.

Twelve studies conducted VBM and 4 studies - SBM.

Seven studies used SPM (Wellcome Trust Center for NeuroImaging, University College, London, UK), one SPM8 and six SPM12. Six studies used CAT12 toolbox in SPM12. Two studies used Freesurfer, and 1 study used both SPM12 and Freesurfer.

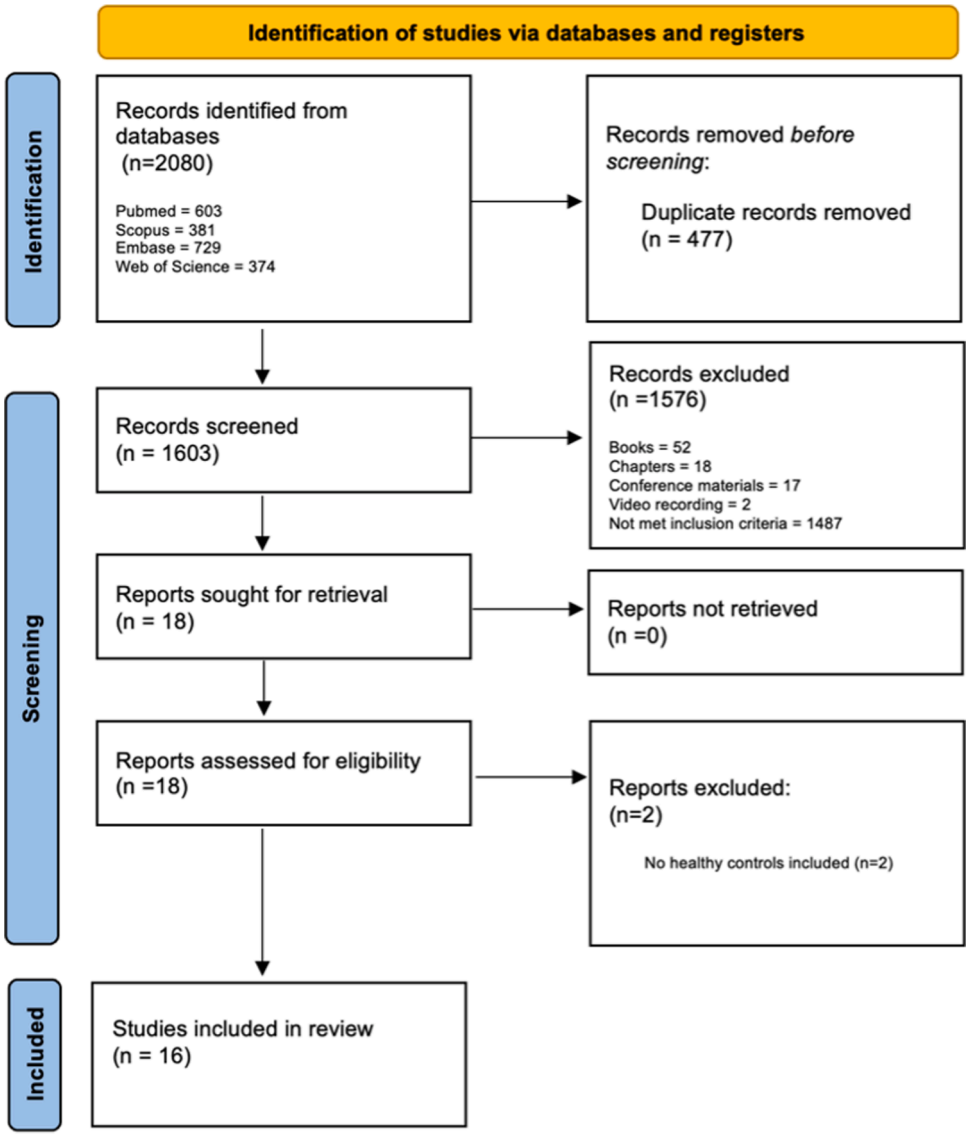

Fig. 1. PRISMA diagram.

Thirteen and the majority of studies were conducted in People's Republic of China. One was done in France, 1 in Italy, and 1 in Japan.

Specific information on the extracted data, including additional analyses performed in collected studies, was demonstrated in Table A.1. The graphical illustration of collected data is presented in Table 1.

3.4. Insular glioma

Two studies analyzed contralateral structures in patients with insular glioma using VBM. Both of them found contralateral increase in insular GMV. Almaiarc et al. [11] found that the GMV and overall volume of the contra-lesional insula in patients with insular LGG are increased compared with HCs. Hu et al. [12] found that in LGG and HGG patients with insular invasion there was increase in GMV of contra-lesional salient network structures, including insula. Interestingly, the precise location of GMV increase was dependent on the side of invaded insula, as it was reported in Table A.1.

3.5. Frontal gliomas

Studies considering frontal gliomas gave various results, frequently dependent on the side of the glioma. Four studies used VBM and two of them used SBM; two studies were of prospective design. Two studies included patients with LGG, whereas four studies analyzed mixed group with HGG and LGG. The results were variable and there were not associated with the design of study.

One study [13] found straightforward structural compensation in contra-lesional frontal lobe, in orbital and rectal gyrus, in patients with diffuse frontal gliomas, regardless of side of tumor. Additionally, there was also increase of GMV in left middle and left inferior frontal gyrus but only in right-sided glioma patients. This was not in line with another study [14], in which authors used SBM and found greater CT in the contra-lesional middle frontal gyrus, but only in patients with left sided frontal glioma. In this paper, in patients with right sided tumors increased CT was found only outside the frontal lobe, in the left middle temporal and cingulate sulci.

Two other VBM studies found increased GMV in cortex outside contra-lesional frontal lobes, in cuneus and superior temporal gyrus [15] and in superior parietal gyrus [16].

Not only increase, but also decrease in CT or GMV of some contralateral structures were found. Two papers found decreased CT in frontal cortex – one study analyzing HGG, in all frontal cortex, mainly in insula and along the Sylvian fissure [17] and one study analyzing LGG in precentral gyrus [14]. Another study found decreased GMV in putamen [15].

Fig. 2. Summary of quality assessment – methodological Index for Non-randomized Studies (MINORS).

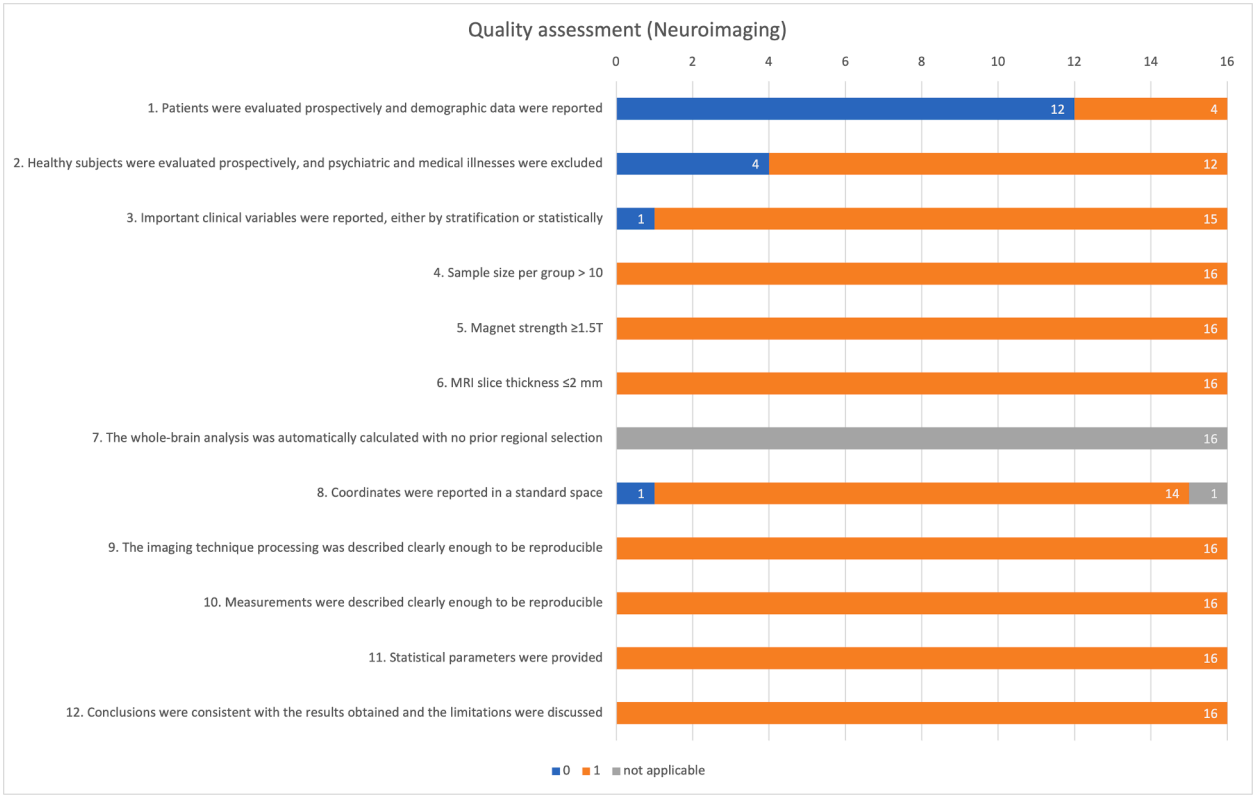

Fig. 3. Summary of quality assessment – neuroimaging scale (Xin et al. [9]).

Finally, Zhang et al. suggested that each frontal lobe glioma patient (WHO 2, 3, 4) develops individual pattern of structural brain atrophy dependent on tumor volume [18].

More precise report on techniques, patients, and compensation patterns is given in Table A.1.

3.6. *Temporal gliomas*

Two studies analyzed temporal gliomas and both of them used VBM. The groups were heterogenous and consisted of patients with both LGG and HGG. They gave contradictory results. One study of a retrospective design [19] found a decrease in GMV of contralateral MTG in

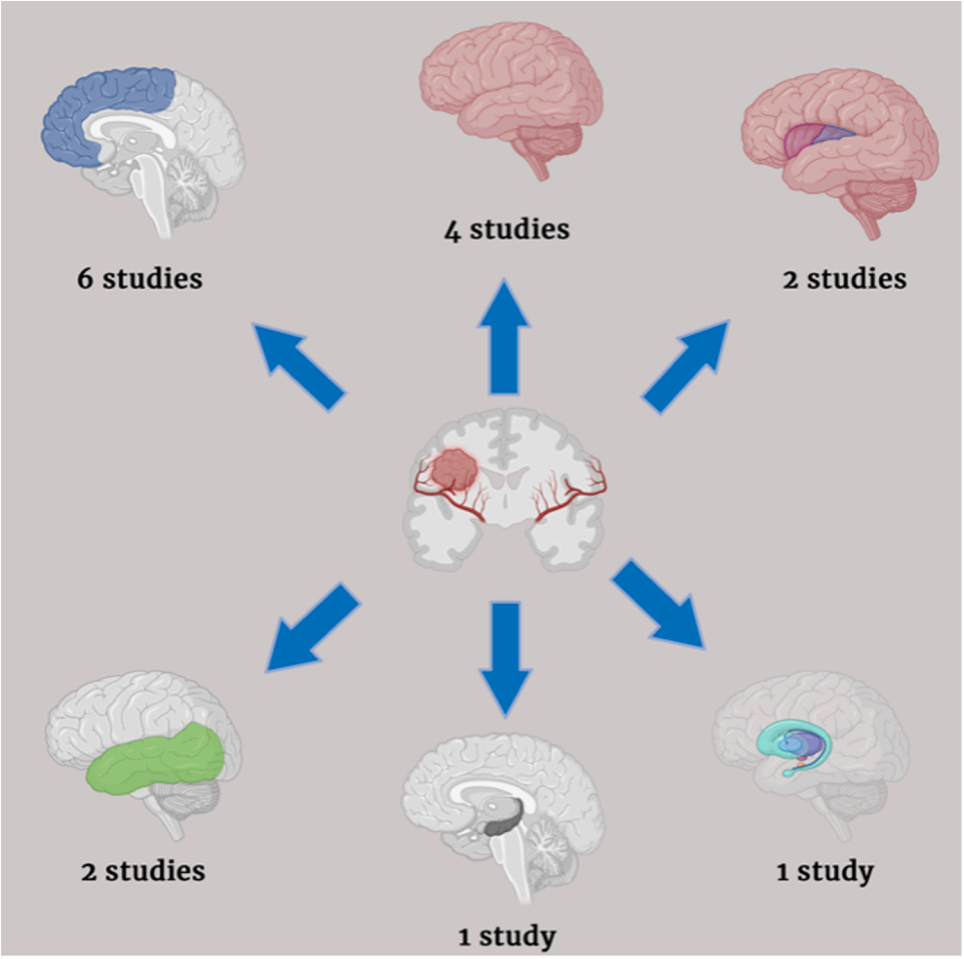

Fig. 4. Included studies – location of glioma. 6 studies included frontal gliomas, 4 - glioma regardless of their specific location, 2 - insular glioma, 2 –temporal lobe glioma, 1 – specifically hippocampal glioma 1 – basal ganglia glioma.

comparison with HCs, whereas a different, prospective study [5] found there was an increase of GMV in this region.

3.7. Thalamus, basal ganglia glioma

Yan et al. [20] performed a retrospective VBM study of patients with HGG invading thalamus and basal ganglia. They found an increase of GMV in contralateral superior frontal and medial superior frontal gyri. Moreover, in left-sided glioma patients, contralateral precuneus had also increased GMV. Again, a decrease of GMV of contralateral structure was found, in hippocampus.

3.8. Hippocampal involvement

Only one retrospective VBM study [21] analyzed GMV of the contralateral hippocampus in patients with hippocampus infiltrated by glioma (WHO type 1, 2, and 3) and found increased GMV in contralateral hippocampus and hippocampal gyri. The authors also analyzed its subfields and found increased GMV in hippocampal fimbria. In patients with left hippocampus invasion, there was also increased GMV in contralesional HATA (hippocampus-amygdalidoid transition region).

3.9. Hippocampus regardless of the location of glioma

Two studies [22,23] the first one with patients with both LGG and HGG tumors, and the second one only with HGGs - analyzed hippocampi in tumors without hippocampal involvement. They were of retrospective design, one used region of interest approach, and the other used VBM. In both of them patients had increased overall volumes in both contra- and ipsilateral hippocampus. Only the first study analyzed GMV, and the increase was found only in ipsi-lesional hippocampus.

3.10. Whole contralesional hemisphere regardless of location of glioma

Yuan et al. [24] performed a retrospective study and used VBM to analyze contralesional GMV and CSFV in patients with low- and high-grade gliomas confined to one hemisphere. They found that in HGGs group there was decreased GMV and increased CSFV in the contralesional hemisphere compared with HCs. There was no difference in studied parameters between LGGs and HCs group. More specified approach was applied by Xu et al. [25] who used VBM to study GMV of the contralesional cortex and bilateral subcortical structures (thalamus and basal ganglia) in patients with left-sided glioma, WHO grades 1, 2, and 3. They found that glioma patients had increased GMV in right cuneus, left thalamus, and trend towards enlargement in left globus pallidus. There were also positive correlations between increase of GMV and glioma volumes.

4. Discussion

In this review we summarized studies on contralateral structural plasticity in patients with glioma. Most of observed papers reported changes in the structure of regions contralateral to glioma and it was mainly due to increase of GMV or CT. However, five studies reported also atrophy in these areas.

Table 1
Structural alterations in patients with glioma. Rows indicate location of studied glioma, columns - changed contralateral sites.

	HYPPOCAMPUS	PG	AMYGDALA	FG	STG	MTG	ITG	INSULA	ISTHMUS CINGULATE	OG	PG	SFG	MFG	IFG	RG	CUNEUS	LG	LATERAL OCCIPITAL CORTEX	SOG	PRECUNEUS	PUTAMEN
TEMPORAL LOBE						[36]↑ [19]↓	[36]														
HIPPOCAMPUS	[37]	[37]																			
INSULA L					[12]	[12]	[12]	[11,12]													
INSULA R					[12]	[12]	[12]												[12]		
FRONTAL LOBE L	[38]	[38]	[39]↑ [38]↓	[7]	[39]	[38]	[38]			[13]	[7]		[7]		[13]	[39]↑ [38]↓	[38]			[38]	[39]
FRONTAL LOBE R	[38]	[38]	[39]	[38]		[7,38]	[38]		[7]	[13]	[7]	[23]	[13]	[13]	[13]	[38]	[38]	[7]		[38]	[39]
THALAMUS BASAL GANGLIA L	[20]											[20]	[20]							[20]	
THALAMUS BASAL GANGLIA R	[20]																				

Blue color indicates grey matter increase in contralateral site (increase of GMV or CT), red – decrease, yellow – ambiguous results (two studies given different results or one study and clusters of increased or decreased GMV in the same region). Only studies with precisely defined locations of tumors and compensation were included. PG – parahyppocampal gyrus, FG – fusiform gyrus, STG – superior temporal gyrus, MTG – middle temporal gyrus, ITG – inferior temporal gyrus, OG – orbital gyrus, PG – paracentral gyrus, SFG – superior frontal gyrus, MFG – middle frontal gyrus, IFG – inferior frontal gyrus, RG – rectus gyrus, LG – lingual gyrus, SOG – superior occipital gyrus.

4.1. Methods of calculation

VBM was the most commonly used method in the found studies. It measures signal intensity in each voxel and using probability maps assigns it to grey matter, white matter, and cerebrospinal fluid. Then it may calculate GMV using volumes of proper voxels [26]. The main drawback of VBM is that the obtained GMV has vague neurobiological meaning. It is a reflection of many factors such as cell size or density, neural or glial cell genesis, changes of blood flow or interstitial fluid [11].

SBM, which measures CT, was used in four studies. CT depicts the shortest distance from the white matter to the pial surface [27], as such being more straightforward parameter. GMV is SBM is calculated from grey matter thickness and area. Therefore, results of SBM are free from many methodological uncertainties characteristic of VBM.

To sum up, it is important to note that discrepancies in included studies can be associated with various methodologies and how the structural compensation was understood by the authors. Differences in CT provided by SBM can be understood very directly, whereas GMV provided by VBM has no straightforwad meaning and is dependent not only on cortical thickness, but also on its surface and histological changes leading to contrast alterations of GM voxels. Therefore, in our opinion the results of SBM can be interpreted and compared more easily. In VBM studies, results may be dependent on various factors and should be taken with greater caution, as provided information is complex and less precise.

In both methods the presence of a lesion in brain parenchyma or the midline shift pose a challenge and this was addressed differently in the studies. Generally, all authors used DARTEL, which was showed to be suitable for normalization and segmentation of a lesioned brain [6,17] Moreover, Yuan et al. [24] masked the lesioned part of brain to exclude it from calculations. Finally, Zhang et al. [14] and Liu et al. [21] used a technique of VBG. This is an open-source workflow which fills lesion with pseudo-normal tissue, using native non-lesioned hemisphere. This approach was shown to outperform non-VBG approach in preprocessing of brains with lesions [28].

4.2. Increase of grey matter amount in contralateral areas

The increase in GMV and CT in contralateral homotopic areas was found in insular, frontal, temporal, basal ganglia and hippocampal glioma. Such compensation is thought to represent secondary changes, in case of insufficient reorganization in the affected and perilesional cortex. It is supposed to be mediated by increased intra-hemispheric connectivity via corpus callosum and its decreased inhibitory role, as some studies showed increased anisotropy in corpus callosum in such cases [13,29,30].

Previous study by Almaiarc et al. [11] analyzed solely a region of contralateral insula in LGG patients and found an increase of GMV, which might be a basis for functional reorganization. This finding fits the hypothesis of recruitment of contralateral homotopic areas in chronic brain injury. However, the results of further papers suggest that such compensation, although seems straightforward, is a complex issue indeed.

Two more recent studies suggest that structural reorganization extends beyond homotopic area and occur in a network-based pattern rather than in isolated regions. Many rs-fMRI studies suggest that regions of the brain act in groups organized in topological networks [31]. Hu et al. [32] studied patients with insular glioma, and found a decrease of anisotropy in white matter tracts, which is a marker of their integrity, of salient network ipsilateral to tumor. This coexisted with increased GMV in contralateral salient network structures. Liu et al. [16] studied frontal gliomas and found functional changes (increased ALFF) in contralateral SPG, an element of cognitive control network, and in left

SPG it was accompanied by increase of GMV. These results imply that gliomas may cause a disruption of topological networks and as such induce structural compensation in contralateral, but not only homotopic, areas included in a given network.

In some of studies the increase of GMV in contralateral region turned out to be dependent on the side of the brain. As an example, in the already mentioned study by Liu et al. [16] the results showed structural changes only in left SPG. Side-dependent differences in structural compensation were observed also in other studies considering frontal glioma [13,15,20], temporal glioma [5] insular glioma [20] hippocampal glioma [21] basal ganglia glioma [20]. There are multiple hypotheses to explain those differences. The reason may be that the structural compensation in unchanged regions may be not apparent yet, as it usually takes time to develop and it follows the functional one. Moreover, the structural reorganization may have its compensatory and decompensatory periods and the patients may be in time of decompensation [16]. It may as well be that the potential of contralateral regions to undergo structural reorganization is just different [13]. Hippocampus may be a good example of an organ with high plasticity potential, as it is believed to contain neural stem cells, and both ipsi- and contra-lateral hippocampi were shown to increase their volume and amount of grey matter even in distant gliomas [22,23].

Importantly, the subregions in contralateral areas may also exhibit different compensatory abilities. Such observations were made in insula of patients with insular glioma, with clusters of decreased GMV in insulas with overall increased GMV [12], and in hippocampus in hippocampal glioma, with various levels of GMV increase in different hippocampal subfields [21].

To sum up, in gathered studies, patients with gliomas frequently exhibited contralateral GM enhancement, both in homotopic and in distant areas. The pattern of compensation is still poorly understood and most possibly dependent on location of glioma, time of disease, compensatory potential of a region or subregion, and on individual attributes of a patient.

4.3. GM atrophy in contralateral areas

The meaning of gray matter atrophy is usually associated with its functional impairment [24]. Previously, the topic of contralateral gray matter atrophy in patients with glioma was analyzed mainly in the context of previous radiation therapy, which was shown to affect the hippocampus [33]. However, five of the above studies reported atrophies of contralateral grey matter in patients before treatment.

Ironically, the presence of atrophy does not necessarily exclude compensation, but they may coexist. Kinno et al. [17] studied patients with left frontal WHO grades II and III gliomas and their only finding was decrease of GMV in contralateral frontal region, irrespective of glioma volume and grade. In the same study, the authors found that decreased GMV was correlated with increased volume of white matter. This may suggest compensatory increased activity of the cortex, as it is often associated with higher amount of oligodendroglia cells, which form white matter in brain [17].

Zhang et al. [14] found grey matter atrophy in contralateral precentral gyrus in frontal LGG patients. They suggested, that synaptic pruning may be responsible for this alteration. Synaptic pruning is a process which eliminates ineffective synapses and allows to strengthen neural transmission and generate finely tuned circuity [34]. The authors suppose that the finding of grey matter atrophy may indicate that the successful synaptic pruning was done, to enhance cortical abilities [14].

Of course, other reasons of atrophy are also possible. It seems to be an expected finding in HGG patients, as in studies by Yuan et al. [24] or Yan et al. [20]. HGGs progress rapidly and the character of brain injury may be rather acute than progressing. As such, there may be no time to develop compensatory changes [4].

Tumor cells may play a role in process of atrophy, as they release abnormally large, toxic amounts of neurotransmitters such as glutamate [24] which may induce distant regions damage. In the study of Yuan et al. [24], a decrease of GMV in contralateral frontal lobe was more advanced in patients with higher glioma grade or with larger contrast enhanced volume, which is thought to contain the most malignant cells.

Moreover, tumor induces potentially damaging inflammation [20] and edema which, even when it is barely identifiable by imaging, may cause contralateral compression and cortical thinning [17].

As increase of contralateral grey matter, also its atrophy may differ by laterality. Lv et al. [15] who analyzed LGG patients, found decreased GMV in left putament and amygdala if a tumor occurred on the right side. This was not true for patients with left-sided tumor, who had increased GMV in contralateral subcortical structures. That suggest that left frontal lobe connections between cortical and subcortical regions may be more prone to injury.

Eventually, it seems that brain atrophy in glioma patients is, again, highly heterogenous process and can depend on individual features of each patient. Zhang et al. [18] calculated structural abnormality maps for each frontal lobe glioma patient to find degree of deviation of every voxel volume from healthy controls. Although patterns of atrophy usually affected regions associated with cognitive function and were dependent on molecular biomarkers, eventually they were found to be individual for each patient.

Different reasons for gray matter atrophy in glioma patients were presented in Fig. 5.

4.4. Limitations of included studies and future directions

In this systematic review we managed to find some limitations of abovementioned studies and thereby indentify directions for the future research. Firstly, the limitation which we most commonly found in the papers was their retrospective character. Only four studies gathered groups prospectively. Authors of one of them, Ge et al. [13], included an impressive group of 101 patients. However, this group was highly heterogenous and consisted of patients with different WHO grades of glioma. It would be desirable to conduct prospective studies on larger homogenous groups, including only low- or high- grade glioma patients, which would allow to draw more specific conclusions.

Heterogeneity of groups was a limitation of most of included studies. Only six studies included groups homogenously consisted of patients with solely low- or high- grade gliomas. Mixed groups make interpretation of results troublesome, as the biological character of types of gliomas differ significantly and may affect process of plasticity, as it was mentioned earlier. Again, finding homogenous groups is an important future challenge.

The methods used by authors in different studies vary significantly. Most of authors used VBM, which interpretation is less straightforward than SBM, and the biological meaning of results is vague [26]. Although all studies used DARTEL in workflow, only two used a method of virtual brain grafting. Use of such new methods would be valuable in future studies, as classic pipelines of both VBM and SBM are usually intended for normal or nearly normal brains and rely on prior anatomical knowledge [14]. Eventually, more studies using SBM or both VBM and SBM would be also preferable.

The majority of studies conducted morphometry for solely regions of interest, not for entire brain. On the one hand, this may be valuable, as it reduces the severity of multiple comparisons correction, but on the other, it ignores changes that are not included in prior hypotheses. As such, it would be interesting to conduct more studies which assess whole brains, as in the study by Zhang et al. [18], where structural abnormality maps were calculated.

Interestingly, only three of VBM studies implemented TFCE as a method for controlling family-wise error, which is an important issue in morphometric research. Most papers used cluster-extend based correction. This could be an important clue for further studies, as TFCE was shown to outperform cluster-extend based correction with improved sensitivity, stability and giving sensible results [35].

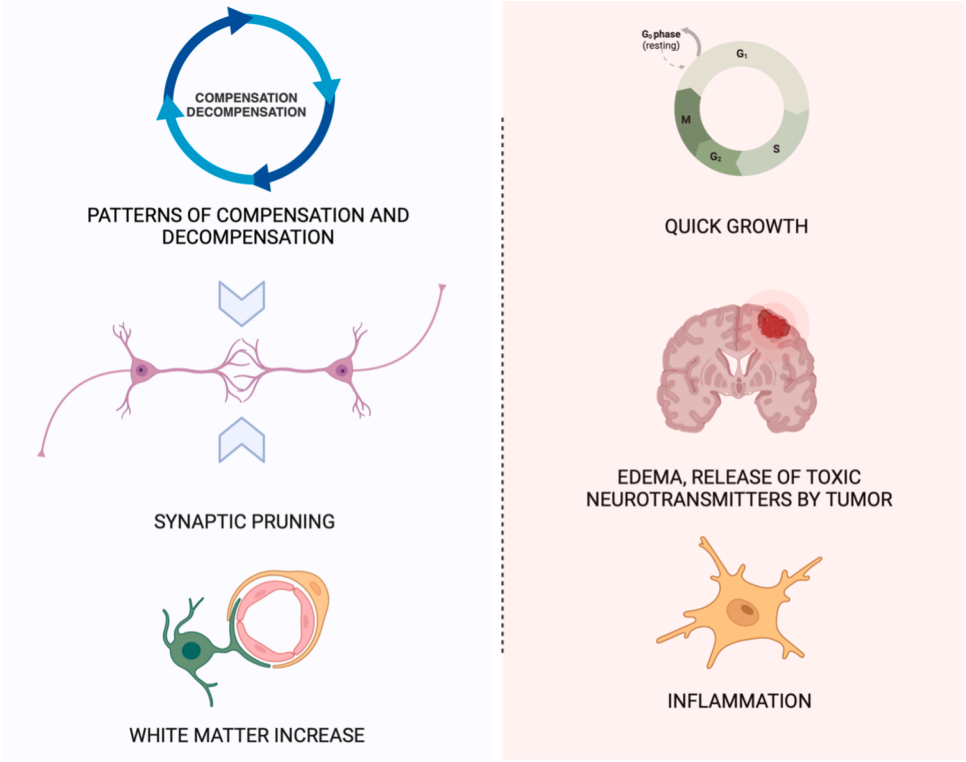

Fig. 5. Possible reasons for no grey matter increase or atrophy in contralateral regions in glioma patients.

Moreover, some of included studies do not include all MNI coordinates or do not specify thresholds for family-wise error correction, as it was presented in Table A.1. This limitation makes comparisons among studies, and specifically among anatomic sites in different patients, limited.

Finally, most (14) of studies were conducted on Asian population, and many in the same city (6 in Nanjing and 4 in Beijing). 13 of them were conducted in China which compose 81 % of found papers. It would be of great value to expand research also on different populations, as there may be potential ethnic differences in results.

4.5. Limitations

The main limitation of our review is due to vastly different methodologies of included studies. Moreover, groups of patients were heterogenous regarding locations and grades of gliomas. Therefore, we have to address many dissimilarities in both presenting results and in discussion. These issues made also conduction of meta-analysis impossible, and even synthetizing results in descriptive way was difficult.

Some of the found studies included also additional analyses, such as: neuropsychological tests, fraction of anisotropy, functional imaging. These were not addressed in this review or were addressed briefly as they were beyond the scope of our research.

5. Conclusions

The development in methods of morphometry makes analyzing brains with gliomas feasible and reliable. The already conducted studies identified changes in hemisphere contralateral to tumor, including increase and atrophy of grey matter. These changes were usually not confined only to region homologous with region infiltrated by glioma, but they affected different parts of contralateral hemisphere. It is possible, that alterations occur in a network-based pattern. They may be dependent on the side of the brain, and on the potential of various regions of brain to compensate. Further research is needed because of many uncertainties and limitations of foregoing studies. We advise to include more homogenous groups, participants of various ethnicities, and to use more advanced methods of analysis in terms of morphometry and statistics.

CRediT authorship contribution statement

Goralewski Mikołaj: Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization. **Barbara Katulska:** Writing – review & editing, Investigation, Data curation. **Mateusz Ciesielski:** Writing – review & editing, Methodology, Investigation. **Sylwia Antczak:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Jacek Wątorek:** Writing – review & editing, Project administration, Methodology, Investigation. **Marcin Stański:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Katarzyna Katulska:** Writing – review & editing, Supervision, Conceptualization. **Jakub Moskal:** Writing – review & editing, Supervision.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix. Table 1. Studies characteristics

Authors	Title	Country	Pro- or retrospective	Studied morphometric parameter	Other analyses	Region of interest	Location/Type of glioma	Number of patients (side of glioma)	HCs	MRI scanners	Preprocessing	FWHM	Covariates of no interest	FWE correction	Results of morphometry
Almaiarc et al. [11]	**Contralesional macrostructural plasticity of the insular cortex in glioma patients**	France	Retrospective	GMV	n.a.	Contralateral insula	Insula/LGG	84 (47 left, 37 right)	24	**1.5 T 3. 0 T**	SPM12 MATLAB DARTEL	8 mm	Age, sex, scanner type, tumor volume, TIV	- cluster-extent based correction (cluster level threshold $p < 0.05$, $k > 200$ contiguous voxels) - small volume correction (only insula included)	- ↑ GMV - left and right insula - ↑ volume - left and right insula
Hu et al. [12]	**Structural alterations of the salience network in patients with insular glioma**	China	Retrospective	GMV	FN and FA networks between ROIs	1. Structures of the salient network: a. ipsi- and contralateral ACC b. Contralateral insula 2. Structures involved in salient network contralateral frontal lobe 3. Contralateral occipital lobe	Insula/LGG, HGG	98 (51 left, 47 right)	21	**3.0 T**	SPM12 MATLAB DARTEL	8 mm	Age, sex	- cluster-extent based correction (corrected $p < 0.001$, $k > 30$)	**Left insular glioma:** - ↑ GMV - left ACC, right ITG, right STG, right temporal pole: MTG and right insula - ↓ GMV - right MTG, right ITG **Right insular glioma:** - ↑ GMV - left ITG, left MTG, left insula, left and right ACC, left MFG, and left SOG, - ↓ GMV - left MTG, left ITG, left temporal pole: STG, and left SOG
Ge et al. [13]	**Synergetic reorganization of the contralateral structure and function in patients with unilateral frontal glioma**	China	Prospective	GMV	Resting state fMRI - mALFF	A ROI containing both contralateral frontal lobe and insula	Frontal lobe/ LGG, HGG	101 (49 left, 52 right)	35	**3.0 T**	SPM12 MATLAB DARTEL	8 mm	Age, sex, TIV	-TFCE ($p < 0.05$, number of permutations = 1000)	**Left frontal glioma:** - ↑ GMV – right OG and right GR **Right frontal glioma** - ↑ GMV - left OG and left LGR - ↑ GMV - left MFG and left IFG
Liu et al. [16]	**Structural and Functional Reorganization Within Cognitive Control Network Associated With Protection of Executive Function in Patients With Unilateral Frontal Gliomas**	China	Retrospective	GMV	n.a.	1. Contralesional CCN: a. dorsal medial PFC b. left anterior PFC c. right anterior PFC d. left SPG e. right SPG	Frontal lobe/ LGG, HGG	37 (16 left, 21 right)	40	**3.0 T**	SPM12 CAT12 toolbox MATLAB DARTEL	8 mm	Tumor volume, TIV, age, gender, and education level	- cluster-extend based correction $p < 0.05$, $k > 30$ voxels	- right frontal lobe invasion (+) - ↑ GMV in the left SFG

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Zhang et al. [18]	**Probing individual-level structural atrophy in frontal glioma patients**	China	Prospective	GMV, WMV, W score (W score reflects the degree of deviation of each patient from healthy controls in every voxel)	correlation with molecular markers and neuropsychological test (MOCA score)	Whole brain, including contralateral structures	Frontal lobe/ LGG, HGG	45	51	**3.0 T**	SPM12 CAT12 toolbox MATLAB DARTEL	4 mm	Age, sex, TIV	$P < 0.05$ - no information on correction	**GMV:** - every patient displayed unique atrophy pattern - ↓ GMV- the temporal lobe, the mesial temporal lobe, (mainly including hippocampus, amygdala and parahippocampus), MTG and ITG, precuneus, LG, FG and insula **WMV:** - WMV ↓ - **bilateral thalamus and pallidum**
Lv et al. [15]	**Contralesional macrostructural plasticity in patients with frontal low-grade glioma: a voxel-based morphometry study**	China	Retrospective	GMV	n. a.	Contralateral hemisphere, including frontal lobe	Frontal lobe/ LGG	44 (19 left, 25 right))	25	**3.0 T**	SPM12 MATLAB DARTEL	8 mm	age, sex, TIV	- cluster-extend based correction $p < 0.05$, $k > 200$ voxels	**Left frontal glioma:** - ↓ GMV - right putamen - ↑ GMV - right amygdala, right cuneus, right STG **Right frontal glioma:** - ↓ GMV - left putamen - ↑ GMV - left amygdala
Zhang et al. [7]	**An MRI Study Combining Virtual Brain Grafting and Surface-Based Morphometry Analysis to Investigate Contralateral Alterations in Cortical Morphology in Patients With Diffuse Low-Grade Glioma**	China	Retrospective	CT, LGI (LGI quantifies the amount of cortex buried within the sulcal folds as compared with the amount of cortex on the outer visible cortex.	n.a.	Whole contralateral hemisphere	Frontal lobe/ LGG	99 (56 left, 43 right)	53	**3.0-T**	VBG - Virtual Brain Grafting Freesurfer 6.0.0	CT - 15 mm LGI - 10 mm	a correlation between CT, LGI and radiomic features of glioma was examined Pyradiomics package (version 3.0.0) (https://pyradiomics.readthedocs.io) 558 features were generated for each patient	Monte Carlo simulation, 10,000 iterations and identify significant contiguous clusters of vertex-wise differences Significance levels: cluster-forming $P < 0.01$, cluster-wise corrected $P < 0.01$	**LF patients** - ↑ CT - right rostral MFG - ↓ CT - right precentral gyrus in the right hemisphere. **RF patients** - ↑ CT - left MTG, LOG extending to isthmus cingulate gyrus **both LF patients and RF patients:** - ↓ CT - left precentral gyrus
Kinno et al. [17]	**Differential Effects of a Left Frontal Glioma on the Cortical Thickness**	Japan	Retrospective	CT, FD (FD assesses complexity of the cortex)	n.a.	Whole brain, including contralateral structures	Frontal lobe/ LGG, HGG	15	15	**3 T**	SPM12 CAT12 toolbox MATLAB DARTEL	20 mm	Not given	TFCE, 10 000 permutations, FDR< 0.05	- ↓ CT in almost all left sided regions except for the left frontal operculum

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Authors	Title	Country	Pro- or retrospective	Studied morphometric parameter	Other analyses	Region of interest	Location/Type of glioma	Number of patients (side of glioma)	HCs	MRI scanners	Preprocessing	FWHM	Covariates of no interest	FWE correction	Results of morphometry
	and Complexity of Both Hemispheres														and left primary motor cortex - ↓ CT - right perisylvian cortex, which extended from the frontal opercular and insular cortex to the entire hemisphere - ↓ FD - in left frontal regions
Yuan et al. [19]	**Structural and Functional Alterations in the Contralesional Medial Temporal Lobe in Glioma Patients**	China	Retrospective	GMV	rsFSC of the memory network of the contralateral hemisphere	Contralesional medial temporal lobe	Medial temporal lobe/ LGG, HGG	68 (33 left, 35 right)	40	**3.0 T**	SPM12 CAT12 toolbox MATLAB DARTEL	8 mm	TIV, age, and sex	cluster-extent based correction ($pFDR < 0.05$, $k > 50$)	- ↓ GMV in contralateral temporal lobe
Hu et al. [5]	**Restructuring of contralateral gray matter volume associated with cognition in patients with unilateral temporal lobe glioma before and after surgery**	China	Prospective	GMV	Several classical neurocognitive tests including DST, memory test, visuospatial test, math exam test, DSST, mapping test, and similarity test.	Contralateral temporal lobe	Temporal lobe/LGG, HGG	26	28	**3.0 T**	SPM12 MATLAB DARTEL	8 mm	age, gender, education, TIV, tumor volume	Cluster-extent based correction Corrected $p < 0.001$, $k > 30$	**Left temporal glioma** - ↑ GMV in right temporal gyrus - ↑ GMV in right temporal pole **Right temporal glioma** - ↑ GMV in left ITG - ↑ GMV in left MTG
Yan et al. [20]	**Synergistic structural and functional alterations in the medial prefrontal cortex of patients with high-grade gliomas infiltrating the thalamus and the basal ganglia**	China	Retrospective	GMV	n.a.	Contralateral default mode network	Thalamus, basal ganglia/ HGG	33 (18 left, 15 right)	24	**3.0 T**	SPM12 MATLAB DARTEL	6 mm	Age, gender, education (age), TBV (total brain volume)	TFCE, 5000 permutations	**Right-sided glioma:** - ↑ GMV in superior frontal gyrus and left medial superior frontal gyrus - ↓ GMV in hippocampus **Left-sided glioma:** - ↑ GMV in superiotr frontal gyrus, left median superior frontal gyrus, and precuneus - ↓ GMV in hippocampus
Liu et al. [21]	**Structural plasticity of the contralesional hippocampus and its subfields in patients with glioma**	China	Retrospective	Hippocampal volume, volume of hippocampal subfields	n.a.	Contralateral hippocampus	Hippocampus/ HGG	55 (27 left, 28 right)	30	**3.0 T**	SPM12 MATLAB DARTEL VBG (the contralateral hippocampus of those patients was segmented into	8 mm	VBM: sex, age, education, TIV Multiple linear regression: tumor hemisphere,	- TFCE-FWE, 1000 permutations, $p < 0.05$ for VBM analyses - Bonferroni correction for hippocampal subfields	- ↑ GMV in hippocampus and parahippocampal gyrus Only right-sided glioma: - ↑ GMV in anterior hippocampal cluster Subregions in both groups:

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Authors	Title	Country	Pro- or retrospective	Studied morphometric parameter	Other analyses	Region of interest	Location/Type of glioma	Number of patients (side of glioma)	HCs	MRI scanners	Preprocessing	FWHM	Covariates of no interest	FWE correction	Results of morphometry
											19 distinct subregions by the segment HA-T1 function implemented in FreeSurfer 7.0)		grade, volume		- ↑ GMV in hippocampal fimbria Subregions in left-sided glioma: - ↑ GMV in HATA
Zilioli et al. [23]	**Volumetric hippocampal changes in glioblastoma: a biomarker for neuroplasticity?**	Italy	Retrospective	ROI volumes	n.a.	Ipsilateral, contralateral hippocampus; mean volume of hippocampus	No specific location/HGG	15	19	**3.0 T**	SPM12 CAT12 toolbox MATLAB DARTEL	8 mm	sex, TIV, and education	cluster-extent based correction ($pFDR < 0.05$, $k > 50$)	- ↑ of both absolute and normalized contralateral hippocampal volume - ↑ mean and absolute ipsilateral hippocampal volume, which did not survive normalization to total intracranial volume - ↓ of volume of ipsi- and contralateral hemispheres of cerebellum
Yuan et al. [22]	**Structural plasticity of the bilateral hippocampus in glioma patients**	China	Retrospective	GMV, hippocampal volume	n.a.	Contralateral hippocampus	No specific location/LGG, HGG	99 (25 left LGG, 27 right LGG, 25 left HGG, 22 right HGG)	80	**3.0 T**	SPM12 CAT12 toolbox MATLAB DARTEL	8 mm	TIV, education, age and sex	cluster-extent based correction ($p < 0.05$, $k > 20$)	- ↑ GMV in ipsilateral hippocampus - no changes in contralateral hippocampus - ↑ hippocampal volume in ipsi- and contralateral hippocampi - for HGG patients - ↑ in the ipsilateral hippocampal volume relative to the contralesional hippocampus
Yuan et al. [24]	**Contrahemis-pheric Cortex Predicts Survival and Molecular Markers in Patients With Unilateral High-Grade Gliomas**	China	Retrospective	Contrahemispheric GMV (CHGMV)	1. IDH1-R132H, MGMT, ATRX, and P53 mutations status 2. Survival analysis	Contralesional hemisphere	No specific location/LGG, HGG	153 (76 left, 77 right)	115	**3.0 T**	SPM12 MATLAB DARTEL	8 mm	not given	Bonferroni correction $p < 0.05$	Both left- and right-sided HGG: - ↓ contrahemispheric GMV - ↑ contrahemispheric CSFV There was no difference between LGG and HCs - patients with higher WHO grade showed more significant decrease in contra-hemispheric GMV - significantly negative correlation between contra-

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Authors	Title	Country	Pro- or retrospective	Studied morphometric parameter	Other analyses	Region of interest	Location/Type of glioma	Number of patients (side of glioma)	HCs	MRI scanners	Preprocessing	FWHM	Covariates of no interest	FWE correction	Results of morphometry
Xu et al. [25]	**Cortical and Subcortical Structural Plasticity Associated with the Glioma Volumes in Patients with Cerebral Gliomas Revealed by Surface-Based Morphometry**	China	Retrospective	Cortical and subcortical GMV	n.a.	Contralateral (right) cortex and bilateral subcortical structures (thalamus, hippocampus, globus pallidus, putamen, caudate)	No specific location/LGG, HGG	13 (13 left)	14	**3.0 T**	FreeSurfer	10 mm	Age, sex	Monte Carlo simulation, treshold < 0.001	hemispheric GMV and contrast enhancing volume - ↑ GMV in right cuneus - ↑ GMV in left thalamus - trend towards enlargement in right globus pallidus

DST - digit span test, DSST - digital symbol substitution test, FA – fractial anisotropy, FN – functional network, FD - fractial dimentionality, FWE – family wise error, FWHM – full width height at maximum, GMV – grey matter volume, HCs – healthy controls, HGG – high grade glioma, LGG – low grade glioma, LGI - local gyryfication index, mALFF - mean amplitude of low frequency fluctuation, rFSC - resting-state functional connectivity, TFCE – threshold free cluster enhancement, TIV – total intracranial volume, VBM – voxel based morphometry, WMV – white matter volume.

ACC - anterior cingulate cortex, FG – fusiform gyrus, GR - gyral rectus, ITG – inferior temporal gyrus, LG – lingual gyrus, LOG – lateral occipital gyrus, OG – orbital gyrus, PFC - prefrontal cortex, SOG – superior orbital gyrus, SPG – superior parietal gyrus, STG - superior temporal gyrus.

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Glossary

CNS: central nervous system
VBM: voxel-based morphometry
SBM: surface-based morphometry
MRI: magnetic resonance imaging
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
MNI: Montreal National Institute
MINORS: the Methodological index for non-randomized studies
MPRAGE: Magnetization Prepared – Rapid Gradient Echo
VOI: volume of interest
GMV: grey matter volume
HCs: healthy controls
LGG: low grade glioma
HGG: high grade glioma
CT: cortical thickness
MTG: middle temporal lobe
CSFV: cerebral spinal fluid volume
DARTEL: Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra algorithm
VBG: virtual brain grafting
rs-fMRI: resting-state functional MRI studies
ALFF: amplitude of low frequency fluctuations
SPG: superior parietal gyrus
TFCE: threshold free cluster enhancement