Glioma migration through the Corpus Callosum and the brainstem detected by DTI and MRI study

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Title:

Glioma migration through the Corpus Callosum and the brainstem detected by DTI and MRI study: initial findings

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Running title: Glioma cell migration along white matter tracts

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Abstract

Purpose: Glioma cell infiltration, in which the glioma tumour cells spread long distances from the primary location using white matter or blood vessels, is known as a significant challenge for surgery or localised chemo- and radiation therapy.

Following the World Health Organization (WHO), the glioma grading system ranges from stages I-IV, in which the lower-grade gliomas represent benign tumours, and higher grade gliomas are considered the most malignant.

Materials and Methods: We gathered MRI and DTI data for 7 patients with right precentral gyrus-located tumours and six age- and sex-matched healthy subjects for analysis. Tract Based Spatial Statistics (TBSS) was utilised to evaluate whole-brain white matter implication due to probable tumour infiltration. Also, along-tract statistics were used in order to trace the implicated WM tracts.

Finally, for cortical evaluation of probable tumour cell migration, Voxel-Based Morphometry (VBM) was utilised, which allowed us to do whole-brain cortical estimation.

Results: The TBSS results revealed significantly higher fractional anisotropy (FA) and lower mean diffusivity (MD) in the left side superior corona radiata. Also, higher fractional anisotropy was observed in the right corticostriatal tract.

Along-tract statistics were also compiled on the corpus callosum (CC), which is anatomically known as a hub between hemispheres. The body of the CC, which connected with the superior corona radiata anatomically, showed significantly higher FA values relative to healthy subjects, which are in line with the TBSS results.

Consistent with these results, whole brain grey matter changes were analysed via VBM, which showed significant hypertrophy of both sides of the brainstem.

Conclusion: In future investigations, focusing on the genetic basis of the glioma patients in line with imaging studies on a larger sample size, which is known as genetics-imaging, would be a suitable approach for tracing this process.

Keywords: Tract Based Spatial Statistics (TBSS), Voxel-Based Morphometry (VBM), Magnetic Resonance Imaging (MRI), Corpus callosum (CC), white matter (WM)

Introduction

Glioma invasion, as the major obstacle for curing patients, is hypothesised to be carried out via extracellular routes to the other brain structures, and causes significant complications for complete surgical resection and chemo- and radiation therapy.

Glioma cell migration, which can occur over long distances via white matter or blood vessels to injure white matter or cortical structures, has been investigated previously in mammalian brains (Cayre, Canoll et al. 2009). In 1938, Hans Joachim Scherer investigated 100 patients with glioma tumours and created criteria for glioma invasion through the brain parenchyma, pre-existing blood vessels, subarachnoid space and white matter tracts. (Scherer 1938).

Diffusion tensor imaging (DTI) is a modern technique which is sensitive to the diffusion of water flow along the white matter (WM) tracts. Hence, it can detect tumour infiltration through the WM tracts when conventional MRI scans appear to be normal (Price, Burnet et al. 2003).

The infiltrating glioma cells extend beyond the surgeon's reach, which can limit the effectiveness of localised therapy (Hochberg and Pruitt 1980, Burger, Heinz et al. 1988, Kreth, Warnke et al. 1993, Shapiro 1999).

Regarding the symptoms of right precentral gyrus glioma patients, sensory deficits in the contralateral side are usually represented in these patients, which could be due to atrophy or

even hypertrophy of sensory cortices, such as the primary and secondary somatosensory cortex (SSC), the brainstem and insula.

The pathway of glial cell migration from the left precentral gyrus to its contralateral side and its effects on cortical regions are the main focus of this study. Therefore, according to the aforementioned findings, we hypothesised that (see Figure 1) the glial cells of left precentral gyrus tumours may migrate along the CC white matter tract, which acts as a hub between hemispheres. The specific region of the CC involved is not yet known, and needs to be clarified in the study.

Next, if glioma migration is proved by the results, the probable cortical changes of the left hemisphere also need to be investigated. That is why we used diffusion tensor imaging techniques (deterministic tractography, TBSS and along-tract statistics) to clarify this probable mechanism.

Materials and methods

Participants

In this study, seven patients with different types of glioma tumours of the right motor cortex (see table1 and figure1) and seven healthy subjects (age- and sex-matched) were included. Subjects with previous neurological problems, such as Parkinson's disease or previous cancer history, were excluded. In addition, in order to prevent statistical problems, we performed a two-tailed t-test, and no significant differences were seen in either the sex (P=0.2) or age (P=0.32) of the groups.

Image Acquisition

Structural MRI and DTI data acquisition

All structural MRI scans were acquired from 3T MRI scanners (Siemens Prisma). The MR anatomical 3D T1-weighted imaging (TE = 3.74 ms, TR = 1810 ms, flip angle = 30 °, 256 ×256 matrix, 1- mmthick slices).

Also, diffusion-weighted imaging (DWI) brain scan done via the same scanner with a 64-channel head coil. Other acquisition parameters were: number of slices, 68; diffusion directions, 30; FOV, 256 × 256 mm^2; voxel size, 2 × 2×2 mm^3; TR/TE, 9000/90 ms.

Data analysis

Structural data preprocessing and Voxel-Based Morphometry

Structural data were analysed using FSL-VBM protocol (Ashburner and Friston 2000, Good, Johnsrude et al. 2001). First, non-brain tissues were extracted using the brain extracting tool (BET) (Smith 2002) and GM segmented before MNI152 standard space registration using non-linear registration.

The resulting GM partial volume images were averaged to create a study template, and then all native GM images were registered non-linearly to this template. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. For the last step, the voxel-wise General Linear Model (GLM) was applied using permutation-based testing. Threshold-free cluster enhancing (TFCE) used for thresholding (Smith and Nichols, 2009). Images were thresholded at $P<0.05$ and corrected for multiple comparisons (see Figure 2).

DTI data preprocessing and Tract Based Spatial Statistics (TBSS)

In order to preprocess the DTI data, we utilised the FMRIB Software Library (FSL 5; http://www.fmrib.ox.ac.uk/fsl). At first, all diffusion-weighted images (DWI) were checked visually for any visible artefacts and then corrected for B_0 inhomogeneities and eddy-current

distortion, with each subject's DWI registered to the corresponding b=0 images via affine transformation.

Secondly, the data were brain-extracted via FSL BET to remove unwanted voxels and finally, fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD, eigenvector L1), L2 and L3 maps were created using DTIFIT.

For analysing white matter changes between groups, TBSS was performed (Smith, Jenkinson et al. 2006) using Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) version 5.0 (Smith, Jenkinson et al. 2004). For the first step, all FA images were non-linearly aligned to a common space (FMRIB58FA_1 mm). In order to create a mean FA skeleton, mean FA images created for each subject, and each FA image was projected onto the mean FA skeleton. TBSS also performed for non-FA data (MD and RD). Nonlinear registration was obtained for FA data and each MD image was projected to the mean FA skeleton.

Statistical analyses

- **Voxel and tract-based statistics**

A voxel-wise GLM was performed for structural T1 data after performing the VBM protocol using 5000 permutations; finally, TFCE was used for finding significant clusters with thresholds set at $p<0.05$, corrected for multiple comparisons (Smith and Nichols, 2009).

Statistical analyses for DTI data were performed using voxel-wise statistical analysis of FA, MD data using TBSS V1.2 part of FSL (Smith, Jenkinson et al. 2006) and FA, MD changes were assessed using permutation-based non-parametric testing with 5000 random permutations (Nichols and Holmes 2002). Our statistical threshold was TFCE and the family-wise error-corrected P-value of 0.05 (Smith and Nichols 2009).

After performing voxel-wise statistics, MNI coordinates of significant clusters in GM were calculated, and anatomical regions were identified using Harvard sub-cortical and Juelich atlases.

- **Along-tract statistics**

VBM and TBSS allowed us to evaluate the cortical and white matter alterations in glioma patients relative to healthy subjects, but in order to achieve the disclosure of glioma invasion patterns along white matter tracts, we used along-tract statistical analyses (Colby, Soderberg et al. 2012) to show the probable hub of this invasion.

Based on this technique, which could be a suitable complement for TBSS, the fractional anisotropy values along the significant tracts that were visualised by TBSS were extracted again separately to determine the WM hypertrophy or demyelination probability in glioma patients versus healthy controls (see figure 5).

According to the small sample size, we decided to use a linear mixed-effects model, in which the FA is the only dependent variable. Hence, using the along-tract statistics Matlab toolbox (http://github.com/johncolby/along-tract-stats) allowed us to extract

FA values and streamlines, and the standard deviation of the WM tract was added to the other variables for application on WM tract data as a serial uni-variate approach. Then fixed effect results containing the position factor, overall intercept and group: position interaction were analysed.

All the procedures of statistical analyses were performed via R version 3.5.0 (*R* Core Team, 2018) and MATLAB (MathWorks, Natick, USA) software.

Results

1. Tract-based spatial statistics (TBSS)

Significant white matter maturation occurred in patients versus healthy controls, and the FA was significantly higher ($P<0.001$) than the MD in patients relative to healthy subjects (see Figure 3), and this result could be a reflection of probable WM maturation due to glioma tumour migration.

According to figure 3, right corticostriatal pathways in the ipsilateral side of the tumour's location showed higher FA but no significant MD changes. Hence, we cannot judge whether there was WM maturation or demyelination.

According to figure 3, the left superior corona radiata showed WM maturation as indicated by the DTI metrics. The FA was significantly higher than the MD values ($P<0.001$), which could be a sign of glioma migration along the CC, which acts as a hub between both hemispheres.

In keeping with our hypothesis diagram (see Figure1), glioma migration into the contralateral side of the tumours' location is observed, but consistent with TBSS limitations (Bach, Laun et al. 2014), specific disclosure of glioma migration along the WM route would not be possible. Hence, we performed along-tract statistics to clarify whether there was a matured white matter hub between hemispheres.

2. Along-tract statistics

In order to verify our probable WM pattern prediction of glioma migration, FA values were analysed along the tract of the CC, which is anatomically known as a hub between hemispheres.

As we show in figure 4 (Part A), streamlines between groups were analysed, and lower streamlines but no signs were found in glioma patients versus healthy subjects (t= -1.87, p= 0.065). According to the visualised results in figure 4 (Part B and C), along-tract statistical analyses were carried out in order to reveal the overall FA versus position curves between the groups.

This analysis showed significant group-position implication (F= 33.3, p= 0.00018) in the body of the CC and right corticostriatal WM, which are illustrated in figure 4 (Part C).

Hence, all the statistical results can be visualised in Part C of figure 4, which is consistent with the TBSS results showing higher FA in the left superior corona radiata in glioma patients.

According to these results and our hypothesis diagram (see figure 1), the body of the CC played a significant role in glioma migration from the precentral gyrus to the contralateral side (see figure 4). This migration would induce cortical changes, such as atrophy or hypertrophy of regions, which need to be verified by cortical imaging techniques, as we have done in this study.

3. Voxel-based morphometry (VBM)

Structural T1 analyses via VBM revealed brainstem hypertrophy on both sides (see figure 7) in glioma patients in comparison to healthy controls (TFCE corrected, P-value<0.05). Our analyses also showed atrophied Brodmann areas 4, 6 and 31, but this was not significant (P>0.05).

As indicated by the TBSS and along-tract statistics results, glioma migration through the body of the CC involved the left side precentral gyrus, and also increased the FA values of the corticostriatal tracts, which could be the reason for the right brainstem hypertrophy.

However, WM analyses of the corticospinal tracts or internal capsule gave no significant results to justify the probable reason for the left side hypertrophy of the brainstem.

Altogether, all the results investigated by WM and grey matter analyses would indicate that the brainstem hypertrophy occurred because of the glioma migration (see figure 6), and in order to trace this transition in vivo, future longitudinal investigations are needed.

Discussion

Present study

In the present study, we had seven patients with right precentral gyrus glioma, and the pathological examinations verified the tumour type. Following our hypothesis diagram (see figure 1) and in keeping with previous literature, we predicted glioma migration through the CC from the left side precentral gyrus into its contralateral side. Subsequently, this probable migration would change in cortical regions, which needs evaluation.

In order to evaluate cortical changes due to glioma migration, we used VBM analyses, which allowed us to determine whole-brain cortical volume. Interestingly, both sides of the brainstem showed hypertrophy, which could be a reflection of glioma cell aggregation in this region.

TBSS analyses were performed for the prediction of glioma migration within whole-brain WM tracts, and the results supported our hypothesis of probable glioma migration along the CC to the right-side superior corona radiata. The involvement of WM tracts in glioma tumour cell migration has been shown to be a significant process (Pedersen, Edvardsen et al. 1995, Bjerkvig, Lund-Johansen et al. 1997, Soroceanu, Manning et al. 1999), which is in line with our TBSS results on superior corona radiata of the left side hemisphere with WM fibre maturation.

The involvement of the CC, which is known as a Scherer's structure in this process (Scherer 1938), needs investigation via a complementary analysis to TBSS, which is carried out by along-tract statistics. The results showed maturation of the body of the CC, in line with TBSS results that showed no significant WM demyelination signs.

As stated in our study's hypothesis (see figure 1), probable cortical changes would occur as a consequence of glioma migration from the right precentral gyrus to its contralateral side, but to the best of our knowledge, no previous glioma cell invasion to the brainstem due to this isolated process has been reported.

White matter tract maturation in the glioma migration process

Consistent with the WM analysis results, WM maturation was seen in the right corticostriatal pathways, left superior corona radiata and the body of the CC, which showed significantly increased FA and decreased MD values. The lack of demyelination signs in WM tracts would be a reflection of glioma cell migration along WM tracts to the contralateral side of the tumour's location, rather than degeneration.

However, we excluded the patients with previous metastatic tumour history or high-grade gliomas, and our WM analyses are in line with a study that reported higher MD and lowered FA in the peritumoral region of metastatic tumour patients (Holly, Fitz-Gerald et al. 2018). Interestingly, higher FA and lower MD values were observed in the ipsilateral peritumoral regions of glioma patients.

A few DTI studies on high-grade glioma patients have also claimed to show signs of glioma cell migration through the CC into the contralateral side (Price, Pena et al. 2004). In an investigation on 31 high-grade glioma patients utilising DTI, the tumour-related area of the CC showed reduced FA and increased ADC values (Kallenberg, Goldmann et al. 2013).

These changes in anisotropy and diffusivity are in line with our results, which suggest tumour spread along the CC, but exclusion of high-grade glioma patients and analysing the CC via along-tract statistics for increasing the accuracy are the novel aspects of our study.

In contrast to our study, in an investigation of glioma infiltrating from edema tissue, no significant difference was seen in FA and MD. However, the study population contained 18

glioblastomas and 22 metastatic tumours, which could be a limitation for this study (Hoefnagels, De Witt Hamer et al. 2014). In addition, the DTI study was carried out between the tumoral and peritumoral site and the contralateral side, which would be another significantly different approach from what we claimed in this study.

Hypertrophy of brainstem and glioma migration

The propagation of tumour cells throughout the whole brain and its overall invasion pattern is not yet clear, and more studies are needed for investigation in this context.

In accordance with the related symptoms of precentral gliomas, the involvement of the cortical homunculus is expected, and obviously, the main sensory projections from the brainstem into the cortical homunculus are also prominent. In keeping with these considerations, grey matter analyses in our study showed significant hypertrophy of the brainstem in glioma patients relative to healthy subjects.

This result may be a reflection of the tumour cell migration, which is line with a histopathological investigation on mouse models that reported the accumulation of tumour cells in regions far from the transplant side (Mughal, Zhang et al. 2018).

However, with the dispersal of glioma cells through the mouse brains, surprisingly, the hippocampus was remarkably free of glioma cell infiltration, which may be in line with our cortical analyses via VBM that showed no involvement of both sides of the hippocampus in this process.

Knowledge of tumour cell aggregation in located regions of the brain is also important in radiotherapy, so that the structures with accumulated tumour cells could receive higher dosage radiation, and the tumour-free structures could be relatively spared (Nourallah, Digpal et al. 2017).

However, glioma invasion has been speculated to occur by invasion along vessels in the perivascular spaces (Cuddapah, Robel et al. 2014), but the present study and our results may not support this hypothesis. Nevertheless, more investigation with different approaches is needed to elucidate this process.

Precision medicine

Precision medicine is currently known as a treatment paradigm considering the molecular and cellular features of a tumour along with its supplementary properties, such as genetics, in order to create a tailor-made treatment. (Yates, Seoane et al. 2018).

According to the WHO, the glioma grading system ranges from stages I-IV, in which the lower grade (I-II) of gliomas are considered to be benign tumours, and higher-grade gliomas (III-IV) are considered malignant (Louis, Ohgaki et al. 2007, Barchana, Margaliot et al. 2012, Ostrom, Gittleman et al. 2014).

However, there is no distinct genetic profile for benign or malignant gliomas to promote tailored therapies for these tumours, so producing new information about glioma cell properties such as migration, behaviour and genetics would be a crucial step toward the realisation of precision medicine.

These considerations along with the modern developed multidisciplinary investigation methods, such as genetic imaging, would be a suitable approach to complement other cellular, molecular and genetic approaches (Mackey, Kan et al. 2016).

Large-scale distributed analyses of magnetic resonance imaging (MRI) scans combined with a voxel-wise genome-wide association approach would be a useful tool in the future to prescribe tailored therapy for gliomas. However, these approaches are currently being adopted in the study of neurological disorders, and the results are quite promising (Thompson, Martin et al. 2010, Jahanshad, Roshchupkin et al. 2018).

Altogether, in gathering glioma genetic, cellular, behaviour and genetic imaging in order to reach a purposed base criterion for the future glioma precision therapy, taking advantage of previous investigations on neurological disorders using the same approach is obviously needed (Hampel, O'Bryant et al. 2017, Titova and Chaudhuri 2017, Hampel, Vergallo et al. 2018, Ferretti, Santuccione-Chadha et al. 2019).

Conclusion

In the present study, the glioma migration hypothesis was evaluated using DTI and structural MRI analyses. Based on the tumour location (precentral gyrus), the body of the CC showed significant alterations according to the DTI analyses. In addition, both sides of the brainstem also showed hypertrophy, which could be a reflection of glioma cell aggregation far from the primary tumour area.

It should be mentioned that the sample size of the present study is a major limitation, and future investigations need to overcome this shortcoming. Genome-wide association analyses in keeping with multimodal imaging analyses, such as genetic imaging, would be a practical approach to moving forward in precision tailored therapy.

AUTHOR CONTRIBUTIONS

GS and AMP contributed equally. AMP acquired, analysed, and explained the data, drafted the manuscript and revised it. HH, TE revised the manuscript.

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Conflict of Interest Statement:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figure 1 | Glioma tumor migration hypothesis between hemispheres and its probable effect on cortical regions of the contralateral side

Abbreviations: CC, Corpus Callosum; SSC: Somatosensory cortex.

Figure 2 | Seven patients with right precentral gyrus glioma (nodes are used for better visualization) are shown in section A. One patient with a 3D-segmented tumor is visualized as an example in part B. Deterministic tractography of corpus callosum is presented in part C, which includes its whole neuroanatomy: 1. Genu of corpus callosum 2. Body of corpus callosum 3. Splenium

Figure 3 | TBSS results showing significant superior corona radiata and corticostriatal tracts alterations in patients versus normal subjects. Significantly higher FA and lower MD values were seen in corpus callosum, which could be a sign of WM maturation.

Figure 4 | Hypothesis of glioma migration from the right precentral gyrus to the contralateral side updated by the along-tract statistics results, which reveal this transition through the body of the CC.

Figure 5 | Along-tract statistical analyses showing significantly lower streamlines in glioma patients relative to normal subjects (Part A). FA values along CC were analyzed between groups which showed a remarkable difference (higher FA along streamlines) in patients versus controls (Part B). All the statistical features visualized show the CC implication as a hub between hemispheres.

Figure 6 | Glioma migration hypothesis which show the transition pattern along the body of the CC and probable influence (hypertrophy) on both sides of brainstem.

Figure 7 | VBM analyses showing significantly hypertrophied brainstem on both sides ($P<0.05$ and TFCE corrected) in glioma patients relative to normal subjects.

Table 1| Demographic and clinical data of the study population.

	Patients	**Controls**	**T value**	**P value**
	7	6	-	-
Age	45±11	45±12	0.30	0.76*
Sex (Male)	5 (2)	4 (2)	-	-
Pathology results				
1. Diffuse astrocytoma with foci of anaplastic transformation (grade II) 2. Oligodendroglioma, WHO grade II 3. Oligodendroglioma, WHO grade II 4. Gemistocytic astrocytoma with anaplastic transformation, WHO grade III 5. Ganglioglioma, WHO grade I 6. Ganglioglioma, WHO grade I 7. Oligoastrocytoma WHO grade II				

Seven patients with no cancer background or metastatic tumor were included in the study. Values are expressed as mean ± SD. ∗P-value calculated independent two-sample t-test.

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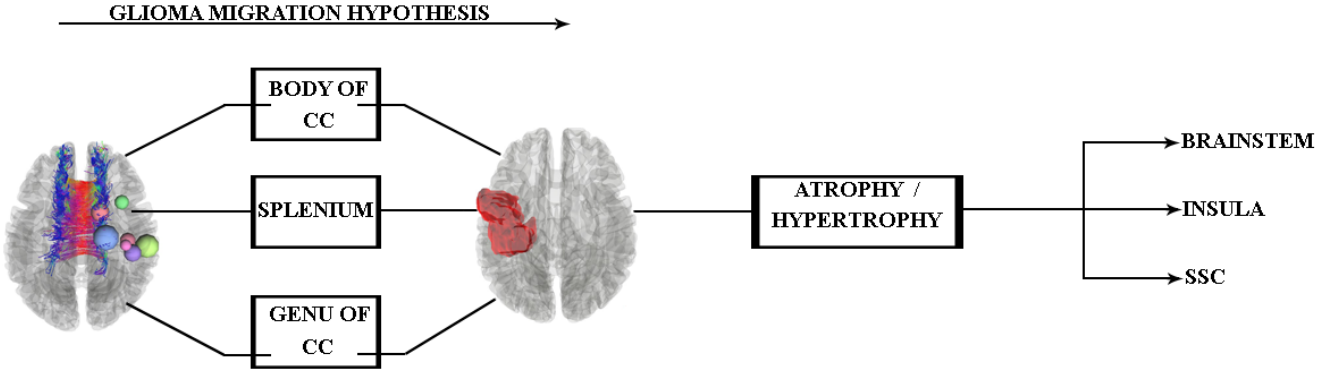
Figure 01.TIF



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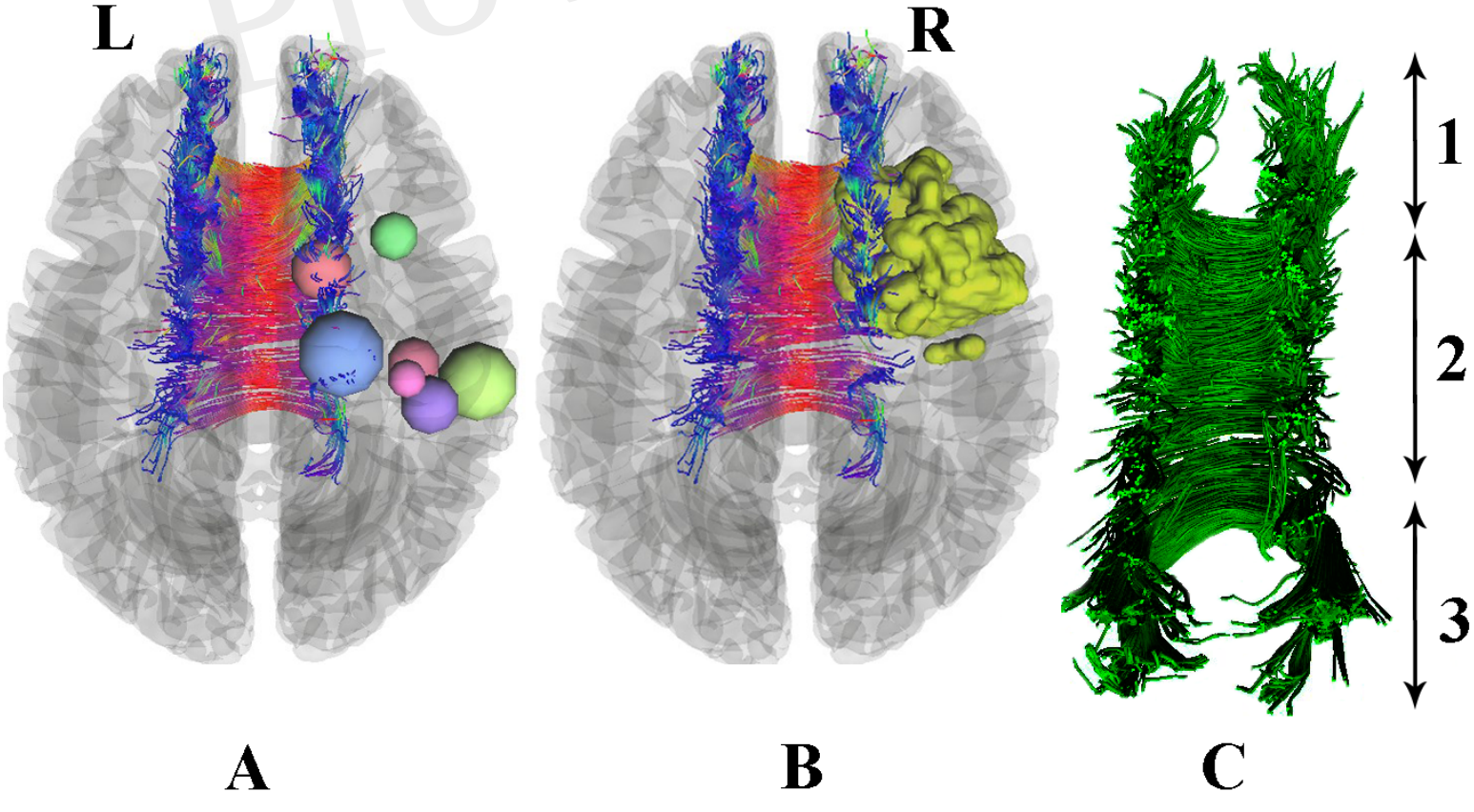

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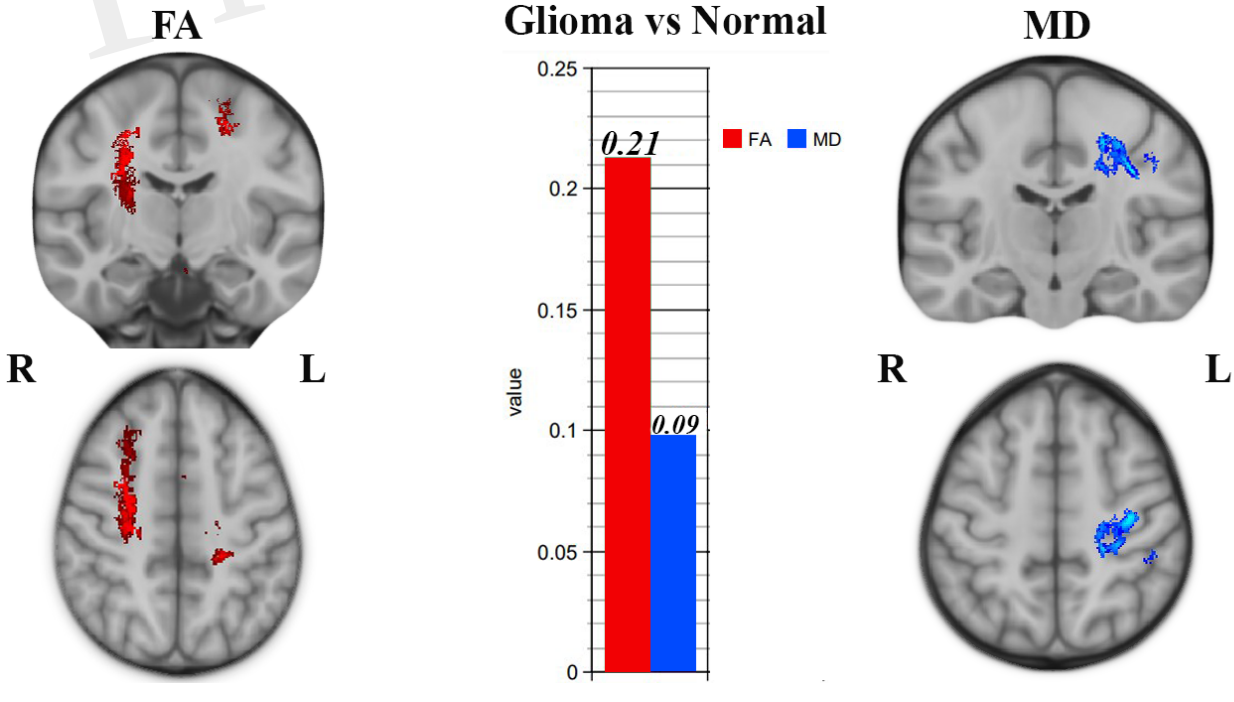

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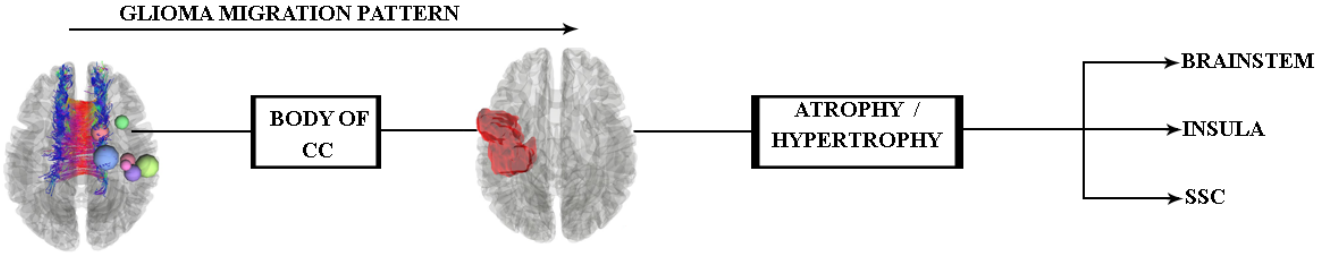

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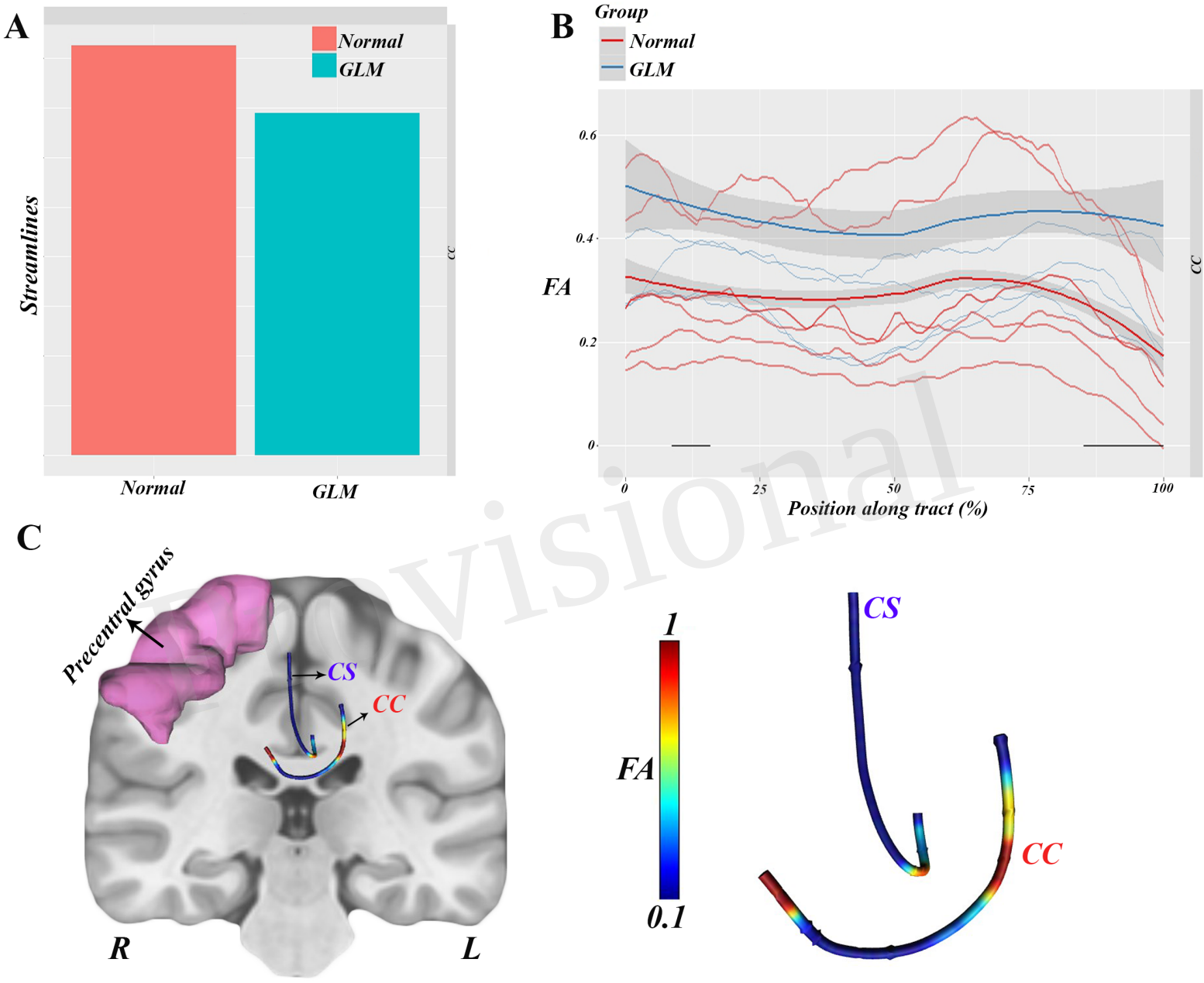

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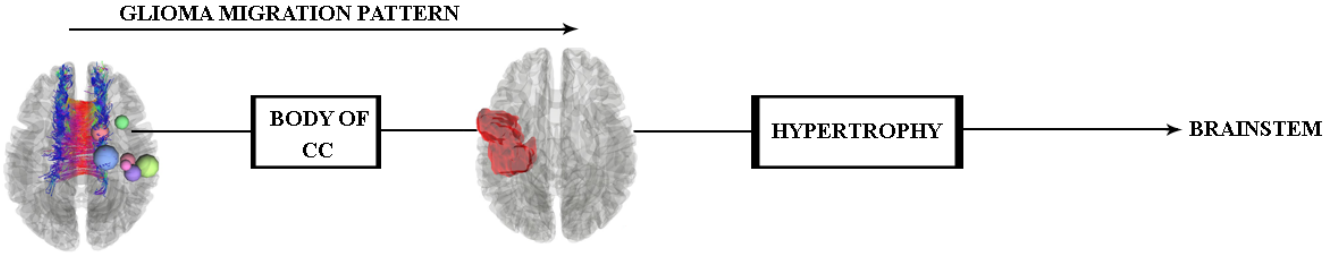

Figure 07.TIF