Published in final edited form as:

J Neuroimaging. 2016 March ; 26(2): 224–231. doi:10.1111/jon.12275.

Corpus Callosum Diffusion and Language Lateralization in Patients with Brain Tumors: A DTI and fMRI Study

Gabriella Tantillo, Kyung K. Peck, Julio Arevalo-Perez, John K. Lyo, Joanne F. Chou, Robert J. Young, Nicole Petrovich Brennan, and Andrei I. Holodny

Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY (GT, KKP, JAP, JKL, RJY, NPB, AIH); Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, NY (KKP); Department of Biostatistics & Epidemiology, Memorial Sloan Kettering Cancer Center, New York, NY (JFC); and University of Puerto Rico, Medical Sciences Campus, San Juan, Puerto Rico (GT).

Abstract

BACKGROUND AND PURPOSE—Examining how left-hemisphere brain tumors might impact both the microstructure of the corpus callosum (CC) as measured by fractional anisotropy (FA) values in diffusion tensor imaging (DTI) as well as cortical language lateralization measured with functional MRI (fMRI).

METHODS—fMRI tasks (phonemic fluency and verb generation) were performed in order to detect activation in Broca's and Wernicke's area. Twenty patients with left-hemisphere brain tumors were investigated. fMRI results were divided into left dominant (LD), right dominant (RD), or codominant (CD) for language function. DTI was performed to generate FA maps in the anterior and posterior CC. FA values were correlated with the degree of language dominance.

RESULTS—Patients who were LD or RD for language in Broca's area had lower FA in the anterior CC than those who were CD for language (median for CD = .72, LD = .66, RD = .65, $P < .09$). Lateralized versus CD group level analysis also showed that CD patients had higher FA in the anterior CC than patients who displayed strong lateralization in either hemisphere (median for CD = .72, lateralized = .65, $P < .05$).

CONCLUSION—Our preliminary observations indicate that the greater FA in CD patients may reflect a more directional microstructure for the CC in this region, suggesting a greater need for interhemispheric transfer of information. Because brain tumors can cause compensatory codominance, our findings may suggest a mechanism by which interhemispheric transfer is facilitated during plasticity in the presence of a tumor.

Keywords

Brain; lateralization; language; diffusion tensor imaging (DTI); functional MRI (fMRI)

Introduction

The role of the corpus callosum (CC) in the organization of brain function and interhemispheric communication is in need of characterization. Some investigators have proposed an excitatory role for the CC, where increased callosal organization would allow greater transfer of information across hemispheres.^{1,2} In contrast, others have suggested an inhibitory role for the CC, where inhibition of the contralateral hemisphere via the CC contributes to the lateralization of different functions, particularly language and spatial processing.^{3,4}

There have been conflicting studies looking at the role of the CC as it related to lateralization of brain function in healthy subjects. Josse found that subjects with a greater midsagittal surface area of the CC displayed greater left lateralization for language in posterior temporal and inferior frontal regions as measured by functional MRI (fMRI).⁵ Likewise, Putnam examined functional activity in the left and right inferior prefrontal cortices in patients performing a verbal encoding task.⁴ They found that the higher fractional anisotropy (FA) group exhibited more left inferior prefrontal cortex activation, while the lower FA group displayed greater activity in the homologous right inferior prefrontal cortex. Furthermore, Westerhausen showed that the molecular diffusion and FA values for the CC were higher in strongly left-lateralized individuals.³ These studies supported an inhibitory model of the CC whereby the dominant hemisphere suppresses the contralateral nondominant hemisphere via functional inhibitory effects mediated by the CC.

In contrast to the aforementioned studies, Haberling, using both fMRI and diffusion tensor imaging (DTI), found reduced FA values in subjects with typical cerebral lateralization (ie, left dominance for language and right dominance for spatial processing) and higher FA values in subjects with atypical cerebral lateralization. These studies suggest an “excitatory” model for CC function, where greater callosal connectivity facilitates information transfer and integration of processes across the hemispheres. Moreover, aside from the controversy seen in healthy subjects, how these relationships hold in patients with brain pathology remains obscure. Studies in populations with epilepsy suggest that the role of the CC may become altered under pathological states.⁶ In one study, greater thickness in the CC was found for strongly lateralized subjects with epilepsy but not healthy controls. The authors postulated that the difference might be due to the need for transcallosal fibers necessary to transfer language function after epilepsy’s injury to the brain.⁶

Though many studies have examined healthy patients and populations with epilepsy, no group has directly investigated how the development of an insidious brain tumor might impact the interhemispheric transfer of information via the CC following language compensation or reorganization. Several case reports have demonstrated the phenomenon of functional language translocations due to the presence of brain tumors, ie, the transfer of the original language cortex towards a new area or hemisphere in response to tumor encroachment.^{7,8} However, the way in which translocation or compensation for language function in the presence of a tumor might be reflected in the microstructure of the CC remains unknown.

We sought to assess the relationship between the CC microstructure as measured by FA and the degree of language lateralization as measured by fMRI in patients with brain tumors in the left typically dominant hemisphere. We hypothesized that patients with strongly lateralized language would display differences in FA values in the CC when compared to patients with bilateral language function.

Methods

Subjects

This retrospective pilot study was granted a Waiver of Authorization from the IRB. Twenty patients (median age 48.1 years, range 24–67 years) with brain tumors in the left hemisphere were studied (clinical data are summarized in Table 1, with additional information on radiation, chemotherapy, and drugs in supplementary table). All patients except one were 100% right handed as determined by the Edinburgh Handedness Inventory⁹ with one patient being left handed. All were native English speakers. The first 20 patients that met the following inclusion criteria were selected: 1) the presence of a tumor in the left hemisphere 2) the presence of a presurgical fMRI and DTI study.

Image Acquisition

The fMRI and DTI data were acquired as part of the routine clinical workup during each patient's preoperative planning. Scanning was performed on a 3T scanner (GE Healthcare, Milwaukee, Wisconsin) with an eight channel head coil. Functional matching T1-weighted (TR/TE = 600/8 ms; thickness = 4.5 mm) and T2-weighted (TR/TE = 4000/102 ms; thickness = 4.5 mm) spin-echo images were obtained. fMRI data were acquired with a single shot gradient echo echo-planar imaging sequence (TR/TE = 4000/35 ms; 128 × 128 matrix; 4.5-mm thickness). DTI data were acquired using a single shot spin echo echo-planar imaging sequence (25 directions, TR/TE = 11000/64 ms, 128 × 128 matrix; 3-mm thickness, 1000 s/mm² *b* value). 3-D T1-weighted images with a spoiled gradient-recalled-echo sequence (TR/TE = 22/4 ms, 256 × 256 matrix, 1.5-mm thickness) were also acquired.

Functional Tasks

Two functional tasks including phonemic fluency and verb generation were used. In the phonemic fluency task, patients were presented a letter aurally and asked to silently generate words beginning with that letter (for example, *t* = tomato, tree, etc.). In the verb generation task, subjects were presented with a noun (for example, “baby”) and asked to silently generate action words (for example, “cry and crawl”) associated with the noun. A block paradigm of 20-second activation epochs and 40-second resting baseline epochs for a total of six cycles each was used. Brain activity and head motion were continuously monitored with Brainwave (Medical Numerics) software in real time.

fMRI Data Analysis—Image processing and analysis were performed using Analysis of Functional Neuroimaging.¹⁰ Head motion correction was performed using 3-D rigid-body registration. Spatial smoothing (Gaussian filter with 4-mm full width of half maximum) was applied to improve the signal-to-noise ratio. Functional activity was generated using a cross-correlation analysis. Signal changes over time were then correlated with a mathematical

model of the hemodynamic response to neural activation. A modeled waveform corresponding to the task performance block was cross correlated with all pixel time courses on a pixel-by-pixel basis to identify stimulus locked responses. Functional activation maps were generated at a threshold of $P < .001$. To reduce false positive activity from large venous structures or head motion, voxels in which the standard deviation of the acquired time series exceeded 8% of the mean signal intensity were set to zero.

Regions of interest (ROIs) were drawn in order to count the number of voxels activated. ROIs were defined using the following anatomical landmarks for Broca's area and Wernicke's area (Fig 1). Broca's area was defined on sagittal slices as the pars opercularis and pars triangularis of the inferior frontal gyrus. The medial border of the area was defined as the insular cortex. Wernicke's area was defined as the posterior portion of the superior temporal gyrus drawn on sagittal images. The anterior borders were defined as Heschl's gyrus, and the posterior border was defined as the termination of the sylvian fissure. The laterality index (LI) was measured using the formula: $LI = (L - R) / (L + R)$, where L and R were the number of activated voxels per drawn ROI in the left and right hemisphere, respectively. An $LI > .2$ was classified as left dominant (LD), $-.2 < LI < .2$ was classified as codominant (CD), and an $LI \leq -.2$ was considered right dominant (RD).^{11,12} Figure 2 shows example cases of (A) LD, (B) CD, and (C) RD language activation.

DTI Data Analysis

Preprocessing including head motion correction and eddy current correction was applied to minimize artifacts. FA and color encoded FA maps were used to draw ROIs in the CC. ROIs of the anterior, posterior, and body of the CC were drawn on axial slices taking the genu of the CC as the Anterior CC, the splenium as the Posterior CC, and the butterfly-shaped midaxial slice as the Body CC. (Fig 2D). The FA values for each ROI were calculated for each voxel, and then averaged per region of the CC. Because of CC segmentation adjacent to the tumor, we segmented portions of the CC instead of using the entire CC.

Effect of Tumor Infiltration of the CC

The tumor was considered to involve the CC if there was enhancement or abnormal T2 or FLAIR signal hyperintensity extending into the CC that was contiguous with the tumor. Discontinuous patchy small stable lesions without mass effect were discounted by a board certified neuroradiologist as representing microvascular disease, demyelination, or other chronic nontumorous lesions. Since 5 of the 20 patients had infiltration of the CC by the tumor, the patients with CC tumor infiltration were also analyzed for differences in the anterior CC and posterior CC FA values when compared with patients with no infiltration.

Statistical Methods

The LI for Broca's and Wernicke's area was assessed separately for each patient and sorted into LD, CD, and RD groups. Because the anterior CC connects homologous Broca's areas across hemispheres, the median FA values for the anterior CC were analyzed for Broca's area ROIs for the three dominance groups. Similarly, because the posterior CC connects homologous Wernicke's areas across hemispheres, the median FA values were compared across the three Wernicke lateralization groups.

Differences in FA and LI values between groups (LD, CD, RD) or between patient characteristics (tumor infiltration, prior radiotherapy, chemotherapy, surgical resection, tumor grade, and gender) were tested by the Kruskal–Wallis test for group with more than two levels or by the Wilcoxon rank-sum test.

To study FA distribution over position and dominance groups, an average histogram of the FA was plotted across position and dominance groups and the descriptive statistics were estimated. To examine the association between position, dominance group, and the distribution of the FA values, a linear mixed-effects model with a robust variance estimate was used to account for the repeated measurement done on the same patients. To evaluate whether the position of the CC modified the association between FA value and language dominance group, we included the position of CC and its interaction with dominance group in the model. All analyses were conducted with SAS version 9.2 (SAS Institute Inc., Cary, NC), with a two-sided $P < .05$ considered to be statistically significant.

Results

fMRI Language Lateralization

For Broca's area, 8 patients were LD for language tasks (median LI = .65), 8 patients were CD (median LI = .05), and 4 patients were RD (median LI = −.54). For Wernicke's area, there were 5 LD patients (median LI = −.34), 8 CD patients (median LI = −.04), and 7 RD patients (median LI = −.56).

FA in the Anterior and Posterior CC

For the anterior CC, median FA values were .66, .72, and .65 for LD, CD, and RD groups, respectively (Fig 3, $P = .09$). Comparison between the LD and CD groups showed no difference in median FA value ($P = .145$), and no difference between LD and RD groups ($P = .67$). The median FA value between the RD versus CD group approached significance ($P = .07$). For the posterior CC, there was no statistically significant difference between any of the three groups (LD, CD, and RD, $P = .90$) or comparing the LD and CD groups and the LD and RD groups.

FA Distribution Over Position and Dominance Groups

The median FA value in the anterior CC was .66 for LD (IQR .61–.75), .72 for CD (IQR .68–.79) and .65 for RD (IQR .62–.67). Overall, there was a significant difference in the distribution of FA value for anterior CC versus posterior CC ($P < .001$) and dominance groups ($P < .001$). The relationship between dominance group and FA value did differ by the position of the CC; P -value for the interaction term was $< .0001$. That is, the position of CC was not only associated with language dominance and FA value but also modified the relationship between the dominance groups and FA value.

FA and Lateralization

Median FA values for the anterior CC were .65 and .72 for lateralized and CD group in Broca's area, with the CD group being significantly higher than the lateralized group ($P = .$

05) (Fig 4). The median FA values for lateralized and CD groups for Wernicke's area were .72 and .77 ($P = .71$).

Effect of Tumor Infiltration on the CC

Although the CC infiltration patients had lower anterior FA values than patients without tumor infiltration on average, there was no significant difference between the average FA values of the anterior or posterior CC in the tumor infiltration patients for different dominance groups.

Effect of Prior Radiotherapy, Chemotherapy, Surgical Resection, and Gender

The effects of prior radiotherapy, chemotherapy, surgical resection, gender, and tumor grade on FA and ROI was summarized in Table 2. We found no difference in the distribution of FA or ROI between these patient and clinical characteristics ($P > .25$).

Effect of Tumor Grade

To examine the relationship between tumor pathology and FA, the patients were additionally sorted by tumor grade. The relationship between tumor grade and the LI was also visualized using a box plot, where tumor grades were plotted against the LI. As seen in Figure 5A as the grade of the tumor increases, the average LI for Broca's area decreases from an average of .37 for grade 2 tumors to an average of $-.04$ for grade 4 tumors. As the tumor grade increased from 2 to 4, the spread of possible lateralization indices for Broca's area also increased in range. Likewise, for Wernicke's area in Figure 5B, as tumor grade increased from 2 to 4, the average LI decreased from .05 to $-.27$. As the tumor grade increases, the spread of possible lateralization values for Wernicke's area shifts downwards toward right dominance.

Discussion

In this pilot study, we sought to investigate how left-hemisphere brain tumors might influence the relationship between language laterality and CC directionality as measured by FA. When patients with brain tumors show atypical CD or RD language function on fMRI, we investigated whether the CC directionality might differ. We found that as a group, patients who were LD or RD for language in Broca's area had lower FA values in the anterior CC than those who were CD for language, although these levels did not reach significance. In contrast, there was no relationship between language dominance and posterior CC FA values for Wernicke's area. When patients were further sorted into Lateralized versus CD groups, CD patients also had significantly higher FA values in the anterior CC than patients who displayed strong lateralization in either the left or right hemisphere.

To examine the relationship between tumor pathology and its potential effects on language reorganization and CC directionality, the patients were additionally sorted by tumor grade. We showed that with greater tumor grade, the variability of lateralization indices for Broca's area increases, with a greater number of patients displaying bilateral language function. The more aggressive the tumor, the more likely it may be to induce cortical reorganization and

recruitment of the contralateral hemisphere for language functions. When examining the effect of tumor grade on Wernicke's LI, we found that with increasing tumor grade, the predominantly CD patients tended to move towards right hemisphere lateralization.

Our study also examined the relationship between language lateralization in Broca and Wernicke's area and FA values in the anterior and posterior CC as a function of several important clinical variables. Specifically, we looked at prior radiation therapy, prior chemotherapy, prior tumor resection, gender, and handedness. While not significant, radiation tended to lower FA values and prior tumor resection tended to increase FA values in the anterior CC. When looking at Wernicke's lateralization, we found handedness to be strongly correlated with lateralization, as the only left-handed patient in our study displayed the strongest right lateralization for both Wernicke and Broca's area. Notably, gender had no significant effect on any of our variables.

Interestingly, while many relationships were found between anterior CC FA values and language lateralization for Broca's area, few analogous results were found to be significant with the companion Wernicke's area. This may be because Wernicke's area has been shown to be less lateralized overall and less reliably measured responsive than Broca's area during fMRI language tasks. The auditory contribution of Heschl's gyrus and the temporal lobe region may limit our ability to discriminate typically lateralized tasks such as semantic and phonological testing in this region.^{13,14}

More research is needed to look in the emergence of codominance in patients with brain pathology. The presence of a brain tumor that encroaches upon functional cortical areas may trigger cortical reorganization as the brain adapts to tumor infiltration.¹⁵ This plasticity may be reflected in codominance as homologous language areas in the contralateral hemisphere may be recruited to assist in functional language tasks. Whether this picture of codominance on fMRI translates to any clinical functional benefit to the patient in the form of preserved language function is unknown.

Two major models for the role of the CC in the lateralization of brain function have emerged over the decades.¹ In the inhibitory model, the CC is posited to inhibit homotopic brain regions in the nondominant hemisphere during the performance of a lateralized task, in order to reduce resource competition and temporal constraints.^{2,5,16} In this inhibitory model, enhanced callosal connectivity would be expected to suppress the nondominant hemisphere and lead to increased functional lateralization. On the other hand, in the excitatory model, the CC transfers information between the two hemispheres, allowing for bilateral functional processing. In this model, enhanced callosal connectivity as measured by callosal surface area or increased FA values would be expected to allow increased interhemispheric transfer of information and greater bilateral functional activity.

The results in our preliminary study may support an increase in information transfer in the CD patients, at least in the anterior portion that might connect homologous Broca's areas. Our data suggest callosal connectivity is reduced in strongly lateralized individuals, where information does not need to be transferred across the hemispheres in order to complete a task successfully. In contrast, in individuals displaying a CD pattern for language tasks,

greater interhemispheric connectivity may be required to transfer information between both hemispheres.

Evidence of the dual excitatory/inhibitory role of the CC comes from studies in bilingual individuals. Evidence of language bilaterality in fMRI can be seen in studies of bilingual individuals when speaking their second acquired, nonnative tongue.¹⁷ For example, in an fMRI study examining Spanish-English bilinguals for whom Spanish was the native language, greater right hemisphere activity was noted in the English (nonnative language) tasks than for the Spanish tasks, with right hemisphere activation being more prominent in phonological rather than semantic tasks.¹⁷ The authors hypothesized that in second-language tasks, the right hemisphere was recruited to assist with the greater task difficulty when compared to analogous tasks in the native language, which were handled completely by the left hemisphere. According to the stage of language acquisition hypothesis, when individuals are acquiring a language in which they are not yet proficient, they rely more on contextual clues for language, and thus, utilize more of the right hemisphere than when speaking their native tongue.¹⁸ After proficiency is attained, however, language becomes more automatic and more left-hemisphere lateralized. Similarly, in patients with brain tumors that encroach upon language and supplementary language cortices, verbal communication assumes a much higher cognitive load, potentially necessitating the use of visuospatial function normally housed in the contralateral right hemisphere.

The reality may in fact be that the role of the CC may be excitatory or inhibitory depending on the health state of the brain and the cognitive demand required of it.¹⁶ For simpler tasks, it may be more efficient to compartmentalize function to the more specialized hemisphere. However, for more cognitively demanding tasks, or when the brain is under increased stress due to pathology such as tumor infiltration, recruitment of the contralateral homologous regions may enhance performance in what would normally be a lateralized task. In cases such as brain tumors that threaten vital language areas, the CC may assume an excitatory role by allowing the recruitment of the non-dominant hemisphere to assist in the completion of a normally lateralized task. In contrast, under healthy conditions and low cognitive demand, the CC may assume an inhibitory role by suppressing the nondominant hemisphere and allowing the more specialized dominant hemisphere to more efficiently carry out the task at hand. In this case, the lack of having to communicate across hemispheres would decrease the transit time and allow for faster and more efficient completion of the task. In either case, connections that are highly inhibitory or excitatory would display stronger callosal organization, reflected by a greater FA value in the CC.

This pilot study has several limitations. First and foremost, the study's small sample size of 20 patients, of which only one is left-handed, limited our ability to draw significant conclusions. Our results are preliminary, therefore, future directions comprise expanding the study to include more patients in order to increase statistical power. In addition, including a longitudinal component where patients are followed over time with fMRI would allow us to track CC morphological changes with tumor progression and clinical language findings. This would allow us to correlate potential changes in the CC with actual changes in language function.

Second, in brain cancer patients, susceptibility artifacts due to prior surgery previously showed to decrease the volume of fMRI activation. Susceptibility artifacts due to surgical hardware, such as titanium plates and blood products, appear to partially mask the fMRI signal. This problem is accentuated since the fMRI sequence is optimized to maximize the susceptibility differences between oxyhemoglobin and deoxyhemoglobin leading to the accentuation of susceptibility-based artifacts. A previous study showed that the presence of significant artifacts arising from surgical hardware placement and/or hemorrhagic products did not independently predict right hemispheric language dominance on the fMRI study.⁸ In addition, it is possible that tumor infiltrated edema could have affected diffusion measurements.¹⁹

Finally, there is the possibility of tumor induced “pseudoreorganization” for language areas as measured by fMRI.^{20,21} In this phenomenon, the tumor pathology causes signal dropout in the blood-oxygen-level-dependent fMRI activation due to neurovascular uncoupling by the abnormal vasculature of the tumor. This phenomenon may manifest itself as artifactual codominance or right dominance for functional language areas due to signal dropout in the dominant left brain. Therefore, the proportion of activation of the right hemisphere may be overestimated with indices such as the LI and artifactually suggest cortical reorganization. However, given that statistically it is expected that the majority of strongly right-handed patients will show left-hemisphere dominance for language, it is unlikely that pseudodominance is a significant issue in the current study. The current study contributes to the growing literature that information transfer between hemispheres is mediated by the CC and can be measured as a function of behavioral variant be them naturally occurring or pathologic in nature.

In such a scenario, right hemisphere activations may not be supporting speech but are in fact just compensatory responses by a struggling brain, which is why we see an increase in fMRI activity. For example, pseudoreorganization has been seen in patients with high-grade brain tumors such as glioblastoma multiforme, of which our sample had 8 patients.²¹

In conclusion, our pilot study indicates that the greater FA in language CD patients may reflect a more directional microstructure for the CC, suggesting a greater need for interhemispheric transfer of information. Because tumors can cause compensatory codominance, our findings may suggest a mechanism by which interhemispheric transfer is facilitated during plasticity in the presence of a tumor. However, a future study with an adequate number of subjects to address the relationship between microstructure for the CC and interhemispheric transfer is required.

Acknowledgments

Funding Sources

Julio Arevalo-Perez was supported by a grant from the Spanish foundation Fundación Alfonso Martín Escudero.

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Fig 1.

(A) An example of a functional image of resulting fMRI localization over Broca's area. ROIs were drawn on sagittal slices in the inferior frontal gyrus pars opercularis and pars triangularis. (B) An example of a Wernicke's area functional image. ROIs were drawn on sagittal slices in the posterior portion of the superior temporal gyrus. The activation map was produced with a threshold of $r > .45$ ($.45 < \text{red} < .65 < \text{yellow}$).

Fig 2.

(A) Example of a LD Broca patient. Axial image clearly shows left-dominance for language in Broca's area just above the insular cortex. Wernicke's area can also be visualized posteriorly on the left side. (B) Example of a CD Broca Patient. Comparable amounts of activated voxels can be seen in Broca's area in both the left and right hemispheres. (C) Example of an RD Broca patient. This patient showed right-hemispheric dominance for language tasks in Broca's area (arrow). This was a left-handed patient whose tumor was located in the left temporal region close to putative Wernicke's area. (D) Color FA map of

white matter tracts. The CC is the red fiber tracts seen on these axial images. ROIs of the anterior CC are drawn around the genu of the CC (first arrow), posterior CC ROIs around the splenium of the CC (second arrow), and body CC ROIs around the body (third arrow) as shown. Distorted architecture of the axonal fibers is shown due to the presence of the left-sided tumor. The color coded FA map was produced with a threshold of $FA > .15$.

Fig 3. Boxplot showing FA values of the anterior CC for LD, CD, and RD Broca's area activity (RD) in patients. The anterior CC FA for Broca's area for RD versus CD patients approached significance ($P = .07$).

Fig 4. Boxplot of Anterior CC FA values for Lateralized versus CD patients for Broca ROIs. For Broca's area, CD patients displayed a higher average anterior FA than lateralized patients ($P = .05$).

Fig 5.

(A) Boxplot showing the Broca LI sorted by tumor grade. Note the descending trend towards codominance with tumor grade. (B) Wernicke LI sorted by tumor grade. As the severity of the tumor increases, the average LI decreases from .05 for grade 2 tumors to $-.31$ for grade 4 tumors and approaches an RD state.

Table 1

Patient Clinical Data

Pt	Gender	Age	Handedness	Tumor Location	Pathology	Grade	Radiation	Chemotherapy	Surgery
1	M	35	Right	Left temporal	Glioma	2	No	No	No
2	M	51	Right	Left posterior temporal	Gliomas	2	No	No	No
3	F	53	Right	Left frontal	Astrocytoma	2	No	No	No
4	M	38	Right	Left fronto-parietal	Astrocytoma	2	No	No	Yes
5	M	24	Right	Left frontal	Glioma with oligodendrioma	2	No	No	No
6	M	44	Right	Left fronto-temporal	Anaplastic astrocytoma	3	Yes	No	Yes
7	M	30	Right	Left frontal	Anaplastic astrocytoma	3	Yes	Yes	Yes
8	F	67	Right	Left insular-temporal	Anaplastic oligodendrioma	3	Yes	Yes	Yes
9	M	59	Right	Left frontal (motor cortex)	Anaplastic astrocytoma	3	No	No	No
10	M	32	Right	Left posterior frontal	Anaplastic oligodendroglioma	3	Yes	Yes	Yes
11	M	35	Right	Left frontal	Anaplastic xanthrocytoma	3	Yes	No	Yes
12	F	64	Right	Left frontal	Glioblastoma	4	No	No	No
13	F	60	Right	Left insula and temporal lobe	Glioblastoma	4	No	No	No
14	M	45	Right	Left frontal	Glioblastoma	4	No	No	No
15	F	58	Right	Left parieto-occipital	Glioblastoma	4	Yes	Yes	Yes
16	M	43	Right	Left temporal	Glioblastoma	4	No	No	No
17	F	51	Right	Left frontal	Glioblastoma	4	No	No	No
18	M	55	Right	Left inferior	Glioblastoma	4	No	No	Yes
19	M	67	Left	Left temporal	Glioblastoma	4	Yes	Yes	Yes
20	F	51	Right	Left frontal	Metastasis	Met	Yes	Yes	Yes

Patient clinical data are summarized for age, gender, handedness, tumor location, tumor grade, pathology, and prior radiation, prior chemotherapy and prior tumor resection. (See Appendix for information on radiation, chemotherapy, and pharmacotherapy.)

Table 2
Association of Prior Radiotherapy, Chemotherapy, Surgical Resection, Gender, Grade, and Tumor on FA and LI

Characteristic	FA						LI					
	Anterior CC			Posterior CC			Broca ROI			Wernicke ROI		
	M	IQR	P	M	IQR	P	M	IQR	P	M	IQR	P
Gender			.14			.93			.53			.53
F (N= 7)	.65	.58, .68	.74	.71, .80	.14	-.13, .81				-.06	-.38, -.01	
M (N= 13)	.69	.67, .77	.72	.68, .82	.1	.005, .35				-.02	-.41, .26	
Prior Radiation			.87			.9			.47			.84
None (N= 12)	.68	.62, .75	.74	.69, .80	.16	-.02, .65				-.08	-.39, .23	
Yes (N= 8)	.69	.65, .74	.73	.70, .80	.02	-.18, .34				-.01	-.32, .06	
Prior Chemotherapy			.51			.34			.9			.71
None (N= 14)	.68	.65, .77	.78	.71, .80	.13	-.13, .63				-.08	-.41, .21	
Yes (N= 6)	.66	.65, .68	.71	.68, .74	.17	.02-.38				-.02	-.12	
	.66											
Prior Surgery			.73			.87			.25			.73
None (N= 10)	.68	.59, .76	.74	.70, .80	.15	.08, .66				-.05	-.38, .26	
Yes (N= 10)	.68	.65, .79	.72	.68, .82	.02	-.37, .35				-.06	-.41, .02	
Tumor Grade			.5			.43			.3			.28
2 (N= 6)	.67	.59, .79	.76	.69, .82	.26	.11, .77				.04	-.41, .34	
3 (N= 5)	.7	.68, .77	.78	.74, .79	.02	.01, .30				-.01	-.02, .26	
4 (N= 8)	.66	.65, .75	.72	.65, .80	-.02	-.52, .38				-.23	-.55, -.02	

Note: M = Median, IQR = Interquartile range.