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## Characterizing the relationship between lesion-activation distance using fMRI and verbal measures in brain tumor patients

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### Abstract

Functional resonance magnetic imaging (fMRI) allows for identification of eloquent cortex in pre-treatment planning. Previous studies have shown a correlation among lesion to activation distance (LAD) measures and morbidity and mortality. This study investigates the relationship between LAD, well-established language centers (Wernicke's and Broca's), and language performance measures. We included a sample population of brain tumor patients that received language fMRI (verbal fluency and sentence verification) for pre-treatment assessment (n = 51). LAD to the nearest language area was measured and divided into groups  $\leq 10$  mm and  $> 10$  mm. Verbal fluency scores were compared between these groups. Additionally, patients were divided into similar groups based on LAD to either Broca's or Wernicke's areas, and the verbal fluency scores and sentence verification accuracy (n = 29) were subsequently compared between groups. Brain tumor patients with LAD  $\leq 10$  mm to either language area had significantly lower verbal fluency scores (p = 0.028). The difference in verbal fluency scores between groups with LAD  $\leq 10$  mm and  $> 10$  mm to Wernicke's area trends toward significance (p = 0.067). The sentence verification accuracy was significantly lower in patients with LAD  $\leq 10$  mm to either language area (p = 0.039). These findings suggest that there exists a significant relationship between LAD to language centers and measures; greater language deficits are seen when LAD  $\leq 10$  mm.

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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.

## Keywords

fMRI; Imaging; Tumor; Language

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## 1. Introduction

Although intraoperative electro-cortical stimulation mapping during awake craniotomy remains the gold standard for identifying eloquent cortex from brain lesions, studies have validated the efficacy of using fMRI in pre-neurosurgical planning [1,2]. Use of fMRI offers a non-invasive and time-consuming method of localizing language and sensorimotor centers during pre-treatment planning. Previous studies by the authors have demonstrated the utility of fMRI as a pre-surgical tool for measuring the distance between brain tumor boundaries and eloquent cortex (Lesion-Activation Distance, LAD) and estimating pre- or post-operative deficits [3]. Furthermore, it has been demonstrated that fMRI can be reliably used in place of the more invasive WADA testing to determine language lateralization [4–6]. These prior studies have assessed LAD to language and sensorimotor centers and determined a corresponding relationship to patient morbidity (aphasia, motor deficits) and mortality in brain tumor patients. For example, Wood et al. demonstrated a significant relationship between motor and language LAD and the existence of pre- or postoperative clinical motor and language deficits [3]. Specifically, they also determined that language deficits increased exponentially as the LAD to primary language centers decreased below 1 cm [3]. Other studies have demonstrated similar findings that deficits significantly increase at an LAD < 1 cm. Haglund et al. found that distance from the resection margin to language areas < 10 mm demonstrated a greater number of persistent language deficits post-operatively [7]. Furthermore, LAD to language areas has also been tied to preoperative language deficits. For example, Kundu et al. demonstrated a significantly increased incidence of preoperative language deficits as LAD to Wernicke's area, one of two primary language centers, decreased [4].

Therefore, based on previous studies, it is reasonable to hypothesize that brain tumor patients with a lower LAD to primary language centers will demonstrate increased language deficits such as aphasia. This study aims to demonstrate the efficacy of fMRI as a pre-treatment tool, which can be used to characterize the degree of preoperative language deficits that are likely to be present based on LAD to primary language centers alone. While past studies have demonstrated relationships between LAD and incidence of aphasia assessed clinically, this study further characterizes the relationship between LAD to language centers and performance on neuropsychological verbal measures. Verbal fluency (VF) tests assessed prior to the fMRI scan and sentence verification (SV) tests performed during the fMRI scan are two measures that can be used to measure language function. Because studies have determined that language deficits substantially increase as LAD drops below 10 mm, this study aims to characterize the relationship between verbal measures and a LAD greater or < 10 mm [3,7].

## 2. Methods

### 2.1. Patient Selection

Fifty-one patient cases were selected from a database of 764 patients with primary brain tumors who underwent fMRI for pre-neurosurgical planning. The fMRI scans for these 51 patients were performed between March 2012 and June 2015. Inclusion criteria selected patients over the age of 18 years who had received VF testing prior to fMRI scan for pre-surgical assessment. The fMRI scans of all selected patients demonstrated activity in at least one of the two primary language centers. Patients with metastatic tumors, multiple lesion foci, and prior history of tumor resection were excluded from the study. Of these 51 patients, 29 patients also received SV testing during the language fMRI scan. All patients provided informed consent according to a protocol approved by the local institutional review board.

### 2.2. Language Paradigms

Activation of Broca's area was tested with word-generation tasks. To assess Broca's area, two types of word-generation tasks were performed: 1) alternating 20-second blocks of covert antonym word generation versus rest, and 2) alternating 20-second blocks of covert letter word generation versus rest. Wernicke's area was identified with receptive language tasks such as alternating 20-second blocks of silent text reading versus scanning symbols. In this task, the patient silently read a short paragraph in the text reading block. During the control/symbols block, the patient was shown a paragraph of symbols and asked to scan and note specific symbols (e.g., dark squares and filled circles). The symbols block controlled for eye movements during reading, which helps in discriminating between eye movement-related activation and the true language areas. Fig. 1 illustrates the examples of fMRI scans demonstrating primary language areas performing tasks such as text symbol, true false, silent word, and antonym. To address mass effect and neurovascular uncoupling issues, which could cause false negative responses on the BOLD tasks, we routinely performed the breath-hold task. All participants that were included in this analysis were able to perform the task well, and fMRI responses were observed in well-established language areas.

### 2.3. Functional MRI image Acquisition

Imaging was done on either a 1.5-T or 3-T commercial MR scanner (GE Medical Systems). Technical parameters were as follows: field of view 24 cm, matrix 64 × 64, TR 2000 msec, TE 40 msec (for 1.5 T) or 27 msec (for 3 T), flip angle 85° (for 1.5 T) or 75° (for 3 T), and 6-mm coronal plane sections (for 1.5 T) or 5-mm axial plane sections (for 3 T), 28 slices. The number of images and the duration of imaging varied with the paradigm. Imaging duration ranged from 3 to 5 min. Additional high-resolution anatomical scans, including 3D volumetric T1- and T2-weighted sequences, were acquired as part of the preoperative assessment. Participants viewed alternating 20 s blocks of fixation '+' ('rest' condition) and a letter of the alphabet (e.g., 'F', 'A', 'S'; 'task' condition) during the silent letter word task scan. During the antonym word generation scan, the participants viewed alternating 20 s blocks of fixation '+' ('rest' condition) and a word (e.g., 'hot', 'far', every 2 s). Participants were asked to silently generate words beginning with the given letter or generate an antonym to the word presented on the screen. Task stimuli were presented using the Prism Clinical

Software package and projected on a screen that was visible inside the scanner via a mirror attached on top of the head coil.

#### 2.4. Post-processing of fMRI Images

AFNI [8] was used for reconstruction, pre-processing, and analysis of the MR images. Anatomical and functional scans were first aligned, and pre-processing included removal of the first 3 volumes, despiking, motion correction, re-sampling to  $3.0 \text{ mm}^3$  and spatial smoothing using a 6-mm full-width at half-maximum Gaussian kernel. Each voxel time-series was scaled to have a mean of 100. First-level single subject activation maps were computed by cross-correlation of the time course of the echo planar imaging (EPI) signal at each voxel with a generalized least square fitting algorithm to a smoothed and temporally delayed boxcar reference function modeling the presumed hemodynamic response. This comparison provided a voxel-wise t-statistic with which images were thresholded individually to optimize visualization of language areas and overlaid on the co-registered anatomical brain volume maps. Unlike in studies where statistical thresholding is applied at the group level, thresholding was individually applied with the intent of optimizing localization of the activation foci because these maps were utilized by the neurosurgeon in preparation of surgical planning, cluster sizes were a minimum of 20 contiguous voxels ( $p < 0.05$ ) with a t-value ranging from 2.15 to 42 (mean 12.63). Clinicians would then view and use these thresholded maps for surgical planning as needed.

#### 2.5. Lesion-Activation distance Measurement

LAD was calculated using the PACS imaging software. The tumor margin was determined to be the edge of the enhancing tumors and determined by architectural distortion on both the T1- and T2-weighted scans for non-enhancing tumors. The shortest distance from the tumor edge to the center of activation for both Broca's area and Wernicke's area was determined between all three planes and recorded. Primary language center activation was determined using the image slice demonstrating the largest area of activation in the corresponding anatomical area for Broca's and Wernicke's areas.

#### 2.6. VF measurement and Adjustment:

Immediately prior to an fMRI scan, each patient's VF was tested. VF outside the scanner was assessed by forms of the Controlled Oral Word Association Test (COWAT) [9], which requires subjects to produce words beginning with the letters, 'F,' 'A,' 'S' in three respective 1-minute trials. Responses to each letter were recorded and letter fluency scores were based on the total number of correct responses produced by the participants across the three letter conditions. Analyses were done using both raw scores and normed scores (corrected for age and education).

#### 2.7. SV Task

The SV task is performed during one of the blocks of a language portion of the fMRI scan. During the task, patients are presented a series of statements (e.g., 'Italy is a country in Southern Europe') and instructed to click a button if the statement is true and do nothing if it is false. In the control condition, participants view two lines of matching symbols and

have to decide if the top and bottom lines match exactly. This task lasts about 4 min with alternating 20 s of task and 20 s of rest. There are several trials in each 20-second task block. The response time to each stimulus is patient-dependent and therefore variable; each stimulus is displayed for 2 s, which includes the time the patient has, to read and respond. The patient's accuracy in correctly responding to true statements is recorded.

## 2.8. Statistical Analysis

All statistical analyses were performed using Microsoft Excel. Analysis included Fisher's exact tests and student's *t*-test as appropriate. In particular, LAD and adjusted VF score standard deviation was calculated with a Fisher's exact test. LAD and adjusted VF scores was assessed using a two-tailed *t*-test. Individual LAD to either Wernicke's or Broca's area and adjusted VF scores were both assessed using a two-tailed *t*-test. LAD and SV accuracy was assessed using a two-tailed *t*-test. LAD to each language center and SV accuracy was conducted using two-tailed *t*-tests. LAD and mini-mental status exam (MMSE) were performed using a two tailed *t*-test.

## 3. Results

### 3.1. Patient sample population Characteristics

All 51 patients (52.9% male) were between the ages of 21 to 78 years old (mean age 50 years, median age 48 years). The patient population was 86.3% right-handed. Average tumor volume was 40.5 mm<sup>3</sup> and 43.1% of patients had high-grade (WHO grade 3 or 4) tumors. Anatomically, 11.8% of tumors were located in the left parietal, 11.8% in the left temporal, 29.4% in the left frontal, 9.8% in the right parietal, 11.8% in the right temporal and 17.6% in the right frontal lobe. Significant activation of Broca's area on fMRI was found and LAD was measured for 50 patients. Activation in Wernicke's area was found, and LAD was measured for all 51 patients. See Table 1 for demographics of the entire sample population.

### 3.2. Patient characteristics among Groups

Within the subject group, 56% had tumors in the left hemisphere, and 40% had tumors localized in the right hemisphere. Language hemispheres were also lateralized, and we found that 84% of our study cohort had language lateralized in the left hemisphere, 4% had language lateralized in the right hemisphere, and 12% of patients had bilateral lateralization. Therefore, 64% patients had tumors ipsilateral to their dominant language hemisphere and 32% patients had tumors contralateral to their dominant language hemisphere. For the purpose of our study, contralateral tumors to language areas are considered LAD > 10 mm. There were 12 patients in the LAD ≤ 10 mm group and 39 with LAD > 10 mm. There existed no significant difference in age between the two groups (48.0 +/- 11.1 vs. 51.0 +/- 15.2; *p* = 0.539). There was no significant difference in percentage male gender between groups (66.7% vs. 48.7%; *p* = 0.276) There existed no significant difference in the percentage of right handedness between groups (91.7% vs. 84.6%; *p* = 0.540). There was no significant difference in tumor volume between patients with LAD ≤ 10 mm than those > 10 mm (45.0 +/- 37.9 vs. 39.0 +/- 42.6; *p* = 0.644). The percentage of tumors which were diagnosed as high grade (WHO classification as grade 3 or grade 4 tumors) was

not significantly different between groups (50% vs.41%;  $p = 0.582$ ). See Table 2 below for patient demographics between groups.

### 3.3. LAD and adjusted VF scores

Patients were divided into two groups based on shortest LAD to either language center. The adjusted verbal fluency scores between patients were compared with an LAD of  $\leq 10$  mm and  $> 10$  mm. Patients with LAD  $\leq 10$  mm were found to have significantly lower adjusted VF scores than those with LAD  $> 10$  mm ( $-1.60 \pm 0.743$  vs.  $-1.078 \pm 0.715$ ;  $p = 0.028$ ). Additionally, a significantly greater percentage of patients in the  $\leq 10$  mm group scored more than one standard deviation below the mean according to the FAS COWA scale (83.3% vs. 51.3%;  $p = 0.049$ ). See Table 3 below for adjusted VF scores to primary language centers.

### 3.4. LAD to individual language centers and adjusted VF Scores

Patients were similarly divided into groups based on LAD  $\leq 10$  mm or  $> 10$  mm to each individual language area (Table 3). When assessing LAD to Broca's area, there existed no significant difference in adjusted verbal fluency scores between groups ( $-1.449 \pm 0.410$  vs.  $-1.168 \pm 0.788$ ;  $p = 0.363$ ). In measuring LAD to Wernicke's area, there was a trend toward significance, as the  $\leq 10$  mm group had lower adjusted VF scores than those with LAD  $> 10$  mm ( $-1.688 \pm 0.948$  vs.  $-1.130 \pm 0.697$ ;  $p = 0.067$ ).

### 3.5. LAD and Mini-Mental status exam (MMSE)

All patients took a MMSE on the day of the fMRI scan. Patients were divided into similar groups based on LAD  $\leq 10$  mm and  $> 10$  mm and MMSE scores were compared. There existed no significant difference in MMSE scores between the two groups ( $p = 0.609$ ).

### 3.6. LAD and SV Accuracy

Patients were divided into groups based on LAD  $\leq 10$  mm and  $> 10$  mm to either language area and accuracy of the SV task was compared. Patients with LAD  $\leq 10$  mm demonstrated significantly lower SV accuracy than those  $> 10$  mm (77.5% vs. 85.9%;  $p = 0.039$ ). There existed no significant difference when comparing similar groups based on LAD to Broca's area alone ( $p = 0.366$ ) or Wernicke's area alone ( $p = 0.155$ ). See Table 4 for the respective SV scores.

## 4. Discussion

Functional MRI is a non-invasive tool that has become more frequently utilized for pre-surgical planning in brain tumor patients. The validity of fMRI has been confirmed in several studies by comparison to electro-cortical stimulation mapping, the current gold standard in determining areas of eloquent cortex [10,11]. Pre-surgical mapping with fMRI has been demonstrated by previous studies to decrease the incidence of post-surgical functional deficits [12,13]. One of the major advantages of fMRI is that it allows for functional mapping of the brain and easy assessment of the proximity from the lesion to eloquent cortex. Prior studies by the authors have demonstrated the utility of fMRI for measuring LAD and predicting surgical outcomes [3,4,14]. This study demonstrated that



there exists a significant relationship between LAD to the two primary language areas of the brain, Wernicke's and Broca's areas, and performance on pre-operative language measures. Patients were divided into those with an LAD  $\leq 10$  mm to the language area of interest and  $> 10$  mm.  $\leq 10$  mm was selected, as previous studies have demonstrated a significantly increased incidence of functional deficits as LAD drops below 10 mm [3,7]. Although other studies have compared LAD and presence of pre- and post-operative clinical language deficits (ex: aphasia), to our knowledge, measures used to characterize language performance neuropsychologically have not been compared in accordance with LAD. Characterizing language performance using neuropsychological measures provides a method of assessing language function in brain tumor patients along a continuum rather than an all or none approach (ex: aphasia, no aphasia). This offers the advantage of predicting the degree of language deficit that will result as LAD measurements decrease in brain tumor patients.

In this current study, it was determined that patients with an LAD  $\leq 10$  mm to either language area had not only significantly lower adjusted VF scores, but also had a greater percentage of patients who scored more than one standard deviation below the mean on the VF test. These findings could be explained by a combined role of both Broca's and Wernicke's areas in the process of retrieving words after being given a letter and sub-vocally expressing those words during the VF test. Perhaps, close tumor proximity to these language centers disrupts white matter tracts between them that are important in combining receptive and expressive language tasks during the VF test. Several studies have suggested that language tasks may be less localized to anatomical areas of the brain than previously believed [15,16]. Rather, the white matter tracts between them may actually be of greater functional significance [15,17]. Considering this possibility, studies of tumor interference with important white matter tracts involved in language, such as the superior longitudinal fasciculus and arcuate fasciculus, could be accurately explored using DTI [18,19]. Further investigation using DTI may demonstrate similar language outcomes as lesion-tract distance decreases in a manner similar to LAD.

Likewise, patients with an LAD  $\leq 10$  mm to Wernicke's area demonstrated a trend toward significantly lower verbal fluency scores while LAD to Broca's area was not found to be of significance. These results mirror the findings by [4] that LAD to Wernicke's area correlates with preoperative language deficits. These findings support the idea that Wernicke's area may hold a role in not only comprehension, but also the recall of words. Additionally, it is possible that important cortical language networks are being disrupted as a tumor encroaches upon Wernicke's area. A previous study suggested that during a verb generation task, Wernicke's area demonstrated activation for both comprehension of speech and word recall [20]. Therefore, involvement of Wernicke's area with these two tasks may partially explain the reduction in VF scores as LAD to Wernicke's area decreases. The lack of significance between LAD to Broca's area and VF scores may indicate that the relationship between anatomical location of Broca's area and language function is more complex than previously thought. Studies have shown that there can be high individual variability in language representation between different patients, a factor which may potentially be demonstrated here [7,15,16].

Accuracy on a sentence verification task, which is routinely performed during the language fMRI, was also shown to correlate with LAD to the two language centers. In patients with an LAD  $\geq 10$  mm to either language center, SV accuracy scores were significantly lower. However, there are no significant differences in SV scores based on LAD to either language area alone. Therefore, both Broca's and Wernicke's areas may play a combined role in reading and comprehending the question presented to the patient and assessing its validity. Again, these findings may suggest an interaction via white matter tracts between the two regions, which may be disrupted as LAD to the two language centers decreases.

The findings of this study help to better characterize the relationship between LAD to eloquent cortex on language fMRI and the degree of presentation of language deficits in patients with primary brain tumors. Several previous studies have affirmed the prognostic value of measuring LAD on fMRI and predicting the likelihood of expected language deficits, both preoperative and post-operative [1,3,4]. Assessing measures of language performance offers a greater insight into the degree to which LAD to language centers may influence language. In agreement with our findings, LAD  $\geq 10$  mm has been established amongst several previous studies as being associated with significantly greater language and motor deficits [1,4,21]. Wood et al. demonstrated a linear relationship between motor deficits and LAD measurements while language deficits were shown to increase exponentially as LAD decreased below 10 mm [3]. Therefore, our findings of reduced scores on tests of verbal measure can be expected, especially when LAD is  $\geq 10$  mm. Further examination of the disruption of important neural networks by brain tumors using DTI may provide a better explanation for the findings in this study. Furthermore, although fMRI task activations do not help us to differentiate between essential from participating areas, there is a high concordance between language activations observed on fMRI tasks and that observed on Wada tests. Several previous studies present concordance findings in the percentages in the range of 75% to 95% between fMRI and Wada test, and currently, solutions to increase its reliability are further being studied [22–26]. Additionally, there was also a study showing enhanced benefits of using fMRI to predict post-operative deficits in comparison to the Wada test [27].

This study has a couple of limitations that needs to be taken into consideration. The study offers a relatively small sample size due to a limited number of patients meeting inclusion criteria. Therefore, our sample size was not determined by an a priori sample size calculation and may be underpowered to detect other significance. A future study with a larger sample size may better characterize the relationship between LAD and language measures in brain tumor patients. Furthermore, the additional analysis to differentiate LAD effects at each language area (Broca's and Wernicke's) has a sample size of 12 patients with LAD  $< 10$  mm. We acknowledge that the sample size is insufficient to make any meaningful assessments on specific language areas and further studies with more subjects in the LAD  $< 10$  mm category may provide important insight to differentiate LAD effects at each language area individually. In addition, another limitation is the fact that two different investigators were involved in the process of collecting and recording patient data and measurement of LAD on fMRI scans. The same protocol for measurement was used by both investigators in an attempt to minimize differences in measurement technique. Another limitation is a lack of characterization of the relationship between the distance from the tumors to white matter



tracts involved in language and verbal measures. Future studies measuring the lesion-tract distance with DTI may provide important insight supporting the findings of this study. Lastly, the SV task recognizes null responses as correct for false statements. As a result, an incorrect response for a true statement in the form of a null response may result from either a prolonged response time depicting a deficit in expressive language fluency, or incorrect interpretation of the statement depicting receptive language problems. This study does not include response time information. Whether the specific delayed response time is indicated as a null or incorrect response is not available for the participants included in the study.

Overall, this study supports the fact that close tumor proximity to language centers, especially when  $\leq 10$  mm correlates with a greater degree of preoperative language deficits. This information can be used by neurosurgeons when deciding whether to pursue surgical versus conservative management in patients with brain tumors. For example, based on this information, a neurosurgeon may decide to intervene if tumor volume is increasing and LAD to primary language areas is approaching 10 mm or less.

## 5. Conclusions

There exists a significant relationship between measurements of tumor boundaries to primary language areas and the degree of preoperative language deficits in patients with primary brain tumors. In particular, LAD measurements less than or equal to 10 mm have been correlated with increased incidence of language deficits. In this study, we found that LAD  $\leq 10$  mm to either language area is associated with worse VF scores. In particular, an LAD  $\leq 10$  mm to Wernicke's area was found to correspond to lower VF scores. LAD  $\leq 10$  mm to either language area was also associated with lower accuracy scores on a SV task during the language fMRI. Therefore, this study indicates that measurements between tumor boundaries and eloquent language cortex can be used to predict the degree of preoperative language deficits in brain tumor patients and be utilized to make treatment decisions.

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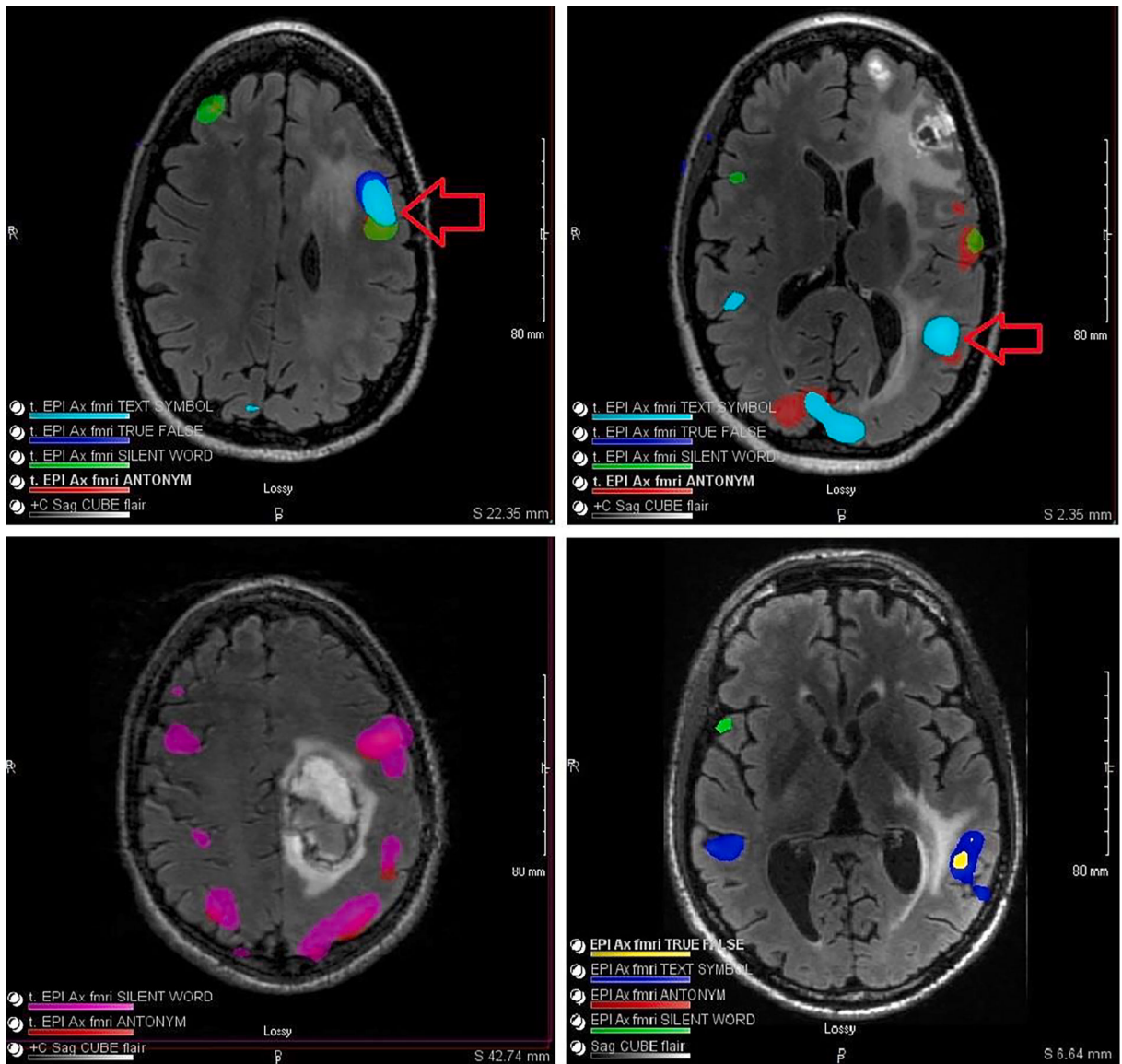
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**Fig. 1.** fMRI images demonstrating Broca's area (left) and Wernicke's area (right). Images are shown in radiological convention. Left side of brain appears on right side of the image.

**Table 1**

Demographics for all 51 patients.

<b>Characteristic</b>	<b>Value</b>
n	51
% Male	52.9%
Age Range (years)	21–78
Mean Age (years)	50
% Right-Handed	86.3
Average Tumor Volume (mm <sup>3</sup> )	40.5
% High Grade Tumors	43.1%
Tumor Location	Percentage Total (%)
Left Parietal	11.8
Left Temporal	11.8
Left Frontal	29.4
Right Parietal	9.8
Right Temporal	11.8
Right Frontal	17.6
Left Hemisphere Tumor	56
Right Hemisphere Tumor	40
<b>Language Laterality</b>	<b>Percentage Total (%)</b>
Left	84
Right	4
Bilateral	12
Ipsilateral Tumor to Language	64
Contralateral Tumor to Language	32

**Table 2**

Patient demographics between groups.

	<b>LAD 10 mm</b>	<b>LAD &gt; 10 mm</b>	<b>P-value:</b>
Number	12	39	
Age	48.0 +/- 11.1	51.0 +/- 15.2	0.539
% Male	66.7% male	48.7% male	0.276
Right Handedness %	91.7	84.6	0.540
Tumor Volume(mm <sup>3</sup> )	45.0+/- 37.9	39.0+/- 42.6	0.644
% High Grade Tumor	50	41	0.582

\*\*  
Significant (p < 0.05)

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**Table 3**

Adjusted VF scores by LAD to primary language centers.

Adjusted VF Scores			
LAD to:	LAD 10 mm	LAD > 10 mm	P-value
**Broca's or Wernicke's	(-1.60 +/- 0.743)	(-1.078 +/- 0.715)	0.028
Broca's only	(-1.449 +/- 0.410)	(-1.168 +/- 0.788)	0.363
*Wernicke's only	(-1.688 +/- 0.948)	(-1.130 +/- 0.697)	0.067
**% Below 1 SD:	83.3	51.3	0.049

\*Trending toward significance (p &lt; 0.1)

\*\*Significant (p &lt; 0.05)

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**Table 4**

SV scores and LAD to primary language centers.

Sentence Verification (SV) Scores (%)			
LAD to:	LAD 10 mm	LAD > 10 mm	P-value
**Broca's or Wernicke's	77.48	85.90	0.039
Broca's only	80.25	84.45	0.366
Wernicke's only	71.50	85.50	0.155

\*\* Significant ( $p < 0.05$ ).

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