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Infiltration of the basal ganglia by brain tumors is associated with the development of co-dominant language function on fMRI

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Abstract

Studies have shown that some patients with left-hemispheric brain tumors have an increased propensity for developing right-sided language support. However, the precise trigger for establishing co-dominant language function in brain tumor patients remains unknown. We analyzed the MR scans of patients with left-hemispheric tumors and either co-dominant (n=35) or left-hemisphere dominant (n=35) language function on fMRI to investigate anatomical factors influencing hemispheric language dominance. Of eleven neuroanatomical areas evaluated for tumor involvement, the basal ganglia was significantly correlated with co-dominant language function ($p < 0.001$). Moreover, among patients whose tumors invaded the basal ganglia, those with language co-dominance performed significantly better on the Boston Naming Test, a clinical measure of aphasia, compared to their left-lateralized counterparts (56.5 versus 36.5, $p = 0.025$). While further studies are needed to elucidate the role of the basal ganglia in establishing co-dominance, our results suggest that reactive co-dominance may afford a behavioral advantage to patients with left-hemispheric tumors.

Keywords

Language Laterality; Co-dominance; Functional magnetic resonance imaging; Brain Tumors; Basal Ganglia; Boston Naming Test

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1. Introduction

During the past decade, functional magnetic resonance imaging (fMRI) has become a mainstay in presurgical planning for brain tumor resection. In addition to providing a way to noninvasively assess the risk of iatrogenic damage, fMRI has proven effective in localizing and lateralizing eloquent areas – e.g. sensory, motor, and language networks – that can be displaced by tumors invading normal tissues (Belyaev, Peck, Brennan, & Holodny, 2013). fMRI is particularly important for planning surgical interventions in putative language regions, given that language is more highly distributed and variable between individuals (Sanai, Mirzadeh, & Berger, 2008).

Beyond serving as a tool in the neurosurgeon's arsenal, fMRI is increasingly being used to elucidate the brain's ability to reorganize following injury. While the literature describing brain plasticity in the context of injury – namely, stroke and epilepsy – is robust, recent neurofunctional imaging studies have demonstrated that major neural reorganizations can also be triggered by tumor invasion (Ius, Angelini, Thiebaut de Schotten, Mandonnet, & Duffau, 2011; Krieg et al., 2013; Petrovich, Holodny, Brennan, & Gutin, 2004; Zheng et al., 2013). To date, four main plasticity patterns have been reported in the study of brain neoplasms: intra-tumoral, perilesional, ipsilateral hemispheric and contralateral hemispheric reorganization (Desmurget, Bonnetblanc, & Duffau, 2007; Krainik et al., 2003; Meyer et al., 2003; Petrovich et al., 2004). In their review of brain plasticity in the context of slow-growing gliomas, *Duffau et al* postulated that these patterns are organized in a hierarchical fashion – that is, local compensations precede remote recruitments (Desmurget et al., 2007). However, the mechanisms underlying such functional reorganization remain enigmatic.

It is reasonable to suggest that there is a “tipping point” where perilesional compensation gives way to an interhemispheric strategy in a hierarchical manner (Duffau et al., 2011). With respect to the language network, several functional imaging studies have already documented the recruitment of the right (nondominant) hemisphere in patients with tumors in the left hemisphere, where most language typically resides (Partovi et al., 2012; Wang et al., 2013). However, the precise anatomical or functional trigger for the recruitment of the contralateral hemisphere and the alteration in language laterality remains to be determined. Thus, we compared two groups of right-handed patients with left hemispheric tumors: in one group, the patients exhibited left-lateralized language function by fMRI and in the other group, the patients exhibited co-dominant language function. We investigated whether certain neuroanatomical structures, when infiltrated by tumor, would correlate with language co-dominance, implying the recruitment of homologous regions in the right hemisphere. Because subcortical injury has been shown to be a predictor of worsening language function in patients subjected to craniotomies (Trinh et al., 2013) and because studies have suggested a critical role of subcortical structures in interhemispheric functional dynamics (Crosson, 1992), we hypothesized that the invasion of subcortical structures would correlate with a greater language deficit and by extension, greater participation of the right hemisphere.

2. Results

2.1 Neuroanatomical correlates of language laterality

Patients with infiltration of the basal ganglia by tumor were significantly more likely than patients without basal ganglia involvement to have co-dominance for language ($p < 0.001$) (Figure 1). The infiltration of the left precentral gyrus and insula, while approaching significance in a single test ($p = 0.023$ and $p = 0.028$, respectively), did not survive multiple comparisons testing (family-wise type I error rate = 0.005). Neither the involvement of Broca's area (inferior frontal gyrus) nor of Wernicke's area (superior temporal gyrus) correlated significantly with the establishment of hemispheric language co-dominance.

No statistical difference in tumor volume was seen between the two groups ($p = 0.58$ by FLAIR, $p = 0.56$ by contrast enhancement), indicating that co-dominance did not correlate with the lesion size.

2.2 Boston Naming Scores

To evaluate the potential behavioral advantages of developing co-dominant language function secondary to tumor, we identified those patients with tumors involving the basal ganglia and analyzed their Boston Naming Test (BNT) scores. Of the patients with documented BNT scores, 10 exhibited co-dominant language function and 10 exhibited left-lateralized language function. Using the Wilcoxon rank sum test, the median BNT score was found to be significantly higher ($p = 0.025$) for the co-dominant group (median = 56.5) than for the left dominant group (median = 36.5), suggesting that co-dominance that is reactive to left hemispheric pathology may afford a behavioral advantage to brain tumor patients.

3. Discussion

The aim of this study was to determine whether pathologic infiltration of certain neuroanatomical structures in brain tumor patients disproportionately contributes to the elicitation of non-dominant language compensation. Our results suggest that the involvement of the basal ganglia factors in the establishment of non-dominant functional language activation. Furthermore, we suggest that in the context of a left hemispheric tumor, co-dominant patients appear to show a behavioral advantage over those who do not elicit right hemispheric support.

To date, the literature regarding language lateralization in the setting of slow-growing tumors remains limited. The few studies that have evaluated the influence of neoplasms on language laterality restricted their analyses to classic language areas like Broca's and Wernicke's areas (Holodny, Schulder, Ybasco, & Liu, 2002; Partovi et al., 2012; Petrovich et al., 2004; Wang et al., 2013). However, studies of patients who suffered acute left-sided ischemic events as well as patients who underwent awake craniotomy procedures in which language function was monitored during cortical and subcortical resection, suggest that subcortical – not cortical – injury is more likely to impart lasting language deficits (P. Lieberman, 2013; Naeser et al., 1982; Trinh et al., 2013). Thus, we were compelled to evaluate the putative relationship between subcortical damage and the elicitation of right hemispheric language compensation defined as co-dominance on fMRI. While our results

chiefly suggest that the involvement of the left basal ganglia by FLAIR and/or contrast is critical for the establishment of co-dominance, the insula and precentral gyrus may also play an essential role. Having survived the first round of statistical testing, these areas failed to pass Bonferroni multiple comparisons testing. However, given our limited sample size (n=35), subsequent studies with a larger cohort of patients may reveal these areas – especially, the subopercular insula with its role in articulatory planning – to be significant (Dronkers, 1996).

In our analysis of those patients whose tumors invaded the basal ganglia, we found that the patients with language co-dominance performed significantly better on the Boston Naming Test, a clinical measure of aphasia, compared to their left-lateralized counterparts. Because this finding is only based on 20 patients, future studies are needed to characterize this effect more completely. However, it is worth noting that this result represents a key difference in the literature regarding brain plasticity induced by acute versus slow-growing lesions. While our findings in brain tumor patients associate clinical co-dominance with *better* behavioral outcomes, several studies have shown that contralateral hemispheric participation post-stroke is associated with *worse* clinical outcomes than if function remains left-lateralized (Martin et al., 2004; Naeser et al., 2005). Some have suggested that the training advantage of a comparably slow-growing tumor may allow for compensatory strategies in a way that acute lesions, such as strokes, do not (Desmurget et al., 2007).

It is worth noting that neither the involvement of Broca's area (inferior frontal gyrus) nor of Wernicke's area (superior temporal gyrus) correlated significantly with the establishment of hemispheric language co-dominance. Given that these regions are both classically and practically considered essential to the brain's language center, it is surprising that their involvement by tumor did not coincide with interhemispheric reorganization. For example, while controversial, Stuss and Benson maintain that aphasia only occurs in the setting of subcortical, and not cortical, damage (Stuss & Benson, 1986). Philip Lieberman goes so far as to argue that the traditional Broca-Wernicke theory is wrong, citing a study performed by Naeser *et al* that described aphasic patients who had suffered strokes that damaged subcortical structures (including the basal ganglia) but spared cortical structures entirely (Philip Lieberman, 2013; Naeser et al., 1982). Our results, which highlight the importance of subcortical structures in the functional reorganization of the language network in brain tumor patients, lend credence to this call for a more complex model of language localization. We hope that future studies will further elaborate the relative importance of cortical and subcortical structures to the brain's language network.

The current study is limited by the challenges of determining language co-dominance by fMRI. It is known that the right hemisphere participates in language even in strongly right-handed, left language dominant individuals (Lindell, 2006). While our validation studies suggest that this degree of right hemispheric activation would elicit speech disruption in the right hemisphere in the setting of intraoperative electrocorticography (IEC), this specific behavioral marker was not assessed in our cohort of patients (Peck et al., 2009). Furthermore, our determination of co-dominant hemispheric activation could have been confounded by tumor-mediated decoupling of the fMRI blood oxygenation level-dependent (BOLD) signal in the left hemisphere. Because left-sided tumors with abnormal tumor

neovasculature and resultant neuro-vascular decoupling are known to obscure perilesional activation, the right hemispheric activity we observed may make the ratio measure seem artifactually rightward biased (Ulmer et al., 2003). However, by controlling for tumor size in the co-dominant and left-lateralized cohorts, we minimized the possibility that this limitation affected one cohort disproportionately.

Studies of handedness and hemispheric language dominance suggest that between 91%–96% of right-handed individuals exhibit left dominant language function (Isaacs, Barr, Nelson, & Devinsky, 2006; Knecht et al., 2000). Thus, the co-dominance we observed is unlikely to be native. Furthermore, while stimulation over the right hemisphere in our fMRI-determined co-dominant patients was not performed for ethical and practical reasons, the significant difference in BNT scores between the co-dominant and left-lateralized cohort does suggest that the co-dominance we observed is associated with a behavioral advantage. Lastly, it is possible that the involvement of varying degrees of white matter surrounding the basal ganglia could factor in establishing co-dominance for language. The corpus callosum for example, has been correlated with co-dominance in brain tumor patients (Tantillo et al., 2015). However, the corpus callosum specifically was only involved in two of our thirty-five co-dominant cases, lessening its contribution. Unfortunately, diffusion tractography was not homogeneously performed in our patient population and as a result, quantitative tractographic analyses could not be performed. While further studies are needed to elucidate the precise role of the basal ganglia in the establishment of co-dominance, our results suggest that its infiltration elicits the recruitment of the right hemisphere to the benefit of the patient.

4. Methods

4.1 Subject Selection

Our institutional review board approved this retrospective study with waiver of informed consent. Electronic medical records were searched for patients with histopathologically confirmed brain tumors, who underwent BOLD fMRI to assess language function for presurgical planning. MR imaging reports from 12/3/07 to 6/1/15 in which language laterality was determined were searched using the keywords “co-dominance” or “left hemispheric dominance.” Inclusion criteria were age > 30 years (no upper limit), right-handed, single left hemispheric brain tumor and English as a first language. Left-handedness and the presence of right hemispheric brain lesions were exclusion criteria. Handedness for all patients was determined using the Edinburgh Handedness Inventory (Oldfield, 1971). Only patients who were 100% right handed were included.

A total of 70 individuals including 35 co-dominant subjects and 35 left-lateralized control patients were identified. The clinical data from these patients is summarized in Table 1. There was no statistically significant difference in age, gender, tumor volume (by FLAIR or contrast), tumor location or tumor pathology.

4.2 MR Image Acquisition

Each patient received an fMRI scan as part of the routine clinical workup for preoperative planning. MR Scan was performed on 1.5T or 3T scanners (GE Healthcare, Milwaukee, Wisconsin) using an 8-channel head coil. Anatomical images including T1-weighted (repetition time (TR)=600 ms; echo time (TE)=8 ms; thickness=4.5 mm) and T2-weighted (TR=4000 ms; TE=102 ms; thickness=4.5 mm) spin-echo axial slices, covering the whole brain and matching with functional images were acquired. Post-contrast 3D T1-weighted images with a spoiled gradient-recalled-echo sequence (TR=22 ms, TE=4 ms, 256×256 matrix, 30° flip angle, 1.5 mm thickness) were also acquired.

Functional MRI data were acquired with a single shot gradient echo echo-planar imaging (EPI) sequence (TR/TE=4000/35 ms; 128×128 matrix; 4.5 mm thickness). There were 90 volumes per task consisting of 5 volumes of activation (20 sec) followed by 10 volumes of rest (40 sec) repeated 6 times (6 min scan total).

4.3 fMRI Paradigm and Data Analysis

Language fMRI was acquired with each patient completing at least two of the following silent speech tasks contrasted with a resting baseline: semantic fluency, phonemic fluency, verb generation or auditory responsive naming. Patients were pre-tested on modified versions of in-scanner stimuli to assure that they understood the task demands and were able to perform the tasks. During the semantic task, subjects were given a supra-ordinate category and were told to generate subordinate words that fit the category (example: subject was presented with the category “country” and may generate words such as ‘Germany,’ ‘Peru,’ or ‘China’). During the phonemic task, subjects generated words that began with the presented letter (example: subject was presented with the letter “A” and may generate words such as ‘Apple,’ ‘Apron’ or ‘Ashtray’). During the verb generation task, subjects were asked to generate action verbs associated with specific nouns (example: subject was presented with the noun “baby” and may generate words such as “cry,” “coo” or “crawl”). During the auditory responsive naming task, subjects were presented with forced choice questions (example: subject was asked to name something with which one shaves). Subjects performed the task silently to avoid motion artifacts. The patient’s brain activity and head motion were monitored using software (Brainwave, Medical Numerics) that permits the observation in real time.

4.4 fMRI Data Pre-Processing

Image processing and analysis was performed using Analysis of Functional Neuroimaging (Cox, 1996). Head motion correction was performed using 3D rigid-body registration. Spatial smoothing (Gaussian filter 4mm full-width half-maximum) was applied to improve the signal-to-noise ratio. Additionally, linear trend and high frequency noise were minimized where necessary. Statistical parametric maps were generated using a cross-correlation analysis. Signal changes over time were 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 $p < 0.001$ (uncorrected). No standard p value was used because individual patient fMRI maps are not

amenable to such practice (Chang et al., 2010). 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. Language laterality was determined as previously described (Ruff et al., 2008).

4.5 Anatomic Assessment

Tumor infiltration into discrete neuroanatomical features was documented by an attending neuroradiologist, who holds a Certificate of Added Qualification (CAQ) in neuroradiology from the American Board of Radiology and has 20 years of experience in fMRI of brain tumors (Figure 2). This neuroradiologist was blinded to the language laterality of each subject. Eleven neuroanatomical areas known to play a role in language were analyzed for tumor involvement (Figure 1) (Price, 2012). These were the inferior frontal gyrus (BA), middle frontal gyrus, superior frontal gyrus, left precentral gyrus, insula, superior temporal gyrus (included the expected location of Wernicke's area), middle temporal gyrus, inferior temporal gyrus, hippocampus/parahippocampal gyrus, basal ganglia and thalamus. Specifically, both fluid-attenuated inversion recovery (FLAIR)-T2-weighted sequences and post-contrast T1-weighted axial images were evaluated. Characteristics of tumor enhancement and the presence of nonenhancing FLAIR signal abnormalities in these regions were characterized. Tumor volume was defined using BrainLab (BrainLab AG, Feldkirchen, Germany), with the area of the tumor defined both by contrast enhancement and by FLAIR abnormality.

4.6 Statistical Analysis

Patient characteristics were compared between the co-dominant and control groups using Fisher's test for categorical variables and the Wilcoxon rank sum test for continuous variables, with a 5% significance level ($p < 0.05$). FLAIR or contrast involvement was compared in 11 neuroanatomical areas between the two groups using Fisher's tests. After Bonferroni adjustment for multiple testing, the p -value was set to $p < 0.005$ ($p < 0.05$ divided by 11 tests). All statistical tests were two-sided, and analysis was done using R (version 3.2.0; R Development Core Team).

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Highlights

- We investigated anatomical factors influencing hemispheric language dominance.
- Basal ganglia involvement by tumor was correlated with co-dominance ($p < 0.001$).
- Insula and precentral gyrus may also play roles in plasticity of language network.
- Involvement of Broca's and Wernicke's areas did not correlate with co-dominance.
- Interhemispheric reorganization of language may confer behavioral advantages.

Figure 1. Relationship between language laterality and tumor location

Differences in the location of tumor infiltrate in the co-dominant versus the left-lateralized cohort are illustrated. The green and orange bars reflect the number of co-dominant and left-lateralized patients, respectively, whose tumors infiltrated a given neuroanatomical area by FLAIR and/or contrast. While involvement of the insula and left pre-central gyrus approach significance in the co-dominant population, they do not survive multiple comparisons testing (** $p < 0.05$). By contrast, involvement of the basal ganglia is significantly associated with co-dominance (*** $p < 0.001$).

Notes: BA: Broca's Area (Pars Orbitalis, Pars Triangularis, Pars Opercularis); MFG: middle frontal gyrus; SFG: superior frontal gyrus; LPCG: left precentral gyrus; STG: superior temporal gyrus; MTG: middle temporal gyrus; ITG: inferior temporal gyrus; H/PH: hippocampus, parahippocampal gyrus; BG: Basal Ganglia

Figure 2. fMRI activation overlaid on T1-weighted imaging

(A) Representative patient scan displays co-dominance for language with FLAIR involvement of the left basal ganglia. (B) Representative left hemisphere dominant patient scan without FLAIR abnormality involving the left basal ganglia. The pars triangularis and pars opercularis of the left inferior frontal gyrus (Broca's area) are involved in both patients. The activation map was generated with $r > 0.5$ as red and $r > 0.6$ as yellow; $P < 0.001$.

Table 1

Patient Clinical Information

	Co-dominant	Left-lateralized	P-value
Gender *			0.81
Female	15 (43)	13 (37)	
Male	20 (57)	22 (63)	
Tumor Location*			0.60
Frontal	20 (57)	20 (57)	
Temporal	6 (17)	6 (17)	
Parietal	3 (9)	6 (17)	
Insula	6 (17)	3 (9)	
Tumor Pathology			0.99
High	25	24	
Low	10	11	
Age	50 (30–79)	50 (23–77)	0.53
FLAIR Volume (cm³)	10.37 (3.12–27.08)	10.84 (0.89–26.32)	0.58
Contrast Volume (cm³)	2.32 (0–7.26)	2.01 (0–9.79)	0.56
BNT score **	56.5 (50–59)	36.5 (0–59)	0.025

Notes: All numbers are median (range) unless otherwise noted:

* =n(%),

** =20 patients (10 co-dominant, 10 left-lateralized) with infiltration of the basal ganglia.