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Abstract

Background and Purpose: Language reorganization has been described in brain lesions with respect to their location and timing, but little is known with respect to their etiology. We used fMRI to investigate the effects of different types of left hemisphere lesions (GL= gliomas, TLE = temporal lobe epilepsy and CA= cavernous angioma) on the topographic intra-hemispheric language plasticity, also considering their location.

Methods: 47 right-handed patients with 3 different left hemisphere lesions (16 GL, 15 TLE and 16 CA) and 17 healthy controls (HC) underwent BOLD fMRI with a verb-generation task. Euclidean distance was used to measure activation peak shifts among groups with respect to reference Tailarach coordinates of Inferior Frontal Gyrus (IFG), Superior Temporal Sulcus (STS) and Temporo-Parietal Junction (TPJ). Mixed-model ANOVAs were used to test for differences in activation peak shifts.

Results: Significant activation peak shifts were found in GL patients with respect both to HC and other groups (TLA and CA). In addition, in the same group of patients a significant effect of tumor location (anterior or posterior) was detected.

Conclusions: We demonstrated that intra-hemispheric language plasticity is influenced by the type of lesion affecting the left hemisphere and that fMRI is especially valuable in the preoperative assessment of such reorganization in glioma patients.

Abbreviations

ANT-GL = Anterior Gliomas

CA = Cavernous Angioma

GL = Glioma

HC = Healthy controls

IFG = Inferior Frontal Gyrus

POST-GL = Posterior Gliomas

STS = Superior Temporal Gyrus

TLE = Temporal Lobe Epilepsy

TPJ = Temporo-Parietal Junction

Introduction

In the 19th century, seminal studies of the linguistic deficits associated with focal cortical lesions demonstrated the critical role of left inferior frontal gyrus and the left temporo-parietal cortex in speech production and comprehension, respectively. The advent of functional neuroimaging (PET and fMRI, especially the BOLD technique) improved our knowledge about the organization of language areas by noninvasively providing a detailed anatomical representation of the language system.

This functional organization can be altered by multiple diseases affecting brain anatomy and physiology. A high degree of anatomical variability in the location of cortical regions supporting speech production and comprehension was firstly observed in patients with intractable epilepsy [1]. Such variability is an example of cerebral plasticity, which is the process regulating brain homeostasis and allowing remodeling of brain networks [2], during both development and learning and in the presence of brain lesions.

Three types of reorganization have since been described: intra-hemispheric, involving cortical regions in the injured dominant hemisphere [3], inter-hemispheric, where language functions shift to the homotopic regions of the contralateral hemisphere [4] and crossed-interhemispheric, where a partial shift of eloquent regions to the right hemisphere occurs [5].

In the presence of a lesion in a functionally eloquent brain region, pre-operative language assessment can thus help minimize perioperative damage.

The language network can be disturbed by gliomas in three different ways: 1) infiltration of critical brain structures by the tumor, 2) disruption of subcortical fiber connections, or 3) displacement of these connections by the tumor [6].

The slow progression of low-grade gliomas possibly allows a thorough language reorganization, which seemingly follows a hierarchical model: language functions could primarily persist within a brain lesion or could be redistributed immediately around the lesion and only subsequently in the contralateral hemisphere [7,8]. For this reason, resection of eloquent cortex in these patients does not necessarily implicate language deficits [9,10].

At the other end of the spectrum, it has been speculated that cavernous angiomas are too small to induce language reorganization [11]. Other lines of evidence suggest that the early onset of left temporal epilepsy induced by cavernous angioma produces a reorganization of left Broca's area [12].

We hypothesize that different pathologies have distinct effects on language reorganization, and may also influence the accuracy of BOLD fMRI in the detection of such reorganization.

In the present task-based BOLD-fMRI study, we evaluated the language reorganization within the left hemisphere induced by three different types of ipsilateral lesions (gliomas, temporal lobe epilepsy and cavernous angioma) by measuring the shift (i.e. distance) of the peak of language-related activations of each group from standard language coordinates and comparing the results with healthy controls. The primary aim of our study was to evaluate the effects of these lesions on the topographic intra-hemispheric reorganization of language function. A secondary aim was to investigate if the topographic reorganization of language is affected by lesion location with respect to Broca and Wernicke.

Methods

This retrospective study was approved by the local ethical committee and conducted in accordance with the declaration of Helsinki. Written informed consent was waived due to its retrospective nature.

Patients and Controls

From a database of 359 patients who underwent a presurgical assessment of language function with fMRI between 2012 and 2020, 47 right handed patients according to the Edinburgh Inventory with a left hemispheric pathology were identified using sharp criteria. Patients were included if they had a pathologically confirmed glioma or cavernous angioma (without extra-capsular bleeding) in the left inferior frontal, superior temporal, supramarginal and angular gyri (axial diameter <2.5 cm) or temporal lobe epilepsy (cryptogenic or secondary either to cortical dysplasia or mesial temporal sclerosis). Patients with hydrocephalus, midline shift, lesions involving both hemispheres, prior treatment (brain surgery/biopsy, chemo and radiotherapy), severe language impairment, tumor or patient-related artifacts (such as susceptibility from hemorrhage, and motion) were excluded.

Also, 17 healthy controls (10 men; age range 22–64 years; mean age 33±12 years) with normal neurological status underwent the same fMRI protocol.

Lesion localization and mass effect definition

Gliomas and cavernous angiomas were divided into anterior and posterior, according to their position with respect to an orthogonal plane passing through the anterior commissure. Glioma patients were also divided into four groups based on the presence of compressive and displacement effects on the neighboring structures on T2-weighted

images as graded by Li [13]: 0, Absent (adjacent tissues are not compressed); 1, Light (enlargement of gyrus, adjacent sulcus is occluded); 2, Middle (adjacent tissues and ventricle are shifted); 3, Heavy (midline shifted to the opposite side). Tumors with heavy mass effect were excluded to limit the possibility that plasticity phenomena were rather due to physical displacement.

Imaging Acquisition

MR images were obtained using a 3T scanner (Philips Achieva X Series; Philips Medical System, Best, the Netherlands) and a sensitivity-encoding eight-channel head coil. BOLD functional images were acquired with a T2*-weighted echo-planar free-induction-decay sequence (TR/TE: 2000/35 ms; FA: 90°; matrix size: 96x96; FOV: 230 mm; thickness: 3 mm; no gap). A total of 115 volumes were acquired for a scanning duration of 3’50’’. Structural images were acquired using a high-resolution 3D Turbo Field Echo T1-weighted sequence (sagittal acquisition; TR/TE 7.6/3.7ms; FA 8°; matrix size 252x240; FOV 250 mm section thickness 1 mm).

fMRI Task

Subjects silently performed an orthographically cued, block-designed, lexical retrieval verb-generation task, with four 30-second task blocks alternated with five 20-second rest blocks. During task blocks, individual nouns were presented for one second in black letters on a gray background at the center of the screen, followed by a two-second fixation dot during which subjects were instructed to think of pronouncing at least one associated verb. During rest periods, subjects were told to relax while fixating a central cross. All participants were asked to silently perform the tasks to avoid head movement. Before scanning, subjects executed a brief overt version of the task to ensure correct comprehension of the instructions and qualitatively assess task performance.

Visual stimuli were presented by using E-Prime, Version 1.1 (Psychology Software Tools, Pittsburgh, Pennsylvania) via an LCD projector and viewed through a mirror placed above the subject's head.

fMRI Analysis

Brain Voyager QX Version 1.9 (Brain Innovation, Maastricht, the Netherlands) was used for data analysis. Preprocessing of functional time series included slice time and head-motion correction, linear detrending to remove slow signal drifts using temporal highpass filtering, co-registration with anatomic images, and transformation into Talairach anatomic space [14] at 3 -mm spatial resolution by a bounded-box rigid body transformation. Spatial normalization of the structural volumes consisted of manually aligning the high-resolution 3D Turbo Field Echo T1 dataset of each subject with the stereotaxic axes: AC-PC and 2 rotation parameters for midsagittal alignment, then the extreme points of the brain (anterior, posterior, right/left lateral, and inferior/superior) were specified. The 8 coordinates were used to scale the 3D datasets to the standard brain of the Talairach atlas.

None of the extreme cerebral points used for spatial normalization were located within the lesions. Statistical activation maps were generated using a General Linear Model (GLM) [15]. The GLM was based on a predictor obtained by the convolution of the boxcar waveform-representing task and rest conditions with the Boynton hemodynamic response function implemented in BrainVoyager QX. The significance of voxel activation was measured by testing the correspondence between the BOLD time series with the predictor expressed in terms of *t*-scores [16].

Activation peaks were identified in each subject's map as the voxels with the highest effect size closest to the three Talairach reference coordinates corresponding to the pars opercularis of the left inferior frontal gyrus (Brodmann area 44/45; IFG = x: -49; y: +17; z:

+5), the left temporal-parietal junction (Brodmann area 22; TPJ = x: -55; y: -36; z: +24) and the left superior temporal sulcus (Brodmann area 50; STS = x: -55; y: -35; z: +3) [17].

Assessment of the shift of the activations

As a measure of reorganization (i.e. “shift” of coordinates), we calculated the Euclidean distance (in mm) between each of the three reference coordinates representing key language regions [pars opercularis of the left inferior frontal gyrus (IFG), left temporal-parietal junction (TPJ), left superior temporal sulcus (STS)] and the closest corresponding peak in the activation map of each patient. For each region, the average distance calculated across patients of each group (glioma, GL; cavernous angioma, CA; temporal lobe epilepsy, TLE) was compared to that of healthy controls (HC), which provided an index of the variability of peak coordinates in the normal population. A mixed-model ANOVA with group (HC, GL, CA, TLE) as the between-subject factor and language region (IFG, TPJ, STS) as the within-subject factor was used to test for differences in activation peak shifts. A further mixed-model ANOVA with group (anterior or posterior) as the between-subject factor and language region (IFG, TPJ, STS) as the within-subject factor, tested for differences in activation peak shifts in patients as a function of lesion location. Additional Duncan post-hoc tests were conducted when applicable.

To assess how mass effect influenced the activation peaks, Pearson’s correlations were performed between measures of activation peak shift obtained in each subject and the corresponding mass effect grading of tumors.

All statistical evaluations were performed with SPSS (SPSS for Mac, version 21.0; IBM, Chicago, Ill). Statistical significance was set at p=.05.

Results

Among the 47 patients, 16 (11 men; age range 25-80; mean age, 51±15) had a histological diagnosis of naive brain glioma. Gliomas were classified into anterior (11/16) and posterior (5/16) and in 0 (2/16; 12%), 1 (7/16, 44%) and 2 (7/16, 44%) based on the mass effect severity scale. 15 patients (5 men; age range 19-62; mean age 38±14) were diagnosed with left TLE: 6 had mesial temporal sclerosis, 4 cortical dysplasia and 5 cryptogenic epilepsy. Patient mean age at seizure onset was 16 years (range, 0.5–30 years). 16 patients (10 men; age range 18-74; mean age 46±14) had a histological diagnosis of cavernous angioma (7 anterior and 9 posterior): they all had a clinical onset with a first ever seizure and underwent brain MRI within a month from the episode.

Variability in the normal population

The mean peak coordinates of the three language areas in the control group were x: -47 ± 3,22, y: +17±6,24, z: +3±2,94 for IFG; x: -53±4,87 , y: -39±5,5, z: +20±4,33 for TPJ; x: -54±2,83, y: -40±6,73, z: +3±3,71 for STS (mean±SD). The corresponding shift of coordinates compared to the coordinates derived from the literature, measured in terms of Euclidean distance (mean±SD) was 7.42±2.66 mm for IFG, 9.02±3.87 mm for TPJ and 8.17±4.48 mm for STS (Fig 1).

Shift of activations in patients

There was a statistically significant main effect of the type of lesion on activation peak shift as determined by the Mixed ANOVA ($F(3, 50) = 6.94$, $p = .001$, $\eta p^2 = .29$). Duncan post-hoc tests revealed significant differences in activation peak shift between GL and all other groups (GL vs HC, p<.001; GL vs CA, p=.003; GL vs TLE, p=.003), whereas no significant differences were found between HC and CA (p=.09) and HC and TLE (p=.08) (Fig 2). Neither a significant main effect of language region ($F(2, 100) = .77$, $p = .47$, $\eta p^2 = .001$),

nor a significant interaction effect (F(6, 100) = .55, p = .77, ηp^2 = .03) on activation peak shift were detected.

Since glioma patients showed significant activation peak shifts, we aimed to explore whether lesion location in this group affected activations. When dividing GL patients in anterior (ANT-GL) and posterior (POST-GL), we found a significant main effect of lesion location on activation peak shift (F(2.3, 30) = 12.06 , p < 10^{-3}, ηp^2 = .45). We also found a tendency towards a significant interaction effect (F(4.6,30) = 2.36, p = .64, ηp^2 = .14). Exploratory Duncan post-hoc test revealed a significant shift of activation between HC and ANT-GL in IFG (p = .004), but not in TPJ nor in STS (p = .09 and p = .3, respectively) (Fig 3).

Conversely, a significant shift of activation was found between HC and POST-GL in STS (p < 10^{-3}), but not in IFG nor in TPJ (p = .8 and p = .09, respectively) (Fig 3).

Representative images of cortical reorganization of language functions in glioma patients are given in Fig 4.

In GL patients, the severity of mass effect did not have any influence on the activation shift (r=.06; p=.43).

Discussion

Former studies on language reorganization in the presence of focal cerebral lesions within or next to eloquent areas focused mainly on temporal factors (time of onset and time-course) [18,19], while limited attention was put on their etiology and location within the dominant hemisphere despite high clinical relevance. Therefore, we evaluated these two latter components of functional variability with BOLD-fMRI, measuring the shift of language-related activation in the left hemisphere in patients with different types of ipsilateral brain lesions involving language regions, namely gliomas, temporal lobe epilepsy and cavernous angiomas.

Our results demonstrate that lesion etiology has an impact on the topographic organization of language function within the affected left hemisphere. Particularly: i) a GL in the left hemisphere induces an intra-hemispheric reorganization of cortical activations for language; ii) this reorganization is observed in proximity of the tumor, as ANT-GL and POST-GL patients show reorganization of anterior and posterior regions, respectively; iii) patients with CA and TLE do not seem to show a significant intra-hemispheric reorganization.

Patients with Gliomas

Following stroke, gliomas are the most studied diseases in terms of cortical plasticity. Data on glioma-driven language plasticity are very heterogeneous [20,9]. In our preoperative study, glioma patients exhibited the highest degree of intra-hemispheric reorganization of language areas as compared to the other groups. In addition to spreading along white matter bundles, gliomas infiltrate the cortex in a progressive way, a feature possibly accounting for their greater ability to induce reorganization of cortical functions [21,9].

When tumor location was considered, local language reorganization was also demonstrated, suggesting that plasticity preferentially operates on functional regions closer to the tumor [22]. Indeed, gliomas are thought to generate a local hyperexcitability which modulates synaptic efficiency and activation of latent connections ultimately recruiting functionally redundant perilesional areas [23,24].

Moreover, the lack of a correlation between the amount of shift and the mass effect of gliomas argues against the possibility that reorganization represents a displacement effect, which has been previously demonstrated for gliomas within motor areas [25].

Patients with Temporal Lobe Epilepsy

Chronic epileptic discharge in TLE leads to significant structural and functional alterations of neuronal circuits which may induce language reorganization [26,27]. TLE patients have long been known to show different degrees of atypical language processing [28], developing either as an adaptive process to mitigate language deficits (compensation) or as a reorganization of language functions per se [29]. Originally inferred from intra-carotid amobarbital test [28], this evidence has received further support from electrical stimulation mapping [1] and fMRI [29].

Differently from the ordered hierarchical plasticity model of gliomas, epilepsy - particularly a temporal lobe focus - has been variably associated with intra-hemispheric, inter-hemispheric and crossed-inter-hemispheric reorganization patterns [26,30].

In our study we found that left TLE patients did not show a significant intra-hemispheric reorganization. On the whole, it must be noted that the report of intra-hemispheric reorganization was consistently lower than that of inter- and bi-hemispheric reorganization across studies [1,29,31,32], possibly due to its more difficult assessment [26,33].

In contrast, it could be argued that the lack of a significant reorganization effect is due to the limited sample size. However, the significant difference between HC and the groups of anterior and posterior gliomas demonstrates that a limited sample size does not prevent the detection of a reorganization effect.

Alternatively, the negative results might reflect the presence of highly individualized patterns of reorganization typical of epilepsy patients. Reorganization patterns were found to vary according to different clinical and demographic factors [29]. These factors, however, were not univocally related to the patterns themselves [29], possibly indicating that they interact in a more complex way, determining a more individualized pattern of reorganization that cannot always be predicted on the basis of lesion location and/or clinical factors alone [34] and that can be hardly identified by a group-level analysis.

Patients with Cavernous Angioma

We also did not find a significant reorganization in CA patients.

Previous research on brain plasticity in CAs has produced mixed results. While multiple studies converge on the idea that CAs induce functional reorganization in motor areas [35], a similar effect on language is still a matter of debate. In line with our results, the only preoperative fMRI study that focused on language-related plasticity in CAs showed no language reorganization [36], hypothesizing the role of the small lesion size and the fact that CAs are thought to spare the cortex. We speculate that the lack of functional reorganization can also be explained by their underlying pathophysiology. Indeed, CA are not infiltrative in nature, therefore less likely to elicit cortical functional modifications. On the other hand, it should also be noted that CAs are highly epileptogenic lesions, with partial seizures present in 50-70% of cases [37] and strongly linked to the peripheral hemosiderin rim [38]. Therefore, one could argue that plasticity in the setting of CAs may ensue as a consequence of epileptic discharge. Nevertheless, the lack of language reorganization in CA may stem from the fact that our patients were included after the first-ever clinical seizure, thus possibly before the establishment of an abnormal functional reorganization.

It is also worth noting that hemosiderin deposition in CAs can impair fMRI sensitivity by producing susceptibility artifacts distorting adjacent BOLD signal [39].

Therefore, the existence of intra-hemispheric language plasticity in the complex scenario of CAs is still a possibility.

Study limitations and future directions

One limitation of our study is its retrospective nature, so that some clinical information - especially regarding the onset and the length of epilepsy - were unavailable.

A second limitation concerns the limited number of patients in each group. However, this choice is explained by our decision to adopt very sharp inclusion radiological criteria (relatively small-sized lesion not exceeding 2.5 cm and absent to moderate mass effect).
Thirdly, as fMRI is based on the assumption that there is a correlation between neuronal activity and local blood flow (neurovascular coupling), its sensitivity may be hampered by the altered reactivity of pathological vessel of brain tumors (neurovascular uncoupling), making the interpretation of activation maps challenging. However, neurovascular uncoupling in the proximity of brain tumors reduces BOLD signal intensity, therefore yielding false negative and not false positive results [40].
In addition to that, we did not consider high and low-grade gliomas separately. Since neurovascular uncoupling is a common feature of high as well as low grade gliomas (although possibly different in nature and of varying degrees) [41,42], we suppose that this should not affect the identification of peritumoral reorganization.
On the other hand, we are aware that this choice prevented us from speculating on differences in functional reorganization related to tumor grading, which may modulate the amount of reorganization [9,43].
Finally, our study explicitly focused on intra-hemispheric plasticity and did not evaluate the presence of inter-hemispheric reorganization. However, we think that the assessment of intra-hemispheric reorganization is the one that counts most in the presurgical planning, given that surgery is aimed at maximizing tumor resection while minimizing post-surgical deficits.

Conclusions

This study demonstrates that left intra-hemispheric language reorganization is influenced by the type of brain lesion. This evidence is crucial in clinical practice for pre-surgical planning and to understand the mechanisms of language reorganization. The preliminary

knowledge of the different patterns of language reorganization may help select those patients who most need an fMRI assessment and increase the confidence of the neuroradiologist and the neurosurgeon with the fMRI pre-surgical mapping.

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Figures and figure legends

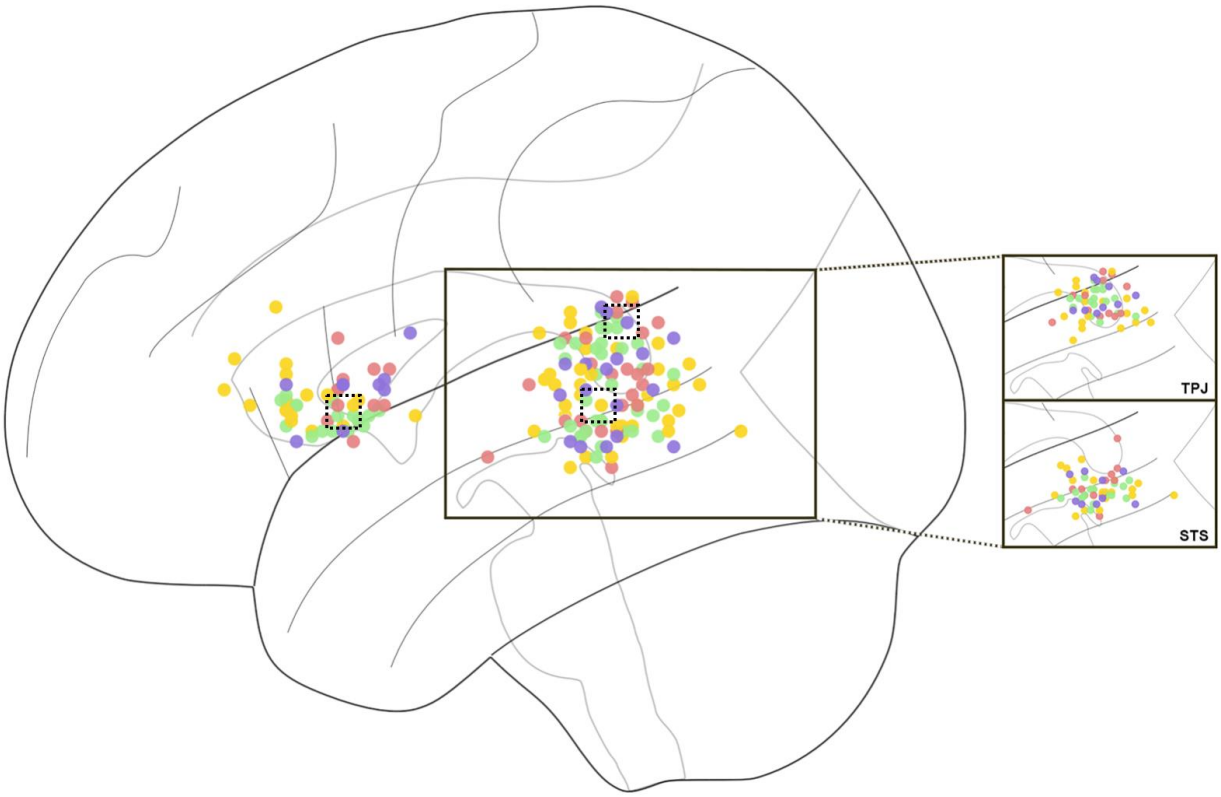

Fig 1. Graphical rendering of fMRI activations on the IFG, TPJ and STS Tailarach coordinates of HC (green) and GL (yellow), TLE (violet) and CA patients (red). Reference coordinates are indicated by dashed boxes. Note how activation peaks in HC are less scattered and closer to reference coordinates than in patients.

CA = cavernous angioma patients; GL = glioma patients; HC = healthy controls; IFG = Inferior Frontal Gyrus; STS = Superior Temporal Gyrus; TLE = Temporal Lobe Epilepsy Patients; TPJ = Temporo-Parietal Junction.

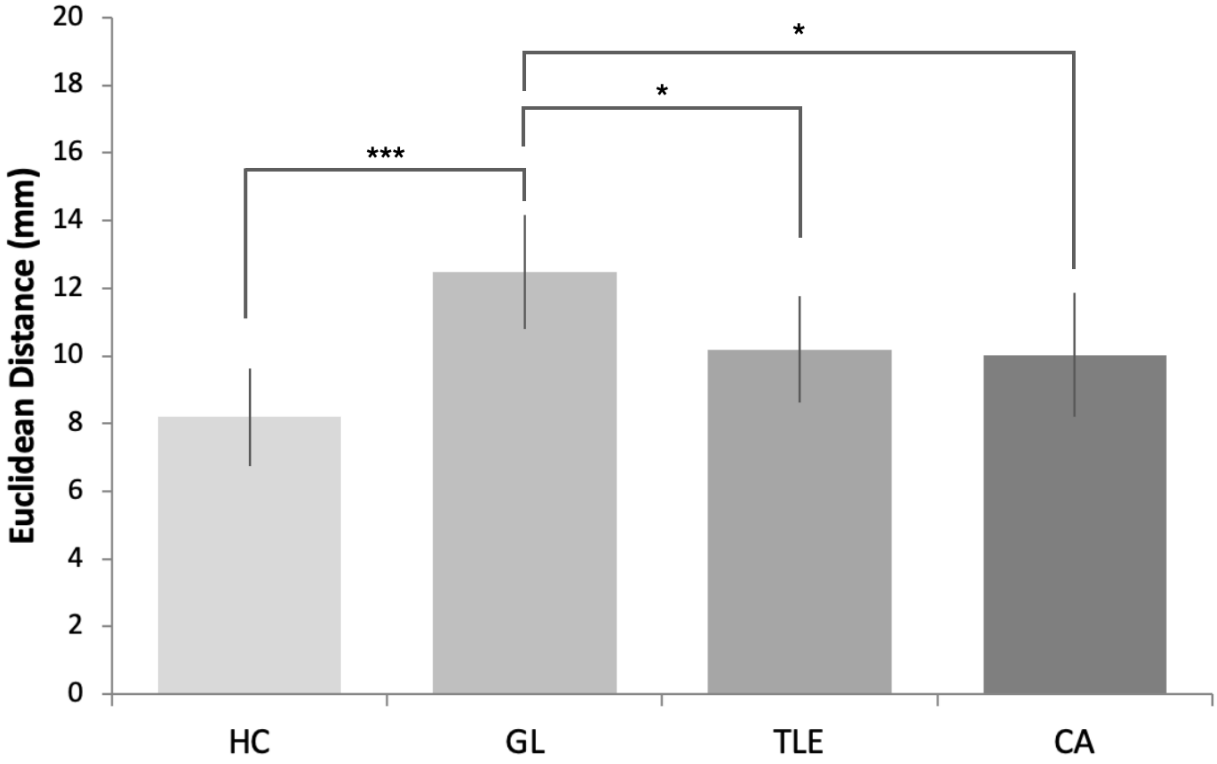

Fig 2. Lesion type affects activation peak shift. The histogram depicts the group difference of the median Euclidean Distance from HC, GL, TLE and CA patients. Bars indicate standard error.

*Indicates $p < 0.05$ and ***indicates $p < 0.001$.

CA = cavernous angioma patients; GL = glioma patients; HC = healthy controls; TLE = Temporal Lobe Epilepsy Patients

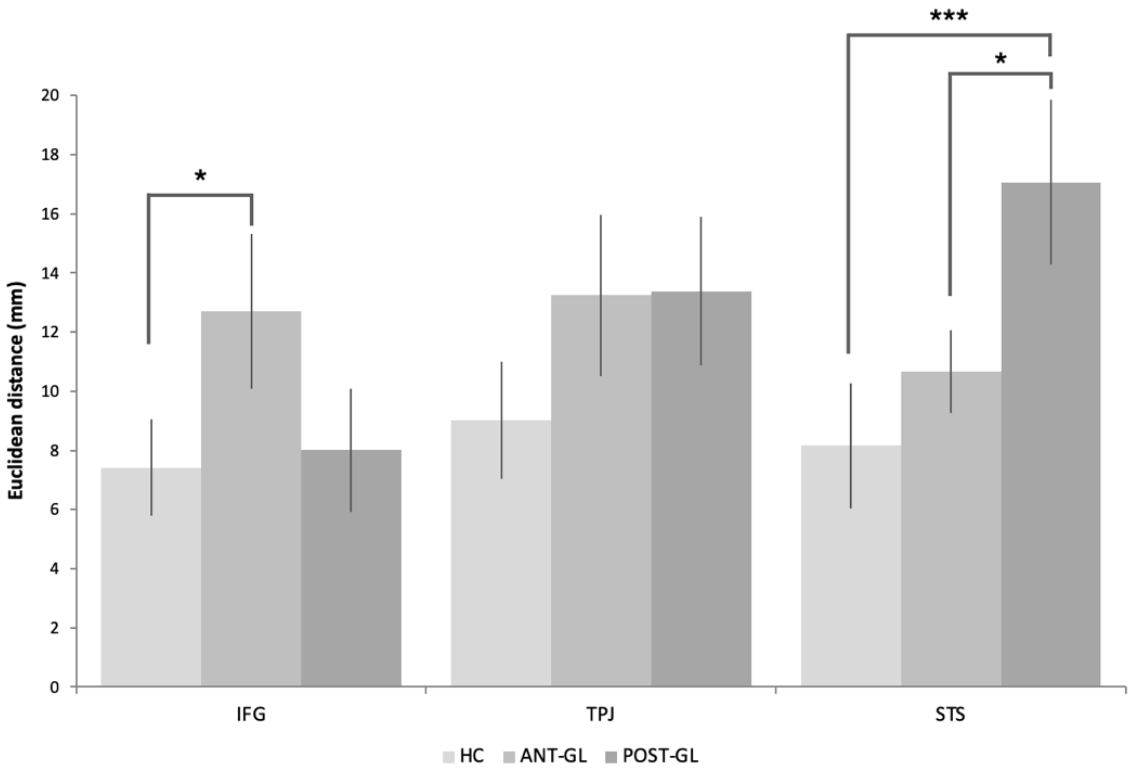

Fig 3. Glioma location affects activation peak shift. The histogram depicts the group difference of the median Euclidean Distance from HC, ANT-GL and POST-GL in each language site (IGF, TPJ, STS). Bars indicate standard error.

*Indicates $p < 0.05$ and ***indicates $p < 0.001$.

ANT-GL = anterior glioma patients; HC = healthy controls; IFG = Inferior Frontal Gyrus; POST-GL = posterior glioma patients; STS = Superior Temporal Gyrus; TPJ = Temporo-Parietal Junction

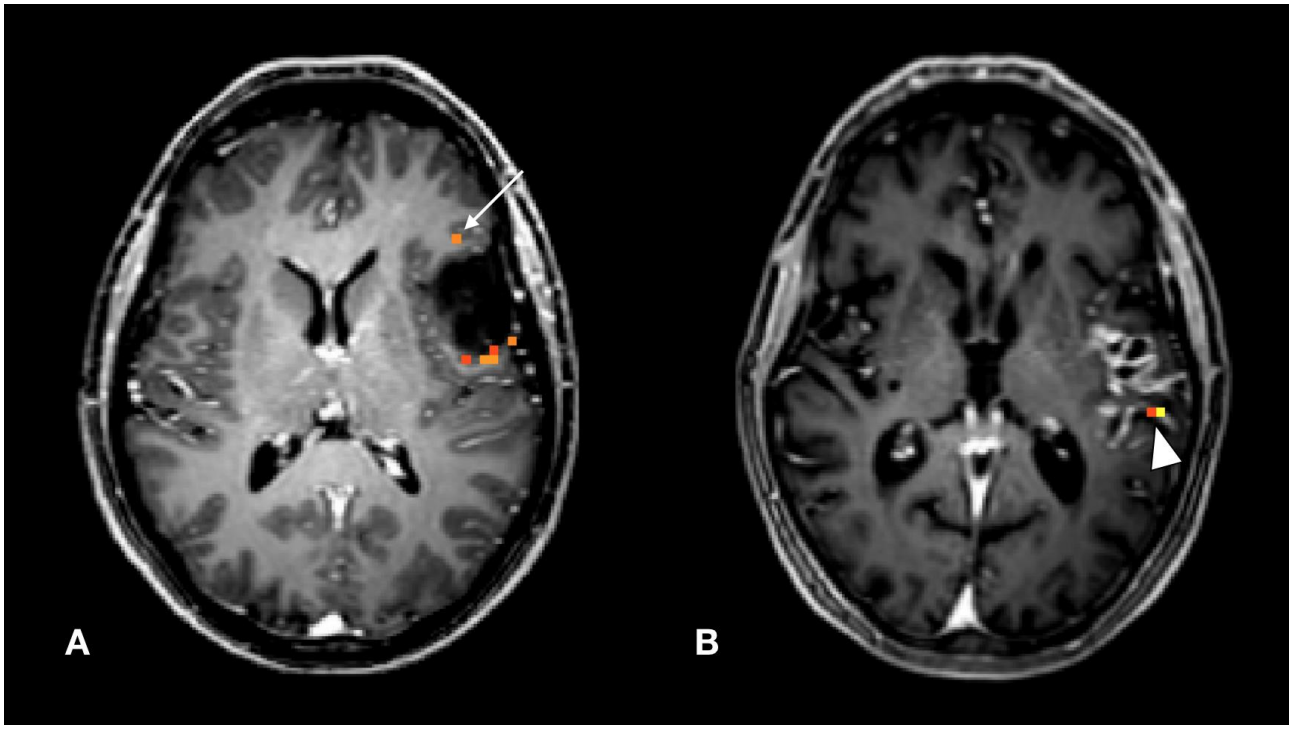

Fig 4. Representative images of cortical activation during a verb generation task in two patients with anterior (A) and posterior (B) high grade gliomas. fMRI is superimposed on the post-contrast axial T1. Patient A) displays activation in the IFG (x: -40, y: 31, z=13) (white arrow) at a Euclidean distance from reference coordinates of 23,32 mm. Conversely, Patients B) displays activation in the STS (x: -58, y: -26, z=5) (arrowhead) at a Euclidean distance from reference coordinates of 8,12 mm.

IFG = Inferior Frontal Gyrus; STS = Superior Temporal Gyrus.