Long-term brain plasticity allowing a multistage surgical approach to World Health Organization Grade II gliomas in eloquent areas

Report of 2 cases

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Although the goal of surgery for World Health Organization Grade II gliomas is maximal extent of resection, complete tumor removal is not always possible when the glioma involves eloquent areas. The authors propose a multistage surgical approach to highly crucial areas that are classically considered inoperable, enabling optimization of the extent of resection while avoiding permanent cognitive deficits due to induced functional reshaping in the interim between the 2 consecutive operations. To demonstrate such plasticity, the authors used a combination of sequential functional MR imaging and intraoperative electrical stimulation mapping before and during surgeries spaced by several years in 2 patients who each underwent 2 separate resections of Grade II gliomas located in the left dominant premotor area. During several years of follow-up after the first procedure, both patients had unremarkable examination results and normal socioprofessional lives. There was no malignant transformation. Based on their experience with these cases, the authors suggest that in cases of incomplete glioma removal, a second operation before anaplasia should be considered, made possible by brain reorganization after the first operation.

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KEY WORDS • brain plasticity • functional magnetic resonance imaging • intraoperative electrical stimulation • language • low-grade glioma • surgery

PATIENTS harboring a WHO Grade II glioma usually present with seizure and no or only mild neurological deficits. Because Grade II gliomas are frequently located in functional areas, resection remains a challenge. Indeed, the goal of surgery is to achieve maximal tumor removal while preserving cerebral functions. To this end, intraoperative cortical and subcortical electrical stimulations are used in awake patients to perform sensorimotor and language mapping, thus permitting a tailored resection according to functional boundaries. These functional limits, however, may force the surgeon to leave tumor residue to avoid permanent deficit when there is invasion into highly eloquent areas. When glioma regrowth occurs in such cases, a second operation is commonly considered impossible because of the excessive risk of major sequelae, and other complementary treatments such as chemotherapy and/or radiotherapy are usually proposed.

Nevertheless, several studies using fMR imaging or intraoperative electrical mapping have shown that slow-growing lesions such as Grade II gliomas can induce functional reshaping due to brain plasticity. This new concept of dynamic brain organization, instead of a fixed model, may play a major role in planning a second operation in patients with Grade II gliomas. Indeed, cerebral plasticity enables us to move from the view that only 1 surgical intervention should be performed in eloquent areas toward a strategy of sequential operations, with the aim of optimizing therapeutic impact on the natural history of the tumor while preserving the patient’s quality of life.
In the present study we show that a multistage surgical approach can be undertaken in eloquent areas without inducing permanent deficits because of the functional re-shaping that occurs between operations. To demonstrate this plasticity, we used a combination of repeated preoperative fMR imaging and intraoperative electrical stimulation mapping before and during 2 surgeries spaced by several years in 2 patients with Grade II gliomas of the left dominant premotor area. To our knowledge, this is the first such study.

Case Reports

Case 1

Examination. This 38-year-old right-handed woman presented with generalized seizure. Her neurological examination was unremarkable. A language assessment using the BDAE was performed by a speech therapist, and the patient was found to have a mild deficit of verbal working memory. Magnetic resonance imaging revealed a precentral tumor that had invaded the posterior part of the left middle frontal gyrus (the dorsal premotor area; Fig. 1). Functional MR imaging was performed to locate the central sulcus and determine the hemispheric dominance for language. Except for the first fMR imaging study in the patient in Case 2, which was obtained at another institution, data analysis for all studies was performed using commercially available software for statistical parametric mapping (SPM99).29 Motor fMR imaging was conducted using right hand movements,29 and showed that the primary motor cortex was posterior to the tumor (Fig. 1). Language fMR imaging was performed using a silent semantic fluency task.30 All activation maps are presented at a probability value < 0.01, uncorrected for statistical comparison. This low threshold was used to favor sensitivity. Functional MR imaging data were compared with electrical stimulation data. An index of hemispheric dominance for language (LI) was computed as described by Lehericy and colleagues.32 Lat- erality indices were calculated for the entire hemisphere (LI_{hemi}), the frontal lobes (LI_{front}), the medial frontal lobe including the SMA (LI_{SMA}), and the lateral frontal lobes without the SMA (LI_{lat}). The LIs were mildly (LI_{hemi} = 0.18) to moderately (LI_{SMA} = 0.4) left-sided, suggesting a moderate left hemispheric dominance for language. In contrast, global (LI_{front} = −0.07) and lateral (LI_{lat} = −0.49) frontal LIs were right-sided suggesting that the tumor was associated with reorganization of lateral frontal language functions to the right hemisphere. In the left frontal lobe, language-related activation was located very close to the tumor, despite the predominant recruitment of the right hemisphere in the lateral frontal cortex (Fig. 2). Because repeated MR images demonstrated tumor volume increases and the seizures persisted, we decided to operate. Due to the tumor’s location within eloquent area, we performed intraoperative electrical mapping on our awake patient.

First Operation. The tumor was delineated on intraoperative ultrasonography, and cortical mapping was done prior to resection using direct electrical stimulation with a 5-mm-tipped bipolar probe (1 msec per phase, 60-Hz bi- phasic current, 1–3 mA; Nimbus, Hemodia). Stimulation allowed the identification of the primary motor and somatosensory areas of the hand. More laterally, stimulation of the primary motor cortex of the face elicited dysarthria associated with face movements, stimulation of the lower part of the precentral gyrus elicited speech arrest on the ventral premotor cortex, and stimulation to the superior part of the inferior frontal gyrus induced paraphasias (Fig. 3A).

The tumor was removed using the precentral sulcus as the posterior limit, preserving the sites that had elicited speech arrest and parapraxia inferiorly, and the medial superior frontal gyrus, which had not been invaded by tumor. Subcortical resection proceeded while the patient continued to perform functional tests. The limit was represented posteriorly by the pyramidal tract arising from the primary motor cortex, medially by the subcallosal fasciculus, which induced transcortical motor aphasia when stimulated, and laterally by the fibers arising from the Broca center, which generated paraphasia during stimulation. Resection was stopped at the level of the periventricular white matter because its subcortical stimulation systematically induced speech arrest (Fig. 3B). The lateral ventricle also could not be opened for this reason.

Postoperative Course. Transient language impairment was observed in the immediate postoperative period. Control MR imaging performed the day after surgery demonstrated a tumor residue evaluated at 3 cm$^2$ in the subcortical part of the precentral gyrus, where language blocking was
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**Fig. 2.** Case 1. A and B: Language fMR imaging performed before the first (Session 1) and second surgery (Session 2) using a silent semantic verbal fluency task. In the left frontal lobe, language-related activation was observed very close to the posterior (arrows) and inferior parts of the tumor (arrowheads). Before the second surgery (center), language-related activation located posterior to the tumor (arrow) was shifted posteriorly compared with Session 1. C: During Session 2, there was greater activation in the bilateral pre-SMA, the right posterior middle and inferior frontal gyri (double arrowheads), the left inferior frontal gyrus (arrowheads), the area that was displaced posteriorly at the posterior border of the tumor (arrow), and in bilateral parietal areas. Images were normalized for easier comparison. Left is right.

**Fig. 3.** Case 1. A: Intraoperative view before resection. The letter tags on the cortex delineate the tumor boundaries. The numbers mark the cortical functional areas from posterior to anterior: primary somatosensory sites in the retrocentral gyrus (10–17); primary motor site of the hand (1) and face (2) in the precentral gyrus; more laterally, ventral premotor cortex (22, 20, 21, and 24) induced speech arrest during stimulation; and language area (25) elicited paraphasia when stimulated in the inferior frontal gyrus. B: Intraoperative view after tumor removal. The cortical functional sites have been preserved (the tag “25” is not visible in this photograph for technical reasons). Three language pathways were identified subcortically: medially, the subcallosal fasciculus, coming from the frontomesial structures that were preserved, joining the anterolateral border of the frontal horn of the ventricle (41), and inducing a transcortical motor aphasia when stimulated; posteriorly, the pyramidal pathways coming from the primary face area (2); and the premotor ventral cortex (22, 20, 21, and 24) joining the lateral wall of the ventricle (42) behind the subcallosal fasciculus. The stimulation of these fibers generated an anarthria or speech arrest, as during the stimulation of the corresponding cortical sites. Thus, the ventricle could not be opened. Laterally, stimulation of the bundles arising from Broca center (40) elicited paraphasia.
elicit ed (Fig. 4 left). On histological examination, a WHO Grade II oligodendroglioma was revealed. According to the deficit demonstrated on postoperative language assessment with BDAE, a specific functional rehabilitation regimen was prescribed, which allowed complete recovery in 3 months. The patient resumed her normal social and professional life without seizures. Because no anaplastic signs were present, no adjuvant treatment was proposed. Regular clinical and MR imaging follow-up was conducted every 6 months.

Chemotherapy. Due to glioma and seizure recurrence, a second surgical intervention was proposed 4 years after the first. However, the patient did not want to have surgery at this time for personal reasons and was consequently started on a course of chemotherapy with 18 cycles of temozolomide. This stabilized tumor growth and epileptic symptoms. At the end of the chemotherapy, however, tumor progression was again observed, with a tumoral volume of 20 cm³ (Fig. 4 right). Functional MR imaging was performed using the same protocol as before. Language fMR imaging during the verbal fluency task showed similar LI values, with left hemispheric and SMA LIs (LI_{left} = 0.16, LI_{SMA} = 0.33) and right global (LI_{right} = −0.13) values, with left hemispheric and SMA LIs (LI_{left} = 0.16, LI_{SMA} = 0.33) and right global (LI_{right} = −0.13) values, with left hemispheric and SMA LIs (LI_{left} = 0.16, LI_{SMA} = 0.33) and right global (LI_{right} = −0.13) frontal LIs. Reshaping of the language map was also noted, with a posterior displacement of activation previously located at the posterior border of the tumor in the precentral sulcus at the level of the face area (Fig. 2).

Direct statistical comparison between the first and second fMR images during the verbal fluency task showed that there was greater activation in the bilateral pre-SMA and in the right posterior middle and inferior frontal gyri when the second set of images were obtained, thus confirming that functional reorganization of language networks had occurred in the frontal lobes after the first surgery. There was also a trend toward fMR imaging activation in the left inferior frontal gyrus and the area displaced posteriorly at the posterior border of the tumor, as well as bilateral parietal areas. Results of BDAE testing did not show any language impairment. Thus, a second awake surgery to reduce the tumor volume to < 10 cm³ was proposed 5 years after the first.

Second Operation. New language mapping tests showed a distribution of the sites in the ventral premotor cortex that elicited speech arrest when stimulated, specifically at the posterolateral limit of the tumor. Stimulation also revealed phonological and semantic paraphasias at the inferior part, that is, the opercular part of the inferior frontal gyrus. No function was found within the tumor. At this cortical stage, the location of the functional sites was slightly more posterior, in agreement with fMR imaging data. Intraoperative language tests were again performed and resection was possible while preserving the eloquent cortical areas, with the possibility this time of removing a part of the tumor behind the precentral sulcus, that is, resection of the anterior part of the precentral gyrus since there was no eloquent site at this level. Subcortical dissection was achieved until stimulation induced transcortical motor aphasia over the subcallosal fasciculus (medial limit) and induced paraphasias over fibers emanating from the Broca center (lateral limit). Posteriorly, we again found that stimulation of the subcortical fibers from the ventral premotor cortex induced anarthria. Interestingly, resection could be pursued farther than the first time at the level of the periventricular white matter, allowing complete opening of the ventricle. Resection was stopped when stimulation of the head of the caudate nucleus elicited perseverations (Fig. 5). There was neither postoperative language worsening (confirmed on tests performed by the speech therapist) nor any motor deficit. Control MR imaging showed a 4-cm³ tumoral residue. Final histological examination of the tumor again confirmed the diagnosis of Grade II oligodendroglioma. There were no other adjuvant treatments. The patient returned again to her normal activities, and at the 1-year follow-up examination, no tumor recurrence was observed.

Case 2

Presentation. This 22-year-old right-handed man presented with generalized seizures. His neurological examination was normal, and no language deficits were revealed on BDAE testing. Magnetic resonance imaging showed...
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First Operation. The surgical method used was the same described for Case 1. Electrical cortical mapping enabled the identification of the primary motor areas of the hand and face. Anarthria was induced with stimulation to the area of the ventral premotor cortex invaded by the tumor, and where preoperative fMR imaging had shown activation (such as at the posterior limit of the tumor). Anomia was also elicited at the level of the opercular part of the inferior frontal gyrus (Broca center). The tumor was thus removed while sparing the primary motor area, the ventral premotor cortex, and the areas in the inferior frontal gyrus for functional reasons. Subcortically, at the posterolateral part of the cavity, stimulation of fibers arising from the premotor cortex elicited anarthria, and posteriorly, stimulation elicited movements of the upper limb (Fig. 7A); tumor resection was stopped.

Postoperative Course and Second Operation. The postoperative course was uneventful, with only slight language impairment and slowness of speech in the first 3 days after surgery, which subsequently improved. Control MR imaging showed subtotal resection with a 2-cm³ residue over the premotor region, posteriorly and laterally to the cavity (Fig. 7B). Histopathological diagnosis confirmed a WHO Grade II oligodendroglioma and no other complementary treatments were performed. Again, the patient received specific language rehabilitation, allowing a complete recovery. He continued his normal socio-professional life with regular clinical and neuropsychological follow-up. The volume of the residue continued to evolve slowly and 4 years later it had reached 15 cm³. Functional MR imaging performed at this time showed that the primary motor area of the face and hand was still spared by tumor infiltration. Language fMR imaging using the silent verbal fluency task showed that all LIs were moderately to strongly left (LI_{hem} = 0.33, LI_{front} = 0.31, LI_{SMA} = 0.8), whereas lateral frontal LI was right (LI_{front} = −0.28) again suggesting that the tumor was associated with reorganization of lateral language functions to the right hemisphere. Only 2 activated areas were observed in the left frontal lobe including the opercular part of the inferior frontal gyrus inferiorly to the tumor and the presupplementary motor area (Fig. 8). In contrast to the first fMR images, no activation was observed at the posterior part of the tumor. No language deficit was shown on BDAE testing. A second operation with intraoperative electrical mapping was then proposed.

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Stimulation of the ventral premotor cortex again induced anarthria, and stimulation of the opercular part of the inferior frontal gyrus elicited anomia. Interestingly, at the posterior limit of the tumor, the invaded premotor cortex showed no response to stimulation (Fig. 9A), so the lesion could be removed partially until subcortical electrical mapping revealed the pyramidal motor tract in the corona radiata. Deeply, the tumor was removed until subcortical stimulation induced perseverations over the head of the caudate nucleus, and the resection was stopped. In the immediate postoperative period, the patient had slowness of speech but no motor deficits. Magnetic resonance imaging demonstrated subtotal resection with an estimated 6-cm³ tumor residue (Fig. 9B). Histopathological studies again showed an oligodendroglioma WHO Grade II, with no anaplastic transformation. One year after this second surgery the patient had returned to a normal socioprofessional life, and was not receiving complementary treatment.

Discussion

Our findings in these cases demonstrate that a multistaged surgical approach in conjunction with brain plasticity can optimize the benefit-to-risk ratio of Grade II glioma removal within so-called eloquent areas when initial complete resection was impossible due to invasion of critical functional structures; that is, a second subtotal resection without permanent deficit can be performed.

Models of Brain Plasticity

Brain compensatory mechanisms have been widely studied, first in animal models, then more recently in humans, especially in stroke victims, due to the development of functional neuroimaging techniques. These studies have shown that recovery is a dynamic process and that activation evolves gradually. Recovery involves both preserved regions in the affected hemisphere and homologous regions in the contralesional hemisphere. Authors of recent longitudinal functional imaging studies generally report that better recovery is often associated with plastic changes in the hemisphere with the lesion, and that early recruitment of contralateral homologous areas decreased with time as the functional deficit is recovered.

In brain tumors, previous imaging and cortical stimulation studies have already shown intra- and interhemispheric compensatory mechanisms. Interestingly, cerebral plasticity was much higher in slow growing lesions, such as Grade II glioma, than in acute lesions. This reshaping may explain why most patients with Grade II gliomas have normal or only slightly impaired neurological examinations. Such reorganization has also been described using intraoperative stimulation in cases of Grade II glioma invading eloquent regions.

Moreover, eloquent structures may persist within the tumor in 7–24% of invasive Grade II gliomas according to recent reports using magnetoencephalography and fMR imaging. This phenomenon can be explained by the Type III spatial configuration of Grade II gliomas described in the Daumas-Duport et al. classification, suggesting the persistence of a functional network within the infiltrated tissue.

Therefore, as summarized by Desmurget et al., if a...
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complete or near complete compensation is usually seen in patients with slow-growing lesions such as Grade II gliomas, even before any treatment, this could be explained by 4 (nonexclusive) mechanisms: 1) the slow infiltrative nature of Grade II glioma makes it possible to find functional areas within the tumor; 2) eloquent areas can be redistributed immediately around the tumor (perilesional plasticity); 3) other distant areas of the network within the same hemisphere can be activated; and 4) the contralateral homologous areas can be also recruited.

This kind of reorganization can also occur in an acute way intraoperatively. For instance, during the resection of Grade II gliomas within the central region, repeated electrical mappings have shown that there are multiple representations of the hand and forearm in the primary motor cortex. Within the short time after tumor resection, these functional redundancies allowed the brain to change its local motor maps by a sudden unmasking of latent sites participating in the same movement.\(^{10,23}\)

**Longitudinal Study Combining fMR Imaging and Intraoperative Electrostimulation**

Although several studies of brain plasticity in neuro-oncology have combined fMR imaging and intraoperative electrostimulation, to our knowledge there is no longitudinal study combining both pre- and intraoperative mapping in 2 consecutive surgeries spaced by several years. Here, we used functional neuroimaging and direct cerebral stimulation to plan a multistage surgical approach for Grade II gliomas in eloquent regions.

Both lesions were located in the left dorsal premotor area (specifically the posterior part of the left middle frontal gyrus), which, as demonstrated on electrostimulation, is a highly functional region not only for the planning of movement, but also for language.\(^{17}\) The mild preoperative language deficit noted by the speech therapist in the first patient, and the postoperative transient language deterioration in both cases confirm this implication and provide further justification for awake procedures.

In the patient in Case 1, reorganization of language maps occurred before the first surgery and between operations, as shown in comparing preoperative fMR images obtained prior to each surgery. Before the first surgery, a reorganization of lateral frontal areas toward homologous regions of the unaffected hemisphere was observed, as shown by the right predominance of LI\(_{\text{pre-SMA}}\) compared with the left right predominance of LI\(_{\text{dom}}\) and LI\(_{\text{SMA}}\). Previous functional imaging studies on language dominance have consistently reported left or, less often, symmetrical dominance in the frontal lobes in healthy right-handed volunteers.\(^{31,40,48}\) Before the second surgery, increased activation was observed in several ipsi- and contralesional brain areas including the right lateral frontal cortex, the bilateral pre-SMA, and the left inferior frontal cortex. These findings suggest that reorganization involved both perilesional and homologous contralateral language-related areas. In the hemisphere with the lesion, intraoperative cortical mapping during the second surgery yielded similar results as in the first one—primary motor cortex of the face, speech arrest in the ventral premotor, and paraphasias in the opercular part of F3—except that the functional sites were slightly more posterior at the posterior border of the tumor, in agreement with fMR imaging findings. Intrasurgical electrical mapping also showed modifications at the subcortical level, where fMR imaging is not able in essence to detect functional activation. During the first operation, the ventricle could not be opened because of repetitive language blocking over the periventricular white matter, while during the second operation, resection could be pursued farther, with opening of the frontal horn, thus allowing stimulation over the head of the caudate nucleus, which elicited perseverations.\(^{25}\) The other subcortical boundaries were unchanged. These data support the implication of a large-scale network in plasticity mechanisms, especially in the involvement of contralateral homologous areas (Fig. 2).

In the patient in Case 2, there was a similar pattern with signs of reorganization in the contralateral hemisphere and the perilesional area. In verbal fluency tests during the first examination a strong activation was present in the left ventral premotor cortex and within the tumor. In the examination conducted just before the second operation, there was a reorganization of frontal areas toward homologous regions of the unaffected hemisphere.

**Fig. 9. Case 2.** A: Intraoperative view before the second resection, 5 years later. Stimulation of the ventral premotor cortex again induced anarthria (11, 12, 20, and 21), and stimulation of the opercular part of the inferior frontal gyrus elicited anomia (29). Interestingly, at the posterior limit of the tumor (letter A), the invaded premotor cortex showed no response to stimulation, so it was possible to remove it partially until subcortical electrical mapping revealed the pyramidal motor tract in the corona radiata. Deeply, the tumor was removed until subcortical stimulation also induced perseverations over the head of the caudate nucleus. B: Gadolinium-enhanced T1-weighted MR imaging obtained after the second surgery showing subtotal resection.
as suggested by the right lateralization of activation in the lateral frontal lobe (LIFL) as compared with the left lateralization of the hemispheric and SMA LIs. Moreover, within the tumoral hemisphere, a reshaping of the language areas was observed more laterally, essentially at the level of the operculum of the inferior frontal gyrus. Thus, there was activation neither at the posterior border of the glioma nor within it (Fig. 8). These results were confirmed on intraoperative electrostimulation during the second procedure. Indeed, during the first operation, the cortical sites at which stimulation induced anoma in the ventral premotor cortex were infiltrated by the tumor and therefore could not be resected. During the second operation 5 years later, these sites were reorganized more laterally, close to the inferior frontal gyrus. Because of this reorganization, the resection could be pursued more posteriorly within the premotor area.

Intrahemispheric and interhemispheric reorganization of language functions that were observed in these 2 patients are in agreement with previous imaging49,50 and cortical stimulation studies.13,14 Here, by comparing pre- and postoperative examinations using longitudinal fMR imaging, combined with intraoperative confirmation with electrostimulation, we have shown that such functional reshaping occurs within several years in individual patients. These results suggest that a multistaged surgical approach to Grade II gliomas is feasible. Such a surgical application could constitute a new indication of fMR imaging, in the repeated perioperative functional assessment of patients with Grade II gliomas in eloquent areas. This application of fMR imaging would be much more useful than obtaining preoperative fMR images to detect functional areas.

To explain this cortical reshaping, 3 types of pathophysiological mechanisms have to be considered. First, the surgical act itself can facilitate cortical hyperexcitability, and thus can be a booster for brain redistribution through the unmasking of latent networks. Thus, there was activation neither at the posterior border of the glioma nor within it (Fig. 8). These results were confirmed on intraoperative electrostimulation during the second procedure. Indeed, during the first operation, the cortical sites at which stimulation induced anoma in the ventral premotor cortex were infiltrated by the tumor and therefore could not be resected. During the second operation 5 years later, these sites were reorganized more laterally, close to the inferior frontal gyrus. Because of this reorganization, the resection could be pursued more posteriorly within the premotor area.

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To explain this cortical reshaping, 3 types of pathophysiological mechanisms have to be considered. First, the surgical act itself can facilitate cortical hyperexcitability, and thus can be a booster for brain redistribution through the unmasking of latent networks.10,23 Second, since the resection was subtotal, the residue continued to grow progressively, and certainly also contributed to the cortical reorganization before and after the first operation. Third, both patients benefited from an intensive and specific program of language rehabilitation following the resection, which probably facilitated brain plasticity.

These observations also show the complementary nature of using both fMR imaging and intraoperative electrical stimulation. Indeed, while functional MR imaging is considered a useful tool for the planning of resections in eloquent regions, Roux et al.44 have reported that it was not yet possible to rely only on its results for reliable language mapping (sensitivity evaluated at 66%). As a result, intraoperative electrical mapping within eloquent regions is still mandatory and remains the gold standard for detecting functional areas. Subcortical stimulation also helped to delineate the limit of the resection in terms of depth, at the level of the white matter tracts and deep gray nuclei. Thus, our results demonstrate that, despite the great potential of cortical reorganization, brain plasticity has some limitations, especially in terms of subcortical connectivity.12,14,20,21 As a consequence, in cases of tumor recurrence, we speculate that it seems possible to continu-
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cal connectivity. However, we acknowledge that our series is too small to represent the definitive statement on brain plasticity with tumors. Larger series of patients with sequential surgeries are needed to confirm these preliminary data, better understand the individual mechanisms of cerebral reorganization, and guide this potential for plasticity, especially using adapted program of rehabilitation.

Disclaimer
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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