ORIGINAL ARTICLE

Functional Outcome after Language Mapping for Glioma Resection

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ABSTRACT

BACKGROUND

Language sites in the cortex of the brain vary among patients. Language mapping while the patient is awake is an intraoperative technique designed to minimize language deficits associated with brain-tumor resection.

METHODS

To study language function after brain-tumor resection with language mapping, we examined 250 consecutive patients with gliomas. Positive language sites (i.e., language regions in the cortex of the brain, 1 cm by 1 cm, which were temporarily inactivated by means of a bipolar electrode) were identified and categorized into cortical language maps. The tumors were resected up to 1 cm from the cortical areas where intraoperative stimulation produced a disturbance in language. Our resection strategy did not require identification of the stimulation-induced language sites within the field of exposure.

RESULTS

A total of 145 of the 250 patients (58.0%) had at least one site with an intraoperative stimulation-induced speech arrest, 82 patients had anomia, and 23 patients had alexia. Overall, 3094 of 3281 cortical sites (94.3%) were not associated with stimulation-induced language deficits. A total of 159 patients (63.6%) had intact speech preoperatively. One week after surgery, baseline language function remained in 194 patients (77.6%), it worsened in 21 patients (8.4%), and 35 patients (14.0%) had new speech deficits. However, 6 months after surgery, only 4 of 243 surviving patients (1.6%) had a persistent language deficit. Cortical maps generated with intraoperative language data also showed surprising variability in language localization within the dominant hemisphere.

CONCLUSIONS

Craniotomies tailored to limit cortical exposure, even without localization of positive language sites, permit most gliomas to be aggressively resected without language deficits. The composite language maps generated in our study suggest that our current models of human language organization insufficiently account for observed language function.

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Although a primary tenet of neurosurgical oncology is that survival can be improved with more extensive tumor resection, this principle must be tempered by the potential for functional loss after radical removal of the tumor. Large, dominant-hemisphere lesions present a particular challenge, especially when they are located within or adjacent to language pathways. The prediction of function through classic anatomical criteria is insufficient because of the variability of cortical organization,[1-4] distortion of the cerebral topography as a result of the mass effect of the tumor, and functional reorganization due to plasticity.[5-7] Because of the infiltrating nature of brain tumors such as gliomas, it is common for a portion of the mass to occupy tissue involved in language function, even if the patient has no aphasia. Furthermore, since functional tissue can exist within the tumor nidus,[8] debulking tumor from within (i.e., staying within the confines of the tumor) is not an acceptable surgical strategy. Taken together, these findings underscore the importance of language mapping not only for dominant frontal-lobe lesions but also for those in proximity to this region.

Techniques for language mapping were first developed in the context of surgery in which intraoperative cortical stimulation guided resection of epileptic foci in patients with epilepsy. In these procedures, large craniotomies exposed the brain well beyond the surgical target in order to localize cortical sites associated with stimulation-induced language and motor function, or "positive" sites, before resection. Until now, such positive sites were thought to be necessary as a control during language mapping before a cortical area could be safely resected. With the use of language mapping, craniotomies performed while the patients were awake have identified positive language sites in 95 to 100% of operative exposures.[2,9,10]

We undertook a different approach to language mapping. Smaller, tailored craniotomies typically did not expose positive sites, and tumor resection was directed by localization of the cortical regions that were not associated with stimulation-induced language or motor function (i.e., "negative" sites). This "negative mapping" strategy represents a paradigm shift in the language-mapping technique by eliminating the neurosurgeon's dependence on the positive sites as controls, thereby allowing minimal cortical exposure, less extensive intraoperative mapping, and a more rapidly performed neurosurgical procedure. We conducted a study to determine the efficacy of negative language mapping in averting new language deficits. We also sought to delineate the distribution of human cortical language sites for speech production (i.e., in Broca's area), naming, and reading; to describe the resolution profile of postoperative language deficits; and to determine whether data from negative language mapping can be relied on for radical brain-tumor resection.

METHODS

PATIENTS

Between June 1997 and September 2005, a total of 245 consecutive patients with left-sided gliomas and 5 patients with right-sided gliomas underwent surgery at the University of California at San Francisco Medical Center, with the use of intraoperative language mapping in English while the patients were awake. All patients with dominant-hemisphere gliomas located within the posterior inferior frontal lobe, anterior inferior parietal lobe, inferior to midportion of the motor cortex, or any portion of the temporal lobe required awake language mapping before tumor resection. A small number of patients (<5%) with dysphasia or aphasia, a severe language barrier, emotional instability, confusion, or a decreased level of consciousness did not undergo language mapping and were not included in our analysis. In the five patients with right-sided glioma, language function was localized to the right hemisphere by means of Wada testing. The institutional review board of the University of California at San Francisco approved this retrospective study. All patients gave written informed consent for the procedure; the requirement for informed consent for this study was waived by the institutional review board.

Preoperatively and at each follow-up appointment, patients underwent neurologic examination. Language testing followed a set protocol: counting numbers from 1 to 50, naming objects pictured on a computer-generated slide show, reading single words projected sequentially on a computer screen, repeating complex sentences, and writing words and sentences on paper. Intraoperatively, the first three tasks were tested three times at each cortical site while the patient's cortex was stimulated as described below.

Language deficits were classified as anomias when the patient was unable to name objects but

was able to repeat sentences and had fluent speech. Alexia was defined as the retention of the ability to write and spell, but with errors in reading words. Aphasias were classified as expressive (i.e., the patient's expression through speech or writing was impaired), receptive (i.e., the patient had fluent but meaningless speech and an impaired ability to understand spoken or written words), or mixed, and they were graded accordingly. Mild language disturbances, such as paraphasic errors, were noted, but these language disturbances were not classified as aphasia and did not influence the resection strategy.

A neuropsychologist conducted all preoperative and intraoperative language testing. Postoperative language testing was conducted by two independent clinicians: an attending neurosurgeon and a neurosurgical resident or an attending neuro-oncologist. These clinicians were unaware of the results of each other's clinical examinations. Differences between the results of the two examinations were adjudicated by accepting the results showing greater impairment, although there was a 98.8% rate of concordance between examiners. After surgery, outpatient clinical examinations were performed at 1 week, 4 to 6 weeks, and 3 to 6 months. Patients with no improvement at their 1-year follow-up visit were considered to have a permanent deficit. Results of magnetic resonance imaging (MRI) were also reviewed to confirm that the patients' symptoms were not a function of tumor recurrence.

TUMOR VOLUME AND EXTENT OF RESECTION

Tumor diameters were measured on MRI with digital calipers. The dimensions were defined visually on the basis of signal abnormalities on T_1-weighted images obtained after the administration of gadolinium (for high-grade tumors) and T_2-weighted images (for low-grade tumors). The formula used to calculate volumes was the standard volume of an ellipsoid.

The extent of resection was determined by comparing MRI scans obtained before surgery with those obtained within 48 hours after surgery. Anything less than a gross total resection, defined radiographically as the absence of contrast-enhancing tissue on T_1-weighted images for high-grade gliomas and the absence of hyperintense tissue on T_2-weighted images for low-grade gliomas, was classified as a subtotal resection.

NEUROANESTHETIC REGIMEN

Before surgery, most patients received midazolam (2 mg) and fentanyl (50 to 100 μg). During surgery, propofol (at a dose of 50 to 100 μg per kilogram of body weight per minute) and remifentanil (0.05 to 0.2 μg per kilogram per minute) were given for sedation. After the bone flap was removed, the dura was infiltrated with lidocaine and all anesthetics were discontinued. The patient was asked to hyperventilate before the dura was opened. No anesthesia was administered during mapping. Topical ice-cold Ringer's solution and a bolus of intravenous propofol (1 mg per kilogram) were available for seizure suppression.[11] When mapping was complete, sedatives were given again; before 2001, propofol was administered with remifentanil, and starting in 2001, primarily dexmedetomidine (0.7 to 2.0 μg per kilogram per hour) was administered with remifentanil (0.05 to 0.1 μg per kilogram per minute).

INTRAOPERATIVE STIMULATION MAPPING AND TUMOR RESECTION

A tailored craniotomy exposed the tumor and up to 3 cm of surrounding brain tissue. Cortical mapping was initiated at a low stimulus (1.5 mA), which was increased to a maximum of 6 mA. A constant-current generator delivered biphasic square-wave pulses in 4-second trains at 60 Hz across 1-mm bipolar electrodes separated by a distance of 5 mm. Stimulation sites were identified with sterile numbered labels and distributed per square centimeter of exposed cortex. During mapping, electrocorticographic readings were monitored after discharge potentials to eliminate the possibility of language errors due to subclinical seizure activity.

Speech arrest was defined as a discontinuation in number counting without simultaneous motor responses (i.e., mouth or pharyngeal-muscle movement). Dysarthria was distinguished from speech arrest by the absence of involuntary muscle contraction affecting speech. For sites associated with naming, stimulation was applied for 3 seconds at sequential cortical sites during a slide presentation of line drawings; for sites associated with reading, the same stimulation was applied during a slide presentation of words. All cortical sites were stimulated three times. A positive site was associated with a patient's inability to count, name objects, or read words during stimulation 66% of the time. The location of the site was recorded with

the use of navigational MRI. The targeted area for resection involved the contrast-enhancing regions for high-grade gliomas and the hyperintense areas on T_2-weighted images for low-grade gliomas; however, when a positive language site was detected, a 1-cm margin of tissue was always preserved around this site.[10] When the field of exposure consisted of only negative sites, greater cortical exposure was not sought in order to identify a positive control site.

STATISTICAL ANALYSIS

Descriptive statistics were used to report the baseline characteristics and outcome profiles of all patients. For each cortical site, the percentage of stimulations that were positive (i.e., that caused interruption in language function) and negative were reported for speech arrest, anomia, and alexia. With the use of intraoperative photography and MRI localization, these sites were integrated into a set of composite language maps for each lobe of the dominant hemisphere.

RESULTS

CHARACTERISTICS OF PATIENTS AND TUMORS

The study population included 146 men and 104 women with a mean age of 41.2 years (Table 1). A total of 151 patients (60.4%) underwent primary craniotomy, and 99 patients (39.6%) had undergone previous craniotomies for either resection or biopsy. Patients most often presented with seizures of recent onset (54.4%), although language deficit (36.4%) was also common at presentation. The most common tumor histologic grade was World Health Organization (WHO) grade IV astrocytoma (also called glioblastoma) (28.4%), followed by grade III astrocytoma (16.4%) and grade II oligodendroglioma (11.6%).

The median time to final clinical examination was 12 months, and the median time to final MRI was 18 months. Of 250 patients, 100% survived to the 4-to-6-week clinical examination. By the 3-to-6-month clinical examination, seven patients (all with grade IV astrocytoma) had died from tumor progression.

DISTRIBUTION OF INTRAOPERATIVE LANGUAGE SITES

A total of 145 of the 250 patients (58.0%) had at least one site with an intraoperative stimulation-

Table 1. Demographic and Clinical Characteristics of the 250 Patients.*

Variable	Value
Age — yr	
Mean	41.2
Range	14–84
Male sex — no. (%)	146 (58.4)
Signs and symptoms at presentation — no. (%)	
Seizure	136 (54.4)
Language deficit	91 (36.4)
Headache	24 (9.6)
Hemiparesis	17 (6.8)
Paresthesia	11 (4.4)
Confusion	6 (2.4)
None	4 (1.6)
Language — no. (%)	
English only	232 (92.8)
English as a second language	18 (7.2)
WHO tumor grade and histologic type — no. (%)	
I, ganglioglioma	11 (4.4)
I or II, astrocytoma	60 (24.0)
II, oligodendroglioma	29 (11.6)
II, oligoastrocytoma	24 (9.6)
III, oligodendroglioma	6 (2.4)
III, oligoastrocytoma	8 (3.2)
III, astrocytoma	41 (16.4)
IV, astrocytoma	71 (28.4)
Tumor volume — cm^3	
Mean	71
Range	1.7–592.7
New or increased postoperative language deficit among survivors — no./total no. (%)	
1 week	56/250 (22.4)
1 mo	24/250 (9.6)
3 mo	6/245 (2.4)
6 mo	4/243 (1.6)
Gross total resection according to WHO tumor grade — no./total no. (%)	
All grades	149/250 (59.6)
I or II	64/124 (51.6)
III	36/55 (65.5)
IV	49/71 (69.0)

* WHO denotes World Health Organization.

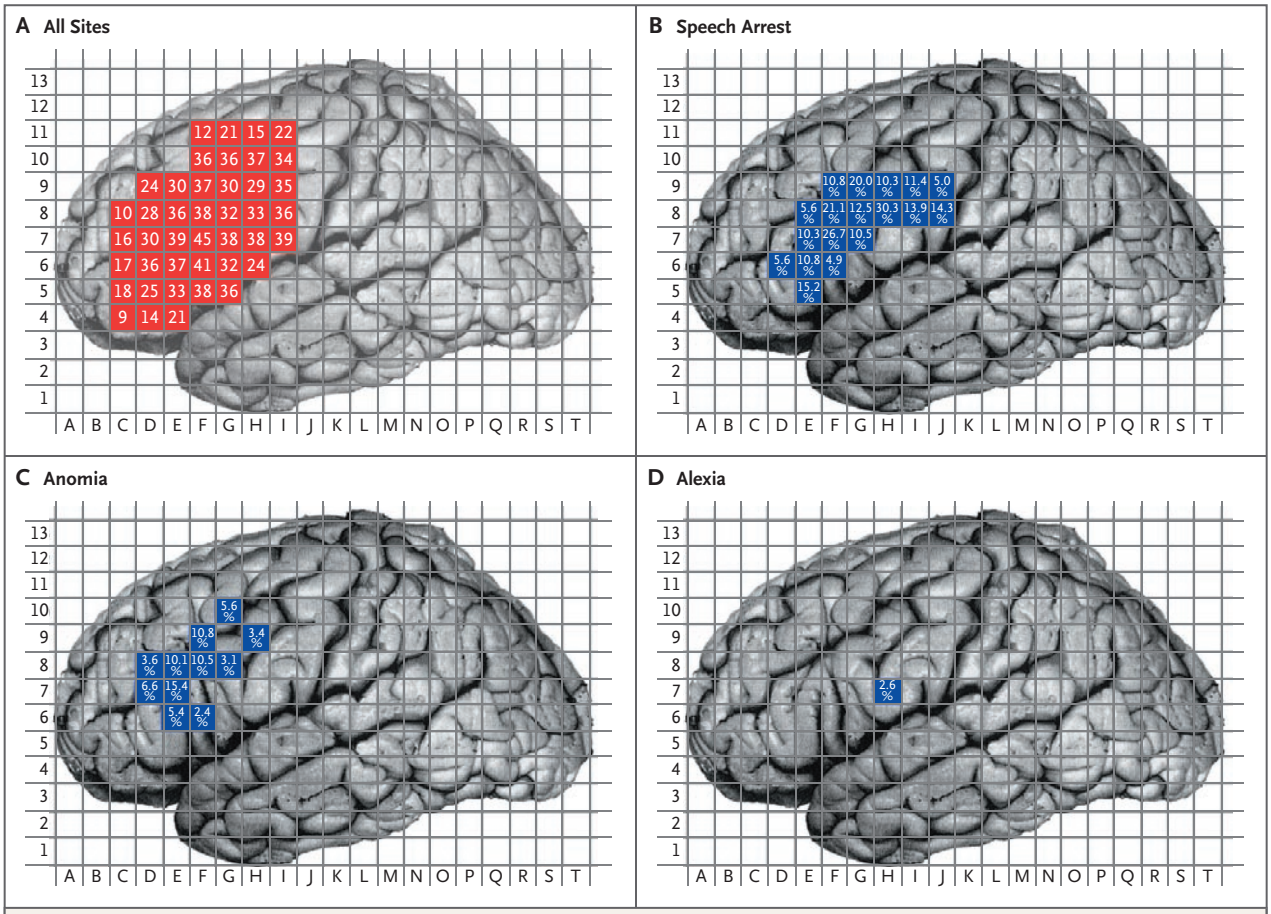

Figure 1. Frontal-Lobe Language Sites.

A total of 1237 cortical sites were stimulated in 151 patients. The red squares indicate the total number of sites that were stimulated, and the blue squares indicate the percentage of total stimulations at that site that induced speech dysfunction. A lateral view of the dominant-hemisphere cortex indicating the total number of stimulations per square centimeter of the frontal cortex is shown in Panel A. The percentage of total stimulations that induced speech arrest (Panel B), anomia (Panel C), and alexia (Panel D) is shown in each square centimeter of the frontal cortex. An interactive graphic showing both the total number of sites that were stimulated and the percentage of total stimulations at that site that induced speech dysfunction is available with the full text of this article at www.nejm.org.

induced speech arrest; anomia occurred in 82 patients and alexia occurred in 23 patients. In most patients, language sites were separated by at least one negative site in which stimulation did not cause a language deficit. Cumulatively, 3281 cortical sites were stimulated among all patients, with 3094 negative sites (94.3%) and 187 positive sites (5.7%).

Stimulation mapping detected at least one frontal-lobe language site in 92 of the 151 patients (60.9%) in whom the frontal lobe was exposed (Fig. 1). In these 92 patients, 111 stimulation-induced language sites were located in the frontal lobe; 82 sites (73.9%) resulted in speech arrest, 28 sites (25.2%) resulted in anomia, and 1 site (0.9%) resulted in alexia. A total of 59 of the 151 patients (39.1%) had no identifiable frontal-lobe language sites (Fig. 2). Transient language deficits developed in 12 of these 59 patients (20.3%) after resection, and a permanent deficit developed in 1 patient (1.7%). A total of 57 of the 186 patients in whom the temporal lobe was mapped (30.6%) were found to have at least one temporal-lobe language site (Fig. 3). Stimulation-induced anomia sites were found in 43 patients, and stimulation-induced alexia sites were found in 16 patients. A total of 129 of the 186 patients (69.4%) had no identifiable temporal-lobe language sites (Fig. 2), and postoperative language deficits developed in 12 of these 129 patients (9.3%). These deficits were permanent in two patients (1.6%).

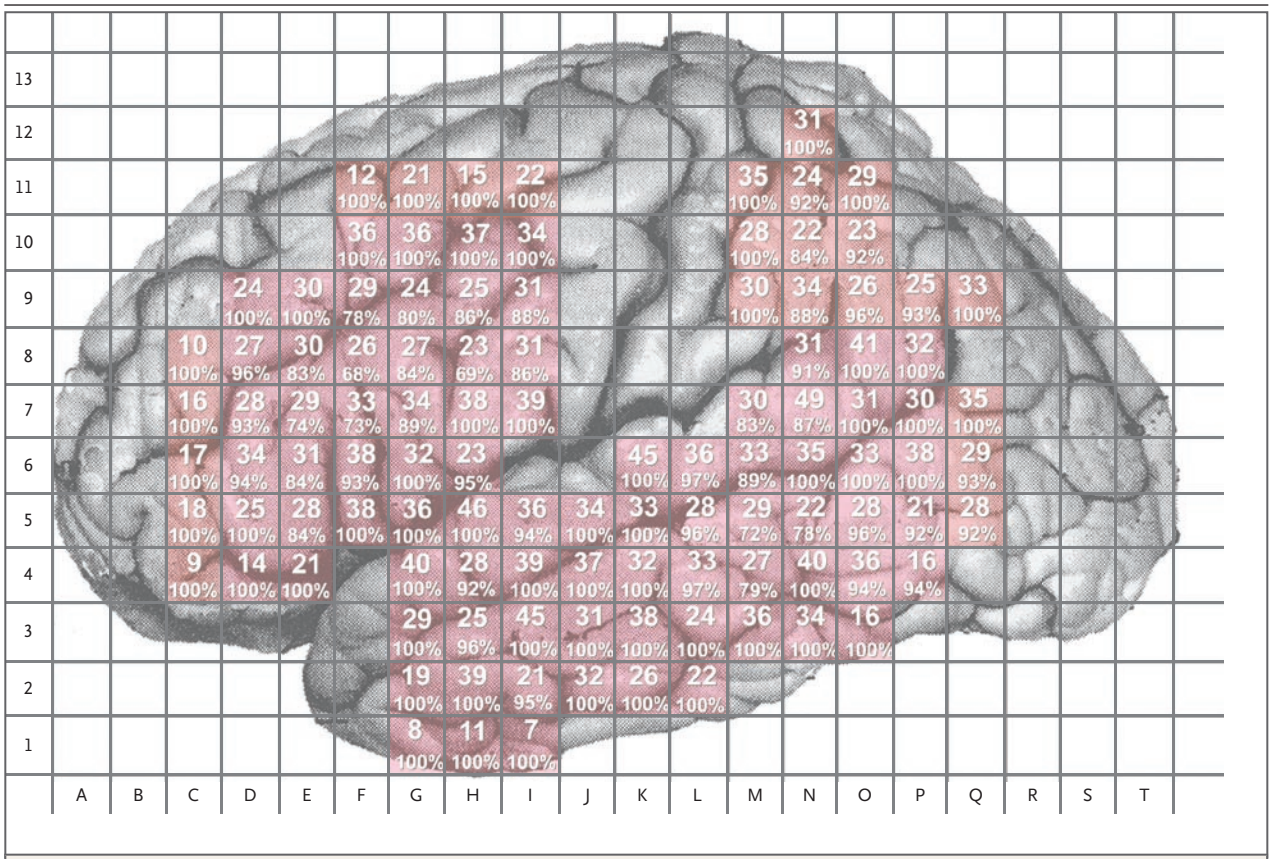

Figure 2. Negative Language Sites.

This lateral view of the dominant-hemisphere cortex shows the location of all negative language sites per square centimeter. In each site, the upper value denotes the total number of patients in whom stimulation did not alter language function, and the lower value denotes the percentage of all patients with no detectable language function at that site.

A total of 13 of 61 patients with parietal-lobe lesions (21.3%) had a parietal-lobe language site (Fig. 4). Of the 17 language sites identified through stimulation, none resulted in speech arrest, 11 resulted in anomia, and 6 resulted in alexia. A total of 48 of these 61 patients (78.7%) had no identifiable parietal-lobe language sites (Fig. 2), and postoperative language deficits, none of which were permanent, developed in 2 patients.

FUNCTIONAL LANGUAGE OUTCOMES AND OTHER NEUROLOGIC MORBIDITY

Overall, 159 of the 250 patients (63.6%) had intact speech preoperatively, and 91 patients (36.4%) had some language deficit at presentation. One week after surgery, the language function in 194 of the 250 patients (77.6%) remained at the baseline level or had improved, it was worse in 21 patients (8.4%), and 35 patients (14.0%) had new speech deficits. At 1 month, however, the number of patients with exacerbated preexisting language deficits had decreased to 16 of 245 (6.4%), and only 8 patients (3.2%) with intact language at baseline had a new language deficit. By 3 months, only 6 of the 245 surviving patients (2.4%) had decreased language function, and no patients had new speech deficits. At 6 months, 4 of the 243 surviving patients (1.6%) had a permanent postoperative language deficit. Thus, 52 of the 56 patients (92.9%) with new or increased language deficits had a return to baseline function or better.

Other neurologic deficits included new, permanent visual deficits in two patients (0.8%) and new, permanent motor deficits in two patients (0.8%). The visual deficits in patients who had undergone temporal-lobe resection were presumably caused by disruption of Meyer's loop. One week postoperatively, 16 patients (6.4%) had new or increased weakness, although only 3 patients (1.2%) had these deficits at 1 month and only 2 patients

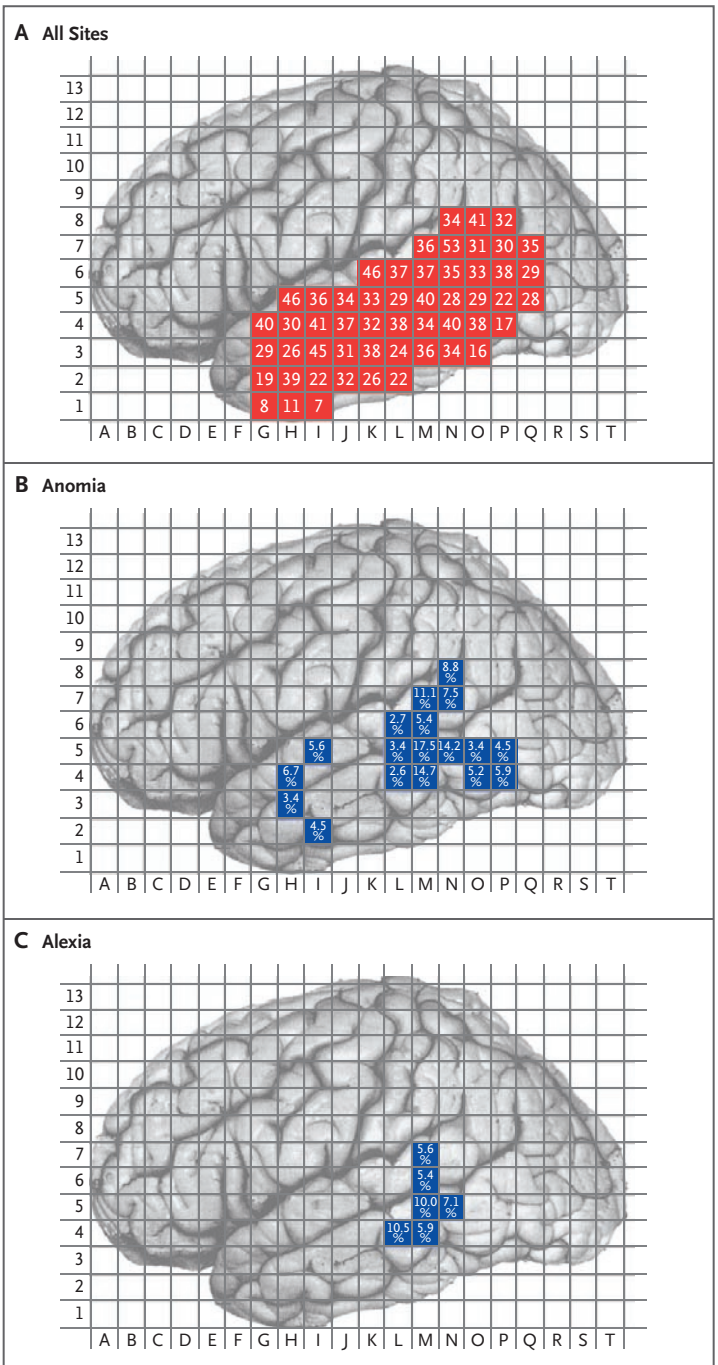

Figure 3. Temporal-Lobe Language Sites.

A total of 1683 cortical sites were stimulated in 186 patients. A lateral view of the dominant-hemisphere cortex indicating the total number of stimulations per square centimeter of the temporal cortex is shown in Panel A. The percentage of total stimulations that induced anomia (Panel B) and alexia (Panel C) is shown in each square centimeter of the temporal cortex. An interactive graphic showing both the total number of sites that were stimulated and the percentage of total stimulations at that site that induced speech dysfunction is available at www.nejm.org.

(0.8%) had them at 3 months. Of the 38 patients with postoperative language deficits who underwent diffusion-weighted MRI after surgery, 5 patients (13.2%) had radiographic evidence of ischemic injury adjacent to the resection cavity, although none of their language deficits were permanent. New postoperative seizure disorders did not develop in any patients, and none died from neurosurgical treatment. A total of seven patients died from their disease before the final 3-to-6-month clinical examination.

EXTENT OF TUMOR RESECTION

Despite an average tumor volume of more than 70 cm^3, the mean area of cortical exposure was only 54.1 cm^2 (range, 15.3 to 88.8), since our mapping strategy permitted a narrow field of exposure. Overall, gross total resection was achieved in 149 of the 250 patients (59.6%) according to postoperative MRI findings. When the extent of resection was stratified according to tumor grade, the rate of gross total resection was 65.5% for WHO grade III tumors and 69.0% for WHO grade IV tumors; the rate was 51.6% for low-grade tumors (WHO grade I and II).

DISCUSSION

Modern theories of language organization in the brain are based on observational data from patients with traumatic, ischemic, infectious, or iatrogenic cortical injuries.[12] This study provides new in vivo data that refine our understanding of cortical language organization. Our findings show that sites associated with speech function are variably located along the cortex and can go well beyond the classic anatomical boundaries of Broca's area. These sites typically involve an area contiguous with the face–motor cortex; however, they can be located several centimeters from the sylvian fissure (Fig. 1B).

In our study, sites associated with anomia were also widely distributed in the frontal lobe, and they often were intermingled with sites associated with speech arrest. We found a paucity of naming sites in the temporal lobe, with only 28 anomia sites identified, predominantly in the superior and middle temporal gyri. This finding differs from those classically described in language studies of the temporal lobe.[13-15] Despite the use of tailored craniotomies, our data confirm that we mapped the entire temporal lobe with repetitive stimula-

tions (Fig. 3). Thus, the small number of anomia sites in the temporal lobe was probably not due to site-selection bias. Reading sites were also sparsely located in the temporal lobe, with just one cluster of 16 sites. More reading sites, however, were located in the inferior parietal lobe, 1 to 2 cm behind the somatosensory cortex (Fig. 4). Overall, our study reveals tremendous variability in language-site localization, but it shows the synthesis of exact language maps based on thousands of cortical stimulations. These data suggest that current models of language localization in the dominant hemisphere insufficiently reflect the true diversity and in vivo patterns of cortical language organization.

The fact that language sites were located intraoperatively in only 58.0% of patients can be attributed to our small, tailored cortical exposures. Historically, neurosurgeons believed it was essential to identify the areas where language was located before any nonfunctional area could be safely resected. However, locating the sites associated with cortical language function with such certainty requires very wide exposures and extensive mapping while the patient is awake, which is tedious and uncomfortable for the patient. We showed that this language localization is no longer needed; nearly half of our patients had no positive language sites in their field of exposure, and more than 94% of the cortical stimulations in these patients were negative, yet their functional outcomes remained acceptable. Only 1.6% of surviving patients had a persistent language deficit 6 months after surgery. Therefore, resection can be based on the areas where language is not located — that is, on negative mapping.

Overall, the morbidity profile in this study compares favorably with that in other studies of hemispheric glioma,[16-22] in which the rate of 30-day neurologic decline had ranged from 7% to 20%. Among our patients, the rate of permanent neurologic morbidity was 3.2%. This difference is probably not the result of conservative tumor resection, since our rate of gross total resection of high-grade gliomas was 67.5% and our rate of gross total resection of low-grade gliomas 51.6%; these findings are similar to those of other studies of gliomas,[23-32] in which the rates ranged from 35% to 63% for resection of high-grade tumors and from 21% to 58% for resection of low-grade tumors. The limited clinical follow-up in some of these studies, however, may have led to an over-

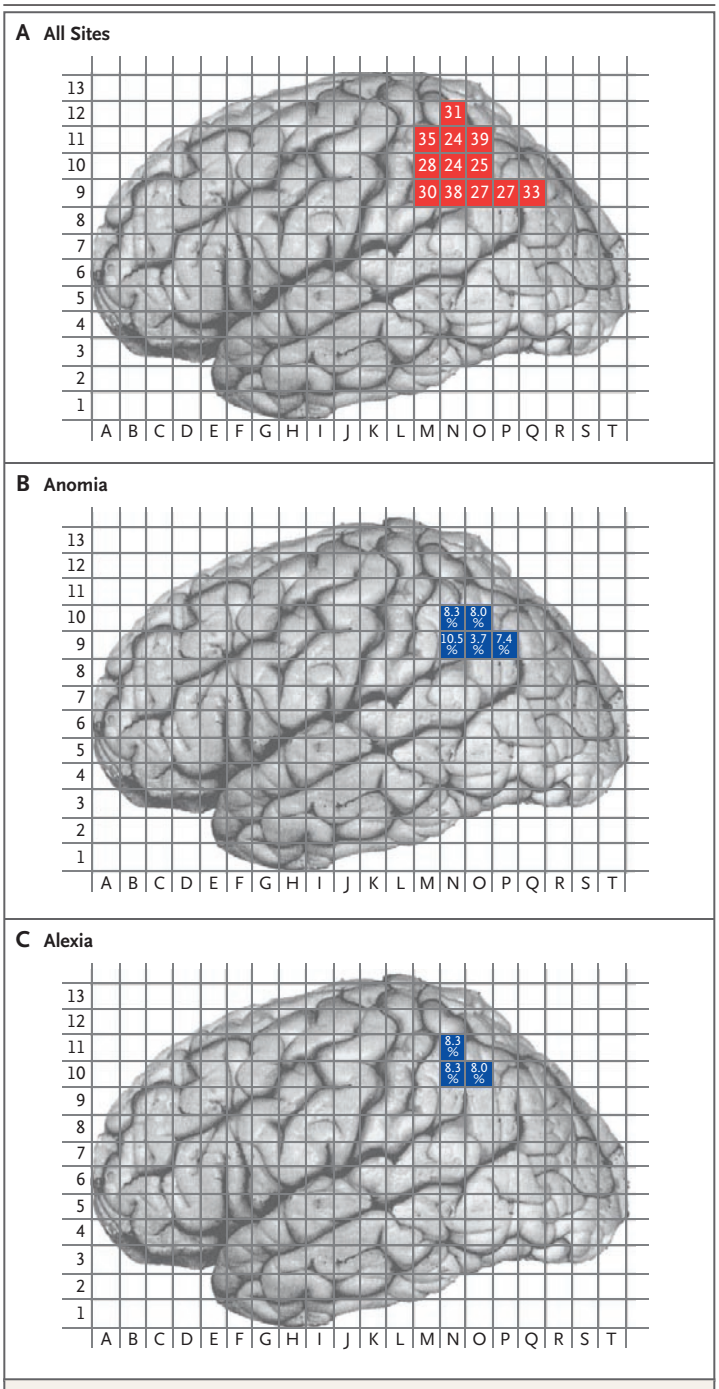

Figure 4. Parietal-Lobe Language Sites.

A total of 361 cortical sites were stimulated in 61 patients. A lateral view of the dominant-hemisphere cortex indicating the total number of stimulations per square centimeter of the parietal cortex is shown in Panel A. The percentage of total stimulations that induced anomia (Panel B) and alexia (Panel C) is shown in each square centimeter of the parietal cortex. An interactive graphic showing both the total number of sites that were stimulated and the percentage of total stimulations at that site that induced speech dysfunction is available at www.nejm.org.

estimation of their complication rates, considering the continued neurologic improvement we observed after the first month after surgery.

A high proportion of patients (92.9%) had complete recovery of language function after an initial decrease in language function. Although perioperative edema may account for some of this recovery, both intraoperative stimulation and data from functional imaging have shown redistribution of functional neural networks in patients with stroke,[6,33,34] brain injury,[35] and tumor progression.[6,7,36] We also cannot rule out the presence of perilesional language sites undetected by intraoperative language testing. Resection of this tissue could have contributed to transient or permanent postoperative language deficits.

Our findings suggest that a tailored craniotomy in conjunction with negative language mapping can be relied on to maximize resection and minimize morbidity when gliomas within or near language pathways are removed. The language deficit that we observed and incurred as a result of this approach improved by 3 months or not at all. The composite language maps generated from this study address the critical question of how cortical language sites for speech production, naming, and reading are distributed within the dominant hemisphere of the cortex.

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Herholz K, Thiel A, Wienhard K, et al. Individual functional anatomy of verb generation. Neuroimage 1996;3:185-94.
2. Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere: an electrical stimulation mapping investigation in 117 patients. J Neurosurg 1989;71:316-26.
3. Ojemann GA, Whitaker HA. Language localization and variability. Brain Lang 1978;6:239-60.
4. Ojemann GA. Individual variability in cortical localization of language. J Neurosurg 1979;50:164-9.
5. Ojemann JG, Miller JW, Silbergeld DL. Preserved function in brain invaded by tumor. Neurosurgery 1996;39:253-8.
6. Seitz RJ, Huang Y, Knorr U, Tellmann L, Herzog H, Freund HJ. Large-scale plasticity of the human motor cortex. Neuroreport 1995;6:742-4.
7. Wunderlich G, Knorr U, Herzog H, Kiwit JC, Freund HJ, Seitz RJ. Precentral glioma location determines the displacement of cortical hand representation. Neurosurgery 1998;42:18-26.
8. Skirboll SS, Ojemann GA, Berger MS, Lettich E, Winn HR. Functional cortex and subcortical white matter located within gliomas. Neurosurgery 1996;38:678-84.
9. Duffau H, Capelle L, Sichez J, et al. Intra-operative direct electrical stimulations of the central nervous system: the Salpetriere experience with 60 patients. Acta Neurochir (Wien) 1999;141:1157-67.
10. Haglund MM, Berger MS, Shamseldin M, Lettich E, Ojemann GA. Cortical localization of temporal lobe language sites in patients with gliomas. Neurosurgery 1994;34:567-76.
11. Sartorius CJ, Berger MS. Rapid termination of intraoperative stimulation-evoked seizures with application of cold Ringer's lactate to the cortex: technical note. J Neurosurg 1998;88:349-51.
12. Berker EA, Berker AH, Smith A. Translation of Broca's 1865 report: localization of speech in the third left frontal convolution. Arch Neurol 1986;43:1065-72.
13. Ojemann GA. Organization of language cortex derived from investigations during neurosurgery. Semin Neurosci 1990;2:297-305.
14. *Idem.* Cortical organization of language. J Neurosci 1991;11:2281-7.
15. Tomaszewki Farias S, Harrington G, Broomand C, Seyal M. Differences in functional MR imaging activation patterns associated with confrontation naming and responsive naming. AJNR Am J Neuroradiol 2005;26:2492-9.
16. Ciric I, Ammirati M, Vick N, Mikhael M. Supratentorial gliomas: surgical considerations and immediate postoperative results — gross total resection versus partial resection. Neurosurgery 1987;21:21-6.
17. Devaux BC, O'Fallon JR, Kelly PJ. Resection, biopsy, and survival in malignant glial neoplasms: a retrospective study of clinical parameters, therapy, and outcome. J Neurosurg 1993;78:767-75.
18. Sawaya R, Hammoud M, Schoppa D, et al. Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. Neurosurgery 1998;42:1044-55.
19. Vorster SJ, Barnett GH. A proposed preoperative grading scheme to assess risk for surgical resection of primary and secondary intraaxial supratentorial brain tumors. Neurosurg Focus 1998;4(6):e2.
20. Taylor MD, Bernstein M. Awake craniotomy with brain mapping as the routine surgical approach to treating patients with supratentorial intraaxial tumors: a prospective trial of 200 cases. J Neurosurg 1999;90:35-41.
21. Brell M, Ibáñez J, Caral L, Ferrer E. Factors influencing surgical complications of intra-axial brain tumours. Acta Neurochir (Wien) 2000;142:739-50.
22. Chang SM, Parney IF, McDermott M, et al. Perioperative complications and neurological outcomes of first and second craniotomies among patients enrolled in the Glioma Outcome Project. J Neurosurg 2003;98:1175-81.
23. Buckner JC, Schomberg PJ, McGinnis WL, et al. A phase III study of radiation therapy plus carmustine with or without recombinant interferon-alpha in the treatment of patients with newly diagnosed high-grade glioma. Cancer 2001;92:420-33.
24. Brown PD, Maurer MJ, Rummans TA, et al. A prospective study of quality of life in adults with newly diagnosed high-grade gliomas: the impact of the extent of resection on quality of life and survival. Neurosurgery 2005;57:495-504.
25. Stark AM, Nabavi A, Mehdorn HM, Blömer U. Glioblastoma multiforme — report of 267 cases treated at a single institution. Surg Neurol 2005;63:162-9.
26. Kowalczuk A, Macdonald RL, Amidei C, et al. Quantitative imaging study of extent of surgical resection and prognosis of malignant astrocytomas. Neurosurgery 1997;41:1028-36.
27. Tortosa A, Viñolas N, Villà S, et al. Prognostic implication of clinical, radiologic, and pathologic features in patients with anaplastic gliomas. Cancer 2003;97:1063-71.
28. Philippon JH, Clemenceau SH, Fauchon FH, Foncin JF. Supratentorial low-grade astrocytomas in adults. Neurosurgery 1993;32:554-9.

29. Nicolato A, Gerosa MA, Fina P, Iuzzolino P, Giorgiutti F, Bricolo A. Prognostic factors in low-grade supratentorial astrocytomas: a uni-multivariate statistical analysis in 76 surgically treated adult patients. Surg Neurol 1995;44:208-21.
30. Scerrati M, Roselli R, Iacoangeli M, Pompucci A, Rossi GF. Prognostic factors in low grade (WHO grade II) gliomas of the cerebral hemispheres: the role of surgery. J Neurol Neurosurg Psychiatry 1996; 61:291-6.
31. Leighton C, Fisher B, Bauman G, et al. Supratentorial low-grade glioma in adults: an analysis of prognostic factors and timing of radiation. J Clin Oncol 1997;15: 1294-301.
32. Peraud A, Ansari H, Bise K, Reulen HJ. Clinical outcome of supratentorial astrocytoma WHO grade II. Acta Neurochir (Wien) 1998;140:1213-22.
33. Chollet F, DiPiero V, Wise RJ, Brooks DJ, Dolan RJ, Frackowiak RS. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. Ann Neurol 1991;29:63-71.
34. Weder B, Seitz RJ. Deficient cerebral activation pattern in stroke recovery. Neuroreport 1994;5:457-60.
35. Grady MS, Jane JA, Steward O. Synaptic reorganization within the human central nervous system following injury. J Neurosurg 1989;71:534-7.
36. Fandino J, Kollias SS, Wieser HG, Valavanis A, Yonekawa Y. Intraoperative validation of functional magnetic resonance imaging and cortical reorganization patterns in patients with brain tumors involving the primary motor cortex. J Neurosurg 1999;91:238-50.