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Magnetoencephalographic Imaging of Resting-State Functional Connectivity Predicts Postsurgical Neurological Outcome in Brain Gliomas

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Abstract

Background—The removal of brain tumors in peri-eloquent or eloquent cortex risks causing new neurological deficits in patients. The assessment of the functionality of peri-lesional tissue is essential to avoidance of postoperative neurological morbidity.

Objective—To evaluate preoperative magnetoencephalography (MEG)-based functional connectivity as a predictor of short- and medium-term neurological outcome after removal of gliomas in peri-eloquent and eloquent areas.

Methods—Resting-state whole-brain MEG recordings were obtained from 79 consecutive subjects with focal brain gliomas near or within motor, sensory, or language areas. Neural activity was estimated using adaptive spatial filtering. The mean imaginary coherence between voxels in and around brain tumors was compared to contralesional voxels and used as an index of their functional connectivity with the rest of the brain. The connectivity values of the tissue resected during surgery were correlated to the early (one week post-operatively) and medium-term (six months post-operatively) neurological morbidity.

Results—Patients undergoing resection of tumors with decreased functional connectivity had a 29% rate of new neurological deficit 1 week after surgery and a 0% rate at 6-month follow-up. Patients undergoing resection of tumors with increased functional connectivity had a 60% rate of new deficit at 1 week and a 25% rate at 6 months.

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Conclusion—MEG connectivity analysis gives a valuable preoperative evaluation of the functionality of the tissue surrounding tumors in peri-eloquent and eloquent areas. These data may be used to optimize pre-operative patient counseling and surgical strategy.

Keywords

Magnetoencephalography; functional connectivity; Intraoperative electrical stimulation; brain tumour; imaginary coherence; magnetic source imaging

Introduction

The goal of brain tumor surgery is to maximize tumor resection while avoiding neurological deterioration. The resection of brain tumors in peri-eloquent and eloquent brain regions is associated with increased risk of neurological impairment. To mitigate this risk, it is critical to obtain preoperative data regarding the functional role of peri-lesional and lesional tissue. The variability of normal anatomy, the inherent distortion of cerebral topography from mass effect, and the functional reorganization due to plasticity all render classic anatomic boundaries insufficient for predicting associated function.[1-3] Consequently, non-invasive functional neuro-imaging techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG) have been developed to generate a functional map of the brain in preparation for a surgical procedure.[4-12] These individualized studies offer an accurate map of eloquent areas and their spatial relationship with the lesion, and have become an integral part of understanding and quantifying the risks associated with possible surgical strategies. Valuable as these techniques may be, the functional data that they yield are incomplete because they focus largely on cortical regions rather than subcortical structures such as white matter tracts and deep nuclei.

Identification of subcortical pathways is critical to preserving function, as permanent neurological deficits following intraoperative injury to white matter pathways have been widely reported.[13-15] Moreover, studies of stroke patients suggest that damage to the white matter tracts may induce more severe deficits than would a cortical injury.[16] Identification of eloquent subcortical fibers in both the pre- and intraoperative setting is therefore important in managing these lesions.[17, 18] Recently, diffusion tensor imaging (DTI) tractography has conferred an ability to visualize white matter tracts and their spatial relationship to a lesion.[18-21] While this technique offers valuable anatomic insights, it is not without limitations. It has yet to be adequately validated, particularly in mapping speech pathways.[22, 23] More importantly, it offers strictly anatomical information—functional “connectedness” cannot be ascertained with DTI. Intraoperative somatosensory evoked potentials and direct cortical stimulation (DCS) are useful for indirect evaluation of the functional significance of subcortical structures during tumor resection. Currently, the gold-standard method for assessing the functional significance of subcortical tissue is intraoperative electrical stimulation (IES). Even with IES, however, recognizing a functionally critical subcortical tract intraoperatively is often challenging because it requires continuous mapping of subcortical tissue as the resection proceeds, thus identifying a safe subcortical boundary for tumor resection.[17, 24-28]

Functional Connectivity

Functional connectivity essentially defines the complex functional interaction between local and more remote brain areas. It is, in effect, an index of functional interaction between these brain areas.[29-31] As we and others have shown, disruptions in functional connectivity occur in patients with brain tumors.[32, 33] Furthermore, these disruptions seem to correlate with neurocognitive effects, particularly in low-grade gliomas.[31, 34] One method by which this effect is posited to occur is through compression of the cortex and subcortical white matter, resulting in cortical de-afferentiation.[35-37] Accordingly, the “connectedness” of this disconnected region would be impaired and basic rhythmic oscillations altered.[38] Based on these observations we hypothesize that when tumor infiltrates and damages sensory, motor or language areas, the functional connectivity of these areas decreases. Thus, measurement of functional connectivity, if conducted with sufficiently high spatial resolution, might yield valuable insights into their relative eloquence.

Our group has recently described a MEG-based approach that quantifies subtle changes in the functional connectivity of peri-lesional and lesional tissue.[39] Subsequently, we reported that the level of functional connectivity in a region can predict IES mapping of that region. Prospectively, we compared MEG functional connectivity maps with IES maps of eloquent cortex in 57 brain tumor patients. Maps of functional connectivity were generated from preoperative MEG recordings. By comparing peri-tumoral regions against the corresponding regions in the contralateral hemisphere, we identified regions of altered connectivity. These maps were then compared with IES-generated maps of language and motor function. Based upon these comparisons, we determined that the negative predictive value of decreased connectivity was 87%, while the positive predictive value of increased connectivity was 64%.[40]

It is our hypothesis that, since levels of functional connectivity correlate with IES mapping, one would also expect resection of highly connected regions to be associated with post-operative deficit. Thus, the aim of the present study is to investigate whether preoperative MEG-based functional connectivity of peri-lesional regions predicts neurological outcome in patients undergoing surgery for glioma in eloquent cortex. To our knowledge, this is the first (and largest) study correlating neurological outcomes with MEG-based functional connectivity analysis in glioma patients.

Materials and methods

Subjects

We included 79 consecutive subjects with unilateral brain gliomas, located near or within motor, sensory or language cortices, who were referred for clinical MEG scanning and magnetic source imaging (MSI) at the University of California San Francisco (UCSF) Biomagnetic Imaging Lab between February 2006 and April 2010, and had a subsequent craniotomy with intraoperative electrical stimulation (IES) mapping and tumor resection. All subjects were treated by the same neurosurgeon (M.S.B.). All participants gave their written informed consent to participate in the research; all procedures were approved by the UCSF Committee on Human Research, and all research was conducted according to the Declaration of Helsinki.

Structural images

Magnetic resonance imaging (MRI) was performed at 1.5 Tesla. The protocol typically included the following sequences: (1) a T1-weighted, three-dimensional spoiled gradient-recalled echo in a steady-state sequence with TR of 34 milliseconds, TE of 3 to 8 milliseconds, and flip angle of 30 degrees; and (2) a T2-weighted, three-dimensional fast spin-echo sequence with TR of 3,000 milliseconds and TE of 105 milliseconds. Both sequences had a slice thickness of 1.5mm, matrix $256 \times 256 \times (108 - 140)$, and a field view of 260×260mm with skin-to-skin coverage to include the nasion and preauricular points.

Tumor diameters were measured on MRI with digital calipers. The dimensions were defined visually on the basis of signal abnormalities on T1-weighted images obtained after gadolinium administration (for high-grade tumors), and T2-weighted images (for low-grade tumors). The formula used to calculate preoperative and postoperative tumor volumes was the standard volume of an ellipsoid (the product of the three largest diameters, two measured in the axial plane and the third measured in the sagittal plane, divided by two).[26, 41, 42] The extent of resection was determined by comparing MRI scans obtained before surgery with those obtained within 48 hours after surgery. The extent of resection was calculated as: (preoperative tumor volume – postoperative tumor volume) / preoperative tumor volume.

Magnetoencephalographic recordings

The participants were lying awake and with their eyes closed in a magnetically shielded room while their continuous resting state MEG was recorded with a 275-channel whole-head CTF Omega 2000 system (VSM MedTech, Coquitlam, British Columbia, Canada), using a sampling rate of 600Hz. From a four-minute recording, an artifact-free epoch of 1-minute duration was selected for subsequent analysis in each subject.

Coils were placed at the nasion and 1 cm rostral to the left and right preauricular points in the direction of the nasion in order to localize the position of the head relative to the sensor array. These points were later co-registered to a high-resolution structural MR image in order to generate the head shape. Head position was monitored by passing a sinusoidal current through the fiducial coils and triangulating these coil positions at the beginning and end of every four-minute run, and scan sessions where head movement exceeded 1cm within a run were discarded and repeated. Participants were lying in a supine position and instructed to remain awake with their eyes closed during a four-minute continuous recording session. Any participant who reported sleeping or feeling sleepy during this scan was re-run, with the initial data being discarded

Signal analysis

Source-space MEG-I reconstructions (adaptive spatial filter) and functional connectivity (imaginary coherence) metrics were computed using the NUTMEG software suite.[43] MEG-I refers to reconstruction of whole brain activity from MEG sensors, which can improve both the spatial resolution and signal detection abilities of MEG. This approach enables precise reconstructions of oscillatory activity in specific brain regions from MEG data.[43-45] From the four minutes of continuous recording, a 60s, artifact-free segment of the data was selected for analysis. Artifact detection was performed qualitatively through a visual inspection of the sensor data after it was broken into four 60s trials, and only trials without excessive scatter (signal amplitude > 5 pT) due to eye blink, saccades, head movement or EMG noise were selected for MEG-I analysis. Previous investigations[39] have determined that this 60s window provides sufficient power for reconstruction of the resting-state data. MEG sensor data were filtered using a phase-preserving bandpass filter (fourth-order Butterworth; 1-20Hz bandpass) and reconstructed in source space using a minimum-variance adaptive spatial filtering technique.[43, 46] This approach provides an amplitude estimate at each element (voxel) derived through a linear combination of a spatial weighting matrix (itself calculated through a forward-field and spatial covariance matrix) with the sensor data matrix.

Tomographic reconstructions of the data were created by generating a multisphere head model based on a head shape obtained from each individual subject's structural MRI. A volume of interest (whole brain VOI) for lead field computation (grid size=2cm; approx. 300 voxels/participant) was automatically generated through a back-transformation of all the points within a spatially normalized MRI that corresponded to locations within the brain and excluding non-cerebral points (e.g. eyes, skull). Therefore, the time-course of activity at each voxel used for functional connectivity was computed for every location within the

VOI, where each voxel within the VOI itself is an estimate of activity derived from inputs from all sensor recordings.

Resting-state functional connectivity estimates were computed from MEG-I reconstructions in each participant. For each subject, alpha frequency bins were selected around a peak power density centered on ~10Hz during the 60s epoch, selected from a broad 1-20Hz band with a frequency resolution of 1.17Hz (512 bins).[39] A peak in the alpha band was easily identifiable from this amount of data in all patients. While peaks in the power spectra corresponding to oscillations in other frequency ranges (e.g. theta, low beta) were occasionally identified from subject to subject, only alpha peaks (power density peak between 8-12Hz) were identified consistently from this sampling window in all participants. Functional connectivity estimates were calculated using imaginary coherence (IC), a technique known to reduce overestimation biases in EEG/MEG data generated from common references, cross-talk and volume conduction.[39, 47] IC is able to sample interactions between source time-series, x(t) and y(t), independent of the class of spatial filter.[40]

Functional connectivity images

Maps of lesion-specific connectivity changes (L-images) were obtained by analyzing all connections between tumor voxels and a centered, equally spaced, whole-brain grid of each fourth voxel within the entire set of voxels (approximately 10,000 –100,000 voxel pairs in total, depending on the individual head and tumor size). As a control, the IC was also calculated for connections between voxels contralateral to tumor voxels and the same whole-brain voxel grid.

The computation time of the maps could be reduced to about 10 minutes by distributing the processing of batches of voxel pairs to a cluster of 10 Linux workstations.

Cortical connectivity analysis and voxel classification

L-images were used to assess tumor voxels of all subjects for within-subject differences with contralateral voxels using two-tailed t tests for one sample, which tested the null hypothesis that the Z-transformed connectivity IC between a given tumor voxel and non-tumor voxels is equal to the mean of the Z-transformed connectivity between all contralateral voxels and the same set of voxels. The resulting probabilities can be corrected easily for multiple testing by using a false discovery rate or other correction procedures. However, in order to avoid masking potentially relevant information in individual subjects, we report here the uncorrected images based on a tertile split of the connectivity measures including upper tertile (high connectivity) and lower tertile (low connectivity) or middle tertile (neutral connectivity).

Functional connectivity of the tissue resected during surgery was analyzed. Preoperative L-images were superimposed on the postoperative structural MRI to analyze the connectivity values of the tissue within the surgical cavity, i.e. the tissue that was resected during surgery. At this point, it is important to remark that the tissue connectivity was analyzed in the preoperative L-images, and the postoperative MRI was only used to define the limits of the surgical cavity.

According to the connectivity values of the resected tissue, the L-images of all subjects were classified in 3 groups: Group 1 (decreased connectivity) = only tissue with decreased connectivity was resected. Group 2 (neutral connectivity) = tissue with “neutral” (i.e. neither increased nor decreased compared to the contralateral tissue) connectivity was resected. Group 3 (increased connectivity) = tissue with increased connectivity was resected.

Intraoperative electrical stimulation mapping

All subjects underwent surgery for tumor resection with IES mapping 24 to 48 hours after the MEG scan. 56 of 79 surgeries (70.9%) were performed under awake anesthesia, and 23 (29.1%) under general anesthesia. Neuronavigation was used in all cases; the craniotomy was tailored according to the exact extension of the tumor with a three cm margin of surrounding brain tissue. Mapping of the motor cortex was performed in 60 of 79 cases (75.9%), mapping of language cortex in 56 cases (70.9%), and mapping of sensory cortex in 38 cases (48.1%). A positive motor site was defined as an area that induced involuntary movement when stimulated, and a positive sensory site as an area that elicited dysesthesias. A positive language site was associated with a subject's inability to count, name objects, or read words during 66% of the stimulation trials. Full details of our IES mapping protocol have been previously described.[48, 49] A bipolar electrode with 5 mm spaced tips delivering a biphasic current (square-wave pulses in 4-second trains at 60 Hz, with single pulse phase duration 1 ms) was applied to the brain. Cortical mapping was initiated at 1.5 mA under awake surgery or 6 mA under general anesthesia, and increased to a maximum of 6 mA under awake anesthesia and 16 mA under general anesthesia. Stimulation sites were identified using sterile numbered labels distributed per square centimeter of exposed cortex. During awake mapping, electrocorticography was used to monitor for after-discharges and to eliminate the possibility of language errors due to evoked or spontaneous subclinical seizure activity. After the cortical mapping was completed, the tumor was removed in a tailored fashion. The targeted area for resection involved the contrast-enhancing regions for high-grade gliomas and the hyperintense areas on T2-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.[50] When the field of exposure consisted of only negative sites, greater cortical exposure was not sought in order to identify a positive control site.[49] During the tumor resection stage, subcortical stimulation was applied in 34 of 79 cases (43%) to identify the pyramidal pathway at the border of the resection.

Subjects' neurological outcome measurements

Preoperatively and at each follow-up appointment, subjects underwent neurological examination. The preoperative Karnofsky Performance Status (KPS) scale was evaluated in all subjects.[51] Each examination was conducted by two clinicians blinded to the MEG data: an attending neurosurgeon and a neurosurgical resident or an attending neuro-oncologist. Our protocol for language function testing has been previously described.[25, 52] There was a 97.1% rate of concordance between examiners. Differences between the results of the two examiners were adjudicated by accepting the results showing greater impairment. After surgery, outpatient clinical examinations were performed at 1 week, 4 to 6 weeks, and 3 to 6 months. Early neurological morbidity was defined as a new onset deficit related to motor, sensory, visual, and language function in the examination 1 week after surgery. Subjects with persistent post-surgical deficit at their 6-months follow-up visit were considered to have a long-term deficit. It should be noted that patients who had worsening in their neurological exam between the first 1 week exam and the 6 month exam were not considered to have a post-surgical deficit, as this worsening was attributed to tumor effect. MR imaging results were also reviewed to confirm that the subjects' symptoms were not a function of tumor recurrence. Specific language and motor rehabilitation was provided after surgery.

Statistical analysis

Frequency distributions and summary statistics were calculated for all variables; values are expressed as mean or median and range. A Kolmogorov-Smirnov test was used to study the distribution of each variable and P-P and Q-Q charts were used to confirm it. The majority did not follow a normal distribution, and non-parametric tests were used for comparisons.

The independent variable of interest was the connectivity pattern of the resected tissue: decreased, neutral, or increased connectivity. The endpoint of this study was the assessment of early and long-term neurological morbidity after surgery. A logistic regression model was used to determine the relationship between neurological morbidity and quantitative variables. The relationship between neurological morbidity and qualitative values was assessed by a Fisher's exact test or a linear association Mantel-Haenszel chi-squared test. A multivariate analysis was performed in order to analyze if the following variables were confounders between the connectivity pattern and early and long-term neurological morbidity: sex, age, preoperative neurological deficits, tumor side, tumor location, histopathology, preoperative tumor volume, postoperative tumor volume, and extent of resection. A significance level of 5% ($p < 0.05$) was accepted in all cases. SPSS software version 15.0 (SPSS, UK) was used for the statistical analysis.

Results

The demographic, clinical, radiological, surgical and pathological characteristics of the subjects and of their tumors are listed in table 1.

Subject characteristics

The study population included 37 men and 42 women, with a mean age of 41.3 years (range 21.1 to 68.5 years). A total of 55 of 79 subjects (69.6%) underwent primary craniotomy, and 24 subjects (30.4%) had undergone previous craniotomies for tumor resection. Eighteen subjects (22.8%) received chemotherapy and five subjects (6.3%) received radiotherapy before the current surgery. Subjects most often presented with seizures of recent onset: partial seizures in 40 subjects (50.6%) and secondarily generalized seizures in 13 subjects (16.5%). Sixty-five subjects (82.3%) had an intact preoperative neurological examination, four subjects (5.1%) had mild motor weakness of the arm and/or leg, two subjects (2.5%) had sensory deficits, and six subjects (7.6%) had mild disorders of language. The median time to the 6-month visit was 19.7 ± 2 weeks. The median preoperative KPS was 90 (range 70 to 100).

Tumor characteristics

Sixty-four of 79 subjects (81%) had left hemisphere tumors and 15 subjects (19%) had right hemisphere tumors. Twenty-nine tumors (36.7%) were located in the frontal lobe (13 in the supplementary motor area and 16 in the lateral premotor cortex/frontal operculum), 19 tumors (24.1%) were located in the paralimbic region with involvement of the insular lobe, 24 tumors (30.4%) were located in the temporal lobe (20 in the posterior temporal lobe and 4 in the mesial temporal lobe), and 7 tumors (8.9%) were located in the parietal lobe (3 in the inferior parietal lobe and postcentral gyrus, and 4 in the superior parietal lobe and postcentral gyrus). Histopathological analysis revealed low-grade glioma in 46 cases (58.2%), anaplastic glioma in 23 cases (29.1%), and glioblastoma in ten cases (12.7%). The mean preoperative tumor volume was 51.2 ml (range 1.2 to 289.6 ml). The differences in preoperative tumor volume between group 1 (mean = 57 ml, range = 1.2 to 124.8 ml), group 2 (mean = 39.3 ml, range = 5.6 to 145 ml), and group 3 (mean = 56.7 ml, range = 2.4 to 289.6 ml) were statistically not significant ($p = 0.348$).

Surgical findings

Functional sites were identified during IES mapping in 44 of 79 subjects (55.7%). In 26 subjects (32.9%), 49 motor functional areas were identified. In 17 subjects (21.5%), 21 subcortical motor functional areas were identified. In 15 subjects (19%), 24 sensory areas were identified. In 20 subjects (25.3%), 29 language areas were identified (25 areas in the frontal lobe and four areas in the temporal lobe). Using the MRI obtained within 48 hours after surgery, the postoperative tumor volume was calculated. The mean postoperative tumor volume was 5.9 ml (range 0 to 64 ml). The mean extent of resection was 92.1% (range 45.6% to 100%). Overall, gross total resection was achieved in 29 of the 79 cases (36.7%). In the immediate postoperative period, one subject developed a wound infection. The wound was cleaned and the bone flap removed with good response to antibiotic treatment. No early or long-term neurological morbidity was observed in this case. No other surgical complications were reported.

Neurological outcome

One week after surgery, new or worsened neurological deficits were observed in 36 of 79 subjects (45.6%). New-onset or worsening of motor deficit was present in 18 subjects (22.8%): facial weakness in 2 cases, mild hemiparesis in 10 cases, and moderate hemiparesis in 6 cases. Twenty-three subjects (29.1%) had new or worsening language deficit: mild dysphasia in 14 cases and moderate dysphasia in 9 cases. Six subjects (7.6%) had new or worsening sensory deficit: leg and/or arm hypoesthesia in all cases. New-onset quadrantanopsia was present in 3 cases (3.8%).

Six months after surgery, 23 subjects had a complete recovery of the deficits, while 13 subjects (16.5%) had a long-term deficit. Five subjects (6.3%) had a long-term motor deficit: mild hemiparesis in all cases. Five subjects (6.3%) had a long-term language deficit: mild dysphasia in all cases. Three subjects (3.8%) had a long-term sensory deficit: leg and/or arm hypoesthesia in all cases. Long-term quadrantanopsia was present in 3 cases (3.8%). At 6 months, the KPS was 100 in 29 subjects (36.7%), 90 in 37 subjects (46.7%), 80 in 11 subjects (13.9%), and 70 in 2 subjects (2.5%).

A comparison was made between subject's sex, age, handedness, previous surgery, preoperative neurological deficits, preoperative KPS, tumor side, tumor location, surgical identification of eloquent cortex, histology, preoperative tumor volume, postoperative tumor volume, and extent of resection in the group of subjects with and without early and long-term neurological morbidity (table 1). Early neurological morbidity was observed more frequently in subjects with a right side tumor compared to subjects with a left side tumor (73% vs.39%, $p = 0.022$), in subjects with preoperative neurological deficits compared to subjects without preoperative neurological deficits (71% vs.40%, $p = 0.041$), and in older subjects ($p = 0.037$). The other comparisons were not statistically significant ($p > 0.05$).

Subjects with long-term morbidity had a greater preoperative tumor volume (mean = 80.5 ml, range = 18.2 to 289.6 ml) compared to subjects without long-term deficits (mean = 45.3 ml, range = 1.2 to 145 ml) ($p = 0.037$). The other parameters were not significantly associated with long-term postsurgical morbidity ($p > 0.05$).

Table 1 and Figure 1 demonstrate that MEG functional connectivity maps were able to predict both 1-week and 6-month neurological deficits. In 40 of 79 subjects (50.6%), tissue with increased connectivity was resected. Within this group, 24 subjects (60%) developed 1-week neurological morbidity, and 10 subjects (25%) had a 6-month deficit. In 25 of 79 subjects (31.6%), tissue with neutral connectivity was resected. Within this group, eight subjects (32%), demonstrated 1-week neurological morbidity, and three subjects (12%) had a deficit at 6-month follow-up. Finally, in 14 of 79 subjects (17.7%), tissue with decreased connectivity was resected. Within this group, four subjects (28.6%) developed 1-week neurological morbidity, and no subject had a long-term deficit.

The proportion of patients with early ($p = 0.016$) and long-term deficits ($p = 0.023$) was significantly different among the 3 connectivity groups. The multivariate analysis revealed that none of the variables studied (sex, age, preoperative neurological deficits, tumor side, tumor location, histopathology, preoperative tumor volume, postoperative tumor volume, and extent of resection) were confounders between the connectivity pattern and 1-week and 6-month neurological morbidity.

In the subgroup of 36 patients with early neurological morbidity, the MEG functional connectivity maps were not predictive of long-term neurological morbidity ($p = 0.36$).

Three Illustrative cases

Case 1: Right frontal oligodendroglioma WHO grade II with decreased functional connectivity within the tumor—Figure 2 shows the brain of a 33-year-old right-handed woman with a 1-month history of partial seizures. The preoperative neurological examination revealed no deficits. A T1-weighted MR image revealed a right frontal hypointense lesion with no gadolinium enhancement. These images were compatible with a low-grade glioma. MEG connectivity analysis revealed decreased connectivity values within the tumor and in the surrounding brain. The subject underwent resection with IES of the motor cortex. Intraoperatively, no functional areas were identified by IES. A subtotal resection of the tumor was achieved. The histological diagnosis was oligodendroglioma WHO grade II. The analysis of preoperative MEG L-images superimposed on the postoperative MRI revealed that the resected tissue had decreased functional connectivity. In accordance with these findings, the subject had no neurological deficits after surgery.

Case 2: Left fronto-parietal oligodendroglioma WHO grade II with increased connectivity in the frontal and parietal lobes—Figure 3 shows the brain of a 51-year-old right-handed man who had a generalized convulsive seizure two weeks prior to admission. No preoperative neurological deficit was observed. MRI revealed an image characteristic of a fronto-parietal low-grade glioma. Areas of increased connectivity were observed within the tumor. Intraoperative electrical stimulation of the cortex superior to the tumor elicited right facial movement and speech arrest, which likely corresponded to a functionally critical expressive language area. A subtotal resection of the tumor was achieved with preservation of the language areas identified. The histological diagnosis was oligodendroglioma WHO grade II. The analysis of preoperative MEG L-images superimposed on the postoperative MRI revealed that the resected tissue had increased connectivity. In accordance with these findings, the patient developed a moderate right upper and lower extremity paresis in the immediate postoperative period. Six months after intensive rehabilitation, the patient continued to have a mild right upper extremity paresis.

Case 3: Left astrocytoma with decreased connectivity within the tumor and negative IES—Figure 3 show the brain of a 26-year-old right-handed woman who presented with a complex partial seizure. MRI was characteristic of a temporal low-grade glioma. IES of the temporal lobe posterior to the tumor elicited anomia. A gross total resection of the tumor was achieved. The histological diagnosis was astrocytoma WHO grade II. The analysis of preoperative MEG L-images superimposed on the postoperative MRI revealed that the tissue resected had decreased connectivity. Cortical and subcortical areas of increased connectivity were evidenced in the vicinity of the tumor. As depicted in the figure, these areas of increased connectivity were not resected. The subject had no neurological deficits after surgery.

Discussion

The surgical options presented to a patient with an infiltrating lesion in peri-eloquent or eloquent cortex depend in part on the risks of neurological morbidity associated with surgery. The present study demonstrates that preoperative MEG-based functional connectivity analysis is a useful tool to evaluate the relative eloquence of a particular brain region and to quantify the neurological risks involved with a given surgical strategy.

The resection of tumors with decreased resting state connectivity has a low risk of postoperative neurological deficits

In the present series, MEG connectivity has an excellent negative predictive value of 100% for 6-month neurological outcome after surgery. We observed that in patients with decreased connectivity in the entire tumor volume, the probability of developing early neurological morbidity is 28.6%, while the probability of a long-term deficit is 0%. These findings are in line with our previous observations, that radical surgery in a tumor with decreased connectivity does not induce new long-term neurological deficits.[39] These observations are also consistent with our observation that damaged brain tissue is associated with decreased values of functional connectivity, and strongly suggest that it is safe to resect a tumor volume with decreased connectivity, as there is a low risk for subsequent long-term functional deficit.[39, 40]

In the last 20 years, the development of an integrative approach to brain function has allowed us to go beyond a one-to-one correspondence of lesion site and deficit. We now understand the consequences of a brain lesion through a variety of topological and hodological mechanisms.[53, 54] A lesion that affects the cortex will generate a topological dysfunction largely limited to the cortical area that overlies the lesion. White matter damage, in contrast, can affect the function of distant cortical regions by interfering with the network of fiber tracts responsible for interconnecting those disparate regions. This hodological perspective of neurological function is consistent with our findings. As gliomas are often located in deep white matter, their infiltration likely damages the surrounding network, reducing the functional connectivity of the corresponding cortical regions. At the same time, particularly in slow-growing lesions, neuroplasticity may recruit regional and distant cortical regions, thus creating new compensatory networks.

Our group has recently reported on the value of negative IES mapping (i.e., the negative predictive value of a negative IES map) in the resection of lesions located in high-risk language areas.[25] In this series, 3.2% of patients demonstrated a long-term language, motor, or visual deficit 6 months after surgery. We thus have shown that negative IES mapping is sufficient to allow for a reasonably safe resection with low rates of impairment in long-term language function. In a series of 200 patients, Taylor and Bernstein[55] report negative IES mapping in 70% of patients, with 3.6% of them developing a long-term deficit. Kim et al[56] recently analyzed the functional outcome in 309 patients operated with IES mapping. Mapping was found to be negative in 109 patients, and 9% of these patients show a long-term deficit. Therefore, despite a high negative predictive value of negative mapping, it fails to guarantee preservation of function postoperatively.

In the present series, decreasing MEG connectivity had a significant correlation with improved long-term outcome. In contrast, IES was not able to distinguish patients who would have postoperative deficits from those who would not (p=0.764, see Table 1). It is also worth noting that 8 of the patients with decreased tumor connectivity and without long-term postsurgical deficits had positive IES mapping. Such is the case of the subject presented in figure 4. The resected tumor tissue had decreased connectivity; however, the surrounding brain demonstrated increased connectivity. IES of the cortex posterior to the tumor, in a region with increased connectivity, elicited anomia during picture naming task. No new or worsened neurological deficits were observed after surgery in this subject. As predicted by MEG connectivity maps, if only tumor areas of decreased connectivity are resected, the risk of a long-term deficit is very low. If these can be replicated in larger series, MEG connectivity maps may obviate the need for IES in this subgroup of patients in whom the entire tumor area shows decreased functional connectivity.

The resection of tumors with increased resting state connectivity is associated with a higher risk of postoperative neurological deficits

In group 3, the patients with increased connectivity in lesional vs. contralesional regions, MEG connectivity maps had a positive predictive value of 60% for early neurological morbidity and 25% for long-term deficits after surgery. Thus, if an area of increased connectivity was resected, the probability of developing early neurological morbidity was as high as 60%, and the probability of developing a long-term deficit was 25%. This relatively low positive predictive value likely results from the fact that MEG analysis, with its reliance on IC, cannot distinguish between functionally active regions and functionally critical regions. Thus, a region may be identified as highly connected, even though its removal is clinically silent.

Functional MRI studies have previously observed that cortical activity can persist even in areas that are infiltrated by a tumor.[12, 57] IES studies have also demonstrated that infiltrative tumor cells can coexist with functional tissue, which may be preserved without initial loss of function.[25, 58] Our MEG results support this finding: the resection of an area of increased connectivity, even if located within a lesion, predicts a postoperative neurological deficit. One must assume that the resected tissue, although diseased, was at least partly functional. Such is the case of the subject presented in figure 3. Areas of increased functional connectivity were observed within the margins of this fronto-parietal low-grade glioma, and the patient developed a moderate postoperative hemiparesis with partial recovery 3 months later. Although it seems likely that functionally connected regions would be limited to slow-growing, low-grade lesions, we found that even high-grade gliomas can harbor functional regions that confer a postoperative deficit if resected. In this series, areas of increased connectivity were resected in 15 subjects with anaplastic glioma and in two subjects with glioblastoma. These results may be explained by the infiltrative nature of gliomas, which often have irregular pseudo-margins. Therefore, the indistinct peripheral regions of a tumor likely still retain functional connectivity. Alternatively, one may also point out that the surgical access to a deep lesion is obtained through normal brain tissue—this tissue may be functional and, despite IES mapping, may confer a deficit when disrupted.

In analyzing the 36-patient subgroup with early postoperative neurological deficit, it was found that lesional connectivity did not predict which patients would improve and which ones would go on to have a long-term deficit. Given that lesional connectivity seems to predict long-term deficit, this result seems counterintuitive. In fact, it is most likely a result of the particular characteristics of this subgroup. Overall, these 36 patients have, on average, a higher average level and narrower spread of connectivity than the overall group of 79 patients. As a result, we are underpowered for detecting significant differences in this smaller, more homogeneous group.

In group 2, those patients with no significant difference between lesional and contralesional connectivity, the probabilities of developing early and long-term neurological morbidity were 32% and 12%, respectively. Consequently, in groups 2 and 3 (those patients with neutral or increased connectivity within the tumor), a careful mapping of the lesional and peri-lesional tissue, with specific attention paid to subcortical mapping, is critical to the avoidance of post-operative morbidity. Although we have previously shown that MEG connectivity maps correlate well with IES,[39, 40] they are not suited to evaluate the exact function of each voxel within the brain. Consequently, we must continue to rely on IES to define the zone of safe resection in these groups of patients. MEG-based analysis of functional connectivity is valuable in in assessing surgical options and in guiding preoperative discussions with patients.

Previous studies have reported a correlation between the extent of tumor resection and the development of neurological morbidity, thus suggesting that greater extent of resection may be safely achieved in tumors far from eloquent areas.[56, 59] In the present study, in order to test the potential bias introduced by the extent of resection, the relationship between the extent of resection and neurological outcome was analyzed. No statistical correlation was found between neurological deterioration and the extent of tumor resection.

One other potential source of error in this study stems from postoperative brain shift. Brain shift is the displacement of the brain that occurs during surgery due to the effect of gravity and tumor resection, and displacements of up to 2.4 cm have been reported.[60, 61] As described above, postoperative MRI was used to define the volume of resection; therefore, brain shift may introduce a discrepancy between the preoperative MEG and the postoperative MRI. Of particular concern would be the tissue at the border of the surgical cavity. This error, however, would not bias the study in a particular direction (i.e. toward inclusion or exclusion of perilesional tissue), and would affect each group similarly.

Conclusion

Comparative decrease in functional connectivity between lesional and contralesional regions reliably predicts the resectability of the lesional tissue with minimal long-term deficit. Increasing levels of functional connectivity in lesional and peri-lesional tissue is predictive of increasing neurological morbidity at 1 week and 6 months postoperatively. Additionally, MEG-based functional connectivity was a better predictor of long-term postoperative morbidity than IES. The present data suggest that, after further validation, MEG connectivity analysis may replace IES in the subgroup of patients in whom the entire tumor area shows decreased functional connectivity.

The resection of lesion and peri-lesional regions with normal or increased functional connectivity significantly increases the risk of neurological morbidity. Careful mapping of cortical and subcortical structures with IES is especially important in these patients. In this subgroup, MEG-based functional connectivity is a valuable tool for planning a surgical strategy and for guiding preoperative discussion with patients about postoperative risks.

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Abbreviations

EEG	electroencephalography
DICS	dynamic imaging of coherent sources
fMRI	functional magnetic resonance imaging
IES	intraoperative electrical stimulation
IC	imaginary coherence
MEG	magnetoencephalography
MRI	magnetic resonance imaging
MSI	magnetic source imaging
PET	positron emission tomography

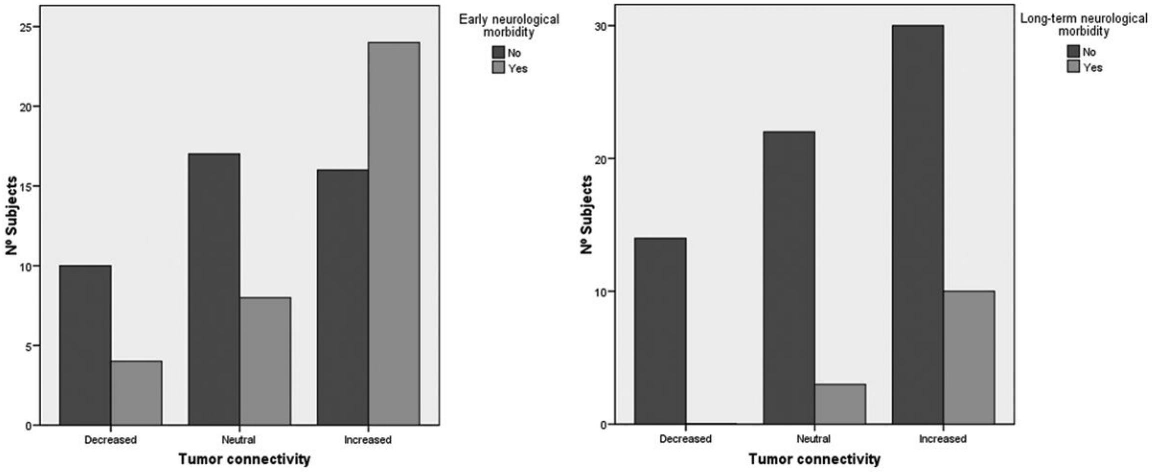

Figure 1.

Bar graph demonstrating early (left) and long-term (right) postoperative morbidity related to the connectivity pattern of the tissue resected during surgery In 40 out of 79 subjects (50.6%), tissue with increased connectivity was resected; 24 of these subjects had early neurological morbidity, and 10 subjects had a long-term deficit. In 25 subjects (31.6%), areas of neutral connectivity were resected; 8 of these subjects developed early neurological morbidity and 3 subjects had a long-term deficit. In 14 subjects (17.7%), only areas of decreased connectivity were resected; 4 of these subjects had early neurological morbidity and none had a long-term deficit.

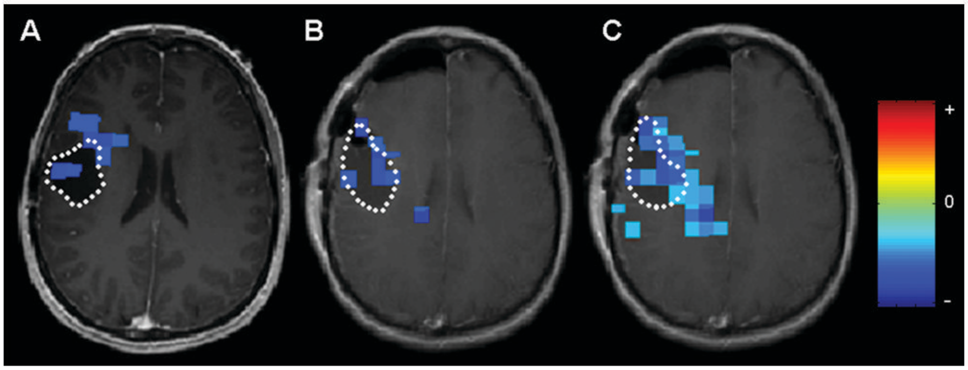

Figure 2.

Right frontal oligodendroglioma WHO grade II in a 33-year-old woman. A) preoperative MEG L-image superimposed on the preoperative T1-weighted MR image. The tumor margin is marked with a white dotted line. Decreased functional connectivity is observed in the tumor and the surrounding brain, thus indicating a functional disconnection of the entire tumor area. B and C) preoperative MEG L-image superimposed on the postoperative T1-weighted MR image. The surgical cavity is marked with a white dotted line. No new or worsened neurological deficits were observed after surgery in this subject, as predicted by MEG connectivity maps showing decreased functional connectivity of the resected tissue. In the right side of the figure is the connectivity scale: red (increased connectivity), green (neutral connectivity) and blue (decreased connectivity).

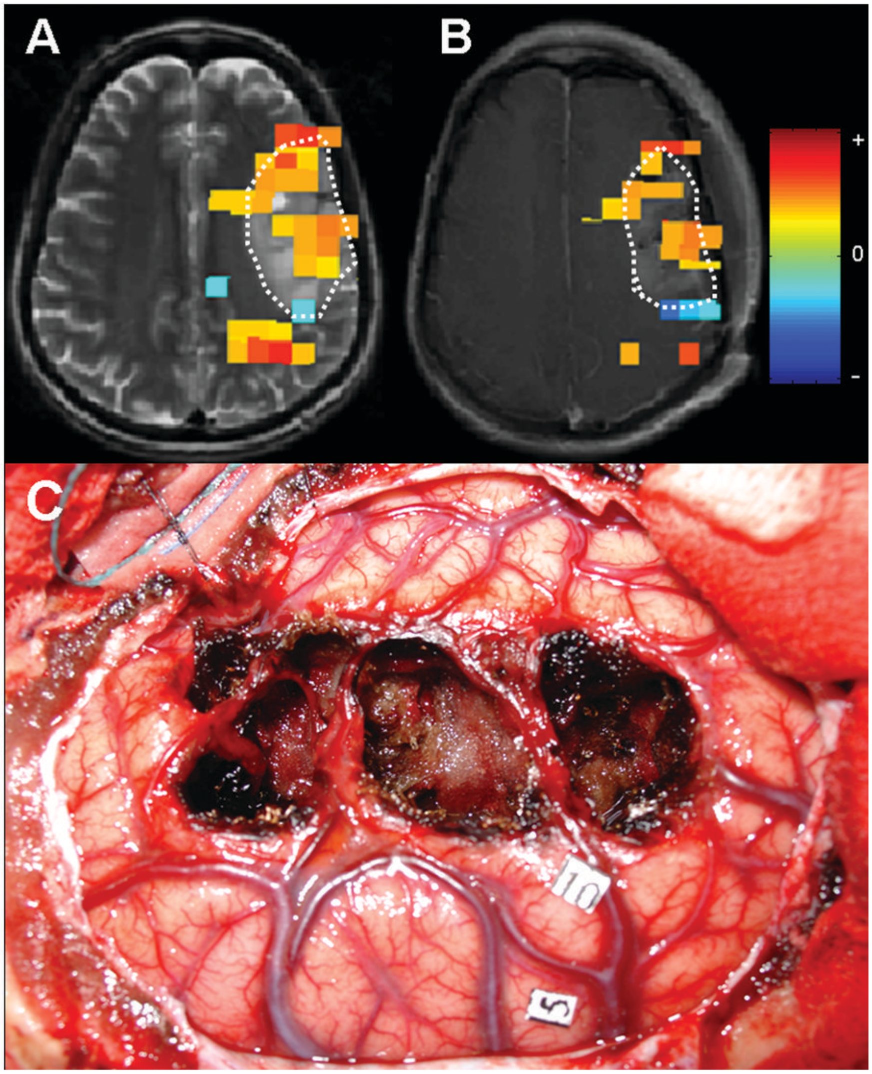

Figure 3.

Fifty-one year old right-handed man with a left fronto-parietal oligodendroglioma WHO grade II. No preoperative neurological deficit was observed. A) preoperative MEG L-image superimposed on the preoperative T1-weighted MR image. The tumor margin is marked with a white dotted line. Increased connectivity values are observed in the tumor and the surrounding brain. B) preoperative MEG L-image superimposed on the postoperative T1-weighted MR image. The surgical cavity is marked with a white dotted line. The resected tissue had increased connectivity. In accordance with these findings, the patient developed a moderate right arm and leg paresis in the immediate postoperative period. Three months after intensive rehabilitation the patient had a mild right arm paresis. C) Intraoperative photograph taken after tumor resection; number 5 marks the area were IES elicited right facial movement, number 10 marks the area where speech arrest was elicited. In the right side of the figure is the connectivity scale: red (increased connectivity), green (neutral connectivity) and blue (decreased connectivity).

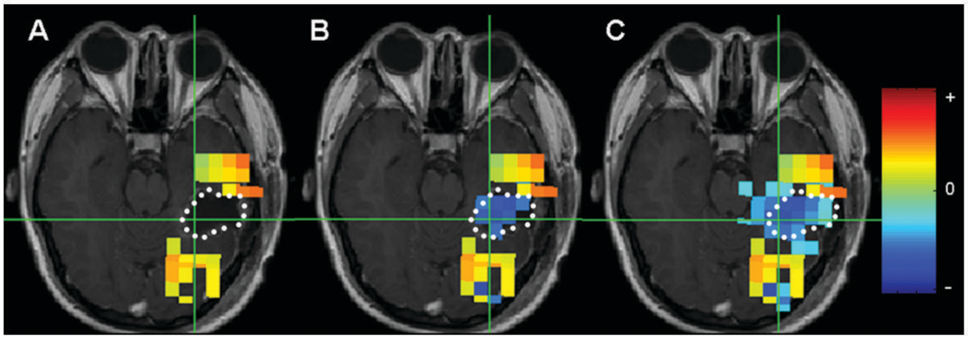

Figure 4.

Left temporal WHO grade II astrocytoma in a 26-year-old woman. A, B and C) Preoperative MEG L-image superimposed on the postoperative T1-weighted MR image. The surgical cavity is marked with a white dotted line. The resected tumor tissue had decreased connectivity; however, the surrounding brain has increased connectivity. Intraoperative pictures were not available in this case, but IES of the cortex posterior to the tumor elicited anomia. No new or worsened neurological deficits were observed after surgery in this subject, as predicted by MEG connectivity maps showing decreased functional connectivity of the resected tissue. In the right side of the figure is the connectivity scale: red (increased connectivity), green (neutral connectivity) and blue (decreased connectivity).

Table 1

Demographic, clinical, radiological, surgical and pathological characteristics of the 79 subjects and tumors.

		Early neurological morbidity			Long-term morbidity		
		No	**Yes**	**p value**	**No**	**Yes**	**p value**
Sex				p = 1			p = 0.238
	Female	23 (54.8%)	19 (45.2%)		33 (78.6%)	9 (21.4%)	
	Male	20 (54.1%)	17 (45.9%)		33 (89.2%)	4 (10.8%)	
Age (years)		38.7 (21.1-63.5)	44.5 (22.5-68.5)	**p = 0.037**	41.3 (21.1-68.5)	41.7 (25.5-63.5)	p = 0.904
Handedness				p = 0.426			p = 0.789
	Right handed	40 (56.3%)	31 (43.7%)		60 (84.5%)	11 (15.5%)	
	Left handed	2 (33.3%)	4 (66.7%)		4 (66.7%)	2 (33.3%)	
	Ambidextrous	1 (50%)	1 (50%)		2 (100%)	0 (0%)	
Tumor side				**p = 0.022**			p = 0.256
	Right	4 (26.7%)	11 (73.3%)		11 (73.3%)	4 (26.7%)	
	Left	39 (60.9%)	25 (39.1%)		55 (85.9%)	9 (14.1%)	
Tumor location				p = 0.107			p = 0.226
	SMA	3 (23.1%)	10 (76.9%)		11 (84.6%)	2 (15.4%)	
	LPMC/FO	10 (62.5%)	6 (37.5%)		15 (93.8%)	1 (6.3%)	
	IPL/RG	1 (33.3%)	2 (66.7%)		3(100%)	0 (0%)	
	SPL/RG	1 (25%)	3 (75%)		1 (25%)	3 (75%)	
	Insula	10 (52.6%)	9 (47.4%)		16 (84.2%)	3 (15.8%)	
	Posterior temporal	15 (75%)	5 (25%)		17 (85%)	3 (15%)	
	Medial temporal	3 (75%)	1 (25%)		3 (75%)	1 (25%)	
Pathology				p = 0.878			p = 0.56
	Grade II glioma	24 (52.2%)	22 (47.8%)		39 (84.8%)	7 (15.2%)	
	Anaplastic glioma	13 (56.5%)	10 (43.5%)		17 (73.9%)	6 (26.1%)	
	Glioblastoma	6 (60%)	4 (40%)		10 (100%)	0 (0%)	
Previous surgery				p = 0.806			p = 0.744

		Early neurological morbidity			Long-term morbidity		
		No	Yes	p value	No	Yes	p value
	No	29 (52.7%)	26 (47.3%)		45 (81.8%)	10 (18.2%)	
	Yes	14 (58.3%)	10 (41.7%)		21 (87.5%)	3 (12.5%)	
Preoperative deficits				**p = 0.041**			p = 0.691
	No	39 (60%)	26 (40%)		55 (84.6%)	10 (15.4%)	
	Yes	4 (28.6%)	10 (71.4%)		11 (78.6%)	3 (21.4%)	
Preoperative KPS		90 (70-100)	87 (70-100)	p = 0.08	89 (70-100)	87 (70-100)	p = 0.38
Preoperative tumor volume (ml)		46.9 (1.2-145)	56.4 (2.4-289.6)	p = 0.399	45.3 (1.2-145)	80.5 (18.2-289.6)	**p = 0.037**
Postoperative tumor volume (ml)		4.5 (0-64)	7.5 (0-39.4)	p = 0.256	5.1 (0-64)	9.5 (0-35.8)	p = 0.235
Extent of resection (%)		93.2 (45.6-100)	90.8 (58.4-100)	p = 0.361	92.3 (45.6-100)	91.3 (67.4-100)	p = 0.757
Tumor connectivity				**p = 0.016**			**p = 0.023**
	Group 1 (decreased)	10 (71.4%)	4 (28.6%)		14 (100%)	0 (0%)	
	Group 2 (neutral)	17 (68%)	8 (32%)		22 (88%)	3 (12%)	
	Group 3 (increased)	16 (40%)	24 (60%)		30 (75%)	10 (25%)	
IES mapping				p = 0.111			p = 0.764
	Negative	23 (65.7%)	12 (34.3%)		30 (85.7%)	5 (14.3%)	
	Positive	20 (45.5%)	24 (54.5%)		36 (81.8%)	8 (18.2%)	

The p-values are derived from logistic regression model, Fisher’s exact tests or linear association Mantel-Haenszel chi-squared test, comparing the influence of the different parameters on post-surgical morbidity.

Negative IES mapping = absence of eloquent cortex identified by IES; Positive IES mapping = presence of eloquent cortex identified by IES; SMA = supplementary motor area; LPMC/FO = lateral premotor cortex/frontal operculum; IPL/PCG = inferior parietal lobe/postcentral gyrus; SPL/PCG = superior parietal lobe/postcentral gyrus; DNET = dysembrioplastic neuroepitelial tumor; KPS = Karnofsky Performance Status scale.