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The Relationship Between Stimulation Current and Functional Site Localization During Brain Mapping

BACKGROUND: Gliomas are often in close proximity to functional regions of the brain; therefore, electrocortical stimulation (ECS) mapping is a common technique utilized during glioma resection to identify functional areas. Stimulation-induced seizure (SIS) remains the most common reason for aborted procedures. Few studies have focused on oncological factors impacting cortical stimulation thresholds.

OBJECTIVE: To examine oncological factors thought to impact stimulation threshold in order to understand whether a linear relationship exists between stimulation current and number of functional cortical sites identified.

METHODS: We retrospectively reviewed single-institution prospectively collected brain mapping data of patients with dominant hemisphere gliomas. Comparisons of stimulation threshold were made using *t*-tests and ANOVAs. Associations between oncologic factors and stimulation threshold were made using multivariate regressions. The association between stimulation current and number of positive sites was made using a Poisson model.

RESULTS: Of the 586 patients included in the study, SIS occurred in 3.92% and the rate of SIS events differed by cortical location (frontal 8.5%, insular 1.6%, parietal 1.3%, and temporal 2.8%; $P = .009$). Stimulation current was lower when mapping frontal cortex ($P = .002$). Stimulation current was not associated with tumor plus peritumor edema volume, world health organization) (WHO grade, histology, or isocitrate dehydrogenase (IDH) mutation status but was associated with tumor volume within the frontal lobe ($P = .018$). Stimulation current was not associated with number of positive sites identified during ECS mapping ($P = .118$).

CONCLUSION: SISs are rare but serious events during ECS mapping. SISs are most common when mapping the frontal lobe. Greater stimulation current is not associated with the identification of more cortical functional sites during glioma surgery.

KEY WORDS: Electrocortical stimulation, Electrocorticography, Glioma, Glioblastoma, Brain mapping, Seizure

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Gliomas are the most common primary intrinsic brain tumor, with approximately 20 000 new cases each year.[1] A hallmark of gliomas is their infiltrative nature whereby they are by definition integrated into the surrounding brain parenchyma. Nevertheless, surgical resection is central to the management of low- and high-grade gliomas. A growing body of evidence suggests that greater extent of resection and smaller volume of residual tumor are associated with enhanced overall and progression-free survival regardless of molecular subtype.[2-6] Therefore, improving the safety of maximal resection has become a central issue in the surgical treatment of gliomas.[7,8] Many gliomas, particularly when they are in the dominant hemisphere, are in close proximity to regions of language, sensorimotor, and cognitive functional significance. Resection of these tumors in eloquent areas has proven to be a challenging task given the high risk of postoperative language and motor deficits.[9] Thus, the gold standard of maximal safe resection must balance the benefits of cytoreduction with the risk of decreasing quality of life.

ABBREVIATIONS: ECS, electrocortical stimulation; **ECOG,** electrocorticography; **IDH,** isocitrate dehydrogenase; **SIS,** Stimulation-induced seizure; **WHO,** world health organization

To improve extent of tumor resection and minimize deficits, intraoperative aids such as fluorescent molecules, intraoperative magnetic resonance imaging, and electrocortical stimulation (ECS) have been employed to distinguish tumor from non-tumor tissue and functional from nonfunctional areas.[7,10,11] Cortical and subcortical ECS mapping permits intraoperative localization of functional sites.[12] Despite its routine use for over 70 yr, it remains largely unknown why stimulation of distinct sites within a broader language, cognitive, and sensorimotor network are able to elicit a behavioral response, whereas others are not. It is known, however, that ECS mapping elicits physiological changes in real time which can be used to guide surgical resections and minimize postoperative morbidity.[12-18] ECS is therefore the gold standard technique used for the identification and preservation of functional sites during glioma resection. ECS mapping, however, is associated with risk. The primary risk and cause of aborted procedures is stimulation-induced seizures (SISs), which have been reported to occur in 2.2% to 54% of published series.[18,19]

There are several different ECS mapping techniques; however, most are based on the identification of a stimulation threshold using intraoperative electrocorticography (ECOG). In this technique, a stimulation threshold is determined based on the level at which after discharge potentials (a precursor to seizure activity) are identified on intraoperative ECOG.[8] One underlying assumption of this technique is that lower cortical stimulation current may identify fewer sites of functional significance (ie, false negative sites with mapping), thereby placing the patient at greater risk for postoperative deficits. The balance between stimulation current, intraoperative seizures, and identification of critical functional sites as determined by a corresponding in behavioral change remains poorly understood.[20] Moreover, the effect of tumor plus peritumor edema volume, hemispheric location, and glioma WHO grade on ECS stimulation current is poorly defined. We therefore used a single-institution retrospective intraoperative brain mapping registry to test the hypothesis that a linear relationship exists between stimulation current and number of cortical language and sensorimotor sites identified during intraoperative mapping.

METHODS

Patient Selection

This study included 586 patients with dominant hemisphere gliomas treated with awake cortical ECS mapping at the University of California, San Francisco, between 1997 and 2018. All surgeries were performed by one of two surgeons using identical technique (M.S.B. and S.H-J.).[8] Patients were identified by querying a retrospective brain tumor registry. Patients were excluded if intraoperative ECS mapping threshold was not recorded. ECS mapping data were obtained directly from the brain tumor registry. Patient demographics and information regarding clinical management were obtained from medical records, operative reports, and pathology reports. The institutional review boards at University of California, San Francisco approved this research protocol and waived the requirement for patient consent given the retrospective study design.

ECS Mapping

ECS mapping and awake craniotomy was performed according to prior published negative mapping protocol.[8,18] Iced Ringer's solution is prepared prophylactically to utilize in the case of a stimulation-induced intraoperative seizure. ECOG is performed using a 16-array cortical electrode and holder assembly (Grass ModelCE1; Natus Medical Inc) designed to record electroencephalography readings from the exposed cortex. An epileptologist is present in all cases to detect after discharge potentials or epileptiform activity following cortical stimulation.

Stimulation is delivered using the Ojemann stimulator (Radionics, Burlington, Massachusetts), a bipolar electrode which consists of 2 1-mm electrodes separated by 5 mm and delivers 1.25-msec biphasic square waves at 60 Hz. The surgeon begins with a 2 mA stimulation and gradually increases in 1-mA increments until after discharge potentials are detected via ECOG, which never occurred above 6 mA. When after discharge potentials are detected, the surgeon performs the mapping procedure at the same amplitude at which after discharge potentials were detected. For this study, stimulation current was determined as the current applied to the cortex during ECS mapping as defined by the level at which after discharge potentials occur on ECOG. According to established protocol, a positive cortical site was defined by its ability to elicit a reproducible behavioral response in at least 2 out of 3 trials during a language or sensorimotor task.

Imaging and Volumetrics

Pre- and postoperative magnetic resonance imaging imaging with and without gadolinium enhancement were obtained for each participant. Brainlab Smartbrush™ (Brainlab, Feldkirchen, Germany) software was used to measure tumor and tumor plus peritumor edema volume. Tumor volume was only determined in contrast-enhancing tumors, as the preoperative T1 postgadolinium sequence was used. A region of interest (ROI) was drawn around the tumor in three planes for each slice in the sequence, and a volume was calculated from the circumscribed region. Tumor plus peritumor edema volume was determined in all tumors using the FLAIR sequence. The same ROI method was used to determine total tumor plus peritumor edema volume.

Statistical Analysis

Categorical contrasts by tumor location were calculated using ANOVA for continuous variables, Fisher's exact test for binary variables, Kruskal-Wallis rank sum test for discrete variables, and Chi square tests for categorical variables. Categorical contrasts of intraoperative seizure rate were calculated using Student's *t*-test for continuous variables, Kruskal-Wallis rank sum test for discrete variables, and Fisher's exact test for categorical variables. Because the rate of intraoperative seizures was so low, we did not control for tumor location in these analyses. Comparisons of stimulation threshold between 2 groups were made using Student's *t*-tests. Comparisons made between 3 or more groups were performed using ANOVA and Tukey's test was employed for post-hoc testing to determine the individual differences that exist while adjusting for multiple testing. Multivariate linear regressions were used to draw associations between ECS mapping level and tumor volume, tumor edema, WHO grade, tumor histology, and IDH mutation status while controlling for cortical location. A Poisson model controlling for location was used to determine the association between stimulation threshold and number of positive sites identifies, with positive sites treated as a Poisson variable. R statistical software version 1.0.136 (R Foundation,

TABLE 1. Characteristics of the Study Population as a Whole and Separated by Tumor Location

Demographic Factor	n	Combined	Frontal	Insular	Parietal	Temporal	*P* value
Age (mean, SD)	586	42.5 (13.8)	41.8 (13.3)	38.1 (10.5)	45.3 (15.5)	44.6 (14.6)	7.96×10^{-5}
Sex (% male, SD)	586	59.0 (2.0)	57.6 (3.8)	55.6 (4.5)	52.5 (5.5)	64.5 (3.2)	.181
History of seizures (% with positive history, SD)	582	71.3 (1.9)	69.7 (3.6)	85.4 (3.2)	66.3 (5.3)	66.4 (3.2)	7.013×10^{-4}
# Anti-epileptic drugs (mean, SD)	582	0.95 (0.7)	0.95 (0.7)	1.12 (0.7)	0.90 (0.6)	0.86 (0.6)	7.065×10^{-3}
Glioma grade	566						7.535×10^{-11}
WHO Grade I (%, SD)	26	4.5 (0.9)	1.3 (0.9)	1.6 (1.1)	4.1 (2.3)	9.0 (2.0)	
WHO Grade II (%, SD)	249	44.0 (2.1)	50.0 (3.4)	56.9 (4.5)	40.5 (5.7)	33.2 (3.2)	
WHO Grade III (%, SD)	146	25.8 (1.8)	27.8 (3.6)	35.0 (4.3)	21.6 (4.8)	20.3 (2.8)	
WHO Grade IV (%, SD)	145	25.6 (1.8)	20.9 (3.2)	6.5 (2.2)	33.8 (5.5)	37.4 (3.3)	
Glioma histology	475						5.672×10^{-15}
Glioblastoma (%, SD)	145	30.5 (2.1)	24.4 (3.4)	5.8 (2.3)	40.3 (6.0)	46.7 (3.8)	
Astrocytoma (%, SD)	200	42.1 (2.3)	36.3 (4.1)	70.2 (4.5)	26.9 (5.4)	35.5 (3.7)	
Oligodendroglioma (%, SD)	130	27.4 (2.0)	39.3 (4.2)	24.0 (4.2)	32.8 (5.7)	17.8 (2.9)	
IDH mutation status (% wild type, SD)	258	37.6 (3.0)	25.6 (4.6)	19.2 (5.5)	37.1 (8.1)	62.3 (5.5)	3.087×10^{-7}
Positive site identified (n, %)	336[a]	336 (57.3)	111 (67.3)	85 (68.5)	62 (77.5)	78 (35.9)	NA
Dysnomia, semantic/paraphasic error (n, %)	90	90 (15.4)	16 (9.7)	11 (8.8)	17 (21.3)	46 (21.2)	
Alexia (n, %)	26	26 (4.4)	0 (0)	0 (0)	5 (6.3)	21 (9.7)	
Sentence comprehension/generation error (n, %)	6	6 (1.0)	0 (0)	2 (1.6)	0 (0)	4 (1.8)	
Speech hesitation, slurring, perseveration (n, %))	23	23 (3.9)	5 (3.0)	8 (6.5)	5 (6.3)	5 (2.3)	
Speech arrest (n, %)	97	97 (16.6)	34 (20.6)	47 (37.9)	4 (5.0))	12 (5.5)	
Motor (n, %)	181	181 (30.9)	82 (49.7)	50 (40.3)	26 (32.5)	23 (10.6)	
Sensory (n, %	118	118 (20.1)	40 (24.2)	29 (23.4)	37 (46.3)	12 (5.5)	

Categorical contrasts are shown.
[a]Many subjects had more than one positive site identified.

Vienna, Austria) was used for all analyses. A *P*-value of less than .05 was considered significant.

RESULTS

Patient Characteristics

This study included 586 patients of which 165 (28.2%) had tumors centered in the frontal lobe, 124 (21.2%) had tumors centered in the insula, 80 (13.6%) had tumors centered in the parietal lobe, and 217 (37.0%) had tumors centered in the temporal lobe. Table 1 summarizes characteristics of the study population in its entirety and separated by tumor location.

Intraoperative SIS Rate

In our assessment of cortical stimulation current and its ability to facilitate the identification of functional sites, we first wanted to understand the overall rate of intraoperative SISs during intraoperative brain mapping. SIS occurred in 3.92% of our study population (n = 23). SIS events were not associated with patient demographic factors such as age (mean age SIS- 41.3 yr, and mean age no SIS- 42.6 yr; $P = .651$) and sex (male- 4.3%, and female- 3.3%; $P = .667$), or previous seizure history (seizure history SIS- 4.8%, and no seizure history SIS- 1.8%; $P = .103$) (Table 2). Additionally, we determined that SIS events were not associated with oncologic factors such as glioma grade (WHO grade I- 3.8%, WHO grade II- 4.8%, WHO grade III- 4.1%, and WHO grade IV- 2.8%; $P = .525$), glioma histology (astrocytoma- 2.5%, oligodendroglioma- 6.2%, and glioblastoma- 2.8%; $P = .204$), or IDH mutation status (IDH wildtype- 10.3%, and IDH mutant- 5.2%; $P = .130$) (Table 2).

We then set out to determine if anatomic location impacts SIS rate. SIS rates during mapping of frontal, insular, parietal, and temporal tumors were 8.5%, 1.6%, 1.3%, and 2.8%, respectively ($P = .009$). To further evaluate whether frontal location was associated with the highest rate of SIS events, we compared SIS rate in the frontal region to SIS rate in the remaining regions. SIS rate was higher during ECS mapping of frontal tumors as compared to all other regions ($P = .001$) (Figure 1).

Stimulation Threshold

We then wanted to determine whether stimulation current (as determined by after discharge potential on ECOG) differs across cortical location. The mean stimulation current employed across all patients was 4.43 mA. The range of stimulation currents employed was 2 to 6 mA for each brain region. Further analysis based on cortical location revealed a mean stimulation threshold of 4.25 mA in frontal cortex, 4.50 mA in insular cortex, 4.32 mA in parietal cortex, and 4.57 mA in temporal cortex ($P = .002$). Stimulation current was significantly lower when mapping in frontal cortex as compared to temporal cortex ($P = .002$),

TABLE 2. Characteristics of Patients With and Without SISs

	n	Patients With SIS (n = 23)	Patients Without SIS (n = 563)	*P* value
Age (mean, SD)	586	41.3 (12.8)	42.6 (13.9)	.651
Sex (% male, SD)	586	65.2 (9.9)	58.8 (2.1)	.667
History of seizures (% with positive history, SD)	582	87.0 (7.0)	70.7 (2.1)	.103
Glioma grade	566			.805
WHO Grade I (%, SD)	26	4.3 (4.2)	4.6 (0.9)	
WHO Grade II (%, SD)	249	52.2 (10.4)	43.6 (2.1)	
WHO Grade III (%, SD)	146	26.1 (9.2)	25.8 (1.9)	
WHO Grade IV (%, SD)	145	17.4 (7.9)	26.0 (1.9)	
Glioma histology	475			.204
Glioblastoma (%, SD)	145	23.5 (10.3)	30.8 (2.2)	
Astrocytoma (%, SD)	200	29.4 (11.0)	42.6 (2.3)	
Oligodendroglioma (%, SD)	130	47.0 (12.1)	26.6 (2.1)	
IDH mutation status (% wild type, SD)	258	55.6 (11.7)	36.3 (3.1)	.130

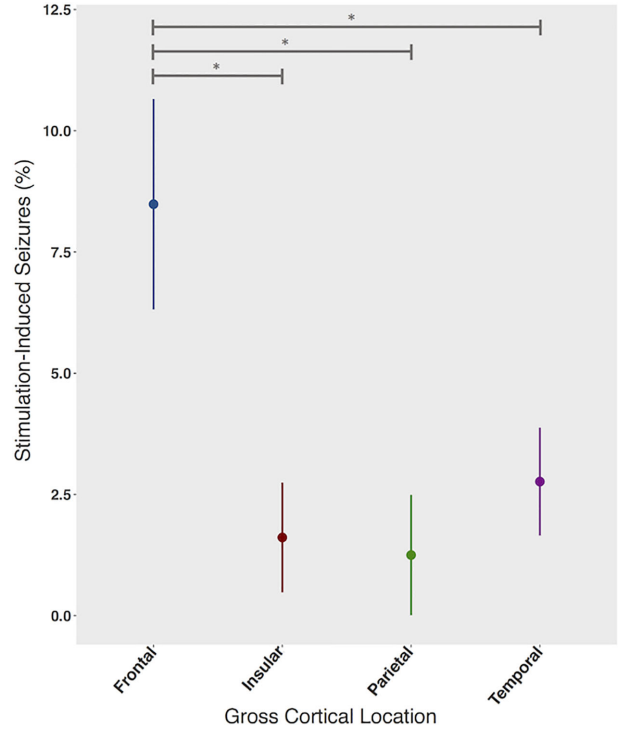

FIGURE 1. *SIS rates by cortical location. SIS were most frequent during ECS mapping of the frontal lobe (n = 165; SIS rate = 8.5%) as compared to ECS mapping of the insular region (n = 124; SIS rate = 1.6%), parietal lobe (n = 80; SIS rate = 1.25%), and temporal lobe (n = 217; SIS rate = 2.8%) (* < 0.05, ** < 0.01, *** < 0.001).*

indicating a small, but significant, difference in stimulation threshold between these regions (Figure 2A). Additionally, stimulation current was lower in patients who experienced SISs (median stimulation threshold SIS- 3.83 mA, and no SIS- 4.46 mA; $P < .001$) (Figure 2B).

Next, we set out to determine if stimulation current was associated with oncological factors such as tumor plus peritumor edema volume, tumor volume, WHO grade of the tumor, tumor histology (glioblastoma vs astrocytoma vs oligodendroglioma), or IDH mutation status. Average peritumor edema volume as determined by the FLAIR sequence was 43.41 cm^3 and varied by tumor location (frontal = 41.96 cm^3, insular = 53.97 cm^3, parietal = 31.20 cm^3, and temporal = 42.89 cm^3) ($P = .005$). After controlling for tumor location, stimulation current was not associated with tumor plus peritumor edema colume ($P = .294$) (Figure 2C). Average tumor volume in contrast-enhancing tumors was 9.85 cm^3 and also varied by tumor location (frontal- 8.09 cm^3, insular- 2.81 cm^3, parietal- 10.53 cm^3, and temporal- 11.37 cm^3) ($P = .043$). When cortical location was controlled for, larger tumor volume was associated with greater stimulation current in contrast-enhancing tumors in the frontal lobe only ($P = .018$) (Figure 2D). Stimulation current was not associated with tumor grade (WHO grade I or II vs WHO grade III or IV) ($P = .095$), tumor histology (astrocytoma vs oligodendroglioma vs glioblastoma) ($P = .849$), or IDH mutation status (wildtype vs mutant) ($P = .243$).

Stimulation Threshold and Functional Site Localization

Finally, we wanted to determine if higher stimulation current results in the identification of a greater number of cortical language and sensorimotor functional sites during surgery. The number of positive functional sites identified per procedure during ECS mapping varied by tumor location (median of frontal = 2, insular = 1, parietal = 2, and temporal = 0.3) ($P < .001$). After controlling for cortical location, stimulation current was not associated with number of positive sites identified (frontal r^2 0.024, $P = .10$; insular r^2 0.001, $P = .71$; parietal r^2 0.002, $P = .72$; and temporal r^2 0.0001, $P = .87$) (Figure 3). Additionally, the stimulation current was not significantly different in patients who had at least one positive site

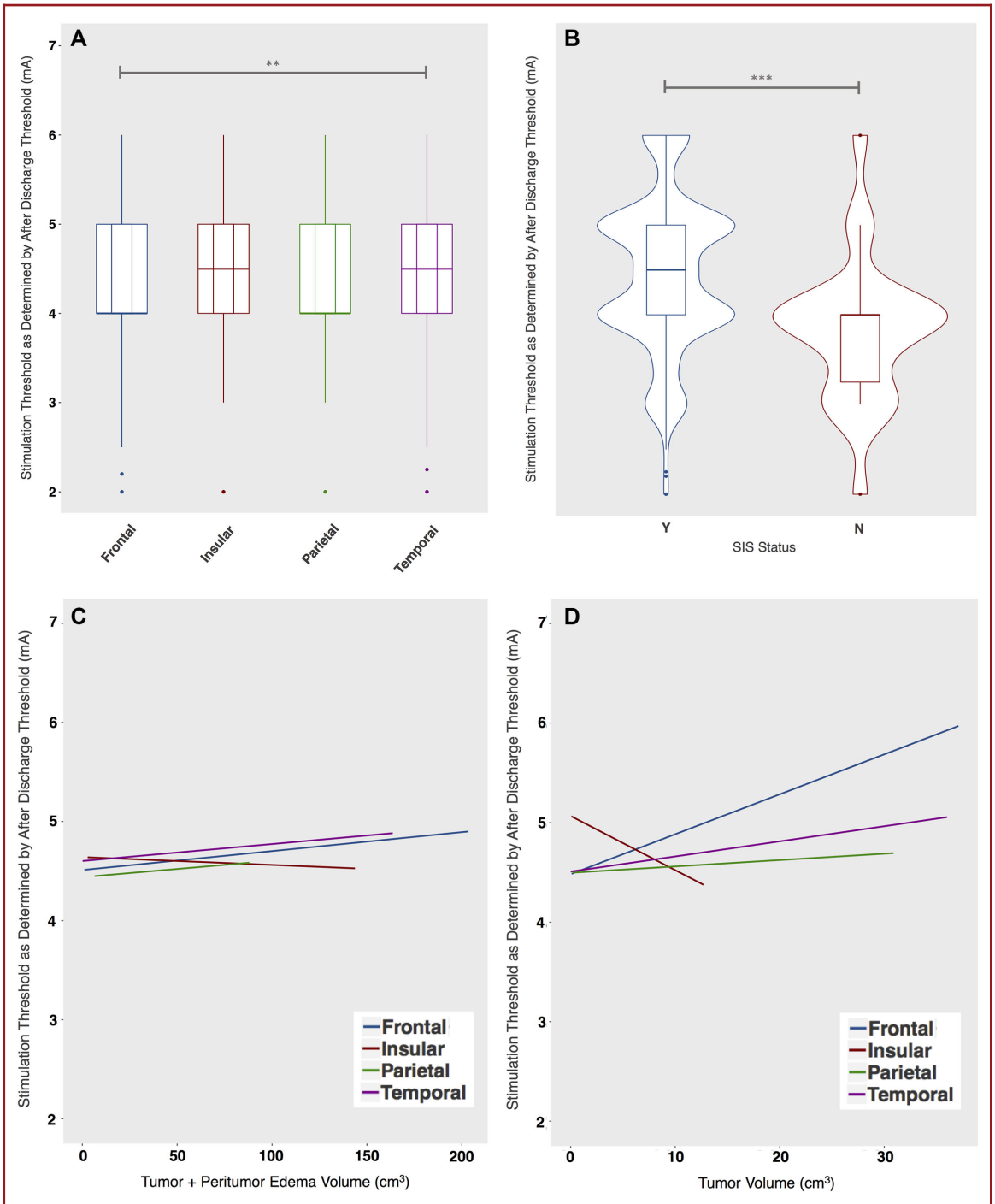

FIGURE 2. **A**, *Stimulation current is lower in frontal cortex (n = 161; mean stimulation threshold = 4.25 mA) as compared to temporal cortex (n = 209; mean stimulation threshold = 4.57 mA).* **B**, *Stimulation current is lower in patients who experienced SISs (n = 23; mean stimulation threshold 3.83 mA) as opposed to those who did not (n = 559; mean stimulation threshold = 4.46 mA).* **C**, *Stimulation current is not associated with tumor plus peritumor edema volume.* **D**, *In contrast-enhancing tumors, stimulation current is associated with larger tumor volume in the frontal lobe (n = 32; R^2 = 0.194; P = .019), but not in the insular lobe (n = 12; R^2 = 0.016; P = .315), parietal lobe (n = 28; R^2 = −0.044; P = .696), or temporal lobe (n = 80; R^2 = −0.033; P = .069) (* < 0.05, ** < 0.01, *** < 0.001).*

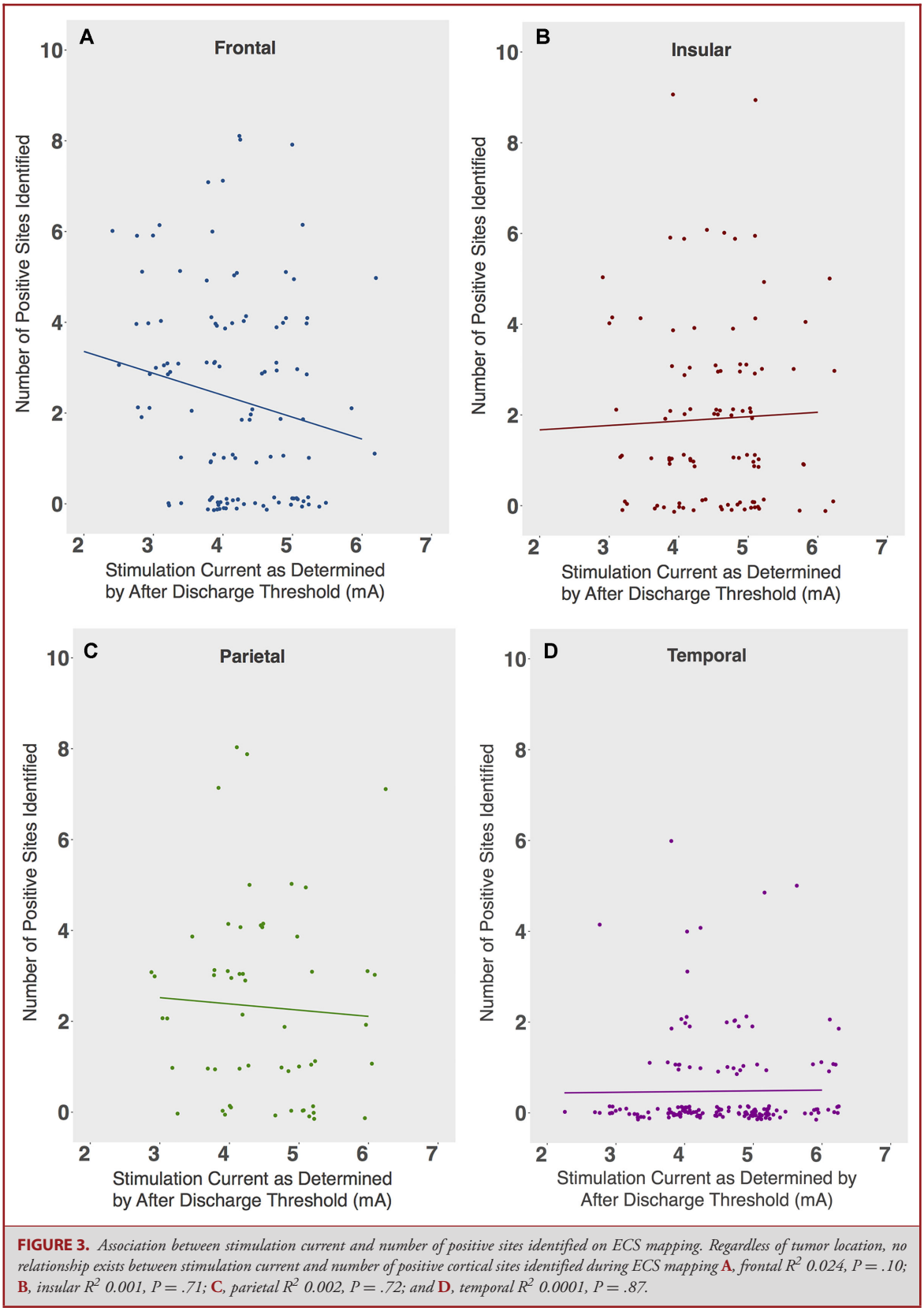

FIGURE 3. *Association between stimulation current and number of positive sites identified on ECS mapping. Regardless of tumor location, no relationship exists between stimulation current and number of positive cortical sites identified during ECS mapping* **A**, *frontal* R^2 *0.024,* $P = .10$; **B**, *insular* R^2 *0.001,* $P = .71$; **C**, *parietal* R^2 *0.002,* $P = .72$; *and* **D**, *temporal* R^2 *0.0001,* $P = .87$.

identified as compared with those with no positive cortical sites identified ($P = .228$).

DISCUSSION

ECS is the gold standard technique to maximize safe tumor removal while preserving functional areas during glioma resection.[21-23] However, previous studies have reported that there is a wide degree of variability for the thresholds of response to cortical stimulation between patients and even within the same patient in different cortical regions.[20-24] Generally, a stimulation current threshold defined by the level at which after discharge potentials are generated is enough to elicit a behavioral response. However, after discharge potentials are typically generated at higher stimulation currents, thereby increasing the risk of SISs. In this study we use a single-institution cortical brain mapping registry to assess SIS and stimulation current across cortical location. We then test the hypothesis that a linear relationship exists between stimulation current and number of cortical language and sensorimotor sites identified during intraoperative mapping.

To our knowledge, we are the first to investigate cortical stimulation current across anatomic location stratified by oncological factors. We found that SISs occur more frequently in frontal gliomas, likely because of stimulation in close proximity to the primary motor and premotor areas. Furthermore, glioma WHO grade, history of seizures, molecular subtype, and tumor IDH status are not associated with SISs. Mean stimulation current is lower in the frontal lobe and in those with intraoperative SISs. The lower current applied for individuals with SISs is a response to initial seizures early on during each brain mapping procedure, as the current applied for the remainder of the case is lower to prevent future seizure events. Volume of tumor plus peritumor edema does not alter the current necessary to achieve adequate cortical mapping. However, within the frontal lobe, there is a statistically significant but weak association between stimulation threshold and tumor volume. This is critical as confidence in the reliability of ECS is a necessity for its use and the lack of variability between tumor type and location allows for a standardized ECS protocol to be employed regardless of oncological variables for a given patient.

Historically, it has been argued by some that the threshold for after discharge potentials varies by cortical location.[25] Additionally, some authors have also suggested that stimulation at currents above those necessary to evoke after discharges may be required for successful mapping in order to avoid false negative sites.[24] We found a slightly lower stimulation threshold within the frontal lobe as compared with other cortical locations. Importantly, we show that a higher stimulation threshold does not lead to a greater number of cortical sites identified. Based on this finding, it follows that using stimulation thresholds greater than the level needed to identify after discharge potentials only increases the risk for a SIS, but does not identify additional functional cortical sites that would have otherwise been undetected. These data raise important considerations with respect to the use of ECOG during surgery for removal of eloquent area tumors. ECOG is critical during intraoperative mapping to ensure that transient behavioral responses are not due to focal seizure activity as result of stimulation, but may be less useful for determining stimulation threshold.

Limitations

One limitation of this study is based on our methods of retrospective analysis of prospectively collected registry data. Additionally, our analysis of the relationship between tumor volume and stimulation threshold is limited to high-grade gliomas, as there is no imaging technique that accurately distinguishes tumor from peritumoral edema in tumors that are not contrast-enhancing.[26] Another limitation of the study is the inclusion of only dominant hemisphere lesions, raising the possibility that the findings are not generalizable to nondominant lesions. Moreover, the results of this study may not be generalizable to the pediatric patient population. For instance, in a series of pediatric epilepsy patients (average age = 12 yr), after discharge threshold has been shown to linearly decrease with age.[27] Additionally, in children, temporal and frontal lobe thresholds for language inhibition were above 7 mA.[28] Thresholds for motor activation were slightly lower than those for language, between 5.3 and 6.1 mA for the face, upper extremity, and lower extremity, suggesting that for children, different stimulation parameters may be necessary for motor and language function. Finally, this study only investigates cortical mapping, as the thresholds necessary for subcortical pathways using low frequency bipolar stimulation remains incompletely understood, and therefore not the focus of this study. Based on the results of this study, stimulation parameters including current applied for cortical language and motor mapping may be standardized for adult glioma patients, independent of the tumor grade and peritumoral edema. Gliomas within the frontal lobe may require lower stimulation current likely because of the lower current required for motor and premotor mapping. There appears to be no added benefit of increasing stimulation current to or beyond the level which generates after discharges, as increasing current does not uncover a greater number of positive cortical sites. The added benefit of ECOG in cortical brain mapping is the ability to correctly identify false positive behavioral responses related to intraoperative seizures. Direct cortical stimulation remains the gold standard technique for intraoperative localization of function areas in real time during glioma removal and these data contribute to the growing body of literature focused on efforts to maximize safety.

CONCLUSION

SIS during ECS mapping is rare when stimulation level is set equal to the stimulation threshold necessary to generate after discharge potentials. SIS is most common when mapping the

frontal lobe. Higher stimulation current applied during cortical mapping does not result in the identification of more functional sites, supporting the practice of keeping stimulation current as low as possible.

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