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Factors that modify the risk of intraoperative seizures triggered by electrical stimulation during supratentorial functional mapping

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HIGHLIGHTS

- Loading with AED before mapping decreases the risk of intraoperative seizures.
- Penfield stimulation and diffuse pathology independently increase this risk.
- Preoperative seizures have no impact, likely due to the protective effect of AED.

ABSTRACT

Objective: Intraoperative mapping via electrical stimulation is the gold standard technique for surgeries close to the eloquent cortex. However, it can trigger seizures which immediately impact patient's safety. We studied whether administration of antiepileptic drugs (AED) prior to and/or at the beginning of the surgery decreases the probability of triggering seizures, while adjusting for other risk factors.
Methods: 544 consecutive intraoperative mapping cases performed at a tertiary care center for epilepsy and brain tumor surgery were included in the study. Using a multivariate logistic regression analysis, we analyzed the independent impacts of AED loading at time of surgery, preoperative AED maintenance, history of seizures, type of stimulation paradigm, lobar location of stimulation, age, opioid administration and pathology on the probability of triggering seizures.
Results: Seizures were identified in 135 patients. Intravenous loading with AED decreased the odds of triggering seizures by 45% (OR = 0.55, p = 0.01), Penfield (versus multipulse train) stimulation and diffuse (versus well circumscribed) pathology increased it twice (OR = 1.97, p = 0.01) and 2.4 times (OR = 2.42, p = 0.003) respectively. No other factors had a significant impact.
Conclusions: Seizures triggered during mapping occur frequently and are multifactorial.
Significance: Loading with AED independently reduces the risk of their occurrence.

1. Introduction

Intraoperative seizures triggered by electrical stimulation during a functional mapping procedure can have adverse consequences for the patient. First, electrographic ictal activity can lead to a generalized tonic clonic seizure. The latter is particularly dangerous during awake craniotomies, where there is no airway protection, hence an increased risk of aspiration and respiratory depression following aggressive medical treatment. Second, even when the treatment is successful, the post-ictal state, characterized by increased somnolence/confusion/dysphasia, either directly related to medication and/or to the postictal phase itself can impede, at least temporarily, the continuation of a reliable mapping. Third, the postictal cortical depression usually results in an increase in the mapping threshold that is hard to predict; this further hinders reliable mapping. Finally, seizures can spread to eloquent cortical regions distinct from those stimulated resulting

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in false localization of eloquent cortex. This is because the positive or negative phenomena observed during stimulation are ictal in origin and not triggered by stimulation of area located directly under the stimulating electrode (Jasper, 1954; Blume et al., 2004; Karakis et al., 2015).

It is well known that high intensity currents applied cortically increase the risk of intraoperative after discharges (AD) and seizures triggered by electrical stimulation (Pinsky and Burns, 1962; Kalamangalam et al., 2014; Karakis et al., 2015). However, newer findings show the major role played in their generation not only by the stimulus amplitude but also by the actual stimulation paradigm used (i.e., the interpulse interval and duration of the pulse), the time left between two consecutive stimulations as well as the timing of stimulation in relationship with existent epileptiform activity (Motamedi et al., 2002; Szelényi et al., 2007; Lesser et al., 2008). It is also conceivable that factors found to modulate baseline cortical excitability will also have an impact on the propensity of triggering seizures via electrical stimulation: type of pathology (Liubinas et al, 2014; Iuchi et al., 2015; Berntsson et al., 2018; Goldstein and Feyissa, 2018); inter-lobar cytoarchitectural and network differences (Pouratian et al., 2004; Lee et al., 2010); age (Lesser et al., 2008; Bhandari et al., 2016; Cueva et al., 2016); pro-epileptogenic agents such as opioids (Brian and Seifen, 1987; Cascino et al., 1993; Tempelhoff et al., 1992; Nielsen and Krøigaard, 2004).

Along these lines, while some authors reported an increased risk of triggering seizures during mapping in patients with epilepsy (Lesser et al., 2008) and/or near epileptic foci (Wyler and Ward, 1981), others found no such correlation (Szelényi et al., 2007).

It is clear that all this knowledge leads to a better understanding of the mechanisms that are at the basis of AD and seizures generation by stimulation. However, such intra and inter-individual variability of the risk factors, makes extremely difficult to reliably predict, let alone reduce their occurrence, on a case by case basis.

Therefore, a better way to avoid the complications associated with intraoperative stimulation triggered seizures is to have a means of preventing them that can be broadly applied to all patients undergoing a mapping procedure and which will be effective regardless of the magnitude of the individual risk.

In our daily practice, we have observed that intraoperative ictal events seem to be more consistently linked to presence or absence of administration of antiepileptic medication at the time of the surgery, than to any of the factors mentioned above.

As such, in the present study we aimed to investigate whether pre-operative administration of antiepileptics (AED), both as maintenance treatment and/or as a loading dose reduces the risk of triggering intra-operative seizures, regardless of presence or absence of a history of epilepsy and while adjusting for other potential confounders, such as stimulation paradigm, patient's state during mapping (i.e., awake versus general anesthesia), lobar location of stimulation, pathology, age, and use of opioids.

2. Methods

2.1. Inclusion criteria

544 consecutive cases of standardized intraoperative functional mapping during brain tumor and/or epilepsy surgery were included in this study. Both awake and asleep (general anesthesia) craniotomies were considered. Mapping was performed via direct cortical electrical stimulation using at least one of the two main stimulation paradigms: (i) repetitive biphasic pulses at 60 Hz, pulse duration of 1 ms, intensities 1–15 mA applied using a bipolar handheld stimulator (Penfield method); or (ii) repetitive trains at 2 Hz, 6 pulses/train, train frequency 250 Hz, pulse duration 0.5 ms, intensity 1–22 mA applied using a monopolar handheld stimulator, with the active electrode connected to the anode (+ positive) and a subdermal needle electrode placed at the margin of the surgical field, connected to the cathode (− negative) (multipulse train technique, also known as high frequency anodal stimulation). All asleep craniotomies were performed under total intravenous anesthesia, maintained with propofol and opioid infusions, without the use of muscle relaxants. Language and parietal functions mapping were performed with the patient awake, while primary somatosensory and motor mappings were done during both awake and asleep craniotomies. Electrocorticographic (ECoG) recordings were performed in all patients, via an 8-contact subdural strip electrode placed directly on the cortical surface, in immediate proximity to the stimulated regions. This allowed early detection and prompt treatment of stimulation triggered AD and seizures. Our standardized mapping procedures using either Penfield or the multipulse train techniques are described in detail elsewhere (Simon et al., 2010a, 2010b, 2012; Simon, 2013; Wang et al., 2011; Simon, 2018).

Of note, we have excluded all cases of pre-operative functional mapping performed at bedside in the video EEG monitoring unit (EMU) as part of the perioperative evaluation for epilepsy surgery. This is because the conditions encountered during such procedures, with direct impact on the risk of triggering seizures, are different than those seen in the operating room.

2.2. Variables

The following variables were retrospectively collected in all the patients 1- gender (male/female); 2- age (younger versus older than 50 years of age respectively); 3- history of pre-operative seizures (yes/no); 4- pre-operative maintenance treatment with AED (yes/no); 5- loading with AED (yes/no); 6-stimulus paradigm (Penfield, multipulse train); 7-patient's state (awake, anesthetized); 8-appearance of the lesions on MRI imaging (i.e. well circumscribed versus diffuse margins); 9- lobar location of mapping (frontal, temporal or parietal);10- type of pathology (primary gliomas; metastatic disease; known highly epileptogenic lesions, i.e. cortical dysplasias (CD), tuberous sclerosis (TS) and mesial temporal sclerosis (MTS); vascular lesions and inflammation/infection); 11- administration of opioids (i.e., remifentanil and/or fentanyl and/or sufentanil and/or alfentanil) during mapping (yes/no); 12- intraoperative seizures triggered by electrical stimulation (yes/no). Seizures were defined as rhythmic runs of self-propagated stimulation triggered AD with a duration of 10 s or more (Fig. 1). Maintenance treatment with AED was defined as daily oral administration of any AED regimen for at least 3 days prior to surgery. Loading with AED was defined as intravenous administration at the beginning of the surgery of: 1–500 mg or more of either levetiracetam, fosphenytoin or valproic acid; or 2–200 mg or more of lacosamide. The study was approved by the Human Institutional Research Committee, Protocol # 2007-P-002376, MGH.

Table 1 details the patients' demographics and their clinical characteristics.

2.3. Statistical analysis

Univariate logistic regression analysis was used first to study the impact of each the above factors on the outcome of interest, i.e. the odds of triggering seizures. A kitchen sink multivariate logistic regression model was employed to analyze the independent effect of all variables on the outcome of interest, while controlling for collinearity and confounding. Of note, inclusion in the final model of factors that did not reach statistical significance in the univariate analysis was a clinical decision, stemming out from observations in our own practice and directly related to contradictory results reported in the literature (e.g. whether a positive history of epilepsy increases the likelihood of triggering seizures

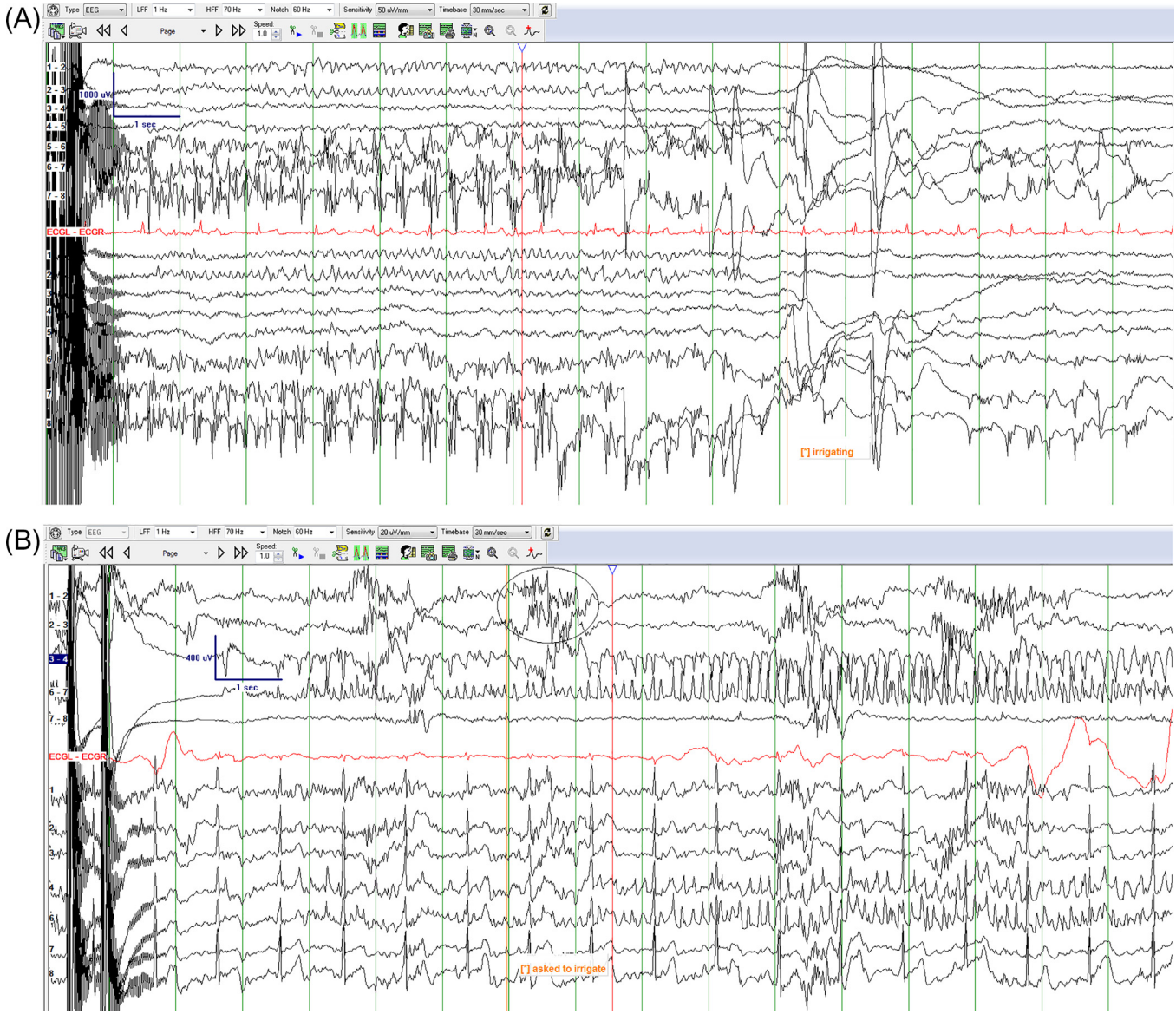

Fig. 1. Intraoperative seizures triggered by electrical cortical stimulation and recorded via an 8-contact subdural strip electrode placed near the stimulated regions. Both bipolar and referential montages are used. The reference is on the contralateral mastoid. (A). Language mapping is performed with the patient awake using the Penfield stimulation paradigm. An electrographic seizure is triggered at 10 mA. It consists of a rhythmic focal run of high amplitude polyspikes, seen at contacts 8 > 7 of the recording electrode. Notice the progressive decrease in the frequency of these discharges, a typical characteristic of seizure evolution. Cortical irrigation with ice cold saline (Sartorius and Berger, 1998) is performed; however, the seizure continues for several seconds afterwards. During this ictal event the patient is noted to have a delay in object naming/card recognition. (B). Motor mapping is performed with the patient under general anesthesia (infusions of propofol and remifentanil) and using multipulse train stimulation. Cortical stimulation, performed via contact 5 of the strip electrode at 14 mA, triggers an electrographic seizure. Notice the clear burst suppression pattern with brief bursts (circled) of sharp, fast frequency activities separated by 1–2 second epochs of electro cerebral silence. The seizure consists of a focal run of rhythmic sharp theta activity seen at contacts 6 > 4. Also, notice the rhythmic ECG artifact seen mainly in the reference montage.

during mapping). A variable of interest was considered collinear with another, if the standard error for estimation of the odds ratio (OR) changed by 20% or more, when analyzing the two factors together (multivariate logistic regression) versus analyzing the variable of interest alone (univariate logistic regression). Similarly, a variable of interest was considered confounded by another, if its OR changed by 20% or more when analyzing the two factors together, versus analyzing the variable of interest alone.

3. Results

There were 294 (54%) males and 250 (46%) females in our study. 301 (55.3%) patients were older than 50 years of age, whereas 243 (44.7%) were younger. The oldest patient was 88 years old (y.o.) and the youngest was 2 y.o. (mean 50 y.o.). 330 out of 544 patients (60.7%) had a history of preoperative seizures, whereas 214 (39.3%) did not. 204 patients (37.5%) were already receiving a maintenance daily AED dose at the time of the surgery, whereas 340 (62.5%) were not. 356 patients (65.4%) received intravenous loading doses of AED whereas 188 patients (34.6%) did not. From all 356 patients who received AED loading, levetiracetam was used in 288 (80.9%); fosphenytoin in 64 (18%); valproic acid and lacosamide in 3 and 1 patients respectively (1.1%). Electrographic seizures were triggered intraoperatively in 135 out of 544 cases (24.9%). Penfield and multipulse train paradigms were used in 178 (32.7%) and 366 (67.3%) cases respectively. 204 mappings (37.5%) were performed in awake patients, whereas 340 (62.5%) were performed under general

Table 1
Patients' Demographics and Characteristics.

Variable	Number of patients (%)
Gender	
Male	294 (54%)
Female	250 (46%)
Age	
Age > 50	301 (55.3%)
Age < 50	243 (44.7%)
History of preoperative seizures	
Yes	330 (60.7%)
No	214 (39.3%)
Maintenance treatment with AEDs	
Yes	204 (37.5%)
No	340 (62.5%)
Loading with AEDs	
Yes	356 (65.4%)
No	188 (34.6%)
Stimulation Paradigm	
Penfield	178 (32.7%)
High frequency anodal	366 (67.3%)
Patient's state	
Awake	204 (37.5%)
General anesthesia	340 (62.5%)
Lesional margins on MRI	
Diffuse	403 (74%)
Well circumscribed	114 (21%)
No lesion seen	27 (5%)
Lobar location of the stimulation	
Temporal	131 (24.3%)
Frontal	340 (63%)
Parieto-occipital	73 (12.7%)
Pathology	
Gliomas	328 (60.3%)
Metastasis	82 (15.1%)
Cortical dysplasia/TS/MTS	18 (3.3%)
Inflammation/Gliosis	42 (7.7%)
Highly vascular lesion/blood products	47 (8.6%)
No pathology reported	27 (5%)
Opioids (administered during mapping)	
Yes	489 (89.9%)
No	55 (10.1%)
Intraoperative Seizures	
Yes	135 (24.9%)
No	409 (75.1%)

anesthesia. In 403 cases (74%) the lesion had diffuse margins on MRI imaging, whereas in 114 cases (21%) the lesions were well circumscribed; in 27 cases (5%) no clear lesion could be appreciated on MRI studies. In 131 cases (24.3%) the electrical stimulation was performed in the temporal lobe regions; in 340 cases (63%) in the frontal lobe regions, in 73 cases (12.7%) in the parietal regions.

Reported histopathological abnormalities were: gliomas in 328 patients (60.3%); brain metastasis in 82 patients (15.1%); pathology associated with high epileptogenicity (i.e. CD, MTS, TS) in 18 patients (3.3%); inflammation and/or gliosis (not including MTS) in 42 cases (7.7%); a highly vascular lesion/acute or chronic blood products in 47 cases (8.6%); no pathology reported in 27 patients (5%). All patients received opioids at some point during the surgery. From these, during the actual mapping 489 (89.9%) received opioids, while 55 patients (10.1%) did not (Table 1).

In the univariate analysis (univariate logistic regression), the following factors were found to significantly increase the risk of triggering intraoperative seizures: 1- Penfield method (OR = 2.16, p = 0.0002); 2-awake state (OR = 1.61, p = 0.01); 3- diffuse pathology (OR = 2.37, p = 0.002); and 4- stimulation in the temporal lobe (OR = 1.72, p = 0.01). However, mapping during awake state was found to be collinear with the use of Penfield paradigm and thus the former was excluded from the final model. Also, the effect of stimulation in the temporal lobe was positively confounded by the use of Penfield paradigm.

Table 2
Univariate analysis: The unadjusted impact of each independent variable on the odds of triggering intraoperative seizures.

Independent Variable (the modeled category)	Univariate Logistic Regression OR (p)
Gender (Male)	1.28 (p = 0.22)
Age (Age > 50)	0.87 (p = 0.47)
History of preoperative seizures (Yes)	0.96 (p = 0.83)
Maintenance treatment with AEDs (Yes)	0.72 (p = 0.11)
Loading with AEDs (Yes)	0.80 (p = 0.28)
Stimulation Paradigm (Penfield)	*2.16 (p = 0.0002)*
Patient's state (Awake)	*1.61 (p = 0.01)*
Lesional margins on MRI (Diffuse)	*2.37 (p = 0.002)*
Lobar location of the stimulation (Temporal)	*1.72 (p = 0.01)*
Pathology (Gliomas)	1.43 (p = 0.08)
Opioids (Any administered during mapping)	0.96 (p = 0.91)

Table 3
Multivariate analysis: The adjusted impact of each independent variable on the odds of triggering intraoperative seizures.

Independent Variable (the modeled category)	Multivariate logistic regression (Kitchen sink) OR (p)
Age (Age > 50)	0.76 (p = 0.2)
History of preoperative seizures (Yes)	0.97 (p = 0.9)
Maintenance treatment with AEDs (Yes)	0.62 (p = 0.06)
Loading with AEDs (Yes)	*0.55 (p = 0.009)*
Stimulation Paradigm (Penfield)	*1.97 (p = 0.01)*
Lesioned margins on MRI (Diffuse)	*2.42 (p = 0.003)*
Lobar location of the stimulation (Temporal)	1.19 (p = 0.5)
Pathology (Gliomas)	0.84 (p = 0.5)
Opioids (Any administered during mapping)	1.57 (p = 0.2)

Neither loading nor pre-operative maintenance treatment with AED reached statistical significance in the univariate analysis. Similarly, positive history of preoperative seizures, age more than 50 years old, administration of opioids at the time of stimulation and gender did not significantly impact the risk of triggering seizures. However, the effect of positive history of seizures on the odds of triggering seizures was negatively confounded by the pre-operative administration of maintenance doses of AED. A trend towards triggering seizures (OR = 1.43, p = 0.08) was associated with mapping during glioma resection (Table 2).

In the final analysis (kitchen sink multivariate logistic regression), intravenous administration of loading doses of AED decreased the odds of triggering seizures by 45% (OR = 0.55, p = 0.009). Presence of diffuse (versus well circumscribed) pathology and using a Penfield (versus multipulse train) stimulation paradigm independently increased this risk 2.4 times (OR = 2.42, p = 0.003) and 2 times (OR = 1.97, p = 0.01) respectively. At the same time, maintenance AED treatment, history of seizures, administration of opioids at the time of mapping, age more than 50 years old, stimulation in the temporal lobe and glioma as pathology did not have a significant impact (Table 3).

4. Discussion

Wada (1977) reported that therapeutic levels of AED significantly reduce the incidence of electroclinical seizures kindled by electrical stimulation in baboons. However, such findings could not be reproduced in other animal models. Our results show that

AED can efficiently protect against electrical stimulation triggered seizures in humans and that such protective effect is independent of other risk factors.

4.1. Intravenous loading with AED

About two thirds (73.3%) of the patients who received intravenous loading with AED at the beginning of the surgery, had not been previously on maintenance AED; however, about a fourth (26.7%) of them had. The loading was performed in this latter group because of lack of information regarding the effectiveness of the AED maintenance (e.g. low or unavailable drug levels, low daily dosage, short length of treatment).

The results of this study support our prior clinical observations that intravenous administration of AED at the beginning of the surgery is an efficient method to decrease the risk of seizures triggered by electrical stimulation during intraoperative mapping across patients. Most patients were loaded with either fosphenytoin and levetiracetam (Keppra). The former had been used earlier in our practice, whereas the latter became the drug of choice over the last several years. The administered doses varied, depending upon pre-existing AED treatment, weight, age and patient's comorbidities, within 500–1500 mg range for fosphenytoin and 500–2000 mg range for levetiracetam. Recent studies have shown that the efficiency in seizure control of the two drugs is comparable (Singh et al., 2018) and that intravenous administration of levetiracetam is safe and well tolerated (Wheless et al., 2009; Kim et al., 2018). This has also been our experience. More so, in comparison with fosphenytoin, keppra has no drug interactions and significantly less severe side effects. This makes the latter an ideal drug to administer routinely across patients at the beginning of the surgery, with the anesthesiologist and the surgeon being comfortable with such approach. As such, our results have recently prompted introduction of standard intravenous administration, prior to incision of a total of ~20 mg/kg of levetiracetam in all patients who are to undergo intraoperative mapping via cortical electrical stimulation. with the appropriate dosage adjustments on a case by case basis (e.g., for presence of renal failure, side effects, age).

4.2. Maintenance treatment with AED and history of pre-operative seizures

Prior studies (Lesser et al., 2008) have found that AD and subsequently seizures are more frequently triggered in patients with intractable epilepsy and that AD are more likely to be triggered when stimulation is performed within the irritative zone (Liu et al., 2017) and/or in close proximity to epileptiform discharges (Karakis et al., 2015) and/or epileptic foci (Wyler and Ward, 1981); however, others found no correlation (Szelényi et al., 2007) between history of epilepsy and likelihood of stimulation triggered seizures. It is logical to assume that patients with epilepsy are already under maintenance AED treatment, whereas those without, are not. Since the role of such treatment is precisely to control the increased cortical excitability present in patients with pre-operative seizures, it will always be difficult to isolate the effects of these two factors (i.e., history of seizures and maintenance treatment with AEDs) on the risk of triggering intraoperative seizures via electrical stimulation. Our results are not surprising in that sense.

We found that positive pre-operative history of seizures as a risk factor for intraoperative seizures was negatively confounded by maintenance treatment with AED. These results suggest that the latter may be protective against the intraoperative seizures. Nevertheless, the results did not reach statistical significance, most likely due to lack of power, with only 20 patients receiving pre-operative maintenance treatment with AED (despite a negative history of seizures). In these patients, administration of AED in the days preceding the surgery was performed prophylactically, at the neurologist's request and in the view of the surgery and intraoperative mapping.

4.3. Stimulation paradigms

Frequency of stimulation modulates the probability of triggering sustained AD and thus seizures. As such, the length of AD runs increases with increases in stimulation frequency from 4 to 64 Hz, with 32 and 64 Hz stimulation triggering the longest trains hence the highest probability to trigger seizures. A further increase from 64 to 512 Hz, results in a decline in the duration of such activity (Pinsky and Burns, 1962). These findings are strikingly concordant with results from other studies showing that inactivation of inhibitory interneurons is more likely induced by electrical stimulation around 50 Hz (Kalamangalam et al., 2014), thus enabling synchronous oscillations of local field potentials (LFP) hypothesized by some authors to be at the basis of AD and seizures generation (Gerin, 1960).

These prior reports explain why in clinical studies low frequency cortical stimulation (50–60 Hz) has been found to be more epileptogenic than multipulse train technique, with incidence of seizures as low as 1.1% for the latter (Neuloh et al., 2004), and as high as 11% (Yingling et al., 1999) and even 20% (Sartorius and Wright, 1997) for the former.

Our results are in accordance with prior work. Also, in our study stimulation during awake state was collinear with the use of Penfield paradigm (as a risk factor for intraoperative seizures). As such, we considered appropriate to eliminate the variable "state" from our final analysis.

4.4. The influence of pathology

We have previously shown that positive mapping of eloquent regions situated near lesional margins, is associated with an increased stimulation threshold (Wang et al., 2011) and that there is a direct positive correlation between the stimulus intensity and propensity of triggering seizures (Karakis et al., 2015). On the other hand, peritumoral cortex has been reported to have increased cortical excitability (Simon et al., 2010b; Simon, 2018). As such, electrical stimulation applied in these regions may be correlated with an increased risk for triggering seizures, particularly for certain types of brain tumors, such as low grade gliomas (Iuchi et al., 2015; Berntsson et al., 2018; Goldstein and Feyissa, 2018), especially in presence of a certain type of molecular biology such as IDH1 mutation (Liubinas et al, 2014). In accord with prior data, we have found that diffuse pathology is more likely to be associated with higher incidence for triggering seizures. In our experience, when compared to other type of pathology, mapping during removal of primary brain lesions seemed to be more frequently associated with intraoperative seizures. This may be due to lack of AED treatment (in comparison with epilepsy patients), a hypothesis that our results support. The other possibility is that glioma as pathology independently increases the risk for stimulus triggered seizures. We were not able to prove the latter relationship. On the other hand, our results suggest that such association may exist for certain types of primary brain tumors (e.g., those with diffuse margins and high infiltrative power). As such, in a future study we are planning to further investigate the relationship between molecular biology of gliomas and propensity of increasing the excitability of the surrounding cortex and thus the risk of seizures.

4.5. Location of stimulation

Well known inter-lobar variations in cortical excitability (Pouratian et al., 2004; Zangaladze et al., 2008; Lee et al., 2010) supported by the correlation between a minimum neuronal cortical density necessary to induce epileptic activity by electrical stimulation (Pinsky and Burns, 1962) explain differences among different cortical regions in the risk of triggering seizures. Thus, we considered important to introduce as a possible predictor of risk, the lobar location of the stimulation. In a univariate analysis, we found that stimulation in the temporal lobe increases the odds of triggering seizures. However, this factor was positively confounded with use of the Penfield paradigm and, after adjusting for the latter, it was no longer found to be a significant predictor.

4.6. Obtaining successful mapping results in patients with triggered intraoperative seizures and the relationship between seizure and mapping thresholds

Current density applied cortically is a major risk factor for triggering epileptic/epileptiform activity (Pinsky and Burns, 1962; Kalamangalam et al., 2014; Karakis et al., 2015.). Thus, one could argue that in the mapping cases where seizures were triggered, significantly higher stimulus intensities were applied. Our results did not find such association. The average stimulus intensity at which intraoperative seizures were triggered, was not higher than the average maximal current applied in patients in whom no seizures were triggered. In fact, the opposite was true: the average maximal current intensity applied in cases where no seizures were triggered was higher by 2 mA than the current at which seizures were triggered (10.5 mA versus 8.5 mA, $p < 0.001$ *t*-test). The average maximal stimulus amplitudes applied in the two groups (i.e. those without and those with triggered seizures) was similar (10.5 mA versus 9.9 mA respectively, $p = 0.27$, *t*-test). These results suggest that the stimulation could be further increased after triggering seizures, to positively map the eloquent regions.

This can be explained by the fact that while increasingly higher current density applied at a certain cortical location in a certain patient is associated with an increased risk for triggering seizures, the likelihood of triggering seizures also depends on other factors such as the timing and frequency of stimulation epochs. Lesser and colleagues (Lesser et al., 2008) showed that regional distribution of AD vary from stimulation to stimulation. The authors concluded that such variations are directly related to extensive dynamic changes of cortical excitability dependent on local brain states and the functional brain architecture at the time of the stimulation.

More so, the threshold for seizures does vary significantly from one cortical location to another within the same patient as well as across patients, due to specific patient related risk factors. Along these lines, the threshold for triggering seizures at one cortical location can be smaller than the mapping threshold of eloquent cortex. As such, from the 135 cases in which intraoperative seizures were triggered, successful mapping of eloquent regions was still achieved in 95 of them at an average mapping threshold that was not significantly different from that obtained in the group without seizures (7.4 mA versus 8.4 mA respectively, $p = 0.12$ *t*-test).

Nevertheless, triggering intraoperative seizures did significantly decrease the odds of achieving positive successful mapping by 42% ($p = 0.01$ logistic regression), mostly because the significant impediments directly associated with triggering intraoperative seizures, as mentioned in the Introduction section. This is in accordance with our prior findings (Sheth et al., 2013) underlining once more the importance of intraoperative seizures' prevention for achieving successful mapping. One legitimate question was whether administration of AED results in an increased mapping threshold. We found no such association (an average threshold of 8.9 mA in the group without AED load versus 7.8 mA in the group with load, $p = 0.07$ *t*-test). This is in accordance with prior reports showing that normal neuronal and synaptic activity are not affected by administration of AED such phenytoin (Wada, 1977).

4.7. Stimulation triggered seizures as outcome

Our goal was not to study the effect of AED on isolated AD but rather on their ability to self-propagate and organize into seizures, with longer runs having an increased likelihood to evolve into a clinical ictal event.

The evolution of epileptiform into epileptic activity lies on a spectrum and a clear delineation between the two types is frequently challenging. However, criteria of organization, such as rhythmicity and dynamic progression of frequency and amplitude of discharges, as well as length of the "self-propagated" run of AD are often applied to define an ictal electrographic event. Along these lines, we used a 10 second cut off as a length criteria for seizure definition (Abend et al., 2013, Sánchez Fernández et al., 2014).

Since the duration and magnitude of an observed electrographic seizure is directly dependent on the position of the recording electrodes vis-à-vis to the ictal onset, we used a standardized ECoG technique involving an 8-contact subdural strip electrode placed in the immediate proximity of the stimulated cortical regions (Wang et al., 2011; Simon et al., 2012; Simon, 2018; Simon, 2013).

4.8. High incidence of triggered seizures

Electrographic seizures were triggered in almost 25% of our cases. Our incidence of seizures is similar to that reported in the literature by some authors (Sartorius and Wright, 1997; Yingling et al., 1999) but significantly higher than that reported by others (Sala and Lanteri, 2003; Neuloh et al., 2004). However, most of these studies relied on clinical identification of intraoperative seizures (e.g., body movements, dysphasia) and some relied on free run EMG recordings to detect motor seizures involving the contralateral hemibody muscles. We believe that our high incidence of observed electrographic seizures is due to, at least partially, to an increased sensitivity of our methodology to detect such activity. All our mapping cases benefit from ECoG recordings during the entire electrical stimulation period; such technique is standard and involves an 8-contact subdural strip electrode that is placed very close to the stimulated area, at all times. This means, the strip is frequently relocated by the surgeon to be near the stimulation sites. These ECoG recordings are interpreted live by a clinical neurophysiologist with expertise in ECoG analysis. Another explanation may lie with the type of population mapped at our tertiary care center. Most of our patients come to the neurosurgeons' attention for a second or even third opinion, and are offered surgery for advanced disease, located near eloquent cortical regions. These are challenging cases, and frequently the local anatomy is distorted by presence of large lesions, many with diffuse margins and perilesional edema.

In our experience, it is in these cases that seizures are triggered more easily; our results support this clinical observation, with diffuse pathology having a higher association with intraoperative seizures.

4.9. Rationale for the effectiveness of AED loading on decreasing the incidence of intraoperative seizures

The impact of AED on stimulation triggered seizures could be understood only in relationship to both the mechanisms of seizure occurrence and that of AED action.

(a) Mechanism of occurrence of stimulation triggered AD and seizures

AD generation, propagation and organization in seizures under general anesthesia were first described more than 80 years ago (Adrian, 1936). Further, Pinsky and Burns (1962) underlined clear similarities between AD triggered by electrical stimulation and epileptiform activity in epilepsy patients; they showed that while AD can be generated in any regions of the cortex, synchronous firing of many neurons is necessary for initiation of an AD. Such repeated firing leads to a state of persistent depolarization. Recovery from this state is uneven, with part of the cell repolarizing towards the normal resting potential faster than the rest of the cell. The mechanism is known as "differential repolarization" and results in an extracellular current flow between the two parts of the neuronal membrane that have different electrical potentials. This hypothesis can explain why the state of neuronal excitability and of the extracellular environment play important roles in AD and seizure generation. The latter also requires neuronal firing and LFP oscillations in a synchronous fashion, events facilitated by inactivation of inhibitory interneurons (Kalamangalam et al., 2014).

(b) AED: Mechanisms of action and pharmacokinetics

Two antiepileptic drugs have been historically used at our institution for intravenous loading in the view of intraoperative mapping: fosphenytoin and levetiracetam (Keppra). As already mentioned, the former has been mainly used earlier in our practice whereas the latter has been consistently and exclusively used over the last several years.

Seizure generation is the result of a positive feedback that enhances neuronal discharges and which is sustained by several mechanisms such as significant increase and decrease in the extracellular concentration of K^+ and Ca^{++} respectively, GABA desensitization and neurotransmitter release potentiation.

Phenytoin efficiently suppresses seizure generation by specifically blocking this feedback: it decreases the neuronal membrane hyperexcitability and depolarization, and the excitatory synaptic transmission; instead, it enhances the synaptic inhibition mediated by GABA. Studies have shown that phenytoin's effectiveness is increased dramatically with the increase in frequency and duration of the neuronal discharges, hence it is ultimately proportional with the magnitude of the generated positive feedback. Since its efficiency is highest on high frequency firing, it explains why the drug is significantly less effective in suppressing brief isolated epileptiform discharges and/or normal neuronal and synaptic activity. As such, we expected no significant changes in the depolarization thresholds for eloquent cortex and thus no negative impact on the efficiency of cortical mapping after AED administration. This is also supported by our findings (see Section 4.6. above). Last, our results support earlier findings (Wada, 1977) showing that therapeutic levels of phenytoin suppress seizures kindled by electrical stimulation in certain animal species.

From a practical perspective, intravenous loading with fosphenytoin is very efficient, being followed by rapid conversion (hydrolysis, dephosphorylation) to the active compound, i.e. phenytoin. The latter reaches therapeutic levels as early as within 15 min of infusion with full conversion occurring within 2 h (Browne et al., 1996). However, its high protein binding, side effects, and interactions with other drugs are major disadvantages.

The mechanism of action of levetiracetam consists of modulation of synaptic neurotransmitter release. Its pharmacokinetics gives it certain advantages over phenytoin including rapid and almost complete absorption, insignificant binding to plasma protein, and absence of enzyme induction and/or interaction with other drugs. Its plasma half life is 7–8 h in adults and up to 10 h in elderly. With intravenous administration, the peak plasma level is usually reached within 15 min, which means roughly by the end of the loading infusion. Such favorable pharmacokinetics and the lack of significant side effects, make levetiracetam a versatile drug to use for perioperative treatment and seizure prophylaxis. It is our experience that both the surgical and the anesthesia teams are usually comfortable using loading doses of levetiracetam at the beginning of the surgery.

4.10. Limitations and future directions

Most of the limitations of this study are inherent to its retrospective nature.

For example, we have found it difficult to assess the effect of each type of pathology on the propensity for triggering seizures. Nevertheless, since our clinical interest has been primarily to study the risk associated with gliomas, particularly those displaying an aggressive behavior, we have dichotomized pathology (i.e. gliomas versus other) and identified lesions more likely to present a higher infiltrative power based on a practical criterion, the appearance of their margins on the MRI.

The information we could retrospectively collect on preoperative AED treatment was sparse and at best incomplete. Thus, we were unable to reliably study the individual effect of different types and doses of AED and/or of the length of AED pre-operative treatment (maintenance).

As previously mentioned, due to sample limitations, we were unable to reliably investigate the independent effect of history of seizures and maintenance AED treatment on the risk of triggering seizures.

Finally, while modeling separately the risk of triggering clinical seizures would have also been informative from a practical perspective, due to incomplete medical records we have not been able to reliably differentiate between purely electrographic and electroclinical seizures.

We are planning to address such shortcomings in future prospective studies.

5. Conclusions

The risk of intraoperative seizures associated with electrical stimulation during functional mapping can be efficiently reduced by administration of a loading dose of AED at the beginning of the surgery. Special attention should be given to cases where mapping is performed via Penfield method of stimulation and in the presence of diffuse pathology.

While we could not prove that positive history of pre-operative seizures is an independent risk factor, this may be because of the protective effect of maintenance treatment with AED. Hence, when mapping patients with epilepsy one should ensure therapeutic AED levels.

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Declaration of interests

None.

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