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# Thermosensitive/thermochromic silicone and infrared thermography mapping in 60 consecutive cases of epilepsy surgery

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### ABSTRACT

**Background:** Epilepsy surgery represents a therapeutic opportunity for those patients who do not respond to drug therapy. However, an important challenge is the precise identification of the epileptogenic area during surgery. Since it can be hard to delineate, it makes it necessary to use auxiliary tools as a guide during the surgical procedure. Electrocorticography (ECoG), despite having shown favorable results in terms of reducing post-surgical seizures, have certain limitations. Brain mapping using infrared thermography mapping and a new thermosensitive/thermochromic silicone (TTS) in epilepsy surgery has introduced a new resource of non-invasive and real-time devices that allow the localization of irritative zones.

**Methods:** Sixty consecutive patients with drug-resistant epilepsy with surgical indications who decided to participate voluntarily in the study were included in the study. We measured brain temperature using two quantitative methods and a qualitative method: the TTS sheet. In all cases, we used ECoG as the gold standard to identify irritative areas, and all brain tissue samples obtained were sent to pathology for diagnosis.

**Results:** In the subgroup in which the ECoG detected irritative areas (n = 51), adding the results in which there was a correlation with the different methods, the efficiency obtained to detect irritative areas is 94.11% (n = 48/51,  $P \le 0.0001$ ) while the infrared thermography mapping method independently has an efficiency of 91.66% ( $P \le 0.0001$ ). The TTS has a sensitivity of 95.71% and a specificity of 97.9% ( $P \le 0.0001$ ) to detect hypothermic areas that correlate with the irritative zones detected by ECoG. No postoperative infections or wound dehiscence were documented, so the different methodologies used do not represent an additional risk for the surgical proceedings.

**Conclusion:** We consider that the infrared thermography mapping using high-resolution infrared thermography cameras and the TTS are both accurate and safe methods to identify irritative areas in epilepsy surgeries.

Keywords: Electrocorticography, Epilepsy surgery, Infrared thermography mapping, Thermochromic silicone, Thermosensitive silicone

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#### INTRODUCTION

Epilepsy surgery represents a therapeutic opportunity for those patients who do not respond to drug therapy or have seizure syndromes remediable by surgery. In some specific cases, such as focal epilepsy, it is the only potentially curative treatment.<sup>[24]</sup> The success of this surgery is closely related to the complete resection of the epileptogenic zone, which depends on the correct delimitation of the region, this being the minimum cortical area that must be resected to achieve seizure suppression<sup>[8]</sup> and avoid morbidity. However, an important challenge in these patients is the precise identification of the area during surgery since the epileptogenic region is usually larger than what is observed in conventional magnetic resonance imaging or hard to delineate even using surgical microscopes, which makes it necessary to use auxiliary tools that function as a guide during the surgical procedure.<sup>[9,17]</sup> In this context, intraoperative electrocorticography (ECoG) has proven to be a useful and effective technique, being currently considered the gold standard for electrical mapping of the epileptogenic zone.<sup>[23]</sup>

Penfield and Jasper first described the ECoG and it is used since then, for the delimitation of the epileptogenic network and the identification of the irritative zones<sup>[15,21]</sup> to guide the neurosurgeon in the resection, confirming a potentially successful disconnection or excision of the epileptogenic mass.<sup>[11,18]</sup> This procedure is useful in adult and pediatric patients, either in temporal or extratemporal lesional focal epilepsy.<sup>[2,5,12]</sup> A meta-analysis including 1070 patients undergoing epilepsy surgery showed that the use of ECoG based on interictal data in patients with focal cortical dysplasia resulted in increased seizure freedom (long-rank test P < 0.001).<sup>[11]</sup> Complete resection of areas showing interictal spikes and ictal spike patterns has been associated with a significant reduction in seizure frequency and intensity in the postoperative outcome.<sup>[8]</sup>

The ECoG, despite having shown favorable results in terms of reduced freedom from post-surgical seizures, has certain limitations.<sup>[11]</sup> Therefore, it is essential to evaluate the use of other methods that allow the precise localization of irritative areas during epilepsy surgery. In this sense, the field of thermography shows a promising panorama, which could provide a valuable tool that allows decision-making in real-time,<sup>[10,13]</sup> overcoming some of the limitations of ECoG, such as the intraoperative time required for its application and its associated costs. The implementation of a standardized and reliable methodology in thermography could represent a significant advance in epilepsy surgery.<sup>[16,20]</sup>

Thermography is based on brain metabolism, where thermal fluctuations during different physiological and pathological processes have been described.<sup>[1,3]</sup> The high consumption of

oxygen and glucose, as well as high blood perfusion, result in a high rate of heat production.<sup>[10]</sup> To explain the correlation of bioelectrical phenomena with metabolic and vascular changes (metabolic neurovascular coupling), it is considered that the brain's temperature may be more closely related to neuronal activity than to changes in cerebral blood flow; therefore, the measurement of the absolute change in local brain temperaure may allow the quantification of neuronal metabolism and synaptic action.<sup>[22]</sup> There are experimental studies where thermography and thermal performance have been used as indicators of physiological activity.<sup>[14]</sup>

In neurosurgery, cortical mapping of functional areas using infrared thermography has demonstrated high sensitivity and specificity, offering an advantage over other discontinuous methods for a sustained evaluation of activation sites simultaneously.<sup>[22]</sup> Experimental studies of infrared thermography in brain tumor surgery reported a temperature difference of 0.5-2.0° in the tumor region, accurately and reproducibly showing the thermal gradients that reflect the physiology of the brain surface and the tumor during the surgical procedure, improved by utilizing thermographic patterns the location of the areas to be resected during surgery.<sup>[10]</sup> Being the case of primary tumors of glial origin that have a lower temperature than the surrounding parenchyma, on the other hand, brain metastases tend to have a hyperthermic behavior, evidencing that the biological heterogeneity of the neoplasms influences the temperature pattern.<sup>[13]</sup> Sadeghi-Goughari et al. performed a surgery based on intraoperative infrared thermal imaging to estimate the temperature and depth of a meningioma, reaching an error of 0.0627 and 0.7015 mm regarding the thermal property and depth.<sup>[19]</sup> The study by Cardone et al., which included 13 patients undergoing resection for brain neoplasms, used an infrared thermography camera to perform intraoperative thermal mapping. The analysis reported an average precision of 90.45%, with a sensitivity and specificity of 84.64% and 93.49%, respectively.<sup>[4]</sup>

Brain mapping of areas using infrared thermography in epilepsy surgery has introduced a new possibility of a noninvasive and real-time tool that allows the localization of irritative zones. Areas with cortical dysplasia with epileptogenic activity identified employing ECoG had lower temperature ranges than normal cerebral cortex and nonirritative dysplastic tissue, usually with a radial heating pattern, where the area of higher temperature is furthest from the irritative zone, with a temperature difference ( $\Delta$ T) of 1.2– 7.1°C. The histopathological results obtained after resection corresponded with diagnoses of type II-A and III-A cortical dysplasia according to the classification of the International League Against Epilepsy (ILAE).<sup>[6]</sup>

In the previous studies, we evaluated a thermosensitive/ thermochromic silicone (TTS) as a qualitative thermographic method. This material provides the observer with a thermal imprint of the contacted surface for 3–30 s, being reactive within a temperature range of 21–38°C. In an initial threestage study, different methods based on thermographic mapping were comparatively tested, including using the TTS. In a series of 10 cases, a 100% correlation was reported between infrared thermography mapping (quantitative method), thermosensitive silicone (qualitative method), and ECoG in the detection of irritative zones in patients with drug-resistant temporal lobe epilepsy.<sup>[7]</sup> Based on this first approach, we sought to establish a cohort of patients that would allow a more precise evaluation and standardize a reproducible thermography mapping method.

#### MATERIALS AND METHODS

Consecutive patients with drug-resistant epilepsy with surgical indications who decided to participate voluntarily in the study were included in the study. We measured brain temperature using two quantitative methods: an infrared thermography camera (Seek Thermal®) and an infrared thermography thermometer with a laser pointer (Fluoreon<sup>®</sup>) and by a qualitative method: the TTS sheet (patent pending). The methodology of this study had three stages for measuring the electromagnetic radiation of the brain using thermography: In the first stage, we used a thermometer with a laser pointer, and the measurements obtained through a perforated silicone grid were recorded and emptied at an Excel table with color gradients, using blue for the coldest point and red for the hottest (Method 1); in the second stage, the use of a high-resolution infrared thermography camera that takes pictures and video was added to the previous methodology (Method 2) and in the third stage, we added the

use of the TTS sheet (Method 3) [Figure 1]. In all cases, we used ECoG as the gold standard to identify irritative areas, and all brain tissue samples obtained were sent to pathology for diagnosis. Three observers evaluated the usefulness of the three methods during the surgeries to reduce kappa errors. Infrared thermography readings were taken as close and perpendicular to the brain as possible, making no contact with the patients. High-resolution photos and videos were taken. The TTS is sterilized and placed directly on the brain surface, as it is flexible and thin. It has a purple basal color and changes to pink when in contact with surfaces with temperatures between 21°C and 38°C with a response time of 3-30 s, depending on the temperature of the surface with which it makes contact, generating a thermal imprint that can be seen with the naked eye, where the purple areas are the coldest areas and the pink areas are the warmest. If the contact of the TTS with the cerebral cortex is maintained for a longer period, it can completely change to pink color by induction and conduction of heat. The relative humidity of the operating room was set at 40%, and its temperature at 20°C in all cases. All patients were within normal vital parameters during the recordings with an anesthetic depth regulated by the bispectral monitor with ranges between 30 and 50.

Bivariate analyses and statistical tests were applied for correlation between the measured variables such as age, age at surgery, gender, chronicity of epilepsy, number of seizures per month, methodology used, type of surgery performed, thermographic pattern obtained, ECoG results, and pathology. The efficacy of the TTS to identify irritative areas identified by the gold standard, that is, ECoG, was analyzed separately.



**Figure 1:** Examples of the three methods described. Method 1: Graph of brain's surface temperatures recorded using the infrared thermometer with laser pointer, where color gradients were added, being red for the warmest point and blue for the coldest point of the recording. Method 2: Example of thermal gradients obtained by the high-resolution thermography camera (capable of taking photos and videos). Method 3: Example of the color contrast achieved by the thermosensitive/thermochromic silicone when in contact with the brain surface. Note that the purple basal color corresponds to the coldest part of the cerebral cortex and pink to the warmest areas, generating a thermal imprint that allows differentiating temperatures with the naked eye, without the need of filters, dyes, contrasts, or special lights.

Table 1: Descriptive demographic statistics.								
	Range	Minimal	Maximal	Media	Standard Error	Standard deviation	Variance	Asymmetry
Age	59	7	66	28.973	1.927	14.934	223.028	0.743
Age at surgery	63	7	70	28.134	1.913	14.818	219.574	0.813
Number of seizures/month	24	2	26	12.45	1.039	8.051	64.828	-0.109
Epilepsy chronicity	42.7	0.3	43	11.871	1.296	10.042	100.846	1.507

#### RESULTS

We included 60 patients, of which 33 were male (55%) and 27 were female (45%). The mean age of the study group was 28.97 years ( $\pm$ 14.93 standard deviation), with a range of 7–66 years. The female average age was 27.82 years and 29.91 for the male, being no considerable variation concerning age and gender. The average seizures per month of the participants were 12.45 ( $\pm$ 8.05 seizures/month) with a range of 2–26 seizures and with a modal interval of 17 seizures in 16 subjects (26.7%), two seizures in 11 subjects (18.3%), and three seizures six subjects (10%) and for the rest of the distribution, the frequency was 2 and 1 monthly seizures. The chronicity of epilepsy was 11.87 years (range 0.3–43 years,  $\pm$ 10.04) [Table 1].

Diverse types of epilepsy surgeries by craniotomy were performed [Table 2]. The frequency and percentage of the thermography methodology applied in the surgeries are detailed in Table 3.

To analyze the average age and its variability concerning histopathology, an error graph was constructed for the distribution of these variables where it is observed that in ILAE type IIIA dysplasia, which was modal, the average age was 30.09 years. Similarly, the highest density interval was recorded in ILAE type III-D dysplasia with an average age of 23.1 years, so there are no correlations between age and histological results. In the last three values of the graph, there was no interval since there was only one subject for each variable [Graph 1].

The Chi-square test was applied from the correlation contingency table versus the methodology, obtaining a significance of  $P \le 0.0001$ . In the subgroup in which the ECoG detected irritative areas (n = 51), adding the results in which there was a correlation with the different methods, the efficiency obtained to detect irritative areas is 94.11%  $(n = 48/51, P \le 0.0001)$  while the infrared thermography mapping method independently has an accuracy of 91.66%  $(P \le 0.0001)$  [Graph 2].

In the subgroup (n = 47) that includes the use of the TTS designed to identify irritative areas due to their lower temperature compared to the rest of the exposed cerebral cortex (methodology 3), we compared its efficacy with the ECoG results, considered the gold standard. In 44 cases (93.61%), the detection of irritative areas by both methods

#### Table 2: Surgeries performed.

Surgery	Number (%)
Right temporal functional lobectomy	14 (23.3)
Left temporal functional lobectomy	21 (35)
Right frontal lesionectomy	5 (8.3)
Left frontal lesionectomy	14 (23.3)
Right frontal lobectomy	1 (1.66)
Right functional hemispherectomy	1 (1.66)
Left functional hemispherectomy	3 (5)
Left biopsy by craniotomy	1 (1.66)

**Table 3:** Frequencies and percentages of the applied thermography methodology.

	Frequency	%
Method 1	2	3.3
Method 2	11	18.3
Method 3	47	78.4
Total	60	100.0



Graph 1: Error bars for pathology result versus age.

coincided completely. In 1 case (2.1%), there was a partial correlation since the ECoG detected only one irritative area, and the TTS detected two areas that were colder than the rest of the cerebral cortex, both being within a dysplasia and in 2 cases (4.2%), there was no correlation between the methods. The TTS has a sensitivity of 95.71% and a specificity of 97.9%



**Graph 2:** Correlation between methodology 1, 2, and 3 and electrocorticography (ECoG) trivariate graphic. (A) Correlation between method 1, method 2, and ECoG; (B) correlation in two hypothermic regions detected with method 1 and 2 with irritative zones detected by ECoG regions; (C) correlation between method 1, 2, and 3 without irritative zones detected by ECoG; (D) only method 2 was used; and (E) correlation between method 1 and 2 in functional hemispherectomy cases. In selected cases, we added contralateral electroencephalography (EEG) in order to document electrical changes after interhemispheric disconnections.

 $(P \le 0.0001)$  to detect hypothermic areas that correlate with the irritative zones detected by ECoG. The time required to make the infrared thermography mappings was 3 min, the TTS 2 min, and the ECoG was 35 min on average. The cost of infrared thermography and the TTS is much lower than that of ECoG.

We independently analyze whether the results of the methodologies used are affected by the number of crises per month or gender, ruling out this possibility. Applying the Chi-square test to the variables of the neuropathology and the methodologies used results, we conclude that the histological diagnosis does not affect the accuracy of infrared thermography mapping or the TTS.

A trivariate histogram was constructed between correlation, thermographic pattern, and epilepsy chronicity, to know the probabilistic intersection between these three variables based on the number of participants, where chronicity does not affect any trend.

When analyzing the frequency and percentage of the thermographic pattern obtained, the modal frequency was radial with 27 cases (45%), followed by tangential with 18 cases (30%) [Table 4].

To analyze the thermographic patterns with the average chronicity, based on age and gender, an error bar graph was constructed. In the radial thermographic pattern concerning gender, the chronicity averages are constant at 15.4 years for males and 14.33 years for females, with very homogeneous distributions. Similar behavior was obtained in the tangential thermographic pattern where the average chronicity in the male was ten years, and in the female, it was 11.6 years, with very compact distributions [Graph 3], so it can be established that neither gender nor chronicity influences the thermographic pattern obtained in this series.

Independently, a scatter graph of the thermographic pattern and age based on chronicity was constructed, where it is observed that there is an increasing trend concerning age and chronicity in the radial and tangential thermographic patterns: As age increases, logically, the chronicity of epilepsy increases, drawing attention to the fact that the tangential thermographic pattern predominates in subjects under 50 years of age [Graph 4].

We did not have any postoperative infections or wound dehiscence, so the different methodologies used do not represent an additional risk for the surgical proceedings.

Table 4: Frequency distribution of thermographic patterns. Cortex temperature values are expressed in Celsius degrees.						
Pattern	Number of cases	Percentage	Example			
Radial	27	45	27.8         29.3         30.5         31.3         32.2         30.4         31.4            27.3         29         30         31.3         32         32.3         31         32.2            27.1         28.2         29.7         30.7         31.7         32         32.4         31.7         32.2           26.6         28.2         29.5         30.4         31         32.2         33.1         32.8         32.1           27.5         28.9         30.5         31.3         31.2         32.2         33.1         32.8         32.1         32.9         33.1         32.8         32.1         33.1         32.9         33.1         33.9         33.1         33.2         32.1         33.1         33.2         33.1         33.9         33.1         33.9         33.1         33.9         33.1         33.4         32.4         33.1         33.4         32.4         33.1         33.4         32.6         33.1         33.4         32.6         33.1         33.4         32.6         33.1         33.4         32.6         33.1         33.4         32.6         33.1         33.4         32.6         33.1<			
Tangential	18	30	30.7         30.8         30.9         30.2         30           30.9         30.7         31         30.4         30.4           31         30.8         31.2         31.1         30.7           31         31.1         31.4         31.3         31.2           30.8         31.3         31.7         31.7         31.3           30.6         31.2         31.8         31.6         31.4           31.1         31.3         31.8         31.7         NV           31.1         31.3         31.8         31.7         NV			
Homogeneous	3	5	°C         °C<			
Hypothermic band	5	8.3	28.2         28.8         28.5         30.2           33.2         32         31.9         31.8           32.9         33.7         33.7         31.9           33.9         33.6         32           34.5         34.2         31.5           34.6         34.1         31.5			
Not performed Total	7 60	11.7 100				

NV: Not valuable. The range of red colors indicates the highest thermal values recorded and the range of blue colors shows the lowest thermal values detected in each case.



**Graph 3:** Error bars for thermographic pattern, gender, and chronicity.



**Graph 4:** Dispersion graphic for age, chronicity, and thermographic pattern.

#### DISCUSSION

The success of epilepsy surgery depends on a delicate balance between disconnection, resection, or efficient inhibition of the epileptogenic mass on the one hand against the preservation of brain tissue to avoid permanent or disabling neurological deficits on the other hand. The challenge is even greater since it is almost impossible to establish these limits with the naked eye or even with the surgical microscope during surgeries. This justifies developing new methods to establish these surgical margins accurately and safely.

Our study population, despite having been diverse in their demographic and pathological variables, had no significant differences, so it represents an adequate study group to establish the usefulness of the different methodologies. We tested three different methods to identify irritative areas, which were compared against the gold standard that is ECoG. Both quantitative infrared thermography mapping (infrared cameras) and qualitative thermography (TTS) methods can identify different brain metabolic patterns due to their heat generation and, therefore, due to their electromagnetic radiation. In general, the  $\Delta T$  is 94.11% correlated with the irritative areas identified by ECoG. Using infrared thermography mapping, four different thermal patterns were obtained, which could be correlated with the metabolic effect of epileptic seizures, and their study may open new lines of research on the pathophysiology of epilepsy.

Few hospitals have the infrastructure to perform ECoG in all epilepsy surgery cases, and in all health systems, it is very important to optimize resources. The TTS costs up to 50 times less than ECoG. Individually, the TTS has a sensitivity of 95.71% and a specificity of 97.9% ( $P \le 0.0001$ ) to detect hypothermic areas that coincide with the irritative zones detected by ECoG.

As none of the thermography techniques used, caused any adverse effects, it can be stated that both infrared thermography mapping and the TTS are safe, with an efficacy comparable to ECoG to identify irritative areas, with a cost and time of application significantly less than the ECoG both in pediatric patients, as in adults, regardless of the chronicity and etiology of epilepsy.

#### CONCLUSION

We consider that the infrared thermography mapping using high-resolution infrared thermography cameras and the TTS are both accurate and safe methods to identify irritative areas in epilepsy surgeries, with the advantage that their application takes only 3 min for infrared thermography and a few seconds for TTS. Both methods have a significantly lower cost than ECoG. The infrared thermography mapping technique and the TTS can also be useful in other neurosurgical indications, in awake surgery, and in general surgery in humans and other species of animals.

#### Ethical approval

Approved on July, 24<sup>th</sup>, 2019, Number: ABC-19-39 by our Institutional Ethics Committee and by our Institutional Review Board at the Centro Medico ABC, Mexico.

#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

#### **Conflicts of interest**

The principal author may apply for a patent of the STT described.

## Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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