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ORIGINAL ARTICLE

Magnetic resonance-guided laser interstitial thermal therapy for the treatment of non-lesional insular epilepsy in pediatric patients: thermal dynamic and volumetric factors influencing seizure outcomes

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Abstract

Purpose To investigate the safety and efficacy of stereoelectroencephalography (sEEG) directed magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) in medically refractory insular epilepsy in pediatric patients, define the relationship between ablation volumes and seizure control, and analyze the relationship between thermal energy and ablation volumes.

Methods A single-institution, retrospective review of pediatric patients with insular epilepsy who underwent sEEG directed MRgLITT over a 10-month period was performed. Perioperative, imaging, and outcome data were analyzed. Seizure outcomes were determined based on Engel score (Engel I versus Engel II–IV). Insula and ablation volumes were measured, and the proportion of insula volume ablated was calculated. Thermal energy was calculated in joules.

Results Four patients underwent sEEG directed MRgLITT of insular epileptogenic foci. The ablation volume was higher in patients with Engel I outcome (3.93 cm^3) compared to Engel II–IV outcome (1.02 cm^3). The proportion of ablation to insula volume was lowest in patients with Engel II–IV outcome (25.09%). The mean energy requirement to create a unit volume of ablation in the insula is 1205.86 J. A linear trend was noted between thermal ablation energy and ablation volume ($R^2 = 0.884$). Over a mean follow-up period of 104 days, three patients were seizure-free (Engel I), and one patient saw significant improvement in seizure frequency (Engel III).

Conclusions The proportion of insula ablated, as well as the volume of ablation, are related to seizure outcome with increasing ablation volumes corresponding to improved seizure control. Further analysis of insula laser ablation thermal dynamics and volumes is needed.

Keywords Stereoelectroencephalography (sEEG) · MRgLITT · Volumetrics · Minimally invasive · Insula

Introduction

Insular epilepsy presents definite diagnostic and therapeutic challenges stemming from anatomic barriers to exploration. The insula is well concealed under the frontal, temporal, and parietal operculum and has extensive reciprocal connections with neighboring epileptogenic areas of the cortex. As a result, scalp electroencephalography (EEG) is unable to adequately localize the epileptic focus to the insula. Clinical and video electroencephalography (vEEG) findings are often misleading due to similarities in symptoms between temporal and insular seizures [1, 2]. Likewise, other non-invasive imaging modalities are helpful but insufficient [3–7]. Invasive intracranial EEG monitoring is often required for precise localization and mapping of insular epileptogenic foci prior to surgical intervention. Subdural grids can provide accurate electrical

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mapping; however, their utility in mapping intrasulcal, deep brain and interhemispheric regions is limited. In addition, implantation of subdural grids requires a large craniotomy, which may be associated with a higher risk of infectious and hemorrhagic complications [8, 9].

The deep seated location of the insula in close proximity to critical structures and vasculature means that open neurosurgical approaches are associated with high risk of complications, particularly strokes, and vascular complications. Thus, minimally invasive techniques are being evolved for the diagnosis and treatment of this challenging form of epilepsy. Stereoelectroencephalography (sEEG) using depth electrodes placed by minimally invasive stereotactic techniques is increasingly favored as a diagnostic tool due to its ability to accurately interrogate deep epileptic foci with high temporal resolution and guide subsequent surgical therapy. Its efficacy and safety profile has been well established in pediatric patients [10–17].

In addition to diagnostic purposes, minimally invasive techniques for destruction of epileptogenic foci using novel energy delivery methods have gained popularity relative to conventional open resection. In addition, these techniques, such as laser ablation, can address multifocal epileptogenic targets [18–22]. Magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) can deliver a precise dose of thermal energy over a predetermined trajectory under real-time MR thermography monitoring. This greatly increases precision while limiting collateral damage [23, 24]. Early evidence of its efficacy and safety is promising in both lesional and non-lesional epilepsy of various etiologies [25–28]. Recently, its use has been extended to insular epilepsy with favorable outcomes [29]. As with any new technique, gaps in knowledge exist. There is limited evidence on the use of sEEG and MRgLITT in concert. To our knowledge, no study has investigated the role of sEEG directed MRgLITT in non-lesional insular epilepsy. There is also a dearth of evidence on the volumetric and thermal dynamic factors influencing seizure control outcomes in patients undergoing this treatment for insular epilepsy.

This study aims to investigate the safety and efficacy of sEEG directed MRgLITT in medically refractory insular epilepsy in pediatric patients, to define the relationship between ablation volumes and seizure control, and to analyze the relationship between thermal energy and ablation volumes.

Materials and methods

Study design

A single-center retrospective study of pediatric patients with medically refractive epilepsy non-lesional insular epilepsy who underwent sEEG directed MRgLITT over a 10-month period was performed. All patients underwent treatment at Children's National Medical Center in Washington, DC. Perioperative, imaging, and outcome data were collected and analyzed. Study approval was received from the Institutional Review Board at Children's National Medical Center (IRB ID Pro00003724).

Patient selection

Patients were selected based on the following inclusion criteria: (1) diagnosed with medically refractory epilepsy defined by the International League Against Epilepsy (ILAE) as "the failure of adequate trials of two appropriately chosen and used anti-epileptic drug schedules to achieve sustained seizure freedom" [30]; (2) absence of a clear lesion on MRI; (3) sEEG confirmed insular epileptogenic focus; and (4) underwent MRgLITT for treatment. Patients were included regardless of prior resections or invasive monitoring.

Presurgical evaluation

All patients underwent video-scalp EEG and brain MRI using our 3T high-resolution epilepsy imaging protocol. Additional tests including functional MRI (fMRI), magnetoencephalography (MEG), and fluorodeoxyglucose-positron emission tomography (FDG-PET) were performed when indicated. Optimal management was determined based on discussions at Multidisciplinary Epilepsy Conference. sEEG was considered when an epileptogenic focus could not be localized from non-invasive methods, insular epilepsy was suspected, discordance was noted between clinical and electrographic findings and in patients with suspected multiple epileptogenic foci. Treatment with MRgLITT was preferred for discrete epileptogenic foci arising from or propagating to the insula and/or opercular cortex and in patients who presented higher risk for open resection.

sEEG technique

All sEEG procedures were performed under general anesthesia using ROSA® robotic stereotactic neuronavigation (Medtech, Montpellier, France) (Fig. 1a). After proper positioning and three-point pin fixation of the head, the patient was registered to previously acquired computed tomography (CT) of the head and brain MRI images. The entry point of each planned trajectory was marked with the assistance of the ROSA robot. A stab incision was made, followed by a 2.4-mm twist drill burr hole. A sEEG depth electrode of standard diameter (1.1 mm) was then introduced into the target point along this trajectory to the appropriate depth and affixed to the skull with a bone anchor (Fig. 1b).

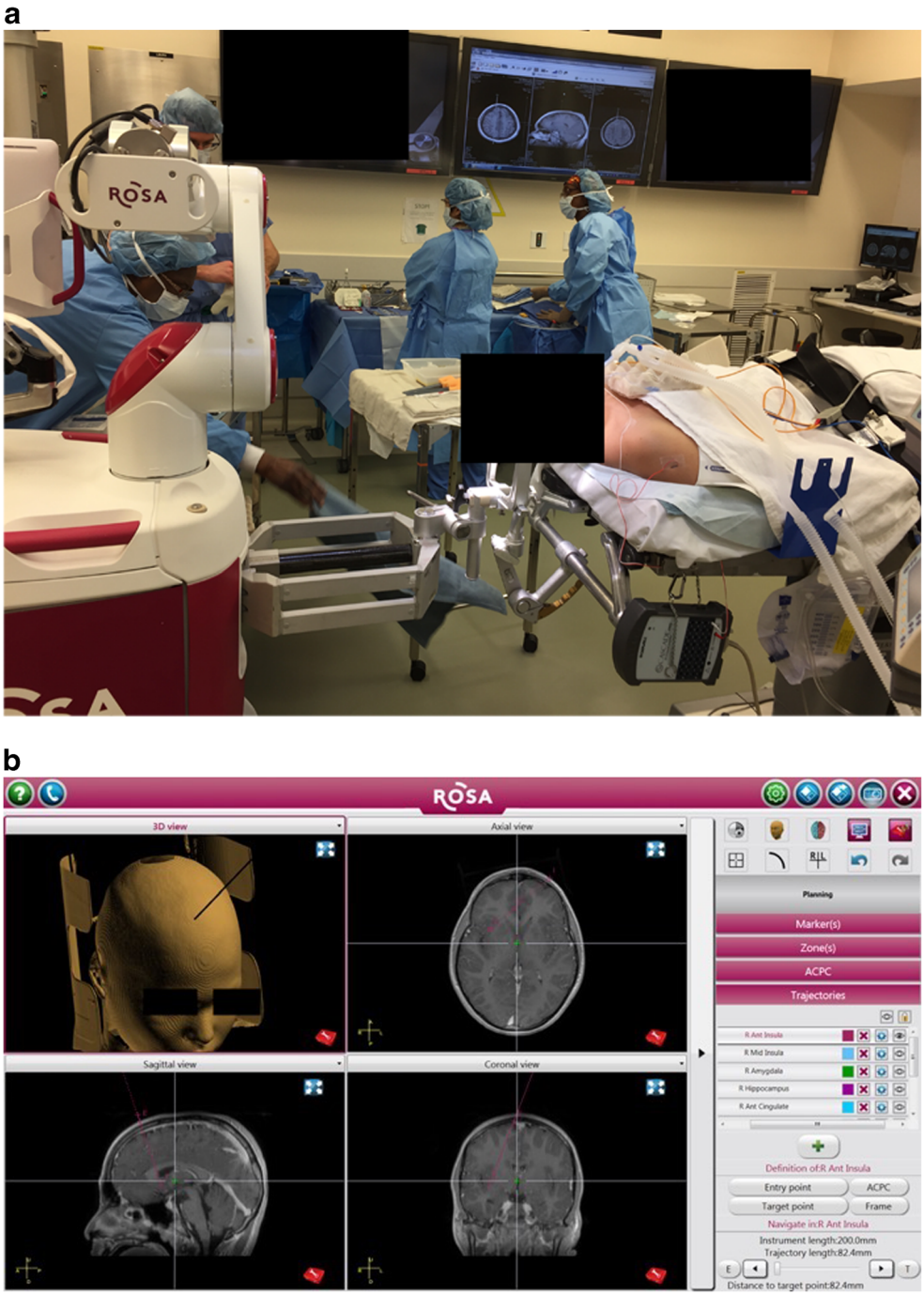

Fig. 1 **a** ROSA robot. **b** Screenshot of ROSA Neuronavigation Software Interface providing stereotactic trajectory guidance at the entry point of each planned trajectory

MRgLITT technique

All MRgLITT procedures were performed using the Visualase® laser interstitial thermal therapy system (Medtronic, Minneapolis, MN) (Fig. 2a). Previously acquired head CT and brain MRI images were used to plan trajectories. Stereotactic trajectory planning was performed using the ROSA robot stereotactic neuronavigation software. Entry and target points were identified using multiplanar reconstructions of the brain. The laser point on the robot was then used to identify the entry point for the insular trajectory. Stab incisions were made at each entry point. A 3.2-mm drill was then used to make a twist drill burr hole, taking into account of the thickness of the bone along this trajectory as determined by CT. Bone anchors were placed and the distance from the upper end of the bone anchor to the target was calculated. Subsequently, 1.6-mm laser cooling tubes were inserted carefully into the target with the metallic stylet in place. Having done this, the metallic stylet was removed, and the laser wire was inserted. Once all the laser wires were inserted, the patient

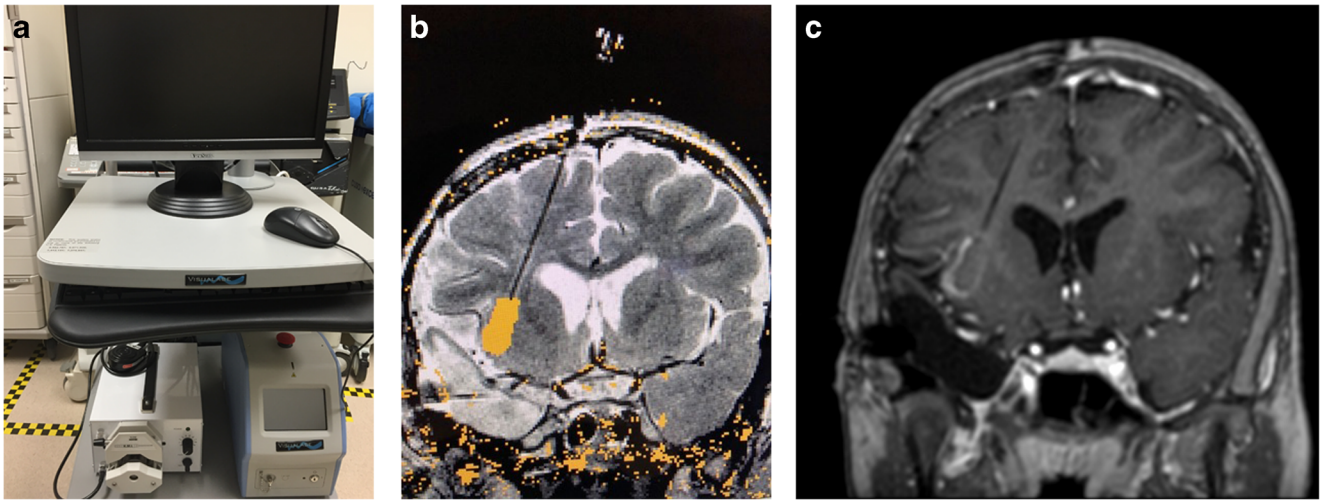

Fig. 2 **a** Screenshot of the ROSA robot software interface. **b** Intraoperative image of the Thermal Damage Estimate (TDE) as shown on the Visualase software system, where the dense orange area depicts the zone of ablation. The trajectory of the laser wire is also visualized. **c** Intraoperative T1 gadolinium enhanced brain MRI depicting the zone of ablation within the right insula

was transferred into the MRI scanner suite to confirm placement. In the MRI suite, T1 SPGR brain scans were obtained. Once placement was verified in the intended targets without any suggestion of bleeding, laser ablation was performed after test doses under real-time MR-guidance (Fig. 2b, c). Following ablation, T1 gadolinium enhanced brain MRI scan was performed to confirm thermal ablation within the intended target. The patient was then returned to the operating room. The cooling tube and bone anchors were removed. A final T1 axial brain MRI was done to confirm no evidence of bleeding following removal of the laser wire. The patient was then brought back to the operating room at the conclusion of the surgery.

Acquisition of volumetric and thermal ablation data

Volumetric measurements of the insula and ablation sites were performed using the OsiriX DICOM Viewer (Pixmeo, Bernex, Switzerland). The insular volume was measured as described by Cohen et al. using preoperative T1 SPGR MRI images [31]. Measurements were made by two independent raters. First, the boundary of the insula was traced in the sagittal view by identifying the orbitoinsular, superior and inferior circular sulci (Fig. 3a). Using the sagittal view as a reference, the insula was then outlined in each slice of the coronal view (Fig. 3b). The coronal view was used for volumetric measurements since it provides the best view of the superior and inferior circular sulci. The insular volume was calculated by aggregating the volumes from each coronal slice. The ablation volumes were measured using T1 contrast-enhanced intraoperative MR images. The boundary of each ring enhancing thermal lesion within the insula or operculum was manually outlined in each slice (Fig. 3c). The ablation volume was then aggregated using Osirix. The proportion of ablation to insula volume was calculated to determine the percentage of insula that had been ablated. The thermal ablation energy deployed

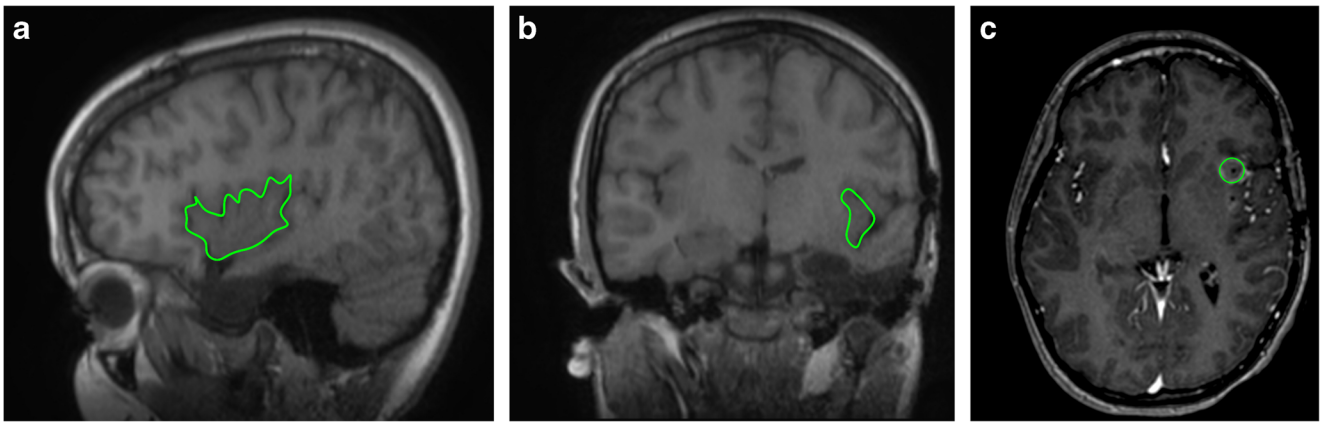

Fig. 3 **a** Preoperative T1 sagittal brain MR imaging depicting the manual tracing of the insula in sagittal section. **b** Preoperative T1 sagittal brain MR imaging depicting the manual tracing of the insula in coronal section. **c** Intraoperative T1 axial brain MR imaging with gadolinium enhancement showing manual tracing of the ring enhancing thermal lesion

Table 1 Summary of patient characteristics and preoperative imaging

Case ID	Age/sex	Prior surgery	vEEG	MEG	FDG-PET	Brain MRI	fMRI
1	18/M	Tailored resection of R frontal lobe epileptic focus	R frontotemporal	R superior frontal and mesio-basal temporal	R anteromedial temporal lobe	Normal	L hemisphere dominant for language
2	15/M	R temporal lobectomy; R amygdalohippocampectomy	R frontotemporal	N/A	N/A	Remnant in R uncus	N/A
3	12/F	Resection of the residual L temporal neocortical seizure focus; L amygdalo-hippocampectomy	L frontotemporal	Multi-focal left hemispheric focus	L anterior temporal	Cavernous malformation in the right mesial temporal lobe, increased in size	L hemisphere dominant for language
4	11/M	None	R frontotemporal	R superior frontal and mesio-basal temporal sources	R anteromedial temporal	Normal	Asymmetric extension of tissue superior and posterior to amygdala. L hemisphere dominant for language

vEEG video EEG, *MEG* magnetoencephalography, *FDG-PET* fluorodeoxyglucose-positron emission tomography, *MRI* magnetic resonance imaging, *fMRI* functional magnetic resonance imaging

was determined by the wattage used at the time of ablation (as entered into the Visualase laser device) multiplied by the duration of application of this energy in seconds. This was reported in joules.

Outcome measurement

The primary outcome was seizure control as determined by the Engel scale. Patients were divided into two groups, Engel I and Engel II–IV, based on reported outcomes at clinic visit and follow-up phone calls. Engel II–IV was grouped together to determine the differences in characteristics between patients that were seizure free and those with persistent seizures.

Statistical analysis

All statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (IBM, Armonk, NY, USA). Significance was set at the 0.05 level. Interrater reliability for insular volumes and ablation volumes as well as the relationship between thermal ablation energy and ablation volume was analyzed using the Pearson correlation. A scatterplot of thermal ablation energy and ablation volume with the best fit line was generated.

Results

Demographics

Four patients ($n = 4$) underwent SEEG directed MRgLITT of insular epileptogenic foci. Mean age at onset of seizure was 3.2 years (range 4 months–7 years), and mean age at surgery was 14 years (range 11–18 years). Two patients had undergone previous invasive EEG monitoring with subdural grid electrodes, subdural strip electrodes, and depth electrodes, while three patients had undergone prior open resections (Table 1). Pathology showed focal cortical dysplasia in two out of the four patients. The number of sEEG electrodes ranged from 5 to 10, and the number of contacts ranged from 28 to 104. Of the four epileptogenic foci, three were located in the island of Reil and one in the operculum (Table 2). Two patients ($n = 2$) underwent MRgLITT of other epileptogenic foci in addition to insular ablation.

Volumetrics and relationship to seizure outcome

The mean insula and ablation volumes across groups were 5.89 ± 1.53 cm^3 and 3.20 ± 1.92 cm^3, respectively. Positive correlation between raters for insula volume ($r = .999$, $p = .001$) and ablation volume ($r = .998$, $p = .002$) demonstrated insignificant interrater variability. The ablation volume was higher in Engel I (3.93 cm^3) compared to Engel II–IV

Table 2 Perioperative data for sEEG

Case ID	Epileptic focus	Laterality	Method of stereotaxy	Electrodes	Contacts
1	Lateral insular operculum	Right	ROSA	5	28
2	Anterior insula	Right	ROSA	6	58
3	Anterior and mid insula	Left	ROSA	10	104
4	Anterior insula	Right	ROSA	9	98

(1.02 cm^3). The percentage of insula ablated was lowest in Engel II–IV (25.10%) (Table 3).

Thermal dynamics and relationship to ablation volume

The energy of ablation was lowest (1417.5 J) in the patient with the lowest ablation volume (1.02 cm^3). The volume-energy curve demonstrated a trend between thermal ablation energy and ablation volume ($R^2 = 0.884$, $p = 0.06$) (Fig. 4). The mean thermal ablation energy across groups (Engel I and Engel II–IV) was 3858.75 J, corresponding to a mean ablation volume of 3.20 cm^3. This translates to an energy requirement of 1205.86 J to create a unit volume of ablation in the insula (Table 4).

Follow-up

The mean duration of follow-up was 104 days. During this time, three patients remained seizure-free (Engel I). Of these three, one patient developed a new type of seizure. Of note, the seizure characteristics seen prior to surgery had resolved completely. One patient had persistent seizures post-MRgLITT, although the seizure frequency had decreased from two to three times per day preoperatively to one episode every 3 weeks (Engel III).

Discussion

MRgLITT is an innovative, minimally invasive strategy for the treatment of non-lesional insular epilepsy in pediatric patients. In our cohort of patients, the proportion of insula ablated, as well as the volume of ablation itself, were found to be related to seizure outcome, with increasing ablation volumes corresponding to improved seizure control. Our work is the first, to our knowledge, to perform a volumetric and thermal dynamic assessment of insular laser ablation and analyze the relationship of these factors to seizure outcomes. Furthermore, this is the first paper to exclusively analyze sEEG directed MRgLITT in pediatric patients with insular epilepsy.

Efficacy and safety of sEEG guided MRgLITT in insular epilepsy

In our cohort, non-invasive monitoring was unable to localize the epileptogenic focus to the insula in all four patients. Subsequent exploration with sEEG accurately led to the insular or opercular epileptogenic focus. Our findings confirm existing evidence that intracranial monitoring is crucial when an insular or perisylvian focus is suspected [2, 17, 21]. At our institution, we have had a positive experience and outcomes with sEEG and MRgLITT, along with a negligible complication rate. Once the insula is implicated, patients are offered the option of open resection or MRgLITT. From our experience, patients often preferred the minimally invasive option. In our series, 75% ($n = 3$) of patients achieved seizure freedom after undergoing MRgLITT. The single patient (case ID 1) whose seizures persisted post-ablation experienced a significant reduction in seizure frequency. It is important to note that this patient has not been compliant with medications. Therefore, it is unclear whether the etiology of the breakthrough seizures is poor compliance, limitations of the ablation, or a combination thereof.

Perry et al. reported 50% seizure freedom in their cohort of pediatric patients with lesional and non-lesional insular epilepsy. This difference in seizure freedom could be attributed to their longer mean follow-up (20 months).

Table 3 Volumetric measurements and relationship to seizure outcome

Case ID	Ablation target	Laterality	Insula volume (cm^3)	Ablation volume (cm^3)	Ablation to insula volume (%)	Engel score
1	Lateral insular operculum	Right	4.06	1.02	25.10	III
2	Anterior insula	Right	7.32	2.16	29.52	I
3	Anterior and mid insula	Left	6.96	4.90	70.45	I
4	Anterior insula	Right	5.21	4.73	90.87	I
	Mean ± SD across groups		5.89 ± 1.53	3.20 ± 1.92	53.98 ± 31.96	

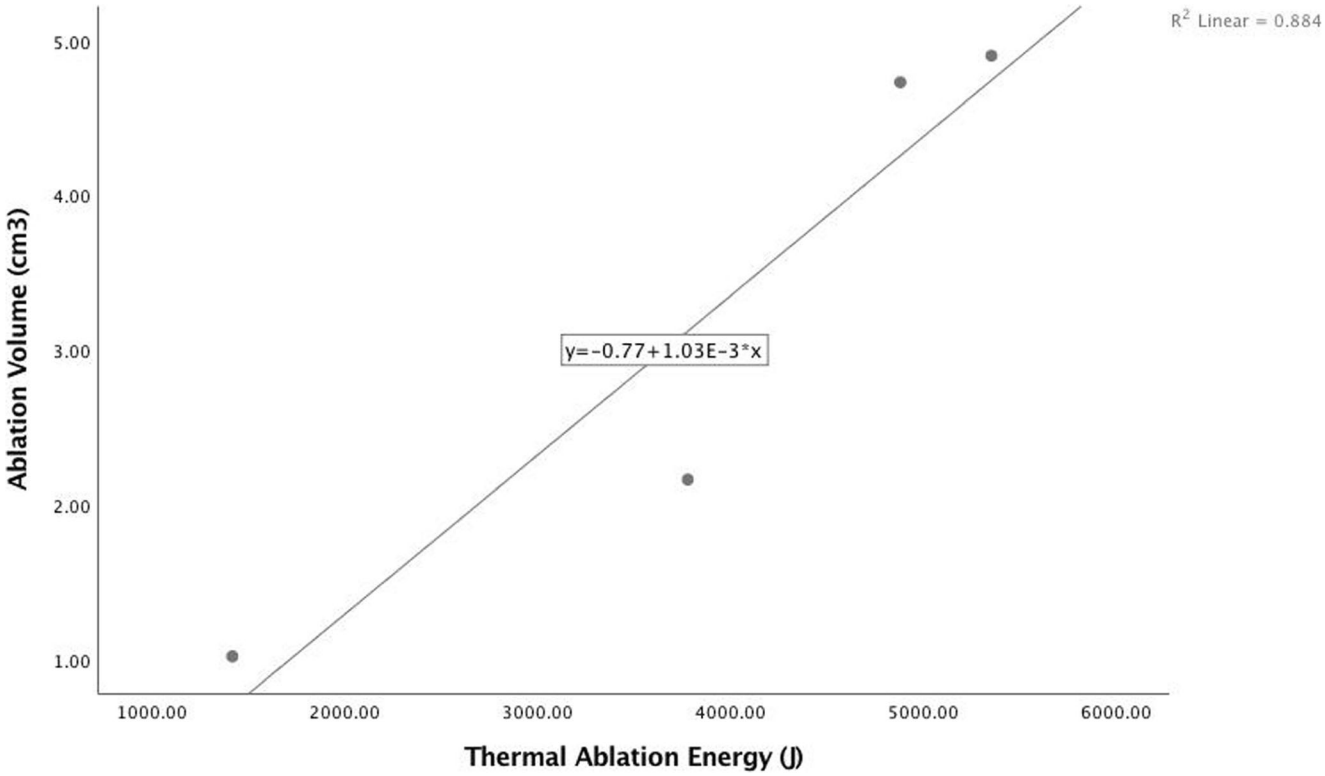

Fig. 4 Volume-energy curve demonstrating a linear association between thermal ablation energy (J) and ablation volume (cm^3)

The authors also reported transient mild hemiparesis in six out of seven patients and expressive language dysfunction in one patient [29]. None of the patients in our series experienced any complications postoperatively. Our success rate was comparable to open insular resection, where seizure freedom rates range from 63 to 89% [18–22, 32]. Despite the small size of our cohort, the results suggest that sEEG directed MRgLITT is a safe and effective initial treatment option in pediatric patients with medically refractory non-lesional insular epilepsy.

Volumetrics and relationship to seizure outcome

Our results suggest that ablating larger volumes of the insula results in improved seizure outcomes. Our patient (case ID 1) with the lowest Engel score in our series (Engel III) also had the lowest ablation volume (1.02 cm^3). This makes intuitive sense since a larger ablation volume is more likely to disrupt a wider array of epileptic networks resulting in a large-scale signal disruption with subsequent improvement in seizure outcome. Although our sample size was not large enough to perform adequately powered statistical analysis, there appears to be a correlation between ablation volume and seizure control. Volume assessments of the amygdala and hippocampus in mesiotemporal sclerosis have not shown a significant difference in total ablation volume or percent ablation volume between Engel groups [33–38]. However, it may not be accurate to extrapolate these results to the insula given the differences in volumes and anatomy of these structures. One can postulate that a critical ablation volume must be reached to disrupt a critical number of epileptic networks, particularly in a large, highly epileptogenic structure such as the insula. Larger studies will be needed to establish this quantitatively.

Table 4 Perioperative data for MRgLITT

Case ID	Ablation target	Laterality	Method of stereotaxy	Wattage and duration of ablation (W/s)	Energy of ablation (J)
1	Lateral insular operculum	Right	ROSA	10.5 W × 135 s	1417.50
2	Anterior insula	Right	ROSA	10.5 W × 180 s, 10.5 W × 180 s	3780.00
3	Anterior and mid insula	Left	ROSA	10.5 W × 180 s, 10.5 W × 165 s, 10.5 W × 165s	5355.50
4	Anterior insula	Right	ROSA	10.5 W × 165 s, 10.5 W × 150 s, 10.5 W × 150 s	4882.50
					Mean = 3858.75

W watts, *J* joules

Thermal dynamics and relationship to seizure outcome

We found a strong linear trend between thermal ablation energy and ablation volume ($R^2 = 0.884$). This suggests that higher ablation volumes could be achieved either by increasing the wattage, by applying this thermal energy for a longer duration, or both. This has implications for seizure control outcomes since both thermal ablation energy and corresponding ablation volumes were higher in our Engel I group. Therefore, it appears that ablation volume, amount of laser thermal energy, and seizure control outcomes are related. Larger studies will be needed to definitively quantify the association between these variables. While reports have tried to understand the thermal dynamics of brain tissue during laser ablation therapy, there is no normative data on the amount of energy required to cause a unit amount of ablation in the insula. Most neurosurgeons assume empirical values for the duration and energy of ablation based on experience and trial and error. Our experience suggests that 1205.86 J of energy is required to achieve 1 cm^3 of ablation in the insula.

Location and seizure outcome

Patients who achieved seizure freedom ($n = 3$) were those in which the seizure focus as identified by sEEG appeared to be restricted to the island of Reil. Our patient (Case ID 1) with persistent seizures post-ablation had an epileptogenic focus localized to the lateral insular operculum. This contrasts the findings of Weil et al. where ablation localized to the insula did not result in significantly different seizure outcomes compared to ablation that included opercular regions [19]. Based on our results, it is possible that a focus outside of the island of Reil is not as amenable to ablation. A case could be made to limit laser guided ablation to the island of Reil and consider resection if the epileptogenic focus extends beyond this region to the opercular regions.

Limitations

Our study has several limitations. (1) The retrospective design of the study introduces an inherent risk of bias in data analysis. (2) Our study was underpowered with an unequal distribution of cases between the outcome groups making it difficult to perform appropriate correlation and predictive statistical analyses. (3) Our follow-up period is short; however, our findings provide an overview of the short-term outcomes following sEEG directed MRgLITT and offer direction for further studies.

Conclusion

The proportion of insula ablated, as well as the volume of ablation, is related to seizure outcome in our cohort of patients. The volume-energy curve shows a strong association between thermal ablation energy and ablation volumes and seems to correspond to improved seizure control. sEEG directed MRgLITT is also an effective and safe minimally invasive technique for the treatment of medically refractory non-lesional insular epilepsy in pediatric patients. Further analysis of ablation thermal dynamics and volumes is critical to define factors related to improved seizure control outcomes for this new and promising treatment modality.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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