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Seizure and anatomical outcomes of repeat laser amygdalohippocampotomy for temporal lobe epilepsy: A single-institution case series

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ABSTRACT

Objective: In patients with treatment-refractory temporal lobe epilepsy (TLE), a single stereotactic laser interstitial thermotherapy (LITT) procedure is sometimes insufficient to ablate epileptogenic tissue, particularly the medial structures often implicated in TLE. In patients with seizure recurrence after initial ablation, the extent to which a second ablation may achieve improved seizure outcomes is uncertain. The objective of this study was to investigate the feasibility and potential efficacy of repeat LITT amygdalohippocampotomy as a worthwhile strategy for intractable temporal lobe epilepsy by quantifying changes to targeted mesial temporal lobe structures and seizure outcomes.
Methods: Patients who underwent two LITT procedures for drug-resistant mesial TLE at our institution were included in the study. Lesion volumes for both procedures were calculated by comparing post-ablation intraoperative sequences to preoperative anatomy. Clinical outcomes after the initial procedure and repeat procedure were classified according to Engel scores.
Results: Five consecutive patients were included in this retrospective case series: 3 with right- and 2 with left-sided TLE. The median interval between LITT procedures was 294 days (range: 227–1918). After the first LITT, 3 patients experienced class III outcomes, 1 experienced a class IV, and 1 experienced a class IB outcome. All patients achieved increased seizure freedom after a second procedure, with class I outcomes (3 IA, 2 IB).
Conclusions: Repeat LITT may be sufficient to achieve satisfactory seizure outcomes in some individuals who might otherwise be considered for more aggressive resection or palliative neuromodulation. A larger study to establish the potential value of repeat LITT amygdalohippocampotomy vs. other re-operation strategies for persistent, intractable temporal lobe epilepsy is worth pursuing.

1. Introduction

Approximately one-third of patients with epilepsy are refractory to medical management [1–3]. Anterior temporal lobectomy (ATL) remains the gold standard for achieving seizure freedom in temporal lobe epilepsy [4]. However, at many institutions, stereotactic magnetic resonance imaging (MRI)-guided laser interstitial thermotherapy (LITT) has rapidly become a first-line option that avoids the morbidity of a craniotomy and potentially unnecessary resection of brain tissue [5]. Inferior outcomes of LITT amygdalohippocampotomy relative to ATL are thought to be due to insufficient ablation of epileptogenic mesial temporal lobe structures, which can at least be partially overcome by using multiple laser trajectories [6,7], but may also be due to a more lateral neocortical epileptogenic zone in some individuals, or extra-temporal ictal

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onset zone. Although estimates have generally been limited by sample size, roughly half of patients who undergo LITT for temporal lobe epilepsy (TLE) do not achieve complete seizure freedom [8]. In patients who do not achieve satisfactory seizure reduction after one LITT procedure, undergoing a second LITT procedure targeting residual tissue may be considered, with risks and benefits weighed against those of alternative therapies such as ATL, deep brain stimulation, responsive neurostimulation, or medical management.

Clinical outcomes for patients who underwent two LITT procedures have thus far been described incidentally and/or within small cohort studies [9]. In these reports, the initial procedure was deemed a technical failure or an inappropriate choice of procedure from the outset, and little interest was taken in the specific volumes that were and were not lesioned [10,11]. Although not directly comparable, the concept of serial LITT procedures as a safe and effective general approach has been described in the field of neuro-oncology [12,13]. There is limited understanding of both the qualitative and quantitative characteristics of targeted structures in the initial and repeat procedures.

In this initial retrospective cohort, we hypothesize that targeting even small volumes of residual tissue in mesial temporal lobe structures after a prior LITT treatment can lead to significant and meaningful clinical improvement, and that this remaining volume of residual tissue is more likely to be the cause of persistent seizures than a lateral/neocortical temporal lobe source. We quantified volumetric anatomical changes and their association with the clinical outcomes to demonstrate the rationality and feasibility of this approach. Through this pilot study, we aim to provide further evidence in support of repeat LITT as an option for patients seeking a minimally invasive treatment for their TLE.

2. Methods

2.1. Patient population

After IRB approval (Lifespan IRB #415821), all patients who underwent two separate LITT procedures for mesial temporal lobe epilepsy (mTLE) at our institution between 2017 and 2022 were included in this study. Patients were deemed candidates for both initial and subsequent repeat stereotactic amygdalohippocampotomy by the institution's comprehensive epilepsy team as well as shared decision-making with each patient, and consent was obtained for the surgical procedures from each patient or their representative. Patients who had previously undergone laser amygdalohippocampotomy but were not seizure free were evaluated for possible additional ablation or resection. Surgical candidacy was determined based on radiological and also, in one case, electrophysiological data [14]. If on postoperative MRI there was evidence of residual medial temporal lobe tissue, a "completion" LITT procedure was offered as a means to achieve the optimal technical result. Patients were informed that anterior temporal lobectomy was a more likely means of achieving seizure freedom, but all preferred at least one more attempt at a minimally invasive approach given their positive experience with the first operation. Given the retrospective nature of this study and that no identifiers of the patients were included, consent for participation in this study was not required.

2.2. Surgical technique

We employed a surgical technique that has been previously described [7,15]. Briefly, a surgical plan for the Visualase (Medtronic, Minneapolis, MN, USA) procedure was created on FHC StarFix (FHC Inc., Bowdoin, ME) planning software, with trajectories roughly concordant with the simulated optimal trajectories. A two-laser or one-laser approach was chosen depending on the number of trajectories required to access the 3-dimensional geometry of the amygdalohippocampal complex, accounting for previously ablated structures for the second procedure. A 3D-printed stereotactic frame was created to guide placement of the fiber optic laser catheters based on earlier-stage implantation of fiducial screw skull anchors. Trajectories were posterior, targeting the length of the hippocampus, and/or postauricular, targeting the amygdala and piriform cortex. After the laser catheter(s) was (were) placed in the OR with intraoperative CT confirmation of trajectory, the patient was transported to the MRI scanner. Laser ablation was started in deep structures and the fiberoptic catheter was retracted stepwise in order to ablate the entire length of the hippocampus and/or width of the amygdala. Protective low-temperature markers were placed on critical structures including the 3rd nerve, midbrain, and optic radiations. After confirmatory post-procedure MRI imaging was obtained, all hardware was removed. Patients were extubated and recovered for generally 1 inpatient day, and then discharged home.

2.3. Lesion analysis

All patients received T1-weighted, gadolinium-enhanced MRI sequences for routine preoperative planning. The post-ablation intraoperative post-gadolinium MRI sequences for each LITT procedure were registered to preoperative MRI sequences using a non-rigid algorithm using the *3dAllineate* and *3dQwarp* commands in AFNI (v23.0.04, National Institute of Mental Health [16,17]). (Details regarding the specific parameters used can be found in the code repository published at https://doi.org/10.5281/zenodo.8122521.) Then, all sequences were transformed to Montreal Neurological Institute (MNI) space (i.e., registrations: intraoperative MRI → preoperative MRI → MNI space). All registrations were verified visually to be well within an acceptable fit. Lesion volumes for both procedures were calculated in AFNI by first subtracting preoperative (i.e., surgery-naive brain) anatomical sequences from post-ablation intraoperative sequences to obtain a voxel-wise comparison. Lesions were then preliminarily segmented by thresholding voxels to isolate the hyperintense gadolinium-enhanced lesion borders. The remainder of the lesion was refined manually to the outer edge of the same boundary (i.e., including the hyperintense lesion border).

The medial temporal lobe (MTL) was defined as the combination of the amygdala, hippocampus, entorhinal cortex, perirhinal cortex, and piriform cortex. The MNI 2009 Glasser atlas in AFNI was used to determine the boundaries of these subcortical structures (Fig. 1). The volume lesioned by each ablation was determined by calculating overlap between each anatomical structure and each lesion.

2.4. Clinical measures

Clinical outcomes were determined by a retrospective chart review of postoperative neurosurgery and neurology office encounters. Seizure freedom after the initial procedure and repeat procedure was classified according to the Engel scale [18]. Required follow-up time was at least 3 months.

3. Results

3.1. Patient characteristics

A total of 5 patients underwent a second LITT procedure for unilateral mesial temporal lobe epilepsy at a single institution

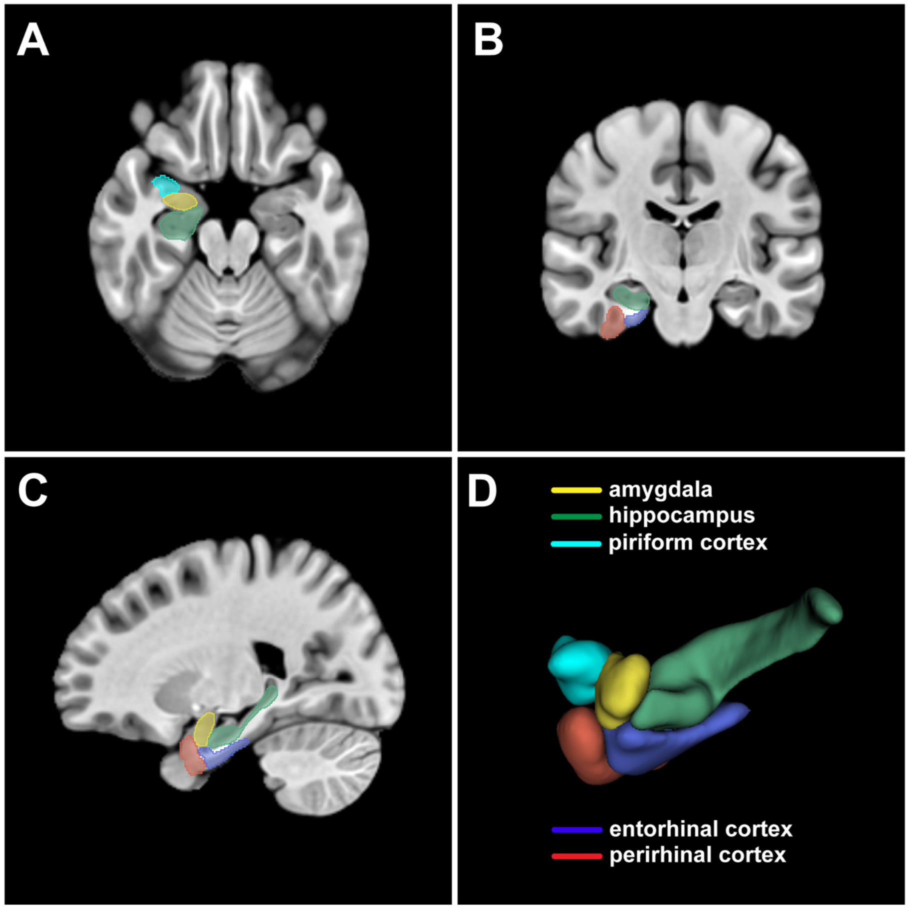

Fig. 1. Segmented medial temporal lobe structures of interest in MNI space. **(A)** Axial, **(B)** coronal, and **(C)** sagittal views of medial temporal lobe structures targeted during LITT. **(D)** Perspective from a superomedial angle view of a 3D model of the amygdalohippocampal complex.

between 2017 and 2022. All patients were female with a median age of 26 years (range: 6–46), with 3 adult and 2 pediatric patients (Table 1, listed chronologically). Three subjects had right-sided disease (mesial temporal sclerosis), whereas the remaining two had left-sided disease, with no bilateral disease. Further details regarding relevant features of their epilepsy are characterized in Table 2. Median follow-up interval was 626 days (range: 184–1193), with a minimum follow-up of 626 days for pediatric patients. Patients who underwent a one-trajectory initial procedure had two trajectories for the subsequent surgery and vice versa. Thus, all five subjects ultimately had three total laser trajectories across two procedures. No complications or adverse effects were attributed to any of the procedures.

3.2. Residual tissues after initial LITT

After the first ablation, 3 of the 5 patients experienced Engel class III outcomes, with 1 patient experiencing a class IB outcome and the last experiencing a class IV outcome (Table 3). Changes to MTL structures for each patient across surgeries are shown in Fig. 2. In each case, residual medial tissue was considered to be the likely source of unsatisfactory outcomes by reviewing intra- or postoperative imaging demonstrating incomplete ablation of mesial structures. Thus, the primary targets of the second procedure were this residual tissue. Depending on the patient, these targeted regions included parts of the medial amygdala, perirhinal cortex, or more broadly, the medial uncus. In general, the volume of newly ablated tissue was less for the second procedure. Subject 3, in particular, only had a change of -77 mm^3 in the amygdala, though this volume may have been slightly underestimated by conservative estimates of the amygdala and hippocampus in the applied atlas. A comparison of intraoperative ablation volumes between procedures for a subject who ultimately achieved class IA outcome is shown in Fig. 3. The second LITT targeted the small volume of medial tissue remaining after the first procedure. One patient (subject 2) was unique in that residual tissue was localized

Table 1
Summary of subject and procedure characteristics.

Subject	Age (years)	Sex	Laterality	1st LITT	Residual Tissue	2nd LITT	Follow-up Duration (days)
1	46	F	R	1-trajectory	Anteromedial amygdala	2-trajectory	219
2	39	F	R	2-trajectory	Lateral hippocampus	1-trajectory	1193
3	6	F	R	2-trajectory	Medial amygdala	1-trajectory	618
4	15	F	L	2-trajectory	Medial uncus	1-trajectory	443
5	26	F	L	1-trajectory	Medial uncus/perirhinal cortex	2-trajectory	184

Median procedure interval = 294 days (range = [227–1918]).

Table 2
Longitudinal characterization of seizure and neuropsychological data for each subject.

Subject	Age of Diagnosis (years)	Seizure Frequency	Seizure Semiology	Imaging Findings	Available Phase II Monitoring Findings	Available Neuropsychological Summaries		
						Initial	After 1st Ablation	After 2nd Ablation
1	18	2–3/month	Complex partial seizures with preceding auras, lip smacking automatisms	MRI with mesial temporal and hippocampal lobe atrophy, PET with hypometabolism of right temporal lobe.	N/A	Low risk for cognitive decline after resective surgery.	N/A	Mild deficits in processing speed and executive function. Intact memory. Self-reported higher levels of depression. (Evaluation completed 3 years post second ablation).
2	10	1/month	Hand twisting with increased tone, predominantly on the left, automatisms of the mouth, followed by post-ictal state.	MRI brain with progressive cerebellar atrophy. PET with hypometabolism of right temporal lobe.	N/A	Low risk for cognitive decline after intervention on right temporal lobe.	N/A	N/A
3	1	2/month	Focal unaware epilepsy, arrest of action, loss of bladder control, and speech impairment.	MRI with increased T2/Flair signal within right hippocampal head and medial temporal lobe. PET with diminished activity in the inferior and medial right temporal lobe.	N/A	Some degree of frontal lobe dysfunction and no clear language/memory impairment.	Stability of skills tested compared with preoperative baseline. (Evaluation completed 8 months post first ablation).	N/A
4	9	3–4/month	Staring spells, abdominal pain, lip smacking.	MRI brain with hyperintensity of left hippocampal formation and diminished size. Consistent with mesial temporal sclerosis.	N/A	Relative weakness in memory function. Cognitive skills average to above average.	Repeat testing commensurate with prior evaluation. No new cognitive or memory deficits. (Evaluation completed 7 months post ablation).	N/A
5	2	2–4/month	Lip smacking, tensed up wrists close to body, visual impressions. Occasional tongue biting.	MRI with left mesial temporal sclerosis, PET with left temporal medial lobe hypometabolism.	SEEG prior to second intervention revealed epileptic activity within the left hippocampal and amygdala regions.	Left-sided language dominance. No cognitive or memory deficits.	No cognitive or memory deficits. (Evaluation completed 14 months post ablation).	N/A.

to the lateral hippocampal body rather than to the medial amygdalohippocampal complex or uncus. (All de-identified imaging data can be found in the repository published at https://doi.org/10.5281/zenodo.8122521.)

3.3. Clinical significance of residual tissue ablation

All patients experienced improved seizure outcomes after a second LITT, with 4 of 5 achieving an Engel class I outcome after initially being classified as Engel class III or worse, and the 5th experiencing a change from a IB to IA outcome. Two subjects (40%) ended the study with class IB outcomes instead of IA outcomes, with the remaining three (60%) subjects experiencing complete seizure freedom. An aggregate of ablation volumes highlighting changes in ablation distribution between the two procedures is illustrated in Fig. 4. While one adult patient (subject 5) experienced a subjective decline in semantic memory following the first procedure that was not reflected on follow-up objective neuropsychiatric testing, there were no further cognitive deficits reported by patients after the second surgery, though formal post-operative neurocognitive assessments and neuropsychiatric evaluations were not routinely performed before and after each procedure, particularly in the adult patients.

4. Discussion

In this small, initial retrospective case series, five subjects with incomplete seizure freedom after an initial stereotactic laser amygdalohippocampotomy for mTLE underwent a repeat ablation. All 5 experienced measurable clinical improvement, with 100% Engel I outcomes at least 3 months for adult patients and at least 12 months for pediatric patients after the second procedure and 3 of 5 achieving complete seizure freedom (Engel IA). Although the volume of additionally ablated tissue was small compared with total lesion volume, the medial tissue targeted by most of the secondary procedure seemed to greatly affect clinical outcomes. In conjunction with previous case series and a developing understanding of epileptogenicity in TLE, the early results presented here provide further imaging-correlated clinical evidence in support of repeat LITT as a viable and potentially highly effective option for

Table 3
Ablation volumes and clinical seizure outcomes.

Subject	Structure	1st Ablation: Residual Volume		Engel Outcome	2nd Ablation: Residual Volume		Additional Ablation		Engel Outcome
		Absolute (mm^3)	Relative (%)		Absolute (mm^3)	Relative (%)	Absolute (mm^3)	Relative (%)	
1 Target:	MTL	10,806	75.2	IIIB	9610	66.9	1196	8.3	IB
	Amygdala	872	76.0		680	59.3	192	16.7	
2 Target:	MTL	10,954	76.3	IIIA	8529	59.4	2425	16.9	IA
	Hippocampus	1522	37.0		740	18.0	782	19.0	
3 Target:	MTL	7892	55.0	IIIA	7815	54.4	77	0.5	IB
	Amygdala	415	36.2		338	29.5	77	6.7	
4 Target:	MTL	12,095	78.7	IB	11,593	75.5	502	3.3	IA
	Amygdala/Hippocampus	3386	59.7		2899	51.1	487	8.6	
5 Target:	MTL	11,252	73.2	IVA	10,283	66.9	969	6.3	IA
	Perirhinal cortex	4465	90.4		3496	70.8	969	19.6	

A complete spreadsheet of ablation volumes can be found in Supplementary Table 1 and the data repository published at https://doi.org/10.5281/zenodo.8125353.

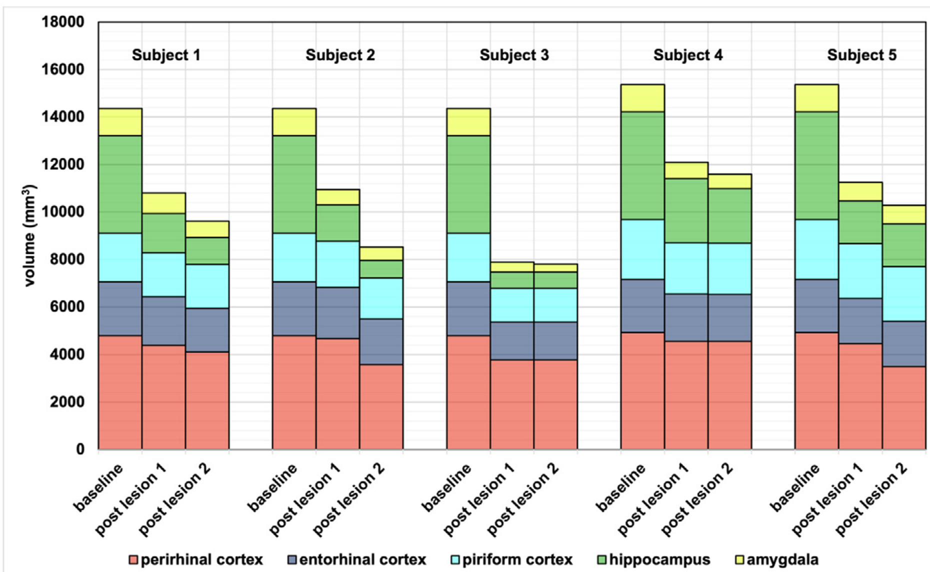

Fig. 2. Changes to MTL structures across LITT procedures for the 5 subjects in this cohort. The volumes of mesial temporal structures are illustrated for baseline anatomy and after each ablation.

addressing incomplete seizure freedom after initial LITT amygdalohippocampotomy.

4.1. Repeat LITT versus ATL

Although ATL has long been the "gold standard" approach with respect to achieving seizure freedom for patients suffering from temporal lobe epilepsy, it can be associated with significant cognitive impairment. In particular, memory deficits have been a known risk after ATL, particularly left-sided resection, for decades [19–21]. LITT, however, has been shown to better preserve verbal memory to a significant degree when directly compared with open resection [22]. Notably, no patients in this cohort reported additional cognitive deficits, including memory impairment, after the second LITT. In addition to achieving complete or near-complete seizure freedom, these patients were spared potentially unnecessary resection of areas in the anterior/lateral temporal lobe as well as the higher morbidity of open craniotomy. Moreover, secondary ablations would pose no hinderance to future ATL if a patient still experienced seizures after the repeat procedure. Conversely, there has been a case report of successful LITT after failed ATL, further demonstrating its utility as a "clean-up" approach to residual medial structures [23]. Nonetheless, patients may decline future surgeries altogether if they undergo any procedure with unsatisfactory results. Indeed, anecdotally, the last patient (subject 5) in this cohort spent several months considering options and sought multiple opinions regarding the risks and benefits of further surgery. Comprehensive epilepsy programs must consider all these factors when treating these particularly challenging cases. We believe this case series to be an initial step in providing support for pursuing LITT as an option in patients in which the procedure did not provide complete seizure freedom previously. This "proof of concept" report aims to provide further insight into this approach for clinicians who may have not considered this procedure as a surgical option and opted instead for ATL.

4.2. Use of multiple trajectories

There are a few known limitations to LITT that are overcome by the described approach of additional ablations. First, the curvilinear contour of the amygdalohippocampal complex may not be sufficiently lesioned by the single rigid laser catheter used in conventional LITT procedures. To that end, multiple laser trajectories can be used to improve coverage [7]. In this case series,

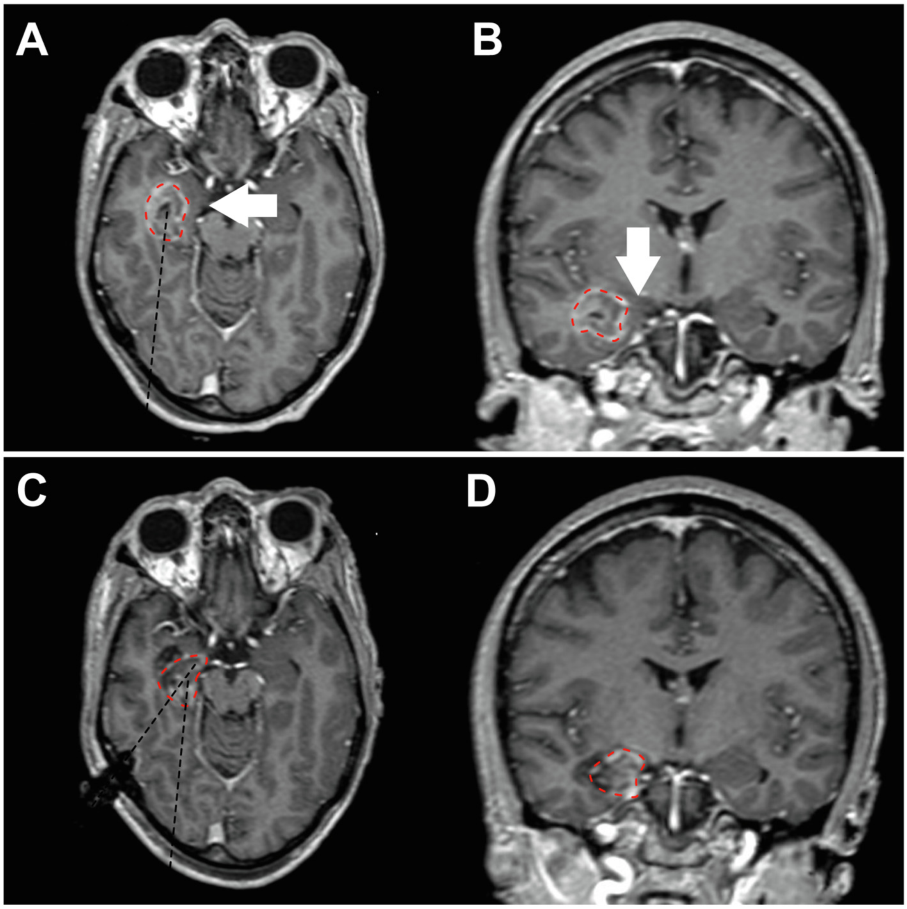

Fig. 3. Post-ablative intraoperative lesions for consecutive LITT procedures. Lesions are outlined in red dashed lines. On axial slices, laser catheter trajectories are projected orthogonally in plane by dashed black lines. **(A, B)** Representative axial and coronal intraoperative sequences with initial results of single-trajectory ablation are shown. A region of amygdala and uncus medially remains unaffected (white arrows). **(C, D)** Equivalent views after a second, two-laser ablation procedure demonstrate expanded coverage encompassing the most medial extent of the mesial temporal lobe. This patient (subject 2) ultimately experienced complete seizure freedom (class IA outcomes).

all subjects eventually required three trajectories to achieve class I outcomes. Theoretically, they may have benefited from additional trajectories during their initial procedure, though the question of whether 1 or 2 lasers should consistently be used is a topic of ongoing interest, with some evidence supporting the use of at least 2 in most cases [7]. Although there was no predetermination that all patients should receive a total of 3 trajectories, this result was simply an artifact of the anatomy of interest and the geometry of safe corridors for access. In other words, for these patients at least, 3 laser trajectories ultimately seemed to provide the most optimal coverage of the MTL. Further, epileptologists and neurosurgeons may preemptively counsel patients about a stepwise approach to achieving an optimal result via "minimally sufficient" intervention, and so highlight the possibility of additional procedures.

4.3. Ablation of additional epileptogenic structures

Selective lesions of the amygdala and hippocampus, both individually and in tandem, are well-established approaches to treating mTLE due to their known epileptogenesis [24]. Lateral trajectories and sparing of the mesial hippocampal head are known risk factors for persistence of seizure after LITT [6]. In this small cohort, the repeat ablations for the two subjects who experienced IB instead of IA outcomes were both specifically targeting residual amygdala tissue. The medial amygdala and uncus may be viewed as easily "missed" epileptogenic tissue after the initial procedure given the residual volumes in Table 1. On the other hand, this result shows that the serial approach would ultimately provide higher specificity than temporal lobectomy, in which resection of eloquent, non-epileptogenic tissue may occur. Another possible distinction between those who experienced IB versus IA outcomes could be that their epileptic networks extended to involve the lateral temporal or extra-temporal cortex. In addition, however, there is emerging clinical evidence to support decades of basic science research that the other (i.e., non-amygdalohippocampal) mesial temporal structures analyzed in this study contribute significantly to epileptogenesis, both independently and via connections with the amygdala and hippocampus.

Specifically, resection or lesions of the piriform cortex have consistently demonstrated association with improved seizure freedom [25–27]. This effect may be mechanistically explained by substantial projections from piriform cortex to amygdala which have been posited to mediate the "kindling" phenomena seen in rodent models of temporal lobe epilepsy [28–30]. Although there is not yet convincing evidence for the independent value of entorhinal cortex resection or ablation, many consider it a critical node in seizure initiation and propagation given its position in the medial limbic circuit along with a considerable number of animal models of mTLE demonstrating its epileptogenic physiology [31–33]. Therefore, to optimize the success of LITT amygdalohippocampotomy, the technical goal should likely include ablation of these structures with as many trajectories as are necessary and safe. Even when small

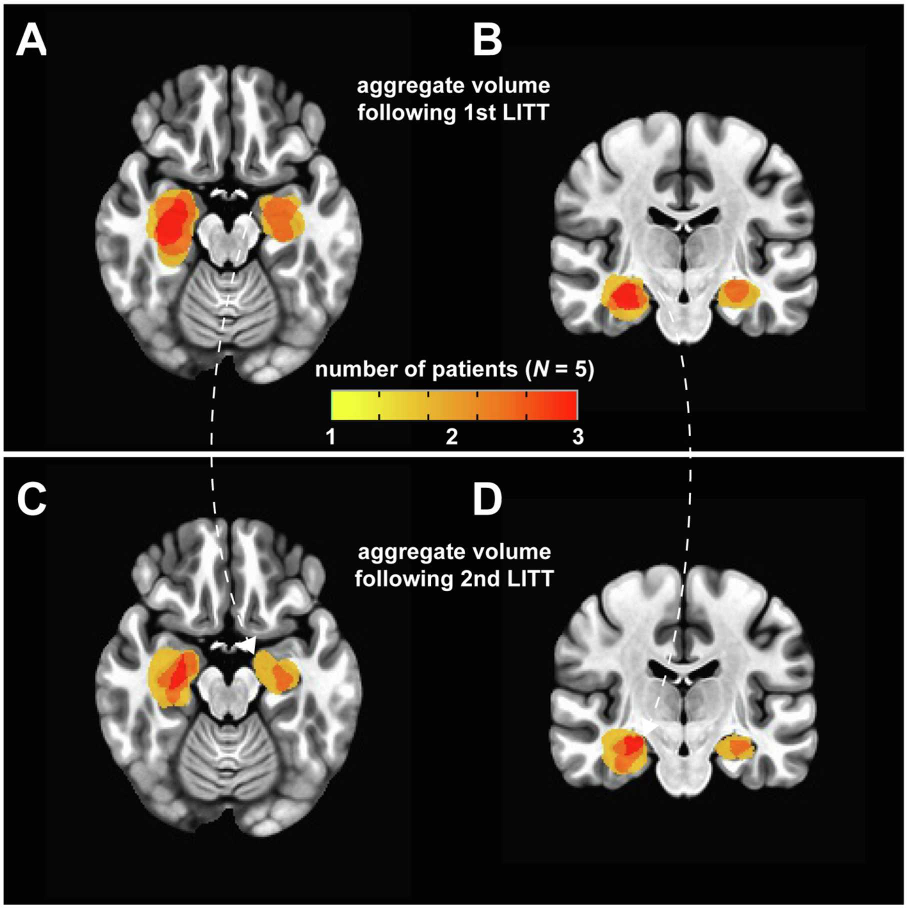

Fig. 4. Aggregated lesions for subjects showing subtle differences in ablation volumes between ablations. Lesions were added together to form a distribution heatmap of ablated regions of the MTL (maximum value is 3 on the right and two on the left reflecting the laterality of subjects' procedures). **(A)** On the left, there was residual tissue left either completely unablated or minimally on axial views. **(B)** On the right, the densest region seen on coronal views (red) does not include the medial most section of the MTL. After a second set of lesions, **(C)** the residual left uncal region is now mostly lesioned (dotted white arrow, left panels) and **(D)** the dense region moves noticeably medially on coronal views (dotted white arrow, right panels).

amounts of medial temporal lobe tissue remain, such residual tissue may nonetheless hold the key to achieving improved seizure outcomes with relatively limited risks compared with ATL.

4.4. Limitations

The primary limitation of this retrospective case series is its small sample size, restricting a fuller quantitative analysis of outcomes. Although LITT amygdalohippocampotomy has become increasingly popular, the subset of patients who undergo two consecutive procedures is small. Because any single institution is likely to have a similarly small number of these individuals, a pooled multi-institutional cohort study of suboptimal initial LITT outcomes would be an impactful next step and ideally include a direct comparison of follow-up treatment alternatives including repeat LITT, ATL, neuromodulation, and medical therapy.

By extension, there were also insufficient data to analyze neuropsychological data meaningfully. With regard to the neuroimaging methods, the subcortical segmentation may encounter difficulty with the hippocampal atrophy associated with mesial temporal sclerosis, which is ubiquitous in patients with mTLE and a known limitation to all similar analyses [34,35]. Lastly, there have been mixed results regarding the relative financial cost of LITT compared with ATL, though the cumulative expense of three laser ablations in these cases is likely relatively high, further cost analysis studies are needed to answer this question [36,37]. Larger studies in the near future will help guide clinicians and patients toward more informed decisions regarding repeat surgical treatment options for maximal seizure benefit.

5. Conclusion

All five patients who underwent repeat LITT in this retrospective case series achieved Engel class I outcomes at 3 months (12 months for pediatric patients), suggesting a second ablation may be preferable to proceeding to anterior temporal lobectomy or defaulting to observation if initial seizure outcomes are unsatisfactory. This series is an initial step that is limited by the number of patients who would qualify for the inclusion criteria at any single institution, but provides a stepping stone for planned larger, multi-institutional studies that are needed to compare and quantify the clinical outcomes more definitively.

Disclosures

None of the authors have any conflict of interest to disclose.

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CRediT authorship contribution statement

Bryan Zheng: Conceptualization, Methodology, Software, Writing – original draft, Writing – review & editing. **Hael Abdulrazeq:** Writing – review & editing. **Belinda Shao:** Writing – review & editing. **David D. Liu:** Writing – review & editing. **Owen Leary:** Writing – review & editing. **Peter M. Lauro:** Methodology, Software, Writing – review & editing. **Luca Bartolini:** Investigation, Writing – review & editing. **Andrew S. Blum:** Conceptualization, Writing – review & editing. **Wael F. Asaad:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2023.109365.

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