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Utility of 7 tesla MRI brain in 16 "MRI Negative" epilepsy patients and their surgical outcomes

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ABSTRACT

The objective is to quantitatively assess surgical outcomes in epilepsy patients who underwent scanning at 7T MRI whose lesions were undetectable at conventional field strengths (1.5T/3T).

16 patients who underwent an initial 1.5T/3T scan that was marked as non-lesional by a neuroradiologist and were candidates for epilepsy surgery were scanned at 7T. The 7T findings were evaluated by an expert neuroradiologist blinded to the suspected seizure onset zone (sSOZ). The relation of the neuroradiologist's findings compared with the sSOZ was classified as *non-definite* (no 7T lesion or lesion of no epileptogenic significance, or lesion of epileptogenic potential which localizes to the patient's sSOZ but is not the definitive cause), or *definite* (7T lesion of epileptogenic potential that highly localizes to the sSOZ and is confirmed through surgical intervention).. Each patient underwent neurosurgical intervention and postoperative Engel outcomes were obtained through retrospective chart review by an epileptologist.

Of the 16 patients, 7 had imaging findings of *definite* epileptogenic potential at 7T while 9 had *non-definite* imaging findings. 15 out of 16 patients had Engel I, II, or III outcomes indicating worthwhile improvement. Patients with *definite* lesion status achieved Engel I surgical outcomes at higher rates (57.1%) than patients with *non-definite* lesion status (33.3%). Patients with normal clinical diagnostic scans at lower field strengths who have *definite* radiological findings on 7T corresponding to the sSOZ may experience worthwhile improvement from surgical intervention.

1. Introduction

About 20–30% of patients with focal epilepsy are "MRI-negative" at conventional field strengths (1.5 or 3T), i.e., they lack a detectable lesion [1]. "Non-lesional" cases have been associated with poor surgical outcomes [2]. Advanced imaging techniques can better define the lesion, which may improve surgical outcomes. Preliminary studies using ultra-high field MRI scanners operating at 7T or higher confer better resolution due to improved signal to noise ratio (SNR) compared to lower field strengths, which may aid detection of more subtle structural abnormalities in epilepsy cases previously labeled non-lesional [3,4]. However, the role of 7T MRI in the neurosurgical management of MRI-negative epilepsy patients remains poorly described in the literature. Prior work has reported qualitative surgical outcomes for 10 patients scanned at 7T [7]. Here, we present our quantitative 6-year single-institution experience in the management of 16 epilepsy patients with MRI-negative epilepsy who underwent imaging with 7T and subsequent epilepsy surgery. We assessed Engel outcomes of epilepsy surgery in our MRI-negative case series at follow-up, and analyzed differences in 7T findings and surgical outcomes.

2. Methods

2.1. Patient population

Following approval from the Icahn School of Medicine Mount Sinai Institutional Review Board, 37 patients were prospectively

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Table 1
Imaging Findings, Surgical Interventions, and Engel Outcomes.

Case No.	Gender	Pt Age at Surgery	7T Imaging Findings	3T Imaging Findings	Invasive EEG	Surgery	Patient Lesion Status	7T Finding Targeted	SOZ Matched Treatment Area	Engel Class at Latest Follow-Up
1	M	21	Ventricle asymmetry. R ventricle bigger	Normal	R GRID/ STRIPS	RNS	Non-definite	no	yes	IC
2	M	25	R parietal polymicrogyria	Thickened cortex visible	R GRID/ STRIPS	Resection	Definite	yes	yes	IIIA
3	F	57	Ventricle Asymmetry	Normal	B/L SEEG	VNS	Non-definite	no	no	IIA
4	M	38	Hippocampal asymmetry, R > L	Normal	B/L SEEG	RNS	Non-definite	yes	yes	IIIA
5	M	51	Hippocampal asymmetry, subtle increased signal and volume R	Indistinct cortex (L)	B/L SEEG	Resection	Non-definite	yes	yes	IA
6	F	32	R Hippocampal sclerosis	Normal	R SEEG	Ablation	Definite	yes	yes	ID
7	F	33	None	Normal	B/L SEEG	RNS	Non-definite	no findings	yes	IIIA
8	F	34	Hippocampal asymmetry R > L; slight R signal hyperintensity. Cortical defect L occipital lobe	Normal	B/L SEEG	Ablation	Definite	yes	yes	IIIA
9	F	65	L MTS, small L inferior temporal meningioma	Normal	No	Ablation	Definite	yes	N/A	ID
10	F	23	Parietal/occipital ventricle asymmetry	Normal	B/L SEEG	RNS	Non-definite	no	yes	IA
11	F	34	Left parietal cortical dysplasia	Normal	B/L SEEG	Resection	Definite	yes	yes	IA
12	M	24	R mid temporal gyrus cavernoma	Normal	No	Resection	Definite	yes	N/A	IA
13	M	52	Hippocampal Asymmetry L > R	Nonspecific cerebral white matter hyperintensities	B/L SEEG	RNS	Non-definite	yes	yes	IIIA
14	F	24	B/L subtle insular polymicrogyria	Normal	B/L SEEG	RNS	Definite	yes	yes	IIIA
15	F	22	Small L anterior arachnoid cyst, small falx meningiomas	Cyst unrelated to epilepsy	L SEEG and STRIPS	RNS	Non-definite	yes	yes	IIIA
16	F	33	None	Normal	B/L SEEG	RNS	Non-definite	no findings	yes	IVB

recruited to undergo 7T imaging between 2013 and 2018. 16 out of 37 patients were MRI-negative focal epilepsy patients who were candidates for epilepsy surgery. These patients underwent subsequent epilepsy surgery and were included in the analysis. Patients with recent neurosurgical intervention or contraindications to MRI were excluded. Demographics, clinical presentation, MRI findings, and long-term surgical outcomes were obtained through review of electronic medical records.

2.2. Imaging methods

The 7T imaging protocol was comprised of T_1-weighted, T_2-weighted and susceptibility-weighted MRI sequences. Four sequences were obtained at a coronal-oblique angle and two sequences were obtained in the axial plane. Sequence details are provided as a supplementary endnote.[3]

[3] Four sequences were obtained at a coronal-oblique angle perpendicular to the angle of the long axis of the body of the hippocampus: 1) MP-RAGE (Voxel Size: 0.7 x 0.7 x 0.7 mm^3, Resolution: 320 x 260), TR: 3000 ms, TE: 2 ms 2) MP2RAGE (0.8 x 0.8 x 0.8 mm^3, 282 x 146) TR: 6000 ms, TE: 5.1 ms 3) T2 TSE (0.4 x 0.4 x 2.0 mm^3, 512 x 416) TR: 6000 ms, TE: 69 ms and 4) FLAIR (0.7 x 0.7 x 3.0 mm^3. 320 x 260) TR: 9000 ms, TE: 123 ms. Two axial sequences were also obtained: 5) susceptibility weighted imaging (SWI) TR: 23 ms, TE: 14 ms and 6) T2 TSE TR: 6000 ms, TE: 69 ms. Total scan time was approximately 55 minutes. When image quality was suboptimal, such as due to motion artifact, a sequence acquisition was repeated a maximum of one time [7].The MPRAGE and the MP2RAGE sequences covered the entire brain with isotropic resolution. From the MP2RAGE sequence, a total of four image sets were produced: 1) Inversion time (TI) of 1050 ms, 2) TI of 3000 ms, 3) T1 maps, and 4) uniform-denoised images. The T1 maps and uniform-denoised images were calculated from both the TI = 1050 ms and TI = 3000 ms images. The SWI sequence produced four sets of images: 1) magnitude images and 2) phase images, which were used to create 3) SWIs and 4) minimum intensity projections (mIPs) through overlapping sets of five contiguous SWI slices [7].

In our case series, 16 patients qualified (6 males, 10 females), with a mean age of 38.5 years (range 23 – 68). The mean age of patients at surgery was 35.5 years and the mean age at follow-up was 37.9 years. To qualify, patients had prior 1.5T and/or 3T MRI scans at our institution reported as non-lesional by neuroradiologists with a certificate of added qualification (CAQ). 7T imaging obtained in this protocol was also evaluated by a CAQ-neuroradiologist blinded to the suspected seizure onset zone (sSOZ) as determined by clinical data, scalp EEG, and other neuroimaging findings (including PET and SPECT). The relation of the neuroradiologist's findings compared with the sSOZ was classified as *non-definite* (no 7T lesion or lesion of no epileptogenic significance, or lesion of epileptogenic potential which localizes to the patient's sSOZ but is not the definitive cause), or *definite* (7T lesion of epileptogenic potential that highly localizes to the sSOZ and is confirmed through surgical intervention) [7]. Each patient underwent neurosurgical intervention with intention of curing seizures through resection, ablation, or RNS or VNS implantation. Engel outcomes were determined at 12 months follow-up through retrospective chart review by our epileptologists [5]. Any findings on the 7T scans prompted re-evaluation of conventional field-strength imaging to validate and confirm the potential new seizure focus. No additional invasive measures were performed on 7T data alone without validation of either scalp EEG and/or standard-of-care clinical diagnostic data.

3. Results

3.1. Clinical presentation and imaging findings of patients

Table 1 lists MRI abnormalities identified on 7T. Nine out of 16 patients exhibited hippocampal or cortical malformations (cortical

dysplasia, cortical thickness abnormalities, or polymicrogyria). Five of those nine patients exhibited hippocampal asymmetry, two exhibited cortical malformations, and two demonstrated hippocampal asymmetry as well as cortical dysplasia. Three patients exhibited ventricle asymmetry. One patient had an arachnoid cyst and a meningioma, and one patient had a cavernoma. Two patients lacked overt imaging abnormality at any field strength. Fig. 1 depicts examples of lesions visible at 7T not identified at lower field strengths.

Of the 16 patients, seven (43.8%) had imaging findings judged to be of epileptogenic potential (*definite*). Nine patients (56.3%) had imaging findings without epileptogenic potential (*non-definite).* Of these nine patients, three demonstrated ventricular asymmetry, three demonstrated hippocampal asymmetry, one had a meningioma and an arachnoid cyst, and two had no imaging findings.

3.2. Surgical interventions and Engel outcomes

The surgical interventions performed on the patients and their Engel outcomes at 12-month follow-up are also summarized in Table 1. Eleven patients received invasive stereo EEG implantation (SEEG) and an additional surgical intervention. Four patients

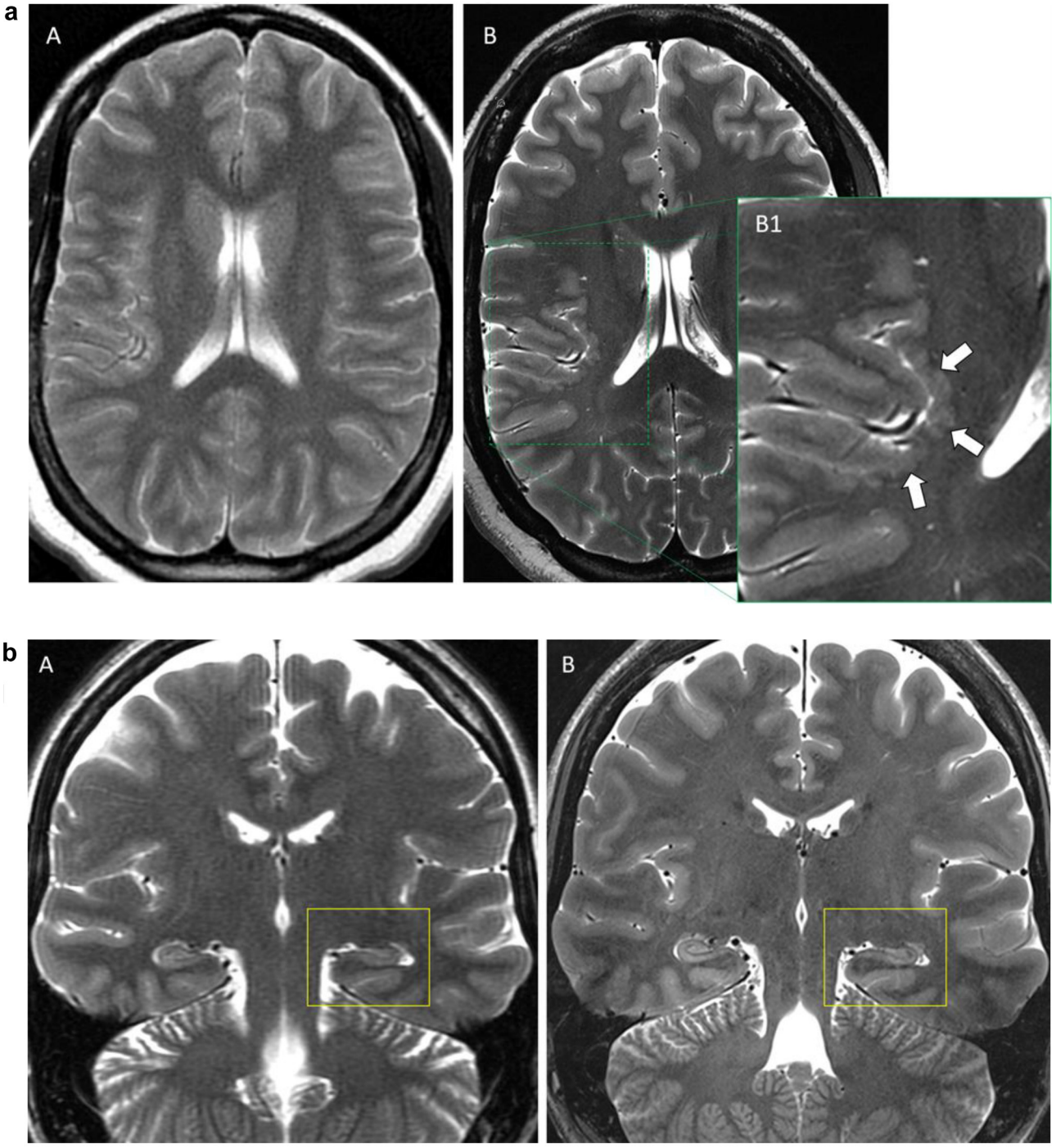

Fig. 1. Sample imaging of lesions visible on 7T imaging. 1a. Patient 14, Polymicrogyria. Axial T2-weighted imaging at 1.5T (A) and 7T (B). The posterior insular polymicrogyria was not detected at 1.5 T but is clearly resolved at 7T (see lobulated gray matter pattern emphasized by arrows in magnified 7T inset, B1) 1b. Patient 8, Hippocampal Asymmetry. Coronal T2 weighted images at 3T (A) and 7T (B). The 7T image has superior visualization of both hippocampal formations, and in particular more precisely highlights the contours of the smaller left side hippocampus better than the 3T scan was able to.

underwent resection, three underwent laser ablation, one received a VNS, and eight were implanted with RNS.

Note that 11 out of 16 patients had their lesion findings targeted during neurosurgical intervention. Of those 11, seven had *definite* imaging findings, and four had *non-definite* findings. In 13 patients, the surgical intervention matched the sSOZ as defined by SEEG. Five of seven patients with *definite* imaging findings received surgical interventions that matched the sSOZ confirmed by SEEG. Two of the seven patients with *definite* findings did not have an SEEG implanted and therefore the sSOZ was not confirmed. Eight of nine patients with *non-definite* findings underwent surgical interventions that matched the sSOZ as defined by SEEG. One patient with a *non-definite* finding was treated with a VNS and their intervention did not match the sSOZ as defined by SEEG.

To analyze surgical outcomes, we grouped patients by Engel class. Postoperative Engel outcomes were obtained through evaluation of medical records by our epileptologists. Following surgery, seven patients were classified as Engel I, one as Engel II, seven as Engel III, and one as Engel IV (see Table 1). Of seven patients with *definite* lesion status, four patients (57.1%) were free of disabling seizures (Engel I), with two of those four achieving complete seizure freedom (Engel IA). Three patients (42.9%) showed reduction in seizure burden (Engel III). All patients with *definite* lesion status demonstrated 'worthwhile improvement' after surgery. Of the nine patients with *non-definite* lesion status, eight (88.9%) demonstrated 'worthwhile improvement' (Engel III and above). Three of these nine patients (33.3%) were free of disabling seizures (Engel I). One patient (11.1%) showed 'no worthwhile improvement' (Engel IV).

4. Discussion

This study analyzed patients with epilepsy with no structural abnormalities detected at 1.5 or 3T MRI. Results suggest that in general 7T imaging, which may be leveraged for higher SNR and/or improved resolution, enabled detection of possible epileptogenic abnormalities not clearly identifiable at lower field strengths. In drug-resistant focal epilepsy patients, localization of a structural lesion on MRI is critical for pre-operative planning and is associated with better surgical outcomes [6]

7T imaging was found to be well-tolerated among the patient population. Prior studies have shown 7T imaging have a similar safety profile to 3T, except for increased acoustic noise and transitory physiological effects [7]. This study was limited to adults over the age of 18 because the 7T scanner used for the case series was approved with respect to the specific absorption rate (SAR) for adults. However, the increased SNR of 7T imaging could be a useful tool in revealing sources of epilepsy in children. Additional technical and safety considerations are required to ensure 7T imaging in children is within conservative SAR limits.

Of the 16 patients studied, a neuroradiologist could detect a *definite* lesion in seven patients (44%), and a *non-definite* lesion in nine patients (56%). 7T imaging was used to complement clinical data to identify neurosurgery candidates. We found 7T MRI a useful additional tool to clinical and electrographic data for planning SEEG electrode placement and identification of the sSOZ, because focal targeting of a potentially epileptogenic lesion may confer lower collateral morbidity. 7T MRI data was not used independently to guide surgical decision making. Findings on 7T were validated with conventional field-strength imaging and clinical data.

Of the 16 patients in the study, 15 (93.8%) had Engel I, II, or III outcomes indicating worthwhile improvement following surgery. Patients with *definite* imaging findings experienced freedom from disabling seizures after neurosurgical intervention at a greater rate (57.1%) than patients with *non-definite* imaging findings (33.3%). This preliminary investigation suggests that patients with epilepsy that is non-lesional at conventional field strength may benefit from 7T imaging. 7T imaging, in conjunction with clinical and EEG data, may be a useful tool in determining whether MRI-negative epilepsy patients are candidates for neurosurgical intervention. Additionally, our study suggests that enhanced detectability of lesions at 7T MRI may be predictive of the likelihood of achieving seizure freedom in patients with MRI-negative drug resistant epilepsy. Further study of 7T imaging in MRI-negative epilepsy patients is warranted to determine its potential role in clinical practice.

5. Limitations

This study does have some limitations. The relatively small number of patients in this case series prevents statistical validation of the diagnostic value of 7T compared to lower field strength imaging.

Additionally, the study is limited by the strength of the patients' initial diagnostic scan. Patients underwent 1.5T or 3T MRI scans at the time of enrollment based on the scanning protocol of the clinical or referring site. Retrospective re-examination of some of the initial scans, particularly those obtained at 3T, may have been re-read as lesional and not qualified for inclusion. However, the initial scans were deemed sufficient clinically when interpreted and non-lesional by the care team. The study was not designed as a comparative 3T vs. 7T study as we did not have control over initial clinical field scans.

This analysis applied only to patients who received surgery. A larger subset of patients did not undergo surgery. In some cases, abnormalities were found and surgery was not pursued. 7T imaging was not conducted postoperatively to objectively measure the effect of surgical intervention because it was beyond the scope of this study and many patients were ineligible due to implanted RNS electrodes at the time of the study. Heterogeneity among patients in the epileptogenic structural abnormality undergoing surgical intervention also limits our assessment of surgical outcomes.

6. Conclusions

Here we detail our institutional experience with surgical treatment of epilepsy patients following imaging using 7T MRIs. We demonstrate that focal epilepsy patients with non-lesional clinical diagnostic scans at lower field strengths who have *definite* radiological findings on 7T corresponding to the sSOZ are likely to experience worthwhile improvement from surgical intervention. Patients whose 7T findings had *non-definite* lesion status in relation to the sSOZ benefited from surgical intervention at lower rates. Our preliminary findings in this case series suggest that there is value in performing a larger study with a greater sample size to assess the utility of 7T in surgical treatment of patients with focal epilepsy.

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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.ebr.2020.100424.

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