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Study of the hippocampal internal architecture in temporal lobe epilepsy using 7 T and 3 T MRI

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ABSTRACT

Purpose: To compare the hippocampal internal architecture (HIA) between 3 and 7 Tesla (T) magnetic resonance imaging (MRI) in patients with temporal lobe epilepsy (TLE), and to investigate the relationship between HIA and hippocampal volume, and postoperative outcomes.

Materials and methods: Thirty-nine TLE patients were recruited with 3 and 7 T MRI scans and a semi-quantitative assessment of the HIA was performed. Differences in HIA scores between 3 and 7 T MRI were evaluated. HIA and hippocampal volume asymmetry were also calculated and compared. The utility of HIA and hippocampal volume asymmetry in epilepsy lateralization, and the predictive value between these two indicators were compared. The relationship between HIA and postoperative outcomes was investigated in 25 patients with amygdalohippocampectomy.

Results: HIA scores of epileptogenic hippocampi were lower than those of non-epileptogenic hippocampi at 3 and 7 T MRI. Higher HIA scores were observed at 7 T MRI. The HIA asymmetry and hippocampal volume asymmetry were both strong predictors for epilepsy lateralization and did not show difference in predictive value. No statistical differences in HIA asymmetry were observed between seizure-free patients (ILAE 1) compared to patients with seizures (ILAE 2–5).

Conclusions: Visualization of hippocampal internal architecture (HIA) may be improved at 7 T MRI. HIA asymmetry is a significant predictor of laterality of seizure onset in TLE patients and has similar predictive value as hippocampal volume asymmetry, however, HIA asymmetry at 7 T does not have extra value in determining epilepsy lateralization and neither does predict surgical outcomes.

1. Introduction

Magnetic resonance imaging (MRI) is a well-recognized diagnostic tool in most brain disorders. Today, high-strength magnetic field (3 T) MRI are standard. Though 7 T MRI are not currently widely used yet, it becomes more and more available for clinical and neuroscientific researchers. However, the higher spatial resolutions that are possible at ultra high field imaging increase scan time as a result, which can result in patient discomfort. The main complaint at ultra high field followed by nausea, light flashes, metallic taste in the mouth, too much noise during image acquisition [1]. Additionally, it may be necessary to extend measurement time due to the higher SAR at field strengths of 7 T. [2]. Despite the fact that there are some distinctive challenges along with ultra-high field imaging, it has been stated that subtle anatomic abnormalities within a wide range of neurologic disorders should benefit from 7 T MRI. The higher resolution of the hippocampus is one important benefit at 7 T. Although, for this brain region near the skull base, MR sequences still need to be optimized due to SAR limitations

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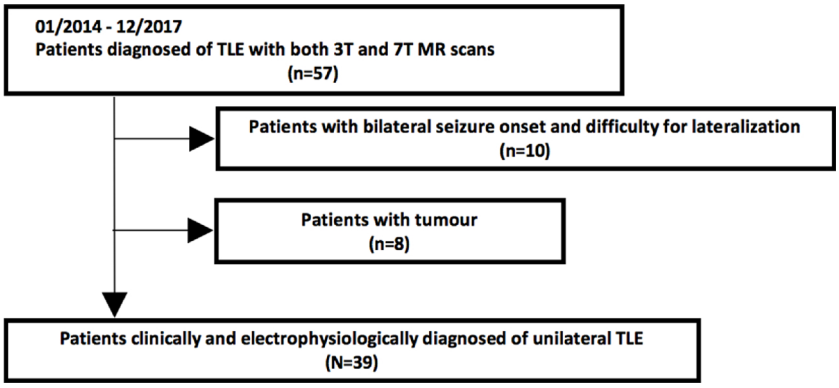

Fig. 1. Flowchart of patient selection.

and increased susceptibility effects. The high-resolution depiction of the hippocampi is possible at 7 T without significant artefacts with T2 sequences [3]. This will enable clinicians to visualize smaller anatomical structures and greater detail of hippocampal internal architecture (HIA) [4,5] from ex vivo or in vivo samples that may not be detectable at lower field strengths. In an ex vivo study of correlations with hippocampal histology, seven clearly recognizable layers and anatomical boundaries were discerned in the non-sclerotic hippocampus on 7 T MRI, while only four layers were recognized in specimens with histopathologically confirmed hippocampal sclerosis (HS) [6]. Another study compared the clarity of HIA at 7 T vs 1.5 T using T2, T2* and FLAIR sequences in three healthy volunteers, and showed that HIA is much more clearly seen at 7 T than 1.5 T due to improved SNR and resolution [7]. Based on these results, 7 T MRI represents a feasible and promising method for obtaining finer anatomical images and therefore a possible earlier diagnosis of a disease compared with 1.5 T or even 3 T MRI. These repots of HIA at 7 T scanners are all based on qualitative assessment.

The hippocampus plays an important role in the formation of both spatial and declarative memory [8], and its damage is associated with many diseases, such as epilepsy [9], Alzheimer's disease [10,11], mood disorders [12], and schizophrenia [13]. In patients with temporal lobe epilepsy (TLE), HS is the major histopathological hallmark with the radiological features of hippocampal atrophy, signal alterations (a hyper-intense T2 signal and hypo-intense T1 signal) and loss of clarity in HIA [14]. A semi-quantitative method to evaluate HIA using a scoring system was first established and reported by Lawrence W. Ver Hoef and his colleagues in 2013 [15]. This semi-quantitative scoring system has 4 grades in total to evaluate the contrast between the grey matter and white matter layers on coronal T2 weighted images across the body of the hippocampus, from "1″ indicating no perceptible internal architecture to "4″ indicating excellent internal architecture. Asymmetry of the HIA calculated at 3 T MRI is a significant independent predictor of the lateralization of seizure onset in patients with TLE even in those without other MRI evidence of HS [16]. However, the HIA scoring system assessments are at 3 T clinical scanners in present literatures. To our knowledge, there are few published reports of HIA scoring system assessment at 7 T or other ultra-high field MRI, and there has been no report on the comparison of HIA assessment between 3 T and 7 T scanners. The aim of the study was firstly to determine if 7 T MRI is superior to 3 T MRI in detecting subtle differences in the HIA by comparing the differences of HIA scores at MR scanners with different field strengths (3 T and 7 T). Secondly, hippocampal volume was measured automatically to investigate the relationship between hippocampal atrophy and HIA asymmetry from MR scanners with different field strengths (3 T and 7 T). Additionally, the relationship between the HIA asymmetry and postoperative seizure outcomes were also studied.

2. Materials and methods

2.1. Patients

Patients were collected retrospectively. From January 2014 through December 2017, 57 consecutive patients were diagnosed of TLE at Neurology Unit of the Peking Union Medical College Hospital. All patients undergoing evaluation for epilepsy were scanned using a 7 T MRI scanner and also underwent standard clinical 3 T MRI, prolonged video-EEG, and neuropsychological testing, as part of the clinical epilepsy evaluation. Of these 57 TLE patients, 18 were excluded for the following reasons: (a) Patients with bilateral seizure onset and difficulty for lateralization (n = 10); (b) Patients with tumour (n = 8). A total of 39 unilateral TLE patients were ultimately included in the study by virtue of seizure semiology and electrophysiological investigations, and had at least a sign of unilateral HS on MRI (including T2 signal hyperintensity, T1 signal hypointensity, atrophy, and/or loss of clarity in HIA based on visual inspection by a neuroimaging expert) with no evidence of a secondary lesion that may be epileptogenic in nature. (Fig. 1). Of the 39 patients included in the study, 20 were male (51%) and 19 were female (49%); the mean age at the time of the 7 T and 3 T MRI scans was 27 ± 8 (standard deviation) years (range 12–47 years). The time interval between 3 T and 7 T scans was less than 24 h for all patients. Twenty-five patients underwent amygdalohippocampectomy and received standardized postoperative follow up for at least one year. International League Against Epilepsy (ILAE) outcome classification system was used for outcome assessments [17]. This study was approved by the Institutional Review Board of Peking Union Medical College Hospital and written informed consent was obtained from all patients.

2.2. MRI acquisition

All patients underwent MRI scans with a 3 T scanner (Discovery MR750 3 T, GE Healthcare, Milwaukee, WI, USA) and a 7 T scanner (Investigational Device 7 T, Siemens, Germany). Thirty-two channel head coils were used with both scanners. For the assessment of HIA, we collected T2-weighted images (T2WI) in the coronal plane located perpendicular to the long axis of the hippocampus (3 T T2WI-fast spin echo(FSE): TR = 7530 ms, TE = 95 ms, resolution 0.4 × 0.4 × 3.0 mm, flip angle 142°, TA 6min23 s; 7 T T2WI-turbo spin echo (TSE): TR = 9640 ms, TE = 72 ms, resolution 0.3 × 0.3 × 2.0 mm, flip angle 60°, TA 11min26 s). We determined the hippocampal volume from 3D T1-weighted images (T1WI) acquired from each patient (3 T T1WI-prepared fast spoiled gradient echo (i.e., BRAin VOlume acquisition, BRAVO): TR = 7.4 ms, TE = 2.8 ms, resolution 1.0 × 1.0 × 1.0 mm, flip angle 12°, TA 6min35 s; 7 T T1WI three dimensional magnetization prepared rapid acquisition gradient echo (3D-MPRAGE): TR = 2200 ms, TE = 2.98 ms, resolution 0.7 × 0.7 × 0.7 mm, flip angle 8°, TA

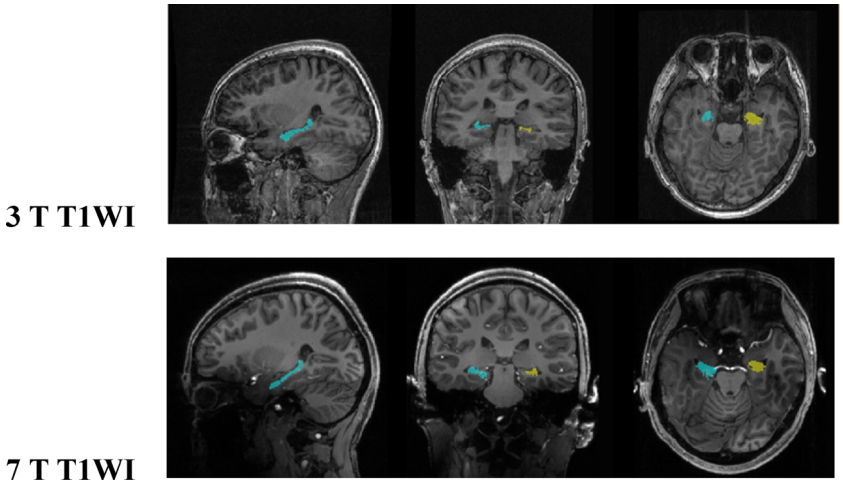

Fig. 2. A typical example of MRI segmentation results from 3 T and 7 T T1WI.

10min16 s).

2.3. Image processing

2.3.1. Automatic segmentation

The hippocampus was segmented, and its volume was calculated using AccuBrain® IV 1.0 software (BrainNow Medical Technology Limited, Hong Kong, China), a brain quantification tool that performs brain structure and tissue segmentation and quantification in a fully automated mode [18]. The examples of the hippocampal segmentation obtained with 3 T and 7 T MRI are given in Fig. 2. Using the T1-weighted MRI data, AccuBrain® segmented the brain structures based on a statistical analysis of previous anatomical data specified by experienced radiologists. This anatomical information was transformed to the individual brain MRI being analysed.

The relative hippocampal volumetric was given adjusted by internal cranial volume (ICV) for each subject and hippocampal volume asymmetry score was calculated by subtracting relative hippocampal volumetric of non-epileptogenic side from the epileptogenic side for atrophy estimation. A positive hippocampal volume asymmetry score indicated a relative loss of hippocampal volume on the epileptogenic side, negative hippocampal volume asymmetry indicated a relative loss of hippocampal volume on the non-epileptogenic side and zero indicated no bilateral volumetric asymmetry.

$$\text{Relative volume hippocampus} = \frac{\text{Absolute hippocampal } \textit{Volume}}{\text{ICV}}$$

$$\text{Asymmetry score (Hippocampal volume)} = \text{Relative volume}_{\text{non-epileptogenic hippocampus}} - \text{Relative volume}_{\text{epileptogenic hippocampus}}$$

2.3.2. Image analysis

HIA was visually assessed in consecutive coronal T2WI according to a previously reported semi-quantitative HIA rating system [16]. There are 4 grades in total from '1' indicating no perceptible internal architecture to '4' indicating excellent internal architecture differentiation. The assessment started with the first slices posterior to the hippocampal head and continuing until the slice in which the inferior and superior colliculi come clearly into view. For each patient, HIA score for each side were averaged the ratings across all the slices of the body of hippocampus. All visual inspections were performed by one board-certified neuroradiologist with over 15 years of experience who was blind to clinical information. Inter-rater reliability studies were performed on ten patients from the main cohort. These ten patients were randomly selected and assessed by another board-certified neuroradiologist with over 20 years of experience who was also blind to clinical information. HIA asymmetry score was calculated by subtracting HIA score of non-epileptogenic side from the epileptogenic side. HIA asymmetry score was calculated. A positive HIA asymmetry score indicated a relative loss of clarity of HIA on the epileptogenic side, and a negative HIA asymmetry score indicated a relative loss of HIA clarity on the non-epileptogenic side. Zero indicated a lack of bilateral asymmetry.

$$\text{Asymmetry score (HIA)} = \text{HIA}_{\text{non-epileptogenic hippocampus}} - \text{HIA}_{\text{epileptogenic hippocampus}}$$

2.4. Statistical analysis

We used SPSS (IBM SPSS Statistics, Version 23.0) for statistical analyses. Differences in HIA scores between epileptogenic and non-epileptogenic hippocampi on 3 T and 7 T MRI were evaluated by Kruskal-Wallis *H* test followed by post hoc comparisons using Mann-Whitney *U* test with Bonferroni correction. A logistic regression model was used to examine the utility of asymmetry score (HIA) in lateralizing the side of seizure onset. Seizure freedom was defined as an International League Against Epilepsy (ILAE) score of 1 (ILAE 1), and persistent postoperative seizures were defined as ILAE 2–6 [17]. The Kruskal-Wallis *H* test was used to compare the HIA asymmetry between 3 T and 7 T MRI and between groups of different surgical outcomes. Spearman's correlation coefficients were calculated to investigate relationship between HIA asymmetry and volumetric asymmetry on both 3 T and 7 T MRI. Fisher's exact test was used to analyse the different predictive value of HIA and volumetric asymmetry on both 3 T and 7 T MRI.

3. Results

Examples of the HIA scoring system using 3 T and 7 T MRI data are shown in Fig. 3. All HIA scores and asymmetry scores (HIA) of 39 patients were shown in Table 1. Twenty-five patients underwent an amygdalohippocampectomy and a surgical outcome evaluation at least one year after surgery.

3.1. Differences in HIA obtained from 3T and 7T MRI

Inter-rater (two raters, YH and FF) reliability studies were performed on ten participants from the main cohort. These ten participants were randomly selected and were evaluated without knowledge of the diagnosis and laterality of seizure onset. Studies indicated high levels of repeatability on both 3 T (inter-rater intra-class coefficient (ICC), two-

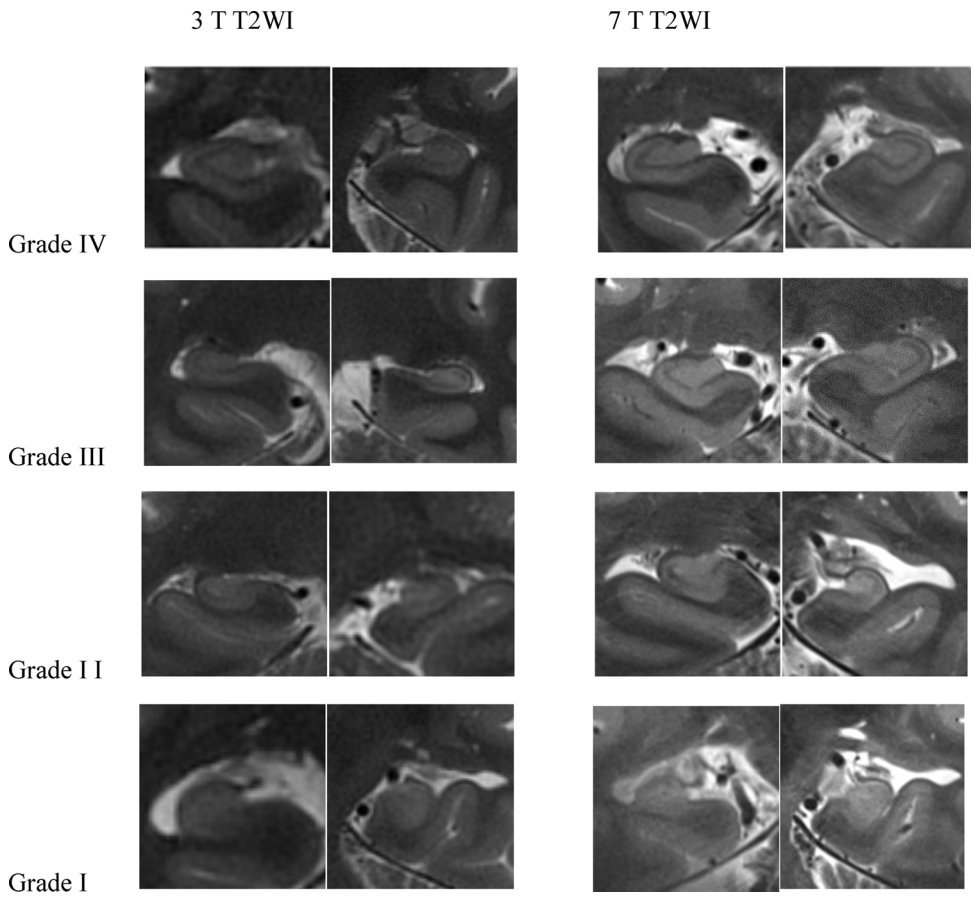

Fig. 3. Images illustrated the different hippocampal grade in our study group.

way random model for consistency: left HIA = 0.931 (95% CI: 0.750-0.983), right HIA = 0.954 (95% CI: 0.827-0.988)) and 7 T MRI (ICC: left HIA = 0.912 (95% CI: 0.688-0.977), right HIA = 0.995 (95% CI: 0.979-0.999)).

Across all patients in the study, HIA scores ranged from 1 to 3.5 (median 2.14, SD 0.64) and 1 to 4 (median 2.86, SD 0.83) for the epileptogenic side of 3 T MRI and 7 T MRI, respectively. HIA scores ranged from 1.67 to 4 (median 2.8, SD 0.61) and 3 to 4 (median 3.67, SD 0.29) for the non-epileptogenic side of 3 T MRI and 7 T MRI, respectively. The HIA scores of the four groups differed ($P < 0.0001$) (Fig. 4). HIA scores of the epileptogenic hippocampi were lower than the non-epileptogenic hippocampi on both 3 T MRI ($P < 0.0001$) and 7 T MRI ($P < 0.0001$). Higher HIA scores for either side of the hippocampus were recorded using 7 T MRI than 3 T MRI (non-epileptogenic side $P < 0.0001$, epileptogenic side $P < 0.0001$).

Eight patients (20.5%) had a negative HIA asymmetry score, 30 (76.9%) patients had a positive asymmetry score, and 1 (2.6%) exhibited symmetry in 3 T MRI. Six patients (15.4%) had a negative HIA asymmetry score. Thirty-one (79.5%) patients had a positive asymmetry score, and 2 (5.1%) exhibited symmetry in 7 T MRI. According to the results from the logistic regression analysis, the HIA asymmetry score was the predictor of laterality of seizure onset on both 3 T and 7 T MRI (3 T MRI: $\beta = 2.303$, SE $\beta = 0.775$, $Z = 8.836$, $P = 0.003$; 7 T MRI: $\beta = 2.621$, SE $\beta = 0.801$, $Z = 10.719$, $P = 0.001$). HIA asymmetry score of 3 T MRI ranging from -1 to 3 and that of 7 T MRI ranging from -0.54 to 2.25 did not show difference statistically ($P = 0.6636$).

3.2. Relationship between HIA and hippocampal volume

Four patients (10.2%) displayed negative hippocampal volume asymmetry, 35 (89.8%) patients displayed positive hippocampal volume asymmetry, and none exhibited symmetry in the 3 T MRI data. Three patients (7.7%) exhibited negative hippocampal volume asymmetry. Thirty-five (89.8%) patients displayed positive hippocampal volume asymmetry, and 1 (2.5%) displayed symmetry in the 7 T MRI data. No significant differences of the hippocampal volume asymmetry indexes were observed between 3 T and 7 T MRI data ($P = 0.2269$).

Based on the results of the logistic regression analysis, the hippocampal volume asymmetry extracted either from 3 T or 7 T MRI data was a predictor of laterality of seizure onset (3 T MRI/7 T MRI: $\beta = 4.270$, SE $\beta = 1.059$, $Z = 16.243$, $P = 0.000056$). A statistically significant correlation was not observed between HIA asymmetry and hippocampal volume asymmetry in 3 T MRI data ($r = 0.217$, $P = 0.185$). However, this correlation was observed in 7 T MRI data ($r = 0.546$, $P = 0.000319$). Additionally, hippocampal volume and HIA asymmetry showed the similar predictive value in laterality of seizure onset in this study (3 T MRI: $P = 0.224$; 7 T MRI: $P = 0.347$).

3.3. Relationship between HIA and surgical outcomes

Of the 25 patients who underwent standard amygdalohippocampectomy and received standard postoperative follow up, 18 (72%) achieved an ILAE outcome of ILAE 1, and 7 (28%) achieved an outcome of ILAE 2–5. No patient had a postoperative outcome of ILAE 6. HIA asymmetry score ranged from −0.46 to 2.83 and −0.5 to 2.25 respectively for patients with ILAE 1 based on 3 T MRI and 7 T MRI. HIA asymmetry score ranged from −0.4 to 1.34 and −0.38 to 2.03 respectively for patients with ILAE 2–5 based on 3 T MRI and 7 T MRI. No statistically significant difference in HIA asymmetry was observed between the patient surgical outcome groups on either 3 T ($P = 0.2764$) or 7 T MRI ($P = 0.4492$). No significant differences in the HIA of non-epileptogenic side (3 T MRI: $P = 0.7111$; 7 T MRI: $P = 0.4291$) and

Table 1
HIA scores and asymmetry scores (HIA) of 39 patients.

Simple ID	Age / Gender	HIA score - 3T (epileptogenic hippocampi)	HIA score - 3T (non-epileptogenic hippocampi)	Asymmetry score (HIA) - 3T	HIA score - 7T (epileptogenic hippocampi)	HIA score - 7T (non-epileptogenic hippocampi)	Asymmetry score (HIA) - 7T	ILAE classification
1	20/M	2.83	2	−0.83	3.5	3.5	0	–
2	29/M	2.5	3.83	1.33	3.83	3.67	−0.16	–
3	24/F	2.4	2	−0.4	2.86	3.17	0.31	4
4	21/F	1.17	4	2.83	1.57	3.67	2.1	1
5	22/M	2.29	2.71	0.42	3	3.78	0.78	1
6	33/F	2.67	2.43	−0.24	3.83	3.29	−0.54	–
7	24/M	2.14	2.2	0.06	3.71	3.33	−0.38	4
8	30/M	2.33	3	0.67	2.83	3.83	1	1
9	13/M	2.43	3.4	0.97	2.17	3.57	1.4	1
10	21/F	3.17	2.67	−0.5	3.33	3.43	0.1	–
11	38/F	1.33	2.2	0.87	1.14	3.17	2.03	4
12	30/F	1.83	3.6	1.77	2.43	3.67	1.24	1
13	35/M	1	2.83	1.83	1	3.14	2.14	1
14	36/M	2	3	1	2.14	4	1.86	2
15	21/F	1.67	2.17	0.5	2.83	3.33	0.5	1
16	21/F	1.5	3.2	1.7	2.83	3.83	1	1
17	25/M	1.33	2.8	1.47	3.14	4	0.86	–
18	18/M	2.17	2.83	0.66	3	3	0	1
19	13/M	1.67	2.6	0.93	2.14	3.33	1.19	–
20	22/M	1.67	2.67	1	3	3.71	0.71	1
21	26/M	1.33	3.67	2.34	1.5	3.75	2.25	1
22	19/M	1	3.5	2.5	1	3	2	1
23	23/F	2.5	3.67	1.17	3.17	3.67	0.5	1
24	21/F	2.33	3.6	1.27	3.2	4	0.8	2
25	47/M	2.29	3.71	1.42	2.2	3.83	1.63	1
26	24/M	1	1.67	0.67	3.25	3.17	−0.08	1
27	25/F	2.43	3.5	1.07	3.75	3.86	0.11	1
28	34/F	2.33	3.67	1.34	3.4	3.8	0.4	3
29	36/F	3.5	3.33	−0.17	4	3.5	−0.5	1
30	18/F	3.17	2.71	−0.46	3.6	3.8	0.2	1
31	27/F	2	3	1	3.43	3.83	0.4	–
32	15/M	2	2.6	0.6	4	3.83	−0.17	5
33	44/F	1.5	2.67	1.17	2.83	3.67	0.84	–
34	41/F	1.4	2.8	1.4	2.8	3.2	0.4	–
35	26/M	2.43	2.43	0	3.14	3.6	0.46	–
36	42/F	3	3.5	0.5	2.83	3.83	1	–
37	29/M	2.17	2.14	−0.03	2.5	3.43	0.93	–
38	12/F	1.29	2.5	1.21	1.625	3.875	2.25	–
39	35/M	2.14	2	−0.14	2	3.6	1.6	–

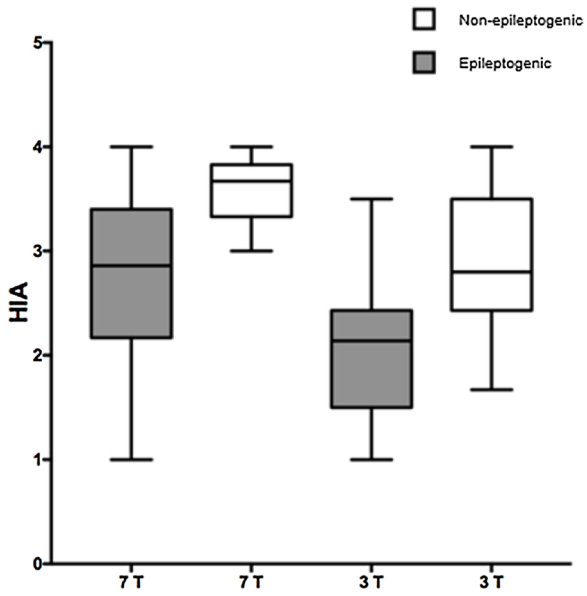

Fig. 4. HIA scores obtained from 3T and 7T MRI.

HIA of epileptogenic side (3 T MRI: $P = 0.2372$; 7 T MRI: $P = 0.3639$) were observed between patient surgical outcome groups (Fig. 5).

4. Discussion

The scoring system used in this study was firstly devised in 2013 to measure the degree of HIA asymmetry in a semi-quantitative way and to evaluate its value in predicting laterality of seizure onset in TLE patients. Its developers have reported the reliability of this scoring system and substantial agreement has been reached among evaluators with expertise in neuroimaging [15,16]. In this study, high reliability of this scoring system between two experienced neuroimaging experts have been confirmed. Additionally, we further investigate the clinical significance of ultra-high field by comparing 3 T and 7 T MRI data with a semi-quantitative HIA scoring system for evaluation to verify whether ultra-high field MRI (7 T MRI) can change the assessment of HIA in TLE patients. HIA scores measured with 7 T MRI were higher than those recorded with 3 T MRI, regardless of the side of the hippocampi. HIA manifests as a hypo-intense (dark) band and is usually 1 mm or less in thickness on coronal sections of T2-weighted images. Histologically, HIA refers to the combination of the strata radiatum, lacunosum and moleculare on the inner surface of the subiculum CA1-CA3 in apposition to the vestigial hippocampal sulcus and stratum moleculare of the dentate gyrus [5,19]. The perfect condition for HIA imaging would be the integration of suitable resolution, tissue contrast, and signal-to-noise ratio. As signal-to-noise ratio increases with the field strength of

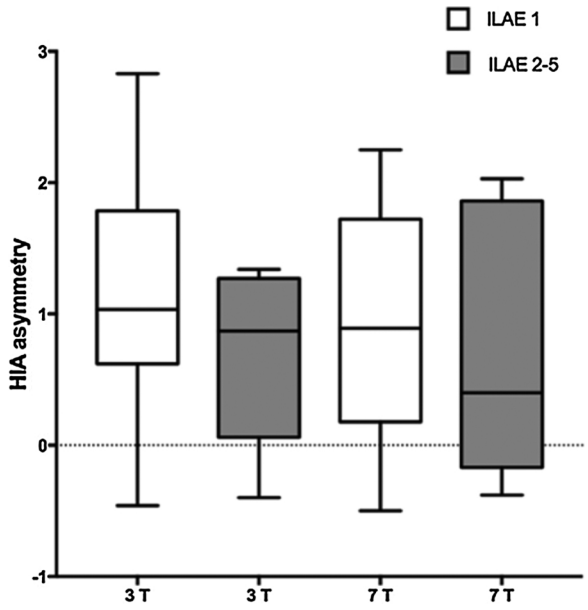

Fig. 5. HIA asymmetries and surgical outcomes.

the MR scanner, a higher spatial resolution of the HIA can be obtained from a higher MR field strength. Previously, studies have shown the superiority of 3 T compared to 1.5 T MRI in detecting lesions in patients with epilepsy [20]. Thus, although the HIA scoring system is relatively stable among different evaluators, it might be affected by MR scanners with different field strengths for detailed morphological delineation of the internal hippocampal structures.

Lower HIA scores for epileptogenic hippocampi have been found compared to non-epileptogenic hippocampi at both 3 T and 7 T MRI. This consistency between these two scanners was not surprising, since the increase in the magnetic field intensity does not affect the radiological feature of loss of HIA clarity in epileptogenic side. When measuring with either 3 T MRI or 7 T MRI, we confirmed that HIA asymmetry is a good indicator of TLE lateralization, when HIA symmetry without lateralization is assumed for normal subjects. Despite the fact that about 20% of the patients had negative asymmetry scores, most of the negative HIA asymmetry scores were quite small (3 T MRI: ranged from -0.83 to 0; 7 T MRI: ranged from -0.54 to 0) compared to the range of positive scores (3 T MRI: ranged from 0.06 to 2.83, 7 T MRI: ranged from 0.1 to 2.25). This suggests that small asymmetry scores may not reliably predict the side of seizure onset but large asymmetry scores do. However, if instead there is a narrow range of asymmetry that may be normal, then a test would not be considered "positive" unless it exceeds a certain threshold. Furthermore, the 7 T data did show a slightly higher beta value in the logistic regression analyses than 3 T (2.6 vs. 2.3) and a slightly higher percent of patients with positive asymmetry scores (79.5% vs 76.9%), however, unfortunately, the truth was that no statistical difference was found in asymmetry scores between 3 T and 7 T MRI ($P = 0.6636$). And this was possibly caused by the fact that 7 T MRI increased the HIA scores on both epileptogenic and non-epileptogenic side, which made asymmetry the same. Therefore, although our findings were consistent with the histological changes of HS and previous studies [21,22], we don't see remarkable evidence that 7 T is better than 3 T MRI at detecting HIA asymmetry and identification of laterality of seizure onset. Although 7 T is not better than 3 T MRI at laterality of seizure onset in TLE patients with the sign of HS in this study, the internal nearly microscopic anatomy of the hippocampus can be visualized with very high resolution indicating possible clinical applications in epileptic patients. Initial clinical investigations have been conducted in patients with known mesial sclerosis showing better depiction of pathologies in this region [23]. Furthermore, cryptogenic epilepsy such as TLE patients without the sign of HS remains an unresolved problem as no structural abnormality can be diagnosed at MRI up to 7 T.

Hippocampal volumetric segmentation was automatically assessed using Accubrain® IV 1.0 software. This quantitative volumetric measurement provides experts with an objective and relatively reliable volumetric standard for laterality of seizure onset. In the present study, the two sets of volumetric data extracted from 3 T and 7 T MRI did not show significant differences in hippocampal volume asymmetry, and the hippocampal volume asymmetry was shown to be a strong predictor of laterality of seizure onset based on both 3 T and 7 T MRI data. Overall, 7 T MRI is not superior to 3 T MRI in performing volumetric analyses of laterality of seizure onset. Additionally, compared with predictive value of HIA asymmetry in seizure onset laterality, hippocampal volume asymmetry performed similarly in this study. However, the correlation between hippocampal volume asymmetry and HIA asymmetry was interesting. It was statistically significant based on 7 T MRI data but not based on 3 T MRI data. This conflicting result may have been caused by the ambiguous relationship between the HIA and hippocampal volume. The previous study revealed significant relationships between loss of HIA clarity and CA3 and CA4 neuronal density, but not between HIA ratings and neuronal density within CA1 [24]. However, pathologically typical HS (ILAE type 1 and 2) with relatively remarkable volume atrophy involve the preferential neuronal loss mainly in CA1 [25,26]. This may lead to the unstable relationship between the HIA and hippocampal volume.

Furthermore, some patients still displayed good HIA clarity in epileptogenic side, even with the features of HS (Fig. 6) in this study, making their HIA asymmetry inconsistent with the epileptogenic side. Historically, HS has been reported and classified into different subtypes based on the subfield distribution and the extent of hippocampal

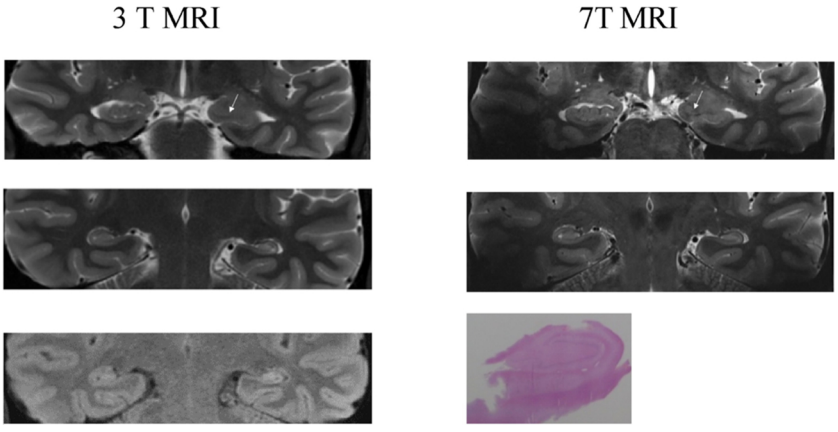

Fig. 6. Eighteen-year-old female patient diagnosed with left-TLE for 4 years underwent amygdalohippocampectomy. This patient had ILAE 1 surgical outcome. The disappearance of hippocampal digitations on the left side can be seen at either 3 T or 7 T MRI (arrow). 3 T MRI T2-FLAIR showed relative hyper-intense signal in left hippocampus compared to the right. However, HIA score of the left hippocampus (average HIA of left side 3T MRI: 3.17; 7T MRI: 3.6) was relatively high. Histological slice also showed relative clear layers of hippocampus.

neuronal loss and gliosis [26]. In terms of radiological aspects, HS is the combination of 3 features: hippocampal atrophy, hippocampal signal alterations (a hyper-intense T2 signal and hypo-intense T1 signal) and the loss of HIA clarity. Many researchers postulate that hippocampal atrophy is associated with the extent of neuronal loss [27] and changes in the hippocampal signal (hyper-intense T2 signal and hypo-intense T1 signal) is correlated with the severity of gliosis [28]. Alterations in the appearance of the HIA might also be the result of a particular microscopic pathological phenomenon that is part of the constellation of findings in HS. The loss of HIA clarity may not or may only be partially influenced by hippocampal atrophy and signal changes. As the loss of HIA clarity is an independent imaging characteristic, it possibly has potential extra value in TLE patients without any other signs of HS on MRI, and further study is in need in this field. Additionally, the determination of an accurate clinicopathological relationship between in vivo imaging findings and ex vivo pathological findings among TLE patients presenting with and without a loss of HIA clarity is still a worthwhile endeavour.

Unfortunately, we were unable to predict postoperative seizure outcomes in TLE patients from the degree of the loss of HIA clarity. Statistically significant difference was not observed between groups with different surgical outcomes. A confident prediction of short-term postoperative seizure outcomes using HIA assessments is difficult to obtain at present. This may due to the reason that in addition to the surgical style, the surgical outcomes may also be influenced by different other factors including surgical age, disease duration, seizure forms [29,30]. Additionally, the 3 T and 7 T MRI did not show any difference in this outcome. This finding was also consistent with an HIA study based on 3 T MRI data [24].

This study had several limitations. First, the higher HIA scores are observed at 7 T MRI compared with those at 3 T MRI and we tend to attribute this difference to higher field strength at 7 T. In fact, besides field strength, there are still other potential confounding variables that could account for these differences. Duration of interval between scans could be the one. However, all of our patients received 3 T scan first and then 7 T scan. The time interval between these two scans is very close, less than 12 h for most of patients and less than 24 h for all patients and no seizures were reported during this time. Therefore, though there are some potential confounding variables, the increased field strength might be the main factor causing the difference. Second, it is known that inhomogeneity artefacts are always more apparent at ultra-high field, and significant signal drop-out can occur in the temporal lobes. B1 and B0 artefacts are significant factors that degrade image quality at 7 T. Unfortunately, these problems indeed exist to some extent in this study and it has to be admitted that 7 T may be not yet a suitable "gold standard" for these imaging methods. Third, two MR scanning sessions were needed in this study. The total acquisition time was relatively long and required a high level of compliance from patients, and the number of recruited patients was restricted by the lengthy scan time to some extent. Although clinicians may experience challenges in bracing patients without inducing discomfort, no serious adverse responses related to 7 T MRI scanning were reported in our study. Additionally, this study included only 39 patients, and only 25 patients received surgical treatment and standard follow up. While most of the results were perfectly explained, some conflicting findings existed, and the results require further confirmation in a larger cohort. And, unfortunately, the histological analysis was not discussed in this study. Further studies are required to analyse the relationships among hippocampal volume, the HIA and its related histological changes, which may help us better understand the pathological process of HS.

In conclusion, the higher HIA scores were obtained on both side of hippocampi on 7 T MRI compared to 3 T MRI and this may mainly due to the clearer picture presented on 7 T MRI, making blurring architectures seen on 3 T MRI clear on 7 T MRI. However, HIA asymmetry at 7 T do not have extra clinical value in determining the epilepsy lateralization in TLE patients with HS. HIA and hippocampal volume asymmetry have similar predictive value in laterality of seizure onset. HIA asymmetry at 3 T does not predict postoperative and neither does HIA at 7 T. The extra clinical benefits of HIA in TLE patients without the sign of HS for epilepsy lateralization is still further studied in the future.

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