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ORIGINAL ARTICLE

Longitudinal hippocampal diffusion-weighted imaging and T2 relaxometry demonstrate regional abnormalities which are stable and predict subfield pathology in temporal lobe epilepsy

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Abstract

Objective: High-resolution (1 mm isotropic) diffusion tensor imaging (DTI) of the hippocampus in temporal lobe epilepsy (TLE) patients has shown patterns of hippocampal subfield diffusion abnormalities, which were consistent with hippocampal sclerosis (HS) subtype on surgical histology. The objectives of this longitudinal imaging study were to determine the stability of focal hippocampus diffusion changes over time in TLE patients, compare diffusion and quantitative T2 abnormalities of the sclerotic hippocampus, and correlate presurgical mean diffusivity (MD) and T2 maps with postsurgical histology.

Methods: Nineteen TLE patients and 19 controls underwent two high-resolution (1 mm isotropic) DTI and $1.1 \times 1.1 \times 1\,mm^3$ T2 relaxometry scans (in a subset of 16 TLE patients and 9 controls) of the hippocampus at 3T, with a 2.6 ± 0.8 year inter-scan interval. Within-participant hippocampal volume, MD and T2 were compared between the scans. Contralateral hippocampal changes 2.3 ± 1.0 years after surgery and ipsilateral preoperative MD maps versus postoperative subfield histopathology were evaluated in eight patients who underwent surgical resection of the hippocampus.

Results: Reduced volume and elevated MD and T2 of sclerotic hippocampi remained unchanged between longitudinal scans. Focal regions of elevated MD and T2 in bilateral hippocampi of HS TLE were detected consistently at both scans. Regions of high MD and T2 correlated and remained consistent over time. Volume, MD, and T2 remained unchanged in postoperative contralateral hippocampus. Regional elevations of MD identified subfield neuron loss on postsurgical histology with 88% sensitivity and 88% specificity. Focal T2 elevations identified subfield neuron loss with 75% sensitivity and 88% specificity.

Significance: Diffusion and T2 abnormalities in ipsilateral and contralateral hippocampi remained unchanged between the scans suggesting permanent microstructural alterations. MD and T2 demonstrated good sensitivity and specificity to detect hippocampal subfield neuron loss on postsurgical histology, supporting the potential that high-resolution hippocampal DTI and T2 could be used to diagnose HS subtype before surgery.

KEYWORDS

diffusion tensor imaging, hippocampal sclerosis, histology, mean diffusivity, postoperative, quantitative T2

1 | INTRODUCTION

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy. While only 20% of TLE patients respond to medications,[1] anterior temporal lobe resection including the hippocampus can provide seizure freedom with resultant improvements in quality of life.[2] However, long-term surgical outcome studies demonstrate that approximately 50% of patients experience seizure recurrence.[3] Finding more accurate predictors of surgical success preoperatively is imperative to advance treatment options and improve outcomes in TLE patients.

Hippocampal sclerosis (HS) is the most common underlying etiology in drug-resistant TLE[1,4] and is categorized into three subtypes based on histological assessment of neuronal loss and gliosis of hippocampal subfields.[4,5] The International League Against Epilepsy (ILAE) HS subtypes include: Type 1 HS with neuronal loss in CA1 and CA4, Type 2 HS with prominent neuronal loss in CA1, and Type 3 HS with prominent neuronal loss in CA4.[4] Notably, postsurgical success has been demonstrated to correlate with HS subtypes.[5–11] Since the HS subtype is currently diagnosed on surgical histology,[5,7,8] it has not been possible to use this information to improve the prediction of surgical outcomes prospectively prior to surgery.[7–9,11]

While conventional clinical magnetic resonance imaging (MRI) can reliably detect HS (volume loss and elevated T2-weighted signal),[6,12] it has not been possible to diagnose HS subtypes using standard in vivo MRI.[1,3–6] Diffusion tensor imaging (DTI) indirectly evaluates brain microstructure[13,14] and has demonstrated elevated mean diffusivity (MD) in the ipsilateral hippocampus of TLE patients with HS,[15–18] correlating with lower pyramidal neuron density in CA4/dentate gyrus (DG).[19] Given the low spatial resolution of most research DTI acquisitions designed for whole-brain (e.g., 2 mm isotropic; 8 mm^3 voxel volumes), it has been difficult to evaluate diffusion changes in hippocampal subregions. Recently, high-resolution (1 mm isotropic) DTI of the human hippocampus using a clinically relevant protocol (~6 minutes at 3T)[20] has shown focal diffusion abnormalities of the hippocampus presurgery that agreed with subfield neuron loss in postsurgical histology in a pilot sample of 4 TLE patients.[21] However, to characterize and validate TLE diffusion findings using high-resolution DTI, a larger sample size of patients with postsurgical histology is required. Increased quantitative T2 relaxation time has also been shown to correlate with neuronal loss in CA1 and CA3,[22] gliosis in DG[23] and granule cell dispersion.[24] Whether diffusion and T2 MRI provide complementary data regarding underlying structural abnormalities in the TLE hippocampus is not known.

It is also unclear whether hippocampal volume, quantitative T2, and diffusion subfield abnormalities persist or worsen in TLE and what the impact of temporal lobe surgery is on the contralateral hippocampus. Some previous longitudinal MRI studies have suggested progressive atrophy of the sclerotic hippocampus[25–27] as well as postoperative reduction in volume and an increase in MD of

Key Points

- Diffusion and T2 abnormalities of hippocampi remain unchanged after ~2.6 years suggesting permanent focal microstructural injury in TLE
- Regional evaluations of MD correlated with regions of higher T2 values
- Focal elevated MD and T2 regions preoperatively are sensitive and specific to subfield neuron loss on postoperative histology

the contralateral nonresected hippocampus.[28–31] However, these findings are not supported by other MRI and histological studies,[32–35] which suggest limited change over time in the hippocampus. Thus, more studies with a longitudinal design are needed to explore these inconsistencies and to improve the understanding of structural changes following epilepsy surgery.

The current longitudinal imaging study of 19 patients and 19 healthy controls acquired high-resolution 1 mm isotropic DTI and $1.1\times1.1\times1\,mm^3$ quantitative T2 to assess whole and focal MRI changes of the ipsilateral and contralateral hippocampus over ~2.6 years in TLE patients (eight of whom had hippocampal resection). To provide insight into focal diffusion abnormalities, the location of preoperative MD abnormalities of the hippocampus was compared with focal T2 abnormalities and areas identified as abnormal (e.g., containing neuron loss) in subfield histopathology following surgery.

2 | METHODS

2.1 | Participants/study demographics

This study included 19 controls (mean age 44 ± 13 years; 18–70 years; 10 females) and 19 patients with TLE (mean age 43 ± 13 years; 18–71 years; 9 females). Of this cohort, 12 patients and 10 controls were recruited from our previous cross-sectional study.[21] All controls were recruited through advertising and had no self-reported history of epilepsy, neurological and psychiatric illnesses, or contraindications to MRI. TLE patients were referred by the neurologists at the University of Alberta Hospital Epilepsy Clinic based on ictal semiology, ictal and interictal EEG, and MRI being consistent with a diagnosis of TLE. All subjects provided written informed consent prior to participation. This study was approved by the Health Research Ethics Board at the University of Alberta.

Temporal lobe epilepsy patients were subdivided into unilateral HS (n = 11), bilateral HS (n = 2), and non-HS (n = 6) based on qualitative review of the clinical MRI (Table 1). Clinical MRI acquisition included: 1 mm isotropic 3D T1 (MPRAGE), coronal T2 with high in-plane resolution, and coronal FLAIR with high in-plane resolution. All MRIs were reviewed by a radiologist with expertise in the field of epilepsy. Non-HS patients showed no evidence of hippocampal atrophy, loss of internal hippocampal architecture, or other structural abnormalities, except for one patient who had a low-grade ganglioglioma (diagnosed on histopathology) with normal hippocampi on MRI (and no evidence of hippocampal pathology on surgical histology).

2.2 | Image acquisition

All 38 subjects underwent two research MRI scans with an inter-scan gap of 2.6 ± 0.8 years (1–4.4 years) for TLE patients and 2.7 ± 0.8 years (1–4 years) for controls. Eight out of 19 TLE patients (seven unilateral HS and one non-HS patients with ganglioglioma) had hippocampal resection surgery at 6.6 ± 7.5 months (1 day-18 months) after scan 1 and then had a follow-up scan at 2.3 ± 1.0 years (1–4 years) after their surgery.

All MRI images were acquired on a Siemens Prisma 3T as per Treit et al.[20] Diffusion images were acquired with single-shot 2D EPI (GRAPPA R2; 6/8 PPF; A/P phase encode), FOV $220\times216\,mm^2$, matrix 220×216, 20 slices at $1\times1\times1\,mm^3$ resolution with no interpolation, TE 72 ms, TR 2800 ms, b 500 s/mm^2, 10 averages of 10 gradient directions and 10 b0s in 5:18 minutes. The slices were manually aligned along the long axis of the hippocampus using a whole-brain 3D T1-weighted MPRAGE for reference ($0.85\,mm^3$ isotropic; 3:39 minutes). A subset of 16 TLE patients and 9 controls also underwent T2 multi-echo spin echo relaxometry scans with 20 slices, 16 echoes, TE 10.7–171.2 ms, 10 ms inter-echo spacing, TR 3560 ms, $1.1\times1.1\times1\,mm^3$, 5:47 minutes. T2 relaxometry scans were acquired along the long axis of the hippocampus (in the same plane as the diffusion acquisition).

Gibbs-ringing, eddy current and motion corrections, and tensor parameter estimations were performed in ExploreDTI v4.8.6 to obtain mean diffusion-weighted image (DWI), MD, and FA maps. Quantitative T2 maps from multi-echo spin echo acquisition were computed using a hybrid model of extended phase graph (EPG)-based indirect and stimulated echo compensation[36] with Shinnar-Le Roux approximation of slice profiles.[37]

2.3 | Hippocampus segmentation

Whole-hippocampi were manually segmented on mean DWIs in native space using ITK-snap v3.6.0[38] by a single user (author SAA), blinded to the subject group and longitudinal scan number. Similarly, hippocampi were traced again by author SAA on echo-summed T2-weighted images. The segmentation protocol followed the guidelines outlined in Alzheimer's Disease Neuroimaging Initiative Harmonized Protocol,[39] including the fimbria/alveus in the procedure but excluding the subiculum. To exclude cerebrospinal fluid (CSF)-containing voxels, an MD threshold of $1.5\times10^{-3}\,mm^2/s$ and T2 threshold of 150 ms (determined based on the lower range of MD and T2 in lateral ventricles) were applied. The volume, MD, FA, and T2 were obtained for

TABLE 1 Characteristics and demographics of 19 temporal lobe epilepsy patients

ID	Hippocampal sclerosis (HS) classification (clinical MRI)	Sex	Age at scan 1 (years)	Scan gap (years)	Age of seizure onset (years)	Disease duration (years)	Telemetry results	Surgery type	Gap surgery – Scan 2 (years)	Pathology	Engel outcome[a]
1	Non-HS	Male	47	2.5	18	29	Bilateral	n/a	n/a	n/a	n/a
2	Non-HS	Male	51	2.5	45	6	Right	n/a	n/a	n/a	n/a
3	Non-HS	Male	53	3.5	51	2.0	Right	n/a	n/a	n/a	n/a
4	Non-HS	Male	34	2.4	28	6	Left	n/a	n/a	n/a	n/a
5	Non-HS	Male	29	2.3	18	11	Left	n/a	n/a	n/a	n/a
6	Non-HS	Female	18	4.0	17	1.0	Right	Right ATL	4.0	Non-HS (Glioma grade 1)	IA
7	Unilateral – Right	Male	44	3.9	2	42	Right	Right ATL	2.5	Type 1 HS	IA
8	Unilateral – Right	Female	39	2.0	28	11	Right	Right SAH	2.0	Type 2 HS	IA
9	Unilateral – Left	Female	19	1.4	6	13	Left	Left ATL	1.4	Type 2 HS	ID
10	Unilateral – Left	Male	28	1.7	4	24	Left	Left ATL	1.1	Type 2 HS	IA
11	Unilateral – Left	Female	54	2.4	37	17	Left	Left ATL	1.6	Type 2 HS	IIIA
12	Unilateral – Left	Female	47	2.7	27	20	Left	Left ATL	2.7	Type 2 HS	IIIA
13	Unilateral – Left	Male	43	4.4	33	10	Left	Left SAH	3.1	Type 2 HS	IA
14	Unilateral – Right	Female	47	2.9	9	37	Right	n/a	n/a	n/a	n/a
15	Unilateral – Right	Female	71	2.7	18	53	Right	n/a	n/a	n/a	n/a
16	Unilateral – Left	Female	44	1.0	7	37	Left	n/a	n/a	n/a	n/a
17	Unilateral – Left	Male	49	2.4	44	5	Left	n/a	n/a	n/a	n/a
18	Bilateral	Male	59	2.6	5	54	Bilateral	n/a	n/a	n/a	n/a
19	Bilateral	Female	36	2.4	0.7	35	Bilateral	n/a	n/a	n/a	n/a

Abbreviation: ATL, anterior temporal lobectomy; SAH, selective amygdalo hippocampectomy

[a]Engel outcomes for eight surgical patients were determined within 4 months of their postoperative scans.

the whole hippocampus. The intrarater dice coefficient (DC) for author SAA was 0.93 ± 0.01, and intraclass correlation coefficient (ICC) for hippocampus volume was 0.98 (0.96–0.99 CI) as measured in 12 subjects (six controls and six TLE) randomly chosen from the sample. Inter-rater reliability between two authors (SAA and ST) showed strong DC (0.83 ± 0.03) and ICC (0.91, 0.64–0.97 CI) scores in the same 12 subjects (Table S1).

2.4 | Registration

To directly compare hippocampal regional changes between the scans, longitudinal mean DWIs for each subject were co-registered using FSL/FLIRT v6.0.[40] Prior to co-registration, 3D Slicer v4.11[41] was used to extract a box region around the hippocampus as a new extracted mean DWI volume given the need to exclude the surgical resection cavity in surgical patients, as this area would significantly disrupt the registration algorithm (Figure S1). For consistency, this method was applied to all subjects (including nonsurgical subjects) and the same transformation was applied to MD using trilinear interpolation. The same method was applied to echo-summed T2-weighted images to co-register longitudinal T2 maps.

2.5 | Identification of focal MD and T2 abnormalities

To characterize focal MD abnormalities at scan 1, an MD threshold of 1.1×10^{-3} mm^2/s was applied, representing two standard deviations (SD) above mean MD ($0.78\pm0.17\times10^{-3}$ mm^2/s) of 19 controls (38 hippocampi). Similarly, regional T2 abnormalities were defined as voxels above a T2 threshold value of 95 ms (2 SD above the control mean, 71 ± 12 ms) measured in 9 controls (18 hippocampi). This identified the location and extent (expressed as percent of the hippocampus volume with abnormal voxels) of hippocampal MD and T2 elevations.

2.6 | Regional MD changes between the scans

To characterize the expected range of inter-scan variability in regional MD maps, a reliability analysis was performed by scanning six healthy subjects (mean age 30 ± 4.9 years; 22–35 years; 3 females) two or three times each over a period of 6 ± 3.8 days (1–17 days) using the high-resolution DTI protocol. This allowed for an estimation of the scan-rescan reliability and the level of noise (e.g., processing and registration variability, etc.) in closely spaced serial scans. Difference MD maps were created by subtracting co-registered hippocampal MD maps for each subject. Voxel-by-voxel MD subtraction maps of the six healthy subjects demonstrated a small mean range of -0.06×10^{-3} to $+0.05\times10^{-3}$ mm^2/s between the serial scans.

2.7 | Statistical analysis

Statistical tests were performed in SPSS v28 (SPSS Corp, 2021) and Prism (GraphPad Software, 2021). Two independent repeated-measures ANOVA (RM-ANOVA) designs were prepared with scans 1 and 2 as repeated factors, hippocampal MRI measures (volume, MD, FA, T2) as dependent variables, and interscan interval as a covariate. The first RM-ANOVA assessed the trajectories of MRI measures in the controls (bilateral hippocampi of 19 healthy subjects, n = 38), non-HS (contralateral hippocampus of 11 unilateral HS and 11 hippocampi of six non-HS TLE patients [one hippocampus was surgically removed]; n = 22) and HS (ipsilateral hippocampus of four unilateral HS without surgery and hippocampi of two bilateral HS TLE patients; n = 8; Figure 1A). The second RM-ANOVA compared the contralateral hippocampus of TLE patients with and without surgery (Figure 1B). One non-HS and both bilateral HS patients were excluded due to the demonstration of independent bilateral seizure onset during inpatient EEG-video telemetry (Table 1). The groups included surgery (contralateral hippocampus of seven unilateral HS and one non-HS patient; n = 8) and nonsurgery (contralateral hippocampus of four unilateral HS who did not undergo resection and four non-HS patients; n = 8). T2 was available in a subset with group numbers shown in Figure 1. Pairwise comparisons adjusted with a Sidak correction for multiple comparisons were conducted for RM-ANOVAs with a significant omnibus effect. Whole-hippocampus measures were plotted against scan number, mean control measurements, and two SD boundaries to assess individual longitudinal changes. Pearson's correlations tested the relationship between whole-hippocampus volume, MD, FA, and T2 with the age of seizure onset and disease duration.

2.8 | Histology

Histological samples of the hippocampus were available for eight TLE patients who underwent surgical resection of the anterior temporal lobe and had pre- and postoperative scans. While the exact location of the histology sample taken from the hippocampus could not be determined, based on the standard surgical procedure used by the neurosurgeon, the histology sample was consistently

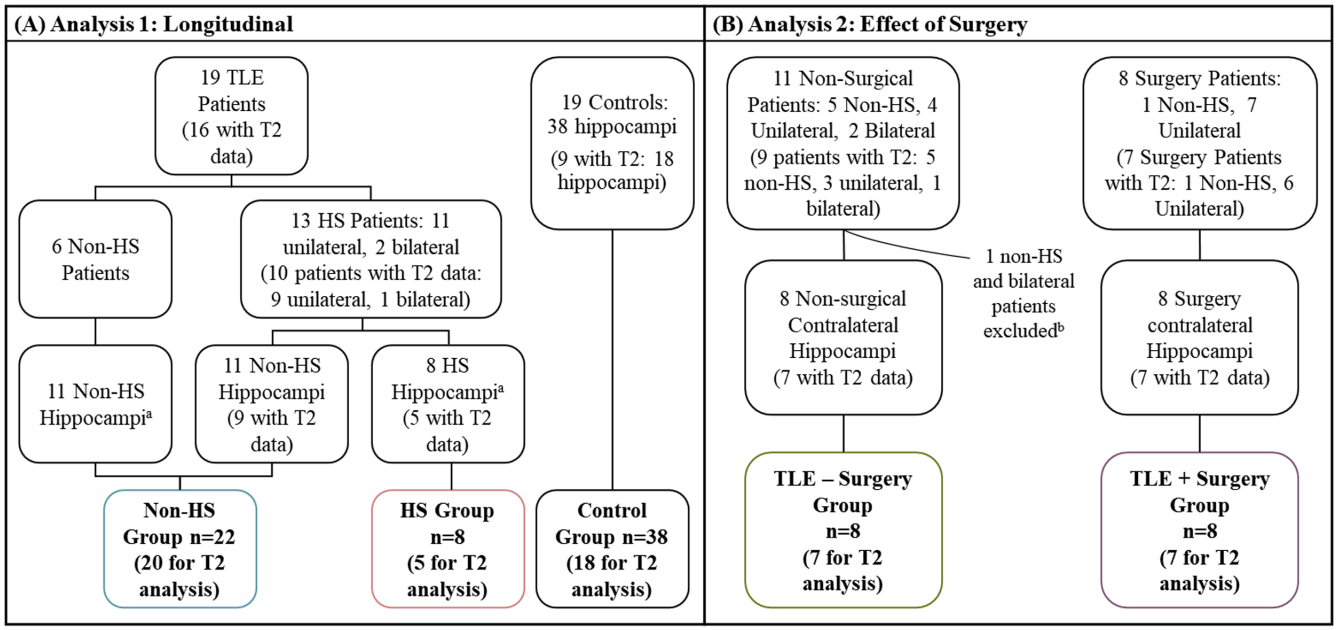

FIGURE 1 Flow chart of the hippocampus groups selected for the repeated-measures ANOVA to assess trajectories of volume, MD, FA, and quantitative T2. (A) Analysis 1 was conducted to assess trajectories of volume, MD, FA, and T2 in the control, non-HS and sclerotic hippocampi. (B) Analysis 2 assessed the effect of surgery on the contralateral hippocampus of HS and non-HS patients. [a]One non-HS patient and seven of 11 unilateral HS patients underwent surgical removal of the ipsilateral hippocampus following their first scan and therefore longitudinal analysis could not be performed on the resected hippocampi. [b]One non-HS and bilateral HS patients were excluded due to the demonstration of independent bilateral seizure onset during inpatient EEG-video telemetry. HS, hippocampal sclerosis

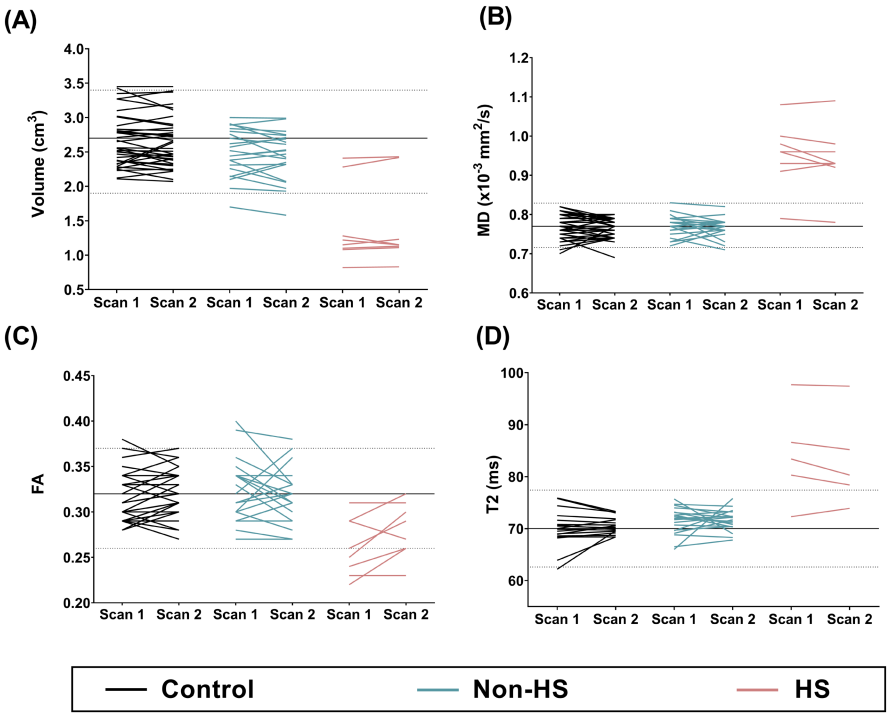

FIGURE 2 Within-individual longitudinal changes of (A) volume, (B) MD, (C) FA, and (D) T2 for whole-hippocampi of all subjects across two scans ~2.6 years apart plotted against mean control (solid line) and 2 SD (dotted lines) at both scans. Volume, MD, FA, and T2 of the non-HS group generally remained within 2 SD of the mean control values at both scans. The HS group demonstrated lower volume in 6/8, higher MD in 7/8, lower FA in 4/8, and higher T2 in 4/5 (scan 1) compared with the control group. The volume, MD, and T2 differences remained consistent between the scans. FA increased by 8%–20% in 5/8 HS hippocampi but was still lower than 2 SD of controls in 3/8 patients

taken from the posterior head and anterior body of the hippocampus. The histological tissues were analyzed by a neuropathologist (LS) blinded to the clinical information. Neuronal nuclei (NeuN) stain was used as a marker of neuronal loss. The HS subtypes were assigned based on the degree of neuronal loss in CA1 and CA4 subfields as per ILAE criteria.[4]

As the pathological specimens were obtained at the hippocampal head-body junction, the comparison to MD and T2 abnormalities was also focused on this region.

Based on anatomical knowledge, it was assumed that the CA1 subfield is located in the lateral aspect of the hippocampus and that the CA4 subfield is located in the mesial hippocampus.[42] To facilitate the analysis of CA1 and CA4 at the head-body junction, where the hippocampus curves mesially, 3D Slicer was used to manually perform curved multiplanar reformatting on mean DWI and echo-summed T2-weighted images.[43] This enabled the reconstruction of diffusion and T2 slices transverse to the long axis of the hippocampus and allowed the identification of CA1 and CA4 with normal or elevated MD and T2 (Figure 5). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MD and T2 to identify subfield pathology were independently determined. False negatives were defined as subfields with histological diagnosis of neuron loss and normal MD and T2. False positives were defined as subfields without neuron loss and abnormally elevated MD and T2.

3 | RESULTS

3.1 | Whole-hippocampus MRI measures remain stable

There was a significant effect of group (control, non-HS, HS) on volume ($F(2) = 32.1$, $P < 0.001$), MD ($F(2) = 84.2$, $P < 0.001$), FA ($F(2) = 11.7$, $P < 0.001$) and T2 ($F(2) = 27.2$, $P < 0.001$). Post-hoc tests revealed significantly lower volume (by 46%, $P < 0.001$), higher MD (by 23%, $P < 0.001$), lower FA (by 15%, $P < 0.001$), and higher T2 (by 19%, $P < 0.001$) in the HS hippocampi compared with the control (Figure 2). The control and non-HS hippocampi did not significantly differ in any of the MRI measures (Table S2). There were no statistically significant differences in hippocampal volumes, MD, and T2 between scan 1 and 2 for any groups. There was a significant interaction effect between the groups and repeat scans for hippocampal FA ($F(2) = 3.49$, $P = 0.038$). Post-hoc analysis showed that hippocampal FA in the HS group at scan 2 was significantly higher (by ~8%–20%, $P = 0.022$) compared with scan 1 (Table S2). There were no significant correlations between MRI measures of sclerotic hippocampi with either age of seizure onset or disease duration at either scan.

3.2 | Heterogeneous regional MD abnormalities of the sclerotic hippocampus persist over time

High-resolution DTI demonstrated substantial heterogeneity of MD values within hippocampal subregions for HS patients (Figure 3). Hippocampi of non-HS patients (Figure 3B,E) showed comparable MD (~0.8×10^{-3} mm^2/s) to the controls (Figure 3A) whereas sclerotic hippocampi in HS patients showed "hotspots" with regional elevations of MD (>1.1×10^{-3} mm^2/s shown in orange and red in Figure 3C,D,F-H).

To identify regions of abnormally high MD at scan 1, a threshold value of 1.1×10^{-3} mm^2/s (2 SD above mean control) was applied while excluding voxels attributed to CSF. The percent of voxels with MD above this threshold was minimal in the controls (mean 5 ± 2% of voxels, range 1%–9%) and non-HS groups (mean 4 ± 1%, range 1%–7%). Conversely, 22 ± 17% (range 4%–59%) of sclerotic hippocampi volume contained voxels with elevated MD (Figure S2). MD elevations were diffuse along the long axis of the hippocampus (e.g., Figure 3C,D-left hippocampus) in 8/15 sclerotic hippocampi, predominantly localized to the head (e.g., Figure 3D-right hippocampus, G, H) in 5/15 sclerotic hippocampi, and were not evident in 2/15 sclerotic hippocampi. MD elevations were localized to the lateral regions in four hippocampi, which were suggestive of Type 2 HS (CA1 abnormalities; e.g., Figure 3G,H) and localized to both lateral and mesial regions in nine hippocampi, which was suggestive of Type 1 HS (CA1 and CA4 abnormalities; e.g., Figure 3C,D,F).

Longitudinal analysis of repeated scans indicated that regional MD abnormalities were consistent over time. MD subtraction maps (scan 2 – scan 1) for TLE patients and control subjects fell in the expected range of scan-rescan noise as determined in six healthy subjects with closely spaced serial scans. This provided quantitative evidence that there is little to no regional hippocampal MD change between the two scans in healthy controls and TLE patients over ~2.6 years.

3.3 | Regional T2 relaxometry increases correspond to regions with elevated MD

Quantitative T2 maps from multi-echo relaxometry were acquired in 16 TLE patients and nine controls. The percent of hippocampal voxels with regions of abnormally high T2 (>95 ms or above 2 SD of mean controls while also excluding CSF-containing voxels) at scan 1 was 2 ± 1% (range 1%–4%) in control, 3 ± 1% (range 2%–5%) in non-HS and 14 ± 12% (range 3%–44%) in HS (Figure S2). Regions of elevated T2 were diffuse along the long axis of the hippocampus in 4/12 sclerotic hippocampi (e.g., Figure 4C), regional and predominately localized on the head in 6/12 sclerotic hippocampi (e.g., Figure 4B), and were not evident in 2/12 sclerotic hippocampi. T2 elevations were localized to the lateral regions of two hippocampi (suggestive of Type 2 HS), to the mesial regions of one hippocampus (suggestive of Type 3 HS), and to both lateral

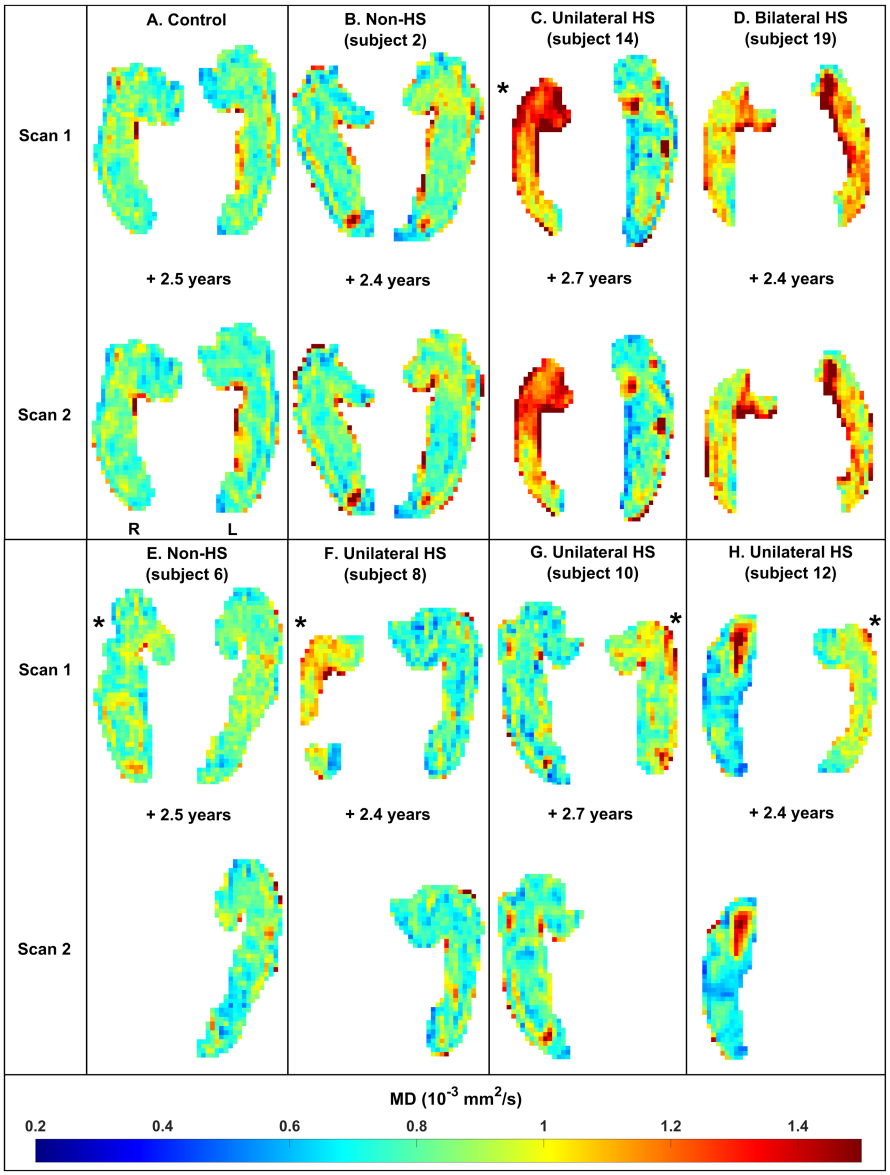

FIGURE 3 The top panel demonstrates longitudinal co-registered MD maps of the hippocampi from a representative (a) control (28 years old), (B) non-HS, (C) right unilateral HS temporal lobe epilepsy (TLE), and (D) bilateral HS TLE. Regional MD maps demonstrate the excellent spatial correspondence between longitudinal scans ~2.6 years apart. The non-HS hippocampi (B) are comparable to the control (mostly green 0.8×10^{-3} mm^2/s) and remain unchanged between the two scans. The ipsilateral hippocampus (indicated by *) of (C) and sclerotic hippocampi of (D) show widespread elevated MD (above 1.1×10^{-3} mm^2/s) throughout the entire hippocampus that remains consistent between the scans. The contralateral hippocampus in (C) shows a focal increase of MD within the hippocampus head, which remains consistent between the scans. The bottom panel demonstrates longitudinal MD maps of four representative (E-H) surgical patients. The MD of the contralateral hippocampus in all examples remains consistent and unchanged between the scans. Non-lesional patient (E) shows hippocampal MD within the control range. Regions of elevated MD are present in the ipsilateral hippocampus (*) of (F-H) and contralateral hippocampus of (H). Note that the maps are not scaled to size between patients but are scaled the same left/right

and mesial regions in seven hippocampi (suggestive of Type 1 HS; e.g., Figure 4B,C).

Regions of elevated hippocampal T2 demonstrated excellent spatial overlap with regions of high MD (Figure 4). While the extent of MD elevated regions (~22%) was larger than T2 elevated regions (~14%), there was a significant correlation ($R = 0.962$, $P < 0.001$) between percent hippocampal regions with high MD and T2 in sclerotic hippocampi (Figure S2).

3.4 | Focal regions of elevated MD and T2 in contralateral hippocampus

While whole-hippocampal MD and T2 of non-HS hippocampi did not differ from the controls, focal regions of elevated MD were detected in 4/11 contralateral hippocampi of unilateral HS patients (e.g., Figure 3H). Regions of elevated T2 were also detected in the contralateral hippocampi of the same four patients (Figure 4B). In all cases, regional

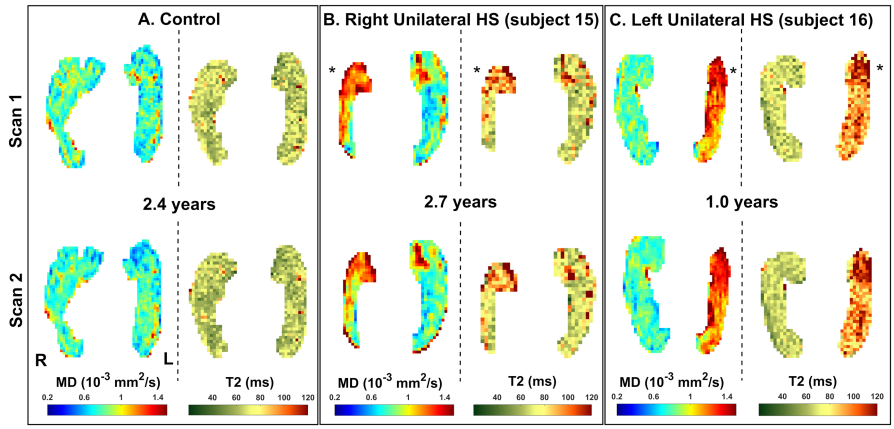

FIGURE 4 Regional MD and T2 maps of the hippocampus in a representative (A) control (32 years old) and two unilateral HS patients. Regions of elevated T2 (above 95 ms) were present in the ipsilateral (indicated by *) hippocampus of (B) and (C) and contralateral head of hippocampus of (B). These elevated T2 regions overlapped with regions of high MD and remained consistent between the longitudinal scans. Note that the maps are not scaled to size between patients but are scaled the same left/right

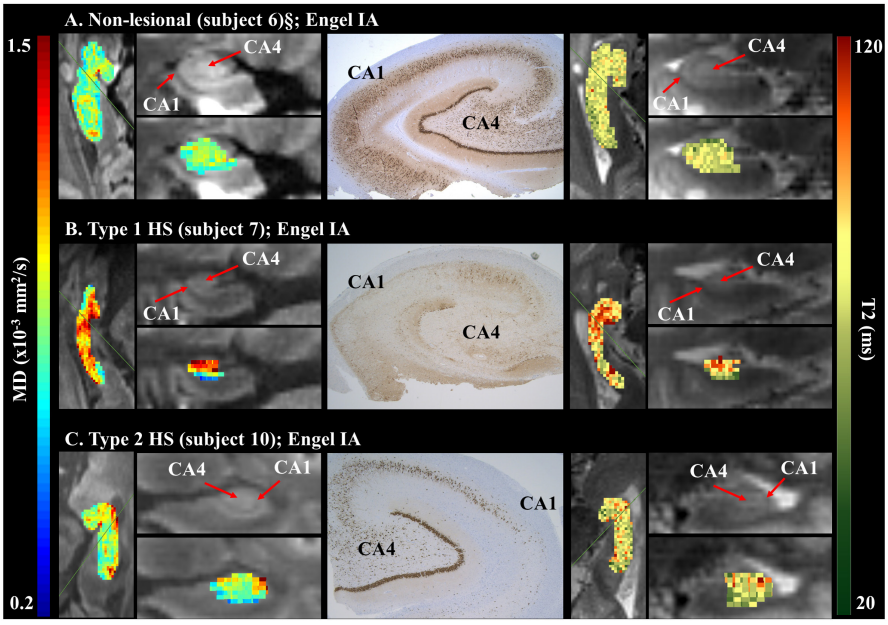

FIGURE 5 Comparison of presurgical MD (superimposed on mean diffusion-weighted image) and quantitative T2 maps (superimposed on echo-summed T2-weighted images) with NeuN (marker of neuronal loss) histology of 3 subjects who underwent surgical resection of the hippocampus. The HS subtypes were assigned by the neuropathologist (coauthor LS) blinded to the clinical information. The histology specimen analyzed was consistently obtained from the posterior head and anterior body of the hippocampus (where the red lines were manually oriented to reconstruct the coronal MRI slices). (A) Non-lesional hippocampus showing typical MD and T2 values (mostly green) and normal neuronal density (dark brown). (B) Type 1 HS with elevated MD and T2 (orange and red) in both CA1 and CA4 regions agreeing with type 1 HS diagnosis. (C) Type 2 HS (neuronal loss in CA1) with MD and T2 elevations in only CA1. (§) denotes the subject reported in our previous study[21]

elevations of MD and T2 were localized to the mesial hippocampal head (suggesting CA4 abnormalities).

3.5 | MRI and histological assessment of surgical patients

Surgery did not result in a significant difference for volume, MD, FA, and T2 in the contralateral whole-hippocampus 2.3 ± 1.0 years after surgery (Figure S3). MD subtraction maps of the contralateral hippocampus in eight surgical patients showed little to no change between the two scans (not shown).

Subject 6 had a brain tumor with no evidence of HS on clinical MRI and the histology showed normal neuron density in CA1 and CA4 (Figure 5A). All seven surgical patients with evidence of HS on clinical MRI had HS confirmed with surgical pathology (one subject with Type 1 HS and six subjects with Type 2 HS; Figure 5B,C).

3.6 | Presurgical regional elevated MD and T2 correspond with NeuN loss on postsurgical histology

Based on the pathologist's assessment of postsurgical histology in eight surgical patients (16 subfields in total), 8/16 subfields were classified as normal (CA1 and CA4 in the tumor case and CA4 for seven Type 2 hippocampi) and 8/16 subfields were classified as abnormal (CA1 and CA4 for Type 1 HS hippocampus, CA1 for seven Type 2 hippocampi).

Regional MD abnormalities ($>1.1\times10^{-3}$ mm^2/s) in the presurgical ipsilateral hippocampus correctly identified 7/8 subfields with reduced neuronal density, demonstrating 88% sensitivity. Likewise, 7/8 subfields with normal neuronal density had normal MD ($\sim0.8\times10^{-3}$ mm^2/s), yielding 88% specificity. Regional MD values were normal in 1/8 subfields with neuron loss (false negative) and abnormally elevated in 1/8 subfield without neuron loss (false positive), yielding 88% PPV and 88% NPV. Regional T2 abnormalities (>95 ms) identified 6/8 subfields with neuron loss, yielding 75% sensitivity and regions with normal T2 (~71 ms) identified 7/8 normal subfields, yielding 88% specificity. Regional T2 values were normal in 2/8 subfields with neuron loss (false negatives) and abnormally elevated in 1/8 subfields without neuron loss (false positive), yielding 86% PPV and 78% NPV. Overall, regional patterns of MD and T2 agreed with HS subtype diagnosis in 6/8 and 5/8 surgical patients, respectively.

4 | DISCUSSION

Hippocampal sclerosis is the most common pathology in medically intractable TLE and the presence of HS is associated with improved seizure-free outcomes with temporal lobe resection.[6,10] However, HS is not homogeneous and has a tremendous amount of variability between patients with respect to the extent of pathological changes within different hippocampal subregions[5] and along the long axis of the hippocampus,[44,45] as well as the presence of pathology in the hippocampus contralateral to the seizure focus.[45–47] Given that approximately 50% of patients have seizure recurrence following surgery on long-term follow-up,[3] it is reasonable to hypothesize that differences in surgical outcomes could be driven by this pathological heterogeneity. This hypothesis is supported by the demonstration of differences in surgical outcomes for different HS subtypes.[7–9,11] These studies highlight the importance of developing noninvasive methods to accurately detect subhippocampal pathological changes in vivo as part of surgical planning. While MRI has been demonstrated to detect HS with high accuracy at the whole-hippocampal level,[6,12] the ability to detect subhippocampal abnormalities with conventional MRI is limited. High-resolution DTI (1 mm isotropic) has shown focal MD abnormalities of the hippocampus presurgery that corresponded with subfield neuron loss in postsurgical histology in four TLE patients.[21] In the current study we have expanded our observations to a larger cohort of eight TLE patients with postsurgical histology and included longitudinal analysis in order to gain further insights into the underlying mechanisms responsible for regional changes in MD of the hippocampus.

Hippocampal volume, MD, and T2 did not show significant differences between scans for all groups (control hippocampi, nonHS hippocampi, HS hippocampi as well as for the contralateral hippocampi of patients who underwent surgery). These findings suggest that the hippocampal imaging parameters were stable at least over the 2.6-year period of this study. These observations suggest that the regional MD changes are associated with structural abnormalities as opposed to functional changes (such as fluid shifts), which could also result in the elevation of MD. Previous longitudinal hippocampal DTI studies postsurgery are limited. In contrast to our findings, two surgical studies demonstrated changes in MD in the postoperative contralateral hippocampus, however, with conflicting findings (one showing an increase in MD[29] and other showing a decrease[31]). Differences in the timing of postoperative scans and the methodology (in particular the spatial resolution of scans and looking at regional as opposed to whole-hippocampal measures) could explain the conflicting findings. Our findings are consistent with TLE not being progressive over a ~2.6 year (1–4.4 year) inter-scan timespan but was limited by a relatively small sample size of 19 TLE patients.

Consistent with two previous studies,[34,35] our results suggest stability of the contralateral hippocampus volume ~2.3 years after the surgery. This differs from other studies that reported postoperative atrophy of the contralateral hippocampus over 0.5–9.6 years.[28,30] The discrepancies in the literature may be related to different segmentation protocols, which limit the comparability of results between studies. Manual segmentation is subject to heterogeneity in the inclusion of different mesial temporal structures (such as how much of the subiculum is included) resulting in differences in the hippocampal volume measurements between studies.[45] The Harmonized Protocol (HarP) for hippocampus segmentation attempts to limit this heterogeneity[46] and has demonstrated high inter- and intra-rater reliability.[39] Our segmentation protocol based on the HarP demonstrated a high degree of inter- and intra-rater reliability (Table S1) and measured mean hippocampal volumes of

the controls consistent with the normative hippocampal volumes (~2.7 mm^3, Table S2) reported in healthy individuals.[39,47] This is in contrast with the previous studies that measured much higher baseline control hippocampal volumes (~3.4 cm^3 and ~5.4 cm^3).[28,30]

Consistent with the pathological literature[48–50] we observed considerable heterogeneity in the extent of MD abnormalities along the long axis of the hippocampus (Figure 3), within the lateral and mesial hippocampus (suggestive of variability in pathological involvement of different hippocampal subfields) as well as in the involvement of the contralateral hippocampus (e.g., Figure 3H). Of note, contralateral MD hippocampal abnormalities were not observed at a whole-hippocampal level and were only seen regionally. When comparing presurgical regional MD abnormalities to postsurgical histology, MD identified subfield neuron loss with excellent sensitivity and specificity (Figure 5B,C).

While visual detection of increased T2-weighted signal can reliably identify HS in TLE patients,[6,12] quantification of T2 relaxation time can detect subtle hippocampal abnormalities with higher accuracy.[51,52] However, T2 relaxometry studies have been limited by the low spatial resolution of acquisitions and while recent studies[24,51,52] acquired T2 scans with high in-plane resolutions (e.g., $0.43 \times 0.43\ mm^2$), these studies still acquired thick slices (4 mm or above), which can result in missed lesions/abnormalities on a regional hippocampal level. Further, these studies used a dual-echo sequence and did not account for stimulated echoes, which leads to an overestimation of T2 values.[36,53] In our study, focal hippocampal T2 abnormalities were demonstrated using a 16-echo T2 sequence with stimulated echo compensation and thin 1 mm slices (1.21 mm^3 voxel volume). These regional abnormalities strongly correlated with the MD findings (Figure 4) and also had good sensitivity and excellent specificity in detecting subfield pathology (Figure 5B,C). These observations suggest that MD and quantitative T2 provided complementary information regarding hippocampal structural changes. Of interest, the extent of the focal abnormalities demonstrated with MD was 1.6× greater than T2, which is consistent with our observation of MD having higher sensitivity than T2 in detecting hippocampal subfield pathology. A larger sample of surgical TLE patients with postsurgical histology is required to confirm the higher sensitivity of MD compared with T2 in the detection of subfield neuron loss.

In summary, our findings demonstrate that high-resolution DTI and quantitative T2 relaxometry can demonstrate structural abnormalities associated with hippocampal sclerosis at a subhippocampal level ipsilateral and contralateral to the seizure focus. While the cohort of patients that underwent surgery was limited, both MD and T2 predicted subfield neuron loss on postsurgical histology with good sensitivity and specificity. Both DTI and T2 acquisitions were acquired at 3T in under 6 minutes making them clinically feasible, potentially providing the opportunity to diagnose precise HS subtypes as well as subtle or regional contralateral hippocampal abnormalities, which could also affect surgical outcomes, preoperatively.

AUTHOR CONTRIBUTIONS

S.A.A. processed all experimental data, performed the analysis, and wrote the paper with input from all authors. S.T. and W.A.W. contributed to MRI acquisitions and data visualization. G.L. contributed to T2 relaxometry data processing and analysis. L.S. analyzed the histology data. A.H.W. aided in the interpretation of the results and worked on the manuscript. C.B. and D.W.G. devised the project and were in charge of overall direction and planning.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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