Received: 23 January 2022 | Revised: 11 May 2022 | Accepted: 14 June 2022

DOI: 10.1111/epi.17333

Epilepsia®

RESEARCH ARTICLE

Superficial and deep white matter diffusion abnormalities in focal epilepsies

Hebel Urquia-Osorio[1,2] | **Luciana R. Pimentel-Silva**[1] | **Thiago Junqueira Ribeiro Rezende**[1] | **Eimy Almendares-Bonilla**[1,2] | **Clarissa L. Yasuda**[1] | **Luis Concha**[3] | **Fernando Cendes**[1]

[1]Department of Neurology, University of Campinas, São Paulo, Brazil

[2]Faculty of Medical Science, National Autonomous University of Honduras, Honduras

[3]Institute of Neurobiology, National Autonomous University of Mexico, Queretaro, Mexico

Correspondence
Luis Concha, Institute of Neurobiology, Universidad Nacional Autonoma de Mexico, Queretaro 76230, Mexico.
Email: lconcha@unam.mx

Fernando Cendes, Department of Neurology, University of Campinas, Campinas, SP 13083-970, Brazil.
Email: fcendes@unicamp.br

Funding information
This study and the authors received financial support from FAPESP (São Paulo Research Foundation) through CEPID/BRAINN grant 2013/07559–3 and scholarship grants 2016/05985–3 and 2013/21056–4.

Abstract

Objective: This study was undertaken to evaluate superficial-white matter (WM) and deep-WM magnetic resonance imaging diffusion tensor imaging (DTI) metrics and identify distinctive patterns of microstructural abnormalities in focal epilepsies of diverse etiology, localization, and response to antiseizure medication (ASM).

Methods: We examined DTI data for 113 healthy controls and 113 patients with focal epilepsies: 51 patients with temporal lobe epilepsy (TLE) and hippocampal sclerosis (HS) refractory to ASM, 27 with pharmacoresponsive TLE-HS, 15 with temporal lobe focal cortical dysplasia (FCD), and 20 with frontal lobe FCD. To assess WM microstructure, we used a multicontrast multiatlas parcellation of DTI. We evaluated fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD), and assessed within-group differences ipsilateral and contralateral to the epileptogenic lesion, as well as between-group differences, in regions of interest (ROIs).

Results: The TLE-HS groups presented more widespread superficial- and deep-WM diffusion abnormalities than both FCD groups. Concerning superficial WM, TLE-HS groups showed multilobar ipsilateral and contralateral abnormalities, with less extensive distribution in pharmacoresponsive patients. Both the refractory TLE-HS and pharmacoresponsive TLE-HS groups also presented pronounced changes in ipsilateral frontotemporal ROIs (decreased FA and increased MD, RD, and AD). Conversely, FCD patients showed diffusion changes almost exclusively adjacent to epileptogenic areas.

Significance: Our findings add further evidence of widespread abnormalities in WM diffusion metrics in patients with TLE-HS compared to other focal epilepsies. Notably, superficial-WM microstructural damage in patients with FCD is more restricted around the epileptogenic lesion, whereas TLE-HS groups showed diffuse WM damage with ipsilateral frontotemporal predominance. These findings

Hebel Urquia-Osorio and Luciana R. Pimentel-Silva contributed equally to this study.

suggest the potential of superficial-WM analysis for better understanding the biological mechanisms of focal epilepsies, and identifying dysfunctional networks and their relationship with the clinical–pathological phenotype. In addition, lobar superficial-WM abnormalities may aid in the diagnosis of subtle FCDs.

KEYWORDS

diffusion tensor imaging, focal cortical dysplasia, frontal lobe epilepsy, superficial white matter, temporal lobe epilepsy

1 | INTRODUCTION

Hippocampal sclerosis (HS) and focal cortical dysplasia (FCD) are among the most frequent brain lesions associated with pharmacoresistant focal epilepsies,[1–4] which can be diagnosed in vivo by neuroimaging.[5] In the past 2 decades, studies have focused on understanding the role of white matter (WM) in epilepsies through diffusion tensor imaging (DTI).[6–9] DTI is a magnetic resonance imaging (MRI) technique widely used to evaluate the brain's WM microstructure by analyzing the preferred direction of water diffusion.[10,11] These studies have demonstrated widespread deep-WM abnormalities in temporal lobe epilepsy with HS (TLE-HS). In FCD patients, the deep-WM abnormalities, although extending beyond the lesion seen on MRI, appeared to be less diffuse than in TLE-HS.[7–9]

The superficial WM (i.e., the region immediately below the cortex) contains a large proportion of corticocortical connections.[12] Emerging evidence suggests that alterations of superficial WM may be implicated in various neuropsychiatric disorders,[13] and few studies have investigated superficial-WM integrity in epilepsy.[14–16] To the best of our knowledge, there have been no studies to date showing alteration patterns of superficial WM in contrast with deep WM in a joint analysis to compare different groups of focal epilepsies.

Most epilepsy DTI studies have used tract-based analysis to evaluate deep WM.[6,7,17] Because the superficial WM is immediately adjacent to the cortex and presents a complex morphology, most DTI processing methods provide limited information about this region.[13] In this regard, DTI region of interest (ROI)-based analysis following cortical morphology can provide regional information about the integrity of superficial WM in patients with epilepsy and allows the investigation of the disease effects on the WM adjacent to the epileptogenic zone. Thus, it may provide further insights into the pathophysiology process according to etiology, ictal onset, and response to antiseizure medication (ASM).[18]

The current study evaluated whole-brain WM integrity through an ROI-based DTI analysis. We aimed to assess superficial-WM and deep-WM diffusion characteristics and identify distinctive patterns of microstructural anomalies in focal epilepsies by including patients with TLE-HS and FCD subdivided according to the response to ASM and localization of the epileptogenic lesion.

Key Points

- TLE-HS groups had more widespread superficial-WM and deep-WM diffusion abnormalities than FCD groups
- The superficial-WM damage patterns differed among epilepsy groups with different epileptogenic lesion topologies (mesial TLE-HS, tFCD, and fFCD)
- Patients with pharmacoresistant TLE-HS had broader multilobar superficial-WM abnormalities across all DTI metrics than pharmacoresponsive TLE-HS
- Superficial-WM analysis showed a gradient of abnormality intensity from the seizure focus toward more distant regions in all epilepsy groups
- The ROI-based superficial-WM analysis seems helpful for a better biological understanding of focal epilepsies and their relationship with the clinical–pathological phenotype

2 | MATERIALS AND METHODS

2.1 | Participants

We enrolled 113 healthy controls, without family or personal history of epilepsy, and 113 patients with focal epilepsies. The patients were divided into four groups: (1) 51 patients with TLE and MRI signs of HS refractory to ASM (refractory TLE-HS), (2) 27 patients with TLE-HS with good seizure control with ASM (pharmacoresponsive TLE-HS), (3) 15 patients MRI signs of temporal lobe FCD (tFCD), and (4) 20 patients with frontal lobe FCD (fFCD). All patients with FCD were refractory to ASM.

The demographic and clinical characteristics of patients and controls are presented in Table 1.

All patients were recruited from the tertiary epilepsy service of the State University of Campinas, Brazil, between 2016 and 2019. The clinical diagnosis of TLE-HS and frontal lobe epilepsy (FLE) was performed by board-certified epileptologists as defined by the International League Against Epilepsy.[19] The response to ASM was categorized according to the frequency and type of seizures into pharmacoresponsive (fewer than three focal seizures per year and no focal to bilateral tonic–clonic seizures) or refractory to ASM (more than three focal seizures or at least one focal to bilateral tonic–clonic seizure per year). We evaluated the seizure frequency from at least 1 year before DTI acquisition. Within the pharmacoresponsive TLE-HS group, 74% of patients were seizure-free for 2.2 ± 2.4 years (mean ± SD, range = 1–10 years). The remaining 26% had fewer than three focal seizures per year for at least 5 years before DTI acquisition.

A comprehensive evaluation was performed to lateralize the seizure focus, as described previously.[20] An epilepsy MRI expert (F.C.) reviewed the images to identify MRI signs of HS and FCD.[5] No patients had lesions other than HS or FCD. All patients in this study had clearly defined scalp electroencephalographic interictal or ictal abnormalities consistent with the MRI findings. Twenty-three of the 51 refractory TLE-HS patients (45%) underwent temporopolar resection with amygdalohippocampectomy. Histological analysis[21] confirmed the presence of HS in all specimens. Six of the 20 frontal (30%) and four of the 15 temporal FCD patients (27%) underwent surgical resection of the suspected dysplastic lesion. The histological findings[22,23] of the specimens revealed that one patient had FCD type IIa, two patients had FCD type IIb, and seven patients showed mild malformations of cortical development with oligodendroglial hyperplasia and epilepsy.

The ethics committee of the University of Campinas approved the study, and all participants signed informed consent.

2.2 | MRI acquisition and DTI analysis

All brain scans were performed using a HARNESS MRI epilepsy protocol[24] on a 3-T Philips Achieva scanner with an eight-channel head coil for the diagnosis of epileptogenic lesions. In summary, we acquired high-resolution three-dimensional (3D) 1-mm T1-weighted and 3D fluid-attenuated inversion recovery images, and high in-plane resolution 2D 3-mm coronal T1-weighted inversion recovery and T2-weighed images perpendicular to the long axis of hippocampi. We performed multiplanar reconstructions to identify MRI signs of FCD, as described previously.[20] For DTI, we acquired a single-shot echo-planar image of 2 x 2 x 2 mm^3 voxel size, interpolated to 1 x 1 x 2 mm^3 (70 slices, echo time/repetition time = 61/8500 ms, flip angle = 90°, 32 gradient directions, $b = 1000\ s/mm^2$).

TABLE 1 Demographic and clinical information of groups included in the study

Characteristic	Controls	Refractory TLE-HS	Responsive TLE-HS	TLE-FCD	FLE-FCD
n	113	51	27	15	20
Age, years, mean ± SD (range)	42 ± 11 (18–65)	46 ± 9 (21–64)	48 ± 8 (31–64)	36 ± 10 (17–54)	30 ± 9 (17–45)
Male, *n* (%)	41 (36%)	14 (27%)	12 (44%)	7 (47%)	8 (40%)
Onset of epilepsy, years, mean ± SD (range)	-	14 ± 10 (1–41)	18 ± 10 (2–37)	11 ± 8 (1–27)	8 ± 7 (1–29)
Duration of epilepsy, years, mean ± SD (range)	-	31 ± 12 (2–49)	28 ± 15 (1–47)	24 ± 12 (7–43)	21 ± 10 (9–42)
Febrile seizures, *n* (%)	-	10 (20%)	5 (19%)	2 (13%)	1 (5%)
FH, *n* (%)	-	25 (49%)	13 (48%)	8 (53%)	8 (40%)
Focal seizures/last year, mean ± SD (range)	-	71 ± 83 (3–365)	.3 ± .5 (0–2)	96 ± 152 (10–540)	183 ± 267 (1–1080)
SzF patients, *n* (%)	-	-	20 (74%)	-	-
Surgical treatment	-	23 (45%)	-	4 (27%)	6 (30%)
Engel I outcome	-	17 (74%)	-	1 (25%)	1 (17%)

Note: Age, onset, and duration are presented in mean ± SD years (range). "Refractory TLE-HS" indicates patients with TLE and hippocampal sclerosis not responding to ASM. Responsive TLE-HS indicates patients with TLE-HS with good seizure control with ASM. "TLE-FCD" and "FLE-FCD" indicate patients with magnetic resonance imaging signs of FCD with TLE and FLE, respectively.

Abbreviations: ASM, antiseizure medication; FCD, focal cortical dysplasia; FH, family history of epilepsy; FLE, frontal lobe epilepsy; HS, hippocampal sclerosis; SzF, seizure-free; TLE, temporal lobe epilepsy.

The raw diffusion tensor-weighted images were processed, segmented, and quantified in MRICloud (www.MRICloud.org), a public web-based software as a service.[25–30] DTI parameter calculations and quality control were performed using the DTI processing pipeline in the same automated cloud service[25,26] through DtiStudio (H. Jiang and S. Mori, Johns Hopkins University, Kennedy Krieger Institute).[27] Next, a DTI MultiAtlas Segmentation pipeline was carried out,[25,26,28] which combines multicontrast large deformation diffeomorphic metric mapping[29] to increase the match between subject imaging and MRICloud template, and multicontrast diffeomorphic likelihood fusion using the multiatlas DTI approach to parcellate the human brain into ROIs based on the diffusion tensor, as described by Tang et al.[30] DTI parameter (fractional anisotropy [FA], mean diffusivity [MD], radial diffusivity [RD], and axial diffusivity [AD]) values were obtained for 42 bilateral ROIs to analyze whole-brain superficial- and deep-WM microstructure integrity (21 and 21 bilateral ROIs, respectively). The parcellation criteria and definition of superficial- and deep-WM labels used in our research were described in previous studies.[18,31,32]

We included the superficial-WM ROIs under the following cortical regions: *frontal* (superior/middle/inferior frontal WMs, gyrus rectus WM, middle fronto-orbital WM, lateral fronto-orbital WM, and precentral WM), *parietal* (postcentral WM, superior parietal WM, precuneus WM, supramarginal WM, and angular WM), *temporal* (superior/middle/inferior temporal WMs and fusiform WM) and *occipital* (superior/middle/inferior occipital WMs, lingual WM, and cuneus WM).

The deep-WM ROIs were categorized into the *limbic* (cingulum [CGC], hippocampal cingulum [CGH], fornix, and fornix/stria terminalis [Fx/ST]), *association* (superior longitudinal fasciculus [SLF], superior fronto-occipital fasciculus [SFO], uncinate fasciculus [UNC], inferior fronto-occipital fasciculus [IFO], sagittal stratum [SS], and external capsule [EC]), *projection* (anterior/superior/posterior corona radiata [ACR/SCR/PCR], anterior/posterior/retrolenticular limb of the internal capsule [ALIC/PLIC/RLIC], and posterior thalamic radiation [PTR]), and *commissural* fibers (genu/body/splenium of the corpus callosum [GCC/BCC/SCC] and tapetum [TAP]).

The ROIs were analyzed ipsilateral or contralateral to the epileptogenic lesion. In the control subjects, left and right ROIs were randomly lateralized into ipsilateral and contralateral ROIs in the same proportion of patients.

2.3 | Statistical analysis

We analyzed the clinical and demographic variables between study groups using the Kruskal–Wallis or Pearson chi-squared tests.

To analyze DTI data, we first removed age and gender effects using linear regression. We then applied a Kruskal–Wallis test to assess group differences in FA, MD, RD, and AD values in superficial and deep WM ROIs. We chose a nonparametric test because the residual for parametric models did not fit appropriately for some variables.

We applied the false discovery rate (FDR) to correct multiple comparisons in the Kruskal–Wallis tests and set corrected p-values $< .05$ as significant. Once the ROIs with significant alterations after FDR correction had been identified, we employed the Dunn–Bonferroni post hoc test for pairwise comparisons between the study groups. Finally, we calculated Cliff delta d effect sizes for the pairwise comparison of the epilepsy group versus controls in those ROIs with significant DTI abnormalities.[33] We interpreted effect sizes according to the equivalent Cohen d criteria as follows: small (.15–.32), moderate (.33–.46), large (.47–.62), and very large (≥.62).[34,35] Only ROIs that showed large and very large effects were included in the main text to demonstrate the most robust group differences. The ROIs with small to moderate effect sizes are detailed in the Supplementary Material (Figures S1–S4).

3 | RESULTS

3.1 | Demographic and clinical data

The demographic and clinical characteristics of patients and controls are presented in Table 1. There were significant differences in age between the five groups (Kruskal–Wallis H-test, $H_4 = 38.72$, $p < .001$) but not between patients and controls ($p > .05$). We also found significant differences in age at disease onset ($H_3 = 12.86$, $p = .005$), disease duration ($H_3 = 11.47$, $p = .009$), and frequency of focal seizures in the year before the MRI ($H_3 = 62.17$, $p < .001$) in the four epilepsy groups. Post hoc comparisons showed that the fFCD patients were younger than both TLE-HS groups and controls (all p-values $< .001$). The tFCD patients were younger than the pharmacoresponsive TLE-HS ($p = .007$) and refractory TLE-HS ($p = .022$) epilepsy groups. The fFCD patients had a significantly earlier disease onset than the pharmacoresponsive TLE-HS patients ($p = .005$) and a shorter disease duration than the refractory TLE-HS patients ($p = .009$).

3.2 | Epilepsy groups versus healthy controls differences

3.2.1 | Whole-brain diffusion abnormalities by anatomical site and fiber type

The global burden of significant superficial-WM and deep-WM diffusion abnormalities relative to controls was more widespread in TLE-HS patients (average ROI altered in 21 of 50 in superficial-WM [42.25%] and 31 of 56 in deep-WM [55.58%]) than in temporal or frontal FCD patients (average ROI altered in 5 of 50 in superficial-WM [9.50%] and 11 of 56 in deep-WM [20.31%]).

The DTI abnormalities consisted of lower FA and higher MD, RD, and AD (Figure 1). In deep-WM, both TLE-HS groups showed bilateral widespread diffusion changes in FA, MD, and RD in all analyzed fiber types (limbic, association, projection, and commissural fibers), although with a lower contralateral burden in pharmacoresponsive TLE-HS patients. Temporal and frontal FCD groups also showed FA, MD, and RD bilateral changes but with a much lower load and predominant damage in projection and commissural fibers. AD alterations were less pronounced than the other DTI metrics, although they followed a similar fiber type pattern (Figure 1B).

Regarding the superficial WM, refractory TLE-HS patients showed diffuse, multilobar, and bilateral diffusion changes in all DTI metrics but with a greater ipsilateral burden. Pharmacoresponsive TLE-HS patients also showed multilobar and bilateral FA abnormalities, but less global MD, RD, and AD change, with more pronounced diffusion change in the ipsilateral frontotemporal regions. Temporal and frontal FCD patients, in general, showed fewer and almost exclusively intralobular alterations, mainly in MD and RD measures (Figure 1A).

3.2.2 | Superficial-WM diffusion abnormalities

Refractory TLE-HS patients had large to very large effect size differences in the superficial WM of ipsilateral middle temporal WM for FA, MD, RD, and AD; superior temporal region for FA, MD, and RD; inferior temporal for MD, RD, and AD; fusiform gyrus for MD and RD; and contralateral middle temporal region for MD and RD. Large effect sizes were also found for ipsilateral inferior frontal and middle occipital region for RD and contralateral middle temporal region for RD (Figures 2 and S1A). See Appendix S1 text and figures for Cliff delta *d* effect size values.

Pharmacoresponsive TLE-HS patients presented large to very large effect size differences in the superficial WM of the ipsilateral inferior temporal region for FA, MD, RD, and AD; inferior frontal region for FA, MD, and RD; and middle temporal, middle frontal, and fusiform gyrus for FA and RD. Large effect sizes were found for FA alone in the ipsilateral superior temporal, frontal, parietal, rectus, and supramarginal gyri, and contralateral superior frontal, superior temporal, lateral fronto-orbital, and superior parietal regions and precuneus (Figures 2 and S2A).

Temporal FCD patients showed large to very large effect size differences in the superficial WM of the ipsilateral middle temporal region for FA, MD, and RD; inferior temporal region for MD, RD, and AD; and FA abnormalities in the ipsilateral supramarginal, middle occipital, contralateral superior parietal, and fusiform gyrus (Figures 2 and S3A).

Frontal FCD patients had superficial-WM diffusion abnormalities with large effect sizes in the ipsilateral inferior and middle frontal regions for FA, MD, and RD; superior frontal region for FA and RD; and superior temporal, precuneus, and angular gyrus for FA (Figures 2 and S4A).

3.2.3 | Deep-WM diffusion abnormalities

Refractory TLE-HS patients had large to very large effect size differences for deep-WM FA, MD, and RD in the ipsilateral IFO, SS, EC, ACR, PTR, GCC, BCC, and contralateral GCC and BCC; for FA and RD in the ipsilateral SCC, SLF, and CGH, and contralateral SCC and PTR; for MD and RD in the ipsilateral UNC and contralateral ACR, EC, and IFO; and for MD and AD in the bilateral SCR. Large effect sizes were found in the ipsilateral RLIC for FA, contralateral ALIC and Fx/ST for RD, and SFO for AD (Figures 2 and S1B).

Pharmacoresponsive TLE-HS patients had large to very large effect size differences compared to controls for FA, MD, and RD in the ipsilateral UNC, IFO, EC, ACR, ALIC, GCC, and bilateral BCC; for FA and RD in the ipsilateral CGH, SS, PLIC, RLIC, SCC, and contralateral UNC, IFO, EC, SCR, GCC, and SCC; and for MD and RD in the ipsilateral CGC and contralateral ACR. Large effect size differences were also found for FA in the ipsilateral PTR; contralateral CGH, SLF, and SS; and ALIC/PLIC/RLIC (Figures 2 and S2B).

Temporal FCD patients had large to very large effect size differences for FA, MD, and RD in the ipsilateral SS and contralateral SCR; for FA and RD in the ipsilateral ACR, SCR, BCC, and SCC, and contralateral PCR and BCC; and for MD and RD in the ACR. Large effect sizes were observed for FA in the ipsilateral ALIC and contralateral Fx/ST, ALIC, BCC, SCC, and TAP; and for RD in the contralateral CGC ($d = .53$; Figures 2 and S3B).

Frontal FCD patients had large effect size differences for FA, MD, and RD in the bilateral genu and body of

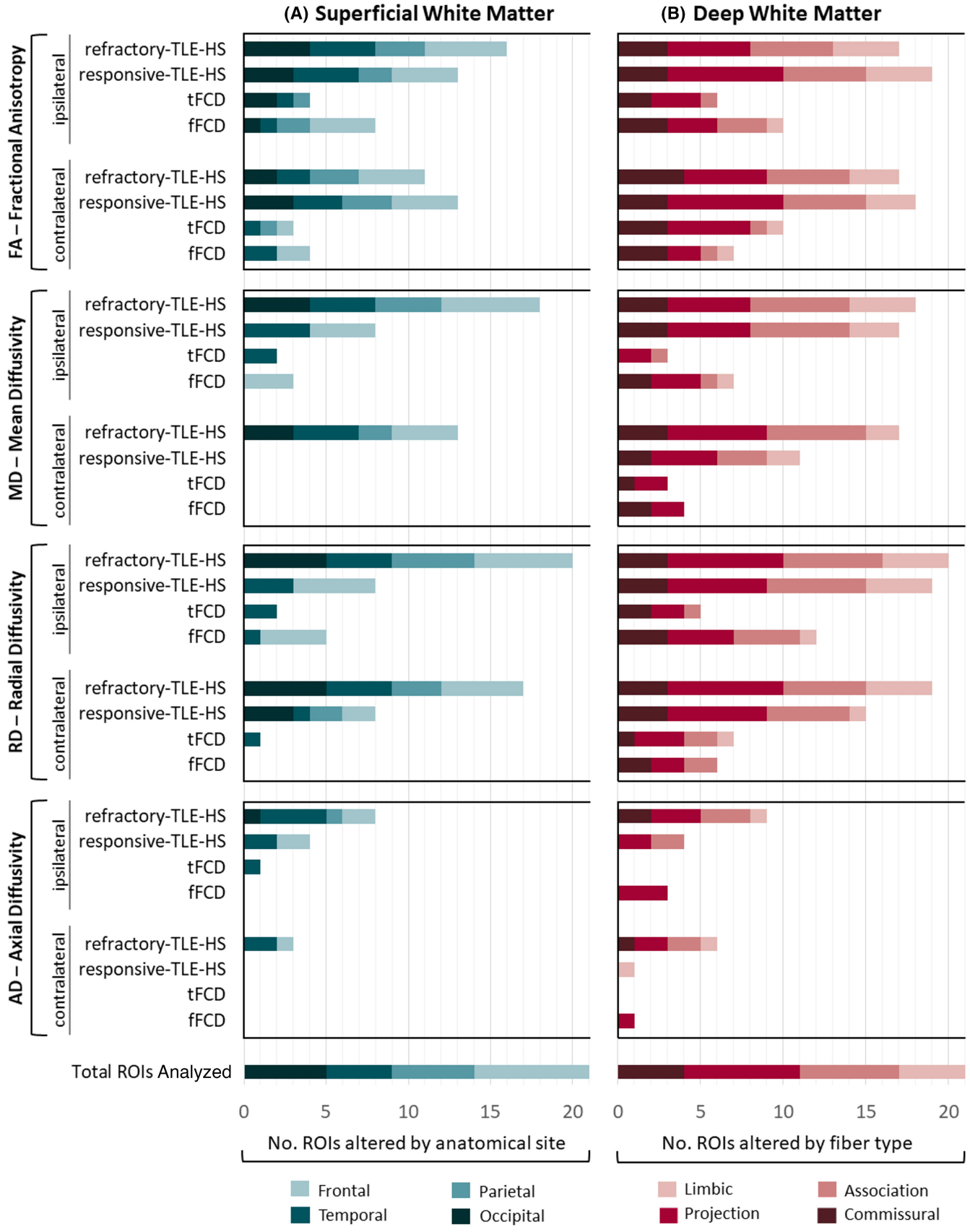
(A) Superficial White Matter
(B) Deep White Matter
FA – Fractional Anisotropy
MD – Mean Diffusivity
RD – Radial Diffusivity
AD – Axial Diffusivity
ipsilateral
contralateral
refractory-TLE-HS
responsive-TLE-HS
tFCD
fFCD
Total ROIs Analyzed
0
5
10
15
20
No. ROIs altered by anatomical site
No. ROIs altered by fiber type
Frontal
Parietal
Temporal
Occipital
Limbic
Association
Projection
Commissural

FIGURE 1 Superficial and deep white matter diffusion tensor imaging whole-brain abnormalities by anatomical site and fiber type, respectively. Number of regions of interest (ROIs) with diffusion abnormalities per patient group is shown compared to controls ($d > .47$, $p < .05$, corrected for multiple comparisons). The superficial white matter (WM) ROIs were categorized into frontal, parietal, temporal, and occipital ROIs. The deep-WM ROIs were categorized into limbic, association, projection, and commissural fibers. ROIs were analyzed ipsilateral and contralateral to the epileptogenic lesion. fFCD/tFCD, patients with frontal and temporal lobe epilepsy with magnetic resonance imaging (MRI) signs of focal cortical dysplasia, respectively; refractory-TLE-HS, patients with pharmacoresistant temporal lobe epilepsy with MRI signs of hippocampal sclerosis; responsive-TLE-HS, patients with pharmacoresponsive TLE-HS.

corpus callosum; for MD and AD in the ipsilateral SCR and SCR; and for MD and RD in the contralateral ACR (Figures 2 and S4B).

3.3 | Pairwise comparisons among epilepsy groups

There were only two ROIs with significant differences in the epilepsy groups' pairwise comparisons. Refractory TLE-HS patients had higher RD in the ipsilateral inferior temporal region ($p = .042$) and higher MD and RD in the ipsilateral UNC ($p = .019$ and $p = .026$, respectively) than fFCD patients. Pharmacoresponsive TLE-HS patients had higher MD and RD in the ipsilateral UNC ($p = .03$ and $p = .018$, respectively) than fFCD patients (Figure 3A). Although the direct comparison between pharmacoresponsive TLE-HS and refractory TLE-HS did not show significant differences after correction for multiple comparisons, the number of ROIs with abnormalities was greater in the refractory TLE-HS, particularly for superficial WM, as shown in Figures 1, S1, and S2.

There was a higher number of alterations in the superficial WM of temporal regions in refractory TLE-HS when compared to refractory fFCD patients (uncorrected $p < .05$). Additionally, we found more altered diffusion metrics in the refractory TLE-HS when compared to the responsive-TLE-HS group, mainly for superficial-WM MD and RD (uncorrected $p < .05$) in the ipsilateral parieto-occipital regions (angular gyrus and middle–inferior occipital regions, respectively; Figure 3B).

4 | DISCUSSION

We found superficial-WM and deep-WM disrupted integrity, including reduced FA and increased MD, RD, and AD in patients with focal epilepsies of different etiologies, lesion localizations, and pharmacoresponse compared to controls. The TLE-HS groups presented more widespread superficial-WM and deep-WM diffusion abnormalities than TLE and FLE with FCD. Ipsilateral changes were more pronounced in the superficial-WM analysis. Also, distinctive peripheral microstructural abnormalities were found between each epilepsy group, which was more evident in the TLE-HS groups than tFCD and fFCD. Whether these WM changes are mainly an epilepsy-related finding or inherent to the nature and location of the lesion, or both, remains to be determined.

When compared to controls, our findings of more diffuse and bilateral deep-WM diffusion abnormalities in TLE-HS groups than FCD groups agree with previous studies.[7–9,17,21] However, we observed that the superficial-WM abnormalities were greater ipsilaterally and with a more robust effect size in the frontotemporal regions of both TLE-HS groups. On the other hand, the FCD groups showed significant superficial-WM abnormalities almost exclusively in areas adjacent to the epileptogenic lesion. These findings align with a few previous studies of superficial WM in pharmacoresistant TLE with hippocampal pathology, showing ipsilateral temporolimbic[14] and frontotemporal[16] diffusion alterations. Another study showed diffusion abnormalities in the perirolandic U-fiber region in children with benign epilepsy with centrotemporal spikes.[15] As in our study, these findings suggest an important local effect of superficial-WM damage in focal epilepsies, especially in structures close to the seizure focus.

MRI–histopathological correlation studies based on deep fibers in animal models and patients have shown reduced FA related to the loss of WM organization over time (i.e., decreased axonal membrane circumference and/or myelin sheath degradations).[10,36] High RD has been consistently associated with myelin degeneration,[37] whereas AD alterations might be related to axonal damage in animal models.[38] Concerning MD, high values are associated with increased extra-axonal space, in line with the reduced overall density of tissue barriers.[39] As opposed to deep fiber studies, little is known about the biological meaning of superficial-WM diffusion abnormalities. A recent study[16] analyzed the relationship between the conventional superficial-WM diffusion metrics and diffusion models that yield more specific metrics for neurite density and myelination,[40,41] and found that diffusion changes (decreased FA and increased RD) were primarily related to reduced neurite density, mostly in the frontotemporal regions.[16] There was also a reduction in myelin water fraction in the ipsilateral temporal pole of pharmacoresistant TLE patients with

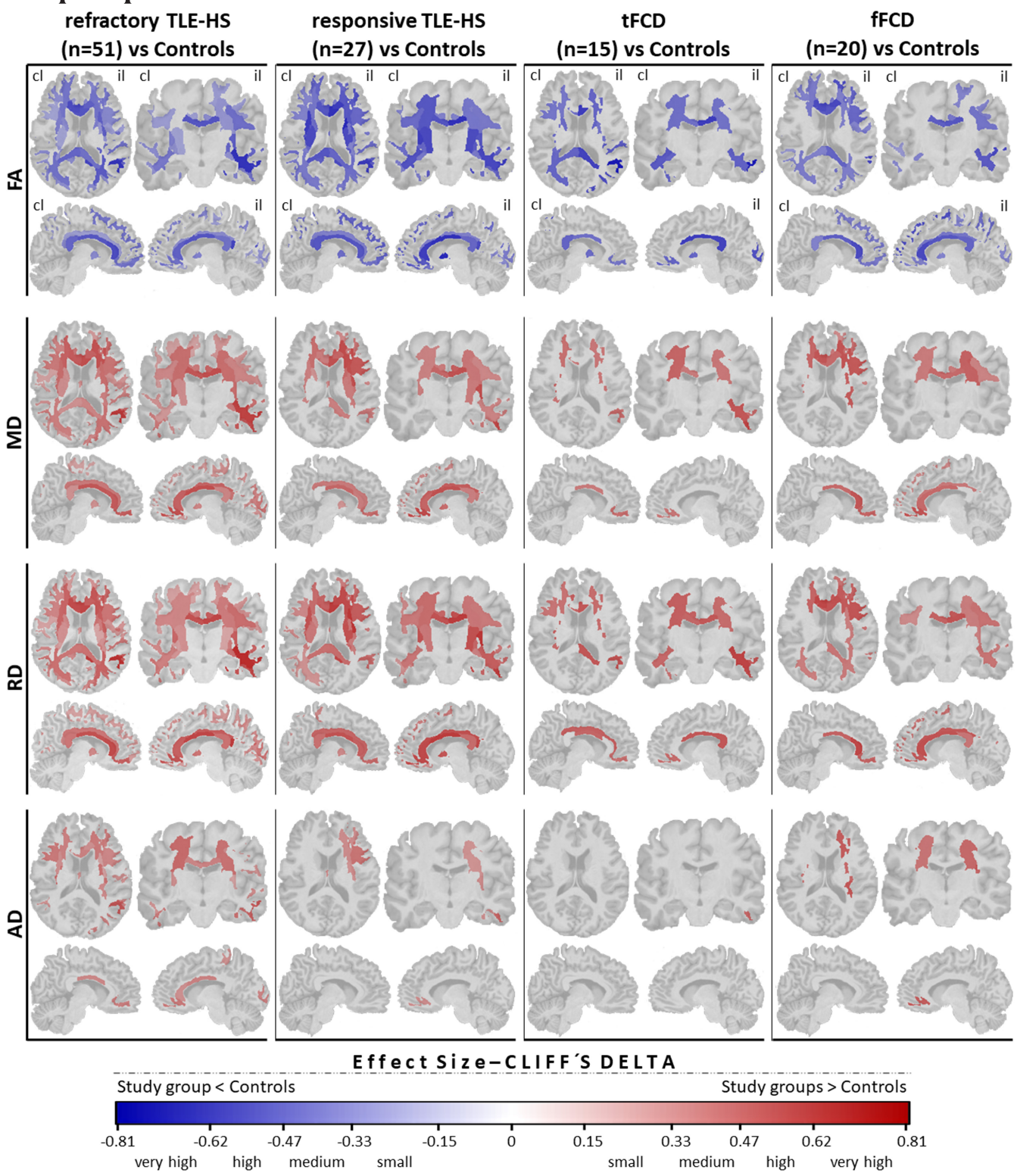

FIGURE 2 The effect size of the superficial and deep white matter diffusion abnormalities. Significant reduction of fractional anisotropy (FA), increase mean diffusivity (MD), increase radial diffusivity (RD), and increase axial diffusivity (AD) in patients' groups relative to controls are shown ($p < .05$, corrected for multiple comparisons). cl, regions of interest (ROIs) contralateral to the epileptogenic lesion; fFCD/tFCD, patients with magnetic resonance imaging (MRI) signs of focal cortical dysplasia with frontal and temporal lobe epilepsy, respectively; il, ROIs ipsilateral to the epileptogenic lesion; refractory TLE-HS, patients with pharmacoresistant temporal lobe epilepsy with MRI signs of hippocampal sclerosis; responsive TLE-HS, patients with pharmacoresponsive TLE-HS.

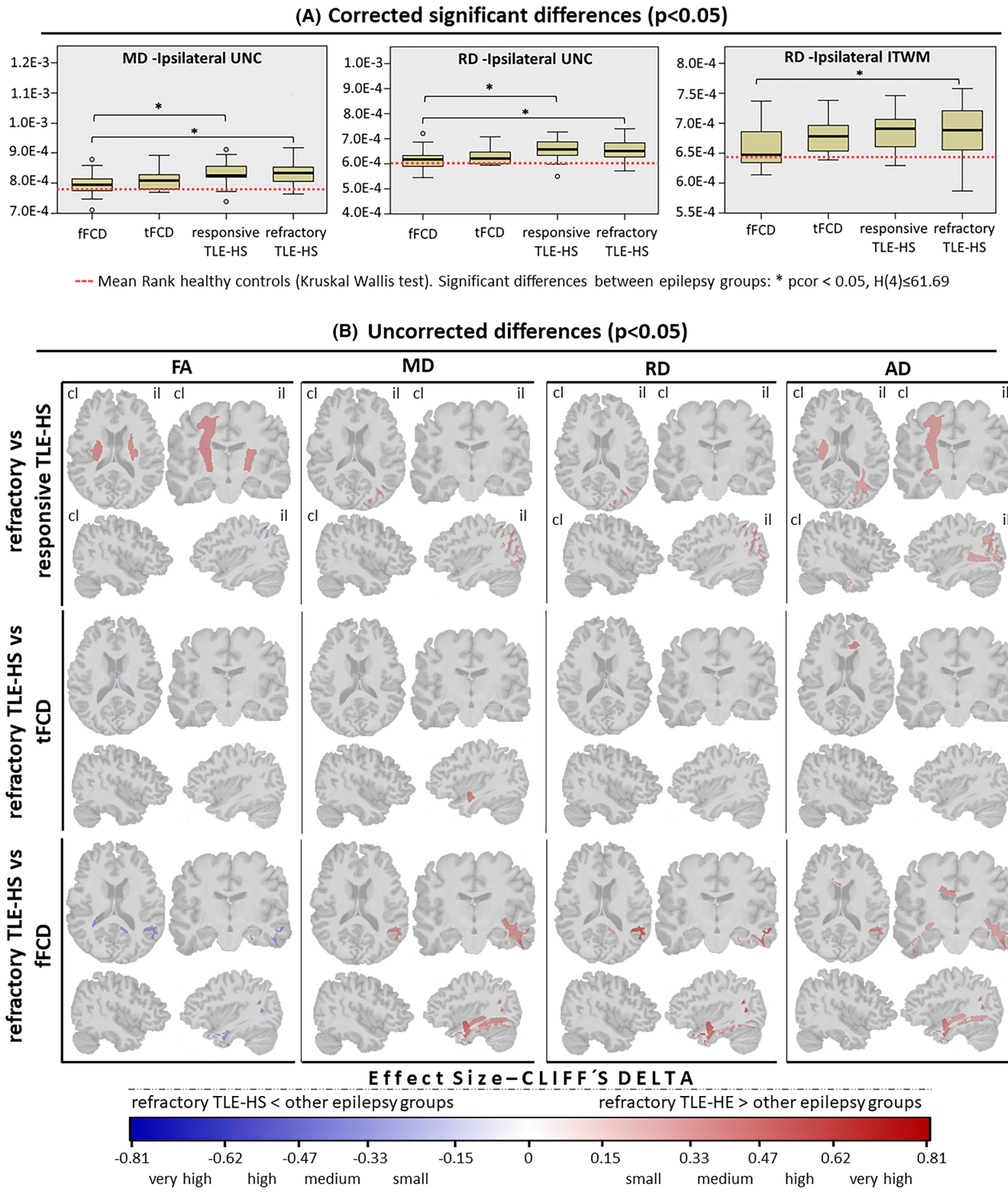

FIGURE 3 Diffusion differences between epilepsy groups. (A) Significant differences in the epilepsy groups' pairwise comparisons ($H_4 \leq 61.69$, $p < .05$, corrected for multiple comparisons). (B) Effect sizes for the regions of interest (ROIs) with significant differences ($p < .05$) between epilepsy subgroups before correction for multiple comparisons. AD, antiseizure medication; cl, ROIs contralateral to the epileptogenic lesion; FA, fractional anisotropy; fFCD/tFCD, patients with magnetic resonance imaging (MRI) signs of focal cortical dysplasia with frontal and temporal lobe epilepsy, respectively; il, ROIs ipsilateral to the epileptogenic lesion; ITWM, inferior temporal white matter; MD, mean diffusivity; RD, radial diffusivity; refractory TLE-HS, patients with pharmacoresistant temporal lobe epilepsy with MRI signs of hippocampal sclerosis; responsive TLE-HS, patients with pharmacoresponsive TLE-HS; UNC, uncinate.

hippocampal pathology. These findings suggest that, despite differences in the structural conformation between the superficial WM and deep WM, the interpretation of superficial-WM diffusion abnormalities observed in conventional DTI metrics in patients with epilepsy may share biological foundations with the changes observed in deep-WM studies, possibly reflecting disturbances of the restricting water barriers. It is also important to consider that the analysis of superficial WM is more complex than deep WM, with fibers entering/exiting the cortex and U-fibers crossing the first. The tensor model is insufficient to capture all this information.

Concerning the conventional DTI metrics altered in our superficial-WM analysis, when comparing epilepsy groups to controls, we observed more distinctive patterns of MD abnormalities. We found exclusively ipsilateral MD abnormalities in both FCD groups and pharmacoresponsive TLE-HS patients (intralobular and frontotemporal regions, respectively). Conversely, the pharmacoresistant TLE-HS group showed bilateral MD changes in the superficial WM. In the RD analysis, the abnormalities were like those reported for MD maps, mainly in ipsilateral structures. Regarding FA, we found mostly diffuse and multilobar changes in all epilepsy groups. Contrary to expectation, pharmacoresponsive TLE-HS patients had diffuse deep-WM changes like refractory TLE-HS patients. These observations may be related to (1) a floor effect or a diluted effect of pharmacoresponsiveness within the effect of HS or (2) the lower specificity of FA metrics.[39] Because MD infers the overall integrity of tissue barriers, thus reflecting the overall degree of water diffusion in all directions, regardless of orientation,[10,42] this might be a more reliable marker of microstructural damage in superficial WM (where deep and peripheral fibers converge from different directions).

We also showed abnormal AD increase in areas surrounding the epileptogenic lesion in all epilepsy groups compared to controls. A possible hypothesis for this finding is that these regions would be more chronically hyperstimulated by epileptic discharges, showing more intense WM damage. Recent studies support the association of an increase in AD with axonal damage in patients with chronic lesions in multiple sclerosis,[43] and correlations with chronic histopathological changes in an intrahippocampal kainate mouse model.[44] The areas surrounding the epileptogenic lesion also showed overlapping FA, MD, and RD alterations with the most robust effect sizes. These changes suggest more chronic abnormalities and a complex pathological process, which could be explained by more than strict axonal or myelinic dysfunction. Nonetheless, further evidence is necessary to unravel the biological underpinnings of AD alterations in epilepsy, particularly for superficial WM, as suggested by other authors.[45,46]

The distribution of the WM damage, with a gradient of abnormality intensity from the seizure focus toward more distant regions, has been observed in previous deep-WM epilepsy studies,[47] and more recently in superficial-WM research.[14,16] Similarly, our results showed more pronounced superficial-WM microstructural damage close to the epileptogenic lesion in TLE-HS and FCD patients (i.e., ipsilateral frontotemporal areas and perilesional alterations, respectively). Moreover, whereas TLE-HS patients presented with broader deep-WM changes in all types of fibers analyzed (i.e., limbic, association, projection, and commissural fibers) and multilobar superficial-WM damage, FCD patients showed predominant deep-WM diffusion alterations in projection and commissural fibers, significantly less damage in association fibers, and rare extralobar superficial-WM damage. These findings may be partly explained by more preserved association tracts involved in connecting ipsilateral interlobular structures. Following this reasoning, we found unique significant deep-WM abnormalities in the uncinate tract, where TLE-HS patients showed higher MD and RD than FCD patients. Uncinate damage is probably related to a preferential pathway of propagating epileptic seizures from the mesial temporal lobe to frontal areas in TLE.[48] These observations suggest a likely and close relationship between deep-WM and superficial-WM alterations in the spatial distribution of damage and open a window to study the correlations between these two WM regions, making it possible to improve our understanding of epileptic networks and possible pathways for microstructural damage spreading from the areas that are closest to the epileptogenic focus to distant regions.

Our study is not without limitations. The direct comparison between pharmacoresponsive TLE-HS and refractory TLE-HS did not show significant differences; however, the number of ROIs with abnormalities was greater in refractory TLE-HS than in pharmacoresponsive TLE-HS, particularly for superficial WM, with robust effect sizes. This lack of significant differences between the two TLE-HS groups was most likely related to our stringent corrections for multiple comparisons and should be interpreted cautiously. Nonetheless, our findings point to target diffusion changes in ROIs that should be further explored by studies with a larger number of patients. Also, including TLE patients with negative MRI would be important to disentangle the microstructural WM changes related to pharmacoresponse and HS. We believe that, based on our findings, a classifier using superficial-WM diffusion measures alone could identify the different types of TLE patients.

Another relative limitation is that our cohort comes from a tertiary center and therefore might be subject to selection bias. Those patients currently showing good seizure control may have had a previous history of pharmacoresistance.[49] Moreover, we could not include pharmacoresponsive patients with both temporal and frontal FCD. Nonetheless, this study included a cohort large enough to show epilepsy-related changes with robust effect sizes. Our results might point toward a better understanding of diffusion changes, in particular for superficial WM. Future studies should focus on disentangling the effects of seizure control and seizure focus, as MRI studies have been showing differential effects on underlying alterations regarding these clinical and pathological features.[7,50]

In conclusion, our findings provide valuable additional information about the WM spectrum of abnormalities in focal epilepsies. The superficial-WM ROI-based analysis might be useful to characterize the local effect, severity, and extent of WM damage and identify distinctive dysfunctional brain networks in focal epilepsies and their relationship to clinical phenotype. The patterns of superficial-WM diffusion abnormalities in both pharmacoresponsive and refractory TLE-HS groups, as well as distinctive alterations in both refractory temporal and frontal FCD groups, suggest that the distinctive superficial-WM dysfunctional brain networks in lesional focal epilepsies might be driven mainly by intrinsic factors specifically related to the connection topology of the epileptogenic lesion.

AUTHOR CONTRIBUTIONS

Hebel Urquia-Osorio and Luciana R. Pimentel-Silva: Conceptualization, data curation, formal analysis, investigation, methodology, software, validation, visualization, writing–original draft preparation, writing–review & editing. Thiago Junqueira Ribeiro Rezende: Methodology, software, writing–review & editing. Eimy Almendares-Bonilla: Writing–review & editing. Clarissa L. Yasuda: Supervision, investigation, writing–review & editing. Luis Concha and Fernando Cendes: Conceptualization (lead), data curation, investigation, methodology, project administration (lead), supervision (lead), writing–original draft preparation, writing–review & editing (lead).

ACKNOWLEDGMENT

None.

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.

ORCID

Hebel Urquia-Osorio https://orcid.org/0000-0003-2386-9449
Luciana R. Pimentel-Silva https://orcid.org/0000-0001-5045-9512
Luis Concha https://orcid.org/0000-0002-7842-3869
Fernando Cendes https://orcid.org/0000-0001-9336-9568

REFERENCES

1. Blümcke I, Aronica E, Miyata H, Sarnat HB, Thom M, Roessler K, et al. International recommendation for a comprehensive neuropathologic workup of epilepsy surgery brain tissue: a consensus Task Force report from the ILAE Commission on Diagnostic Methods. Epilepsia. 2016;57(3):348–58. https://doi.org/10.1111/epi.13319
2. Blumcke I, Spreafico R, Haaker G, Coras R, Kobow K, Bien CG, et al. Histopathological findings in brain tissue obtained during epilepsy surgery. N Engl J Med. 2017;377(17):1648–56. https://doi.org/10.1056/NEJMoa1703784
3. Sommer W. Erkrankung des Ammon's horn als aetiologis ches moment der epilepsien. Arch Psychiatr Nurs. 1880;10(3):631–75. https://doi.org/10.1007/BF02224538
4. Taylor DC, Falconer MA, Bruton CJ, Corsellis JA. Focal dysplasia of the cerebral cortex in epilepsy. J Neurol Neurosurg Psychiatry. 1971;34(4):369–87. https://doi.org/10.1136/jnnp.34.4.369
5. Cendes F, Theodore WH, Brinkmann BH, Sulc V, Cascino GD. Neuroimaging of epilepsy. Handb Clin Neurol. 2016;136:985–1014. https://doi.org/10.1016/B978-0-444-53486-6.00051-X
6. Eriksson SH, Rugg-Gunn FJ, Symms MR, Barker GJ, Duncan JS. Diffusion tensor imaging in patients with epilepsy and malformations of cortical development. Brain. 2001;124(Pt 3):617–26. https://doi.org/10.1093/brain/124.3.617
7. Hatton SN, Huynh KH, Bonilha L, Abela E, Alhusaini S, Altmann A, et al. White matter abnormalities across different epilepsy syndromes in adults: an ENIGMA-Epilepsy study. Brain. 2020;143(8):2454–73. https://doi.org/10.1093/brain/awaa200
8. Fonseca VC, Yasuda CL, Tedeschi GG, Betting LE, Cendes F. White matter abnormalities in patients with focal cortical dysplasia revealed by diffusion tensor imaging analysis in a voxelwise approach. Front Neurol. 2012;3:121. https://doi.org/10.3389/fneur.2012.00121
9. Slinger G, Sinke MR, Braun KP, Otte WM. White matter abnormalities at a regional and voxel level in focal and generalized epilepsy: a systematic review and meta-analysis. Neuroimage Clin. 2016;12:902–9. https://doi.org/10.1016/j.nicl.2016.10.025
10. Beaulieu C. The basis of anisotropic water diffusion in the nervous system—a technical review. NMR Biomed. 2002;15(7–8):435–55. https://doi.org/10.1002/nbm.782
11. Ciccarelli O, Catani M, Johansen-Berg H, Clark C, Thompson A. Diffusion-based tractography in neurological disorders: concepts, applications, and future developments. Lancet Neurol. 2008;7(8):715–27. https://doi.org/10.1016/S1474-4422(08)70163-7
12. Schuez A, Braitenberg V. The human cortical white matter: quantitative aspects of cortico-cortical long-range connectivity. In: Schüz A, Miller R, editors. Cortical areas: unity and diversity. London, UK: Taylor and Francis; 2002. p. 377–86.

13. Guevara M, Guevara P, Román C, Mangin JF. Superficial white matter: a review on the dMRI analysis methods and applications. Neuroimage. 2020;212:116673. https://doi.org/10.1016/j.neuroimage.2020.116673
14. Liu M, Bernhardt BC, Hong SJ, Caldairou B, Bernasconi A, Bernasconi N. The superficial white matter in temporal lobe epilepsy: a key link between structural and functional network disruptions. Brain. 2016;139(Pt 9):2431–40. https://doi.org/10.1093/brain/aww167
15. Ostrowski LM, Song DY, Thorn EL, Ross EE, Stoyell SM, Chinappen DM, et al. Dysmature superficial white matter microstructure in developmental focal epilepsy. Brain Commun. 2019;1(1):fcz002. https://doi.org/10.1093/braincomms/fcz002
16. Winston GP, Vos SB, Caldairou B, Hong SJ, Czech M, Wood TC, et al. Microstructural imaging in temporal lobe epilepsy: diffusion imaging changes relate to reduced neurite density. Neuroimage Clin. 2020;26:102231. https://doi.org/10.1016/j.nicl.2020.102231
17. Otte WM, van Eijsden P, Sander JW, Duncan JS, Dijkhuizen RM, Braun KP. A meta-analysis of white matter changes in temporal lobe epilepsy as studied with diffusion tensor imaging. Epilepsia. 2012;53(4):659–67. https://doi.org/10.1111/j.1528-1167.2012.03426.x
18. Oishi K, Zilles K, Amunts K, Faria A, Jiang H, Li X, et al. Human brain white matter atlas: identification and assignment of common anatomical structures in superficial white matter. Neuroimage. 2008;43(3):447–57. https://doi.org/10.1016/j.neuroimage.2008.07.009
19. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512–21. https://doi.org/10.1111/epi.13709
20. Campos BM, Coan AC, Beltramini GC, Liu M, Yassuda CL, Ghizoni E, et al. White matter abnormalities associate with type and localization of focal epileptogenic lesions. Epilepsia. 2015;56(1):125–32. https://doi.org/10.1111/epi.12871
21. Blümcke I, Thom M, Aronica E, Armstrong DD, Bartolomei F, Bernasconi A, et al. International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: a Task Force report from the ILAE Commission on Diagnostic Methods. Epilepsia. 2013;54(7):1315–29. https://doi.org/10.1111/epi.12220
22. Blümcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, Palmini A, et al. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. Epilepsia. 2011;52(1):158–74. https://doi.org/10.1111/j.1528-1167.2010.02777.x
23. Schurr J, Coras R, Rössler K, Pieper T, Kudernatsch M, Holthausen H, et al. Mild malformation of cortical development with oligodendroglial hyperplasia in frontal lobe epilepsy: a new clinico-pathological entity. Brain Pathol. 2017;27(1):26–35. https://doi.org/10.1111/bpa.12347
24. Bernasconi A, Cendes F, Theodore WH, Gill RS, Koepp MJ, Hogan RE, et al. Recommendations for the use of structural magnetic resonance imaging in the care of patients with epilepsy: a consensus report from the International League Against Epilepsy Neuroimaging Task Force. Epilepsia. 2019;60(6):1054–68. https://doi.org/10.1111/epi.15612
25. Mori S, Wu D, Ceritoglu C, Li Y, Kolasny A, Vaillant MA, et al. MRICloud: delivering high-throughput MRI neuroinformatics as cloud-based software as a service. Comput Sci Eng. 2016;18(5):21–35.
26. Li Y, Shea SM, Lorenz CH, Jiang H, Chou MC, Mori S. Image corruption detection in diffusion tensor imaging for post-processing and real-time monitoring. PLoS One. 2013;8(10):e49764. https://doi.org/10.1371/journal.pone.0049764
27. Jiang H, van Zijl PC, Kim J, Pearlson GD, Mori S. DtiStudio: resource program for diffusion tensor computation and fiber bundle tracking. Comput Methods Programs Biomed. 2006;81(2):106–16. https://doi.org/10.1016/j.cmpb.2005.08.004
28. Tang X, Oishi K, Faria AV, Hillis AE, Albert MS, Mori S, et al. Bayesian parameter estimation and segmentation in the multi-atlas random orbit model. PLoS One. 2013;8(6):e65591. https://doi.org/10.1371/journal.pone.0065591
29. Ceritoglu C, Oishi K, Li X, Chou MC, Younes L, Albert M, et al. Multi-contrast large deformation diffeomorphic metric mapping for diffusion tensor imaging. Neuroimage. 2009;47(2):618–27. https://doi.org/10.1016/j.neuroimage.2009.04.057
30. Tang X, Yoshida S, Hsu J, Huisman TA, Faria AV, Oishi K, et al. Multi-contrast multi-atlas parcellation of diffusion tensor imaging of the human brain. PLoS One. 2014;9(5):e96985. https://doi.org/10.1371/journal.pone.0096985
31. Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, et al. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. Neuroimage. 2008;40(2):570–82. https://doi.org/10.1016/j.neuroimage.2007.12.035
32. Oishi K, Faria A, Jiang H, Li X, Akhter K, Zhang J, et al. Atlas-based whole brain white matter analysis using large deformation diffeomorphic metric mapping: application to normal elderly and Alzheimer's disease participants. Neuroimage. 2009;46(2):486–99. https://doi.org/10.1016/j.neuroimage.2009.01.002
33. Macbeth G, Razumiejczyk E, Ledesma RD. Cliff's delta calculator: a nonparametric effect size program for two groups of observations. Univ Psychol. 2011;10(2):545–55. https://doi.org/10.11144/Javeriana.upsy10-2.cdcp
34. Marfo P, Okyere GA. The accuracy of effect-size estimates under normals and contaminated normals in meta-analysis. Heliyon. 2019;5(6):e01838. https://doi.org/10.1016/j.heliyon.2019.e01838
35. Sawilowsky SS. New effect size rules of thumb. J Mod Appl Stat Methods. 2008;8(2):597–9. https://doi.org/10.22237/jmasm/1257035100
36. Concha L, Livy DJ, Beaulieu C, Wheatley BM, Gross DW. In vivo diffusion tensor imaging and histopathology of the fimbria-fornix in temporal lobe epilepsy. J Neurosci. 2010;30(3):996–1002. https://doi.org/10.1523/JNEUROSCI.1619-09.2010
37. Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage. 2002;17(3):1429–36. https://doi.org/10.1006/nimg.2002.1267
38. Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage. 2003;20(3):1714–22. https://doi.org/10.1016/j.neuroimage.2003.07.005
39. O'Donnell LJ, Westin CF. An introduction to diffusion tensor image analysis. Neurosurg Clin N Am. 2011;22(2):185–96. https://doi.org/10.1016/j.nec.2010.12.004

40. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage. 2012;61(4):1000–16. https://doi.org/10.1016/j.neuroimage.2012.03.072
41. Deoni SC, Rutt BK, Arun T, Pierpaoli C, Jones DK. Gleaning multicomponent T1 and T2 information from steady-state imaging data. Magn Reson Med. 2008;60(6):1372–87. https://doi.org/10.1002/mrm.21704
42. Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. Magn Reson Med. 2000;44(4):625–32. https://doi.org/10.1002/1522-2594(200010)44:4<625::aid-mrm17>3.0.co;2-o
43. Klistorner S, Barnett MH, Wasserthal J, Yiannikas C, Barton J, Parratt J, et al. Differentiating axonal loss and demyelination in chronic MS lesions: a novel approach using single streamline diffusivity analysis. PLoS One. 2021;16(1):e0244766. https://doi.org/10.1371/journal.pone.0244766
44. Janz P, Schwaderlapp N, Heining K, Häussler U, Korvink JG, von Elverfeldt D, et al. Early tissue damage and microstructural reorganization predict disease severity in experimental epilepsy. Elife. 2017;6:e25742. https://doi.org/10.7554/eLife.25742
45. Uddin MN, Figley TD, Solar KG, Shatil AS, Figley CR. Comparisons between multi-component myelin water fraction, T1w/T2w ratio, and diffusion tensor imaging measures in healthy human brain structures. Sci Rep. 2019;9(1):2500. https://doi.org/10.1038/s41598-019-39199-x
46. van Eijsden P, Otte WM, van der Hel WS, van Nieuwenhuizen O, Dijkhuizen RM, de Graaf RA, et al. In vivo diffusion tensor imaging and ex vivo histologic characterization of white matter pathology in a post-status epilepticus model of temporal lobe epilepsy. Epilepsia. 2011;52(4):841–5. https://doi.org/10.1111/j.1528-1167.2011.02991.x
47. Concha L, Kim H, Bernasconi A, Bernhardt BC, Bernasconi N. Spatial patterns of water diffusion along white matter tracts in temporal lobe epilepsy. Neurology. 2012;79(5):455–62. https://doi.org/10.1212/WNL.0b013e31826170b6
48. Rodrigo S, Oppenheim C, Chassoux F, Golestani N, Cointepas Y, Poupon C, et al. Uncinate fasciculus fiber tracking in mesial temporal lobe epilepsy. Initial findings. Eur Radiol. 2007;17(7):1663–8. https://doi.org/10.1007/s00330-006-0558-x
49. Coan AC, Campos BM, Bergo FPG, Kubota BY, Yasuda CL, Morita ME, et al. Patterns of seizure control in patients with mesial temporal lobe epilepsy with and without hippocampus sclerosis. Arq Neuropsiquiatr. 2015;73(2):79–82. https://doi.org/10.1590/0004-282X20140199
50. Pimentel-Silva LR, Casseb RF, Cordeiro MM, Campos BAG, Alvim MKM, Rogerio F, et al. Interactions between in vivo neuronal–glial markers, side of hippocampal sclerosis, and pharmacoresponse in temporal lobe epilepsy. Epilepsia. 2020;61:1008–18.

SUPPORTING INFORMATION

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

How to cite this article: Urquia-Osorio H, Pimentel-Silva LR, Rezende TJR, Almendares-Bonilla E, Yasuda CL, Concha L, et al. Superficial and deep white matter diffusion abnormalities in focal epilepsies. Epilepsia. 2022;00:1–13. https://doi.org/10.1111/epi.17333