Published in final edited form as:

Acta Neurol Belg. 2020 December ; 120(6): 1323–1331. doi:10.1007/s13760-019-01074-x.

White Matter Microstructural Differences between Right and Left Mesial Temporal Lobe Epilepsy

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Abstract

Purpose: Mesial temporal lobe epilepsy (mTLE) is a chronic focal epileptic disorder characterized by recalcitrant seizures often necessitating surgical intervention. Identifying the laterality of seizure focus is crucial for pre-surgical planning. We implemented diffusion MRI (DMRI) connectometry to identify differences in white matter connectivity in patients with left and right mTLE relative to healthy control subjects.

Method: We enrolled 12 patients with right mTLE, 12 patients with left mTLE, and 12 age/sex matched healthy controls (HCs). We used DMRI connectometry to identify local connectivity patterns of white matter tracts, based on quantitative anisotropy (QA). We compared QA of white matter to reconstruct tracts with significant difference in connectivity between patients and HCs and then between patients with left and right mTLE.

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Conflict of interest

The authors declare that they have no conflict of interest.

Informed consent

De-identified retrospective data, approved by the HFHS IRB Committee, was used in this research.

Ethical approval

Ethics approval was provided by Henry Ford Health System Institutional Review Board, Detroit, Michigan, USA.

Results: Right mTLE patients show higher anisotropy in left inferior longitudinal fasciculus (ILF) and forceps minor and lower QA in genu of corpus callosum (CC), bilateral corticospinal tracts (CSTs), and bilateral middle cerebellar peduncles (MCPs) compared to HCs. Left mTLE patients show higher anisotropy in genu of CC, bilateral CSTs, and right MCP and decreased anisotropy in forceps minor compared to HCs. Compared to patients with right mTLE, left mTLE patients showed increased and decreased connectivity in some major tracts.

Conclusions: Our study showed the pattern of microstructural disintegrity in mTLE patients relative to HCs. We demonstrated that left and right mTLE patients have discrepant alternations in their white matter microstructure. These results may indicate that left and right mTLE have different underlying pathologic mechanisms.

Keywords

Temporal lobe epilepsy; Diffusion Magnetic Resonance Imaging (DMRI); Connectometry

1. Introduction

Mesial temporal lobe epilepsy (mTLE) is the most common form of localization-related epilepsy. mTLE is characterized by focal seizures arising from the inner aspect of the temporal lobe, most commonly from the hippocampal formation itself. After a short duration of pharmaco-responsive seizure, most patients with mTLE develop intractable seizures accompanied by progressive memory deficits and mesial temporal lobe (MTL) sclerosis, necessitating surgical resection of the instigating focus (1). Functional alterations in MTL as a result of prolonged spontaneous discharges, as well as MTL sclerosis, yield to microstructural disintegrity in MTL and adjacent/interconnecting white matter tracts. Diffusion tensor imaging (DTI) has provided clear evidence on white matter disintegrity both in temporal and extra-temporal regions, even in patients with no apparent sclerosis or atrophy in MTL (2). Overall, reduced white matter integrity is seen bilaterally, but is more prominent in ipsilateral white matters adjacent to the epileptogenic focus and more severe in patients with MTL sclerosis (2, 3). Changes are commonly seen in corpus callosum, external capsule, uncinate and arcuate fasciculi and correlate with disease duration especially in patients with no MTL sclerosis. Data on contralateral temporal lobe white matter involvement have been inconclusive.

Even with invasive EEG monitoring to identify epileptogenic focus, again one-fourth of patients undergoing surgery re-experience medication resistible seizures, which is attributed to multilobar/multifocal seizure foci (4). Interest is increasing to identify white matter abnormalities as biomarkers of drug refractoriness in mTLE (5) and epileptogenic foci (6). This might obviate the need for invasive EEG monitoring used for pre-surgical planning which is also aimed to reduce risk of post-surgical memory and cognitive deficits. Non-invasive lateralization and fiber tracking might also help estimate postsurgical prognosis, as left mTLE patients are found to have more severe language problems, whereas right mTLE patients have disruptions mainly in the tracts related to the limbic circuitry and emotional regulation (7). Of interest, diffusivity in the ipsilateral corpus callosum has helped with surgical planning of patients with and without MTL sclerosis (8).

Diffusion MRI (DMRI) connectometry is a novel approach in the analysis of diffusion MRI that uses density of water diffusion along different directions of a voxel as a measure to identify similarity in local connectivity patterns and track white matter pathways. Unlike conventional diffusion tensor imaging, DMRI connectometry is concerned with the density of water diffusion, not water diffusivity, i.e., how fast the water diffuses in any direction. This gives DMRI additional spatial resolution to identify white matter fibers in areas with kissing or crossing tracts, a situation often confronted in long associational white matter fibers, projecting in and out of the temporal lobe (9). In a commonly used protocol, the spin distribution function (SDF) is calculated based on a predefined atlas of diffusion density, for any given direction of each white matter voxel (9), and SDF is then used to reconstruct a connectomics fingerprint of all voxels for each subject. Connectometry converts SDF to a new variable, quantitative anisotropy (QA) which is a density based index used for further analyses (10). QA is used to extract fiber tracts, calculate between group differences, or correlate diffusion density with a variable of interest. Importantly, DMRI connectometry does not use average diffusion variables to extract statistical significance (11). Connectometry instead, tracks significant difference/correlations based on QA measures alongside voxels, to build up significant tracts. One major advantage of this notion is significant reduction in type 1 error, higher spatial resolution, and lower susceptibility to partial volume effect of DMRI connectometry compared to conventional DTI (12).

Previous evidence regarding the white matter microstructural disintegrity in left and right mTLE patients are scarce and inconclusive (13–15). Herein we used retrospective imaging data from presurgical planning of a group of patients with unilateral mTLE. Using model-free DMRI connectometry approach we aimed to identify white matter microstructural changes in each group compared to the healthy controls (HCs) and to the other. We hope to identify potential signature white matter area(s) to be used for pre-surgical planning of patients of unilateral mTLE.

2. Materials and Methods

2.1 Participants

This research study was approved by the Henry Ford Health System Institutional Review Board and used the data of 24 patients with mTLE, in two age/sex matched groups: 12 right mTLE patients (male/female: 7/5, mean age: 43.3 ± 11.4 years) and 12 left mTLE patients (male/female: 6/6, mean age: 40.1 ± 13.7 years) (16). All patients had undergone mesial temporal lobe resection surgery and achieved an Engel class I outcome following resection of their mesial temporal structure. TLE laterality had been determined in all patients devising conventional invasive and non-invasive EEG as well as postsurgical histopathology to divide patients into the left and right mTLE groups (Table 1). Detailed history was obtained from all subjects before MTL resection, regarding co-morbid neuropsychological disorders, history of brain tumors or brain surgery. Importantly, patients in both groups has similar rates of MTL sclerosis, which has been shown to interfere with white matter diffusivity by other studies.

We also recruited a group of 12 age and sex-matched individuals with no history of neurological disorders (male/female: 6/6, mean age: 42.2 ± 11.5 years), as healthy control

(HC) group. DTI data for HCs was obtained from the freely available “information extraction from images” database (<http://biomedic.doc.ic.ac.uk/brain-development/>).

2.2 Data Acquisition

Both patients groups underwent pre-surgical imaging using a 3 Tesla MRI scanner (GE Medical Systems, Milwaukee, USA) producing: 1) DMRI images at 25 diffusion angles obtained with echo planar imaging (EPI) with a $b=1,000$ s/mm², along with null images at b -value of 0 s/mm² (repetition time = 10,000 ms, inversion time = 0 ms, echo time = 76 ms; voxel size: $1.96 \times 1.96 \times 2.6$ mm³; field of view = 224×224 mm), and 2) 3D T1-weighted structural images using the spoiled gradient echo protocol (SPGR) (repetition time = 10,400 ms, inversion time = 4500, echo time = 300 ms; flip angle = 15°, voxel size: $0.39 \times 0.39 \times 2.0$ mm³) (16).

DTI for HC group was obtained from the freely available “information extraction from images” database (<http://biomedic.doc.ic.ac.uk/brain-development/>). Ethical approval of this data base was granted by the Thames Valley multicenter ethics committee. Healthy subjects were scanned at 3 Tesla MRI scanner (Philips Medical Systems Intera). Imaging parameters were: 15 diffusion-weighted images, 1,000 mm/s diffusion-weighting, 1 b_0 images, 56 axial slices, 2.35-mm slice-thickness, 128×128 acquisition matrix, 1.75×1.75 mm voxels, and repetition time (TR)/echo time (TE) of 11.9 s/51 ms.

2.3 Diffusion MRI Data Processing

DMRI data were corrected for subject motion, eddy current distortions (17), and susceptibility artifacts due to the magnetic field inhomogeneity using Explore DTI toolbox (12). Further, a visual quality control was performed in T1-weighted images to rule out macrostructural brain abnormalities, including excessive white matter lesions, silent brain infarction, tumors, hydrocephalus, etc. None of the patients in either groups were excluded after quality check.

2.4 Between-Groups Analysis

The diffusion data were reconstructed using the publicly available software DSI Studio (<http://dsi-studio.labsolver.org>), in the MNI space. Reconstruction was performed by q-space diffeomorphic reconstruction (QSDR) using an enhanced version of SPM normalization using Fourier basis to construct the diffeomorphic field for each subject. The QSDR protocol in DSI Studio allows for a simultaneous registration, normalization and construction of SDF maps in any given template, such as the MNI space. QSDR converts raw SDF measures to a new variable called QA which gives the peak value of water density in each fiber direction. Unlike conventional diffusivity measures like fractional anisotropy (FA) that are calculated for the main fiber direction, QA has a “fiber orientation” component meaning that is defined for each of the given directions of a voxel (18). This implicates a better spatial resolution for QA to detect microstructural disturbances in kissing or crossing fibers. Our patients and HCs are from different databases and have undergone different technical procedures, thus we have applied normalized QA, in comparison between mTLE patients with HCs. Normalized QA use spatial normalization to calibrate QA and ensure a better consistency/reproducibility (<http://dsi-studio.labsolver.org/Manual/diffusion-mri-indices>).

Comparing subjects QA in each voxel to the MNI QA map, DSI studio records an R-squared value that can be used to detect possible registration errors. We excluded all fiber with less than 0.6 average R-square difference to template, as an additional measure of quality control.

2.5 DMRI Connectometry

As mentioned, connectometry builds up a “local connectomics” based on calculated QA for any given fiber orientation, as a proxy of water diffusion density along that direction. Connectometry can then track the difference of white matter tracts between groups, or correlation of white matter fibers with a variable interest. Using the DSI studio software, the DMRI connectometry protocol was adopted to identify tracts with significant difference in QA between the two groups (contrast analysis), based on local connectome/diffeomorphic map (19). Next, we performed a deterministic fiber tracking algorithm along the core pathway of the fiber bundle to connect the selected local connectomes. A length threshold of 20 voxels distance and a tract density of 20 per voxel were adopted to select tracts. All tracts with $QA > 0.1$, angle threshold smaller than 40° and tract length greater than 40 mm were included. A T-score threshold of 2.5 was assigned to select local connectomes. All tracts with $FDR < 0.05$ were reported, as recommended by the software developer.

As a final measure, the resulting output was corrected for multiple comparisons by false discovery rate (FDR). In order to estimate the FDR, a total of 2,000 random permutations were applied to the group label to obtain the null distribution of the tract length. Permutation testing allows for estimating and correcting the FDR for Type-I error inflation due to multiple comparisons.

3. Results

Results of comparison analysis of local connectivity maps in patients with right and left mTLE, and HCs are summarized in Table 2. Comparing patients with right mTLE and HCs, higher connectivity was found in patients in left inferior longitudinal fasciculus (ILF), left uncinate fasciculus (UF), left anterior limb of internal capsule (ALIC), and forceps minor with a FDR of 0.0112 . In contrast, genu of corpus callosum (CC), bilateral corticospinal tracts (CSTs), bilateral middle cerebellar peduncles (MCPs), left arcuate fasciculus (AF), and left posterior limb of internal capsule (PLIC) showed lower connectivity in right mTLE compared to HCs ($FDR=0.0024$). When comparing connectivity of white matter fibers between left mTLE patients and HCs, connectivity of forceps minor, right ALIC, and left UF was higher in the patients group ($FDR=0.0024$), and connectivity of the genu of CC, bilateral CSTs, right MCP, left AF, and left PLIC was higher in HCs ($FDR=0.0116$).

Comparing two groups of patients with right and left mTLE, left mTLE patients showed increased connectivity in the subgenual part of bilateral cingulum and parts of the CST, genu of CC, left ILF, left UF, and left AF ($FDR = 0.042$) (Figure 1). As shown in Figure 2, right mTLE patients on the other hand, showed preserved connectivity in the right MCP, right ILF, and right inferior-fronto occipital fasciculus (IFOF) compared to left mTLE patients ($FDR = 0.038$).

Among fibers where connectivity is increased or decreased in both groups, the left AF, left UF, bilateral CST, genu of corpus callosum, and right MCP have the potential to be used to differentiate right from left mTLE patients.

4. Discussion

To our knowledge, this is the first DMRI-based connectometry that investigates the alterations in brain white matter connectivity of left and right mTLE patients compared to HCs and to each other. Our results from DMRI connectometry analysis revealed microstructural differences between the left and right mTLE patients. Use of DMRI connectometry enabled us to identify microstructural alterations in white matter of mTLE patients with higher spatial sensitivity compared to conventional DTI. In simple words, DMRI connectometry tracks changes through individual white matter voxels, instead of comparing diffusometric measures along predefined trajectories, i.e. track-based extraction of diffusometric measures (20). DMRI connectometry is a model-free method, using statistical significance of the reconstructed local connectome of white matter in a comparison of interest, as a clue to track voxels along a white matter trajectory (9). Using DMRI connectometry, we were able to identify both increased and decreased white matter connectivity in patients with mTLE compared to HCs, unlike previous studies using conventional DTI.

Areas with increased connectivity overlapped, when comparing either right or left mTLE patients to healthy controls. Likewise, white matter regions with decreased connectivity compared to controls were similar in right and left mTLE patients, independent of the affected side. This result is compatible with bilateral disruption of white matter integrity in patients with mesial temporal sclerosis, which is also shown to be independent of the seizure side (21). Furthermore, fiber tracing through DMRI has shown high correlation and cross-validity with “tract-tracing data” and myelin staining, suggesting validity of DMRI in brain architectural mapping (22). Herein, DMRI connectometry has identified widespread white matter microstructural demise, as is seen in mTLE patients with mesial temporal sclerosis.

We have previously developed a “response-driven lateralization model” based on DTI metrics of the cingulate, fornix, and corpus callosum that could differentiate laterality of epileptogenic focus in patients with unilateral mTLE from other subtypes (23). Considering the above findings in right and left mTLE patients and the HC group, we believe that a connectivity map based on left AF, left UF, bilateral CST, and genu of corpus callosum, could help differentiate between left and right mTLE patients. Considering higher spatial resolution of DMRI compared to conventional DTI, this model could yield a higher sensitivity in recognition of epileptogenic side.

Furthermore, it is known that age of onset and duration of disease can negatively impact ability of EEG modalities to identify the epileptogenic focus, as these are associated with medial temporal sclerosis and multilobar engagement (24, 25). It is therefore crucial to discriminate age related changes in white matter structure from those resulting from abnormal electrical discharge from the epileptogenic focus. Q-space measurements and

DMRI are shown to have high sensitivity to microstructural alterations related to age and sex and correlate with DTI indices in healthy individuals (26).

One interesting result of this study was finding “increased” connectivity in white matter fibers contralateral to the seizure focus, i.e., increased connectivity in left ILF, left UF, and left ALIC in right mTLE patients compared to HCs. These fibers are part of or in close proximity to the limbic and language circuitry, which has been shown to undergo early connectivity changes in mTLE patients (27). It is reasonable to postulate that abnormal electrical discharge from seizure focus is the reason for adaptive changes in structure and function of the adjacent white matter fibers to the epileptogenic focus in MTL (28, 29), and henceforth in the limbic system. Also, functional alterations in the connectivity between MTL structures might also lead to structural disruption of the white matters fibers projecting in and out of MTL (27, 30), and thus affect structural connectivity of remote fibers in the contralateral side. These changes could also reflect early phases of structural disruption and neuroinflammation in white matter fibers in the contralateral side, which is associated with reduced overall diffusivity, increase in FA (31), and potentially increased connectivity. Indeed, conventional DTI studies have found only slight changes in temporal white matter, in terms of increased mean diffusivity of the ipsilateral fibers, with no changes in FA or white matter volume in early mTLE (31).

Finally, hemisphere laterality/dominance in functional circuitry, such as language network, could confer a difference in susceptibility of ipsi- and contralateral white matter fibers to microstructural changes (32). This can also provide a clue to seizure laterality, as functional connectivity of white matter fibers within the medial temporal lobe is decreased in the ipsilateral side and increased in the contralateral side relative to the seizure focus (33, 34). On the other hand, functional connectivity of the seizure focus to extra-MTL areas is less liable to the laterality of seizure focus (33). This is in line with our finding of bilateral decreased connectivity in CST, right MCP, and genu of CC in both patient groups.

In light of these findings, our results can be interpreted in a network-based fashion considering that both ILF and UF, mediate structural connections of MTL/hippocampus, to extra-MTL regions in the occipital and frontal lobes, respectively. ILF connects the temporal pole to the cuneus and precuneus regions, which are also parts of the default mode network (35), and UF mediates the connections from the medial temporal gyri to the frontal regions, namely the medial prefrontal cortex (36). ILF and UF converge in their frontal connections and essentially share their connectivity to the frontal lobe with ALIC (37). Therefore, the observed DMRI changes in these fibers are more consistent with increased contralateral functional connectivity of white matter fibers of MTL and limbic circuitry, rather than diffusometric changes revealed by DTI. Conclusively, DMRI connectivity patterns appear to reflect network-based patterns of disruption, with increased connectivity of intra-MTL white matter in the contralateral side of seizure focus and decreased connectivity in extra-MTL regions of both hemispheres.

In a view of literature, left mTLE patients appear to have more severe and lateralized connectivity interruptions and greater degree of white matter atrophy relative to right mTLE patients. Patients with left mTLE have demonstrated widespread dysconnectivity in terms of

reduced FA in major temporal lobe white matter tracts, namely the AF from the language circuitry, and in the temporal pole white matter fibers such as IFOF, which has a significant overlap with ILF and UF (15). Accordingly, results of a recent meta-analysis of DTI-detected white matter changes in TLE patients demonstrated reduced FA and increased mean diffusivity (MD) in a majority of white matter regions, both ipsilateral and contralateral (38). Reduced FA and increased MD were seen in UF both ipsi- and contralateral to the epileptic focus, as well as the bilateral internal capsule and bilateral cingulum. It appears that right mTLE patients show lower levels of white matter connectivity in tracts related to the limbic circuitry, but overall, have less dysconnectivity and atrophy compared to patients with left mTLE.

Putting this fact together with the above explanations that the internetwork connections are more likely to obey connectivity alterations based on the epileptogenic domain, our results reiterate the fact that the network architecture of the brain as well as proximity to epileptic focus are necessary to determine the extent of dysconnectivity of white matter tracts in patients with mTLE. Based on the above explanations and in light of findings of the current study, there is a potential for the DMRI-connectometry parameters of the mentioned white matter fibers to be used as a proxy to display the epileptogenic focus in mTLE patients.

Patients with left mTLE also have showed widespread grey matter atrophy in frontal, parietal, and occipital regions (39), besides MTL. This might as well reflect the extent of extra-MTL connections of the epileptogenic focus in the left hemisphere. Patients with left mTLE also show a stronger volume-function correlation in medial temporal lobe nodes, with atrophy in hippocampal and parahippocampal formation, which is associated with memory dysfunction in these patients (15, 40).

Once again, it is reasonable to deduce that increased regional homogeneity and network integrity seen in ipsilateral temporal lobe white matter including cingulum (41), as well as in their respective cortical areas, including ipsilateral frontal and temporal gyri (42), is behind increased connectivity in adjacent white matter fibers to the language networks, namely the AF, and UF. Although it has been suggested that QA in DMRI connectometry is analogous to FA in conventional DTI (18), it appears that DMRI connectometry has a predilection to identify changes in “functional” network architecture, rather than structural networks. Consistent with our results, studies have demonstrated that the seizure network might affect contralateral language structures more severely than ipsilateral fibers to the epileptogenic area (43). In the next final paragraphs, we explain significance of our findings in a fiber-wise manner with an overview on relevant literature.

Our results indicated reduced anisotropy in bilateral CST and genu of CC in patients with right mTLE compared to left. CC is the largest white matter structure of the brain, anatomically composed of four sections: splenium in the posterior, trunk in the middle, and genu and rostrum in the anterior. Interestingly, genu of CC is postulated to be the main pathway for generalization of focal seizures including TLE (44, 45). Studies have demonstrated a reduced anisotropy in CC in different epileptic syndromes including mTLE, and juvenile myoclonic epilepsy (JME) (46). Again, in accordance with our findings, anterior part of the CC shows a significant reduction in FA along with reduced volume in

TLE (46), along with decreased FA and increased MD in ipsilateral CST in mTLE patients (44). Previous studies have also reported a correlation between atrophy and structural alteration and remodeling in bilateral CST and CC in mTLE patients (49). To our knowledge, our study is the first one reporting the differences in the connectivity of CST between the left and right mTLE patients, with ipsilateral predominance in QA in left mTLE patients.

Regarding MCP, as previous studies have observed no lateralized pathologic differences or asymmetry in the structure of the cerebellum, in right and left mTLE patients (47, 48), the observed difference in connectivity of MCPs can be attributed to disruption of motor networks, mainly in the dominant hemisphere (41).

Moving onto the ILF, the connecting fiber between temporal and occipital lobe, it has been shown to undergo microstructural alternations in mTLE patients. In a recent study (50), Kreilkamp, et al. exhibited more severe structural changes in bilateral ILF, in left mTLE patients compared to right mTLE. Herein, we found that right mTLE patients have higher connectivity in right ILF and left mTLE patients have increased connectivity in left ILF, compatible with the fact that internetwork white matter connections are more prone to structural disruption in the ipsilateral side of the seizure focus. To our knowledge, there are few previous studies investigating the diffusion feature of IFOF in mTLE patients. We found that right IFOF has a higher QA in right mTLE patients relative to left mTLE patients, which is justifiable considering significant spatial overlap of this fiber with ILF.

Finally, cingulum, a key component of limbic system, has been postulated to be one of the key fibers accounting for anisotropy asymmetries between the left and right hemispheres in healthy individuals (51, 52). In a study on TLE with hippocampal sclerosis (TLE-HS), researchers reported that several structures in left TLE-HS, but not right TLE-HS, including the ipsilateral posterior cingulum demonstrate loss of integrity and reduced connectivity (53). We observed a reversed relationship in bilateral subgenual parts of cingulum in left compared to right mTLE patients, which could attribute to difference in susceptibility of different parts of cingulum to seizure pathology or attribution of different cingulum subsections to different functional networks in the brain.

Results of the current study should more or less be interpreted considering major methodological limitations of this work, namely: DMRI data of patients and healthy subjects were extracted from different databases.

5. Conclusion

Over the past decade, various white matter microstructural changes have been detected in mTLE patients. Left and right mTLE patients have discrepant involvement of white matter microstructure, which could potentially contribute to discovering the pathological underpinnings of mTLE pathophysiology. Our study is the first one to address this issue, using DWI connectometry as an excellent method for detection of distinct white matter connectivity in left and right mTLE. Our results demonstrated the disruptions in the connectivity of white matter fibers in mTLE patients compared to HCs. More importantly,

we demonstrated that several major white matter tracts were differently involved in the left and right mTLE patients; the main affected structures located contralateral to the epileptic focus and also within the midline components. The main limitation of this study is the limited number of patients in each group. Follow-up studies with a larger number of patients and HCs will clear whether small regional diversities observed between the patient groups are linked to specific patterns of mTLE or justified by the small sample size.

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Figure 1. White matter pathways with significantly increased anisotropy in left mTLE patients compared to right mTLE patient (FDR = 0.042): (a) left subgenual part of cingulum, (b) left corticospinal tract, (c) right subgenual part of cingulum, (d) right corticospinal tract, and (e) genu of corpus callosum.

Figure 2.

White matter pathways with significantly increased anisotropy in right mTLE patients compared to left mTLE patient (FDR = 0.038): (a) right inferior longitudinal fasciculus, (b) right inferior fronto-occipital fasciculus, and (c) middle cerebellar peduncle.

Table 1.

Demographic and baseline clinical information of TLE patients and healthy controls

Characteristic	Right-sided TLE [n=12]	Left-sided TLE [n=12]	HC [n=12]	p-value
Age at surgery, mean (SD) [95% CI], in years	40.1 (14.3) [31.0–49.2]	43.4 (11.4) [36.1–50.6]	42.2 (12.0) [34.2–49.8]	0.816 ^a
Female/male, No. (% male)	6/6 (50.0)	5/7 (58.3)	6/6 (50.0)	0.895 ^b
Disease duration, mean (SD) [95% CI], in years	21.8 (16.8) [11.1–32.4]	31.8 (15.9) [21.7–41.9]	-	0.178 ^c
Follow-up duration, mean (SD) [95% CI], in years	4.5 (0.8) [4.0–5.0]	3.5 (1.0) [2.9–4.2]	-	0.039 ^c
MTS–/MTS+ (%MTS+)	7/5 (41.7)	2/10 (83.3)	-	0.089 ^d

Abbreviations: TLE, Temporal lobe epilepsy; MTS, Mesial temporal sclerosis.

^a Based on one-way ANOVA test.^b Based on Pearson χ^2 test.^c Based on Mann-Whitney U test^d Based on Fisher's exact test.

Table 2.

Results of multiple regression analysis of quantitative anisotropy of white matter fibers from MNI atlas in patients with right and left temporal lobe epilepsy and healthy controls (> indicates higher quantitative anisotropy)

Left PLIC	Left AF	Left UF	Left Subgenual Cingulum	Left ILF	Left ALIC	Left MCP	Left CST	Forceps Minor	Genu of CC	Right CST	Right MCP	Right ALIC	Right ILF	Right IFOF
	L>R	L>R	L>R	L>R			L>R		L>R	L>R	R>L		R>L	R>L
HC>L	HC>L	L>HC					HC>L	L>HC	HC>L	HC>L	HC>L	L>HC		
HC>R	HC>R	R>HC		R>HC	R>HC	HC>R	HC>R	R>HC	HC>R	HC>R	HC>R			
	HC>L>R	L>R>HC		L>R>HC			HC>L>R		HC>L>R	HC>L>R	HC>R>L			

* TLE= temporal lobe epilepsy; R = right temporal lobe epilepsy; L=left temporal lobe epilepsy; HC= healthy control; PLIC= posterior limb of internal capsule;ALIC= anterior limb of internal capsule;AF= arcuate fasciculus; UF= uncinate fasciculus; MCP= top cerebellar peduncle; CST= corticospinal tract; CC= corpus callosum; IFOF= inferior frontooccipital fasciculus

** FDR=false discovery rate; significant FDR of comparisons were as follows: **R>HC**: 0.0112; **HC<R**: 0.0024; **L>HC**: 0.0116; **L<HC**: 0.0024; **R>L**: 0.038; **L>R**: 0.042

*** The second row shows significant results comparing QA maps of patients with right TLE and HC, the third row shows comparison of left TLE patient and HC; and the fourth row compares left and right TLE. The fifth row summarizes significant findings from the three comparisons (L vs. HC, R vs. HC, and L vs. R). Only significant comparisons are listed.