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Diffusion Tensor Imaging Shows More Extensive White Matter Changes in Frontal than in Temporal Lobe Epilepsy

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Abstract

Introduction: FLE is known to have a poorer prognosis than TLE. We compared the extent of white matter changes in these groups using diffusion tensor imaging-based tractography. ***Methods:*** 20 tracts each were made in five TLE and six FLE patients (bilateral FORX, CGC, PH, UF, SLF, ILF, IFOF, ATR, CST; FMajor and FMinor) and their FA values compared. ***Results:*** The TLE group had decreased FA of all ipsilateral fibres except IFOF, with a statistically significant decrease in FORX and UF. The FLE group had a significant decrease ($p< 0.05$) in the FA values of contralateral ATR and CST. A few contralateral tracts (PH, UF, SLF, IFOF) and ipsilateral FORX and ILF also showed (statistically nonsignificant) decreased mean FA. Mann-Whitney U test comparing ipsilateral nine fibre pairs of FLE vs. TLE was non-significant and significant ($p<0.05$) only for CST in contralateral fibre comparison. However, a generalised decrease in all fibre FA in FLE vs. TLE was noticed, except for the 'intimate' temporal fibres, viz., FORX and PH. The mean FA of all tracts was 0.4982 and 0.5201 for FLE and TLE, respectively ($p<0.05$). The mean FMajor and FMinor FA were 0.6146 vs. 0.6702 and 0.5598 vs. 0.5917 in FLE vs. TLE, respectively. ***Conclusion:*** Tractography based FA value comparison reveals more extensive and severe white matter changes in FLE than in TLE.

Keywords: diffusion tensor imaging, tractography, fractional anisotropy, epilepsy, temporal lobe epilepsy, frontal lobe epilepsy

1. Introduction

Epilepsy is a common neurological disease, affecting 0.5%–1% of the population, being refractory to medical therapy in 15%–30% of cases, in some of whom, neurosurgical treatment can be superior to long-term drug treatment, (Lefkopoulos A, Haritanti A, Papadopoulou E, Karanikolas D, Fotiadis N, Dimitriadis AS, 2005; Wiebe S, Blume WT, Girvin JP, Eliasziw M., 2001) especially in temporal lobe epilepsy (TLE) which is the most common form of focal epilepsy refractory to medical therapy in adults. (Engel J Jr., 2001) Patients with frontal lobe epilepsy (FLE), however, have a poorer outcome. (Jeha LE, Najm I, Bingaman W, Dinner D, Widdess-Walsh P, Lüders H., 2007)

Diffusion tensor imaging (DTI) is a special sequence of clinical magnetic resonance imaging (MRI) that generates multiple parameters like apparent diffusion coefficient (ADC) and fractional anisotropy (FA), which can be used to study the pathological as well as the normal-appearing areas of the brain. (Lee SK, Kim DI, Kim J, Kim DJ, Kim HD, Kim DS, Mori S., (2005) Tractography utilizes the DTI data to visualize white matter tracts and generate DTI parameters viz. ADC and FA etc. Thus, creating a large group of tracts in both cerebral

hemispheres can generate information about a large part of the brain's white matter. (Lee SK, Kim DI, Kim J, Kim DJ, Kim HD, Kim DS, Mori S., 2005)

It implies that refractory focal epilepsy, which is known to have widespread white matter changes and can even appear normal on conventional MRI, can be studied using DTI and tractography, and that pattern(s) of change(s) can be derived in both TLE and FLE patients to identify differences in disease extent.

2. Materials and Methods

Patients: The study was done after taking due approval from the Institute Ethics Committee of the All India Institute of Medical Sciences, New Delhi (Ref No T-14/12.06.2009), as part of a thesis protocol, and included patients with epilepsy received for MR imaging over a period of six months. All methods were carried out according to approved guidelines and as per the Helsinki declaration. An "informed consent" was obtained from all study participants and/or their legal guardian(s).

Only right-handed patients with a history of focal seizures for at least two years and multiple drug intake (at least four) were included. All study participants came from well-educated families (at least one parent was a graduate). However, the education of the participants themselves was not considered a deterrent for enrolment as many were school dropouts. Cases with gross neurological deficits or significantly asymmetrical deficits were not included. Only patients with temporal or frontal localization were included in the study, based on matching clinical findings, electroencephalogram/video-electroencephalogram (EEG/VEEG), and single photon emission computed tomography (SPECT), if done. Any patient in whom there was discordance in these three profiles, bilateral discharges/SPECT findings, or varying areas of electrical activity, was not taken. Cases with tumors, calcification, or bleeding as seen on MRI were not considered. Thus, a total of eleven patients formed the study group. Patients with identifiable unilateral mesial temporal sclerosis (MTS) only were included in the TLE group, and patients with non-lesional or extra-mesial TLE were not included. Patients with FLE were included, whether MRI showed a focal lesion or not.

MRI and DTI data acquisition: Patients were examined on a 1.5T MRI scanner (Avanto, Siemens, Erlangen, Germany). Initially, all patients had routine clinical pulse sequences, including axial T1W (TR/TE 500/27 ms), T2W (TR/TE, 4000/90 ms), FLAIR (TR/TI/TE, 6000/2000/120 ms), and oblique coronal 3mm thick FLAIR images perpendicular to the hippocampal plane. DTI acquisition consisted of a diffusion-weighted spin-echo pulse sequence with a single-shot EPI readout with a TR/TE of 9.4 sec./80 ms. Three mm thick, 52 axial sections parallel to the anterior/posterior commissure line were acquired, covering the entire brain (Lee SK, Kim DI, Kim J, Kim DJ, Kim HD, Kim DS, Mori S., (2005). The maximal b-value was 800 seconds/mm2, used in a 12-gradient direction scheme. The FOV was 230x230 mm. All images were of a 128x128 matrix. Four repetitions were performed. 3D-MPRAGE images (TR/TE/flip angle 6.8–8.8/3.3–3.7 ms/8°) were also obtained with the same section localization and FOV.

Postprocessing: The collected data was transferred to a Windows-based computer, sorted, and anonymized (DicomWorks v 1.3.5b). DTI-Studio v 2.4.01 was then used to process the DTI data.

The technique of tractography: Twenty tracts in each patient were reconstructed—Right and Left Fornix (FORX), Cingulum in Cingulate gyrus (CGC), Cingulum in Parahippocampal gyrus (PH), Uncinate fasciculus (UF), Superior Longitudinal fasciculus (SLF), Inferior longitudinal fasciculus (ILF), Inferior FrontoOccipital fasciculus (IFOF), Anterior thalamic radiation (ATR), Cortico-Spinal tract (CST); and Forceps Major (FMajor) and Minor (FMinor).

Tracts were made using a region of interest (ROI) placement technique, following previously described methods by Wakana, Concha, and Yasmin. (Wakana S, Caprihan A, Panzenboeck MM, Fallon JH, Perry M, Gollub RL, Hua K, Zhang J, Jiang H, Dubey P, Blitz A, van Zijl P, Mori S., 2007; Concha L, Beaulieu C, Gross DW., 2005; Yasmin H, Aoki S, Abe O, Nakata Y, Hayashi N, Masutani Y, Goto M, Ohtomo K. 2009) For tract reconstruction, the fibre assignment by continuous tracking (FACT) method described by Mori et al. and Xue et al. was used, and the fibre tracking was stopped if the FA reached less than 0.20 and/or the fibre turning angle exceeded 80 degrees. (Mori S, Crain BJ, Chacko VP, van Zijl PCM. 1999; Xue R, van Zijl PCM, Crain BJ, Solaiyappan M, Mori S. 1999) A multi-ROI approach was used to reconstruct tracts using the existing anatomical knowledge of tract trajectories, which has been described in detail and 'standardized' by Wakana et al.; (Wakana S, Caprihan A, Panzenboeck MM, Fallon JH, Perry M, Gollub RL, Hua K, Zhang J, Jiang H, Dubey P, Blitz A, van Zijl P, Mori S., 2007) however, the CGC and FORX were made according to Ahmadi et al. and Concha et al. (Concha L, Beaulieu C, Gross DW., 2005; Ahmadi ME, Hagler DJ Jr, McDonald CR, Tecoma ES, Iragui VJ, Dale AM, Halgren E. 2009; Concha L, Beaulieu C, Collins DL, Gross DW. 2009) Tracking was performed from all pixels inside the brain—The Brute-Force Approach—described by Conturo et al. and Huang et al., (Conturo TE, Lori NF, Cull TS, Akbudak E, Snyder AZ, Shimony JS, McKinstry RC, Burton H, Raichle ME. 1999; Huang H, Zhang J, van Zijl PC, Mori S. 2004) and results passing through the manually defined ROIs were assigned to the

specific tracts associated with the anatomically located ROIs. The ROI placement and tract reconstruction were done on color-coded maps, however, many times the identification of anatomical landmarks was difficult when trace images were used- especially for drawing the UF, ILF, and IFOF.

Statistical analysis: Mann-Whitney U test was performed to compare the FA values of all the tracts in both groups. Paired t-tests were also performed for each pair of tracts (classified as ipsilateral and contralateral) in both groups. Fmajor and Fminor FA values were compared separately.

3. Results

A total of 11 patients were evaluated (Table 1). The average durations of epilepsy were 9 and 16 years for TLE and FLE, respectively. The numbers appear significant in isolation, although the Mann-Whitney U test showed a nonsignificant comparison ($p>0.05$). The average age of FLE and TLE patients was 21.2 years and 15.4 years, respectively (statistically non-significant with $p>0.05$).

Table 1. Localization of seizure focus and MRI diagnosis

Localization	Side of localization	MRI diagnosis	Number (n)
Temporal	Left	Left mesial temporal sclerosis	2
	Right	Right mesial temporal sclerosis	3#
Frontal	Left	Left frontal focal cortical dysplasia	2
		Normal	1
	Right	Diffuse atrophy	1
		Diffuse atrophy and bilateral fronto-temporal encephalomalacia	1
		Normal	1
Total			11

one patient also had focal cortical dysplasia in the ipsilateral superior temporal lobe; n = number of patients

The mean FA of all tracts was 0.4982 for FLE and 0.5201 for TLE (both statistically significant with ($p < 0.05$). (Figure 1)

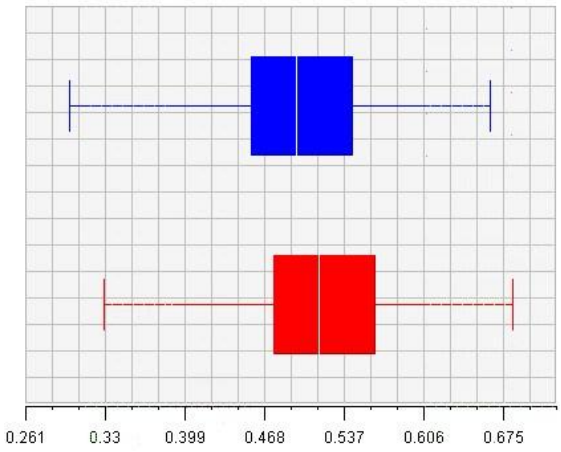
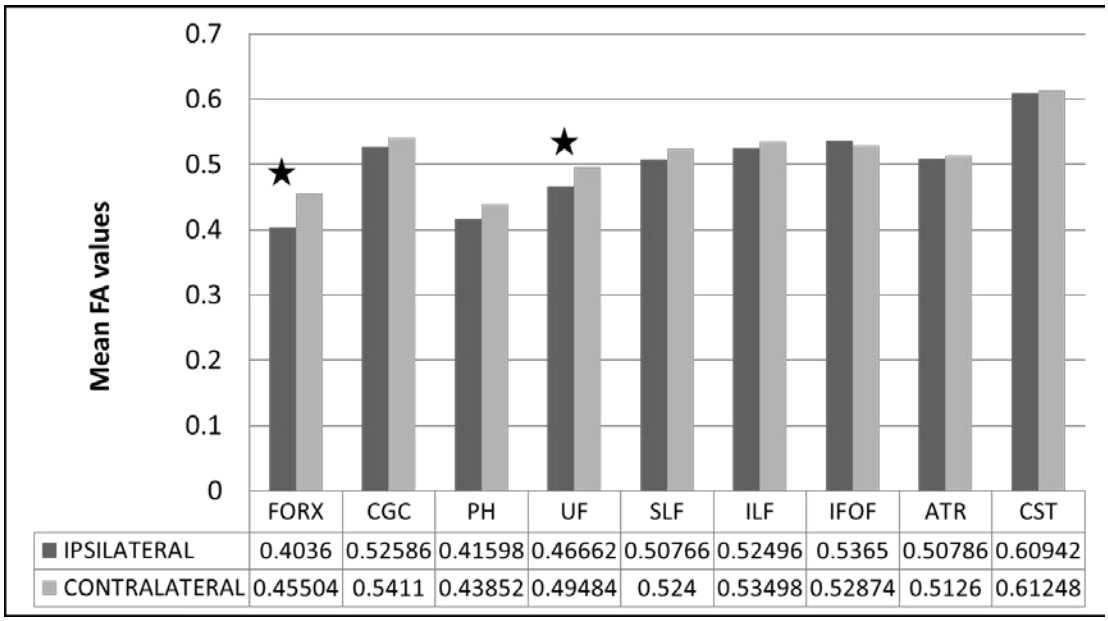


Figure 1. Box and Whisker plot of FLE (upper) and TLE (lower) patients for FA values of all 20 tracts

All the values are comparatively decreased in FLE patients as compared to TLE patients. FLE-frontal lobe epilepsy, TLE-temporal lobe epilepsy, FA-fractional anisotropy.

The FA values of individual fibres on both sides of the TLE group were subjected to the paired t-test. (Figure 2)

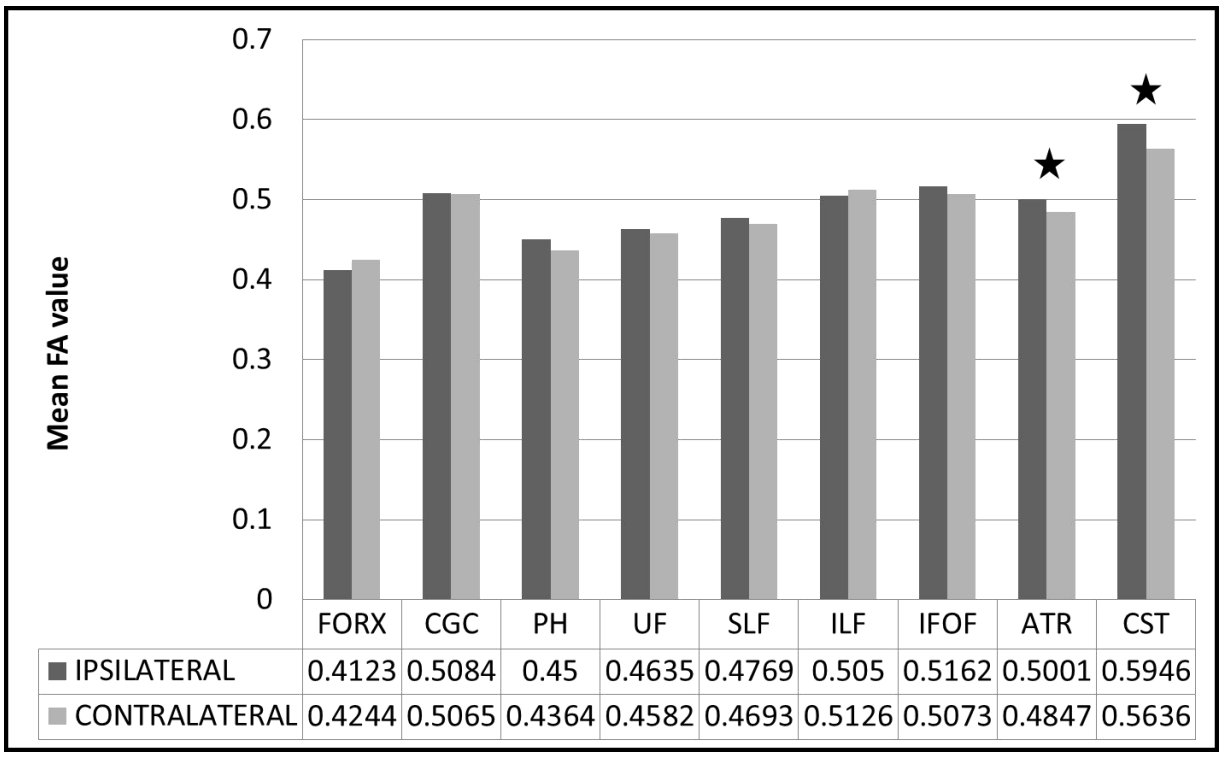


	FORX	CGC	PH	UF	SLF	ILF	IFOF	ATR	CST
IPSILATERAL	0.4036	0.52586	0.41598	0.46662	0.50766	0.52496	0.5365	0.50786	0.60942
CONTRALATERAL	0.45504	0.5411	0.43852	0.49484	0.524	0.53498	0.52874	0.5126	0.61248

Figure 2. Mean FA values of ipsilateral and contralateral fibers in patients with TLE (unilateral MTS)

Indicates a significant difference ($p<0.05$). FA-fractional anisotropy, TLE-temporal lobe epilepsy, MTS-mesial temporal epilepsy, FORX-fornix, CGC-cingulum in cingulate gyrus, PH-cingulum in parahippocampal gyrus, UF-uncinate fasciculus, SLF-superior longitudinal fasciculus, ILF-inferior longitudinal fasciculus, IFOF-inferior fronto-occipital fasciculus, ATR-anterior thalamic radiation, CST, corticospinal tract.

A generalised decrease in FA of all ipsilateral fibres except the IFOF was seen with a statistically significant difference obtained for FORX and UF. The FLE group was similarly analysed with the paired t-test. (Figure 3)



	FORX	CGC	PH	UF	SLF	ILF	IFOF	ATR	CST
IPSILATERAL	0.4123	0.5084	0.45	0.4635	0.4769	0.505	0.5162	0.5001	0.5946
CONTRALATERAL	0.4244	0.5065	0.4364	0.4582	0.4693	0.5126	0.5073	0.4847	0.5636

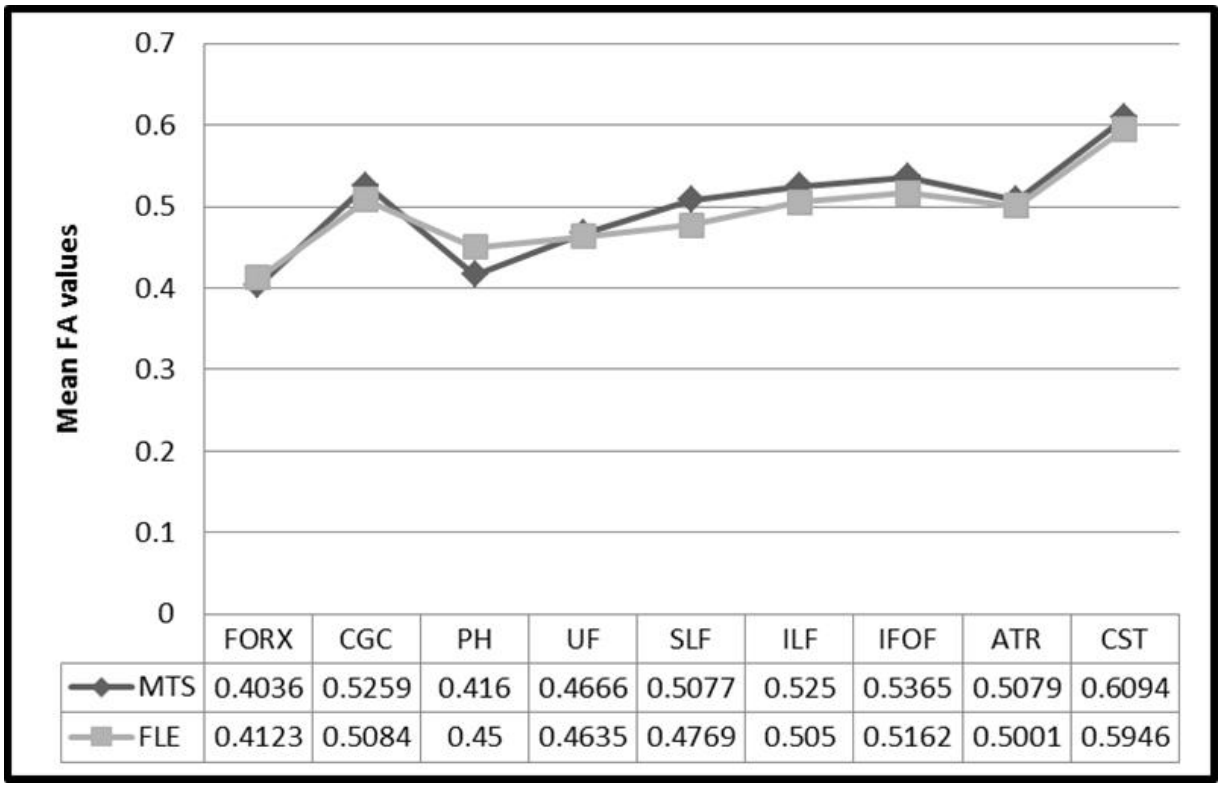
Figure 3. Mean FA values of ipsilateral and contralateral tracts in patients FLE.

($p<0.05$). FA-fractional anisotropy, FLE-frontal lobe epilepsy, FORX-fornix, CGC-cingulum in cingulate gyrus, PH-cingulum in parahippocampal gyrus, UF-uncinate fasciculus, SLF-superior longitudinal fasciculus,

ILF-inferior longitudinal fasciculus, IFOF-inferior fronto-occipital fasciculus, ATR-anterior thalamic radiation, CST, corticospinal tract.

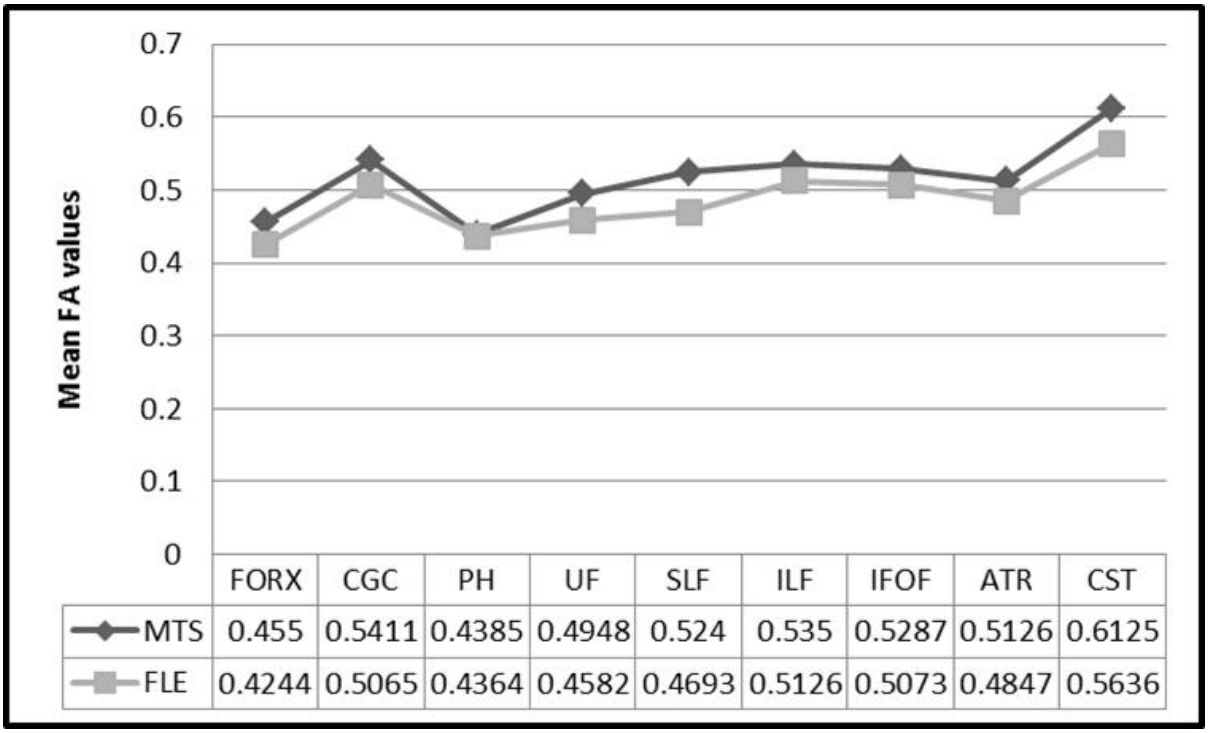
There was a significant decrease ($p<0.05$) in the FA of contralateral ATR and CST, with some other contralateral tracts (PH, UF, SLF, IFOF) also showing decreased mean FA values, but not reaching statistically significant levels. The mean FA values of ipsilateral FORX and ILF were lower than their contralateral counterparts, but not statistically significant.

Mann-Whitney U test for ipsilateral fibres of FLE vs. TLE groups was non-significant for any of the 9 fibre pairs, while a significant decrease ($p<0.05$) for CST only was seen in a comparison of contralateral fibres. (Figures 4 and 5, respectively). However, there was a generalised decrease in all ipsilateral and contralateral fibre FA values in FLE patients compared to TLE patients (Figure 4 and Figure 5) except for the fibres intimately related to the mesial temporal lobe viz., FORX and PH, which were decreased ipsilaterally for TLE patients.



	FORX	CGC	PH	UF	SLF	ILF	IFOF	ATR	CST
MTS	0.4036	0.5259	0.416	0.4666	0.5077	0.525	0.5365	0.5079	0.6094
FLE	0.4123	0.5084	0.45	0.4635	0.4769	0.505	0.5162	0.5001	0.5946

Figure 4. Ipsilateral tract mean FA values in TLE (with MTS) and FLE patients



	FORX	CGC	PH	UF	SLF	ILF	IFOF	ATR	CST
MTS	0.455	0.5411	0.4385	0.4948	0.524	0.535	0.5287	0.5126	0.6125
FLE	0.4244	0.5065	0.4364	0.4582	0.4693	0.5126	0.5073	0.4847	0.5636

Figure 5. Contralateral tract mean FA values in TLE (with MTS) and FLE patients

The Fmajor and Fminor were also evaluated in all patients; the mean FA of the FMajor was 0.6146 and 0.6702 in FLE and TLE, respectively ($p<0.05$). Mean FMinor FA was lower in FLE (0.5598) than in TLE (0.5917), although nonsignificant statistically.

4. Discussion

Although epilepsy is predominantly considered a gray-matter disorder, the underlying white matter connections also have abnormalities with important implications for seizure generation and propagation and can be studied with DTI and tractography (Concha L, Beaulieu C, Collins DL, Gross DW. 2009). Zhong et al. first reported the use of diffusion MRI in epilepsy (Zhong J, Petroff OAC, Prichard JW, Gore JC. 1993), since then the field has grown rapidly such that now DTI is useful in all aspects of epilepsy evaluation including understanding the basic pathophysiology, identifying and localizing the epileptogenic foci, defining the surgical resection volume, and predicting postoperative neurological deficits.

Most of the studies in epilepsy utilising DTI and tractography have been done in TLE with or without MTS. (Ahmadi ME, Hagler DJ Jr, McDonald CR, Tecoma ES, Iragui VJ, Dale AM, Halgren E. 2009; Concha L, Beaulieu C, Collins DL, Gross DW. 2009; Yu Y, Chu L, Liu C, Huang M, Wang H. 2019; García-Pallero MA, Hodaie M, Zhong J, Manzanares-Soler R, Navas M, Pastor J, Vega-Zelaya L, Delgado-Fernández J, Sola RG, Torres CV. 2019; Kreilkamp BA, Weber B, Richardson MP, Keller SS. 2017; Gross DW, Concha L, Beaulieu C. 2006; Rodríguez-Cruces R, Concha L., 2015; Kimiwada T, Juhasz C, Makki M, et al. 2006; Urquia-Osorio H, Pimentel-Silva LR, Rezende TJR, Almendares-Bonilla E, Yasuda CL, Concha L, Cendes F. 2022; Concha L, Gross DW, Beaulieu C. 2005; Alizadeh M, Kozlowski L, Muller J, Ashraf N, Shahrampour S, Mohamed FB, Wu C, Sharan A. 2019; Londoño A, Castillo M, Lee YZ, Smith JK. 2003; Assaf BA, Mohamed FB, Abou-Khaled KJ, Williams JM, Yazeji MS, Haselgrove J, Faro SH. 2003; Yoo SY, Chang KH, Song IC, Han MH, Kwon BJu, Lee SH, Yu IK, Chun CK. 2002; Kantarci K, Shin C, Britton JW, So El, Cascino GD, Jack CR. 2002; Arfanakis K, Hermann BP, Rogers BP, Carew JD, Seidenberg M, Meyerand ME. 2002; Rugg-Gunn FJ, Eriksson SH, Symms MR, Barker GJ, Duncan JS. 2001) Mostly, these studies are simple and have focused on perior interictal alterations of diffusion and anisotropy in the temporal and extratemporal white matter.

Assaf et al. have reported increased diffusivity and reduced anisotropy in eight and four out of 12 cases, respectively, in the hippocampus ipsilateral to the seizure focus, as compared with the unaffected temporal lobe of the same patient, as well as significantly increased diffusivity in five out of 12 cases in the ipsilateral hippocampi compared with those of the control subjects. (Assaf BA, Mohamed FB, Abou – Khaled KJ, Williams JM, Yazeji MS, Haselgrove J, Faro SH. 2003)

The changes in diffusion in epilepsy cases are not localised in all patients but extend to involve the otherwise

normal-appearing brain. In the series of Assaf et al., two cases had normal routine MR imaging findings (Assaf BA, Mohamed FB, Abou – Khaled KJ, Williams JM, Yazeji MS, Haselgrove J, Faro SH. 2003). Arfanakis et al. explored the extratemporal white matter with DTI in 15 TLE cases and 15 age-matched healthy controls and found reduced anisotropy in the external capsule and posterior corpus callosum of the TLE cases, structures that are not in direct continuity with the site of the disease. (Arfanakis K, Hermann BP, Rogers BP, Carew JD, Seidenberg M, Meyerand ME. 2002) Studies have also attempted to differentiate MTS from non-MTS TLE.

Concha et al. studied 17 TLE cases harbouring an MTS, 13 TLE cases without any MRI visible lesion, and 25 healthy controls to evaluate the DTI findings of the FORX, cingulum, external capsules, and the corpus callosum and found that the white-matter abnormalities seen in the FORX, represented by decreased FA and increased diffusivity, appear to be exclusive to the cases with MTS. (Concha L, Beaulieu C, Collins DL, Gross DW. 2009). The cingulum had high overall diffusivity in both MTS and non-lesional TLE cases, but decreased FA was only seen in MTS cases, following a pattern similar to that of the FORX. In both groups of patients, they found reduced FA in the frontal and temporal components of the corpus callosum, as well as the external capsules. They concluded that some white-matter structures are affected in TLE regardless of the presence or absence of MTS. However, DTI changes in the white matter tracts directly related to the mesial temporal structures (i.e., the FORX and CG) appear to be unique to the MTS harboring TLE cases.

Lateralization of the seizure focus is also a goal of imaging studies. Ahmadi et al. studied the FA values of eight pairs of white matter tracts in TLE cases and were able to lateralize the seizure focus even if the MRI was normal. (Ahmadi ME, Hagler DJ Jr, McDonald CR, Tecoma ES, Iragui VJ, Dale AM, Halgren E. 2009) They have reported widespread changes in the connectivity of both cerebral hemispheres, albeit the findings were more pronounced ipsilateral to the seizure focus. Interestingly, they also reported more extensive bilateral changes in left TLE as opposed to right TLE, the latter showing predominantly right-sided alterations in the FA values.

The frontal lobes have been rather overshadowed by the temporal lobes in the epilepsy literature. Only a few diffusion-based reports on FLE exist. (Okumura A, Fukatsu H, Kato K, Ikuta T, 2004; de la Roque AD, Oppenheim C, Chassoux F, Rodrigo S, Beuvon F, Daumas-Duport C, Devaux B, Meder JF. 2005; Guye M, Ranjeva JP, Bartolomei F, Confort-Gouny S, McGonigal A, Régis J, Chauvel P, Cozzone PJ. 2007; Wang XQ, Lang SY, Hong LU, Lin MA, Yan-Ling MA, Yang F. 2011; Braakman HM, Vaessen MJ, Jansen JF, Debeij-van Hall MH, de Louw A, Hofman PA, Vles JS, Aldenkamp AP, Backes WH. 2014)

In contrast to TLE, frontal lobe seizures are more difficult to define, both clinically and on EEG, which can be normal in either the ictal or the inter-ictal state. (Williamson PD, Spencer DD, Spencer SS, Novelly RA, Mattson RH. 1985) The seizures in FLE tend to spread rapidly and widely, and also manifest inter-ictal discharges bilaterally, thus further complicating accurate seizure localization. (Rasmussen T. 1983) FLE seizures can also have bizarre behavioural manifestations and can be mistaken for pseudoseizures. (Saygi S, Katz A, Marks DA, Spencer SS. 1992) Neuroimaging studies are often normal and do not contribute much to the clinical diagnosis. (Swartz BE, Halgren E, Delgado-Escueta A, Mandelkern M, Gee M, Quinones N, Blahd WH, Repchan J. 1989)

The clinical syndromes in FLE have been subject to various classification schemes, with a large group of investigators, such as Bancaud and Tailarach, focusing to define the anatomical-electrographic-clinical state during the FLE-associated seizures. Bancaud et al., (Bancaud J, Talairach J. 1992) and others, e.g., Williamson et al., (Williamson PD, Spencer DD, Spencer SS, Novelly RA, Mattson RH. 1984) have proposed using an original anatomic subdivision of the frontal lobes with possible association to distinct clinical syndromes. The proposed regions are rolandic, inferior frontal, intermediate medial frontal, intermediate dorsolateral frontal, cingulate gyrus, supplementary motor area, frontopolar, and orbitofrontal. These eight regions have been recombined into three working groups-motor, premotor, and prefrontal. Physicians typically identify the prefrontal lesions as the source of the “frontal lobe syndromes.” While this approach to anatomical subdivision partially fulfils our tendency to assign a clear anatomical location to all diseases, it fails to consider the dynamic nature of seizures in FLE. The seizures in FLE spread rapidly and widely with the presence of silent areas, thus making this approach even more difficult to justify. Nevertheless, it forms a starting point in our endeavour to understand the complex behavioural and electrographic seizure patterns.

The frontal lobes are massive, usually estimated at between 24 and 30% of the total cortical surface and up to 50% of the whole brain weight. (Stuss DT, Benson DF. 1986) The superficial cortical anatomy is highly complex. In addition, the various areas of the frontal lobes are connected by many fast-conducting pathways. The three major white matter tracts, the SFOF, the IFOF, and the SLF, connect the prefrontal area structures with the unimodal association cortex of all sensory modalities as well as the posterior heteromodal association areas, the flow of information being reciprocal. (Petrides M, Pandya DN. 1984) In addition, the prefrontal areas also have connections with three limbic system pathways: (1) the corticolimbic regions such as the subiculum, entorhinal area, and parahippocampal structures; (2) the subcortical limbic regions such as the thalamic and hypothalamic

nuclei; and (3) the visceral-endocrine peripheral nervous system via a series of ill-defined pathways in the spinal cord and lower brain stem. (Benson DF. 1994) Thus, the prefrontal area is a major, and probably the only area in the central nervous system, to receive and integrate information from both the somatic and the limbic-sensory systems, which can be a significant factor in the study of epilepsy. (Nauta WJH. 1971)

While FLE can be produced by the entire range of conditions affecting the brain, most commonly gliosis and encephalomalacia, neoplasms, dysplasias, and vascular lesions, the issue in studying FLE is the presence of extensive and/or multilobar changes. In Mathieson's series of 503 general epilepsy pathology cases, a frontal lobe pathology was present in 47 study participants. (Mathieson G. 1975) However, another 100 had multilobar as well as frontal-temporal lesions. (Mathieson G. 1975) Hence the importance of strict seizure localization and the need for a study like ours.

We found altered FA profiles of the CST and the ATR with significantly fewer values on the contralateral side of the seizure localization (Table 2).

Table 2. MRI findings and FA values of CST and ATR in patients with frontal lobe seizures

Localization	MRI	Ipsi-CST	Contra-CST	Ipsi-ATR	Contra-ATR
Lt	Lt frontal CD	0.6168	0.5413	0.4922	0.4886
Lt	Lt frontal CD	0.6034	0.6207	0.5871	0.5551
Lt	Normal	0.5704	0.554	0.4992	0.484
Rt	Global atrophy	0.5819	0.5644	0.4711	0.46
Rt	Global atrophy, BL	0.5797	0.5297	0.4612	0.4278
	frontal-temporal encephalomalacia				
Rt	Normal	0.6152	0.5712	0.4897	0.4926

Lt-left, CD-cortical dysplasia, Ipsi-ipsilateral, Contra-contralateral, CST-corticospinal tract, ATR-anterior thalamic radiation.

This finding is "unlikely" to be due to any confounding factors or the effect of any one or two patients having large value changes dragging down the mean values of the whole group because the findings were similar for both right and left-sided localizations, unrelated to the presence or absence of focal lesion or MRI predicted pathology.

Such specific contralateral tract 'involvement' in FLE could not be found in the literature. In an excellent DWI-based study of a cohort of 14 cases with refractory FLE (Guye et al., (Guye M, Ranjeva JP, Bartolomei F, Confort-Gouny S, McGonigal A, Régis J, Chauvel P, Cozzone PJ. 2007)), nine did not have any MRI abnormality, yet areas of significantly increased diffusivity were reported in 13 cases. Diffusivity changes were reported in both ipsilateral and contralateral sides, including the frontal, temporal, parietal, and occipital lobes as well as the cerebellum, basal ganglia, and thalamus, albeit they were significantly less widespread in negative-MRI patients ($p=0.028$). The sensitivity of diffusion imaging in defining regions that were the sites of electrical abnormalities was about 57% for the epileptogenic zone. Their data suggest that increased diffusivity is not a simple correlate of the presence of an MRI visible pathological lesion, rather it may reflect structural changes not necessarily directly linked to the epileptogenic zone itself, the possible explanation being that it may represent secondary changes in the connected areas. The correlation found between the duration of epilepsy and the spatial extent of increased diffusivity tends to suggest an evolving process. Further, they did not find a relation between seizure frequency and raised diffusivity, but reported more widespread diffusivity alteration if the duration of seizures was longer than 18—20 years. This might be explained by silent inter-ictal epileptiform discharges with widespread propagation.

The work of Luat et al. offers a possible explanation. (Luat AF, Chugani HT. (2008) They studied the role of the thalamus in seizures associated with tuberous sclerosis and demonstrated that the ipsilateral tracts connecting the tuber harbouring region of the brain to the thalamus showed high FA values compared with the opposite side, and hypothesised the presence of aberrant connections as the cause. (Luat AF, Chugani HT. 2008) In the study by

Lin et al., the thalamo-occipital connection had similar alterations in both TLE and FLE. (Kimiwada T, Juhasz C, Makki M, et al. 2006) The thalamus has been associated with seizure-associated diffusion abnormalities and proven pathologic changes, (Kimiwada T, Juhasz C, Makki M, et al. 2006) a finding not entirely unimaginable, it is the chief relay centre of the brain and is involved to some extent in virtually every imaginable neural circuit.

While it can be said that cortical dysplasias have anomalous connections, with resultant haphazard values, even the four other cases in our study have a consistent pattern of decreased values in ipsilateral CST and ATR. Do they have MRI-hidden dysplasias? Are the findings really due to increased FA as opposed to decreased FA or a combination of both or due to some entirely different possibility?

While the findings are obvious, they will have to be validated because we have not correlated them with the clinical profile of the patients.

5. Summary and Conclusion

Working on the premise of region-specific white matter tract involvement in refractory focal seizures, the study analysed fractional anisotropy changes in 20 tracts in five TLE and six FLE patients. The tracts assessed were: Bilateral Fornix; Cingulum, cingulate gyrus part; Cingulum, hippocampal part; Uncinate fasciculus; Inferior longitudinal fasciculus; Superior longitudinal fasciculus; Inferior fronto-occipital fasciculus; Anterior thalamic radiation; Cortico-spinal tract; Forceps major and Forceps minor.

Five patients had unilateral MTS on MRI and a significant ($p<0.05$) decrease in ipsilateral from contralateral Fornix and Uncinate fasciculus FA.

In the six patients with FLE, a significant decrease in FA values ($p<0.05$) was seen in contralateral ATR and CST. There was a general trend of decreased FA values of all the ipsilateral and contralateral tracts compared with TLE patients.

For generalization of results, the authors recommend studies with larger sample size.

Author Contributions

SK conceived and analyzed, acquired data, contributed data tools, performed analysis, wrote and finalized the article; SBG contributed data tools and finalized the article; NKM conceived and analyzed, performed analysis, wrote and finalized the article.

Data Availability

The data is already available in the article; raw data can be sought from the corresponding author (SK) on reasonable request.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

Abbreviations

Temporal lobe epilepsy (TLE), frontal lobe epilepsy (FLE), Fornix (FORX), Cingulum in Cingulate gyrus (CGC), Cingulum in Parahippocampal gyrus (PH), Uncinate fasciculus (UF), Superior Longitudinal fasciculus (SLF), Inferior longitudinal fasciculus (ILF), Inferior Fronto-Occipital fasciculus (IFOF), Anterior thalamic radiation (ATR), Cortico-Spinal tract (CST), Forceps Major (FMajor), Forceps Minor (FMinor), fractional anisotropy (FA).

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