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Hippocampal Abnormalities in Adults with Unilateral Temporal Lobe Epilepsy: A Diffusion Tensor Imaging Study

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Abstract: ***Aims & objectives: To compare the fractional anisotropy and mean diffusivity of ipsilateral and contralateral hippocampus of unilateral temporal lobe epilepsy patients with age matched normal controls. Materials and methods: The study was conducted in the department of Radiology, Government Mohan Kumaramangalam Medical College, Salem. This study was done as an analytic, prospective case control study for a period of 3years from September 2016 to August 2019. Patients with a clinical picture of temporal lobe epilepsy, with either structural abnormalities in temporal lobe on MR imaging or EEG consistent with temporal lobe epilepsy were included. Our control group consisted of 30 adults. Imaging protocol: The examinations were performed in 1.5T Philips MRI system. Results: This study reveals increased mean diffusivity (ADC) and decreased fractional anisotropy (FA) in ipsilateral and contralateral hippocampi in patients with unilateral hippocampal sclerosis. Conclusion: In patients with clinical history of temporal lobe epilepsy and equivocal conventional MRI, significantly altered DTI values adds to the diagnosis.***

1. Introduction

A seizure is defined as the signs/symptoms due to the abnormal excessive neuronal activity in the brain. Epilepsy is the tendency to have unprovoked seizures. About 1% of people worldwide have epilepsy[6] and the sensitivity of conventional MRI in identifying the epileptogenic focus with the current epilepsy protocol is only slightly greater than 50%[3]. So there is a need for additional sequences like diffusion tensor imaging in cryptogenic cases of epilepsy.

Temporal lobe epilepsy is the most common form of focal epilepsy. The etiology can be varied like hippocampal sclerosis, malformations of cortical development, mass lesions, AV malformations, gliosis etc. Previous studies with diffusion tensor imaging have shown increased apparent diffusion coefficient and decreased fractional anisotropy in the seizure focus[3].

Diffusion weighted imaging was introduced in 1986 by Le Bihan et al. By introducing directionality into diffusion weighted images, diffusion tensor images are obtained[1]. It assesses the molecular and biochemical environment of cerebral tissue noninvasively and is capable of demonstrating microstructural alterations in a variety of disorders.

We have intended to explore the utility of diffusion tensor imaging in temporal lobe epilepsy, and depict the focal abnormalities that occur in our population. The study might establish the diagnostic value of diffusion tensor imaging in epilepsy, and incorporate it in routine protocol. DTI might show the extent of microstructural alterations when the imaging features are normal.

1.1 Hypothesis

Mean diffusivity is increased and fractional anisotropy is decreased in hippocampus in patients with mesial temporal sclerosis.

1.2 Need for the Study

To explore the role of diffusion tensor imaging of hippocampus in temporal lobe epilepsy and establish the diagnostic value in regular epilepsy protocol.

1.3 Aims & Objectives

To compare the fractional anisotropy and mean diffusivity of ipsilateral and contralateral hippocampus of unilateral temporal lobe epilepsy patients with age matched normal controls.

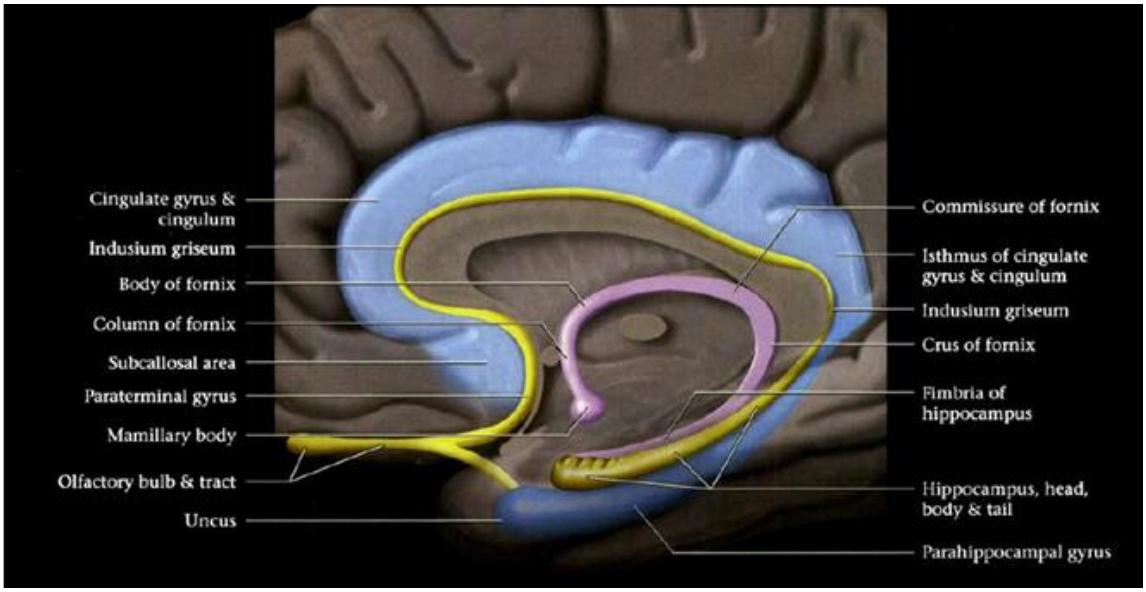
2. Review of Literature

2.1 Anatomy of the limbic system:[27]

Limbic lobe is phylogenetically older cortex and contains few layers than the neocortex. It plays a major role in memory, olfaction and emotion. It is composed of the hippocampus, the parahippocampal gyrus, dentate gyrus, subiculum, cingulate gyrus and the subcallosal area. Limbic system consists of the limbic lobe and some subcortical structures like the amygdala, mammillary bodies and the septal nuclei.

The limbic lobe consists of three arches surrounding the diencephalon and the basal ganglia.

The outer arch extends from the temporal to frontal lobes and consists of the uncus, parahippocampal gyrus, cingulate gyrus and the subcallosal area. The middle arch consists of the hippocampus proper (ammons horn), dentate gyrus, indusium greiseum and the paraterminal gyrus. The inner arch is the smallest and consists of fornix and fimbria, and extends from the temporal lobes to mamillary bodies.



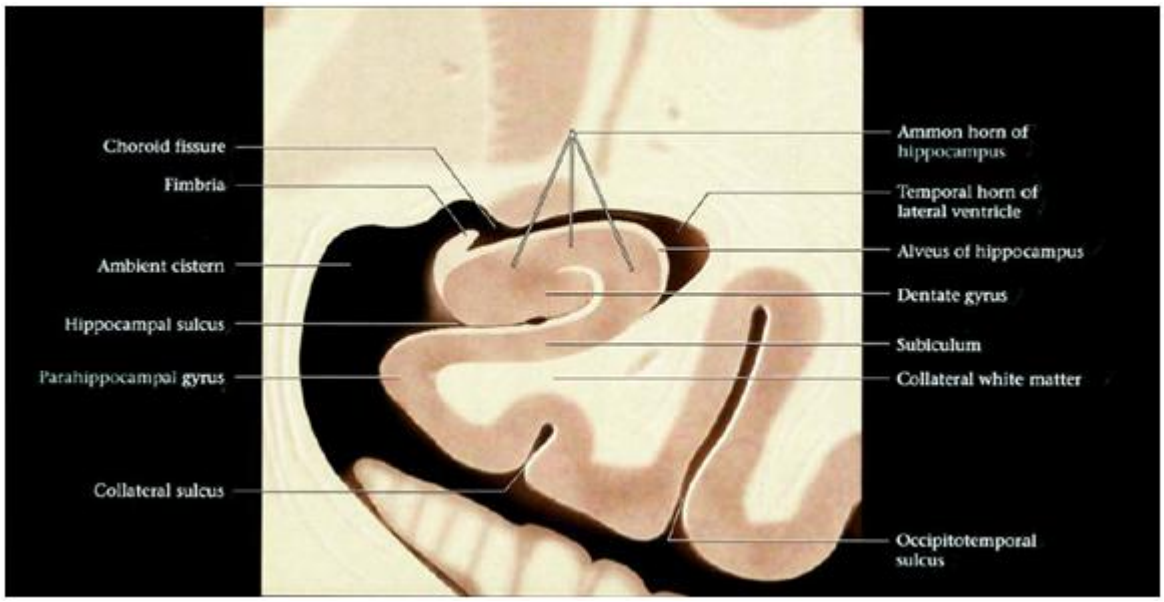
Diagrammatic representation of the limbic system

2.2 Imaging anatomy[27]:

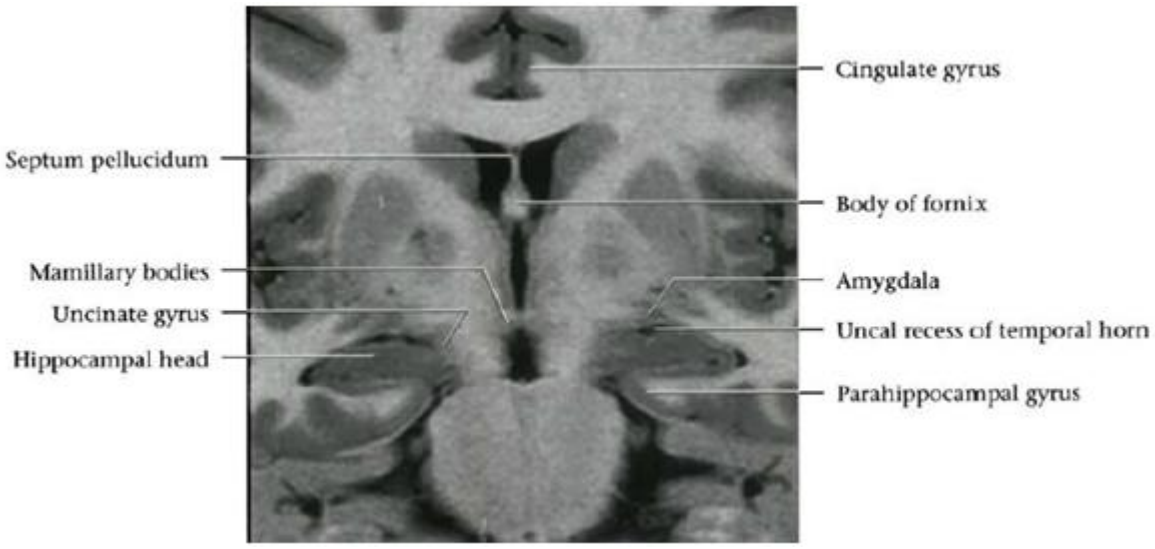
Hippocampus lies on the medial aspect of temporal lobe and bulges into floor of the temporal horn. It consists of two interlocking U shaped grey matter structures, the hippocampus proper or the Ammons horn and the dentate gyrus. It has a head which consists of 3-4 digitations on the superior surface, a cylindrical body oriented parasagitally, and a tail. The Ammons horn continues laterally into the subiculum. Subiculum is the transition into the parahippocampal gyrus or the entorhinal cortex, which is part of the neocortex. A thin layer of white matter covers the hippocampus called alveus, which consists of the efferent fibres continuing as the fimbria and fornix.

Amygdala is a large grey matter nucleus which is situated anterior and superior to the hippocampus, lateral to uncus. Uncinate gyrus connects amygdala to the hippocampus.

The fimbria thickens posteriorly and splits off from the hippocampus to form the crus. The crus of the fornix attaches to the anterior surface of the splenium of corpus callosum. The crura of both sides unite to form the hippocampal commisure, and continues anteriorly as the body.



Coronal diagrammatic representation of the hippocampus

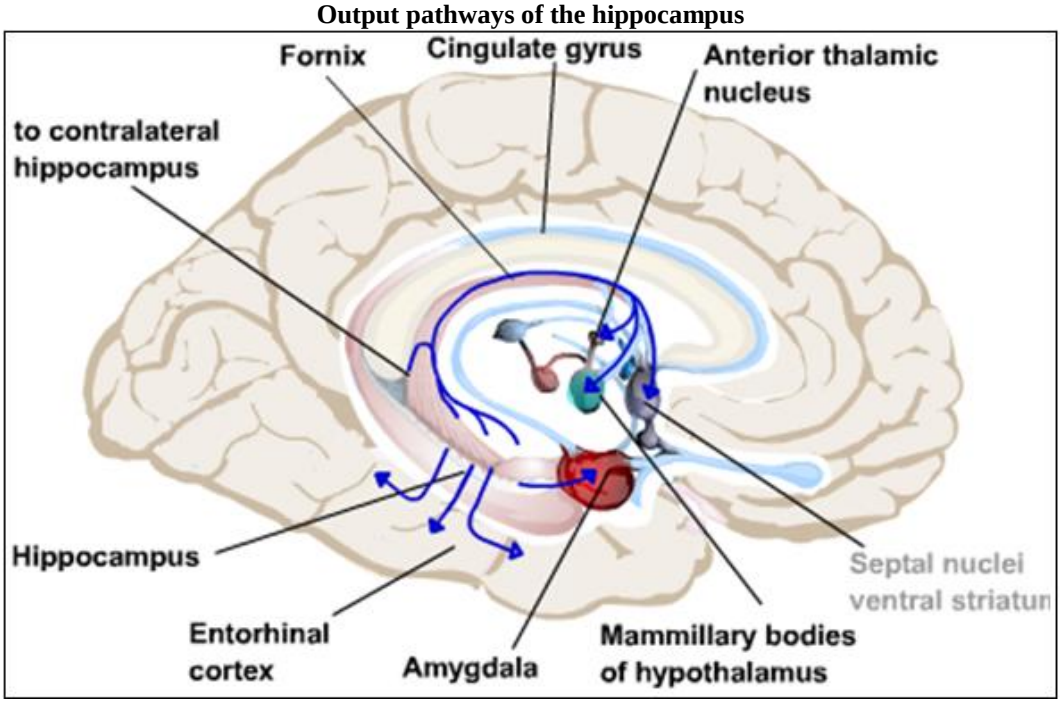


Coronal T1 IR image at the level of hippocampal head

2.3 Connections of the hippocampus:[26]

The hippocampus is directly connected to the para hippocampal gyrus through the subiculum, and to the amygdala through the uncinate gyrus. Two major hippocampal pathways are the fornix and the para hippocampal gyrus.

Output pathways of the hippocampus



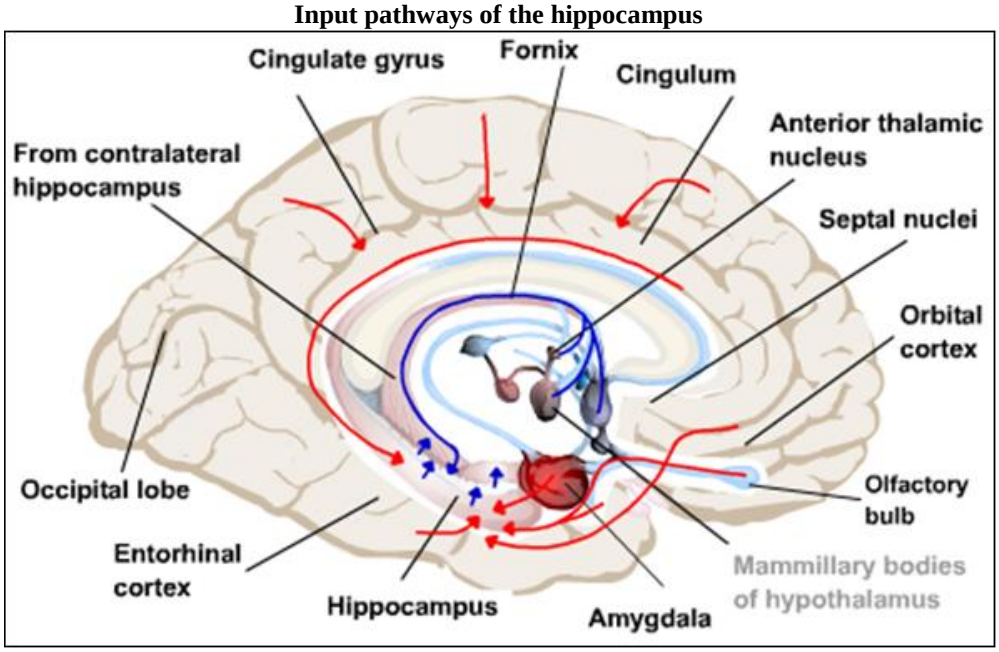
The crus of fornix contacts the contralateral fornix and forms the hippocampal commissure, through which bilateral hippocampi connect with each other. They then continue as body of the fornix to the anterior commissure where it splits into three parts.

1) Pre commissural fornix, just before the commissure which goes to the septal nuclei, preoptic nuclei, orbital cortex, anterior cingulate cortex and the ventral striatum.
2) Anterior commissure, the second pathway connecting bilateral hippocampi.
3) Post commissural fornix going to mammillary bodies and the anterior nucleus of the thalamus. Anterior thalamic nuclei connect to the cingulate cortex.

The cingulate cortex in turn projects to the entorhinal cortex or the para hippocampal gyrus, completing the Papez circuit. The Papez circuit is involved in learning, memory, emotion and social behaviour.

Para hippocampal gyrus is a major source of input to the hippocampus. The cingulate gyrus, neocortex, amygdala, orbital cortex and the olfactory bulb have inputs through the para hippocampal gyrus to the hippocampus.

Input pathways of the hippocampus



Physics:[1,8,22]

Diffusion is a process of random motion of molecules called as Brownian motion[1]. It is thermally driven, the rate of diffusion given by the equation,

$<r^2> = 6Dt$

$<r^2>$ denotes the mean squared displacement of the molecules, t the diffusion time and D the diffusion constant. The diffusion constant is the average displacement of the molecule in the observed time. Higher values indicate more mobility.

In the clinical setting, ADC is measured which reflects in vivo diffusion that cannot be separated from active transport, changes in membrane permeability and movement along the pressure gradient.

Stejskal – Tanner Diffusion Encoding:

A pair of diffusion sensitising, equal and opposite motion probing gradients, are applied to a T2-weighted spin-echo sequence, before and after the 180 degree refocusing pulse. If there is molecular motion, there is change in phase position during the application of diffusion sensitising gradients, resulting in incomplete rephasing and signal loss. The diffusion contrast is given by the equation,

$S_i = S_0 . e^{-b.ADC_i}$

S_i is the signal intensity along the direction i

S_0 is the signal intensity without the diffusion gradient

ADC_i is the ADC in the direction i

b is given by the formula,

$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)$

where γ is the gyromagnetic ratio

G is the amplitude of diffusion measured in millitesla per meter

δ is the duration of diffusion gradient in milliseconds

Δ is the interval between the onset of diffusion gradient before and after the rephasing pulse.

Units of b is seconds per square millimeter, ADC is millimeter square per second.

Raising b values increases the diffusion weighting.

ADC is the apparent diffusion coefficient given by the formula,

$$ADC_i = -\ln (S_i/S_0)/b$$

ln is the natural logarithm

S_i is the signal intensity in a given voxel in direction i with a given b value

S_0 is the signal intensity in a given voxel without diffusion sensitising gradients.

Isotropy and anisotropy

The tendency of molecules to move equally in all directions is called isotropy. In brain, isotropic diffusion is seen in CSF spaces. In clinical range of b values, grey matter is considered to show isotropic diffusion. Here, the direction of diffusion sensitising gradient is considered unimportant because ADC_i is same for all directions i.

In white matter, diffusion is strongly anisotropic, occurring maximally in the same direction as white matter tracts. Larger ADC values are seen in the direction parallel to the tracts compared to the orthogonal direction. It is a property of the integrity of myelin sheath and axonal membrane[1]. So, more than one direction is required to characterise anisotropic diffusion. To overcome this problem, rotationally invariant measures like trace ADC and geometric mean DWI are used. It is derived from the DWIs in minimum of three directions S_1, S_2 and S_3

$S_{DWI} = S_0 . e^{- b.ADC}$

Where $ADC = (ADC_1 + ADC_2 + ADC_3)/3$.

ADC is the average of three ADCs along three orthogonal directions and is rotationally invariant. It is also known as the mean diffusivity, trace ADC or ADC.

ADC mapping in healthy brain and pathology:

In clinical range of b values, in healthy adult brain, there is little difference between grey and white matter. Mean diffusivity of grey matter is 0.67- 0.83 x $10^{-3}mm^2/s$ and 0.64 – 0.71 x $10^{-3}mm^2/s$ for white matter. In neonates, ADC is very high at term, dropping steeply in first 2 years, gradually reaching the normal values in adulthood, at varying rates in different parts of the brain. ADC values tend to increase again after the age of 40.

The diffusion tensor

White matter tracts are highly anisotropic and this property can be exploited for characterisation and anatomic mapping of these tracts. White matter is subjected to motion probing, diffusion sensitising gradients in at least 6 non collinear directions, and with one b 0 image, a tensor is obtained. The tensor, 3 x 3 matrix of vectors is a mathematical model of 3 D diffusion anisotropy.

The diffusion ellipsoid that describes the ADC of water molecules at a particular time, is defined by 6 variables in different directions. It is a sphere for isotropic diffusion, and ellipsoid for anisotropic diffusion. The elements of a tensor above the diagonal are same as that below the diagonal, termed as conjugate symmetry.

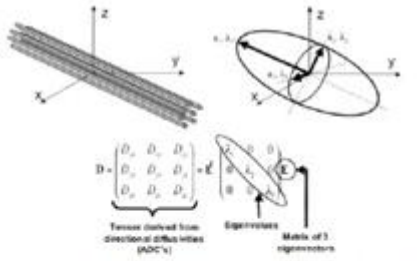


Fig. 1. *Top left*, Fiber tracts have an arbitrary orientation with respect to scanner geometry (*x*, *y*, *z* axes) and impose directional dependence (anisotropy) on diffusion measurements.
Top right, The three-dimensional diffusivity is modeled as an ellipsoid whose orientation is characterized by three eigenvectors (ε_1, ε_2, ε_3) and whose shape is characterized three eigenvalues (λ_1, λ_2, λ_3). The eigenvectors represent the major, medium, and minor priniciple axes of the ellipsoid, and the eigenvalues represent the diffusivities in these three directions, respectively.
Bottom, This ellipsoid model is fitted to a set of at least six noncollinear diffusion measurements by solving a set of matrix equations involving the diffusivities (ADC's) and requiring a procedure known as matrix diagonalization. The major eigenvector (that eigenvector associated with the largest of the three eigenvalues) reflects the direction of maximum diffusivity, which, in turn, reflects the orientation of fiber tracts. Superscript *T* indicates the matrix transpose.

Diffusion tensor parameters:

By subjecting the tensor matrix to diagonalization, a set of **three Eigen values** representing major, medium and minor principle axes are obtained with their corresponding Eigen vectors. They describe the directions and lengths of the three diffusion ellipsoids axes. The largest vector is the primary Eigen vector, with its Eigen value $\lambda 1$, denotes the magnitude and direction of the greatest water diffusion. It is also termed **longitudinal diffusivity** and used in fibre tractography indicating the orientation of axons. The second and third vectors, $\lambda 2$ and $\lambda 3$ are orthogonal to the primary vectors and their mean represents **radial diffusivity.**

Trace D is the sum of the three eigen values, $D = \lambda 1 + \lambda 2 + \lambda 3$. The **mean diffusivity** is the mean of the three eigen values and is given by the formula,

$$ADC = D_{av} = \frac{\lambda 1+\lambda 2+\lambda 3}{3}$$

Fractional anisotropy (FA):

FA is derived from the standard deviation of the three Eigen values and is given by the formula,

$$FA=\sqrt{\frac{3}{2}}\, x\, \frac{\sqrt{(\lambda 1-\lambda)^2+(\lambda 2-\lambda)^2+(\lambda 3-\lambda)^2}}{\sqrt{\lambda 1^2+\lambda 2^2+\lambda 3^2}}$$

$\lambda 1, \lambda 2, \lambda 3$ are the three eigen values and λ is the mean value.

Fractional anisotropy FA ranges from 0 to 1[1].

Decreased anisotropy is a common feature of white matter tract disease. Diffusion tensor imaging exploits this property of reduced anisotropy to recognise diseased neurons before they show up on conventional imaging.

Diffusion tensor imaging in seizures:

During the ictal phase of seizures, there is an increase in oxygen consumption in the seizure focus, which is more than the increased blood flow. It results in relative ischemia and cytotoxic edema which is shown to result in increased ADC. As time progresses, epilepsy results in neuroglia, increased extracellular space and increased interictal ADC[9].

Diffusion tensor imaging of Hippocampal formation in temporal lobe epilepsy:

The hippocampus is an important structure in temporal lobe epilepsy, and hippocampal sclerosis is the etiology in non lesional temporal lobe epilepsy.[2] In addition to visual inspection of high resolution MR images taken orthogonal to hippocampal formation, quantification of hippocampal volume and T2 signal can increase the sensitivity of detection of hippocampal sclerosis[19]. Assaf et al [2] in 2003 analysed the mean diffusivity and fractional anisotropy of 12 patients with unilateral temporal lobe epilepsy and compared them with 14 healthy controls. They found significant increase in mean diffusivity and decreased fractional anisotropy in the Hippocampal formation of ipsilateral side compared to contralateral side in patients. Comparing with the controls, the mean diffusivity remained statistically higher but the fractional anisotropy did not reach significant differences, though they were lower.

Thivard L et al in 2005[17] with 35 patients of TLE with hippocampal sclerosis found increased diffusivity in the epileptogenic hippocampus and temporal lobe structures. The anisotropy was reduced in the ipsilateral temporal lobe. Contralateral Hippocampal formation, amygdala and rest of temporal lobe showed reduced diffusion. They found no correlation between the age at onset, duration of epilepsy and the frequency of seizures.

Correlation of Diffusion tensor imaging with histopathology of fimbria - fornix in temporal lobe epilepsy patients:

Fimbria - fornix is a major afferent- efferent pathway of the hippocampus. Concha L et al [24] in 2010 studied the histopathology of fimbria - fornix in 11 medically intractable temporal lobe epilepsy patients with and without mesial temporal sclerosis. They found strong positive correlation between the fractional anisotropy of fimbria – fornix with cumulative axonal membrane circumference and axonal density. The myelin thickness was negatively correlated. The changes were bilateral suggesting etiology other than degeneration alone. Their study provides a strong validation for DTI as a measure of white matter pathology.

3. Materials and methods

Study area: The study was conducted in the department of Radiology, Government Mohan Kumaramangalam Medical College, Salem.

Study design and period: This study was done as an analytic, prospective case control study for a period of 3years from September 2016 to August 2019.

Study population: Patients with a clinical picture of temporal lobe epilepsy, referred to our department for an MRI examination. The patients were referred from neurologists, neurosurgeons and general physicians. Irrespective of treatment status, both previously treated and untreated patients were included in the study.

4. Cases

Inclusion criteria:
Adults, both males and females, with a clinical history of unilateral temporal lobe epilepsy and with either structural abnormalities in temporal lobe on MR imaging or EEG consistent with temporal lobe epilepsy.

Exclusion criteria:
1) Presence of intra axial structural abnormalities in locations other than temporal lobe, as it might interfere with the diffusion tensor imaging values.
2) Presence of a major psychiatric disorder, as uncinate fasciculus is shown to be involved in psychiatric disorders.

Of the 39 patients referred to us with a clinical picture of temporal lobe epilepsy, patients with lesions in regions other than temporal lobe and patients with bilateral hippocampal sclerosis were excluded from the study.

Finally, our case group consisted of 30 patients with unilateral temporal lobe epilepsy, 14 males and 16 females, aged between 22 to 49 years, with a mean of 29.9 yrs. 19 (63%) patients had unilateral hippocampal sclerosis, four (13%) had gliosis of the temporal lobe, four (13%) had focal cortical dysplasia, one (3%) had dysplastic neuro epithelial tumour, one (3%) had infiltrative glioma and one (3%)had persistent seizures after temporal lobectomy for hippocampal sclerosis. 18 cases had EEG localised to the ipsilateral temporal lobe. All patients underwent conventional MRI, temporal lobe protocol and diffusion tensor imaging. All of them were seizure free for more than a week at the time of imaging. The duration of seizures ranged from one month to 15 years.

Controls:
Our control group consisted of age matched adults with no neurologic deficit and normal by MR imaging.

Our control group consisted of 30 adults, of whom 19 were males and 11 were females, aged between 23 to 46 years, with a mean of 32.9 years.

There was no statistically significant difference between the ages of the two groups.

The control group underwent conventional MRI and diffusion tensor imaging.

Imaging protocol
The examinations were performed in 1.5T Philips MRI system, using the head coil. Our conventional imaging protocol consists of T1W sequence in the sagittal plane, T2W in the axial plane and FLAIR in the coronal plane. Temporal lobe protocol for epilepsy consists of 3 mm oblique coronal sections orthogonal to hippocampus in T2W, T1 inversion recovery and FLAIR sequences.

DTI images were acquired in the axial plane using spin echo – echo planar imaging sequence. Diffusion sensitive gradients are applied in 15 directions.T1W 3D TFE imaging was done for superimposing over the colour coded FA maps. Imaging is performed after a minimum of 7 days after the ictus as ADC values are known to alter in the peri ictal period.

Imaging analysis:
All DTI images were transferred to a workstation where image reconstruction and post processing analysis was performed. ROIs of similar size were placed in colour coded FA map superimposed over isotropic T1W images over bilateral hippocampi and body of fornix. FA and ADC values from each of these ROI from coronal images was recorded.

Statistical analysis
- All the continuous variables were tested for the normality using Shapiro Wilk's test. Variables were normally distributed and expressed as mean ± SD. Categorical variables were expressed either as percentage or proportion.
- Comparison of categorical variables (age) was done by Chi - square test or Fisher's exact test based on the number of observations.
- Comparison of normally distributed continuous variables between cases and controls was done by independent sample T test.
- Comparison of right and left sided variables within controls was done by paired T test.
- All the P values less than 0.05 were considered statistically significant.
- Data entry was done in MS excel worksheet.
- Data analysis was done by SPSS software version 11.0.

5. Result

The FA and ADC values of right and left sides of controls were compared. There was no statistically significant difference between the two. Their mean was used to represent the controls.

Table 1: FA of Hippocampus and Fornix

Site	Cases (30)	Cases (30)	Controls (30)	Controls (30)	P value
	Mean	SD	Mean	SD	
FA of ipsilateral hippocampus	.14	.06	.18	.05	.005*
FA of contralateral hippocampus	.13	.05	.18	.05	.001*
FA of ipsilateral fornix	.37	.21	.33	.16	.398
FA of contralateral fornix	.38	.19	.33	.16	.304

*statistically significant

Compared to controls, patients' bilateral hippocampi had significantly reduced FA values, the values of fornix were not statistically significant.

Table 2: ADC of Hippocampus and Fornix

Site	Cases (30)	Cases (30)	Controls (30)	Controls (30)	P value
	Mean	SD	Mean	SD	
ADC of ipsilateral hippocampus	1.18	.22	.909	.186	.000*
ADC of contralateral hippocampus	1.05	.17	.909	.186	.004*
ADC of ipsilateral fornix	1.67	.71	1.81	.51	.412
ADC of contralateral fornix	1.86	.79	1.81	.51	.726

*statistically significant

Compared to controls, patients' bilateral hippocampi had significantly increased ADC values, the values of ipsilateral fornix was lower and contralateral fornix was higher but did not achieve statistical significance.

6. Discussion

Hippocampal diffusivity and anisotropy

The hippocampal indices of 30 patients with hippocampal sclerosis were compared with the 30 age matched controls. Patients' both ipsilateral and contralateral hippocampi had statistically significant reduced FA and increased ADC values. The results of our ipsilateral hippocampus is in line with the results of Thivard et al[17] and Assaf et al[2] in 2003 who also found increased mean diffusivity(ADC) in the ipsilateral hippocampus. Assaf et al [2] with 12 patients of unilateral temporal lobe epilepsy found diffusivity measurements more sensitive than anisotropy. They observed that the selection of region of interest (ROI) in the anterior body of hippocampus yielded accurate and consistent measurement. ROI was placed in the anterior body of hippocampus in our study as per their recommendations. Bilateral hippocampi are connected with each other through the hippocampal commissure and the anterior commissure through the fornices[27]. Many studies have demonstrated widespread propagation of seizure activity through the neuronal networks[9,10,11,12,13]. We have observed increased ADC and reduced FA in the contralateral hippocampus, the electrical activity possibly utilising the commissures. Previous studies with contralateral hippocampus have yielded varying results as observed by Thivard et al[17]. The results were either normal or reduced mean diffusivity. All our patients had visually recognisable mesial temporal sclerosis, compared to Assaf et al[2] where one third had normal conventional MR findings. This reflects higher degree of structural damage in our cases and explain the bilaterally significant hippocampal values.

Though the contralateral hippocampus shows statistically significant diffusion tensor imaging indices, no such changes could be demonstrated in the fornices in our study. We had technical difficulties in placing the voxel exclusively within the fornix without contamination from the CSF, which might be responsible for the insignificant values. But our results concur with those of Thivard et al[17] who did not find significant values in bilateral fornices. Concha L et al [24] in 2010 with 11 medically intractable TLE patients with and without hippocampal sclerosis, found positive correlation between diffusivity of fimbria - fornix and histology. DTI was acquired following an inversion pulse (TI 2200 ms at 1.5T) to suppress the cerebrospinal fluid signal, which likely yielded them accurate results.

7. Conclusion

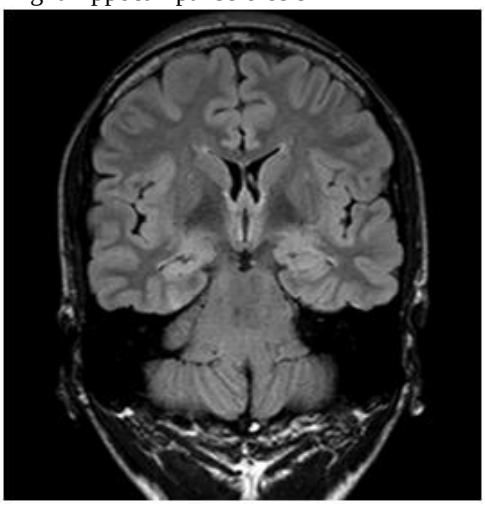
This study reveals increased mean diffusivity (ADC) and decreased fractional anisotropy (FA) in ipsilateral and contralateral hippocampi in patients with unilateral hippocampal sclerosis. In patients with clinical history of temporal lobe epilepsy and equivocal conventional MRI, significantly altered DTI values adds to the diagnosis.

8. Recommendations

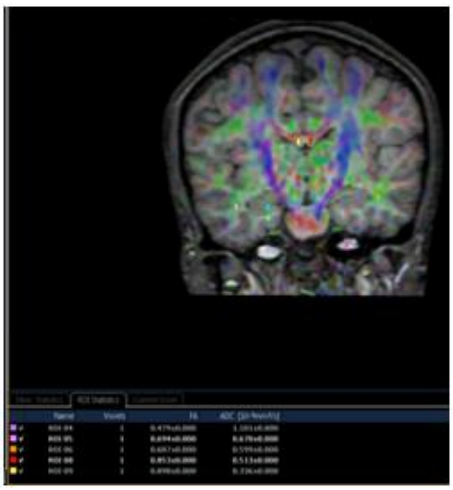
Diffusion tensor imaging can be incorporated in routine epilepsy protocol as altered hippocampal values adds to the diagnosis in equivocal cases.

Representative Images

Case 1: Right hippocampal sclerosis

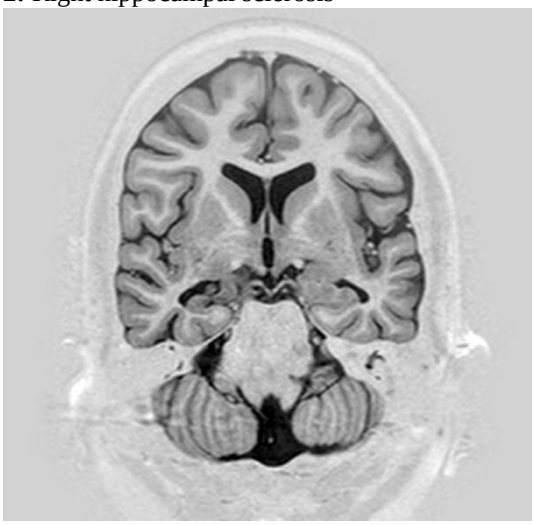


FLAIR Coronal showing right hippocampal sclerosis

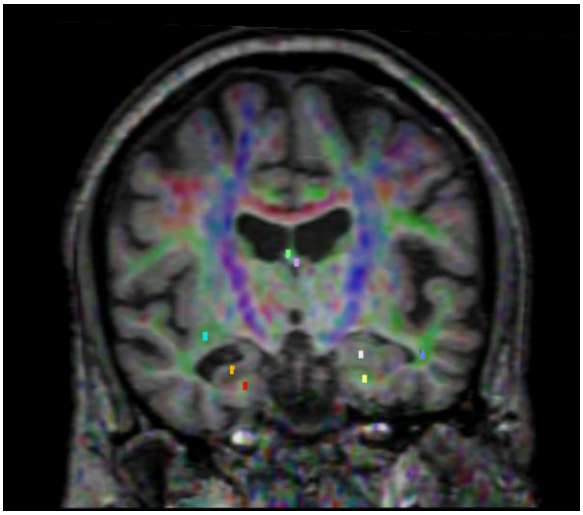


Colour coded FA map superimposed on isotropic T1W image – coronal showing ROIs at hippocampus, uncinate fasciculus, para hippocampal gyrus and fornix

Case 2: Right hippocampal sclerosis

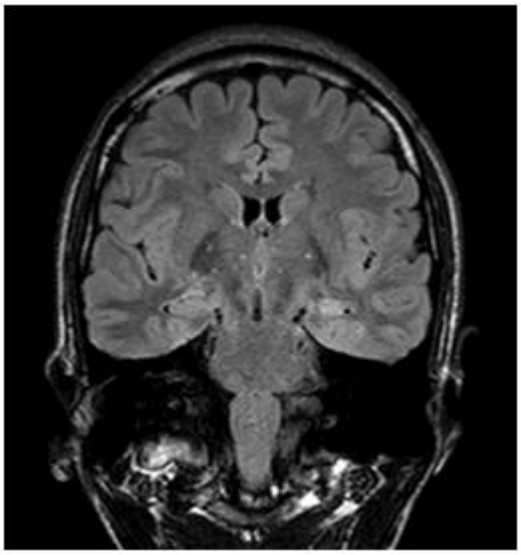


Coronal T1W IR showing hippocampal sclerosis

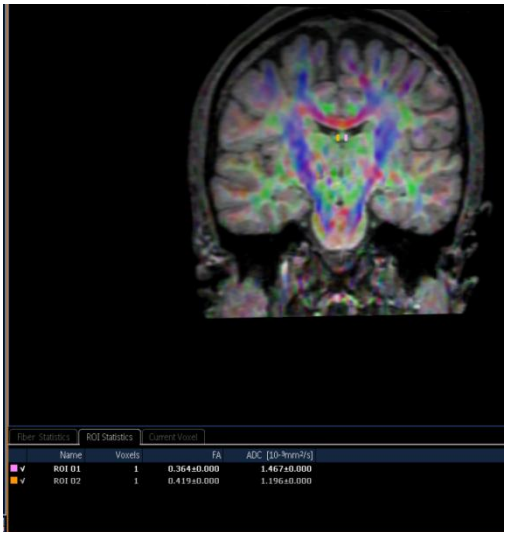


Colour coded FA map superimposed on isotropic T1W image - Coronal showing ROIs at hippocampus, uncinate fasciculus, parahippocampal gyrus and fornix

Case 3: Left hippocampal sclerosis



Coronal Flair image showing left hippocampal sclerosis



Coronal image with ROI at fornix

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