Original Research Article

Role of diffusion tensor imaging in dementia

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Abstract

Background: Dementia, with high morbidity and significant socioeconomic effect, is a debilitating disease of the elderly. Therefore, early diagnosis and early onset of treatment for cases of dementia can greatly decrease the morbidity associated with the disease. And Diffusion Tensor Imaging provides a promising future in this matter. Diffusion Tensor Imaging gives qualitative and quantitative information of the white matter tracts and hence can be useful to detect early micro-structural changes associated with dementia before obvious clinical features are appreciated.**Method:** Diffusion Tensor Imaging of 50 patients with clinical suspicion of dementia was done SIEMENS 3T MAGNETOM VIDA SCANNER.**Results:** There was an apparent correlation between the clinical dementia rating score and the FA values in the parahippocampal cingulum and uncinate fasciculus, with higher CDR score showing lower FA values in the above mentioned fibers.**Conclusion:** Our study showed that Diffusion Tensor Imaging is a very useful tool in the detection of the early microstructural changes seen in dementia even before the obvious clinical symptoms appear and hence aids in early diagnosis and treatment of the disease.

Keywords: diffusion tensor imaging and 'dementia.

Introduction

Dementia, with high morbidity and significant socioeconomic effect, is a debilitating disease of the elderly. Dementia has a multi-factorial etiology, heterogeneous presentation, and variable prognostic prediction. It is defined in many domains by a reduction in output and cognitive disability and affects the independence of a person in everyday life activities.[1] It also leads to substantial costs of healthcare and the increased responsibility on caregivers, making it a priority for public health.On an average, one in five people from middle and low income countries is expected to be over 60 years of age by the year 2050. In countries such as India, older people are cared for by families and 10 people of working age is accounted for 1 elderly person, but by 2100 this ratio would rise closer to one elderly person for every 3 people of working age.[2]

With the increase in the elderly population, there will be a proportionate increase in people suffering from dementia.In simple terms, there are currently around 35.6 million people living with dementia in the world with new cases accounting to 7.7 million annually[3], i.e. for every 4th person, one person is suffering from dementia in South Asian nations such as India and China (countries showing the highest projections).[4] The number of people affected by dementia worldwide is estimated to double by 2030 and more than triple by 2050, with the majority expected to be residing in the above mentioned developing countries[5].

Therefore, early diagnosis and early onset of treatment for cases of dementia can greatly decrease the morbidity associated with the disease. And Diffusion Tensor Imaging provides a promising future in this matter. Diffusion Tensor Imaging gives qualitative and quantitative information of the white matter tracts and hence can be useful to detect early micro-structural changes associated with dementia before obvious clinical features are appreciated.

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Aim and objectives

Aim: To study the role of Diffusion Tensor Imaging (DTI) in evaluation of suspected cases of dementia.

Objectives

- Assessment of micro-structural changes in brain parenchyma related to dementia.
- To identify findings seen on diffusion tensor imaging in early cases of dementia.
- To correlate findings with clinical dementia rating scale.

Materials and methods

- Place of study: Padmashree Dr. D. Y. Patil Medical College and Hospital and Research Centre, Pimpri, Pune
- Type of study: Prospective Study.
- Period of study: September 2018 to October 2020
- Period required for data collection: 20 months.
- Period required for data analysis and reporting: 5 months
- Sample Size: 50 Cases
- Study Design : Observational study

Inclusion criteria

- All patients clinically suspected with early dementia

Exclusion criteria

- Postoperative presence of MRI incompatible orthopedic hardware.
- Patient having history of cardiac pacemakers, metallic foreign body and cochlear implants insitu.
- Patients with history of claustrophobia.
- Method of diagnosis: Siemens Magnetom Vida (3T)

Fig 1:SIEMENS 3T MAGNETOM VIDA MRI

MRI SCAN Technique

Patient positioning:

- Supine with head first
- Head positioned in head coil and immobilized with cushions.
- Laser beam localizer centered over glabella.

Sequences Used: All patients in the study underwent MR brain using 3T MR scanner (Siemens Magnetom Vida). The imaging protocols included T1 weighted, T2 weighted, FLAIR sequences, diffusion weighted imaging and diffusion tensor imaging (DTI).

- **Diffusion tensor imaging:**The primary sequence in our study to obtain Diffusion Tensor Imaging was "ep2d_diff_mddw_20_(DTI)" in which multiple diffusion gradients are applied in 20 different directions on an Echo Planar Imaging (EPI) Sequence. Diffusion tensor imaging was done in the axial plane using the parameters mentioned below on the 3T scanner;
  - Repetition time(TR):3700 milliseconds(ms)
  - Echo time(TE) : 92ms
  - Diffusion gradient encoding in 20 directions: b – 0: b- 1000(tensor value) seconds/mm^2; Higher the number of directions, higher are the number of fibers assessed and greater is the acquisition time.
  - Voxel size – 1.7x1.7x4mm;
  - Slice thickness – 4mm with distance factor of 30
  - Total of 25 slices without gaps were used for obtaining the cerebral hemispheres, cerebellum and upper brainstem.
  - The acquisition time on the 3T MR scanner for this diffusion weighted sequence was 4 minutes 39 seconds.
  - Software used- Syngo via XA 11
  - Subsidiary software – Syngo via Neuro 3d
  - Hardware – Magnet: MAGNETOM VIDA XG Coil –Coil: Head and Neck 64 channel coi

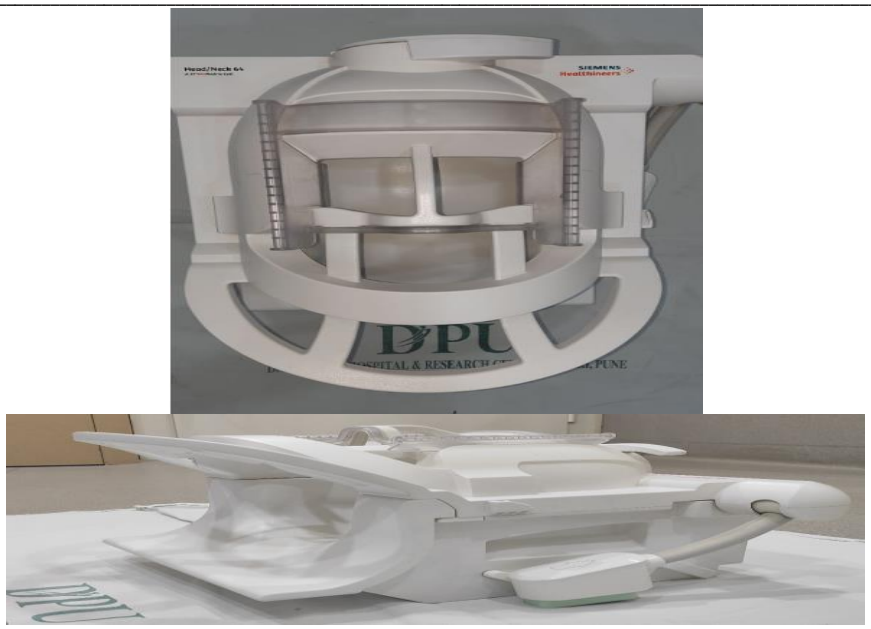
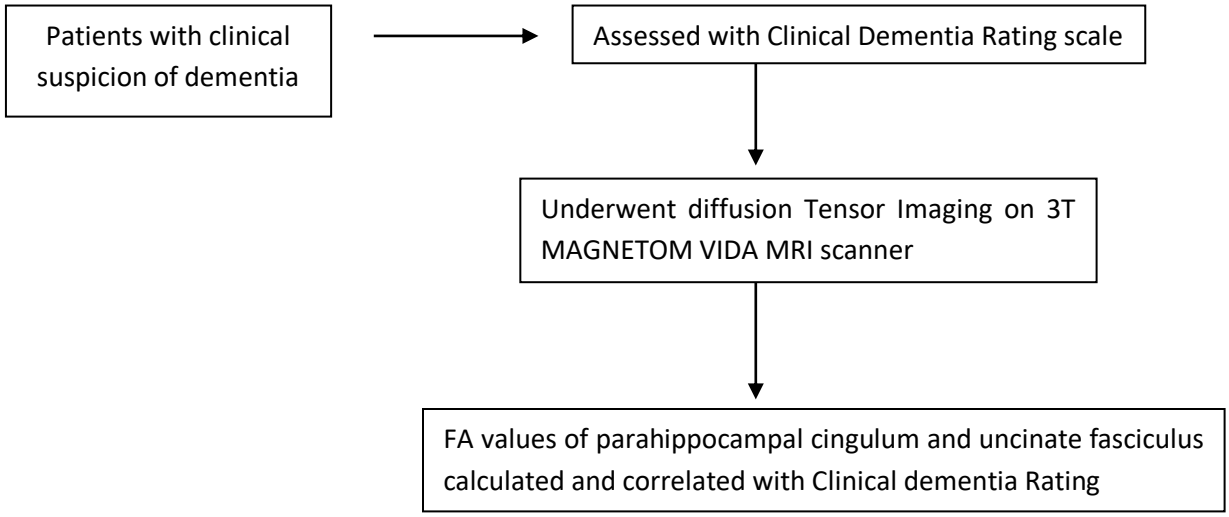


Fig 2: Head and neck 64 channel coil used to perform DTI studies of the brain.

Methodology

Patients coming to the Psychiatry/Neurology OPD with clinical suspicion of dementia were assessed based on the Clinical Dementia Rating scale and a score from 0.5 – 3 was given (questionable – severe dementia). The patients were then referred to the Department of Radiology where they underwent Diffusion Tensor Imaging after having satisfied the inclusion and exclusion criteria.Region of Interest (ROI) was placed over the required white matter tracts (parahippocampal cingulum and uncinate fasciculus) and Fractional Anisotrophy (FA) values were calculated. These values were then correlated with the clinical dementia rating score



Data collection method and statistical analysis

Data has been collected from the subjects on a pretested Performa enclosed at Appendix-A. Data were entered in Microsoft Excel and analyzed. Continuous variables like FA values in parahippocampal cingulum and uncinate fasciculus were expressed as mean (standard deviation). The distribution of categorical variables like age categories, gender and clinical dementia rating scores were summarized as proportions.

Observations

1. Sex distribution

Table 1: Sex distribution

Male	Female
26	24

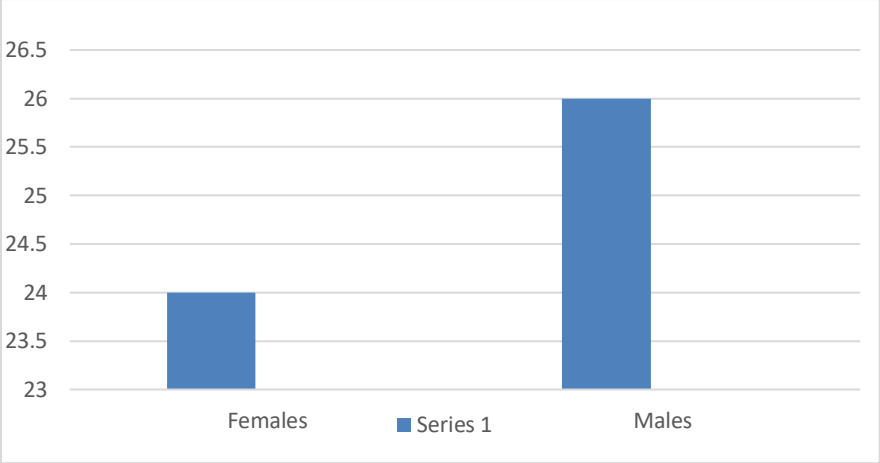


Fig 3:Sex distribution

2.Age categories

Table 2:Age distribution

<50	50 and above
22	28

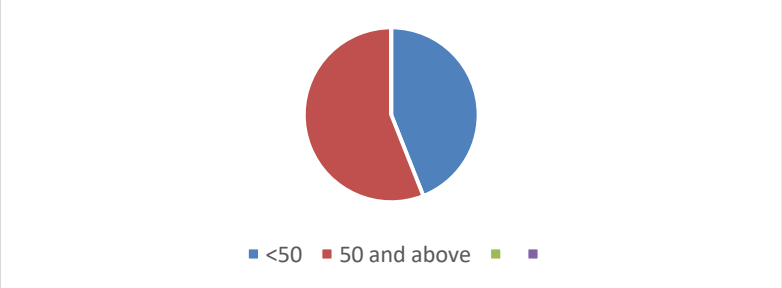


Fig 4:Age distribution

3.Clinical Dementia Rating Score

Table 3:Clinical Dementia Rating (score)

0.5	1	2	3
19	26	5	0

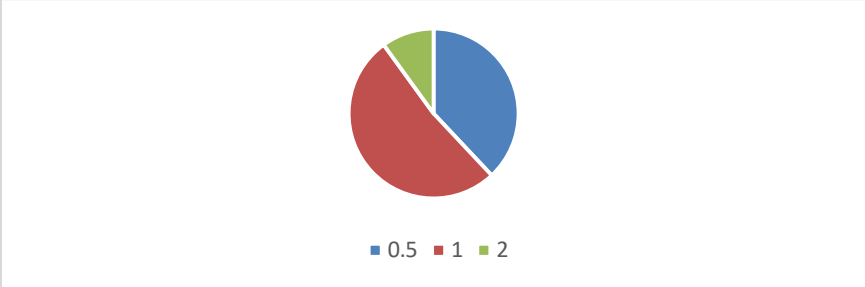


Fig 2:Clinical Dementia Rating (score)

4. Clinical Dementia Rating

Table 4:Clinical Dementia Rating

Questionable	Mild	Moderate	Severe
19	26	5	0

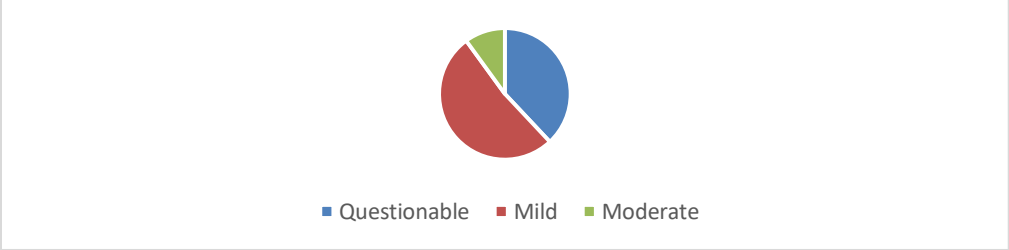


Fig 6: Clinical Dementia Rating

5. Distribution of FA values observed in Parahippocampal Cingulum

Table 5:FA value of Parahippocampal Cingulum

<0.5	0.5-0.59	0.6-0.69	>0.69
5	25	18	2

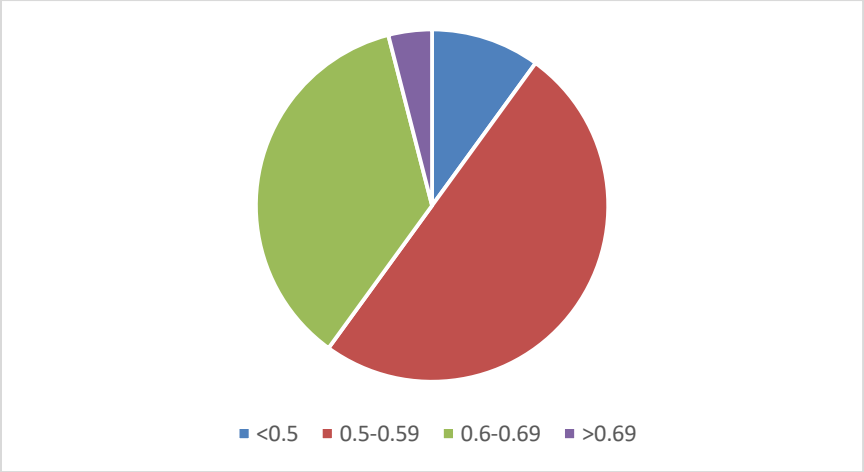


Fig 7: FA values observed in Parahippocampal Cingulum

6. Distribution of FA values in Uncinate Fasciculus

Table 6:FA value of Uncinate Fasciculus

<0.5	0.5-0.59	0.6-0.69	>0.69
5	23	22	0

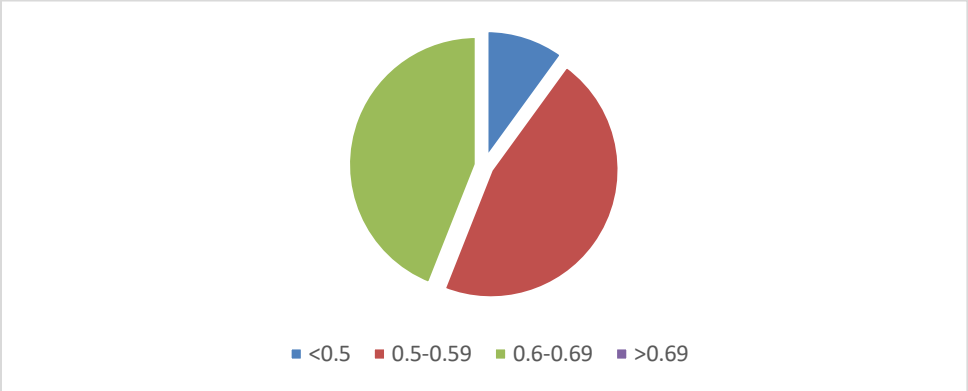


Fig 8: FA values observed in Uncinate Fasciculus

7. Correlation between FA values in parahippocampalcingulum and age.

Table 7:Correlation between FA values in parahimmpocampalcingulum and age

FA values in parahippocampalcingulum	>50 years of age	<50 years of age
<0.5	5	0
0.5-0.59	13	12
0.6-0.69	9	9
>0.69	2	0

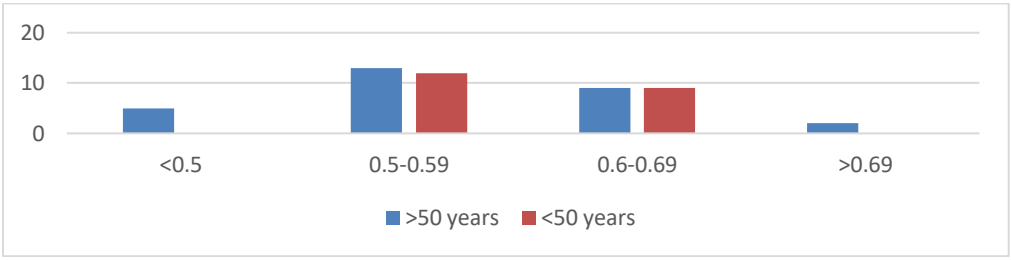


Fig 9: Correlation between FA values in parahippocampal cingulum and age

8. Correlation between FA of uncinate fasciculus and age.

Table 8: Correlation between FA of uncinate fasciculus and age

FA values in uncinate fasciculus	>50 years	<50 years
<0.5	5	0
0.5-0.59	13	12
0.6-0.69	9	9
>0.69	2	0

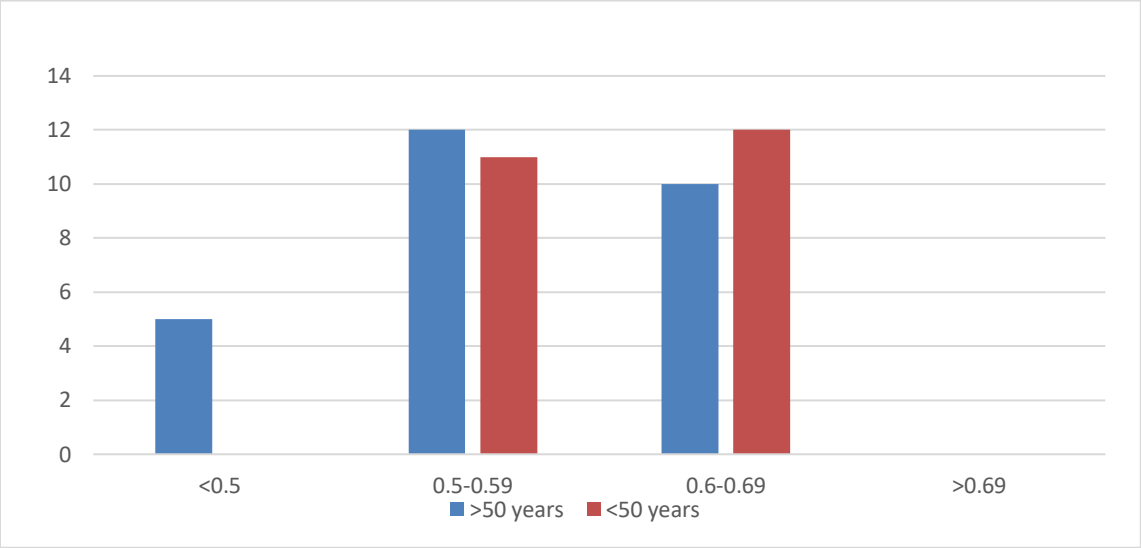


Fig 10:Correlation between FA values in Uncinate Fasciculus and age

9.Correlation between FA values of parahippocampalcingulum and Clinical Dementia Rating Score

Table 9: Correlation between FA values of parahippocampalcingulum and Clinical Dementia Rating Score

FA values in parahippocampalcingulum	Clinical Dementia Rating score			
	0.5	1	2	3
<0.5	0	2	3	0
0.5-0.59	8	16	1	0
0.6-0.69	11	6	1	0
>0.69	0	2	0	0

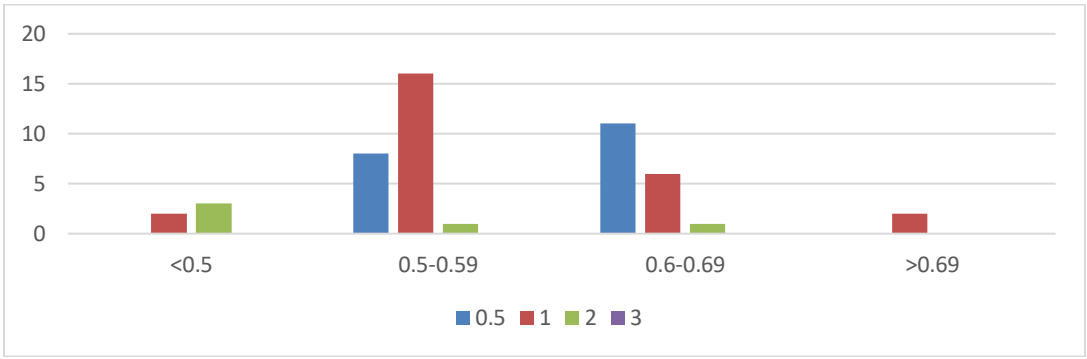


Fig 11:Correlation between FA values in parahippocampal cingulum and Clinical Dementia Rating score

10.Correlation between FA values of uncinate fasciculus and Clinical Dementia Rating Score

Table 10:Correlation between FA values of uncinate fasciculus and Clinical Dementia Rating Score

FA values in uncinate fasciculus	Clinical Dementia Rating score			
	0.5	1	2	3
<0.5	0	2	3	0
0.5-0.59	13	16	1	0
0.6-0.69	6	8	1	0
>0.69	0	0	0	0

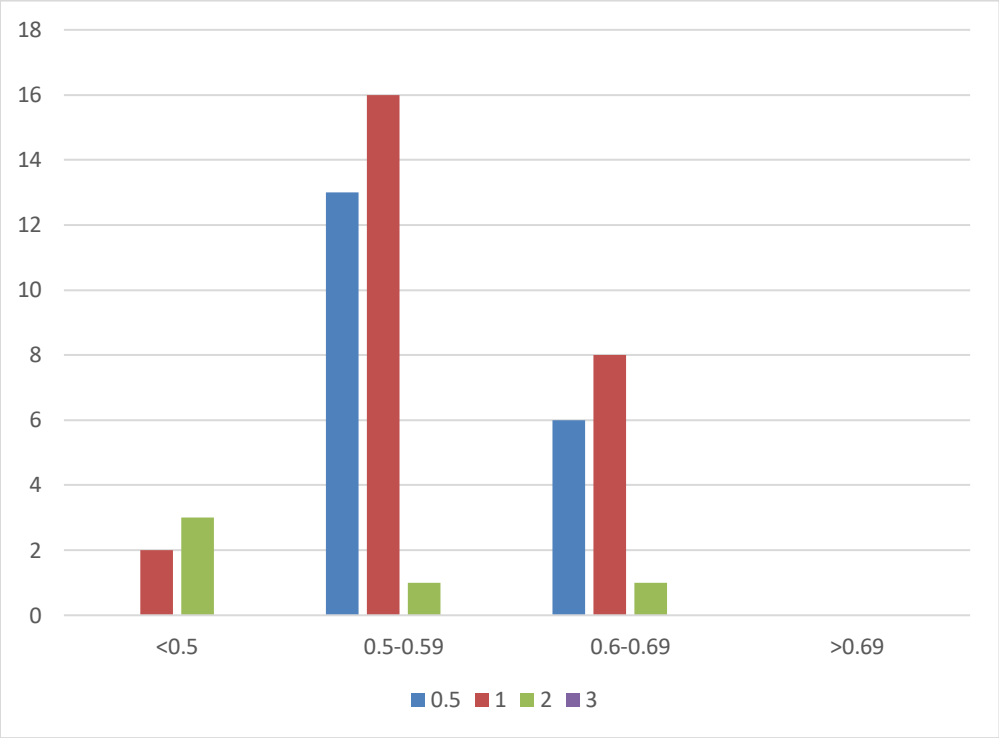


Fig 12:Correlation between FA values in Uncinate Fasciculus and Clinical Dementia Rating score

CASE 1

63 year old female with complaints of forgetfulness since 2 years. Her CDR score was 1(mild)

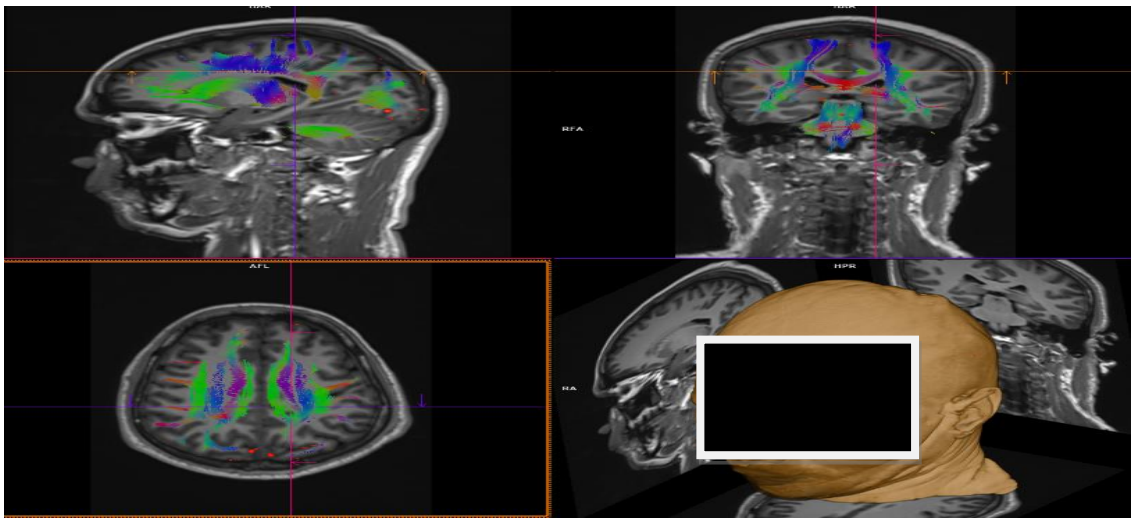
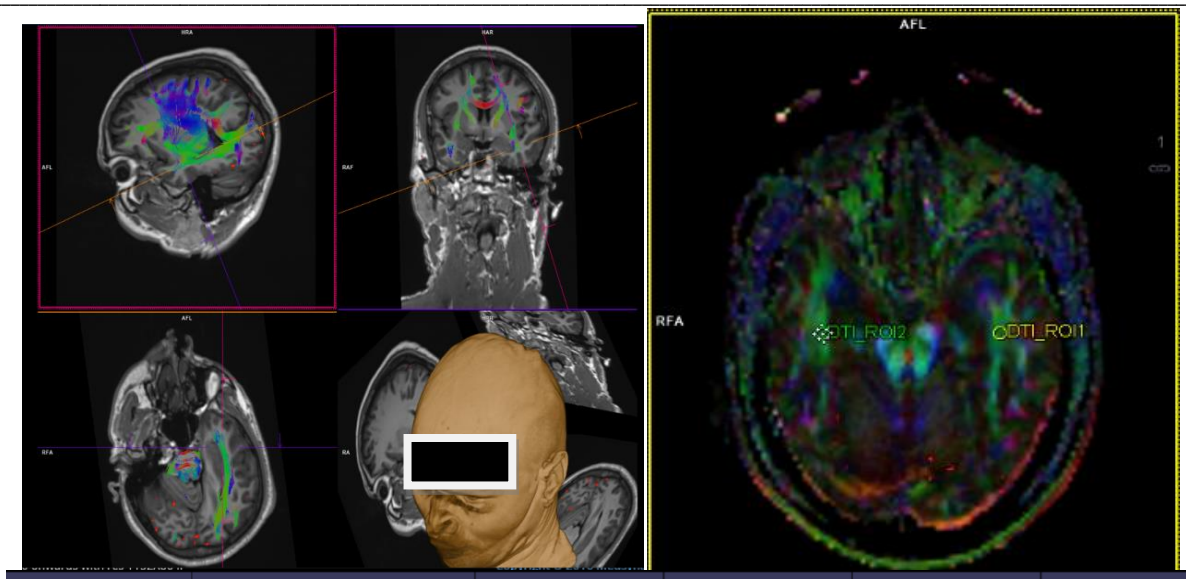


Fig 13: Post processed DTI images in sagittal, coronal and axial plan



ID	Measurements	t1_mprag…	FA	ADC	B0
DTI_ROI1	Mean	318.82	408	841.83	245.83
	StdDev	21.96	60.7	37.07	4.84
	Min / Max	272 / 341	322 / 488	803 / 893	242 / 256
	(Area cm2)	0.2	0.2	0.2	0.2
DTI_ROI2	Mean	283.3	489	825.71	236.29
	StdDev	31.01	53.11	28.05	4.59
	Min / Max	207 / 316	403 / 551	775 / 868	229 / 244
	(Area cm2)	0.2	0.2	0.2	0.2

Fig 14:Diffusion Tensor images and tractography (Top left and top right) were obtained for the patient and FA values (bottom) of the parahippocampal cingulum and uncinate fasciculus which showed lower FA values (0.4 and 0.48)

CASE 2

58 year old female with complaints of memory loss and poor personal care with a CDR score of 2(moderate)

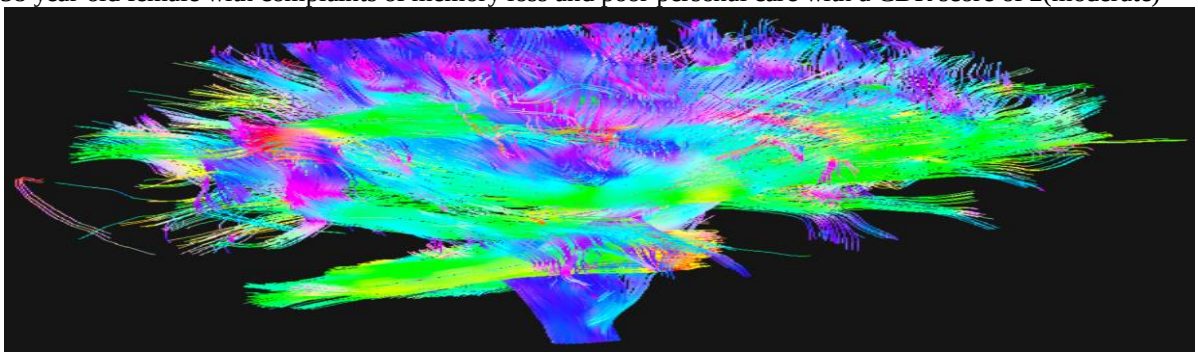
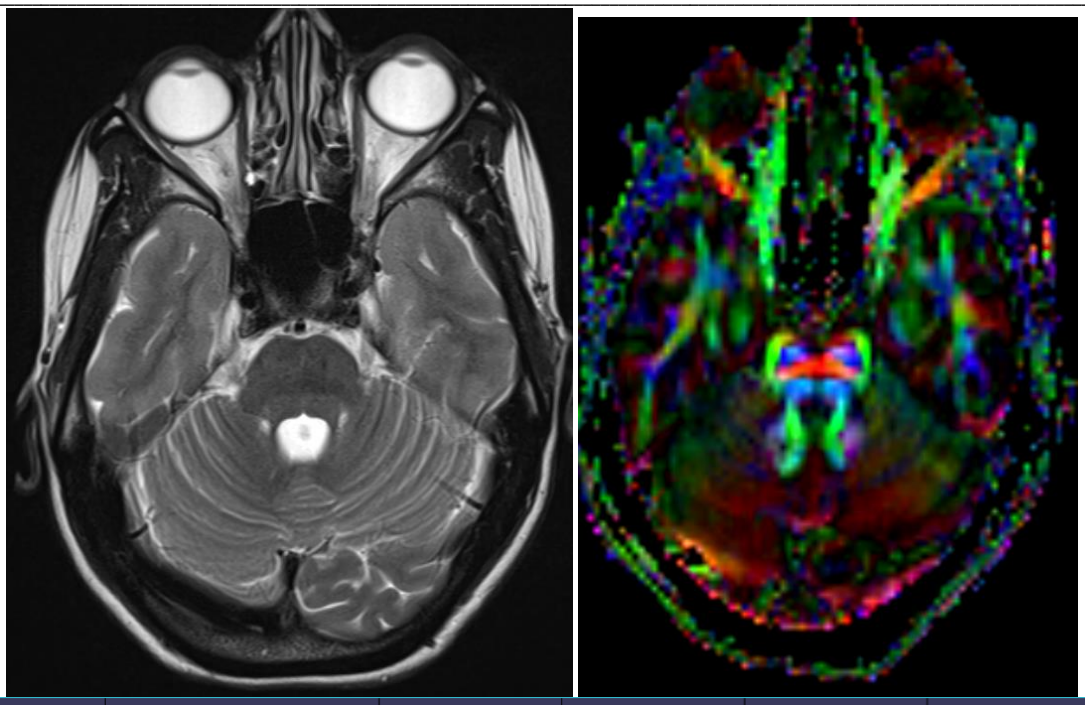


Fig 15:Post processed 3D tractography of the white matter tracts of brain



ID	Measurements	t1_mprag…	FA	ADC	B0
DTI_ROI1	Mean	250.09	435.38	806.77	199.31
	StdDev	34.83	40.14	46.68	11.75
	Min / Max	165 / 295	374 / 497	738 / 872	183 / 216
	(Area cm2)	0.41	0.41	0.41	0.41
DTI_ROI3	Mean	282.81	445.63	813	242.5
	StdDev	24.88	70.19	28.82	11.58
	Min / Max	206 / 315	340 / 572	769 / 855	223 / 262
	(Area cm2)	0.27	0.27	0.27	0.27

Fig 16:T2WI and tractography (Top left and top right) is depicted at the level of the parahippocampal cingulum and FA values (bottom) of bilateral parahippocampal cinguli were reduced (0.45 and 0.48)

CASE 3

43 year old female with complaints of forgetfulness since 6 months. Her CDR score was 0.5(questionable)

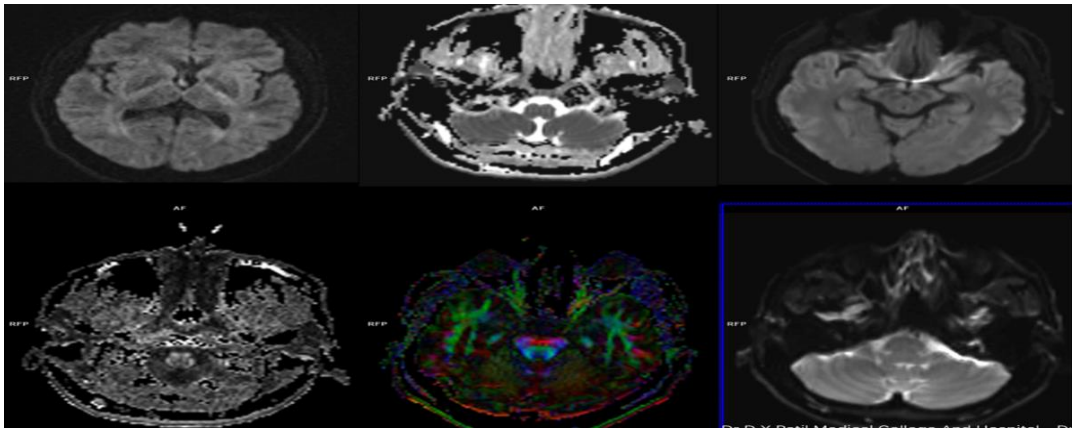
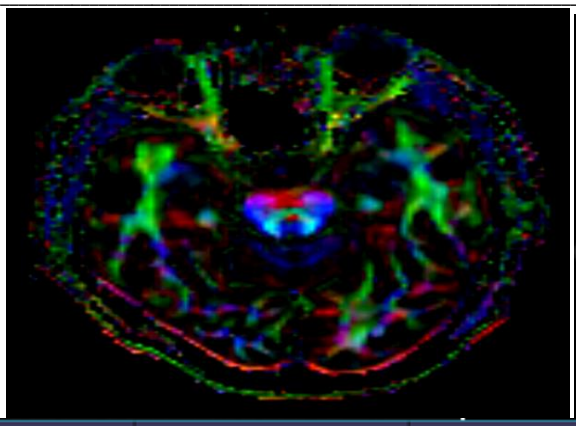
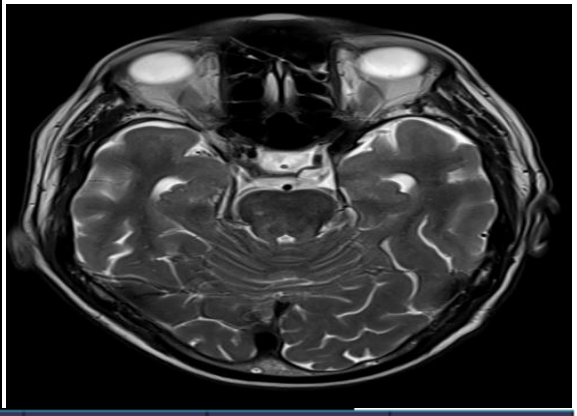


Fig 17:Pre processed acquisition DTI images of the white matter tracts of brain.

ID	Measurements	t1_mprag…	FA	ADC	B0
DTI_ROI4	Mean	258.92	587.5	807.31	274.5
	StdDev	16.74	129.19	55.76	13.76
	Min / Max	194 / 284	356 / 735	728 / 957	247 / 306
	(Area cm2)	0.78	0.78	0.78	0.78
DTI_ROI5	Mean	204.35	621.33	893.58	259.63
	StdDev	62.15	180.92	157.9	27.99
	Min / Max	66 / 292	216 / 845	674 / 1294	221 / 323
	(Area cm2)	0.79	0.79	0.79	0.79

Fig 18: T2WI and tractography(Top left and top right) is depicted at the level of the parahippocampal cingulum and FA values (bottom) of bilateral parahippocampal cinguli were normal (0.58 and 0.62)

CASE 4

49 year old male with complaints of forgetfulness since 3 months. Her CDR score was 0.5(questionable)

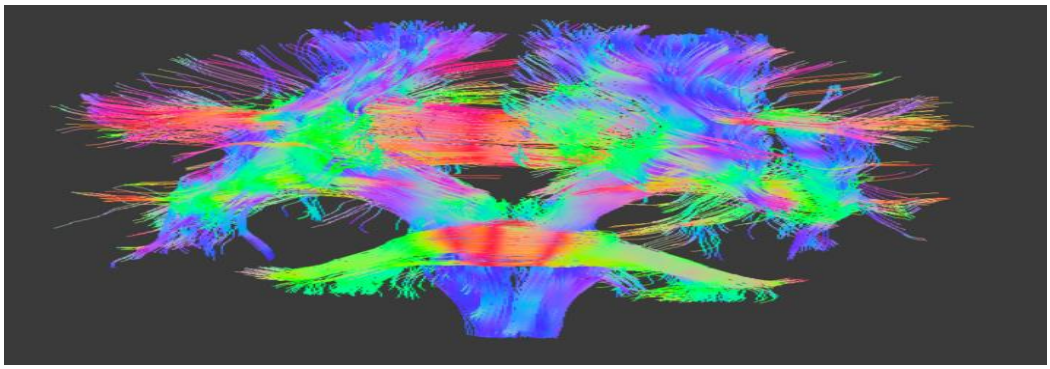
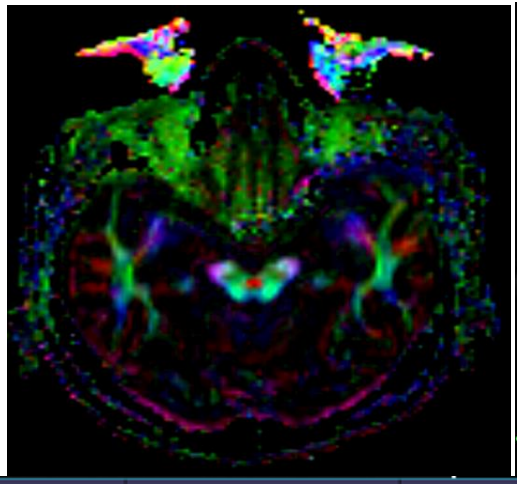
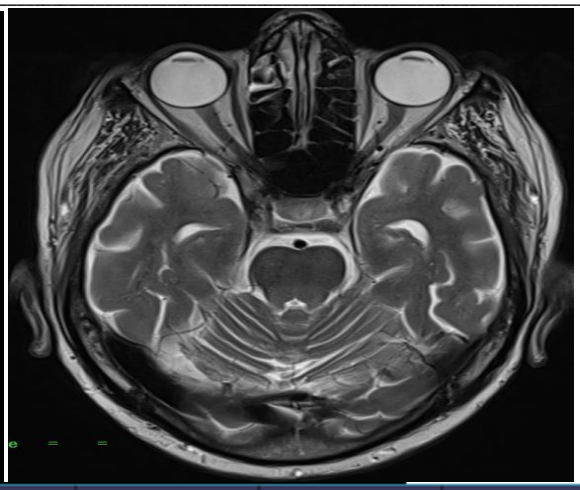


Fig 19:Post processed 3D tractography of the white matter tracts of brain.





ID	Measurements	t1_mprag…	FA	ADC	B0
DTI_ROI7	Mean	207.05	691	907.83	254.67
	StdDev	81.83	88.97	144.39	23.42
	Min / Max	51 / 305	514 / 780	797 / 1221	232 / 303
	(Area cm2)	0.19	0.19	0.19	0.19
DTI_ROI8	Mean	282.36	629.44	815	262.33
	StdDev	8.22	129.55	27.41	34.31
	Min / Max	267 / 297	446 / 815	779 / 861	196 / 307
	(Area cm2)	0.29	0.29	0.29	0.29

Fig 20:T2WI and tractography (Top left and top right)is depicted at the level of the parahippocampal cingulum and FA values (bottom) of bilateral parahippocampal cinguli were normal (0.69 and 0.63)

CASE 5

42 year old male with complaints of loss of memory, decreased problem solving skulls and poor personal care since 1 year. His CDR score was 2(moderate)

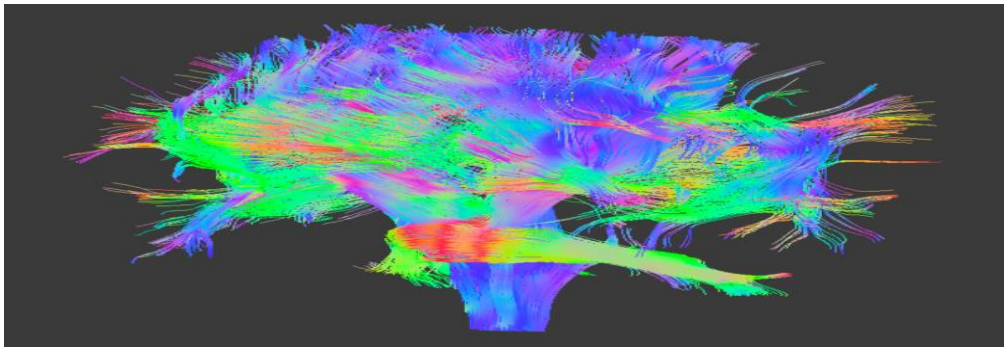
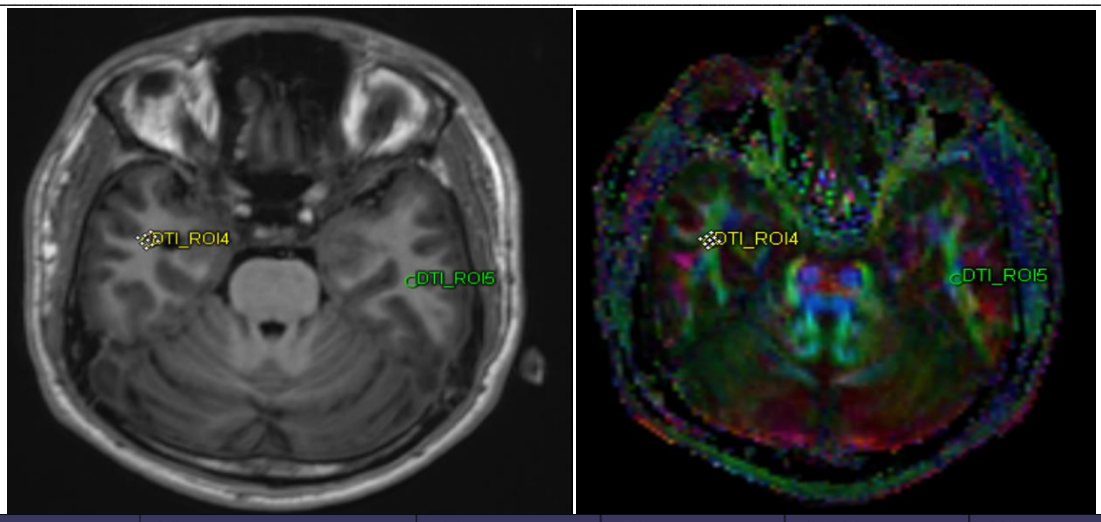


Fig 21: Post processed 3D tractography of the white matter tracts of brain



ID	Measurements	t1_mprag…	FA	ADC	B0
DTI_ROI4	Mean	285.8	416.67	799.17	241.17
	StdDev	12.39	88.48	27.75	5.34
	Min / Max	241 / 297	309 / 558	759 / 848	234 / 247
	(Area cm2)	0.14	0.14	0.14	0.14
DTI_ROI5	Mean	273.71	515	854.25	192.25
	StdDev	7.19	39.1	26.33	4.6
	Min / Max	261 / 285	464 / 571	812 / 882	188 / 200
	(Area cm2)	0.12	0.12	0.12	0.12

Fig 22: T1WI and tractography (Top left and top right)is depicted at the level of the parahippocampal cingulum and FA values (bottom) of bilateral parahippocampal cinguli were reduced (0.41 and 0.51)

CASE 6

43 year old male patient with complaints of forgetfulness since 6 months. No comorbidities. Family history was not significant. On clinical examination, his CDR score was 0.5(questionable).

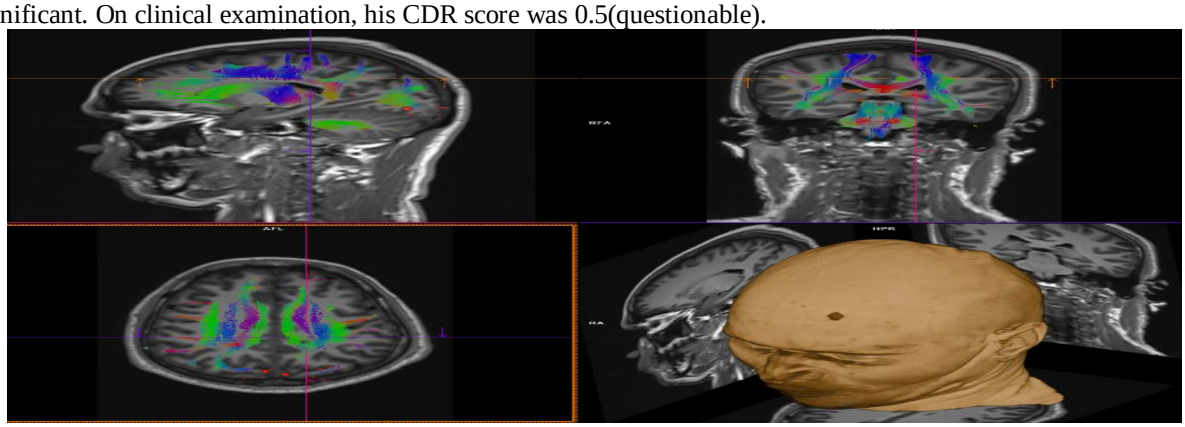


Fig 23: Post processed DTI images reveal normal configuration of visualized white matter tracts. FA values of visualized white matter tracts were within normal limits

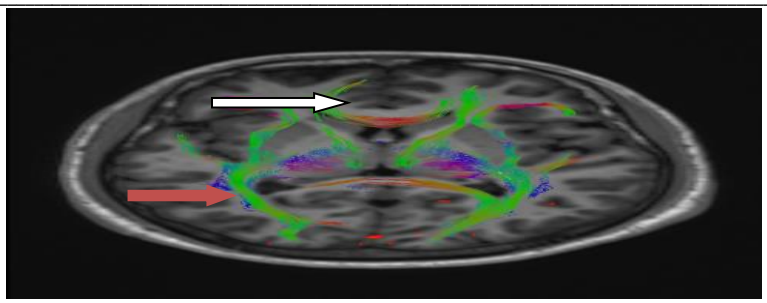


Fig 24:Axial MRI DTI images of the same patient at the level of internal capsule reveals normal fibers of internal capsule (White arrow) and optic radiation (red arrow).

CASE 7

52 year old male patient with complaints of loss of memory since 1 year. No comorbidities. Family history was not significant. On clinical examination, his CDR score was 0.5(questionable).

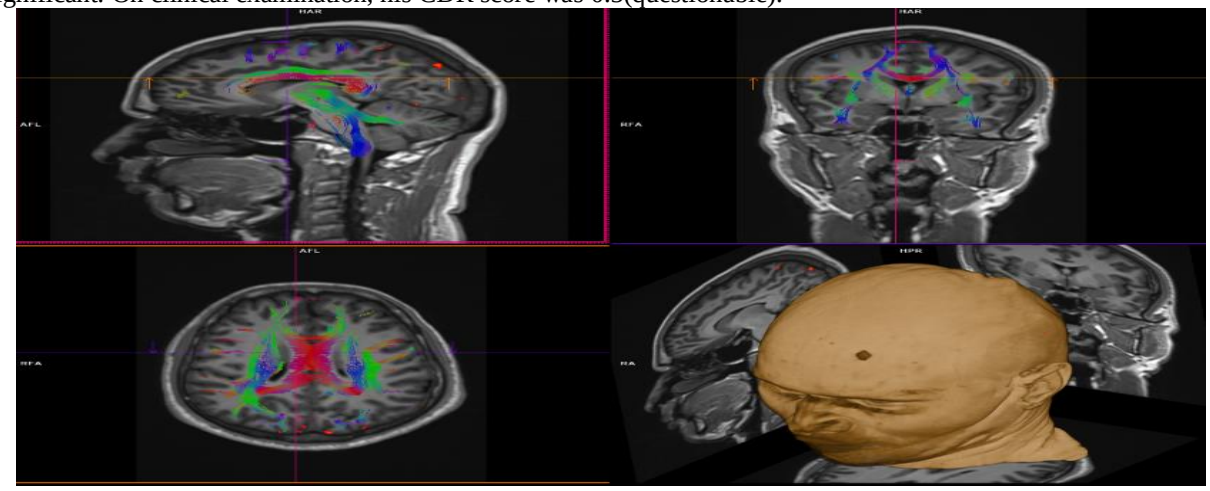


Fig 25:Post processed DTI images reveal normal configuration of visualized white matter tracts. FA values of visualized white matter tracts were within normal limits

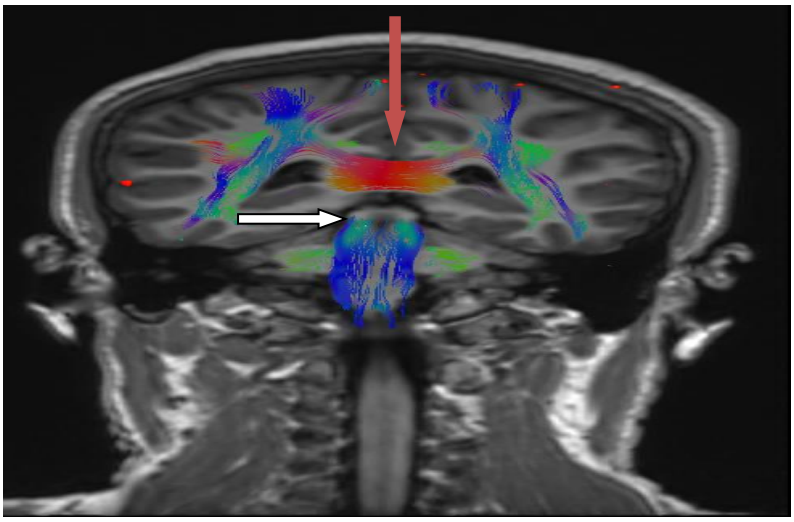


Fig 26:Coronal MRI DTI images of the same patient reveals normal fibers of corticospinal tract (White arrow) and corpus callosum (red arrow)

CASE 8

52 year old male patient with complaints of reduced problem solving skills since 3 years. No comorbidities. Family history was not significant. On clinical examination, his CDR score was 1(mild).

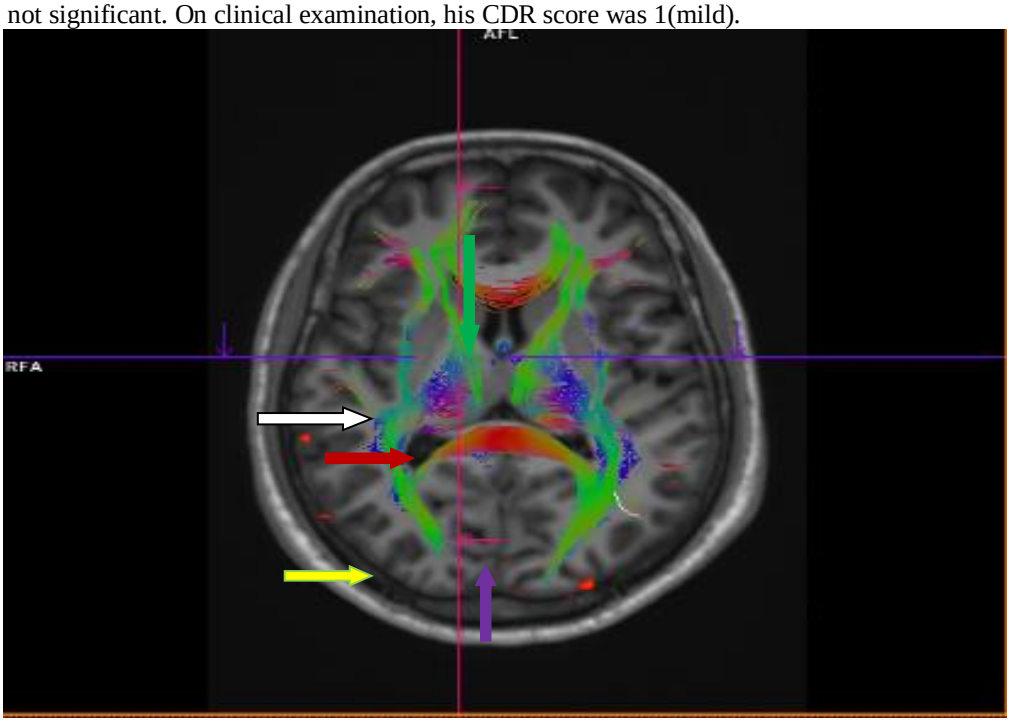


Fig 27:Post processing axial DTI images showing normal fiber volume and brightness (FA) of visualized inferior occipitofrontal fasciculus (white arrow), internal capsule (red arrow), optic radiation (yellow arrow) and genu (green arrow) and splenium of corpus callosum (purple arrow)

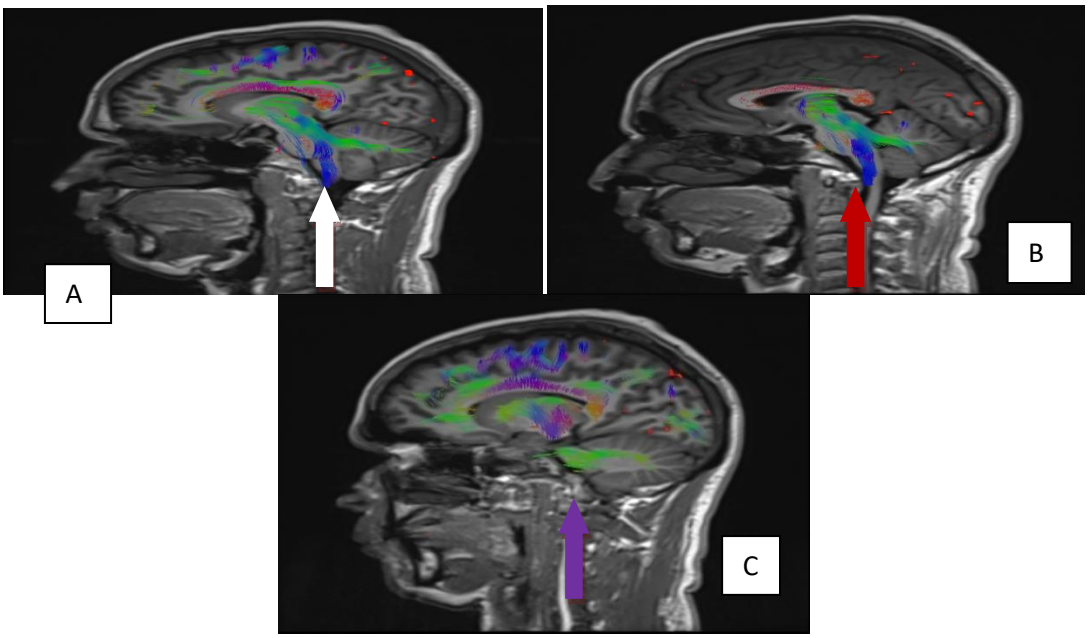


Fig 28: Post processed sagittal images of the same patient; *A*-Superior cerebellar peduncle (white arrow). *B* – Middle cerebellar peduncle (red arrow). *C* – Inferior cerebellar peduncle (purple arrow).

Discussion

This observational study was carried out in "Dr. D.Y.Patil Medical College, Hospital and Research Centre, Pimpri, Pune-18" over a period of two years in patients who were referred for Magnetic Resonance Imaging of the brain to department of radio-diagnosis for further examination. Patients were evaluated using Siemens Magnetom VIDA Magnetic Resonance Imaging scanner (3Tesla).

Age: In our study, 22 participants were less than 50 years and 28 above 50. 41 year old male was the youngest patient in the study and 63 year old female was the oldest patient in the study group.

Gender: Total 50 participants were evaluated, out of which there were 26 (52%) males and 24(48%) females (all age groups).

Findings

Total 50 participants were evaluated initially clinically to determine their clinical features and ascertain a Clinical Dementia Rating score. The participants then underwent Diffusion Tensor Imaging and the FA values of the parahippocampal cingulum and Uncinate Fasciculus were measured. We then made correlations between ages as well as Clinical Dementia Rating to the FA values in the above mentioned white matter tracts. It was observed that those with a higher clinical dementia rating score tend to have a lower FA value in the parahippocampal cingulum and uncinate fasciculus. Out of the 5 participants having a clinical Dementia rating of 2 (moderate rating), 3 showed a significantly lower FA value of less than 0.5. 18 of 26 (69.2%) participants with a Clinical Dementia Rating score of 1 (mild) show FA values in parahippocampal cingulum and uncinate fasciculus of <0.59.

These findings concur with study conducted by Sexton et al [6], who conducted one of the earliest meta-analyses of 41 regions of interests and found extensive changes in FA and MD using Diffusion Tensor imaging.

The white matter of para-hippocampal cingulum the temporal and frontal lobes, the corpus callosum (genu and splenium), uncinate fasciculus, middle, anterior and posterior cingulum and the superior longitudinal fasciculus were found to be low with respect to FA values.

A report on major discrepancies in microstructure para meters of white matter in people diagnosed with dementia relative to matched stable older adults was conducted by Mayo et al., 2017[7].

In particular, it was found that people with dementia sh owed higher MD and lower FA in the hippocampal cingulum compared to healthy older adults, internal an d externalcapsule,the corpus callosum, fronto-occipital fasciculus, cingulate gyri, fornix, posterior thalamic radiation,corona radiata, inferior and superior longitudinal fasciculi, ,tapetum and uncinate fasciculus. These changes in the integrity of white matter were in agreement with dementia related Diffusion Tensor Imaging studies done in the past [8-14].

In a systematic analysis of probabilistic tractography and diffusion tensor indices obtained in a population of healthy controls, Minimal Cognitive Impairment and probable Alzheimer's Disease subjects, a study conducted by Dounad et al, 2011[9] recorded whole-brain performance. As predicted, all diffusion indices converged to demonstrate that the most affected white matter tracts in AD are the uncinate fasciculus, the superior longitudinal fasciculus, the whole corpus callosum, and cingulum bundle. Significant differences were essentially restricted to the corpus callosum between MCI and AD.Meta study of white matter (WM) alterations in amnestic mild cognitive impairment (aMCI) studied by Yu J et al, 2017[15] abounds. In aMCI, reliable FA and MD changes in the parahippocampal cingulum, fornix and the uncinate fasciculus were observed among the several important ROI-related findings. Larger effects relative to FA in MD were observed. The ALE meta-analysis showed a substantial decrease in FA in the posterior corona radiata among subjects with aMCI. Such findings provide clear proof of the existence of WM anomalies in aMCI.In 2011, Shu et al[13] used tract-based spatial statistics (TBSS) and diffusion tensor imaging to research improvements in WM in various diffusion indices in both AD and MCI patients (e.g., fractional anisotropy, axial, radial and mean diffusivity). The AD patients had decreased FA and increased radial, axial and mean diffusivity in widespread white matter structures, including lateral temporal cortex and corpus callosum, fronto-parietal regions and precuneus/ posterior cingulated cortex relative to standard controls. In MCI patients, related white matter regions with decreased anisotropy were also found, but with a lower degree than in Alzheimer's Disease. There were substantial variations between the AD and MCI classes in the mean and axial diffusivity of the white matter tracts in close proximity to the posterior cingulate cortex/precuneus without changes in anisotropy. Hence, these results based on the different diffusion indices (FA, mean, axial and radial diffusivity) indicate distinct white matter degeneration characteristics in MCI and AD.Another research conducted in 2019 by Mayo et al.[16]found that as predicted, people with Alzheimer's disease showed lesser composite scores on executive and memory function measures, as well as

reduced integrity of white matter compared to healthy elderly adults in widespread regions, including the hippocampus. Important relationships between memory scores and DTI metrics across different regions of the brain was observed, including the medial temporal regions, when the Alzheimer's disease and stable elderly adult groups were put together and important relationships between executive function and DTI values was shown.

Limitations of study

This study had few limitations. First, the sample size is small, which limits the generalization of the results to the population in large.Second, follow up was not possible; hence the disease progression could not be assessed.Third, participants who had associated claustrophobia or MRI incompatible implants, cochlear implants etc., were excluded from the study.

Conclusion

This is an observational study of 50 patients performed for a period of two years (September 2018 to September 2020) at "Dr.D.Y.Patil Medical College, Hospital and Research Centre, Pimpri, Pune". This study was carried out using Siemens Magnetom VIDA Magnetic Resonance Imaging scanner (3Tesla). The aim of the study was to assess the "Role of Diffusion Tensor Imaging in dementia" The patients who were fulfilling the inclusion and exclusion criteria were included in the study and the study group comprised 50 patients. Out of total 50 patients, 26(52%) males and 24(48%) females (all age groups).Our study has shown the utility of Diffusion Tensor Imaging in evaluating the early micro-structural changes that are seen in early dementia before obvious clinical features can be appreciated.We hope that our findings will lead to more studies investigating evaluation of diffusion tensor imaging in suspected cases of early dementia and hence significantly decrease the cost of treatment as well as morbidity associated with the disease.

Abbreviations

AD - Alzheimer's Disease
ADC - apparent diffusion coefficient
aMCI - Amnestic mild cognitive impairment
AxD - axial diffusivity
DTI – Diffusion Tensor Imaging
FA- fractional anisotrophy
GM - gray matter
MCI - mild cognitive impairment
MD - mean diffusivity
MRI – Magnetic resonance Imaging
RD - radial diffusivity
TBSS - tract based spatial statistics
WM -White matter

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