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A STUDY ON THE AGE-RELATED LOSS IN WHITE MATTER INTEGRITY USING DIFFUSION TENSOR IMAGING PARAMETERS

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ABSTRACT

Background

With increase in the proportion of aging dependent population, the need for understanding the pathogenesis of aging and the risk factors related to age related neurodegeneration is increasing with definite certainty. Studies pertaining to age related neurodegeneration will play a role in mitigating the impending issues related to aging population. Studies have shown the relatively greater involvement of white matter compared to the grey matter with age and therefore the evaluation of white matter tracts will further shed light onto the processes that occur with aging.(1)

Methodology

MRI was performed on a 3T MR scanner (General Electric, Signa Pioneer) with a head‑neck 45 coil. The subjects' brains were evaluated with conventional imaging using routine axial T2/T1‑weighted and diffusion-tensor imaging (DTI) sequences. The DTI acquisition protocol which was used is a dual-spin echo single shot echo-planar imaging sequence with the following parameters: Forty 3mm thick slices with no inter-slice gap. TR=6400ms, TE=88ms. FOV= 220x220mm^2, matrix of 128x128 zero filled to 256x256. DTI was performed with b=1000s/mm^2 using 25 different encoding directions. The Total scanning time was 11 mins. Various white matter tracts were evaluated from the DTI sequences using fibertractographyfollowing which the average Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA) values of each fiber was computed and tabulated with respect to age.

Results

Mean age of subjects was 63.49 ± 7.080 years. In the study majority of subjects were in the age group 61 to 70 years (42.9%). There was significant positive Correlation Distribution of Age and ADC in both the hemispheres and the corpus callosum. With increase in Age there was increase in Superior Longitudinal Fasciculus, Cingulum, Corticospinal Tract, Anterior Limb of Internal Capsule and corpus callosal ADC values and vice versa.There was a significant negative Correlation between Age and FA of Bilateral Superior Longitudinal Fasciculus, Cingulum, Corticospinal Tract, Anterior Limb of Internal Capsule and corpus callosum.With increase in age there was decrease in FA Values of Superior Longitudinal Fasciculus, Cingulum, Corticospinal Tract, Anterior Limb of Internal Capsule and corpus callosum and vice versa. The average ADC values of all the individual tracts on the right

cerebral hemisphere was greater when compared to the corresponding tracts in the left cerebral hemisphere.
Keywords: Diffusion Tensor Imaging, white matter, aging, Apparent Diffusion Coefficient, Magnetic Resonance Imaging

INTRODUCTION

With ageing, the brain undergoes microstructural and macrostructural changes that result in cognitive and functional decline. There is loss of brain volume and there is both white matter and grey matter degeneration. Histological studies demonstrate a decrease in myelin density and in the number of myelinatedfibers. Autopsy and volumetric neuroimaging studies suggest that White Matter changes are more prominent than cortical changes with aging, at least during certain segments of the age span and in certain regions of the brain. More recently, the role of cerebral white matter in neurodegeneration has increasingly been acknowledged. Imaging studies investigating cerebral white matter changes have initially focused mainly on macrostructural changes, such as white matter atrophy or the formation of white matter lesions (WML), which have both been linked to cognitive decline and dementia. However, these macrostructural changes are likely only the tip of the iceberg of the white matter pathology present and are thought to be preceded by microstructural changes.

Investigating tissue microstructure in a population-based setting of aging could thereby offer insight into earlier stages of neurodegeneration, potentially before irreversible damage has occurred. Furthermore, with ageing population in the future, neurodegenerative diseases will become more common and will cause burden on the society. Collection of data related to normal ageing will help future research to better understand pathological degeneration and the pathogenesis of ageing.

Diffusion Tensor Imaging is a promising modality, wherein one is able to quantify the diffusion of water molecules along the nerve tissue and thereby its microstructure. Additionally, it is possible to create 3- dimensional images of the trajectory of nerve fiber tracts. With increasing computational capabilities of machines, the accuracy of Diffusion Tensor Imaging has improved over the years. Diffusion Tensor imaging and fibertractography can be used to assess the relationship between microstructure of white matter and age.

This study was done, focussing on the importance of white matter with respect to aging by obtaining data relating to the relationship between the Diffusion Tensor Imaging parameters and aging.

MATERIALS AND METHODS

Study Design

This study was a cross sectional study done on patients attending Yenepoya Medical College Hospital, Mangalore who met the inclusion criteria. MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) were used to analyse data. EPI Info (CDC Atlanta), Open Epi, Med calc and Medley's desktop were used to estimate sample size.

Minimum required sample size was estimated to be 21. Therefore the sample size taken was 49.

Imaging Technique adapted and data processing

MRI is performed on a 3T MR scanner (General Electric ,Signa Pioneer) with a head‑neck 45 coil, located at Yenepoya Hospital- Deralakatte, Mangalore, India. The subjects' brain is evaluated with conventional imaging using routine axial T2/T1‑weighted and diffusion-tensor imaging imaging (DTI) sequences. The DTI acquisition protocol which is used is a dual-spin echo single shot echo-planar imaging sequence with the following parameters: Forty 3mm thick slices with no inter-slice gap. TR=6400ms, TE=88ms. FOV= 220x220mm^2, matrix of 128x128 zero filled to 256x256. DTI is performed with b=1000s/mm^2 using 25 different encoding directions. The Total scanning time is 11 mins. Various white matter tracts are evaluated from the DTI sequences using fiber tractography, following which the average Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA) values of each fiber is computed and tabulated with respect to age. Data is entered into Microsoft excel data sheet. MS Excel and MS word were used to obtain various types of graphs such as bar diagram, Pie diagram and Scatter plots.

Statistical analysis

Data is analyzed using SPSS 22 version software. Pearson correlationis done to find the correlation between two quantitative variables and qualitative variables respectively. p value (Probability that the result is true) of <0.05 is considered as statistically significant after assuming all the rules of statistical tests.

Images:

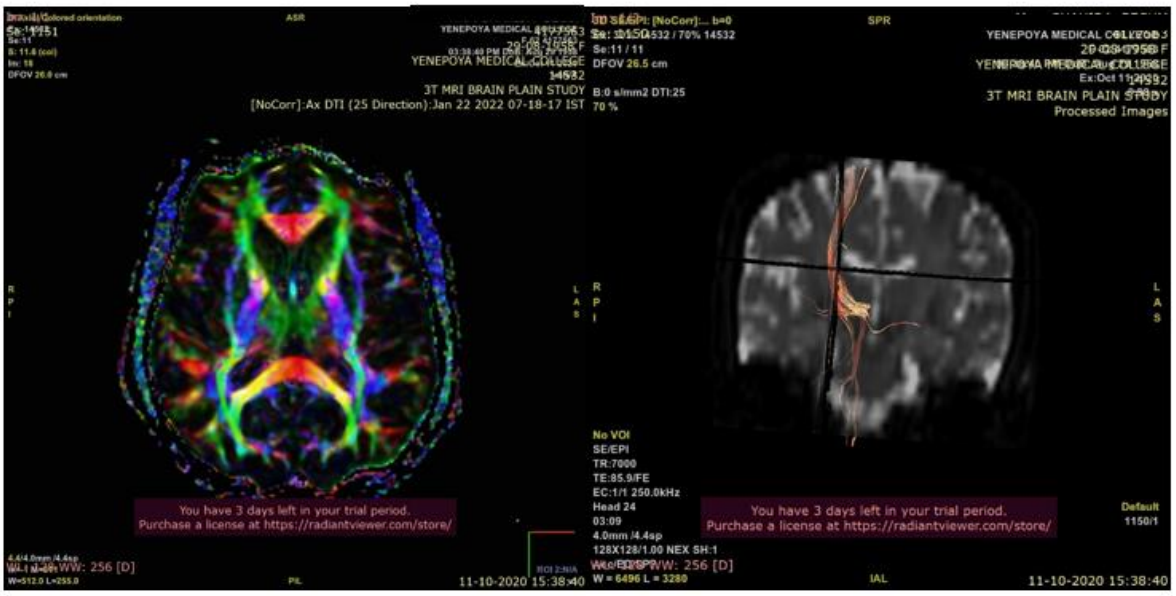

Figure 1 showing the ROI placement on the colour coded FA map and the resultant corticospinal tract

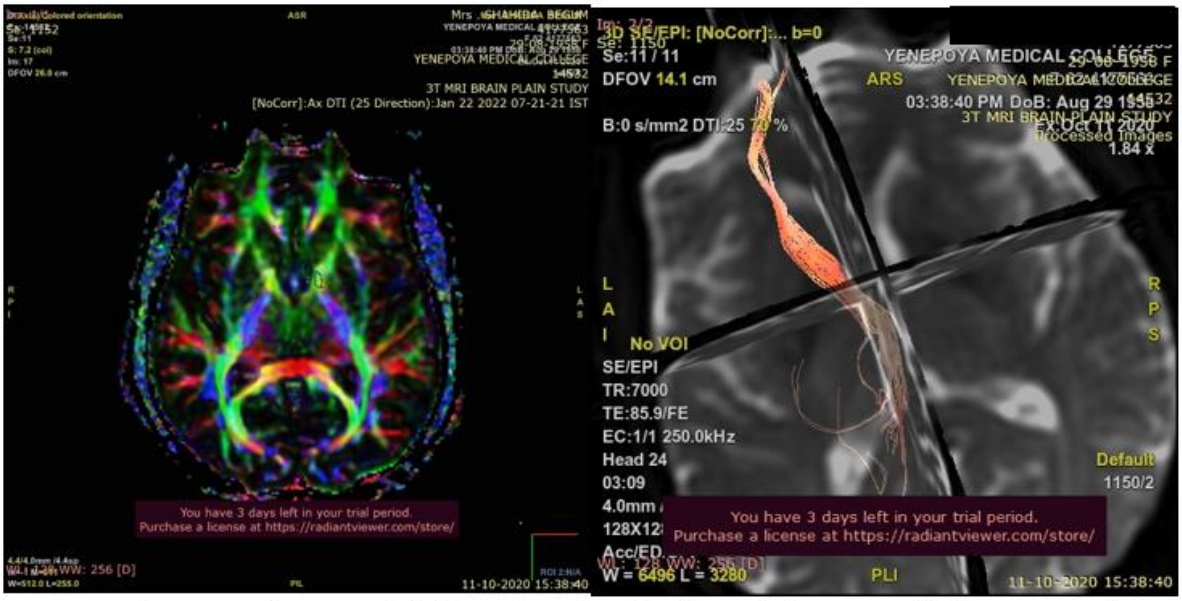

Figure 2: ROI placement on the anterior limb of internal capsule in the colour coded FA maps and the fibers generated.

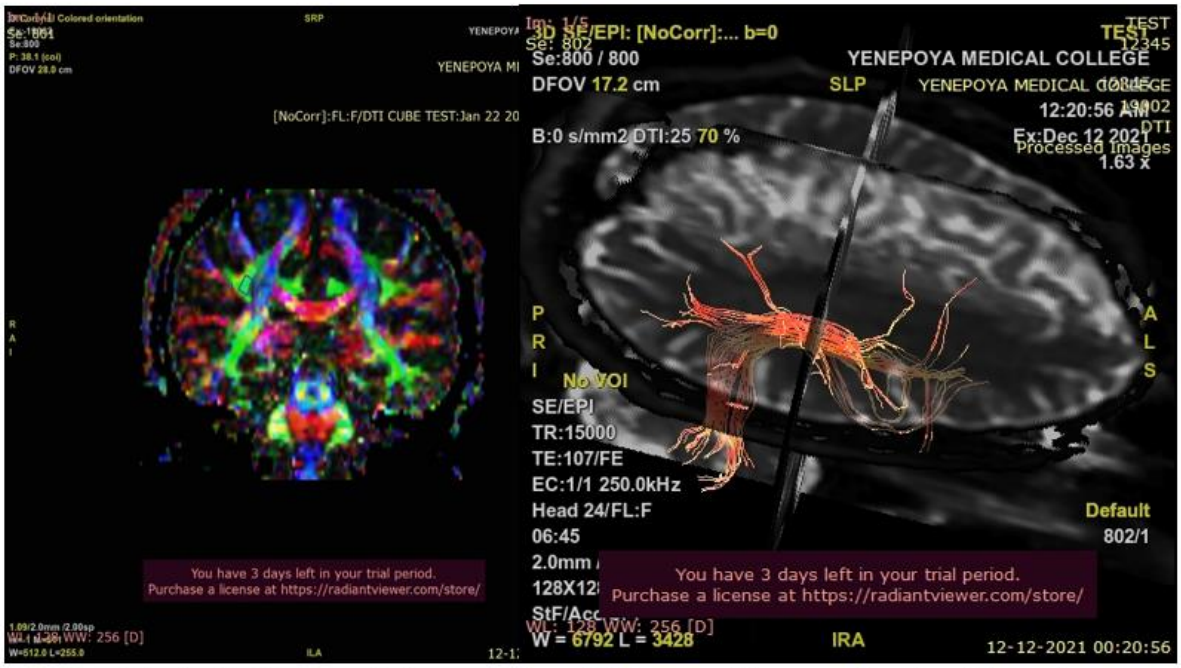

Figure 3 showing the ROI placement in the coronal colour coded FA maps and the corresponding fibers of the Superior longitudinal fasciculus

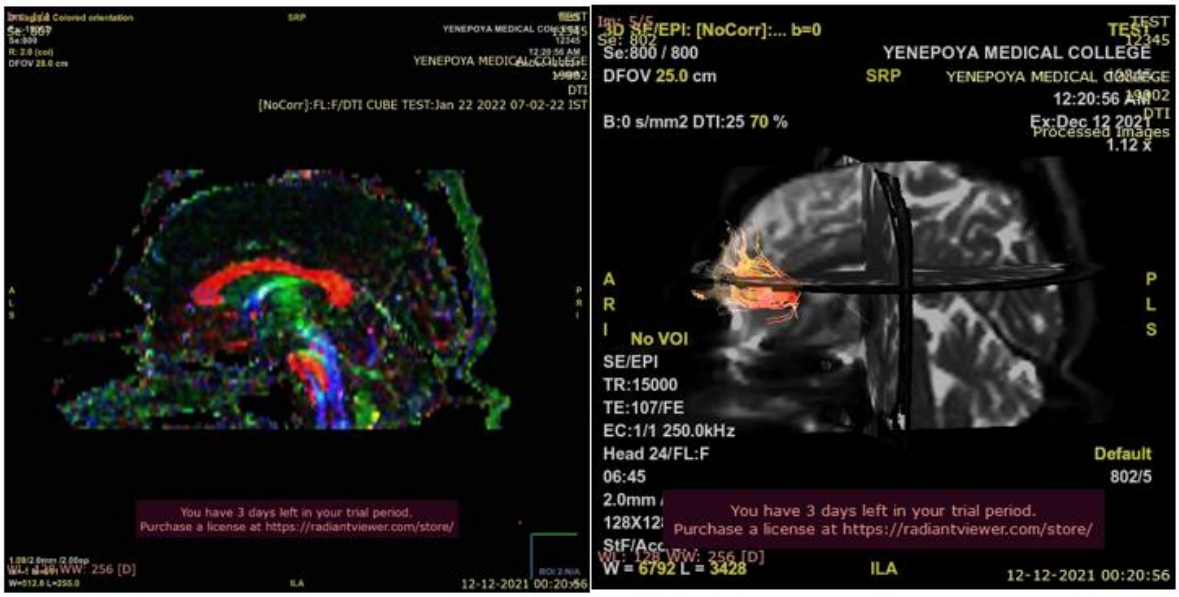

Figure 4: The ROI placement in the sagittal colour coded FA map and the corresponding tract of the genu of corpus callosum

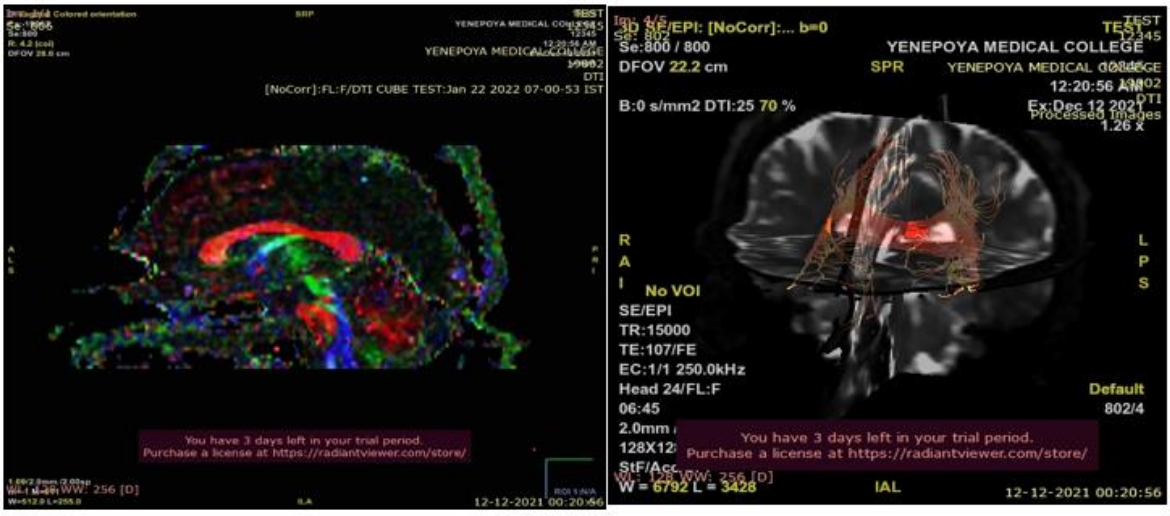

Figure 5: The ROI placement in the sagittal colour coded FA map and the corresponding tract of the splenium of corpus callosum

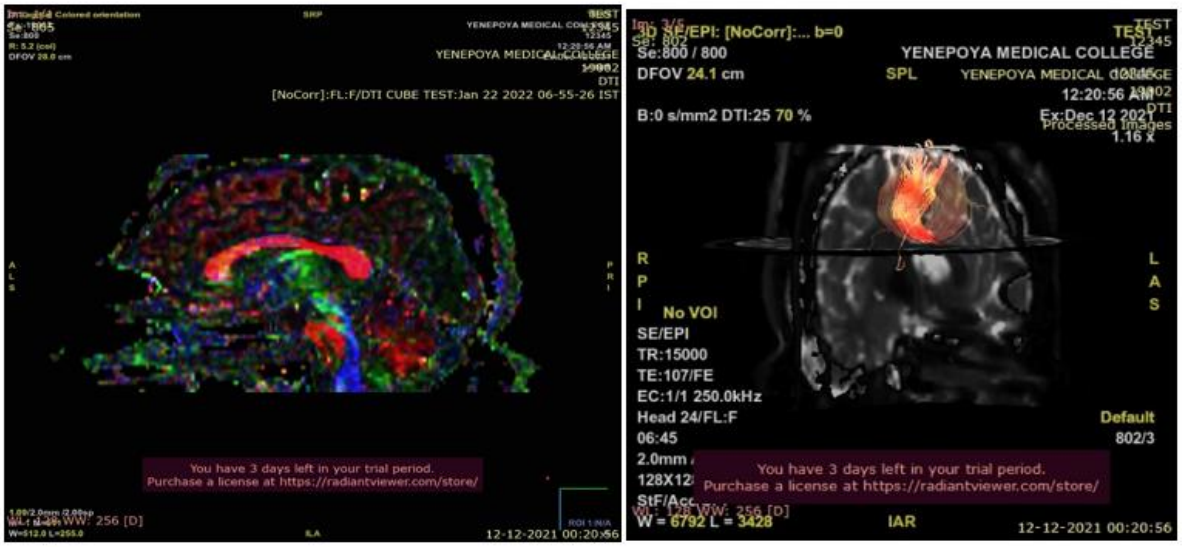

Figure 6: The ROI placement in the sagittal colour coded FA map and the corresponding tract of the body of corpus callosum

Results

Mean age of subjects was 63.49 ± 7.080 years. In the study majority of subjects were in the age group 61 to 70 years (42.9%).

There was significant positive Correlation Distribution of Age and ADC in both the hemispheres and the corpus callosum.

With increase in Age there was increase in Superior Longitudinal Fasciculus, Cingulum, Corticospinal Tract, Anterior Limb of Internal Capsule and corpus callosal ADC values and vice versa.

There was a significant negative Correlation between Age and FA of Bilateral Superior Longitudinal Fasciculus, Cingulum, Corticospinal Tract, Anterior Limb of Internal Capsule and corpus callosum.

With increase in age there was decrease in FA Values of Superior Longitudinal Fasciculus, Cingulum, Corticospinal Tract, Anterior Limb of Internal Capsule and corpus callosum and vice versa.

The average ADC values of all the individual tracts on the right cerebral hemisphere was greater when compared to the corresponding tracts in the left cerebral hemisphere.

Table 1: Age distribution

		Count	%
Age	<60 years	20	40.8%
	61 to 70 years	21	42.9%
	70 to 80 years	8	16.3%
	Total	49	100.0%

Mean age of subjects 63.49 ± 7.080 years. In the study majority of subjects were in the age group 61 to 70 years (42.9%).

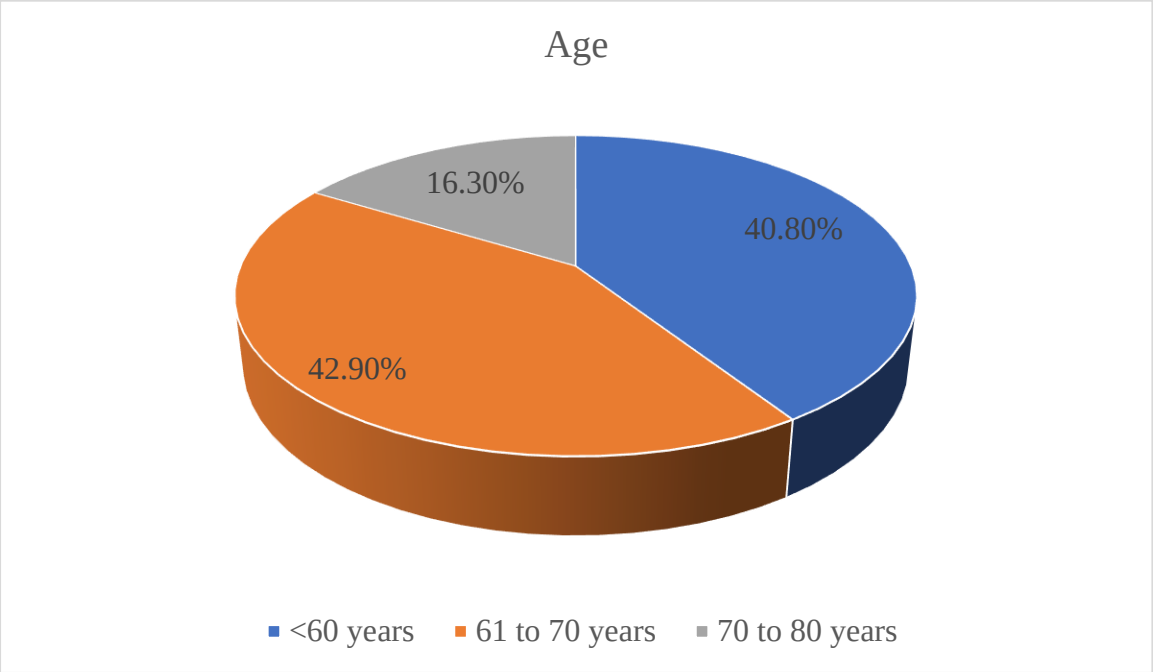

Figure 7: Pie diagram showing Age distribution

Table 2: Sex distribution

		Count	%
Sex	Female	22	44.9%
	Male	27	55.1%
	Total	49	100.0%

In the study, 44.9% were Female and 55.1% were Male.

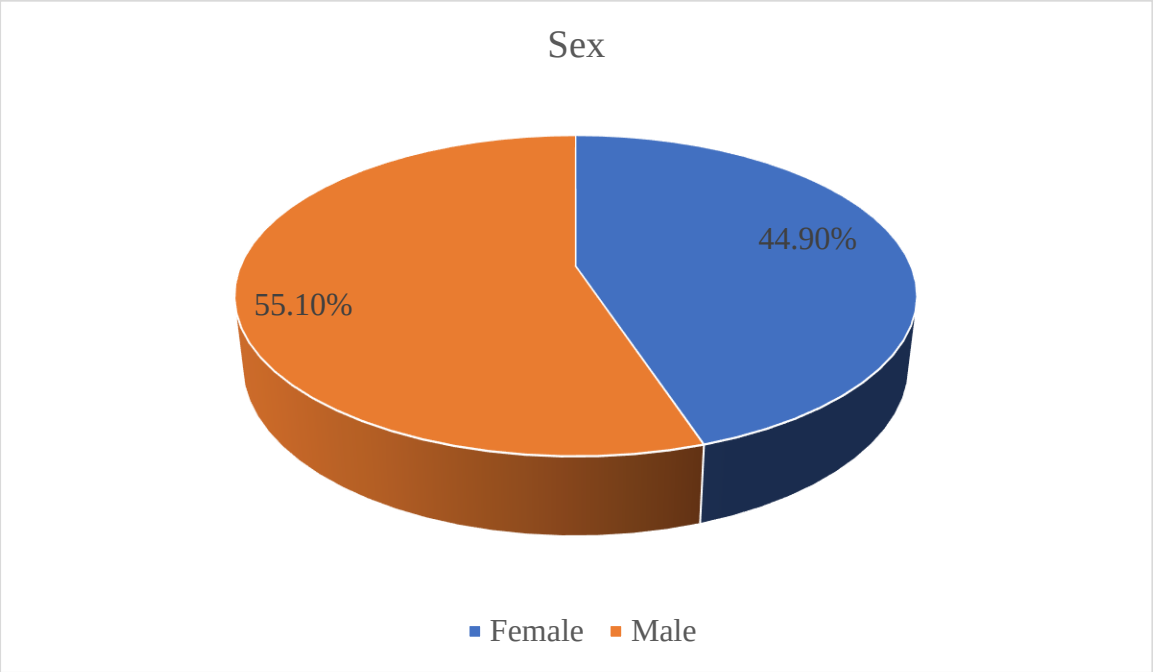

Figure 8: Pie diagram showing Sex distribution

Table 3: ADC distribution on Right and Left Hemisphere and Corpus Callosum

		Mean	SD	Median
Right Hemisphere	Superior Longitudinal Fasciculus	9.36	1.41	9.000
	Cingulum	9.37	1.46	9.000
	Corticospinal Tract	9.43	1.46	9.000
	Anterior Limb Of Internal Capsule	9.41	1.45	8.900
Left Hemisphere	Superior Longitudinal Fasciculus	9.21	1.37	8.800
	Cingulum	9.20	1.45	8.800
	Corticospinal Tract	9.22	1.43	8.900
	Anterior Limb Of Internal Capsule	9.28	1.35	8.900
Corpus Callosum	Genu	9.44	1.26	9.200
	Body	9.60	1.37	9.100
	Splenium	9.54	1.23	9.700

In Right Hemisphere, Mean Superior Longitudinal Fasciculus was 9.36 ± 1.41, Cingulum was 9.37 ± 1.46, Corticospinal Tract was 9.43 ± 1.46 and Anterior Limb of Internal Capsule was 9.41 ± 1.45.In Left Hemisphere, Mean Superior Longitudinal Fasciculus was 9.21 ± 1.37, Cingulum was 9.2 ± 1.45, Corticospinal Tract was 9.22 ± 1.43 and Anterior Limb of Internal Capsule was 9.28 ± 1.35. In Corpus Callosum, Mean Genu was 9.44 ± 1.26, Body was 9.6 ± 1.37 and Splenium was 9.54 ± 1.23.

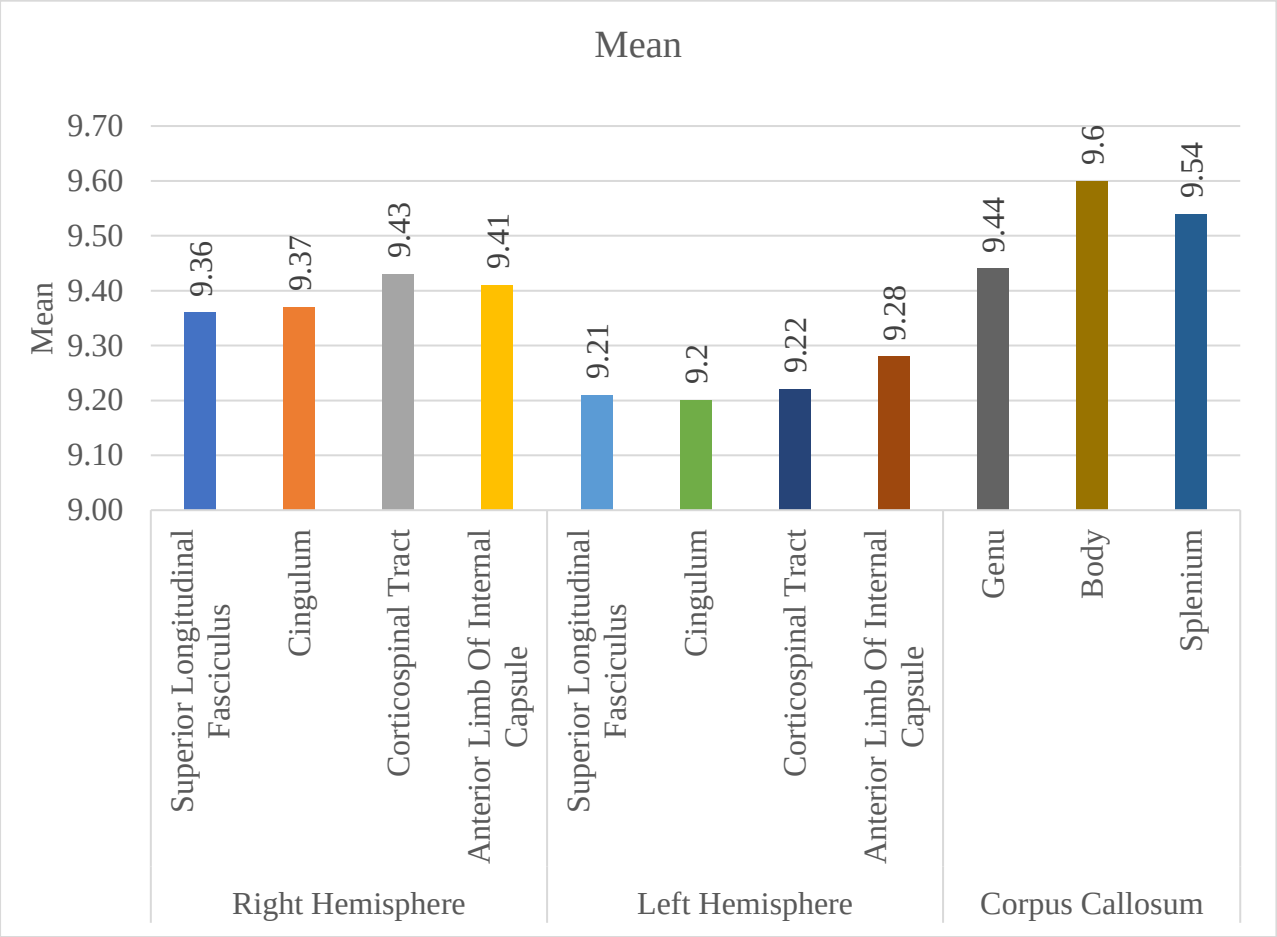

Figure 9: Bar Diagram showing ADC distribution on Right and Left Hemisphere and Corpus Callosum

Table 4: Correlation between Age and ADC in Right hemisphere

		Age (years)
Age (years)	Pearson Correlation	1
	P value	
	N	49
Superior Longitudinal Fasciculus	Pearson Correlation	0.839**
	P value	<0.001*
	N	49
Cingulum	Pearson Correlation	0.829**
	P value	<0.001*
	N	49
Corticospinal Tract	Pearson Correlation	0.861**
	P value	<0.001*
	N	49
Anterior Limb of Internal Capsule	Pearson Correlation	0.842**
	P value	<0.001*
	N	49

There was significant positive Correlation Distribution of Age and ADC of Right hemisphere distribution. With increase in Age there was increase in Superior Longitudinal Fasciculus, Cingulum, Corticospinal Tract and Anterior Limb of Internal Capsule ADC Values and vice versa.

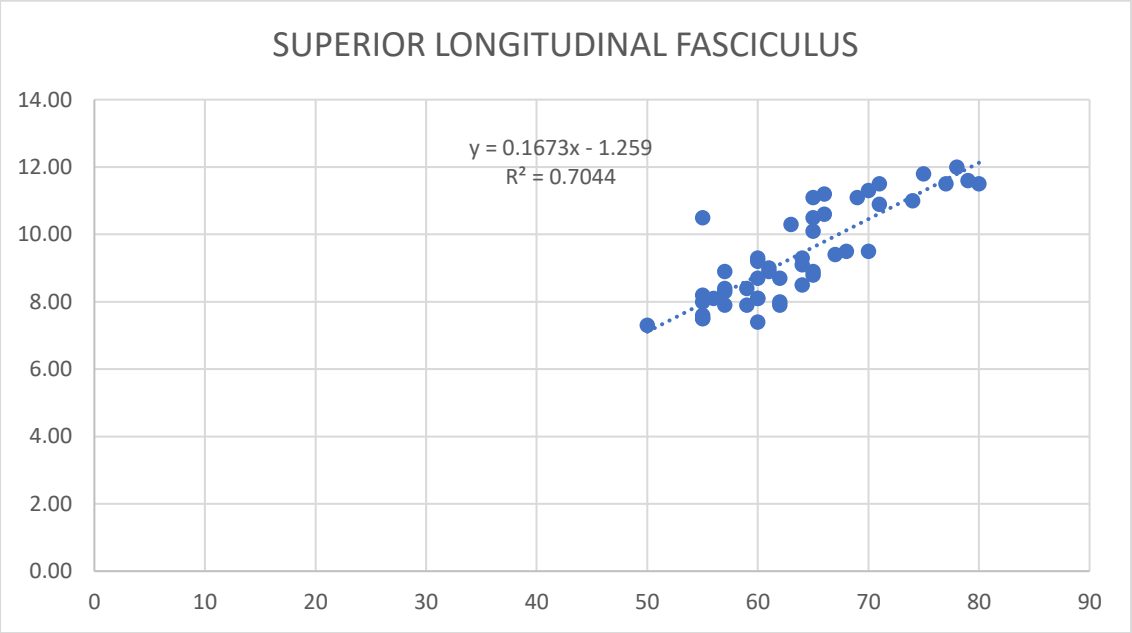

Figure 10: Scatter Plot showing Positive Correlation between Age and ADC of Superior Longitudinal Fasciculus on Right hemisphere.

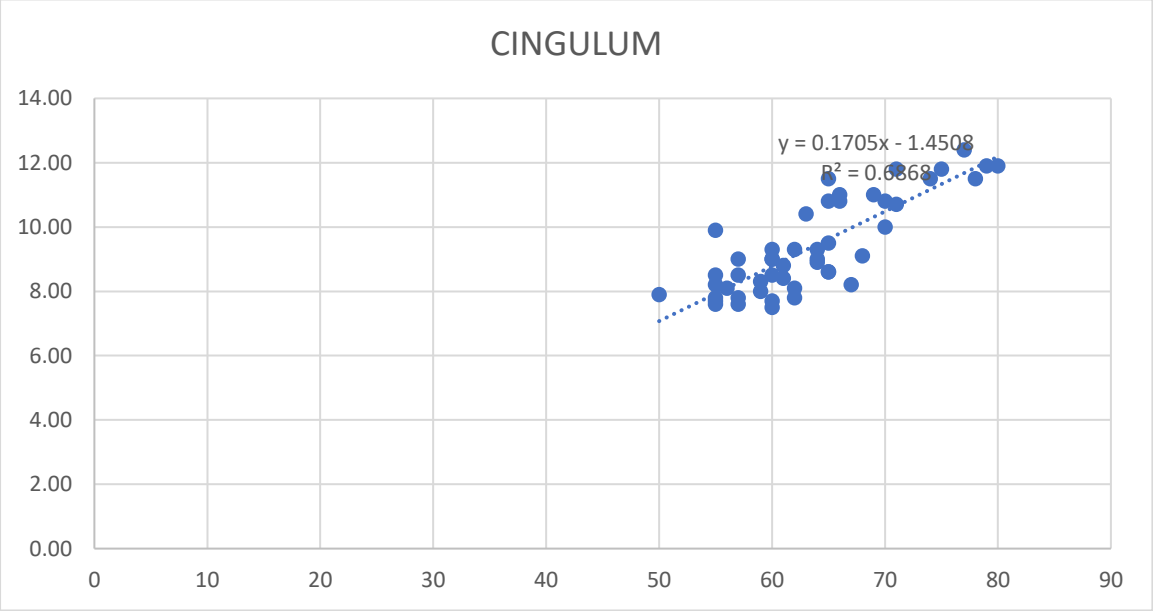

Figure 11: Scatter Plot showing Positive Correlation between Age and ADC of Cingulum on Right hemisphere.

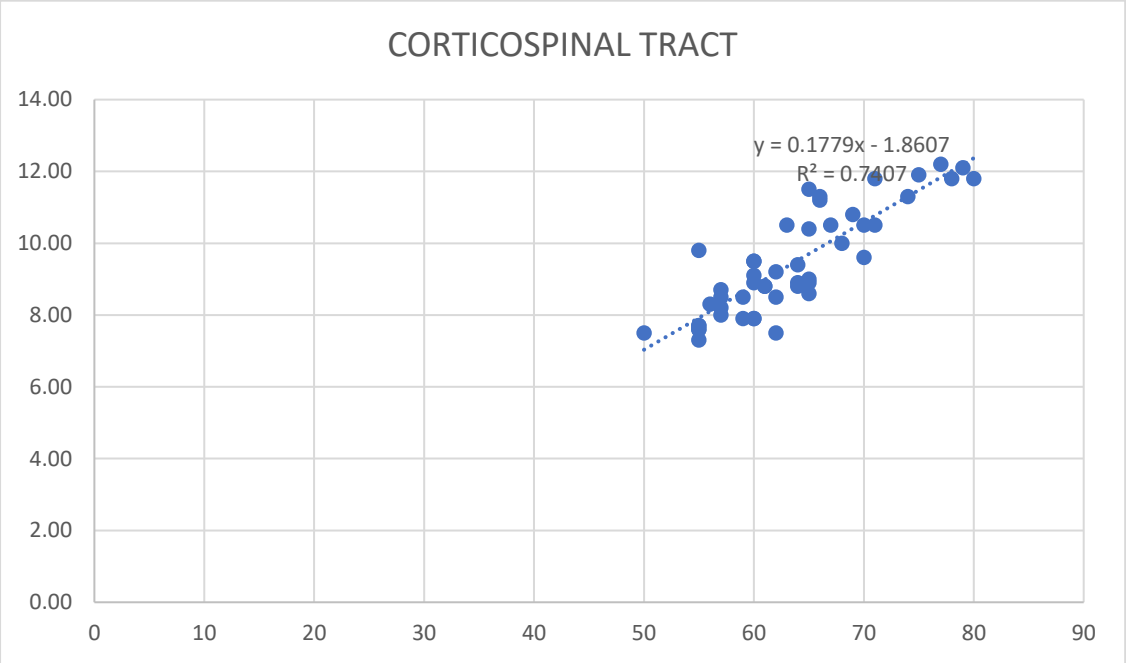

Figure 12: Scatter Plot showing Positive Correlation between Age and ADC of Corticospinal tract on Right hemisphere.

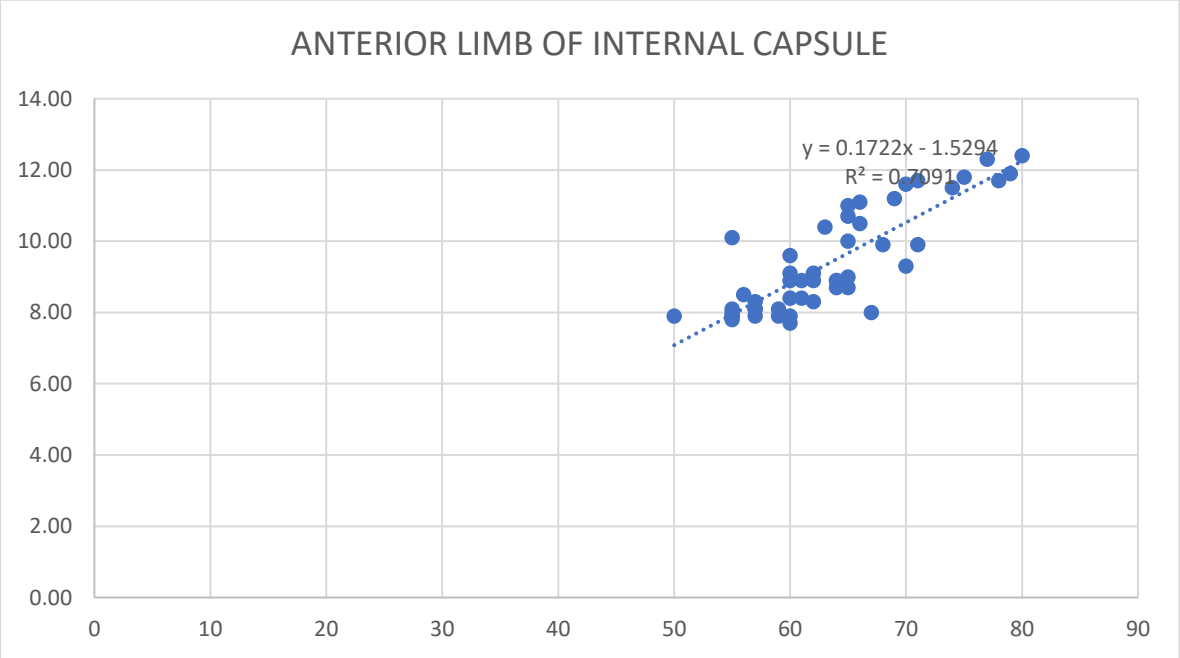

Figure 13: Scatter Plot showing Positive Correlation between Age and ADC of Internal Capsule on Right hemisphere.

Table 5: Correlation between Age and ADC in Left hemisphere

		Age (years)
Age (years)	Pearson Correlation	1
	P value	
	N	49
Superior Longitudinal Fasciculus	Pearson Correlation	0.854**
	P value	<0.001*
	N	49
Cingulum	Pearson Correlation	0.806**
	P value	<0.001*
	N	49
Corticospinal Tract	Pearson Correlation	0.856**
	P value	<0.001*
	N	49
Anterior Limb of Internal Capsule	Pearson Correlation	0.808**
	P value	<0.001*
	N	49

There was significant positive Correlation Distribution of Age and ADC of Left hemisphere. With increase in Age there was increase in Superior Longitudinal Fasciculus, Cingulum, Corticospinal Tract and Anterior Limb of Internal Capsule ADC Values and vice versa.

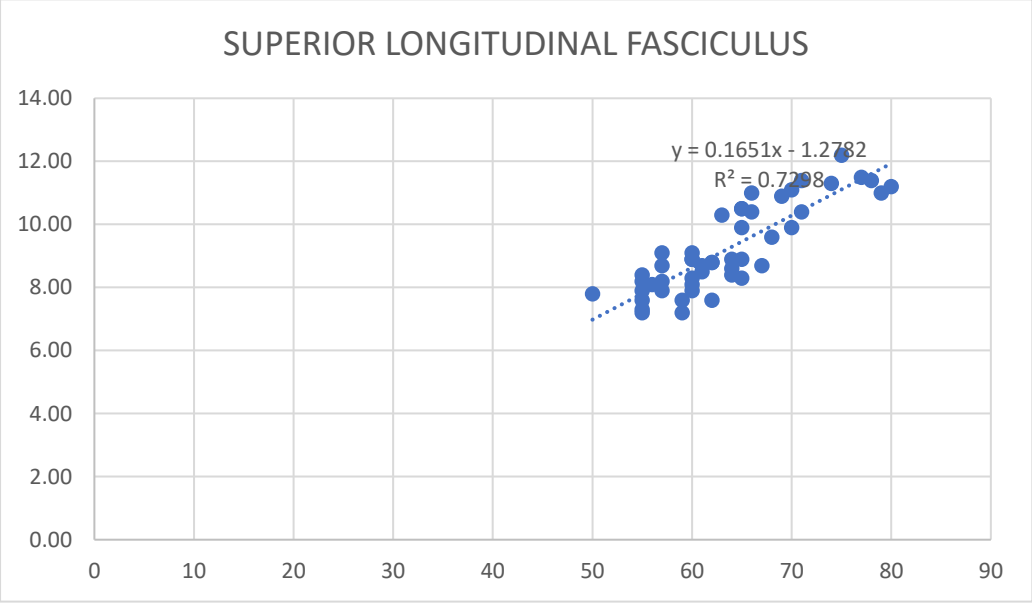

Figure 14: Scatter Plot showing Positive Correlation between Age and ADC of Superior Longitudinal Fasciculus on Left hemisphere.

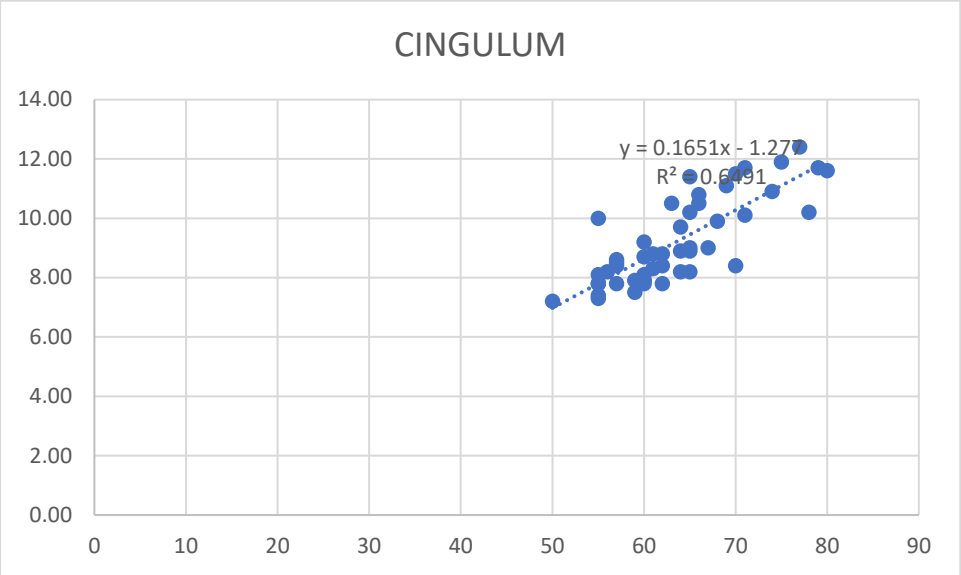

Figure15: **Scatter Plot showing Positive Correlation between Age and ADC of Cingulum on Left hemisphere.**

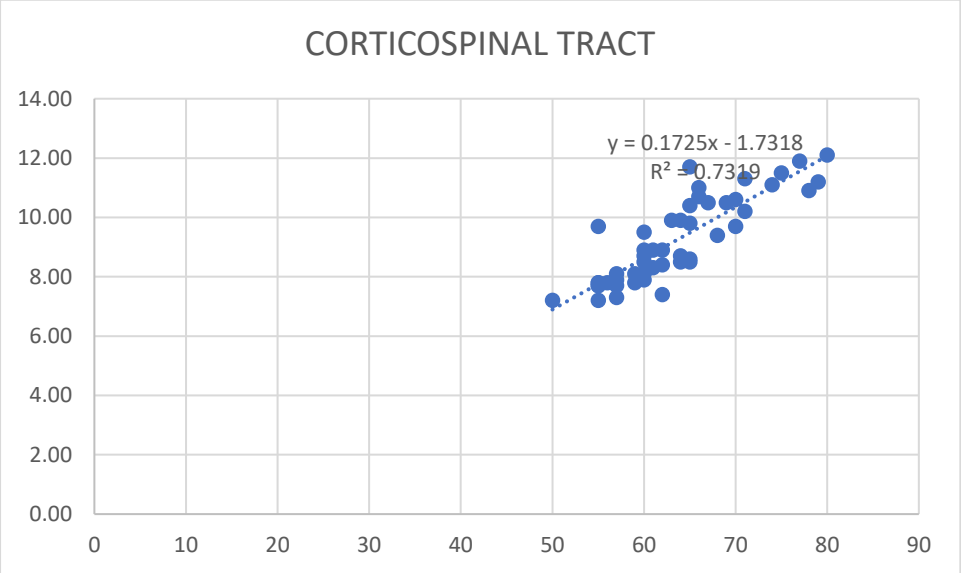

Figure 16: **Scatter Plot showing Positive Correlation between Age and ADC of Corticospinal tract on Left hemisphere.**

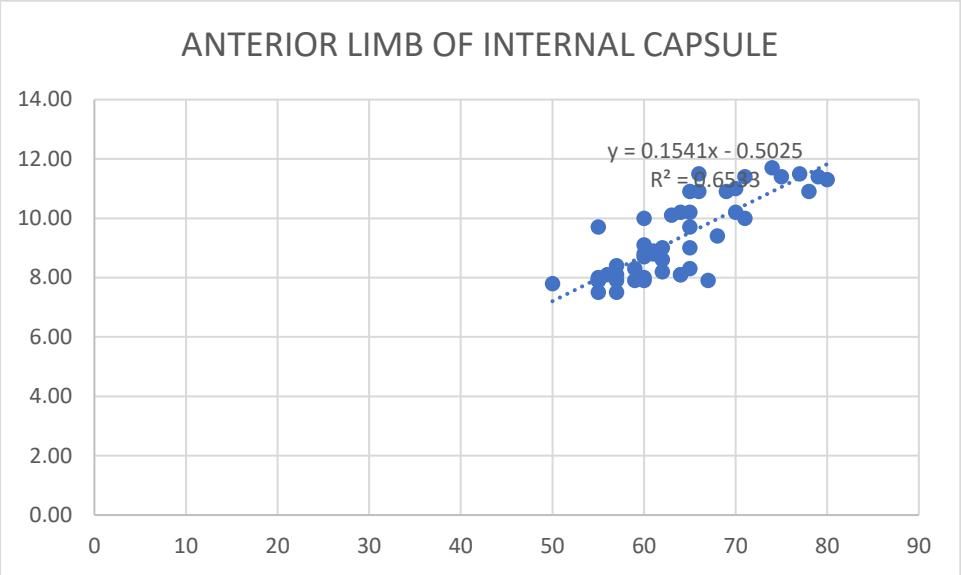

Figure 17: Scatter Plot showing Positive Correlation between Age and ADC of Anterior limb of internal capsule on Left hemisphere.

Table 6: Correlation between Age and ADC values of Corpus Callosum

		Age (years)
Age (years)	Pearson Correlation	1
	P value	
	N	49
GENU	Pearson Correlation	0.816**
	P value	<0.001*
	N	49
BODY	Pearson Correlation	0.747**
	P value	<0.001*
	N	49
SPLENIUM	Pearson Correlation	0.799**
	P value	<0.001*
	N	49

There was significant positive Correlation Distribution of Age and ADC of Corpus Callosum.

With increase in Age there was increase in ADC of Genu, Body and Splenium and vice versa.

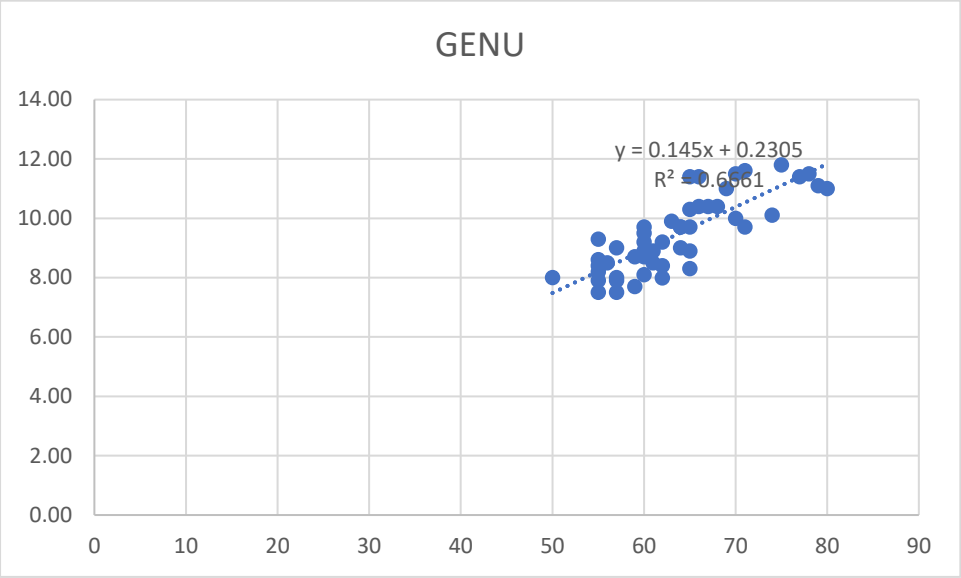

Figure 1: Scatter plot showing Positive Correlation between Age and ADC value of Genu Corpus Callosum

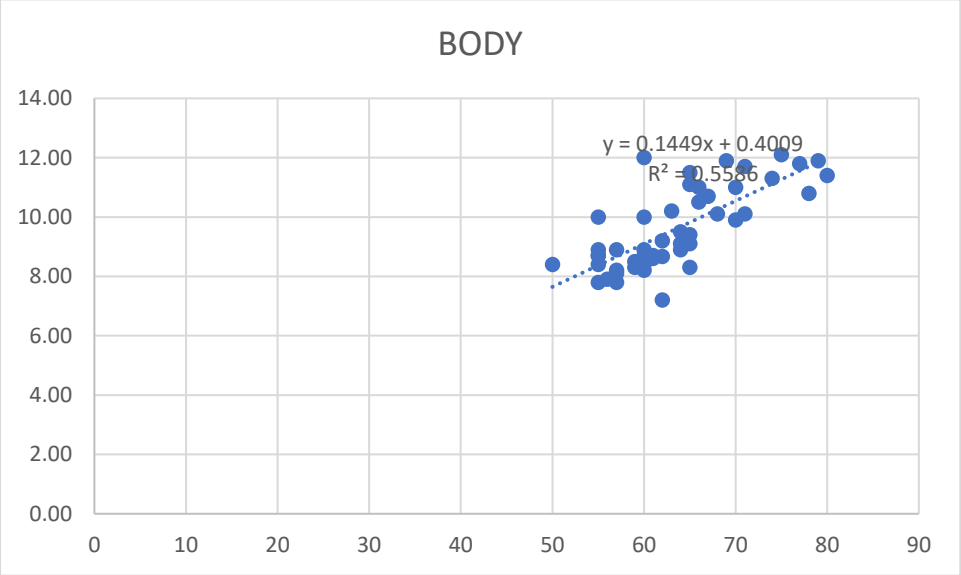

Figure 2: Scatter plot showing Positive Correlation between Age and ADC value of Body Corpus Callosum

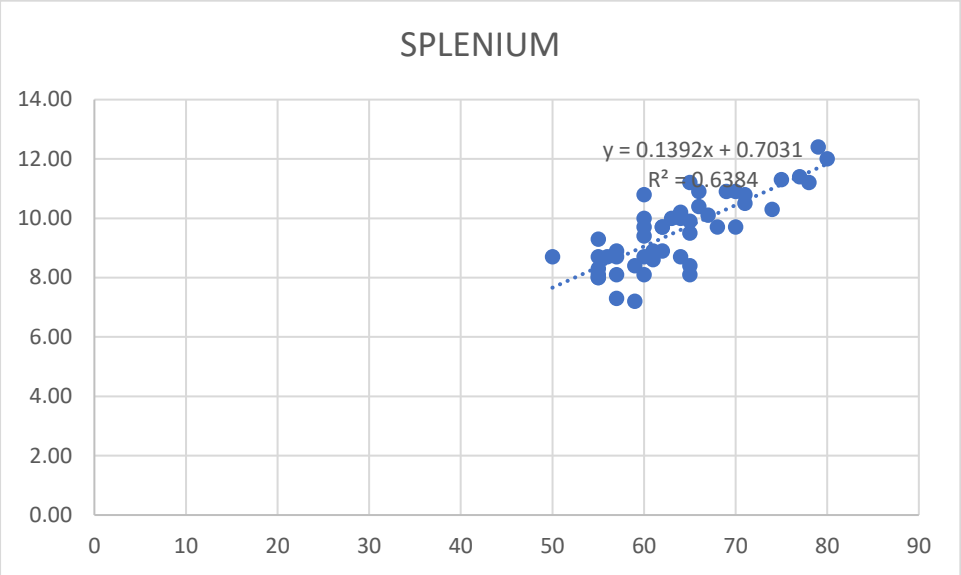

Figure 20: Scatter plot showing Positive Correlation between Age and ADC value of Spleium Corpus Callosum

Table 7: Correlation between Age and FA Values in Right hemisphere

		Age
Age	Pearson Correlation	1
	P value	
	N	49
Superior Longitudinal Fasciculus	Pearson Correlation	-0.666**
	P value	<0.001*
	N	49
Cingulum	Pearson Correlation	-0.646**
	P value	<0.001*
	N	49
Corticospinal Tract	Pearson Correlation	-0.776**
	P value	<0.001*
	N	49
Anterior Limb of Internal Capsule	Pearson Correlation	-0.730**
	P value	<0.001*
	N	49

On Right side there was a significant negative Correlation between Age and FA of Superior Longitudinal Fasciculus, Cingulum, Corticospinal Tract and Anterior Limb of Internal Capsule.

I.e. with increase in age there was decrease in FA Values of Superior Longitudinal Fasciculus, Cingulum, Corticospinal Tract and Anterior Limb of Internal Capsule and vice versa.

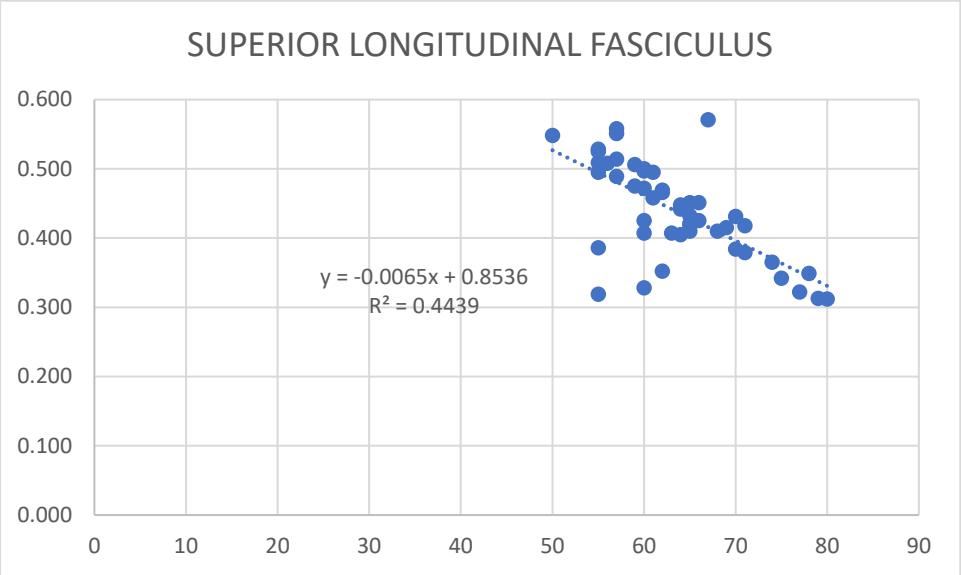

Figure 21: Scatter plot showing Correlation Distribution of Age and Superior Longitudinal Fasciculus of FA of Right hemisphere

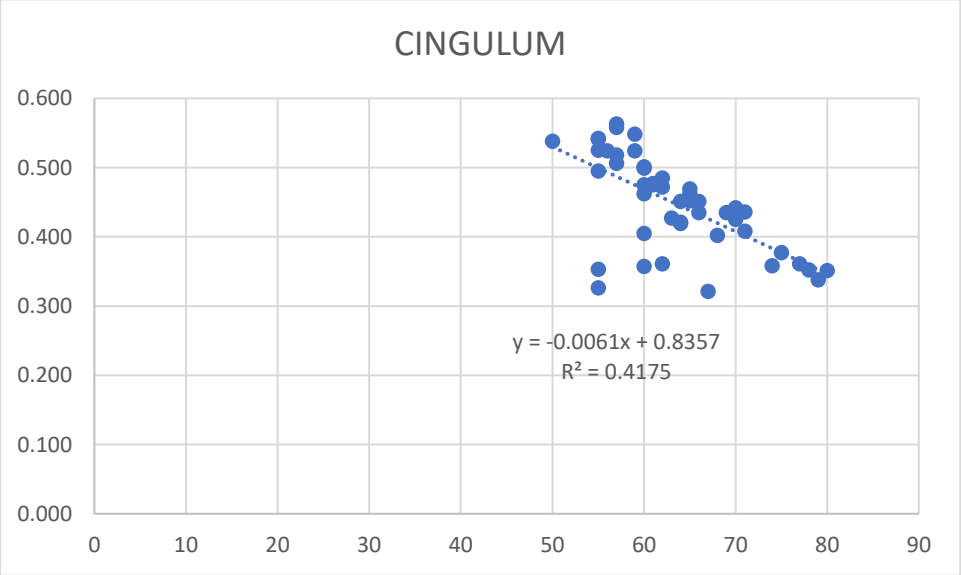

Figure 22: Scatter plot showing Correlation Distribution of Age and Cingulum of FA of Right hemisphere

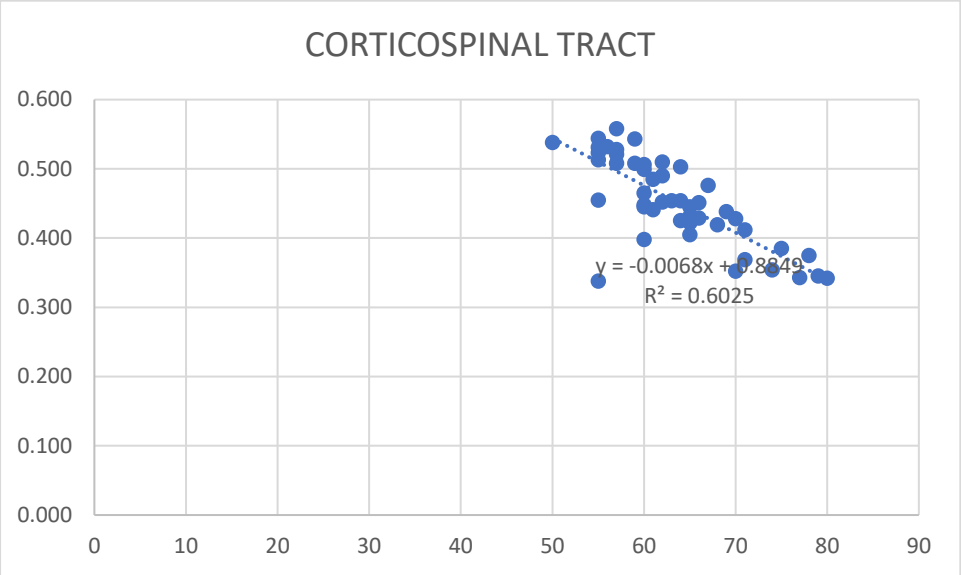

Figure 23: Scatter plot showing Correlation Distribution of Age and Corticospinal Tract of FA of Right hemisphere

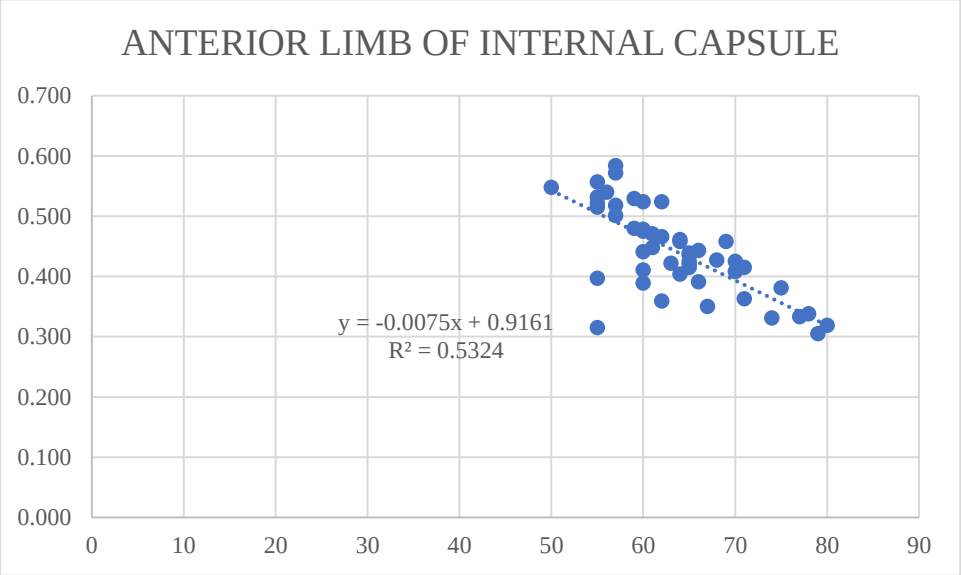

Figure 24: Scatter plot showing Correlation Distribution of Age and Anterior limb of internal capsule of FA of Right hemisphere

Table 8: Correlation between Age and FA in Left hemisphere

		Age
Age	Pearson Correlation	1
	P value	
	N	49
Superior Longitudinal Fasciculus	Pearson Correlation	-0.746**
	P value	<0.001*
	N	49
Cingulum	Pearson Correlation	-0.682**
	P value	<0.001*
	N	49
Corticospinal Tract	Pearson Correlation	-0.813**
	P value	<0.001*
	N	49
Anterior Limb of Internal Capsule	Pearson Correlation	-0.772**
	P value	<0.001*
	N	49

On Left side there was a significant negative Correlation between Age and FA of Superior Longitudinal Fasciculus, Cingulum, Corticospinal Tract and Anterior Limb of Internal Capsule.

I.e. with increase in age there was decrease in FA Values of Superior Longitudinal Fasciculus, Cingulum, Corticospinal Tract and Anterior Limb of Internal Capsule and vice versa.

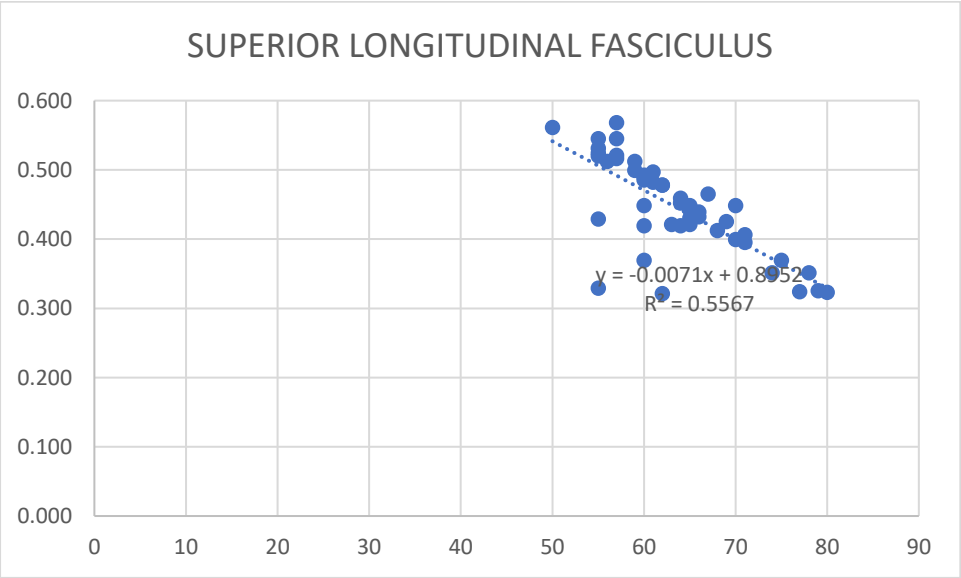

Figure 25: Scatter plot showing Correlation Distribution of Age and Superior Longitudinal Fasciculus of FA of Left hemisphere

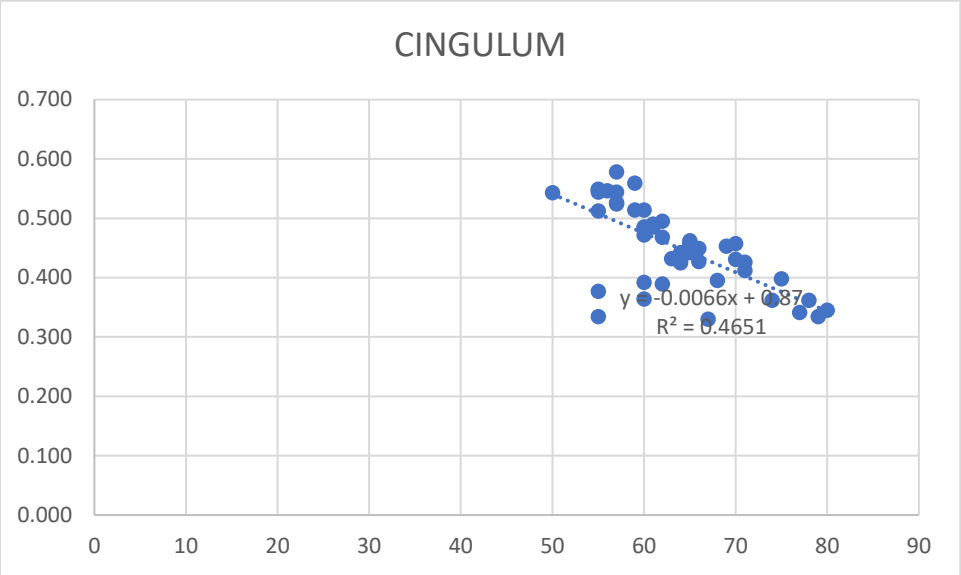

Figure 26: Scatter plot showing Correlation Distribution of Age and Cingulum of FA of Left hemisphere

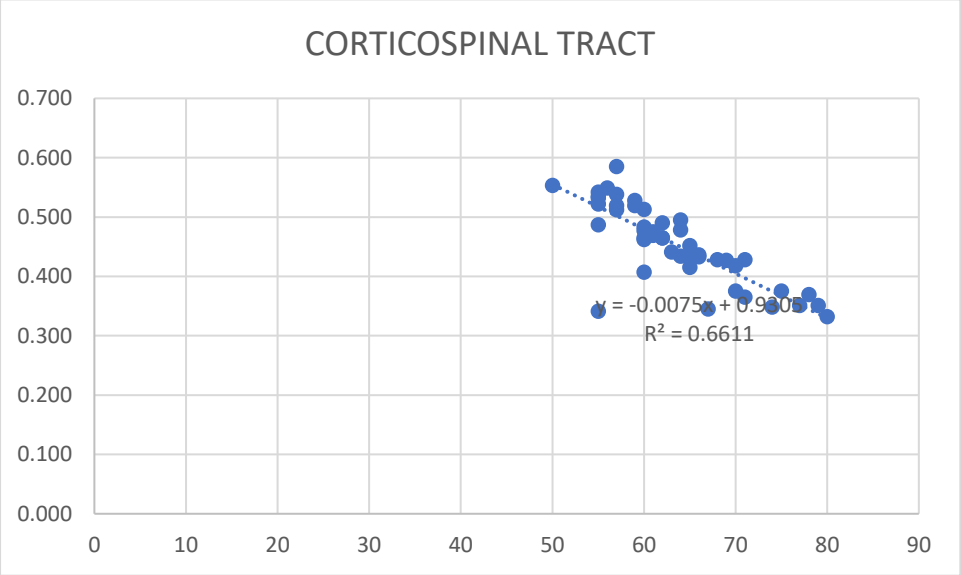

Figure 27: Scatter plot showing Correlation Distribution of Age and Corticospinal Tract of FA of Left hemisphere

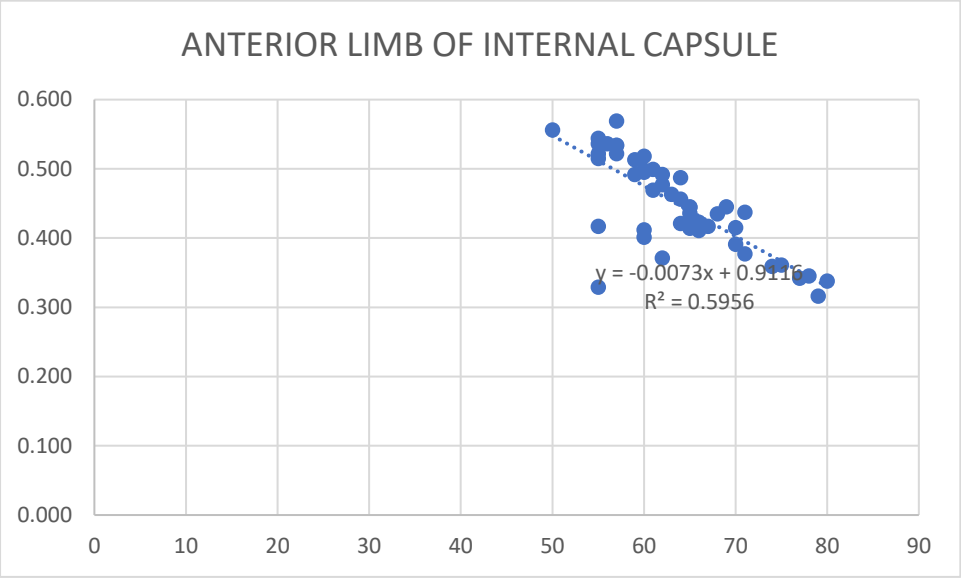

Figure 3: Scatter plot showing Correlation Distribution of Age and Anterior limb of internal capsule of FA of Left hemisphere

Table 9: Correlation between Age and FA values in Corpus Callosum

		Age
Age	Pearson Correlation	1
	P value	
	N	49
Genu	Pearson Correlation	-0.661**
	P value	<0.001*
	N	49
Body	Pearson Correlation	-0.830**
	P value	<0.001*
	N	49
Splenium	Pearson Correlation	-0.796**
	P value	<0.001*
	N	49

There was significant negative Correlation between Age and FA Genu, Body and Splenium of Corpus Callosum.

I.e. with increase in age there was decrease in FA Values of Genu, Body and Splenium of Corpus Callosum and vice versa.

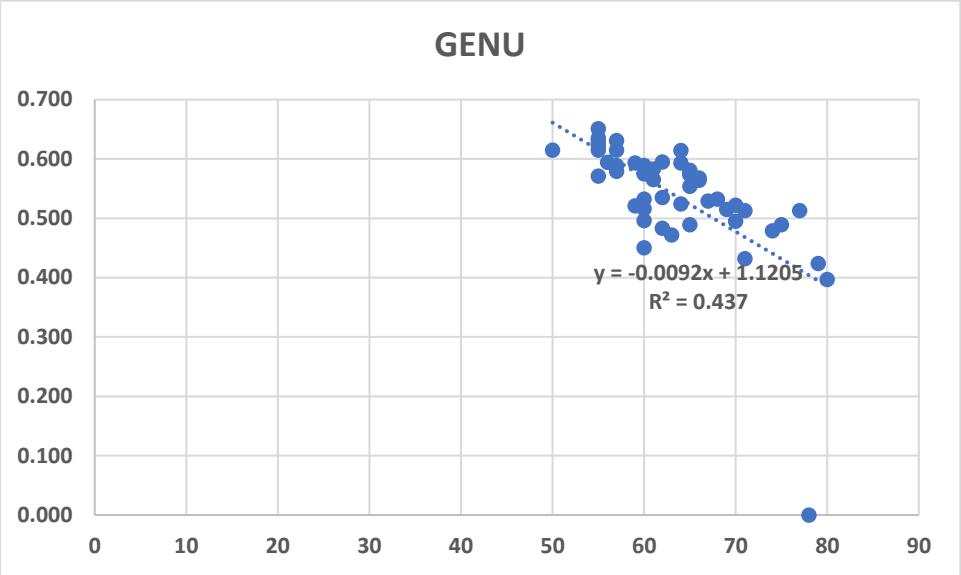

Figure 4: Correlation Distribution of Age and Genu Corpus Callosum of Left hemisphere distribution.

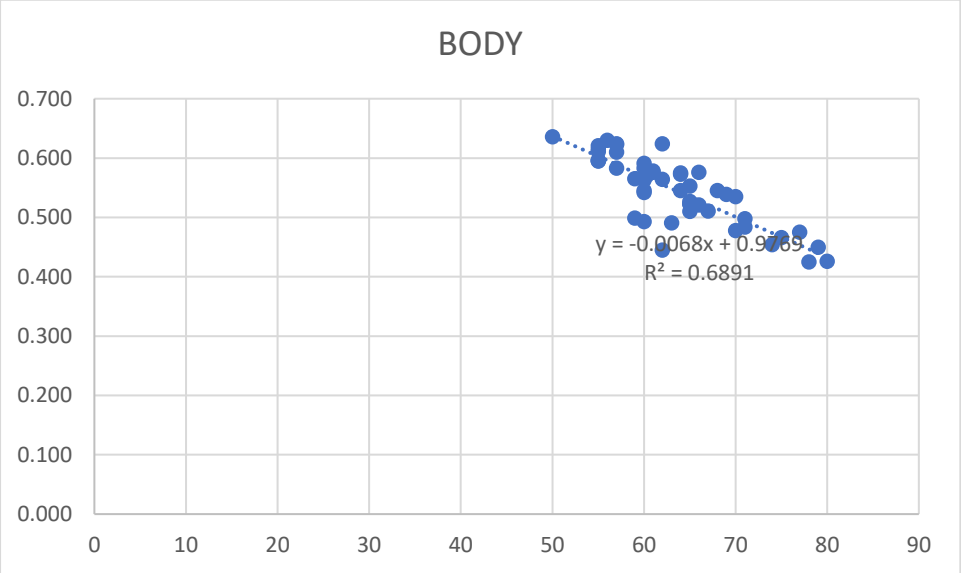

Figure 30: Correlation Distribution of Age and Body Corpus Callosum of Left hemisphere distribution

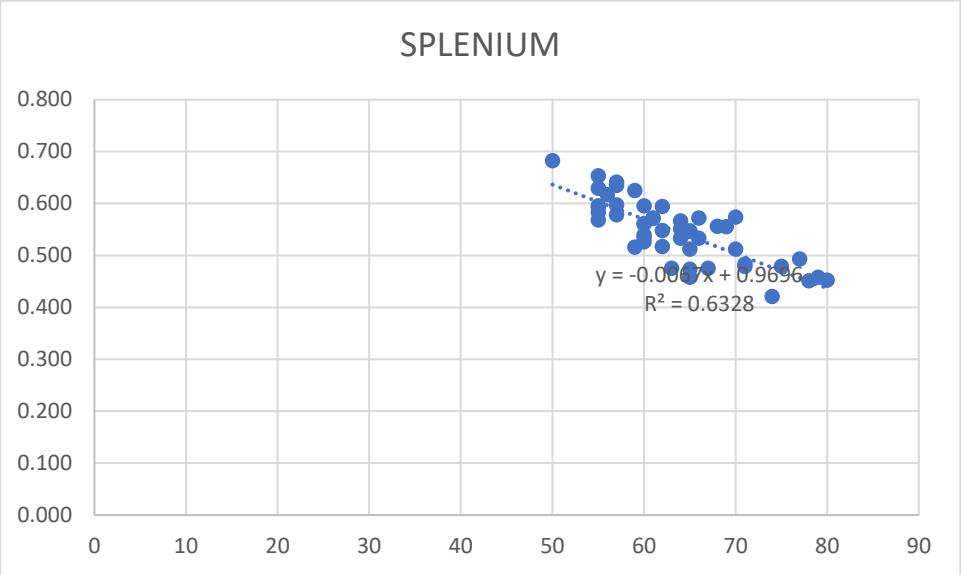

Figure 31: Correlation Distribution of Age and Splenium Corpus Callosum of Left hemisphere distribution

Discussion

Out of the 49 individuals we had examined, 27 (55.1%) were male and 22 (44.9%) were female. Majority of the individuals were between 55 and 70 years of age.

Coming to the individual white matter tracts, it was seen that the superior longitudinal fasciculus in both hemispheres showed statistically significant rise in mean ADC and reduction in Fractional anisotropy values with increase in age, showing a strong positive Pearson's correlation of age and ADC and a strong negative correlation of age and FA values. A similar trend was also observed in the mean ADC values and Fractional Anisotropy values of the Cingulum, Corticospinal tract and Anterior limb of the internal capsules of both hemispheres and the genu, body and splenium of the corpus callosum.

The above findings suggest that all the visualised white matter tracts show changes in white matter microstructure and resultant loss of their integrity when an individual ages. This finding of global loss of white matter integrity was in agreement with a study done on 38 individuals by D.H. Salat et al. [(1)]which also showed global loss of integrity of white matter tracts. However, our study showed uniform loss in white matter integrity across all the fibers in both hemispheres and corpus callosum which was in contrast to the above mentioned study, which showed notable loss of integrity in the posterior limb of the internal capsule and the anterior fibers of the corpus callosum.

It was also observed that the mean ADC values of the right hemisphere was higher than the left cerebral hemisphere. Hence there was an asymmetry of white matter integrity, with fibers in the dominant hemisphere (left) being less susceptible to loss of integrity. This finding was in agreement with a study by H Takao[(2)] and the above study.

The fibers of the corpus callosum showed the highest mean ADC values, when compared to the association and projection fibers which was in agreement with the above study.

While comparing our study with a study involving 79 individuals above 55 years of age by Lebel et al. [(3)], our findings pertaining to the relationship of ADC and FA values of all the white matter tracts with age were in agreement with their findings.

In contrast to our study, a study by Sullivan et. al[4]in 2010 demonstrated that the changes in the corpus callosum with respect to aging was isolated to the premotor sections unlike our study which showed loss of integrity in the genu, body and splenium of the corpus callosum.

The potential concern related to our study is the partial volume effect, influenced by the shape and size of the tracts. Partial voluming with the adjacent CSF or grey matter voxels bring down the FA values near the edges of the tracts, thereby: i. excluding them from reading if their value drops below the threshold for tractography resulting in higher FA valuesand ii. causing reduction in the overall FA value or increase in the overall Mean Diffusivity.

Also, diffusion tensor imaging is prone to artifacts. Diffusion tensor imaging is extremely sensitive to patient movement and minimal movement may result in artifacts.

The basis of diffusion tensor imaging which relies on the calculation of the principal eigen vector to identify the direction of the fibers cannot be used for fibers that intersect each other. This may result in false values or additional tracts with no anatomic correlation.

Another limitation of this study was the long-time involved in calculating the tensor parameters for each individual fiber which involves placement of adequate ROI for each fiber tract, requiring repeated trial and error in spite of trying to use a uniform protocol for placement of the ROI.

Pertaining to future studies, using a larger sample size and doing a meta-analysis of multiple studies across various ethnic groups and ages, it is possible to create an age-wise normative value for fractional anisotropy and average ADC.

Conclusion

1.Diffusion tensor imaging Tractography of 11 major white matter tracts in individuals aged above 55 years of age showed consistent reduction with fractional anisotropy and increase in Apparent Diffusion Coefficient (Mean diffusivity) with increase in age.

2.The corpus callosalfibers and the fibers within the non-dominant hemispheres have lower Fractional anisotropy and a higher Apparent Diffusion Coefficient when compared to the dominant hemispheres, raising a possibility that the effect of aging on these fibers will be more pronounced.

References:

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4. Sullivan EV, Rohlfing T, Pfefferbaum A. Longitudinal study of callosal microstructure in the normal adult aging brain using quantitative DTI fiber tracking. Dev Neuropsychol. 2010 Jan 1;35(3):233–56.