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A Diffusion Tensor Imaging Study to Estimate Normative Fractional Anisotropy Values in Different Age Groups of Normal Brain White Matter

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Abstract: Background and purpose: DTI is one of the most sophisticated and relatively new neuroimaging technique that allows in vivo quantification of water diffusion properties. It can also assess the integrity of white matter microstructure. In our study, we investigated normative data from a large number of healthy participants in three different age groups to examine the developmental trends in diffusion tensor imaging during this white matter maturation period.

Title: A Diffusion tensor imaging study to estimate normative Fractional anisotropy values in different age groups of normal brain white matter.

Materials and Methods: DTI data in 85 healthy subjects in three different age groups were analyzed retrospectively using 1.5 T MRI system. FA values were measured at the corpus callosum, centrum semiovale and pons using fixed ROI technique with a b-value of 1000 s/mm^2 and TE = 100 millisecond.

Results: FA values showed regional variation between different white matter regions of the brain namely the corpus callosum, centrum semiovale and pons. The highest and lowest values found varied with each region studied in the brain white matter.

Conclusions: In a normal adult population FA values of the brain white matter showed regional variation. These points should be taken into consideration while interpretation in clinical patients. We demonstrate a relationship between FA and normal ageing which is a key feature to detect early white matter changes. We propose that FA may provide an early means for the detection of age-related change and suggest a need for elaborate data to explore this association with comparison with a diseased population.

Keywords: FA, fractional anisotropy; DTI, diffusion tensor imaging; b-value; TE, echo time, ms, milli second, MRI, diffusion imaging.

Discloser: This paper was presented by Mr. Rahul P Kotian[1*] at the 3rd International Conference on Global Issues in Multidisciplinary Academic Research (GIMAR-February 01-02, 2017) at Tokyo, Japan.

1. INTRODUCTION

Diffusion tensor imaging (DTI) is a rapidly developing and relatively new method for evaluation of brain white matter integrity as well as for identifying focal lesions in white matter tract in both clinical and research applications. A detailed and age specific knowledge with normal and regional variation of fractional anisotropy (FA) values between different white matter structures in the brain is very important when DTI measurements are correlated for treatment and diagnosis in clinical patients. DTI is the sole imaging technique which is highly sensitive to Brownian motion of water as it diffuses in the brain. Diffusion which equally occurs in all directions is said to be isotropic compared to its counterpart which is restricted by a barrier where it is said to be anisotropic. The most common diffusion parameter derived from DTI is Fractional anisotropy (FA) (Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996). FA is a measure of the directionality of diffusion with values ranging from 0 to 1, where 0 represents totally isotropic diffusion and 1 represents highly anisotropic diffusion respectively. Despite the widespread use of DTI imaging techniques, there are still very few reports that have assessed normative FA values (Lee, Danielian, Thomasson, & Baker, 2009)(Huisman, Loenneker, Barta, Bellemann, Hennig, Fischer, & Il'yasov, 2006)(S Hunsche, Moseley, Stoeter, & Hedehus, 2001)(Snook, Paulson, Roy, Phillips, & Beaulieu, 2005)(van Norden et. al., 2012)(Sullivan, Rohlfing, & Pfefferbaum, 2010) (Treit, Chen, Rasmussen, & Beaulieu, 2014)(Sexton et. al., 2014) (Williams, Paul, Clark, & Gordon, 2007) (Paper, 2015) and (Jun et. al., 2013).

Objective of the Study

The main aim of our study is to estimate and report normative FA values of brain white matter in the genu, body and splenium of the corpus callosum, right and left centrum semiovale and pons respectively in a wider age group of young adult population to late adult population. The brain white matter may experience changes in myelination and other changes as age progresses. This study will add an insight on the behaviour of FA values in different age groups in a large number of healthy participants which is lacking in the current literature.

Materials and Methods

Subjects: The present study included 85 healthy participants without any neurological brain abnormalities in three different age groups of 18-40 mean age (26.66), 17 male, 16 female; 41-60 mean age (47.79) 14 male, 15 female and 61-75 mean age –67.13; 11 male, 12 female. They were recruited after a preliminary screening and who did not have any neurological abnormalities. They were excluded if they had structural brain abnormalities and space occupying lesions seen on conventional MR brain imaging sequence. They were included if they have no contraindications for MRI and sufficient co-operation without claustrophobia to participate in the study. The Kasturba Hospital, Manipal institutional committee granted ethical approval.

Study Procedure: Healthy participants without any neurological abnormalities were included in the study after an oral interview and by obtaining written informed consent. A double check confirmation was made to rule out neurological abnormalities by a routine MR brain imaging sequence Flair axial and T1 Sagittal sections. The data collection was done at the Department of Radiodiagnosis and Imaging, Kasturba Hospital, Manipal using a 1.5 Tesla Superconducting Philips MR system. 85 participants were scanned using 1.5T MRI unit and FA values were obtained at three different regions of normal brain white matter of the corpus callosum, right and left centrum semiovale and right and left pons. For corpus callosum the sagittal section was chosen to obtain FA values while the axial section was used to obtain FA values for both centrum semiovale and pons. A fixed *b*-value of 1000 s/mm^2 and TE = 100 millisecond were used to obtain FA values.

Study Design: Cross-sectional study.

Instrument: MRI data was acquired using a Philips MRI 1.5T Achieva, class IIA series, 16 channel system.

Image Acquisition: Healthy participants were scanned with a 1.5-T 5T Achieva, class IIA series, 16 channel system for approximately 15 minutes for anatomical and DTI imaging**.** The DTI data was acquired using a single shot echo-planar imaging sequence with 2 mm slice thickness, no inter-slice gap (interleaved acquisition), TR = 8602 ms, TE = 100 ms, field-of-view 224 mm, 15 non collinear diffusion-sensitizing gradient directions with diffusion sensitivity $b = 1000$ s/mm^2, and a matrix of 112×108. The entire brain was included during MRI image acquisition. Total DTI acquisition time was approximately 5.06 min with 40 contiguous axial slices for full brain coverage. A routine flair axial and T1 sagittal sequence was also acquired for anatomy correlation while computing FA values. The white matter areas which were assessed were the corpus callosum, right and left centrum semiovale and right and left pons which is shown in Figure 1-3.

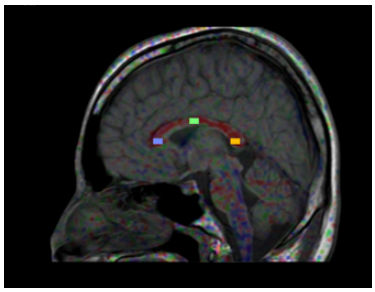


Figure 1: ROI placement at the Corpus callosum

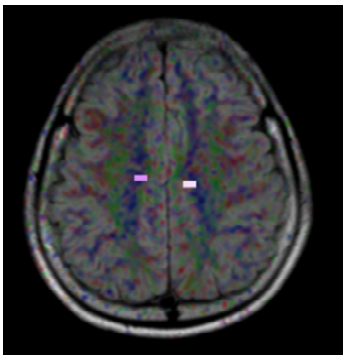


Figure 2: ROI placement at the right and left Centrum Semiovale

Region-of-interest: A fixed ROI technique was used to estimate fractional anisotropy values using a rectangular ROI with eight voxel size at the following white matter regions of the brain: corpus callosum (three regions namely genu, body and splenium), centrum semiovale (two regions namely left and right), and pons (2 regions namely left and right).

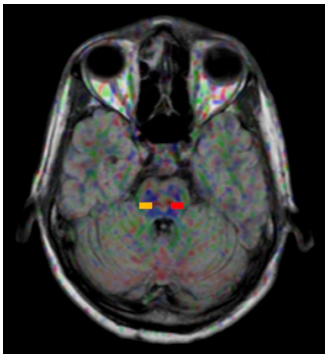


Figure 3: ROI placement at the right and left Pons

Image Analysis: The DTI image analysis was done on the Philips extended workstation using the fixed ROI technique. The DTI image sets were loaded along with sequence Flair axial and T1 Sagittal for anatomy correlation to visualize and calculate fractional anisotropy values.

Statistical Analysis: Statistical analysis was performed using SPSS software.

Descriptive Statistics: For assessment of normal regional values, the results of measurements were averaged. Mean, standard deviations (SDs), Mean and SD fixed and lastly Mean±SD for FA values of the studied regions were calculated.

Left/right asymmetry: Left and right FA values were compared using paired t tests (P<0.05>) namely for right and left centrum semiovale and pons respectively. A paired-samples t-test was conducted to compare the left and right side hemispheres in centrum semiovale and pons respectively.

Manova: MANOVA was used to test the difference between age groups and gender across FA values from five regions simultaneously. A significant MANOVA was followed by a one way ANOVA to determine specifically in which group the difference existed.

Results: Table 1 depicts normative FA values in three different age groups of normal brain white matter. When comparing FA in different age groups, decreases in FA was seen in the corpus callosum centrum semiovale and pons (Table 1). To summarize FA values tend to continually decrease from young adulthood to late adulthood and above. Table 3 depicts the total number of participants and gender distribution across different age groups.

Table 1
Mean Regional FA values in age groups 18-40; 41-60 and 61-75 years

White matter region	*Mean ± SD Age group 18-40*	*Mean ± SD Age group 41-60*	*Mean ± SD Age group 61-75*
Genu of CC	0.69 ± 0.10	0.63 ± 0.11	0.59 ± 0.14
Body of CC	0.68 ± 0.10	0.68 ± 0.09	0.65 ± 0.15
Splenium of CC	0.77 ± 0.07	0.77 ± 0.05	0.75 ± 0.08
CS right	0.60 ± 0.08	0.60 ± 0.07	0.58 ± 0.08
CS left	0.64 ± 0.07	0.61 ± 0.06	0.56 ± 0.06
CS[a]	0.62 ± 0.02	0.61 ± 0.01	0.57 ± 0.01
Pons right	0.60 ± 0.08	0.58 ± 0.07	0.55 ± 0.10
Pons left	0.60 ± 0.08	0.58 ± 0.09	0.57 ± 0.09
Pons[a]	0.60 ± 0.00	0.58 ± 0.00	0.56 ± 0.01

CS, centrum semiovale; CS[a] = Left/right combined value is presented for centrum semiovale;
Pons[a] = Left/right combined value is presented for pons

Left/right asymmetry: Table 2 depicts interhemispheric differences calculated using paired *t* test to rule out differences between right and left side of pons and centrum semiovale respectively. Overall, there was very little hemispheric asymmetry in FA in both centrum semiovale and pons. There was no statistically significant difference between right and left side of the centrum semiovale and pons, except for centrum semiovale (right and left) in age group 18-40 (P = 0.037) as shown in Table 2.

Effect of age and gender on FA values: MANOVA revealed that there was statistically significant difference in all the regions between age groups F (14, 146) = 1.858, $p = 0.04$; Wilk's $l = 0.72$]. However, there was no statistically significant difference in gender across all regions F (7, 73) = 0.702, p value = 0.67; Wilk's $l = 0.937$. In order to determine how the regions differed among the age groups, Univariate ANOVA with bonferroni correction was performed and we accepted statistical significance at $p < 0.007$ (0.05/7 = 0.01). We found that there was statistically significant difference in left and right centrum semiovale between the age groups ($p = 0.001$) and in rest of the regions it was found to be insignificant. Further Tukey's HSD post-hoc test was

Table 2
Interhemispheric differences in Centrum Semiovale and Pons (Age groups 18-40; 41-60 and 61-75)

White matter region	Age group 18-40		P value	Age group 41-60		P value	Age group 61-75		P value
	Mean	SD		Mean	SD		Mean	SD	
CS right	0.60	0.07	0.037	0.60	0.06	0.323	0.58	0.08	0.559
CS left	0.64	0.07		0.61	0.06		0.56	0.06	
Pons right	0.60	0.08	0.660	0.58	0.07	0.699	0.55	0.02	0.419
Pons left	0.60	0.67		0.58	0.08		0.57	0.02	

CS, centrum semiovale

performed to identify which of the age groups the left and right centrum semiovale differed. We found that it differed statistically between 18-40 and 60-75 age group ($p < 0.001$) but not between 18-40 & 41-60 ($p = 0.327$) and 41-60 & 61-40 ($p = 0.03$).

We also found the same test analysis when left and right centrum semiovale and pons FA values were averaged. MANOVA revealed that there was statistically significant difference in all the regions between age groups F (10, 150) = 2.09, $p = 0.03$; Wilk's $l = 0.77$]. However, there was no statistically significant difference in gender across all regions F (5,75) = 0.96, p value = 0.45; Wilk's $l = 0.84$. In order to determine how the regions differed among the age groups, Univariate ANOVA with bonferroni correction was performed and we accepted statistical significance at $p < 0.01$ (0.05/5 = 0.01). We found that there was statistically significant difference in average centrum semiovale FA values between the age groups ($p = 0.006$) while rest of the regions it was found to be insignificant. Further Tukey's HSD post-hoc test was performed to identify which of the age groups the average centrum semiovale FA values differed. We found that, it differed statistically between 18-40 and 61-75 age group ($p = 0.005$) but not between 18-40 & 41-60 ($p = 0.571$) and 41-60 & 61-75 ($p = 0.068$). Graphical representation of age effects on FA is shown in Table 3.

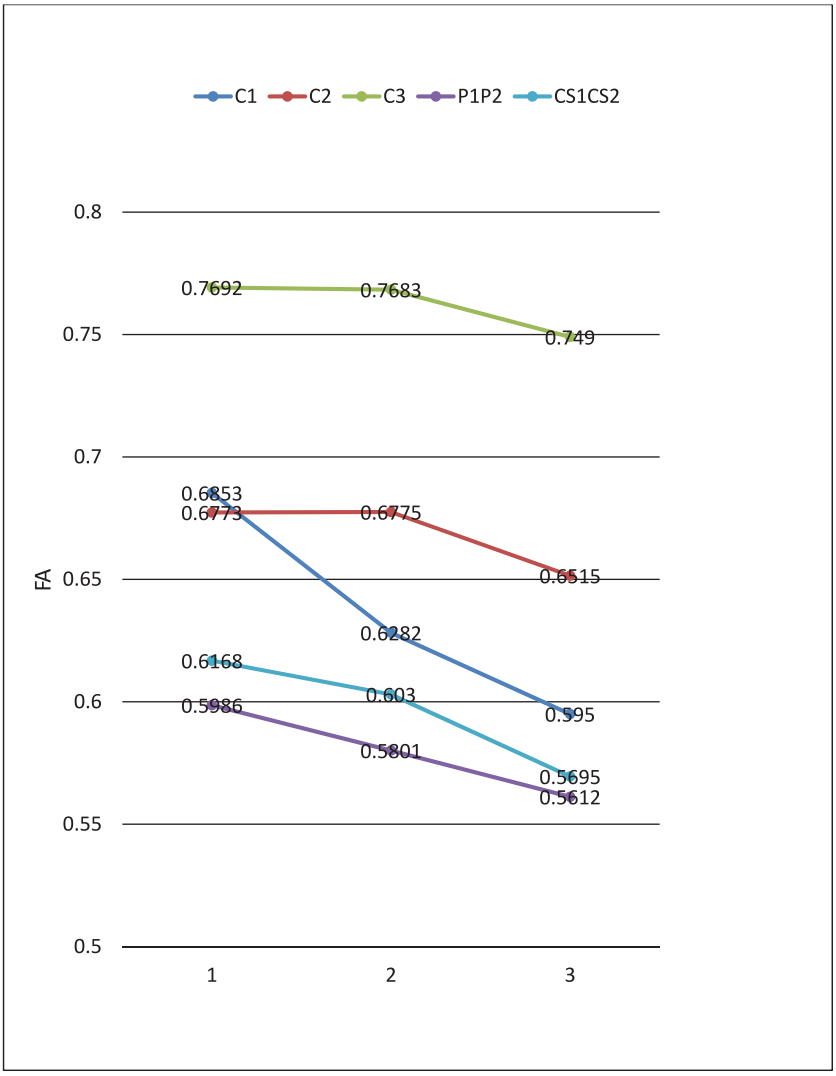
2. DISCUSSION

The changes in DTI derived parameters were studied to find major changes in white matter tracts and study the effects of myelinations and axonal development. We chose to specifically focus on the genu, body and splenium of the Corpus callosum, as it is one of the major and largest interhemispheric connections in the human brain. The corpus callosum is also highly susceptible to ischemic changes and other neurodegenerative abnormalities (Cancelliere et. al., n.d.; Mendez, 2015; De Leon, Urgel, Ed. Cuevas, and Dasalla, 2016). The vast clinical applications and reliability of DTI techniques and FA values in particular are still being studied and at present

Table 3
Participants demographics and Gender distribution across different age groups

Group	Gender	n	%
18-40	Male	17	51.52
	Female	16	48.48
41-60	Male	14	48.28
	Female	15	51.72
61-75	Male	11	47.83
	Female	12	52.17
Total		85	100

Table 4
Age effects on FA



C1-Genu of corpus callosum, C2-Body of corpus callosum, C3-Splenium of corpus callosum, CS1-Right centrum semiovale, CS2-Left centrum semiovale, P1-Right pons and P2-Left pons
1-Age group 18-40 years
2-Age group 41-60 years
3-Age group 61-75 years

only few reports of normative regional FA values are available in literature. Data accumulated from such studies form the basis of DTI region of interest measurements in clinical patients. It is always wise to be aware of regional variation in FA values based on normal ageing when DTI is performed in clinical patients. FA is considered as the most comparable DTI measurements across different MRI magnets (Fox et. al., 2012). This study has tried to present normative FA values using a fixed combination of *b*-value of 1000 and TE = 100 millisecond; as these two parameters quantitatively affect FA values and normative values were obtained in three different age groups of 18-40, 41-60 and 61-75 respectively. Current study was conducted on the normal brain white matter of the corpus callosum (genu, body and splenium), centrum semiovale and pons. Our study results add to previously published studies of regional FA values and measurement reliability in the normal population of normal brain white matter in the corpus callosum, centrum semiovale and pons.

The regional variation seen in healthy brain white matter exists and is well known. FA is one of the scalar indices of DTI and is used as an indicator of white matter tissue integrity (Virta, Barnett, & Pierpaoli, 1999). A paired *t* test was done in the current study to rule out interhemispheric differences between right and left centrum semiovale and pons respectively. Overall there was no statistical significant difference found between the right and left hemispheres but in age group 18-40 a statistical difference was found between right and left centrum semiovale ($p = 0.037$). This finding might be a mere difference in the hemispheres as this age group included subjects from young adulthood and we are not able to draw a conclusive finding from the difference obtained. Moreover we did not see any differences in both hemispheres in centrum semiovale and pons in other age groups namely 41-60 and 61-75. In the current study FA was slightly greater on the left centrum semiovale in the 18-40 age group and 41-60 age group respectively.

This study has formulated regional normative FA values in the brain white matter regions of the corpus callosum (genu, body and splenium), right and left centrum semiovale and pons respectively. A noteworthy observation was a slight and a gradual decrease in FA values across all white matter regions studied as age progresses which is a very important indicator in detecting brain white matter abnormalities which is in line studies conducted by (Haydee Guadalupe Garcia-Lazaro, Ivonne Becerra-Laparra, David Cortez-Conradis, & Ernesto Roldan-Valadez, MD, MSc, PhDa, n.d.); (Imperati et. al., 2011); (Löbel et. al., 2009); and (Williams et al., 2007). This finding and association of FA values among all different age groups is not available in literature which is one of the strengths of our study. MANOVA was used to test the difference between age groups across FA values from five regions simultaneously which showed FA values in all white matter regions studied decreased as age increased. Generally high FA values are found where dense packing of fibers are present and it also depends upon the orientation of the fibers. Corpus callosum is a tightly packed thick bundle of fibers which connects both the cerebral hemispheres, hence FA values are expected to be slightly higher than other white matter structures. In our study we found higher FA values in the posterior part of the corpus callosum (splenium) compared to anterior parts which is in line with studies conducted by (Chepuri et. al., 2002) age group 23-81, (Löbel et. al., 2009) age group 3weeks-19 years; (Bonekamp et. al., 2007) age group 5-19. FA values reported at the splenium of the corpus callosum in the current study in age groups 18-40, 41-60 and 61-75 respectively is in line with studies reported in literature by (Snook et. al., 2005) age group 21-27;(Huisman, Loenneker, Barta, Bellemann, Hennig, Fischer, & Il 'yasov, 2006) age group 26-31;(S Hunsche et. al., 2001) age group 30-35;(Lee et. al., 2009) age group 19-62 ; while FA at the genu of the corpus callosum in age groups 18-40, 41-60 and 61-75 was also in line with (Löbel et. al., 2009) age group 3weeks-19 years and lastly FA obtained at the body of the corpus callosum in age groups 18-40, 41-60 and 61-75 respectively is in line with (Brander et. al., 2010) age group 19-61. FA at the genu obtained in the current study is slightly lower compared to values reported in literature (Huisman, Loenneker, Barta, Bellemann, Hennig, Fischer, & Il'yasov, 2006)(Huisman, Bosemani, & Poretti, 2014)(Stefan Hunsche, Moseley, Stoeter, & Hedehus, 2001)(Brander et. al., 2010)(Snook et. al., 2005). However on the other hand FA in some regions is inherently low due to complex and crossing fiber orientation. Fa values obtained in the current study at the centrum semiovale and pons is low compared to FA values at the genu, body and splenium of the corpus callosum. Similarly FA values at the genu and body of the corpus callosum reported in the current study are slightly lower than FA values reported in literature (Snook et. al., 2005)(Hakulinen et. al., 2012)(Huisman, Loenneker, Barta, Bellemann, Hennig, Fischer, & Il 'yasov, 2006) (Huisman et. al., 2014)(S Hunsche et. al., 2001). This slight difference in FA values obtained in the genu and body of the corpus callosum might be due to different geographic population of the participants studied, technical parameters, equipment specifications, type of ROI method and age group studied. FA at the centrum semiovale in the current study at age group 18-40 is slightly higher to FA reported by (Snook et. al., 2005) in the cenrtrum semiovale in the age group of 21-27 years (0.44 ± 0.05 and 0.47 ± 0.05 at right and left side respectively) while (Brander et. al., 2010) showed a FA value of (0.539 ± 0.06 and 0.567 ± 0.07) at right and left side respectively in

the age group of 19-61. While FA in the pons showed a mix of increase and decrease in FA values on right and left side. FA values in the current study at the right and left pons are slightly lower than FA at the pons reported by (Brander et. al., 2010). Centrum semiovale showed leftward asymmetry of FA In the age group of 18-40 and 41-60 but age group 61-75 had rightward asymmetry. Pons showed leftward asymmetry of FA In the age group of 41-60 and 61-75 but age group 18-40 had rightward asymmetry.

Strengths of the current study includes the use of a sample size of 85 healthy participants, with a healthy sample size in all three age groups and a fixed ROI of 8 voxel size which were the limitations reported in literature (Taylor et. al., 2010)(Bisdas, Bohning, Besenski, Nicholas, & Rumboldt, 2008). Moreover we had a wide range of participants and they were double screened to rule out any neurological abnormalities. The other advantage was the use of the same MRI scanner and software for imaging throughout the course of the study. Current finding in the study and association of FA values among different age groups is not available in literature which is the main strengths of our study. The only anticipated limitation in our study is the use of DTI medium sequence with 15 weighting directions, DTI medium with 32 weighting directions could also be used. Our study helped us in comparing the interregional and interhemispheric differences of normal development in the brain white matter regions studied. Our main aim was to provide a normative data of FA values in healthy participants without any known neurology related abnormalities. Future longitudinal studies with comparison of these physiological changes in brain white matter with pathological conditions will be very useful for interpretation in clinical cases which is lacking in our current study. The vast clinical application of DTI and fractional anisotropy in particular will continue to grow as we learn and study in depth about anisotropy and diffusivity.

3. CONCLUSION

We demonstrate a relationship between FA and normal ageing which is a key feature to detect early white matter changes. We propose that FA may provide an early means for the detection of white matter age-related changes and suggest a need for explorative in depth data to explore this association in comparison with a diseased population. This normative data on FA values obtained with this system specifications should be checked for reliability with other MRI systems with higher tesla strength magnets.

Conflict of interest statement: The authors declare that they have no conflict of interest in this research.

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