A diffusion tensor imaging software comparison and between control subjects and subjects with known anatomical diagnosis

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A DIFFUSION TENSOR IMAGING SOFTWARE COMPARISON AND BETWEEN CONTROL SUBJECTS AND SUBJECTS WITH KNOWN ANATOMICAL DIAGNOSIS

by

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Master of Combined Sciences
Mississippi College
Bachelor of Science
Mississippi State University

A thesis submitted in partial fulfillment of the requirements for the

Master of Science in Health Physics

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Division of Health Sciences

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A Diffusion Tensor Imaging Software Comparison and Between Control Subjects and Subjects with Known Anatomical Diagnosis

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Diffusion weighted imaging (DWI) is a magnetic resonance imaging (MRI) method that produces in vivo images of biological tissues weighted with the local micro-structural characteristics of water diffusion. Diffusion tensor imaging (DTI), a form of DWI, is useful when a tissue, such as the neural axons of white matter in the brain, has an internal fibrous structure that allows water to diffuse more rapidly in alignment with the fibers. Changes in the water diffusion pattern indicate changes in the fiber structure which can result from damage to the fibers. Measurements of the water diffusion patterns include overall diffusivity, Apparent Diffusion Coefficient (ADC), and the linear component of the ADC known as the Fractional Anisotropy (FA). The purpose of this study is three fold: (1) to evaluate the reproducibility of ADC and FA values obtained from the same dataset between two Diffusion Tensor Imaging analysis software packages (Analyze 10.0 and Philips PRIDE), (2) to use the results of the Analyze 10.0 software analysis to characterize the corpus callosum (CC) and anatomical regions of the CC from a dataset of control subjects with no known anatomical abnormalities obtained via 3.0 Tesla (3T) MRI, and (3) to identify and characterize patterns present in ADC and FA values of subjects with known anatomical abnormalities by comparing the results to the control
datasets. In this DTI software analysis study, Analyze 10.0 produced significantly different results for mean ADC and mean FA when compared to the PRIDE software package. Pearson correlation values show that Analyze 10.0 provides reliably similar mean ADC and mean FA values. Regardless of the software package, gender and age of the subjects did not provide significantly different values for mean ADC and mean FA. Using results from Analyze 10.0 on the control group, provides a baseline of comparison for subjects with CO, MS, or TBI diagnosis. Comparisons of seven anatomical and physiological regions of the CC between control and non-control subjects show that medial regions of the CC (AMB, PMB, Isthmus 1 and Isthmus 2) are most likely to show significant differences in mean ADC and FA; while the genu and splenium regions are less likely to show significant differences.
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1.1 Magnetic Resonance Imaging of the Brain

Magnetic resonance imaging of the brain is a common MR examination that provides detailed images of the brain and nerve tissues. MR imaging provides high soft tissue contrast, unmatched by other modalities. MR brain imaging is often done to detect or monitor birth defects of the brain, hemorrhaging, tumors, or damage from injury. Brain function can also be detected and monitored with MR imaging techniques. Diffusion imaging measurements of cellular fluid diffusing through cell membranes has developed into an important, non-invasive clinical application for assessing the human brain.

1.2 Diffusion Tensor Imaging

Diffusion MR imaging of the brain was first adopted for use in clinical neuroradiology in the early 1990’s. Articles on diffusion tensor imaging (DTI) in neurologic and other system-based conditions are consistently and increasingly being generated. A PubMed literature search for diffusion tensor imaging, diffusion tensor tractography, diffusion tensor MR tractography, and MRI fiber tracking conducted on March 21, 2007 yielded 1,490 references dating from 1994 to 2007 to over 4,500 references in mid-2011. Application of DTI continues to expand for research and clinical purposes. DTI has become a valuable tool in the diagnosis and monitoring of numerous pathological processes, as well as surveillance of brain development, maturation and aging. DTI analysis results can provide non-invasive information about
axonal integrity for white matter (WM) fiber connections of the brain, changes in axons of WM over time, organization of axons of WM, alignment of axons of WM, and changes in myelination over time.\textsuperscript{11,12,13,14,15} Changes in the water diffusion pattern indicate changes in the fiber structure which can result from damage to the fibers. Diffusion tensor imaging measurements of the water diffusion patterns include overall diffusivity, Apparent Diffusion Coefficient (ADC), and the Fractional Anisotropy (FA). There have been many publications of ADC and FA values for various regions of the brain including the corpus callosum, either as a whole or in parts, but there is not a set method for determining these regions or their DTI measurements.

1.3 Basic Physics of Magnetic Resonance Imaging

The tissues of the human body contain large amounts of water. Body tissues contain large proportions of hydrogen atoms from the water molecules they contain. Spin properties of the hydrogen nuclei produce a magnetic moment for the nucleus which can be interpreted when placed in an external magnetic field.\textsuperscript{1,16}

The magnetic spin properties of the protons in water molecules can be detected when placed within a strong magnetic field such as that of a magnetic resonance imaging (MRI) machine. The proton spin property allows the protons to excite and absorb photon energy and their alignments with the magnetic field can be utilized to gain valuable information about their microenvironment. Excitation and de-excitation of the resonating protons via radio frequency (RF) pulses provides a signal that can be detected and measured which indicates proton density and movement, and thus location and flow of water molecules.\textsuperscript{1,16}
1.4 T1 and T2 Weighted Magnetic Resonance Imaging

T1-weighted and T2-weighted MR imaging are standard, basic images that highlight T1 or T2 property differences of the tissues being imaged. T1 images of the brain provide good contrast between grey matter and white matter due to their longer T1 relaxation times, while T2 images rely on shorter relaxation times to control tissue contrast enhancing cerebrospinal fluid contrast. T1-weighting refers to return of the spinning proton from its excited, aligned state to an equilibrium state as it releases energy to the surrounding tissue.\textsuperscript{1,16} The transverse relaxation of the spinning protons is the basis of T2-weighted imaging.\textsuperscript{1,16} T1 and T2 relaxation times are fundamental properties of the local tissue; T1 is significantly longer than T2 relaxation times.\textsuperscript{1} Images produced with T1-weighting show tissues with a high water content to be darker while tissues with high fat content are lighter in grayscale. T2-weighting shows water as light and fat as dark in grayscale tone.\textsuperscript{1}

1.5 Diffusion Anisotropy Measurement

The transport of water molecules between spatial locations over time can be mapped by the motion of the hydrogen nuclei.\textsuperscript{1} Random molecular motion of water molecules due to heat, also known as Brownian motion, can be quantified and reflects intrinsic features of tissue microstructure in vivo.\textsuperscript{17} Mapping hydrogen nuclei transport can thus provide micro-structural information.\textsuperscript{16,18}
1.6 Diffusion Weighted Imaging

Diffusion weighted imaging (DWI) uses two gradient pulses to change the resonance phase of the water molecule protons to observe a signal change in moving water molecules.\textsuperscript{16} The gradient pulse allows the protons to resonate at different RF frequencies as the RF photon excites the protons. The first gradient pulse dephases the precession of the protons in the water molecules and the second rephases them if the water molecules have not moved. The molecule will not see the same magnitude of the gradient pulse if it has changed position. With molecular movement through a small region of space, a voxel (volumetric picture element), water molecules resonate with different RF frequencies.\textsuperscript{6,16} As the protons relax and de-excite, RF pulses are emitted and detected as a returning RF signal. The signal intensity measured from the protons within a voxel is proportional to the sum of the magnetization components of all the differently phased water molecules within a volume. This intensity of diffusing molecules varies compared to stationary molecules, and the changes in the signal intensities are measured and recorded.\textsuperscript{18} Adjacent voxels will contain varying water molecule densities allowing for the mapping of water molecule diffusion through neighboring voxels.\textsuperscript{16}

1.7 Diffusion Tensor Imaging Physics

Diffusion tensor imaging (DTI) collects the DWI information on the diffusion of the water molecules in at least six directions, and sums them to describe the diffusion of water with respect to a reference direction within a voxel of space in the tissue of interest, primarily the brain.\textsuperscript{16,18,17,19} Water diffusion can be isotropic or unrestricted producing a
sphere shaped model. If the diffusion is restricted and allowed to be more along one axis than the others, it is an ellipsoid and the resulting diffusion is anisotropic. In brain tissue, however, water diffusion can be constrained by structures such as myelin sheaths, cell membranes, and axonal tracts. In general, diffusion of the water molecules is less restricted along the long-axis of a group of aligned tissue fibers (such as those of WM) than perpendicular to it. Figure 1 shows models of both isotropic and anisotropic diffusion. Axonal fibers in the brain constrain the diffusion of water and channel the diffusion along the length of the fibers themselves. Understanding the anisotropic diffusion of water along the fibers provides knowledge of the axonal fiber structure and integrity.

Figure 1: Isotropic and anisotropic diffusion water trajectories and geometric ellipsoids.

As the water diffuses more along a single axis, the diffusion pattern becomes ellipsoidal. A diffusion tensor can provide the mathematical description of the spherical or ellipsoidal diffusion of the water molecules. The directionality of water diffusion is
quantified by applying diffusion gradients in a minimum of six non-collinear directions in three dimensional space and is referred to as tensors.\textsuperscript{3,16} Basser et al. first proposed the application of diffusion tensors in measurement of the anisotropic diffusion of water with the presentation of an ellipsoid mathematical model.\textsuperscript{3} The diffusion tensor is a 3x3 covariant matrix which shows the movement of water molecules in three dimensions normalized by time. The diagonalization of the diffusion tensors yield eigenvalues ($\lambda_1$, $\lambda_2$, $\lambda_3$) that correspond to the three main major axes (x, y, z) of an ellipsoid. Calculations of eigenvalues of the ellipsoid vectors are made for each voxel of space for the area being examined. Isotropic diffusion is represented by equal eigenvalues, while different magnitudes of the three eigenvalues indicate anisotropy.\textsuperscript{1,3} Eigenvalue changes correlate to changes in the microstructures of the WM. An eigenvector defines the eigenvalues and the rotation angles of each eigenvalue that describe the ellipsoid (v_1,v_2,v_3). Each voxel is then a matrix with eigenvectors that show the magnitude and direction of the water diffusion along each axis, ultimately producing a tensor description of the anisotropic diffusion of water within the voxel.\textsuperscript{18} Equation 1 shows example matrices for the possible water diffusion: $D$ is the diffusion tensor in an isotropic model, $D_{xy}$ is the anisotropic diffusion tensor measurement along the z axis, and $D_{\text{eff}}$ is the effective, restricted diffusion tensor ($D_{\text{eff}} < D$).\textsuperscript{16x,18x}

$$
\begin{pmatrix}
D & 0 & 0 \\
0 & D & 0 \\
0 & 0 & D
\end{pmatrix}
\begin{pmatrix}
D_{\text{eff}} & 0 & 0 \\
0 & D_{\text{eff}} & 0 \\
0 & 0 & D_{\text{eff}}
\end{pmatrix}
\begin{pmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{yx} & D_{yy} & D_{yz} \\
D_{zx} & D_{zy} & D_{zz}
\end{pmatrix}
$$

Eq. 1
1.8 Apparent Diffusion Coefficient

The Apparent Diffusion Coefficient (ADC) measures the mobility of water molecules through a region of interest (ROI), comparing the average displacement of a water molecule over an area during the observation duration.\textsuperscript{16} Eigenvalues and their corresponding eigenvectors are used to describe the directions of the apparent diffusivities along the principal axis of the diffusion. The ADC is a calculated average of the three diagonal axial eigenvalues. The ADC represents the average diffusivity of water within the constrained, restricted ROI. The lower the ADC value; the more restricted or less diffuse the water movement (anisotropic).\textsuperscript{4,11,18} Equation 2 represents the calculation of the ADC value:

\[
S = S_o e^{-\gamma^2 G^2 \delta^2 (\Delta-\delta/3)} D
\]

\(S_0\) is the initial RF signal intensity, \(S\) is the measured RF signal intensity with the gradient returning from the de-exciting hydrogen nuclei, \(\gamma\) is the gyromagnetic ratio unique to hydrogen, \(G\) is the gradient strength, \(\delta\) is the gradient pulse duration, \(\Delta\) is the time between pulses, and \(D\) is the apparent diffusion coefficient.\textsuperscript{11,16} ADC measurement units are mm\(^2\)/s.\textsuperscript{16}

1.9 Fractional Anisotropy

Fractional Anisotropy (FA) is the portion of the magnitude of the diffusion tensor that is due to anisotropy.\textsuperscript{11,16} FA is calculated by dividing the sum of the squares of the differences between the three axial eigenvalue to the two shorter ones on the ellipsoid by
the mean of the three eigenvalues ($\lambda$) (Eq. 3).\textsuperscript{11,16} FA provides a linear description of the ADC values. The unitless values of FA range from 0.0 for a purely isotropic medium to a value close to 1.0 for a highly symmetric anisotropic medium. The fractional anisotropy of the medium can infer the microstructure of the surrounding tissue that constrains the diffusion.\textsuperscript{3,4,22,23,24,25,18,19}

$$\text{FA} = \sqrt{1/2} \frac{\sqrt{((\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2)}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \quad \text{Eq. 3}$$

In addition to ADC and FA values, the predominant diffusion direction can also be determined, which is used as an input to fiber tracking algorithms. Typical DTI map parameters do not include the total diffusion patterns in every direction, but they do include directional descriptions of the ellipsoidal water diffusion. Common DTI maps such as eigenvector maps are directionally encoded color (DEC) images that show the direction of the diffusion from each voxel tensor, developed by Pajevic and Pierpaoli\textsuperscript{26} (Figure 2).
Figure 2: Coronal view of an eigenvector map of the human brain. Motion along the x-axis is red, motion along the y-axis is green, and motion along the z-axis is shown as blue.\textsuperscript{16,26}

The location and orientation of major WM fiber tracts can be revealed from water molecule diffusion paths with these full tensor-based color methods. This process is often referred to as fiber tracking.\textsuperscript{18,25,27} These orientation values can be calculated in 2D with use of one slice while a 3D based valuation can be obtained from integration and calculation of several slices (Figure 3).

Figure 3: Fiber tracts of a control subject’s CC ROI. Each color represents a different region of the CC (Genu -Splenium).
1.10 The Corpus Callosum

The corpus callosum is a large bundle of white matter neural fibers, beneath the cortex. It effectively divides the left and right hemispheres of the brain and facilitates communication between the two sides with hundreds of millions of axonal projections spreading away from the corpus callosum to all other regions of the brain.\textsuperscript{10,20,27,28} The size and shape of the corpus callosum varies greatly between individuals and sexes. Different regions of the CC have differing densities of axons originating from them, with a large number of fibers extending from the anterior and posterior, known as the genu and splenium, respectively (Fig. 4). Physiologically, the regions of the CC correspond to the regions of the cortex and brain lobes that they communicate to (Broadmann’s functional regions).\textsuperscript{10,20,27} MR imaging and measurement of the anatomy and physiology of the CC is at the forefront of MRI-brain research. Figure 4 is an adapted sagittal view of the CC with some of the anatomical and physiological regions of the CC identified.
1.11 Research Goals

There are three goals of this research: 1) Compare the accuracy of commercially available DTI metrics software to industrially provided software. 2) Develop FA and ADC models for seven regions of the CC from a control subject data set. 3) Compare FA and ADC models for non-control subjects to control subjects.

Fractional anisotropy and apparent diffusion coefficient values calculated with Analyze, a commercially available software package, (AnalyzeDirect Inc., Overland Park, Kansas).
Park, KS, USA) were compared to Philips PRIDE (Philips Healthcare, Andover, Massachusetts, USA) software values from the same DTI dataset to evaluate accuracy and reliability. Data were measured and collected from a Philips 3.0 Tesla (3T) magnetic resonance imaging (MRI) scanner from a region of interest (ROI), namely the corpus callosum (CC) of patients without anatomical abnormalities on MRI as determined from the radiological reports completed by a staff neuroradiologist.

Using a multiple region of interest template approach for assessment of the CC, the CC is divided into seven regions based on anatomical, functional, and physiological sections to determine ADC and FA values for each ROI among the dataset.

Data from patients with one of three known abnormalities were also analyzed to establish criteria for using ADC and FA values of the CC to quantitatively determine the extent of axonal damage to patients. The three abnormalities investigated were carbon monoxide poisoning (CO), multiple sclerosis (MS), and traumatic brain injury (TBI).

This research will show that Analyze 10.0 will produce ADC and FA values that can be favorably compared to the industry standard software, PRIDE. Using the Analyze 10.0 results, this research will produce a normative comparison model of the CC including 2D single, sagittal, midline slice; and 3D, composite of five adjacent slices; values of the CC overall; and of seven anatomical/physiological regions of the CC. Using this normative model of the CC developed by Analyze 10.0 this research will identify and characterize subjects with clinical and radiological evaluations of CO, MS, or TBI based on FA and ADC values.
CHAPTER 2

MATERIALS AND METHODS

This retrospective and anonymized study was performed with Institutional Review Board (IRB) exemption approval and was Health Insurance Portability and Accountability Act (HIPAA) compliant. Identifying patient information was removed from the imaging studies and was not used in the analysis or interpretation of the data.

Fifty control subjects (age 40.3 years ± 10.7) without anatomical or structural findings on a 3.0T MRI were analyzed using PRIDE and Analyze 10.0 DTI analysis software to determine ADC and FA through regions of interest (ROI) of the corpus callosum. Seventy four percent of the control subjects were female (age 41.3 years ± 11.2) and twenty six percent were male (age 37.5 years ± 8.7). Subjects were imaged for diagnosis of traumatic brain injuries, nervous system disorders, or various developmental or vascular anomalies, and revealed no anatomical abnormalities. Two additional patients were imaged, evaluated, and included in the control subjects group to be compared to the diseased subject group, bringing the number of control subjects to 52, but were not included in the head to head comparisons of Analyze and PRIDE.

Abnormal datasets are those with anatomical, structural, and/or a history of findings that correlate to either carbon monoxide poisoning (CO), multiple sclerosis (MS), or traumatic brain injury (TBI). One hundred and twenty six TBI subjects were studied as were sixty five CO subjects and one hundred and sixty MS subjects. Gender and age stratification was not done on the diseased subjects.
2.1 Image Interpretation

MR data files from the Philips 3.0T MR scanner were imported into the Analyze 10.0 software as raw data files (Par/Rec format files or DICOM format files). Base images and diffusion weighted images were used to develop DTI map data.

2.2 ROI Development

Eigenvector maps of the midsagittal brain were used to develop a ROI of the corpus callosum (CC) for the 2D data calculations in the Analyze 10.0 software package. The Analyze auto-trace feature with a set contrast range was utilized to ensure consistency of the ROI of each subject. The Object Extraction function was used to create a 3D ROI of the whole CC based on the same voxel criteria as the 2D ROIs. Extracted 3D ROIs for the subdivided regions of the CC proved to be excessively time consuming to create and collect data. An approximation of the true 3D data was produced by combining the five midsagittal slices. This integration of the five 2D slices provides our 3D information from the Analyze software package when collecting data from the CC regions and is denoted as 3D (5 slice). A true, extracted 3D ROI may include up to 30 slices depending upon the subject. The same auto-trace feature was used for each data file to ensure the corpus callosum was characterized without the addition of adjacent tissue. ROIs for PRIDE were similarly selected from the midsagittal slice using eigenvector maps to include the whole CC. PRIDE software incorporates the 2D ROI of the midline CC to include adjacent slices for the 3D ROI. An instructional guide to ROI development and analysis for Analyze 10.0 is included in Appendix I.
2.3 Multiple ROI

The body of the corpus callosum was divided into seven distinct anatomical and physiological regions. Anatomical regions are made up of the Genu in the anterior position and the rostrum which extends beneath the Genu, Ventral Rostral Body (VRB), Anterior Mid Body (AMB), Posterior Mid Body (PMB), Isthmus 1, Isthmus 2, and Splenium. Figure 5 shows the divisions of the CC created with Analyze.

![Greyscale Eigenvector map of the Midline Slice of the Corpus Callosum divided into Seven Regions that approximate Physiological, Functional Regions of the Corpus Callosum](image)

Figure 5: Greyscale Eigenvector map of the Midline Slice of the Corpus Callosum divided into Seven Regions that approximate Physiological, Functional Regions of the Corpus Callosum: A is the Genu and Rostrum, B is the Ventral Rostral Body (VRB), C is the Anterior Mid Body (AMB), D is the Posterior Mid Body (PMB), E is the Isthmus I region, F is the Isthmus 2 Region, and G is the Splenium.

2.4 DTI Data Collection and Initial Analysis

Automated subdividing the CC into regions was accomplished only with the Analyze software. PRIDE only allows for manually drawn subdivisions of the CC and is not automatically reproducible. ADC and FA values for the whole, undivided, CC were calculated for both the 2D and 3D ROIs. ADC and FA values from the Analyze and PRIDE software packages were compared for reproducibility. The dataset was stratified
by age and by gender. A correlation between differences of both Analyze techniques (3D extracted and 3D 5 slice) and PRIDE was evaluated for a common trend or differences.

The age differentiation datasets were separated by age from 18-39 and 40+. These datasets were analyzed between the two age groups for regional differences as a whole using both Analyze 10.0 and PRIDE software packages. Both mean FA and ADC values for the different age groupings were compared for significance.

Gender differentiation among the datasets was also produced and analyzed. These datasets were evaluated between the two gender groups for regional differences using both Analyze 10.0 and PRIDE software packages. Both mean FA and ADC values for the different gender groupings were compared for significance.

2.5 Diseased State Subjects

Both whole corpus callosum ROI and ROIs for the seven subdivided regions of the CC were created for each dataset. Both 2D and 3D(5 slice) values for ADC and FA were produced and compared to control values to establish criteria for identifying differences between the control and disease state (CO, MS, TBI) groups. Gender and age stratification was not done for these comparisons.

2.6 Statistical Analysis

Statistical analysis was performed using Excel (Microsoft Corporation, Redmond, WA) and Minitab (Minitab Inc., State College, PA). Two sample independent t-tests were used for comparisons of quantitative values and a p-value of less than 0.05 at the 95% confidence interval was used to determine significance. A Pearson correlation test was
applied to the Analyze and PRIDE data to find reliability and precision in the ADC and FA values. Significance of correlation was determined by using a Pearson correlation value greater than 0.500. ²⁹
CHAPTER 3

RESULTS

3.1 Analyze and PRIDE Software Comparison

The Analyze 2D FA values for the normal data set range from 0.680 ± 0.173 to 0.813 ± 0.133 with a mean value of 0.756 ± 0.023 while the PRIDE 2D FA values range from 0.619 ± 0.210 to 0.823 ± 0.110 with a mean value of 0.734 ± 0.031. The Analyze mean values for 2D FA data sets were increased when compared to the PRIDE mean 2D FA values (Figure 6). The differences of Analyze to PRIDE values for the 50 dataset group 2D FA calculations were found to be significantly different (p < 0.001). The differences of Analyze to PRIDE mean values for the stratified groups divided by gender were also significant for male (p = 0.023) and female (p < 0.001) groups. The same was true for the age stratified groups as the 18-39 (p < 0.001) and 40+ (p = 0.027) groups showed significance in difference of Analyze and Pride mean values. Even with the increased 2D FA values with Analyze, the Pearson correlation between the Analyze and PRIDE analysis techniques was 0.626 meaning there is a strong correlation between the two data sets even with the significantly different measurements.
Figure 6: 2D FA comparison between Analyze and PRIDE. Mean FA value from Analyze was 0.756 and the mean PRIDE value was 0.734. The Pearson correlation value was 0.626. FA values are on the y axis and the fifty subjects are arranged on the x axis.

The Analyze 3D (extracted) FA mean values range from 0.738 ± 0.152 to 0.865 ± 0.084 with a overall mean value of 0.812 ± 0.021 and the Analyze 3D (5 slice) FA mean values range from 0.730 ± 0.0002 to 0.802 ± 0.0001 with a overall mean of 0.760 ± 0.017 for the 50 normal group individuals while the PRIDE mean 3D FA values range from 0.755 ± 0.113 to 0.907 ± 0.038 with an overall mean value of 0.835 ± 0.029 for the 50 dataset group. The difference in mean 3D FA values for the 50 dataset group was shown to be significantly different (p < 0.001). The all male (p = 0.017) and all female (p = 0.001) gender groups and the 18-39 (p = 0.002) and 40+ (p = 0.004) age groups also showed significance in difference of Analyze and PRIDE values. The Pearson correlation test value between Analyze (extracted) and PRIDE was 0.690 and between
Analyze (5 slice) and PRIDE was 0.648. Both demonstrate strong correlations between the two analysis techniques. The mean PRIDE values were shown to be greater compared to both of the mean Analyze values for the 3D FA (Figure 7).

![Pride vs Analyze 3D FA Control (n=50)](image)

Figure 7: 3D FA comparison between the two Analyze techniques and PRIDE. Mean values for Analyze (extracted) was 0.812, mean value for Analyze (5 slice) was 0.760 and the mean value for PRIDE was 0.835. Pearson correlation value for Analyze (extracted) and PRIDE: 0.690; and for Analyze (5 slice): 0.648. FA values are on the y axis and the fifty subjects are on the x axis.

The Analyze 2D ADC mean values range from $0.578 \pm 0.148$ to $0.750 \pm 0.213$ and the PRIDE 2D ADC mean values range from $0.654 \pm 0.267$ to $1.020 \pm 0.379$. The Analyze mean 2D ADC value for all 50 samples is $0.624 \pm 0.032$ while the PRIDE 2D mean value for all 50 samples is $0.767 \pm 0.058$. ADC measurement and units are $10^{-3}$ mm$^2$/s. The 2D ADC data showed significance in difference between the Analyze and PRIDE values as the 50 datasets and both stratified gender and age groups had ($p < 0.001$) values. The Pearson Correlation test value between Analyze and PRIDE for 2D
ADC was 0.654 which is a strong correlation for the similarity of the data. The PRIDE values were shown to be increased compared to the Analyze values for all normal individuals (Figure 8).

![2D ADC Pride vs Analyze Controls (n=50)](image)

Figure 8: 2D ADC comparison between Analyze and PRIDE. ADC values on the y axis are measured in \(10^{-3}\) mm\(^2\)/s units and the subjects are on the x axis. Mean 2D ADC Analyze value was 0.624 and for PRIDE was 0.767. Pearson correlation value: 0.654.

The Analyze 3D (extracted) ADC mean values range from 0.640 ± 0.181 to 0.826 ± 0.231 with an overall mean value of 0.702 ± 0.031 for all 50 datasets. The Analyze 3D (5 slice) ADC mean values range from 0.563 ± 0.008 to 0.731 ± 0.008 with an overall mean value of 0.615 ± 0.028. The Pride 3D ADC mean values range from 0.568 ± 0.121 to 0.841 ± 0.187 with an overall mean value of 0.682 ± 0.043 for all 50 datasets (Figure 9). The difference between the Analyze and Pride 3D ADC values were shown to be significant for the 18-39 age group (p = 0.008) and the 50 sample dataset (p = 0.010).
However, the difference of 3D ADC values of Analyze and PRIDE for Male (p = 0.074) and Female (p = 0.051) stratified gender groups and the 40+ age group (p = 0.14) was shown not to be significant. The Analyze mean values for the 50 dataset group and all stratified groupings were shown to be increased compared to the PRIDE mean values.

![3D ADC Pride vs Analyze Controls (n=50)](image)

Figure 9: 3D ADC comparison between the two Analyze techniques and PRIDE. ADC values on the y axis are $10^{-3}$ mm$^2$/s with the fifty subjects on the x axis. 3D (extracted) Analyze mean value was 0.702. 3D ADC Analyze (5 slice) mean value was 0.615. PRIDE 3D ADC mean value was 0.682. Pearson correlation between Analyze (Extracted) and PRIDE: 0.677; and for Analyze (5 slice): 0.747.

Summary data for the Analyze (extracted), Analyze (5 slice), and PRIDE software comparison for 2D and 3D FA and ADC with gender and age stratification is presented in Tables 1-2. Table 3 provides additional comparisons between the Analyze (5slice), Analyze (extracted), and PRIDE software techniques.
Table 1: Gender and Age comparison for Mean FA between Analyze (extracted) and PRIDE with t-Test values and Pearson correlation values.

<table>
<thead>
<tr>
<th>Gender and Age Stratification</th>
<th>Mean 2D FA</th>
<th>Analyze</th>
<th>SD</th>
<th>PRIDE</th>
<th>SD</th>
<th>t-test p-Value</th>
<th>Pearson</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.759</td>
<td>0.023</td>
<td>0.734</td>
<td>0.031</td>
<td>&lt;0.001</td>
<td>0.626</td>
<td></td>
</tr>
<tr>
<td>All Males</td>
<td>0.768</td>
<td>0.022</td>
<td>0.744</td>
<td>0.028</td>
<td>0.023</td>
<td>0.470</td>
<td></td>
</tr>
<tr>
<td>All Females</td>
<td>0.755</td>
<td>0.023</td>
<td>0.730</td>
<td>0.032</td>
<td>&lt;0.001</td>
<td>0.647</td>
<td></td>
</tr>
<tr>
<td>18-39</td>
<td>0.762</td>
<td>0.020</td>
<td>0.732</td>
<td>0.022</td>
<td>&lt;0.001</td>
<td>0.590</td>
<td></td>
</tr>
<tr>
<td>40+</td>
<td>0.756</td>
<td>0.025</td>
<td>0.735</td>
<td>0.038</td>
<td>0.027</td>
<td>0.671</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender and Age Stratification</th>
<th>Mean 3D FA</th>
<th>Analyze</th>
<th>SD</th>
<th>PRIDE</th>
<th>SD</th>
<th>t-test p-Value</th>
<th>Pearson</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.812</td>
<td>0.022</td>
<td>0.835</td>
<td>0.029</td>
<td>&lt;0.001</td>
<td>0.690</td>
<td></td>
</tr>
<tr>
<td>All Males</td>
<td>0.820</td>
<td>0.021</td>
<td>0.846</td>
<td>0.030</td>
<td>0.017</td>
<td>0.659</td>
<td></td>
</tr>
<tr>
<td>All Females</td>
<td>0.810</td>
<td>0.022</td>
<td>0.831</td>
<td>0.028</td>
<td>0.001</td>
<td>0.679</td>
<td></td>
</tr>
<tr>
<td>18-39</td>
<td>0.813</td>
<td>0.020</td>
<td>0.833</td>
<td>0.024</td>
<td>0.002</td>
<td>0.223</td>
<td></td>
</tr>
<tr>
<td>40+</td>
<td>0.812</td>
<td>0.024</td>
<td>0.836</td>
<td>0.033</td>
<td>0.004</td>
<td>0.685</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Gender and Age Comparison for Mean ADC between Analyze (extracted) and Pride with t-Test values and Pearson correlation values (ADC is $10^{-3}$ mm$^2$/s).

<table>
<thead>
<tr>
<th>Gender and Age Stratification</th>
<th>Mean 2D ADC</th>
<th>Analyze</th>
<th>SD</th>
<th>PRIDE</th>
<th>SD</th>
<th>t-test p-Value</th>
<th>Pearson</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.624</td>
<td>0.032</td>
<td>0.767</td>
<td>0.058</td>
<td>&lt;0.001</td>
<td>0.654</td>
<td></td>
</tr>
<tr>
<td>All Males</td>
<td>0.613</td>
<td>0.029</td>
<td>0.758</td>
<td>0.052</td>
<td>&lt;0.001</td>
<td>0.564</td>
<td></td>
</tr>
<tr>
<td>All Females</td>
<td>0.628</td>
<td>0.032</td>
<td>0.771</td>
<td>0.060</td>
<td>&lt;0.001</td>
<td>0.674</td>
<td></td>
</tr>
<tr>
<td>18-39</td>
<td>0.623</td>
<td>0.025</td>
<td>0.754</td>
<td>0.041</td>
<td>&lt;0.001</td>
<td>0.414</td>
<td></td>
</tr>
<tr>
<td>40+</td>
<td>0.625</td>
<td>0.038</td>
<td>0.780</td>
<td>0.068</td>
<td>&lt;0.001</td>
<td>0.758</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender and Age Stratification</th>
<th>Mean 3D ADC</th>
<th>Analyze</th>
<th>SD</th>
<th>PRIDE</th>
<th>SD</th>
<th>t-test p-Value</th>
<th>Pearson</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.702</td>
<td>0.031</td>
<td>0.682</td>
<td>0.043</td>
<td>0.010</td>
<td>0.797</td>
<td></td>
</tr>
<tr>
<td>All Males</td>
<td>0.692</td>
<td>0.035</td>
<td>0.663</td>
<td>0.045</td>
<td>0.074</td>
<td>0.798</td>
<td></td>
</tr>
<tr>
<td>All Females</td>
<td>0.705</td>
<td>0.030</td>
<td>0.688</td>
<td>0.041</td>
<td>0.051</td>
<td>0.789</td>
<td></td>
</tr>
<tr>
<td>18-39</td>
<td>0.698</td>
<td>0.025</td>
<td>0.678</td>
<td>0.027</td>
<td>0.008</td>
<td>0.590</td>
<td></td>
</tr>
<tr>
<td>40+</td>
<td>0.705</td>
<td>0.036</td>
<td>0.685</td>
<td>0.054</td>
<td>0.140</td>
<td>0.747</td>
<td></td>
</tr>
</tbody>
</table>
Table 3: Comparison of both Analyze techniques with PRIDE for FA and ADC determination with Pearson correlation values (ADC is \(10^{-3}\) mm\(^2\)/s and Pearson correlation value >0.500 = strongly correlated).

<table>
<thead>
<tr>
<th>Technique</th>
<th>Maximum</th>
<th>Minimum</th>
<th>Mean</th>
<th>t-Test p-value</th>
<th>Pearson correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D FA</td>
<td>0.813</td>
<td>0.680</td>
<td>0.756</td>
<td>&lt;0.001</td>
<td>0.626</td>
</tr>
<tr>
<td>2D PRIDE FA</td>
<td>0.823</td>
<td>0.619</td>
<td>0.734</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D (extracted) FA</td>
<td>0.865</td>
<td>0.738</td>
<td>0.812</td>
<td>&lt;0.001</td>
<td>0.690</td>
</tr>
<tr>
<td>3D PRIDE FA</td>
<td>0.907</td>
<td>0.755</td>
<td>0.835</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D (5 slice) FA</td>
<td>0.802</td>
<td>0.730</td>
<td>0.760</td>
<td>&lt;0.001</td>
<td>0.677</td>
</tr>
<tr>
<td>2D ADC</td>
<td>0.750</td>
<td>0.578</td>
<td>0.624</td>
<td>&lt;0.001</td>
<td>0.654</td>
</tr>
<tr>
<td>2D PRIDE ADC</td>
<td>1.020</td>
<td>0.645</td>
<td>0.767</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D (extracted) ADC</td>
<td>0.826</td>
<td>0.640</td>
<td>0.702</td>
<td>0.010</td>
<td>0.797</td>
</tr>
<tr>
<td>3D PRIDE ADC</td>
<td>0.841</td>
<td>0.568</td>
<td>0.682</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D (5 slice) ADC</td>
<td>0.731</td>
<td>0.563</td>
<td>0.615</td>
<td>&lt;0.001</td>
<td>0.747</td>
</tr>
</tbody>
</table>

3.2 Analyze 10.0 Age Differentiations

None of the differences in mean FA values between the age groups 18-39 and 40+ of 2D and 3D data using Analyze 10.0 were found to be significant. The 2D FA difference between the age groups 18-39 and 40+ had a \(p = 0.339\) while the 3D FA was \(p = 0.900\). The 3D FA values were increased compared to the 2D FA values using the Analyze software (Table 4).

Table 4: FA and ADC age stratification comparison of Analyze values with t-Test values (ADC is \(10^{-3}\)mm\(^2\)/s).

<table>
<thead>
<tr>
<th></th>
<th>18-40</th>
<th>SD</th>
<th>40+</th>
<th>SD</th>
<th>t-Test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 2D FA</td>
<td>0.762</td>
<td>0.020</td>
<td>0.756</td>
<td>0.025</td>
<td>0.339</td>
</tr>
<tr>
<td>Mean 3D FA</td>
<td>0.813</td>
<td>0.020</td>
<td>0.812</td>
<td>0.024</td>
<td>0.900</td>
</tr>
<tr>
<td>Mean 2D ADC</td>
<td>0.623</td>
<td>0.025</td>
<td>0.625</td>
<td>0.038</td>
<td>0.848</td>
</tr>
<tr>
<td>Mean 3D ADC</td>
<td>0.698</td>
<td>0.025</td>
<td>0.705</td>
<td>0.036</td>
<td>0.478</td>
</tr>
</tbody>
</table>
The difference in Analyze ADC values between the age groups 18-39 and 40+ were also not significant for both 2D and 3D image data. The 2D ADC difference had a p=0.848 and p = 0.478 for 3D ADC. The 3D ADC values were increased compared to the 2D ADC values using the Analyze software.

3.3 PRIDE Age Differentiations

The differences of FA values between age groups 18-40 and 40+ using the Philips PRIDE software had p = 0.710 for 2D and p = 0.770 for 3D and were not significant (Table 5). The mean 3D FA values were increased when compared to the mean 2D FA values for both 18-40 and 40+ age groupings. The differences of ADC values between age groups 18-40 and 40+ using the PRIDE software were also not significant for both 2D (p = 0.115) and 3D (p = 0.527) image slices. The mean 2D ADC values were increased compared to the mean 3D ADC values for both 18-40 and 40+ age groupings.

Table 5: FA and ADC age stratification comparison of PRIDE values with t-Test values (ADC is $*10^{-3}$mm$^2$/s).

<table>
<thead>
<tr>
<th></th>
<th>18-40</th>
<th>SD</th>
<th>40+</th>
<th>SD</th>
<th>t-Test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 2D FA</td>
<td>0.732</td>
<td>0.022</td>
<td>0.735</td>
<td>0.038</td>
<td>0.710</td>
</tr>
<tr>
<td>Mean 3D FA</td>
<td>0.833</td>
<td>0.024</td>
<td>0.836</td>
<td>0.033</td>
<td>0.770</td>
</tr>
<tr>
<td>Mean 2D ADC</td>
<td>0.754</td>
<td>0.041</td>
<td>0.780</td>
<td>0.068</td>
<td>0.115</td>
</tr>
<tr>
<td>Mean 3D ADC</td>
<td>0.678</td>
<td>0.027</td>
<td>0.685</td>
<td>0.054</td>
<td>0.527</td>
</tr>
</tbody>
</table>

3.4 Analyze 10.0 Gender Differentiations

There were no significant differences in FA values between the female and male gender data for both 2D (p = 0.089) and 3D (p = 0.138) image slices using Analyze 10.0 (Table 6). The Analyze 3D FA mean values in the gender groupings were increased in
comparison of 2D gender group FA values. There were also no significant differences in
Analyze ADC mean values between females and males in examination of using both 2D
(p = 0.150) and 3D (p = 0.216) data. The Analyze 3D ADC mean values were increased
compared to the 2D ADC values.

Table 6: FA and ADC gender comparison of Analyze (extracted) values with t-Test
values (ADC is *10⁻³mm²/s).

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>SD</th>
<th>Male</th>
<th>SD</th>
<th>t-Test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 2D FA</td>
<td>0.755</td>
<td>0.023</td>
<td>0.768</td>
<td>0.022</td>
<td>0.089</td>
</tr>
<tr>
<td>Mean 3D FA</td>
<td>0.810</td>
<td>0.022</td>
<td>0.820</td>
<td>0.021</td>
<td>0.138</td>
</tr>
<tr>
<td>Mean 2D ADC</td>
<td>0.628</td>
<td>0.032</td>
<td>0.613</td>
<td>0.029</td>
<td>0.150</td>
</tr>
<tr>
<td>Mean 3D ADC</td>
<td>0.705</td>
<td>0.030</td>
<td>0.692</td>
<td>0.035</td>
<td>0.216</td>
</tr>
</tbody>
</table>

3.5 PRIDE Gender Differentiations

There were no significant differences between female and male mean FA values
for either 2D (p = 0.164) or 3D (p = 0.097) images using the Philips PRIDE software
(Table 7). The PRIDE 3D FA image values were increased compared to the 2D FA image
values. There were also no significant differences between female and male mean ADC
values for either 2D (p = 0.511) or 3D (p = 0.065) images using the PRIDE software. The
PRIDE 2D ADC data was increased compared to the PRIDE 3D ADC data for both male
and female stratified gender groupings.

Table 7: FA and ADC gender comparison of PRIDE values with t-Test values and
Pearson correlation values (ADC is *10⁻³mm²/s).

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>SD</th>
<th>Male</th>
<th>SD</th>
<th>t-Test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 2D FA</td>
<td>0.730</td>
<td>0.032</td>
<td>0.744</td>
<td>0.028</td>
<td>0.164</td>
</tr>
<tr>
<td>Mean 3D FA</td>
<td>0.831</td>
<td>0.028</td>
<td>0.846</td>
<td>0.030</td>
<td>0.097</td>
</tr>
<tr>
<td>Mean 2D ADC</td>
<td>0.771</td>
<td>0.060</td>
<td>0.758</td>
<td>0.052</td>
<td>0.511</td>
</tr>
<tr>
<td>Mean 3D ADC</td>
<td>0.688</td>
<td>0.041</td>
<td>0.663</td>
<td>0.045</td>
<td>0.065</td>
</tr>
</tbody>
</table>
3.6 Control subjects compared with TBI subjects

There were significant differences in 2D FA mean values between control subjects and TBI subjects in CC regions A-F. Region G, the splenium, was the only region with not significantly different FA values (p = 0.515) between control subjects and TBI subjects. Region D, E, and F, which are PMB, Isthmus 1 and Isthmus2 respectively, showed the greatest differences (Figure 10).

![2D FA Controls vs TBI by Regions](image)

**Figure 10:** 2D FA comparison between control subjects and TBI subjects. Mean FA values of the CC regions are on the y axis and the CC regions are on the x axis.

Comparisons of the 3D (5 slice) FA show the Genu, region A, was the only region that was not significantly different between the control subjects and TBI subjects (p = 0.072). The remaining regions of the CC were shown to be significantly different (p < 0.05) (Figure 11). The greatest differences occurred in the PMB, Isthmus 1, and Isthmus 2 regions.
Figure 11: 3D (5 slice) FA comparison between control subjects and TBI subjects. Mean FA values of the CC regions are on the y axis and the CC regions are on the x axis.

Regional 2D ADC comparisons between control subjects and TBI subjects show regions A, C, and D (Genu, AMB, and PMB) to not be significantly different. T-Test p values for each are as follows: Genu p = 0.072, AMB p = 0.061 and PMB p = 0.392. The remaining regions of the CC were significantly different (Figure 12). TBI values showed a peculiar variation in that some values were increased and some were decreased compared to the control subjects. This 2D ADC plot shows an interesting crossing of the TBI values across the Control subject plot implying changes in the diffusion patterns include both increased water diffusion (higher ADC values) and decreased ADC values for a constricted water diffusion. Large differences in mean 2D ADC values were found in the Isthmus 1, Isthmus 2, and Splenium regions.
Regional 3D (5 slice) ADC comparisons between the control subjects and TBI subjects show regions A, D, E, F, and G were significantly different. Regions B and C, the VRB and AMB, were not significantly different; $p = 0.061$ and $p = 0.065$ respectively (Figure 13). The Isthmus 1 region showed the greatest difference in mean 3D ADC values between the TBI and Control subjects.
Figure 13: 3D (5 slice) ADC comparison between the control and TBI subjects. Mean ADC values of the CC regions are on the y axis, measured in mm$^2$/s, and the CC regions are on the x axis.

Table 8 provides the t-Test values for each region of the control subject and TBI subject comparisons. Values less than 0.05 confirm that the mean TBI and Control datasets for each region of the CC are significantly different.

Table 8: t-Test values for significance between control and TBI subjects for the seven regions of the CC.

<table>
<thead>
<tr>
<th>CC Region</th>
<th>2D FA</th>
<th>2D ADC</th>
<th>3D FA</th>
<th>3D ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genu</td>
<td>0.023</td>
<td>0.187</td>
<td>0.072</td>
<td>0.026</td>
</tr>
<tr>
<td>VRB</td>
<td>&lt;0.0001</td>
<td>0.014</td>
<td>0.005</td>
<td>0.061</td>
</tr>
<tr>
<td>AMB</td>
<td>&lt;0.0001</td>
<td>0.061</td>
<td>0.002</td>
<td>0.065</td>
</tr>
<tr>
<td>PMB</td>
<td>&lt;0.0001</td>
<td>0.392</td>
<td>&lt;0.0001</td>
<td>0.002</td>
</tr>
<tr>
<td>Isthmus 1</td>
<td>&lt;0.0001</td>
<td>0.007</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Isthmus 2</td>
<td>&lt;0.0001</td>
<td>0.001</td>
<td>&lt;0.0001</td>
<td>0.001</td>
</tr>
<tr>
<td>Splenium</td>
<td>0.515</td>
<td>&lt;0.0001</td>
<td>0.019</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
3.7 Control subjects compared with MS subjects

MS patients provide lower 2D FA values throughout the entire range of CC regions. Only the Splenium, region G, approached non-significantly different results ($p = 0.017$), but still proves to be significantly different (Figure 14). The VRB, AMB, PMB, Isthmus 1 and Isthmus 2 regions show the greatest differences in mean 2D FA values.

![2D FA Controls vs MS by Regions](image)

Figure 14: 2D FA between the control subjects and the MS subjects. Mean FA values of the CC regions are on the y axis and the CC regions are on the x axis.

Regional 3D FA comparisons between control subjects and MS subjects show a reduced 3D (5slice) FA values for MS subjects across all regions of the CC (Figure 15). All values were found to be significantly different with the greatest differences found in the PMB, Isthmus 1, and Isthmus 2 regions of the CC. Genu and Splenium values were least different.
Figure 15: 3D (5 slice) FA comparisons between control subjects and MS subjects. Mean FA values of the CC regions are on the y axis and the CC regions are on the x axis.

Two dimensional ADC comparisons show regions A, C, E, F, and G are significantly different while regions B and D, VRB and PMB, are not significantly different, $p = 0.218$ and $p = 0.076$ (Figure 16). Although the differences in posterior regions are noticeable and significant (except for the VRB and PMB regions), the greatest differences occur in the Isthmus 1, Isthmus 2, and Splenium regions of the CC.
Figure 16: 2D ADC comparison between control subjects and MS subjects. Mean ADC values of the CC regions are on the y axis, measured in mm$^2$/s, and the CC regions are on the x axis.

Comparisons between control subjects and MS subjects, for 3 ADC (5 slice), show that all CC regions are significantly different ($p < 0.001$) (Figure 17). Genu and Splenium regions show the least differences while the VRB, AMB, PMB, Isthmus 1, and Isthmus 2 regions show the largest differences.
Figure 17: 3D (5 slice) ADC comparisons between control subjects and MS subjects. Mean ADC values of the CC regions are on the y axis, measured in mm²/s, and the CC regions are on the x axis.

Two variable t-Test results for region comparisons between control subjects and MS subjects are provided in Table 9. Considerable, significant differences in MS and Control subject values exist within many of the CC regions as evident by the t-Test values less than 0.05.

Table 9: t-Test results for each region comparison between control and MS subjects.

<table>
<thead>
<tr>
<th>2 Variable t-Test p values for Regions</th>
<th>2D FA</th>
<th>2D ADC</th>
<th>3D FA</th>
<th>3D ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genu</td>
<td>&lt;0.0001</td>
<td>0.016</td>
<td>&lt;0.0001</td>
<td>0.001</td>
</tr>
<tr>
<td>VRB</td>
<td>&lt;0.0001</td>
<td>0.218</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AMB</td>
<td>&lt;0.0001</td>
<td>0.032</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PMB</td>
<td>&lt;0.0001</td>
<td>0.076</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Isthmus 1</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Isthmus 2</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Splenium</td>
<td>0.017</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
3.8  Control subjects compared with CO subjects

Comparisons between control and CO subjects for 2D FA show that regions B, C, D, E, and F are significantly different while regions A and G are not significantly different. Regions A and G, the Genu and Splenium, report t-Test p values of 0.988 and 0.390 respectively (Figure 18). The Isthmus 1 region shows the greatest difference in mean values for 2D FA.

![2D FA Controls vs CO by Regions](image)

Figure 18: 2D FA comparisons between control and CO subjects. Mean FA values of the CC regions are on the y axis and the CC regions are on the x axis.

Fractional Anisotropy comparisons between control and CO subjects show that regions C, D, E, and F are significantly different for 3D (5 slice) measurements while regions A, B, and G were not significantly different. The t-Test p values for these regions include: Genu p = 0.343, VRB p = 0.103, and Splenium p = 0.671 (Figure 19). The most significant difference occurred in the mean 3D FA values for the Isthmus 1 region.
Figure 19: 3D (5 slice) FA comparison between control subjects and CO subjects. Mean FA values of the CC regions are on the y axis and the CC regions are on the x axis.

Carbon monoxide subject values show variation with the Control subjects with both increased and decreased values compared to the Control individuals. Mean 2D ADC comparisons between control and CO subjects show CC regions B, C, D, F, and G are significantly different and regions A and E are not significantly different. The t-Test p values for regions A and E, the Genu and Isthmus 1, are 0.174 and 0.906 respectively (Figure 20). Again there is the criss-cross of the two plots as previously seen with the TBI-Control subject comparison for 2D ADC.
Figure 20: 2D ADC comparison between control and CO subjects. Mean ADC values of the CC regions are on the y axis, measured in mm$^2$/s, and the CC regions are on the x axis.

Regional 3D (5 slice) ADC comparisons between control and CO subjects show regions A, C, D, E, F, and G are significantly different with PMB, Isthmus 1, and Isthmus 2 CC regions showing the greatest variance. Regions B and C, the VRB and AMB, provide mean ADC values that are not significantly different. The t-Test p values for these two regions were 0.211 and 0.228 respectively (Figure 21).
Figure 21: 3D (5 slice) ADC comparison between control and CO subjects. Mean ADC values of the CC regions are on the y axis, measured in mm$^2$/s, and the CC regions are on the x axis.

Table 10 provides a summary of all t-Test data for FA and ADC comparisons between control and CO subjects. Test values less than 0.05 confirm that mean values for the regions are significantly different.

Table 10: t-Test results for FA and ADC comparisons between control and CO subjects for CC regions.

<table>
<thead>
<tr>
<th>2 Variable t-Test p values for Regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D FA</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>Genu</td>
</tr>
<tr>
<td>VRB</td>
</tr>
<tr>
<td>AMB</td>
</tr>
<tr>
<td>PMB</td>
</tr>
<tr>
<td>Isthmus 1</td>
</tr>
<tr>
<td>Isthmus 2</td>
</tr>
<tr>
<td>Splenium</td>
</tr>
</tbody>
</table>

Tables 11 provides a summary of mean FA and mean ADC values for all regions of the CC, including whole CC, and for control, CO, MS, and TBI subjects with appropriate t-Test p values.
Table 11: Mean FA and mean ADC for all subjects and regions. (ADC is in mm$^2$/s, shaded values are p<0.05 for significantly different comparison with Control subjects)

### Control Subjects (n=52)

<table>
<thead>
<tr>
<th></th>
<th>Genu</th>
<th>VRB</th>
<th>AMB</th>
<th>PMB</th>
<th>Isthmus 1</th>
<th>Isthmus 2</th>
<th>Splenium</th>
<th>Whole CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D FA</td>
<td>0.739</td>
<td>0.730</td>
<td>0.765</td>
<td>0.785</td>
<td>0.785</td>
<td>0.784</td>
<td>0.766</td>
<td>0.758</td>
</tr>
<tr>
<td>3D FA</td>
<td>0.739</td>
<td>0.729</td>
<td>0.762</td>
<td>0.777</td>
<td>0.765</td>
<td>0.775</td>
<td>0.775</td>
<td>0.762</td>
</tr>
<tr>
<td>2D ADC</td>
<td>0.000627</td>
<td>0.000660</td>
<td>0.000616</td>
<td>0.000622</td>
<td>0.000638</td>
<td>0.000631</td>
<td>0.000604</td>
<td>0.000624</td>
</tr>
<tr>
<td>3D ADC</td>
<td>0.000620</td>
<td>0.000636</td>
<td>0.000591</td>
<td>0.000598</td>
<td>0.000630</td>
<td>0.000635</td>
<td>0.000608</td>
<td>0.000615</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.030</td>
<td>0.030</td>
<td>0.041</td>
<td>0.028</td>
<td>0.034</td>
<td>0.030</td>
<td>0.023</td>
<td>0.020</td>
</tr>
</tbody>
</table>

### Carbon Monoxide Subjects (n=65)

<table>
<thead>
<tr>
<th></th>
<th>Genu</th>
<th>VRB</th>
<th>AMB</th>
<th>PMB</th>
<th>Isthmus 1</th>
<th>Isthmus 2</th>
<th>Splenium</th>
<th>Whole CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D FA</td>
<td>0.738</td>
<td>0.688</td>
<td>0.714</td>
<td>0.713</td>
<td>0.692</td>
<td>0.726</td>
<td>0.772</td>
<td>0.733</td>
</tr>
<tr>
<td>3D FA</td>
<td>0.746</td>
<td>0.715</td>
<td>0.742</td>
<td>0.740</td>
<td>0.715</td>
<td>0.743</td>
<td>0.772</td>
<td>0.747</td>
</tr>
<tr>
<td>2D ADC</td>
<td>0.000641</td>
<td>0.000620</td>
<td>0.000559</td>
<td>0.000583</td>
<td>0.000640</td>
<td>0.000668</td>
<td>0.000649</td>
<td>0.000628</td>
</tr>
<tr>
<td>3D ADC</td>
<td>0.000664</td>
<td>0.000077</td>
<td>0.000084</td>
<td>0.000077</td>
<td>0.00091</td>
<td>0.00090</td>
<td>0.00069</td>
<td>0.00048</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.044</td>
<td>0.052</td>
<td>0.059</td>
<td>0.058</td>
<td>0.079</td>
<td>0.059</td>
<td>0.039</td>
<td>0.041</td>
</tr>
</tbody>
</table>

### Multiple Sclerosis Subjects (n=160)

<table>
<thead>
<tr>
<th></th>
<th>Genu</th>
<th>VRB</th>
<th>AMB</th>
<th>PMB</th>
<th>Isthmus 1</th>
<th>Isthmus 2</th>
<th>Splenium</th>
<th>Whole CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D FA</td>
<td>0.688</td>
<td>0.643</td>
<td>0.647</td>
<td>0.666</td>
<td>0.642</td>
<td>0.666</td>
<td>0.742</td>
<td>0.688</td>
</tr>
<tr>
<td>3D FA</td>
<td>0.677</td>
<td>0.667</td>
<td>0.683</td>
<td>0.700</td>
<td>0.668</td>
<td>0.689</td>
<td>0.738</td>
<td>0.703</td>
</tr>
<tr>
<td>2D ADC</td>
<td>0.000668</td>
<td>0.000691</td>
<td>0.000664</td>
<td>0.000658</td>
<td>0.000712</td>
<td>0.000742</td>
<td>0.000696</td>
<td>0.000686</td>
</tr>
<tr>
<td>3D ADC</td>
<td>0.000118</td>
<td>0.000176</td>
<td>0.000154</td>
<td>0.000141</td>
<td>0.000169</td>
<td>0.000180</td>
<td>0.000110</td>
<td>0.000120</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.074</td>
<td>0.096</td>
<td>0.100</td>
<td>0.096</td>
<td>0.120</td>
<td>0.115</td>
<td>0.067</td>
<td>0.074</td>
</tr>
</tbody>
</table>

### Traumatic Brain Injury Subjects (n=126)

<table>
<thead>
<tr>
<th></th>
<th>Genu</th>
<th>VRB</th>
<th>AMB</th>
<th>PMB</th>
<th>Isthmus 1</th>
<th>Isthmus 2</th>
<th>Splenium</th>
<th>Whole CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D FA</td>
<td>0.716</td>
<td>0.683</td>
<td>0.699</td>
<td>0.706</td>
<td>0.660</td>
<td>0.718</td>
<td>0.760</td>
<td>0.719</td>
</tr>
<tr>
<td>3D FA</td>
<td>0.723</td>
<td>0.705</td>
<td>0.734</td>
<td>0.736</td>
<td>0.700</td>
<td>0.732</td>
<td>0.757</td>
<td>0.733</td>
</tr>
<tr>
<td>2D ADC</td>
<td>0.000646</td>
<td>0.000622</td>
<td>0.000585</td>
<td>0.000608</td>
<td>0.000696</td>
<td>0.000682</td>
<td>0.000665</td>
<td>0.000643</td>
</tr>
<tr>
<td>3D ADC</td>
<td>0.000101</td>
<td>0.000102</td>
<td>0.000109</td>
<td>0.000112</td>
<td>0.000141</td>
<td>0.000097</td>
<td>0.000069</td>
<td>0.000075</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.058</td>
<td>0.058</td>
<td>0.061</td>
<td>0.067</td>
<td>0.087</td>
<td>0.071</td>
<td>0.052</td>
<td>0.052</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Genu</th>
<th>VRB</th>
<th>AMB</th>
<th>PMB</th>
<th>Isthmus 1</th>
<th>Isthmus 2</th>
<th>Splenium</th>
<th>Whole CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D FA</td>
<td>0.068</td>
<td>0.065</td>
<td>0.076</td>
<td>0.078</td>
<td>0.101</td>
<td>0.084</td>
<td>0.055</td>
<td>0.056</td>
</tr>
<tr>
<td>3D FA</td>
<td>0.072</td>
<td>0.058</td>
<td>0.061</td>
<td>0.067</td>
<td>0.087</td>
<td>0.071</td>
<td>0.052</td>
<td>0.052</td>
</tr>
<tr>
<td>2D ADC</td>
<td>0.000648</td>
<td>0.000666</td>
<td>0.000620</td>
<td>0.000643</td>
<td>0.000709</td>
<td>0.000682</td>
<td>0.000653</td>
<td>0.000653</td>
</tr>
<tr>
<td>3D ADC</td>
<td>0.000087</td>
<td>0.000110</td>
<td>0.000107</td>
<td>0.000102</td>
<td>0.000133</td>
<td>0.000098</td>
<td>0.000652</td>
<td>0.000077</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.026</td>
<td>0.061</td>
<td>0.065</td>
<td>0.002</td>
<td>&lt;0.0001</td>
<td>0.001</td>
<td>&lt;0.0001</td>
<td>0.001</td>
</tr>
</tbody>
</table>
CHAPTER 4

DISCUSSION

DTI has demonstrated clinical utility in the diagnosis, evaluation and monitoring in numerous neurological and psychiatric disorders by revealing decreased FA and increased ADC values due to changes in the white matter integrity allowing an increase in the radial diffusion of water, as well normal anatomical and physiological changes such as brain development and aging through changes in FA and ADC.\textsuperscript{2,4,5,6,8,11,15,20,28,30,31} Numerous CNS conditions have been studied by DTI, including Alzheimer’s disease\textsuperscript{24,32}, amyotrophic lateral sclerosis (ALS)\textsuperscript{33}, cerebral adrenoleukodystrophy\textsuperscript{34}, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)\textsuperscript{35}, epilepsy, Krabbe disease\textsuperscript{36}, multiple sclerosis\textsuperscript{37,14,21}, traumatic brain injury\textsuperscript{38,23,39,40,41,42} and several psychiatric disorders\textsuperscript{15} such as anxiety\textsuperscript{15}, attention deficit hyperactivity disorder (ADHD)\textsuperscript{43}, fetal alcohol syndrome\textsuperscript{44}, depression\textsuperscript{41}, obsessive compulsive disease (OCD)\textsuperscript{15}, schizophrenia\textsuperscript{15}, and autism\textsuperscript{2,45}

4.1 Normative, Control Subjects

Normative, healthy, control subject values (n=52 subjects) for the whole CC and the seven approximations of the anatomical regions of mean ADC and mean FA DTI measurements acquired with the Analyze software package, from Table 11, provide a considerable basis of comparison for typical values found in publicized literature. Values from the 3D (5slice) acquisition are not very different from the 2D values for ADC and FA as the 3D (5 slice) technique represents less than 20\% of the entire width of the CC and is thus a poor approximation of a true 3D model of the CC or of the CC regions.
Studies have also been conducted on healthy subjects to produce a control data set that can be used for comparison. Lee et al. found normative data for 31 individuals without known neurologic disorders using the Philips MRI scanner (Intera 3T MRI) and the PRIDE analyzing software. In the Lee et al. study, the average FA value for the genu of the corpus callosum for the 19-39 age group was 0.806 ± 0.065 and the 40-65 age group was 0.786 ± 0.076. The average FA value for the splenium of the corpus callosum for the age group 19-39 was 0.775 ± 0.052 and for the 40-65 age group was 0.777 ± 0.085. Lee et al. found average ADC values (×10⁻³ mm²/s) of the genu of the corpus callosum to be 0.780 ± 0.041 for the 19-39 age group while the 40-65 age group had an average ADC 0.747 ± 0.085 value. The splenium of the corpus callosum had a mean ADC value of 0.774 ± 0.069 for the 19-39 age group while the 40-65 age group had a 0.757 ± 0.099 mean ADC value (×10⁻³ mm²/s). These values fall within a standard deviation of the mean 2D ADC values obtained in this study. LeBihan et al. report mean FA and ADC values of the healthy splenium to be 0.860±0.050 and .690± 0.050 (×10⁻³ mm²/s). Normative data for 19 additional individuals without known neurologic disorders from the peer-reviewed literature that used Siemens and GE 3T MRI 2D FA values for the corpus callosum ranged from 0.748-0.800. The range of 2D FA values of 0.720-0.806 for Philips 3T MRI systems and 0.748-0.800 for 3T GE and Siemens systems are comparable. The comparable numbers between the “healthy” volunteers in the study conducted by Lee et al. and to our 50 normal control patients confirm a similar range of normal values for FA and ADC data using the Philips PRIDE software. Six regions of the CC and whole CC values for 2D FA and 2D ADC were produced by Hasan et al. Mean 2D FA values from 0.403 to 0.589 characterize the CC regions which are
considerably lower than the same values determined with PRIDE and this Analyze technique. Comparative literature values for FA and ADC are summarized in Table 12.

The t-Test and Pearson correlation comparisons between PRIDE and the extracted Analyze values confirm that the results are significantly different between the two methods, but with strongly similar correlation trends between the analysis methods. The t-Test and Pearson correlation comparisons between PRIDE and the 5 slice Analyze technique confirm that FA and ADC results are significantly different but with strongly similar comparison trends.

Table 12: Comparative Literature Values of FA and ADC.

<table>
<thead>
<tr>
<th>This Study</th>
<th>FA</th>
<th>SD</th>
<th>ADC</th>
<th>SD</th>
<th>Studies</th>
<th>FA</th>
<th>SD</th>
<th>ADC</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 52 subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D Genu</td>
<td>0.739</td>
<td>0.030</td>
<td>0.000620</td>
<td>0.000038</td>
<td>Lee\textsuperscript{35}</td>
<td>Genu (19-39)</td>
<td>0.806</td>
<td>0.065</td>
<td>0.000780</td>
</tr>
<tr>
<td>3D VRB</td>
<td>0.729</td>
<td>0.030</td>
<td>0.000636</td>
<td>0.000048</td>
<td>Genu (40-65)</td>
<td>0.786</td>
<td>0.076</td>
<td>0.000747</td>
<td>0.000085</td>
</tr>
<tr>
<td>3D AMB</td>
<td>0.762</td>
<td>0.041</td>
<td>0.000591</td>
<td>0.000057</td>
<td>Genu (40-65)</td>
<td>0.775</td>
<td>0.052</td>
<td>0.000774</td>
<td>0.000069</td>
</tr>
<tr>
<td>3D PMB</td>
<td>0.777</td>
<td>0.028</td>
<td>0.000598</td>
<td>0.000048</td>
<td>Splenium (19-39)</td>
<td>0.777</td>
<td>0.085</td>
<td>0.000757</td>
<td>0.000099</td>
</tr>
<tr>
<td>3D Isthmus 1</td>
<td>0.765</td>
<td>0.034</td>
<td>0.000630</td>
<td>0.000045</td>
<td>Splenium (40-65)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D Isthmus 2</td>
<td>0.775</td>
<td>0.030</td>
<td>0.000635</td>
<td>0.000055</td>
<td></td>
<td>0.715</td>
<td>0.047</td>
<td>0.000697</td>
<td>0.000033</td>
</tr>
<tr>
<td>3D Splenium</td>
<td>0.775</td>
<td>0.023</td>
<td>0.000608</td>
<td>0.000037</td>
<td></td>
<td>0.748</td>
<td>0.019</td>
<td>0.000781</td>
<td>0.000027</td>
</tr>
<tr>
<td>3D whole CC</td>
<td>0.762</td>
<td>0.020</td>
<td>0.000615</td>
<td>0.000027</td>
<td></td>
<td>0.800</td>
<td>0.034</td>
<td>0.000653</td>
<td>0.000041</td>
</tr>
<tr>
<td>2D Genu</td>
<td>0.739</td>
<td>0.036</td>
<td>0.000627</td>
<td>0.000044</td>
<td>Hunsche\textsuperscript{34}</td>
<td>Genu</td>
<td>0.800</td>
<td>0.080</td>
<td>0.000853</td>
</tr>
<tr>
<td>2D VRB</td>
<td>0.730</td>
<td>0.042</td>
<td>0.000660</td>
<td>0.000071</td>
<td>Splenium</td>
<td>0.770</td>
<td>0.070</td>
<td>0.000728</td>
<td>0.000084</td>
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<tr>
<td>2D AMB</td>
<td>0.765</td>
<td>0.053</td>
<td>0.000616</td>
<td>0.000073</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2D PMB</td>
<td>0.785</td>
<td>0.046</td>
<td>0.000622</td>
<td>0.000053</td>
<td>Hasan\textsuperscript{35}</td>
<td>Splenium</td>
<td>0.492</td>
<td>0.028</td>
<td>0.001020</td>
</tr>
<tr>
<td>2D Isthmus 1</td>
<td>0.785</td>
<td>0.059</td>
<td>0.000638</td>
<td>0.000087</td>
<td>2D whole CC</td>
<td>0.541</td>
<td>0.040</td>
<td>0.000955</td>
<td>0.000677</td>
</tr>
<tr>
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<td>0.784</td>
<td>0.048</td>
<td>0.000631</td>
<td>0.000076</td>
<td>2D Genu</td>
<td>0.416</td>
<td>0.035</td>
<td>0.001039</td>
<td>0.000943</td>
</tr>
<tr>
<td>2D Splenium</td>
<td>0.766</td>
<td>0.033</td>
<td>0.000604</td>
<td>0.000043</td>
<td>2D Rostral Body</td>
<td>0.403</td>
<td>0.042</td>
<td>0.001036</td>
<td>0.000087</td>
</tr>
<tr>
<td>2D PMB</td>
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<td>0.042</td>
<td>0.001036</td>
<td>0.001011</td>
<td>2D AMB</td>
<td>0.431</td>
<td>0.057</td>
<td>0.001120</td>
<td>0.001101</td>
</tr>
<tr>
<td>2D Isthmus 1</td>
<td>0.589</td>
<td>0.037</td>
<td>0.001016</td>
<td>0.000753</td>
<td>2D Splenium</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2D Isthmus 2</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2D whole CC</td>
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</tbody>
</table>

4.2 Gender and Age Comparisons

Liu et al. found normative data for 10 male and 10 female subjects for FA and mean diffusivity. Only the genu of the CC of male subjects revealed a significantly increased FA (p < 0.05) compared to female subjects with no significant differences in ADC among male and female subjects.\textsuperscript{8} In this study, both PRIDE and Analyze
(extracted) analysis showed no significant differences in FA or ADC values, for both the 2D and 3D measurements, between male and female subjects.

Sullivan et al. reported a study of DTI metrics of the adult aging brain and showed a decrease in FA in five of six regions of the CC with an increase in ADC in the same five regions of the CC among 8 elderly and 8 young subjects. Elderly patients in Sullivan’s study had a mean age of 74.6 ± 5.1 years, while young patients were 28.6 ± 5.2 years. This study showed no significant differences in 2D ADC, 2D FA, 3D ADC, or 3D FA from either PRIDE or the extracted Analyze methods for the two age groups that were imaged (18-39 years and 40+ years). It should be noted that the oldest patient in this study was only 61 years old at the time of imaging and the youngest was 18.

As a result of the non significant difference in Analyze 10.0 results for the control subjects, continued gender and age differentiation was discontinued for the comparisons between control subjects and TBI, MS, and CO subjects.

4.3 Analyze 10.0 Comparisons between Control and Diseased Subjects

When comparing the 52 control subjects to the TBI (126 subjects), MS (160 subjects) and CO (65 subjects) groups, significant differences between FA and ADC values were found in multiple regions of the CC and well as whole CC comparisons. Both 2D and 3D (5 slice) analysis was completed on all 403 subjects for these comparisons with the Analyze software.

Compared with the control subjects, TBI subjects show significant differences (t-Test p < 0.05) for all regions except the splenium (region G) for 2D FA. 2D ADC shows
differences in the VRB, isthmus 1, isthmus 2, and splenium. Only the genu region is not
significantly different for 3D FA values. 3D ADC values are significantly different for all
regions except the VRB, and AMB. Whole CC comparisons show a decreased FA and
increased ADC for both 2D and 3D measurements. Literature consistently shows a
reduced FA value in TBI subjects.\textsuperscript{23,38,39,40} Miles et al. reports FA values for TBI subjects
of 0.66 ± 0.02 with 0.71 ± 0.03 for controls and only reports mean diffusivity increases
for TBI subjects.\textsuperscript{42} Maller et al. reports a consistent decrease in FA over various regions
and whole CC studies with associated increases in ADC measurements in his literature
review study of 40 DTI-TBI articles.\textsuperscript{41}

Multiple Sclerosis subjects also show a global reduction in FA and increase in
ADC over the whole CC.\textsuperscript{8,14,21,37} Liu et al. and Roosendaal et al. both report in their
DTI-MS studies an increase in ADC values for MS subjects compared to control subjects,
and a decrease in FA measurements for MS subjects.\textsuperscript{8,14} All 2D and 3D values for FA
were significantly different for all regions of the CC. 3D ADC values were significantly
different for all regions of the CC. Only the VRB and PMB showed no significant
differences for 2D ADC comparisons.

Terajima et al. reports that structural changes in white matter cause an increase in
ADC for CO subjects with a resulting decrease in FA for the CC.\textsuperscript{46} Chang et al. report
that not all white matter damage could be detected by DTI metrics just after onset of CO
poisoning.\textsuperscript{47} Some subjects only showed decreases in FA and associated increases in
ADC after some time had passed and that changes in ADC and FA values continued for
patients measured 3 month post poisoning to 10 months post poisoning.\textsuperscript{47} CO subjects
show many significant differences with control subjects, both whole CC and regionally, for FA and ADC values.\textsuperscript{47,46} 2D FA values for the genu and splenium were not significantly different, but the remaining mid-regions were significantly different. 3D FA measurements showed the same but with the VRB also showing non-significantly different values. Only the PMB, isthmus 2, and splenium were significantly different for both 2D and 3D ADC measurements.

Literature did not often report absolute values of ADC and FA for their control or other subjects, but often only reported significant and non-significant changes in ADC and FA, and most often showed whole CC changes or changes in major regions of the CC such as the genu, rostral body, or the splenium.\textsuperscript{4,6,14,23,24,32,46} This study concludes that DTI metric values depend heavily upon the software creating them and absolute values of ADC and FA for ROIs do not exist yet due to ROI definitions from these two software packages. Report of changing ADC and FA values is only a qualitative description of the WM changes in the CC which this study supports these similar literature findings.
CHAPTER 5

CONCLUSIONS

The use of DTI has provided a noninvasive and in vivo approach for the detection and evaluation of WM changes or damage in the human brain.\textsuperscript{2,3,4,5,18} DTI has shown to be more sensitive in detecting micro structural changes in WM than T2-weighted MRI.\textsuperscript{2,3,6,12,36}

5.1 Comparing Analyze 10.0 to PRIDE

This DTI metrics study of FA and ADC values from an off the shelf software package, Analyze 10.0, provides corroborative data for using FA and ADC measurements in detecting and quantifying differential damage to the seven various CC regions and the whole CC. Presently, PRIDE is not capable of creating autonomized, multiple region ROI’s. Both the extracted ROI and 5 slice Analyze techniques produced significantly different values for ADC and FA than the PRIDE software package, the proprietary software supplied with the Philips MR imaging system. Analyze does provide reliable results for FA and ADC measurements that correlate strongly with the PRIDE software data. Trend lines between the two software packages are nearly parallel for all FA and ADC comparisons. The 5 slice Analyze technique does provide reduced FA values and slightly increased ADC values compared to the extracted ROI and PRIDE techniques due to the lack of slices that are included in the ROI. It is just a partial 3D collection of the CC. PRIDE and extracted ROI’s could include as many as 20 to 30 slices to recreate the entire width of the CC; whereas, the 5 slice only contains the 5 most central slices. Pearson correlation values show that each of the Analyze analysis techniques is strongly
similar to the PRIDE values and thus can be a reliable tool in producing ADC and FA values even though Analyze produces significantly different values for ADC and FA.

5.2 Carbon Monoxide, Multiple Sclerosis, and Traumatic Brain Injury subjects compared to Control Subjects with Analyze 10.0

Control subjects were characterized with the Analyze 5 slice technique. Fifty two data sets were measured for both mean 2D and 3D FA and ADC for whole CC ROI and seven ROI sub regions of the CC. These control subjects were used as a benchmark for comparisons with 378 subjects previously determined to have TBI, MS, or CO damage to WM regions of the brain. Changes in mean FA and mean ADC for various regions of the CC were indicated in the non-control subjects. These mean FA and mean ADC changes imply damage or at least changes in WM integrity for the corresponding CC regions. Figure 22 provides evidence of significant differences in mean, whole CC 3D FA between the control subjects and non-control subjects suggesting the need to evaluate regional influences on mean 3D FA for the individuals to determine if localized CC damage influences the whole CC. Figures (23-26) show some of the significant variations in values between control and non-control subjects for the seven regions of the CC. Deviation from normal values for ADC and FA could prove to be a useful measurement in the detection, diagnosis, and treatment planning for WM damaged subjects. Since the accuracy of DTI measurements such as ADC and FA depend upon the software package, it is important for future evaluation of ADC and FA values that the DTI analysis is conducted with the same software. This will be especially important if ADC and FA variations are used to determine a diagnosis of WM damage in patients.
Figure 22: Mean 3D (5slice) FA comparison of all subjects. Mean FA values are on the y axis while the y axis indicates the number of subjects in the study. Significant variation in CO, MS, and TBI subjects compared to control subjects suggest white matter damage within the corpus callosum region of interest to some of the non-control subjects while some appear undamaged.

Figure 23: 2D ADC comparison by regions for Controls, TBI, MS, and CO subjects. Mean ADC values of the CC regions are on the y axis, measured in mm$^2$/s, and the CC regions are on the x axis.
Figure 24: 2D FA comparison by regions for Controls, TBI, MS, and CO subjects. Mean FA values of the CC regions are on the y axis and the CC regions are on the x axis.

Figure 25: 3D ADC comparison by regions for Controls, TBI, MS, and CO subjects. Mean ADC values of the CC regions are on the y axis, measured in mm$^2$/s, and the CC regions are on the x axis.
Figure 26: 3D FA comparison by regions for Controls, TBI, MS, and CO subjects. Mean FA values of the CC regions are on the y axis and the CC regions are on the x axis.

5.3 Future Considerations

Other off the shelf DTI analysis software exists. Like Analyze and PRIDE, each has its own unique differences.\textsuperscript{25,48} Future and continued development of these DTI software packages should progress to a more universal and systematically congruent analysis package yielding significantly similar results. Software packages use the same equations for determining DTI metrics like ADC and FA, but ROI developments used in the analysis are different enough to create significant differences in the calculations. DTI metric values will remain software dependant and ambiguous until a systematic ROI development is established.

ROI manipulation is also a complication to overcome. Analyze and PRIDE do not create 3D ROIs in a universal manner, nor does either package allow for an ROI to be easily and automatically divided into regions. Multiple ROIs have to be geometrically created into equal width or equal angular sections, or must be created by hand.
anatomical/pathological markers of the CC can be used to create accurate ROI representations, more accurate DTI metrics of the CC regions will be attainable.

Clinical outcome comparisons for each of the non-control subjects (TBI, MS, and CO) with DTI metrics (severity scores with quantifiable changes in FA or ADC) should be included in future studies to produce a scale of FA and ADC changes that correlate with mild, moderate, and severe damages to the ROI. This could aid in the diagnosis, evaluation, and treatment of various conditions.
APPENDIX I

Analyze 10.0 Directions

1. Importing Phillips Par/Rec files

- From the main workspace:
- File - Import Export
- Tools - Raw Data
- Browse to find the appropriate Rec file (always the 38.2 Mb file)
- R:/Par Rec
- Select the Image Parameters Tab
- check the display, clear, scale, and offset boxes (all 4)
- Input width and height to 128x128, depth to 36 and volumes to 34
- Change data type to unsigned 16-bit
- Click the Load button on the Files Tab

![Image of the Analysis window showing data parameters]

- A volume of data will appear on the main workspace, close out of the Import/Export windows
- Exit the Import/Export window
- Again from the main workspace:
- File - Load As
- Select and drag the volume from the workspace to the Load As window
- If an error pops up about using default info or calculating it, cancel and unload the image from the workspace and start over; the image parameters were not set right
- Select the Sub/Region tab
- change the Low V from 1 to 33 and the High V to 33
• uncheck the auto exit after load box
• click the Load button
• Create new volume
• A second volume of data now appears on the main workspace, this is the base volume and appears brighter than the first
• Again from the main workspace:
• Again drag the first 34 volume data to the Load As window
• Select the Sub/Region tab
• Change the High V from 34 to 32
• check the exit upon load box
• Load
• Load as a single multi volume (1st option on left)
• create new
• there are now 3 volumes of data on the main workspace
• Hold down the Shift key, then select the 2nd and 3rd volumes (the two you just created): must select the 2nd then 3rd in order----cannot flip flop
• Right click on the mouse and select the Append option from the drop down menu
• Select Create a MultiVolume with 33 volumes
• don't unload other files
• A 4th volume appears on the main workspace, THIS IS THE BASE VOLUME WITH THE 32 DW FILES THAT YOU WILL USE FOR DTI STUDIES (you know it was done correctly if the brighter base volume map is showing in this new volume)

2. Creating DTI maps

• From the main workspace:
• Load data into the workspace
• Select the 4th volume on the screen (Base volume and the additional DW volumes)

• Goto the Apps Menu
• Select the DTI add-on
• Click the Load Gradient Directions button
• From the desktop of the computer, select the text file Analyze gradients(Patton)
• Load the gradient directions
• Leave the B value at 1000
• Flip the Gradients Signs for Z
• Click the Apply button
• Select the Map Processing Tab
• Adjust the Background Threshold slider to remove the skull from the calculations (about 12-20)
• Click the Compute DTI Maps button
• ADC, FA, and Eigen Vector maps can be viewed from the menu button in the middle of the screen
• As a check, Select the eigen vector maps from the central drop down menu, in the sagittal view, the CC should appear distinct and bright red
• To save DTI maps:
  • File - Save DTI Maps
  • Save Volume
  • Done
  • Exit the DTI APP
  • DTI Maps will be saved onto the main workspace

3. **To create a grey scale eigen vector map**
   • from the main work space (with all volumes now present --11 volumes)
   • File - Load As
   • Drag the Eigen Vector map (AppendedFiles_EVCM), of the newly created DTI maps, onto the Load As window
   • Change the 24 bit conversion from None to Red Channel
   • Select Load - Create New
   • This new volume is called AppendedFiles_EVCM0

4. **Defining an ROI**
   • From the main workspace:
   • Select both the colored and grey scale eigen vector maps
   • Go to the ROI button at the top (both maps will appear in the ROI window)
   • Go to the Generate menu
   • Change the orientation to Sagittal, then Done
   • Again go to the Generate menu and change the slice to about 64 Use the +magnification to magnify the image (also maximize the window at the top right)
   • Select the appropriate orientation and slice (typically for a corpus callosum - Sagittal, 64 or 65 is usually the middle of the CC and the best to pick...look for more of the colored map to be dark, indicating that you are at the middle of the
CC, and look for the green ‘triangular’ formation to appear just below the CC. If 2 slices look the same, default to the lower slice number as the midline

- Set Object To Define to ***New*** (bottom center of screen)
- Select the 3D Mode
- Select the Auto Trace Drawing tool to define the region on the current slice (3rd from top on left side)
- Click on a region of the CC on the grey scale EVCM0 map,
- On Edge should be checked
- In the box just above, input a low threshold of 100 and on the far side of the slide, an upper threshold of 255
- the low end value of 100 may need tweaking for some CC, especially a damaged CC
- Click Apply when done
- Copy ROI to each slice that is adjacent to this midline slice (64, and 66 if middle is 65), use the **Use the Copy Current Region Forward and Backward Buttons next to the Exit button**: Click one of the buttons to copy the region then click on the CC region, then click the apply button for it to set.

- You must have an ROI defined on 5 consecutive slices, and the ROI is defined using the midline slice
- Save the ROI object map now if using the whole CC region (File-Save Object Map...)
4b. **To create an extracted ROI of the whole CC**

- from the ROI workspace, select the Object Extraction button
- load the grey scale eigen vector map of the midline slice
- select a region of the whole CC to be extracted
- set the intensity range minimum to 100 and the maximum to the maximum value
- click apply when done to extract all of the voxels within the intensity range on either side of the midline slice
- arrow forward and back to view the resulting extracted CC (will be in between 20 to 30 slices now)
- save the new extracted ROI object map

5. **To create a multi-segment ROI**

- from the ROI workspace
- load both the colored and grey scale eigen vector maps
- create the sagittal images at the same slice that was used to create the total ROI object
- File - Load Object Map
- select the total object map that was just created in the previous section (may already be at this step from part 4)
- Select the Grid Divider button
- Change Rows to 1 and Columns to 6
- Point and click anywhere within the object map loaded onto the two images, notice the ROI is now divided into 6 regions
- Repeat for the other two slices; use the slice slider or the Show button t move to the other slices
- Region 4 (should be 2nd from the right) needs to be divided into half
- Change Object to Define to 3, change columns to 2 then click on this region to split it
- Move to the other two slices and repeat...use the slice slider of the Show button to move then click on the ROI to divide it
- All of the regions need to be renamed from their object numbers to letter designations
- Click View - Objects
- In the Name box, type A
- Click the Add object Button of the window
Repeat this renaming procedure for the regions B - H

- click the Rename Region Button in the bottom left
- From the Object to Define drop down menu, Select the region name A, then click on the region of the CC you want to be called A
- Repeat for all regions and all slices

If “H region” voxels appear in on slice, but not the others, absorb it into the adjacent region by renaming it as that same region; if it appears in two slices but not one, then keep it as the H region and DO NOT absorb it into A; do the same for any spare voxels that may be sticking off of the G region on the other side unless it looks like an island extension of the F region, then label it F.
• MAKE SURE THE REGIONS ARE LISTED IN ORDER (A-H) IN THE OBJECT TO DEFINE LIST (CENTER OF SCREEN) IF NOT, REDO THIS NAME ASSIGNMENT SECTION

<table>
<thead>
<tr>
<th>Original</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.Object</td>
<td>D</td>
</tr>
<tr>
<td>2.Object</td>
<td>E</td>
</tr>
<tr>
<td>3.Object</td>
<td>F</td>
</tr>
<tr>
<td>4.Object</td>
<td>G</td>
</tr>
<tr>
<td>5.Object</td>
<td>13.Object</td>
</tr>
<tr>
<td>A</td>
<td>*** New ***</td>
</tr>
<tr>
<td>B</td>
<td></td>
</tr>
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</table>

• Clean out all other objects from the list: View-Objects-Remove Unused

<table>
<thead>
<tr>
<th>Original</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>F</td>
</tr>
<tr>
<td>B</td>
<td>G</td>
</tr>
<tr>
<td>C</td>
<td>*** New ***</td>
</tr>
<tr>
<td>D</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Object To Define:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
</tr>
</tbody>
</table>

• If you need to start over from scratch: File - Reset Object Map - continue Without Saving
• **IF THE H REGION EXISTS**: we also want data when H is absorbed into the A region (so we can look at it both with and without the H region). Rename each H region that exists as A so that it is absorbed into A,
• Exit the ROI editor
6. To Determine ADC, Axial, FA, RA, Radial, and VR

- from the main workspace:
- select and highlight the ADC, Axial, FA, RA, Radial, and VR maps in this order and all highlighted together (they must be in this, alphabetical order before you append them together)
- Right Click and select Append
- select Multi volume, then Don't Unload
- This creates a new multivolume map called AppendedFiles0, select this volume
- Measure - Region of Interest
- maximize window, use generate orientation and slice to select the Saggital slice that is the first of the 5 slices in the ROI, and magnify image. Use the slider bar beneath the image to get to the right slice #, images may appear black
- File - Load Object Map to load the *_divided_total.obj object map you created in part 5
- The divided object map will appear in the image with regions labeled A-G

In this example, slice 64 is the first of the 3 slices, since slice 65 was determined to be the midline slice

- Click the Sample Opt (sample options) to change from 2 decimal places to 10 (bottom of pop up window that appears)
- Change Log Stats to On
- Change the Sample type to Object(s), and select the objects A-H; leave this window open
Go to Generate - Slice; Change the Volume Number to 6 (3rd slider), and change the Slice Number to 3 (6th slider)
Click Done to close this window
Go back to the Sample options window and prepare to collect data!
Configure Log Stats to: Vol. No., Slice, Region Name, Mean, St. Dev., Number of Voxels, Area, Volume (this is set as the default already)
Change Combine objects to No and Summing to Off; Click the Sample Images to get Data
A ROI Stat Log window will appear as data is collected
When the first round is over, go back to the Sample Options window, change Summing to On, click the Sample Image button again, new data is added to the data log
Then change Combining Objects to Yes and Summing to Off and click Sample Images, more new data
Then change Combing Objects to Yes and Summing to On and click Sample Images
A summary of these four rotations would look like this:
1. Combine: off; Summing: off
2. Combine: off; Summing: on
3. Combine: on; Summing: off
4. Combine: on; Summing: on
File-Reset Object Map will remove the object map and allow you to load the new one

All of the data has now been collected! If A-G regions have been collected, there will be nearly 200 lines of data, and if A-H are collected it will be just over 215
lines of data. In the **ROI Stat Log** click the **Save button** and save the data with the appropriate file name and location!

- Click Done to close the ROI Stat Log window
- Collecting stats for extracted ROIs is the same once you load the new extracted ROI

7. **Fiber Tracking and collecting fiber tracks from the multi-segment ROI**

- Repeat Part 2 of the procedure to create the appropriate DTI maps then:
  - Select the Fiber Tracking tab
  - Adjust parameters (.30, .35, 40 degrees, 5 mm)
  - Click the Load Object Map
  - Select *.*_divided_total.obj object map created in part 5
  - Click the Select All
  - Click the Compute Fibers button
  - Click the Display Fibers button
  - Fiber Track displays can be saved:
    - File - Save Displayed Fibers
    - Browse to find the location to save the file
    - Orient the image (top Right) to show fibers in sagittal plane
    - Move the other two planes out of the way of the fibers
    - Check the auto save box to save the DTI fiber image on the Main workspace
    - Select and highlight the image with Print screen (greenshot software)
    - File - Save As
    - Select *.PNG format
    - Browse to select the location to save the image
    - Return to the DTI Screen
    - Uncheck Auto Save box and close out of the DTI app window

8. **Collecting an image of the CC with the multi-segment ROI**

- from the Main Workspace
- Select and highlight the colored Eigen vector map
- Click the ROI tool button
- Maximize the window, Generate a Sagittal slice at the midline (slice 64 or 65)
- File - Load Object map: *._divided_total.obj
- Enlarge the image with the ROI
- Collect screen shot (print screen key)
- click and drag around image
- Browse to select the location to save the image
- Return to the ROI window and close out of the window

Miscellaneous Instructions

To Clear the Main Workspace of any volume files
- Select and highlight all the files you wish to remove from the main workspace
- right click and select Unload
- select unload all

Save Data
- From the main workspace:
  - File - Save
  - Select the appropriate directory, filename, and format
  - Click the Save button

Collecting Images (Greenshot software)
- Hit the printscreen key on the keyboard
- click and drag to create a region around the image
- browse to location to save the image

Create and Load a DICOM database
- From the main workspace:
  - File - DICOM Tool
  - File - Create a new local database (each new set of images for a patient)
  - Create database name, define a directory location and name, and source of original DICOM images
  - Dicom Receiver and Dicom Server are optional operations and may not be needed (refer to Quick Start Guide on the Resource disk)
  - Click to Create Local Database
  - Click OK when done, Database has been created
  - Within Patient name, ID box, select the appropriate patient database
• If, there is more than one set of Dicoms for this patient within the database, Select the appropriate series in the bottom box.
• The Slice Number slide bar can be used to review the images
• To load the selected Dicom data set into the main workspace, select Load Volume at the end of the slide bar
• The data set will now appear in the main workspace
• Importing Different File Formats
• From the main workspace:
  • File - Import/Export
  • To see which formats are actively supported: Help - Formats
  • Select the appropriate format(s)
  • To add to the default list: Tools - External Libraries
  • Select formats to be added to the default list
  • Formats must be loaded and accepted before they are configured
• IF RAW DATA (unsupported format):
  • File - Import/Export
  • Tools - Raw Data
  • Input Raw Data file location and file name
  • Select the Image Parameters Tab
  • Input width and height values, data type, adjust byte offset to the header information size, adjust byte swap (to pairs for PC’s)
  • Check the Display, Clear, Scale boxes (do in this order)
  • Click the Load button to load the data into the main workspace
  • Close the Import/Export window(s)
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