Chapter 9

Diffusion Tensor Tractography in Cerebral White Matter

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Additional information is available at the end of the chapter

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Abstract

Conventional magnetic resonance imaging (MRI) allows researchers and clinicians to observe the anatomy and injuries of the cerebral white matter (CWM) in dogs. However, dynamic images based on the diffusion tensor (DT) technique are required to assess fiber tract integrity of the CWM. Diffusion tensor tractography (DTT) produces a three-dimensional representation in which data are displayed on a colored map obtained from the anisotropy of water molecules in the CWM tracts. Fractional anisotropy (FA) is a value that measures changes in water diffusion, which can occur if the CWM tracts are displaced, disrupted, or infiltrated. The goal of this study was to determine the feasibility of DTT for in vivo examination of the normal appearance of CWM in dogs through visual and quantitative analysis of the most representative CWM tracts.

Keywords: diffusion tensor, cerebral white matter, dog, tractography, in vivo

1. Introduction

Magnetic resonance imaging (MRI) is the best imaging technique for the evaluation of the neurologic system due to the ability to diagnose central nervous system (CNS) diseases in both humans and animals, especially diseases affecting cerebral white matter (CWM), providing in vivo markers for disease severity or response to therapy and shedding light on progression and recovery processes. The broad spectrum of magnetic resonance contrast mechanisms makes MRI one of the most important and widely used imaging tool for diagnosis in the CNS. However, one of the disadvantages of conventional MRI is that it does not allow the visualization of the cerebral White matter constituent fiber tracts and their connectivity in the brain in vivo [1].

Previously, the anatomy of the cerebral white matter tracts could only be studied by postmortem dissection or through invasive methods, and said methods could only reveal a few tracts in vivo (neurosurgery) and no tracts could be observed in vivo via conventional imaging studies [1–6].

Diffusion tensor tractography (DTT) is a useful noninvasive imaging technique that can identify and represent fiber tracts of the cerebral white matter and their connections in the brain in vivo [1]; also, it can give us information that cannot be achieved by conventional anatomical MRI or histology. In addition to displaying specific cerebral white matter fiber tracts, this technique can also improve the quantification of diffusion characteristics within these fibers [1, 7–9].

DTT provides a three-dimensional representation of diffusion tensor imaging (DTI), and data can be displayed on a colored map obtained from information on the directionality of the movement of water molecules along the main fiber tracts of cerebral white matter [1].

1.1. Diffusion tensor imaging

DTI uses the property of the water diffusion anisotropy in axonal fibers allowing the analysis and tracking of said fibers in the brain [1, 4, 10, 11].

DTI permits the exploration of microstructural tissue features through the observation of water molecular diffusion, thus furnishing information about the anatomy, microstructural features, and damage of the main brain bundles, useful in several pathological animal models. DTI-based tractography permits the virtual reconstruction of the white matter fiber bundles in-vivo, following the principal diffusion direction [12, 13].

This technique is commonly used in human medicine to study the anatomy and maturation of the normal, aging brain, but it also can be used to help diagnose neurological conditions, including brain ischemia, multiple sclerosis, diffuse axonal injury, epilepsy, metabolic disorders, certain mental illnesses, and brain tumors, as well as establish a prognosis for patients with these conditions [14, 15]. Though DTI has been extensively used to investigate brains of the dogs ex vivo [11]; there is only one report of the in vivo use of DTT to study cerebral white matter fiber tracts in dogs [1].

The ability to trace cerebral white matter fibers in the dog generates a number of opportunities for potential clinical applications, and has both diagnostic and prognostic [1].

2. Diffusion anisotropy measurement and tensor analysis

Diffusion is a physical process that involves the translational movement of molecules via thermally driven random motions, the so-called Brownian motion. The factors influencing diffusion in a solution (or self-diffusion in a pure liquid) are molecular weight, intermolecular interactions (viscosity), and temperature [16, 17]. Diffusion is a random transport phenomenon, which describes the transfer of material from one spatial location to other locations over

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time. The direction of water molecules diffusion in living tissues is always limited to some degree. Water diffusion in biological tissues occurs inside and outside of cellular structures, and it is caused primarily by random thermal fluctuations. The water diffusion is affected by the interaction with cellular and subcellular membranes and with organelles. Cellular membranes deter water diffusion, decreasing the water mean squared displacement. The diffusion hindering and corresponding apparent diffusivity may increase by either cellular swelling or increased cellular density [3].

On the other hand, breakdown of cellular membranes caused by necrosis or other ailments increases the apparent diffusivity. Intracellular water tends to be more contained by cellular membranes, rather than deterred. This restricted diffusion also decreases the apparent diffusivity, but plateaus with increasing diffusion time [3]. In fibrous tissues, including white matter, water diffusion is relatively unimpeded in the parallel direction to the fiber orientation. On the contrary, water diffusion is highly restricted and deterred in directions perpendicular to the fibers. Hence, the diffusion in fibrous tissues is anisotropic [3, 18].

The property by which the rate of diffusion varies with direction is called diffusion anisotropy or anisotropic diffusion [4]. Isotropic diffusion occurs when the magnitude of diffusion is the same in all directions. Conversely, anisotropic diffusion is when the magnitudes of diffusion are significantly different [19].

In some tissues, for example cerebrospinal fluid (CSF), Brownian motion leads water molecules to diffuse freely in any direction. For other tissues, like white matter, water diffusion occurs along the fiber orientation rather than across it due to the highly organized fibrous structure that restricts water diffusion [20]. The underlying tissue cellular microstructure influences the overall mobility of the diffusing molecules by providing numerous barriers and by creating various individual compartments (e.g., intracellular, extracellular, neurons, glial cells, axons) within the tissue [16]. Early diffusion imaging experiments used measurements of parallel and perpendicular diffusion components to characterize the diffusion anisotropy [3].

The behavior of the anisotropic diffusion using diffusion tensor (DT) is described by a multivariate normal distribution, which describes the covariance of diffusion displacements in three dimensions normalized by the diffusion time [3]. Water diffusion cannot be characterized by a single value in an anisotropic voxel given its directional dependence; thus, the tensor model was developed. A tensor may assist in obtaining different parameters. For example, a three-dimensional principal eigenvector indicates the gradient of water diffusion within a voxel. In a similar manner, scalar eigenvalues signify the magnitude of the diffusivities along the principal and two orthogonal eigenvectors [21]. The diagonal elements are the diffusion variances along the axes x, y, and z, and the off-diagonal elements are the covariance terms and are symmetric about the diagonal [21]. The diffusion tensor can be represented as an ellipsoid, with its principal axis being defined by the eigenvectors and the ellipsoidal radii defined by the eigenvalues. If the eigenvalues are nearly equal, the diffusion is considered isotropic; if significantly different, anisotropic. Local tissue microstructure modifications such as injury, disease, or normal physiological changes may alter the eigenvalue magnitudes. Hence, the diffusion tensor allows the characterization of both normal and abnormal tissue microstructure [3]. In the CNS, water diffusion is usually more anisotropic in white matter regions and isotropic

in both grey matter and cerebrospinal fluid (CSF). The major diffusion eigenvector is assumed to be parallel to the tract orientation in regions of homogeneous white matter [3].

Diffusion-weighted imaging (DWI) is an important technique of functional magnetic resonance (fMR) imaging, which has the ability to assess changes in random motion of water protons in vivo. It is useful to diagnose several diseases in the central nervous system of humans and animals, specially canines [2, 22]. To detect lesions by DWI, the anisotropy is deliberately reduced using imaging techniques and processing to avoid detecting the signals from normal white matter [4].

DWI can be used to detect and visualize water molecules diffusion in tissues by adding a bipolar gradient pulse called a motion-proving gradient (MPG). Diffusion-weighted MRI differs from conventional MRI in that it provides high-contrast resolution based on diffusion, which allows new information on lesions to be obtained [4]. In the 1970s, water diffusion MRI was introduced and later used for medical applications [5]. Reports on diffusion MRI of the brain for neurological disorders were first published in the 1980s [23]. In the 1990s, its use was extended [4]. With the introduction of DTI, it was proposed to represent the water diffusion coefficient distribution in all the directions of space as a tensor in each voxel. A reconstruction of the white matter pathways was later proposed based on this tensor model [5].

DTI is an advanced technique of DWI sequence that displays vectors corresponding to the strength and direction of the movement of water molecules [2]. Recently, the DTI technique has permitted the detailed visualization of white matter structural integrity and connectivity [24]. One of the advantages of DTI is the reconstruction of axonal tracts in the brain in vivo [10]. DTI uses water diffusion anisotropy in axonal fibers allowing the analysis and tracking of said fibers in cerebral white matter.

Cerebral white matter anatomy can be studied in detail using DTI; it shows a complete anatomical and statistical fiber atlas of the white matter [15]; and it can explain, in combination with functional MRI, some anatomical and functional connectivity between different parts of the brain [11].

Pathologic conditions such as edema, inflammation, myelin loss, and gliosis may cause disruption in white matter tracts or changes in the membrane permeability which can alter DTI measurements, such as fractional anisotropy (FA) and apparent diffusion coefficient (ADC) [25].

Several studies have demonstrated the validity of quantitative diffusion imaging of the large white matter tracts in the brain in vivo [2]. FA provides information about the shape of the diffusion tensor at each voxel. The FA relates the differences between isotropic and anisotropic diffusion and is a scalar value between 0 and 1 indicating the degree of anisotropy in water diffusion. If FA value is close to 0, the diffusion is isotropic or random, and if it is close to 1, the diffusion is highly directional. The diffusion coefficient measured by nuclear magnetic resonance is best known as apparent diffusion coefficient (ADC). ADC depends greatly on the interactions of the diffusing molecule with the cellular structures over a given time; it could also be influenced by active processes within the tissue. ADC is calculated by acquiring two or more images with a different gradient duration and amplitudes, quantified as b-values.

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Also, one can calculate the eigenvalues corresponding the various imaging axis in order to find if the water diffusion is either anisotropic or not. With the obtained data, a tensor map is generated and tractography can be performed. This entire process is called DTI [2, 3, 16, 25, 26]. DWI uses an ADC map; given that DTI is an extension of DWI, it also uses an ADC map [16]. The difference between DWI and DTI is that in DWI encodes water diffusion in three spatial directions and DTI uses up to six directions.

The strength of the signal in FA maps represents the magnitude of FA, and, unlike conventional DWI, it is quantitative. FA decreases at lesion sites. Diffusion tensor analysis has the novel feature of not only quantifying anisotropy by FA and other parameters, but also of analyzing directionality.

Colored FA maps represent anisotropy in different colors according to the direction of the principal axis. These maps make it possible to differentiate fibers based on the direction in which they run. The colors are assigned to nerve fiber tracts depending on the direction of water displacement. The colors represent the predominant orientation of the fibers in a three-dimensional coordinate system in the three axes of space (x, y, and z); where red indicates a right-left direction, green indicates a dorsoventral direction, and blue indicates a rostrocaudal direction. This type of representation is called an anisotropic [1, 4, 27].

2.1. Construction of diffusion tensor tractography (DTT)

Methods for tracing connections in the brain have a long history, beginning with those based on lesions and the resulting retrograde or anterograde degeneration. The ensuing methods exploited the axonal transport of specific molecules like the horseradish peroxidase, and it was followed by a host of other tracers including small fluorescent molecules, lectins, neurotrophins, neurotoxins, dextrans, carbocyanine dyes, latex microspheres, and viruses. Although these methods allow the study of the brain connections, they are highly invasive. Moreover, any histological visualization of the transported substance requires sacrifice of the experimental animal [5]. Magnetic resonance images that make use of tensor analysis, such as FA maps and color maps, are collectively called DTI. A recent extension of DTI is fiber tracking, or tractography, which has been applied in the brain to noninvasively identify specific white matter pathways and connections in the brain in vivo. In the broadest sense, DTT can be considered a subtype of DTI, but it is often deliberately differentiated from DTI.

DTI and DTT provide us with a new opportunity to investigate such structures and to assess changes due to brain disease [4, 7, 15, 27]. DTT is a method of noninvasively tracing neuronal fiber bundles, and it integrates voxel-by-voxel orientations into a pathway that connects distant brain regions. The DTT technique can be used to analyze the trajectory, shape, fiber structure, location, topology, and connectivity of neuronal fiber pathways in vivo [28–30]. DTT can be used to simultaneously delineate cerebral white matter tracts in three dimensions and to identify alterations in connectivity. By tracing fiber pathways throughout the entire brain, diffusion tractography provides information that cannot be achieved by conventional anatomical MR imaging or histology [8, 9]. DTT refers to 3D models of white matter pathways generated from diffusion weighted MRI data, most commonly diffusion tensor imaging (DTI). Here, the term DT is used to refer to all forms of tractography derived from diffusion MRI data

including but not limited to DTI. Given that white matter is highly anisotropic, the nerve fibers can be tracked and visualized with DTT. To perform a DTT, parameters such the ADC and the FA must be calculated. To calculate these parameters, tensor analysis is employed [4, 27, 31]. The orientation of the component of the diagonalized diffusion tensor represents the orientation of the dominant axonal tracts, DTI provides a 3D vector field, and each vector represents the fiber orientation. Actually, there are different ways to reconstruct cerebral white matter tracts, these reconstructions are divided in two different types. The first type is based on line propagation algorithms that use local tensor information for propagation step. The main differences found throughout these techniques are due to the way they incorporate information from neighboring pixels in order to define smooth trajectories and to reduce noise contributions. The second one is based on global energy minimization to find the most favorable energetic pathway between two pixels [15]. The orientation of the diffusion tensor major eigenvector is generally assumed to be parallel to the local white matter fascicles. These directional patterns may be simply visualized using the color maps representing the major eigenvector direction. Such color maps are useful for assessing the organization of the cerebral white matter in the brain and for the identification of the major cerebral white matter tracts in 2D sections [3]. Another approach to visualize the white matter connection patrons in 3D is using diffusion tensor tractography. White matter patterns are estimated by starting at a specified location, this location is called seed point, also estimating the direction of propagation that is called major eigenvector, and moving a short distance in that direction called tract integration. The tract direction is then re-evaluated and another small step is taken until the tract is finished. Fiber tracts can be obtained using different number of regions of interest (ROIs) [3]. Diffusion tensor tractography have been used to produce anatomically fiber tract reconstruction of the most important proyection pathways. The primary applications of tractography to date have been the visualization of WM trajectories in 3D (particularly, in relation to brain pathology) and segmentation of specific brain regions [3, 32]. In human medicine, this technique has great potential for studying numerous diseases because the results of DTT and clinical symptoms can be compared directly. This technique is commonly used in human to study the anatomy and maturation of the normal, aging brain, but it also can be used to help diagnose neurological conditions, including brain ischemia, multiple sclerosis, diffuse axonal injury, epilepsy, metabolic disorders, certain mental illnesses, and brain tumors, as well as establish a prognosis for patients with these conditions [1]. FA and ADC are measurements that may be altered by disruption of white matter tracts or changes in membrane permeability as a result of pathologic conditions such as edema, inflammation, myelin loss, and gliosis. We can visualize the physical displacement of axon bundles employing tractography maps and are evaluated for surgical planning. Also, using axonal diffusivity, we can quantified noninvasively and correlate with histopathology axonal injury without demyelination [1, 2, 11, 25, 33].

2.2. DTI in human medicine

DTI is a widely used technique for the detection of several central nervous system diseases. It is the tool of choice because it is highly sensitive, highly specific, and noninvasive while providing a diagnosis within the therapeutic window [34].

http://dx.doi.org/10.5772/66249

It is expected to become even more useful due to the recent development of diffusion-weighted whole-body imaging with background body signal suppression, which can be used to evaluate the metastases of malignant tumors in three dimensions.

DTI is commonly used in order to study the normal anatomy of normal brain maturation and aging [11].

Normal white matter brain anatomy can be studied in detail using DTI; on one side, it shows a complete anatomical and statistical fiber atlas of the white matter, and on the other hand, it can explain in combination with functional MRI, some anatomical and functional connectivity between different parts of the brain [11, 15].

Aside detecting diseases in the central nervous system, DTI has been used for different applications in human medicine.

DTI was applied presurgically in human medicine to plan function-preserving brain surgery by saving special areas of motor and speech function, actually the application of the DTI is also possible for white matter tract reconstruction in 3D images for the spinal cord and brain [22].

Some applications of DTI in normal brain are demonstrating the relationship between the white matter structure and its function; for example, IQ has been positively correlated with anisotropy in cerebral white matter association tracts. Reading ability has been correlated with anisotropy of the left temporoparietal white matter, where tractography has localized the language areas. In visual pathways, increase in anisotropy has been correlated with improved reaction time. Tractography findings have demonstrated an excellent correlation with functional data; for example, probabilistic tractography has been used for segmentation of the thalamus according to its cortical connectivity, which corresponds well to segmentation of the thalamus.

DTI has shown additional abnormalities in patients with several types of dementia and neurodegenerative disease.

Several researches have use DTI to demonstrate a variety of white matter abnormalities often correlated with performance in neuropsychiatric test.

For demyelinating disease, the use of DTI is often used for diagnosing multiple sclerosis; several groups have demonstrated increased diffusivity and decreased anisotropy in demyelinating lesions.

In the case of ischemic disease, DTI is used for the detection of early acute ischemia into the domain of prognosis and long-term management of ischemic sequelae.

DTI has important implications in the delineation of tumor margins beyond what is currently demonstrated with conventional MRI [21].

2.3. DTI in animals

DTI has been used in an experimental model in cats, rats, mice, dogs, pigs, and marmosets [2, 5, 8–10, 12, 17, 20, 30, 31, 34]. DTI has generally been used following the creation of spinal cord trauma to serve as a model to aid in evaluating human spinal cord trauma victims [4, 35–37].

In dogs, it has been used for the evaluation of the spinal cord and its pathologies, providing statistically and visually different images when evaluating fractional anisotropy and ADC in normal dogs compared against dogs with lesions localized in the spinal cord using different types of scanners and software [19, 22, 24, 38–40].

DTI technique has also been applied to image animal brains in vivo and ex vivo [1, 10, 11, 20, 34]. Previous work shows consistent results between diffusion anisotropy of in vivo and ex vivo formalin-fixed mouse brains. This offers a new opportunity to study the brain microstructure with ex vivo DTI, as it avoids motion artifacts and allows for longer imaging time [20].

The use of DTI in white matter tracts found in dog and human brains has the potential for studying several pathologies by correlating DTI findings with clinical symptoms [11].

The corpus callosum has been also studied in dogs with DTI because its aging and pathologies are similar of those found in the human corpus callosum. In Pierce's work, the corpus callosum was segmentated into six major White matter tracts, which will provide grounds for new research in both species [34].

Tracing tracts by DTI is relative new, and it is expected that further research will develop new technologies soon. However, recent studies have demonstrated that even simple methodologies are able to visualize cerebral white matter tracts connections in situ for both human and animals [15].

2.4. DTI limitations

To date, DT remains the only noninvasive method for visualizing human brain and spinal cord connections. DT suffers from both fundamental and practical limitations that limit its use for modelling brain connections. Unlike many invasive modalities, DT is incapable of determining the direction of information flow, nor can it distinguish single- and multineuron connections. DT may also have difficulty in resolving complex intravoxel fiber crossings or nondominant fiber populations due to limitations in scan time, hardware, or processing methods. Despite its many limitations, DT has been successfully used to model human neuronal connections for over two decades, including several pathways that are putatively deep brain stimulation targets. DT generation can be divided into three separate steps: data acquisition, data processing, and tracking. Each of these steps has several variables that must be considered in order to ensure accurate DT [41].

2.5. New research on DTI

Different methods for the acquisition and analysis of DTI have been developed and have improved the precision of diffusion tensor measurements in recent years, so, new innovations can be expected. New pulse sequences and diffusion tensor encoding schemes are being developed to improve the spatial resolution, accuracy and to decrease artifacts in diffusion tensor measurements [3].

http://dx.doi.org/10.5772/66249

Even though DTI provides quantitative parameters of clinical relevance, it is limited in representing complex diffusion schemes. Methods based on high angular resolution diffusion imaging (HARDI) provide a more precise diffusion profile visualization [36].

Q-ball imaging (QBI) allows the detection of subtle anatomical features of the spinal cord that were not seen with DTI.

QBI has also been applied to the injured spinal cord, demonstrating its ability to detect directional abnormalities. Metrics derived from QBI may therefore provide useful markers of diffusion characteristics in the healthy and injured SC [36, 37].

3. Diffusion tensor tractography of cerebral white matter in the dog

Several studies have demonstrated the validity of quantitative diffusion imaging of the large white matter tracts in the brain in vivo [25]. DTI has been extensively used to investigate brains of the dogs ex vivo [11, 34].

There is only one report of the use of DTT in dogs to determinate the feasibility for in vivo examination of the normal appearance of the cerebral white matter.

MRI allows investigators and clinicians to observe the anatomy and injuries of the cerebral white matter (CWM) in dogs. However, dynamic images based on the diffusion tensor (DT) technique are required to assess fiber tract integrity of the CWM. The goal of this study was to determine the feasibility of DTT for in vivo examination of the normal appearance of CWM in dogs through visual and quantitative analysis of the most representative CWM tracts [1].

3.1. Materials and methods: experimental animals

Nine healthy canine patients of varying breeds and genders were prospectively recruited for the study. The dogs received a general physical and neurological exam, and blood samples were taken for a preanesthetic profile. During the imaging procedure, the dogs were anesthetized with diazepam (2 mg/kg IV, valium, Roche, Nutley, New Jersey) and propofol (4 mg/kg IV, recofol, Bayer, Turku, Finland) [1].

3.2. Image acquisition technique

The MRI protocol was carried out in the same 3 Tesla scanner for all dogs. Diffusion tensor imaging was performed on each patient. Moreover, T1- and T2-enhanced images were acquired to obtain a high-resolution anatomical reference. T1- and T2-weighted images and DTI were obtained in different planes (transverse, dorsal, and sagittal). Three-dimensional reconstructions, FA, and ADC values were obtained for the left and right corticospinal tracts, the corpus callosum, the cingulum, and the right and left fronto-occipital fasciculus to visually evaluate and quantify these fiber tracts [1].

3.3. Diffusion tensor imaging tractographies

Diffusion tensor tractography was performed by importing DTI into image analysis software. Cerebral white matter tracts were identified using regions of interest (ROIs). The software identified tracts based on finding the most favorable path between two manually placed ROIs. Regions of interest were positioned where trajectories of the cerebral white matter fiber tracts were estimated to be, based on veterinary anatomy guides and a human DTI atlas. High-resolution T1-images were placed on top of the colored map to identify connections between anatomical structures. The different tracts were identified, delineated, and reconstructed at different points along their trajectory using the color map in the sagittal, dorsal, and transverse planes, which were reconstructed using a fiber-tracking algorithm. Data were coded in red to indicate a right-left direction, green to indicate a dorsoventral direction, and blue to indicate a rostrocaudal direction. The cerebral white matter tracts were assigned to three groups of fibers: projection, commissural, and association fibers [1].

3.4. Data analysis

Statistical analyses were selected and performed using a commercially available statistical software package (SSPS, version 19, Microsoft, Chicago, IL). Mean tract FA and ADC values, their standard errors, and standard deviation were calculated. A confidence interval of 95% or a significance value of $P < 0.05$ was used for the mean. A quantitative assessment of ventricular volume (VV) in relation to the brain volume (BV) was also performed using manual segmentation in regions of interest (ROIs) on the image analysis freeware (OsiriX v.3.9.4) in the nine healthy dogs. The means, standard errors, standard deviations, and 95% confidence intervals for the means of the VV in relation to the BV of the right and the left side were obtained [1].

3.5. Results

Three-dimensional reconstructions of the corticospinal tract, corpus callosum, cingulum, and fronto-occipital fasciculus were generated for each of the nine dogs. Fibers in the corticospinal tract component of the projection fiber group were displayed in blue and green (**Figure 1A–C**) [1].

Blue fibers connected cortical areas in the cerebral cortex, the brain stem, and spinal cord. Green fibers connected the corona radiate, internal capsule, and cerebral peduncle. Fibers in the corpus callosum component of the commissural fiber group were displayed in red and connected the two cerebral hemispheres (**Figure 2A–C**).

The cingulum component of the association fiber group appeared as long fibers, and these were displayed in blue (**Figure 3A–C**) [1].

These fibers had a rostrocaudal orientation and connected cortical areas in each hemisphere. Fibers in the superior and inferior fronto-occipital fasciculus component of the association fiber group were long and displayed in blue (**Figure 4A–C**) [1].

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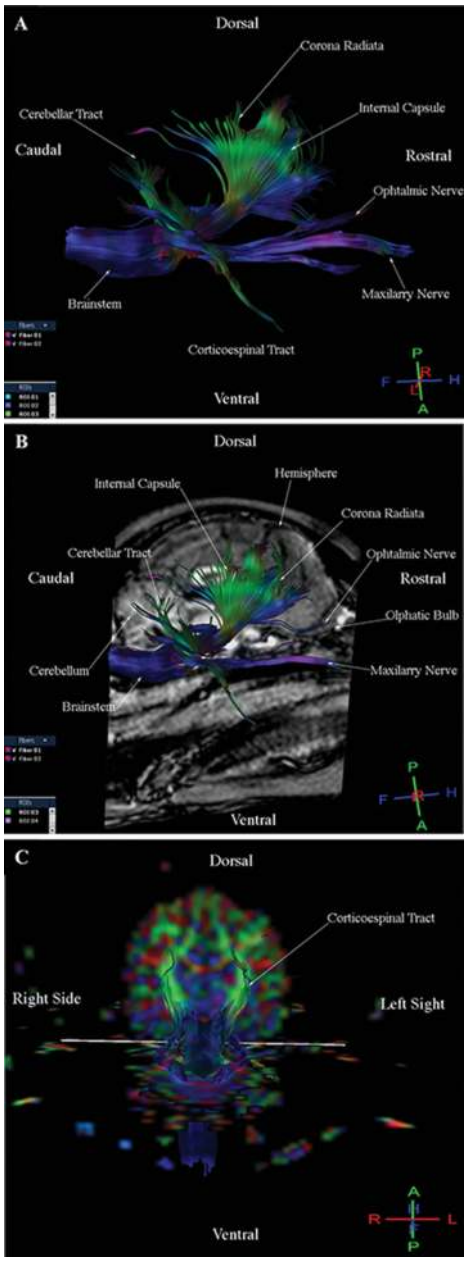

Figure 1. Images illustrating the corticospinal tract in a healthy dog. (A) DTT image, side view. (B) T1-weighted image, sagittal view. (C) Colored map, transverse sectional view [1].

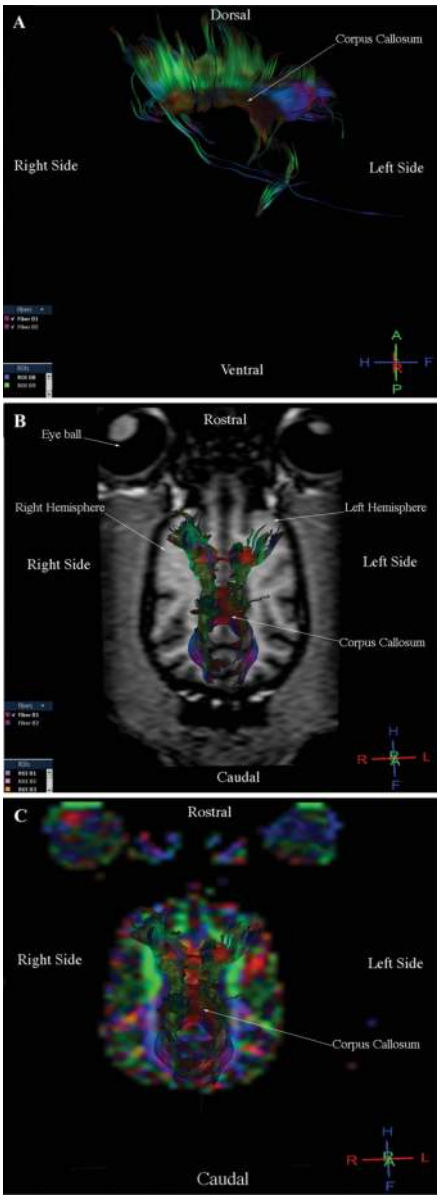

Figure 2. Images illustrating the corpus callosum in a healthy dog. (A) Diffusion tensor tractography (DTT) image, side view. (B) T1-weighted image and diffusion tensor tractography (DTT) image, dorsal view. (C) Diffusion tensor tractography (DTT) image on the colored map, dorsal view [1].

http://dx.doi.org/10.5772/66249

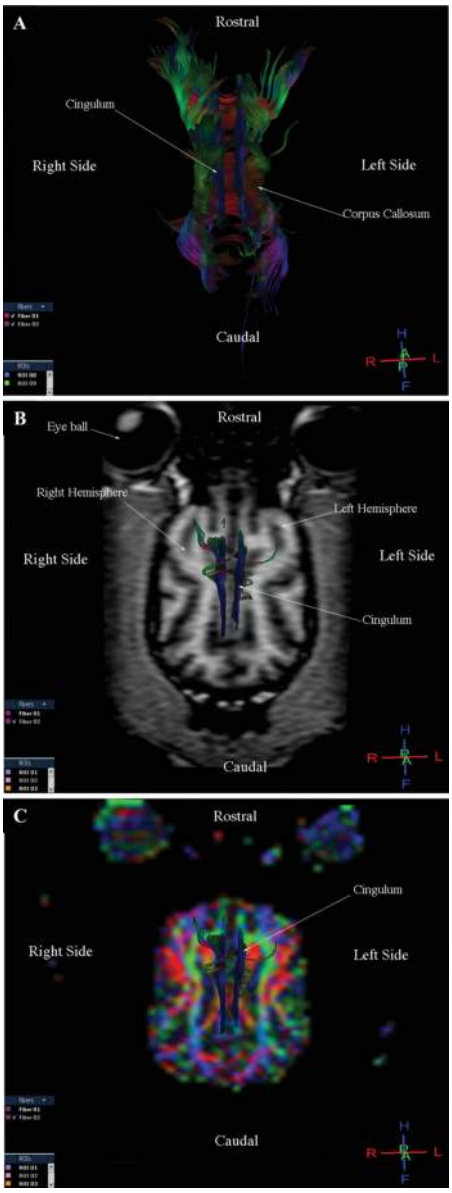

Figure 3. Images illustrating the cingulum in a healthy dog. (A) Diffusion tensor tractography (DTT) image, dorsal view. (B) T1-weighted image and diffusion tensor tractography (DTT) image, dorsal view. (C) Diffusion tensor tractography (DTT) image on the colored map, dorsal view [1].

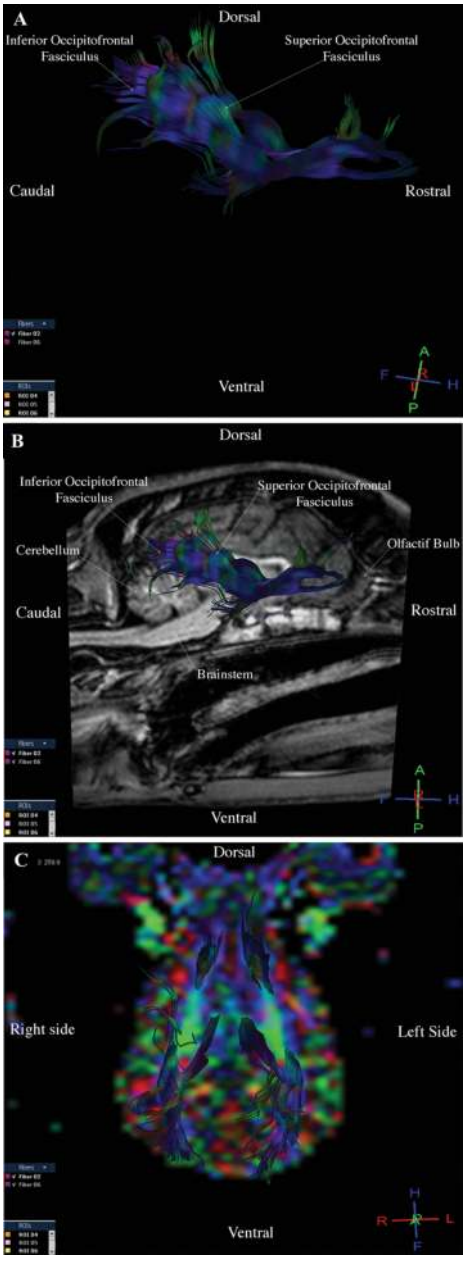

Figure 4. Images illustrating the fronto-temporo-occipital tract in a healthy dog. (A) Diffusion tensor tractography (DTT), side view. (B) T1-weighted image and diffusion tensor tractography (DTT) image, sagittal view. (C) Diffusion tensor tractography (DTT) image on the colored map, dorsal view [1].

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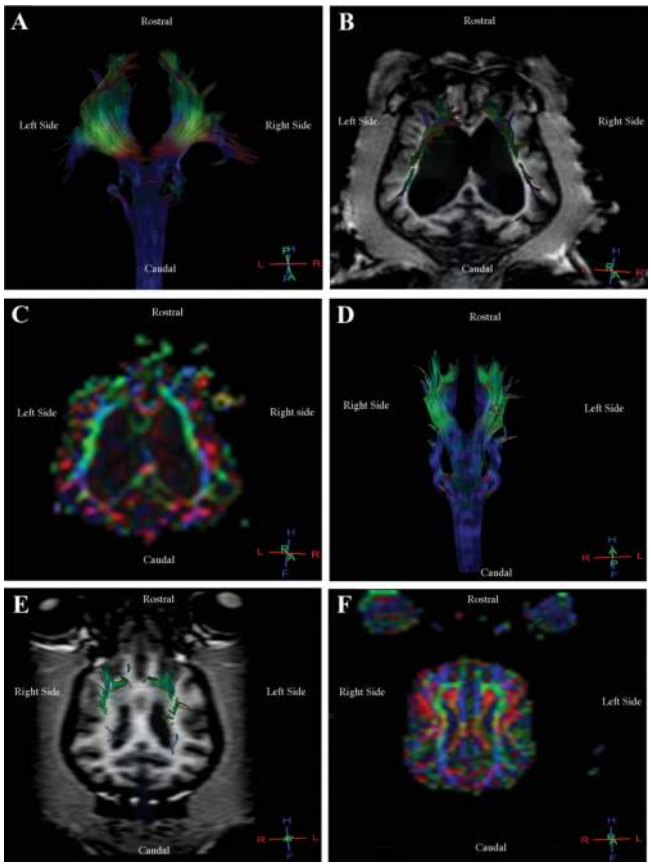
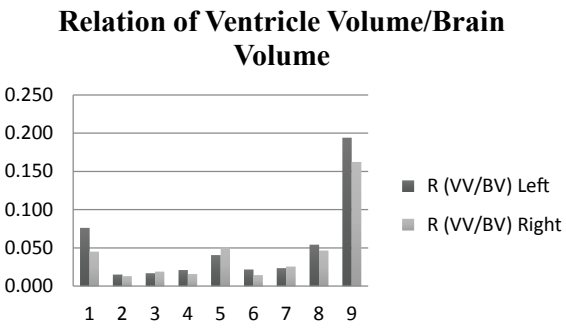


Figure 5. Comparison between a healthy dog with large lateral ventricles and a healthy dog with normal ventricles. (A) Diffusion tensor tractography (DTT) image, corticospinal tract with altered topography and corpus callosum due to large lateral ventricles, dorsal view. (B) Diffusion tensor tractography (DTT) image, corticospinal tract with normal downward topography of the fibers, dorsal view. (C) T1-weighted image and diffusion tensor tractography (DTT) image, corticospinal tract with anterior and lateral displacement of the fibers and of the corpus callosum due to large lateral ventricles, dorsal view. (D) T1-weighted image and diffusion tensor tractography (DTT) image, corticospinal tract with normal downward topography of the fibers, dorsal view. (E) Diffusion tensor tractography (DTT) image of the corticospinal tract on the colored map with anterior and lateral displacement of the fibers and of the corpus callosum due to large lateral ventricles, dorsal view. (F) Diffusion tensor tractography (DTT) image, corticospinal tract on the colored map with normal topography of the fibers, dorsal view [1].

These fibers had a rostrocaudal orientation and connected cortical areas in each hemisphere and in the frontal and occipital lobes. Three-dimensional reconstructions of the tracts were homogeneous and uniform in geometry and spatial orientation in eight of the nine healthy dogs. In one dog, tract reconstructions were not homogeneous or uniform because the fibers were displaced, most evident in the corticospinal tract and corpus callosum (**Figure 5**) [1].

There was a significant difference in the VV in relation to the BV in this dog (**Table 1**) [1].

Relation ventricle volume/brain volume	Healthy dogs (n = 9)			
	X	SE	SD	C.I. 95%
RVV/BV (left)	0.051	0.019	±0.057	(0.007, 0.095)
RVV/BV (right)	0.044	0.016	±0.047	(0.007, 0.080)



R, relation; VV, ventricle volume; BV, brain volume; X, mean; SE, standard error; SD, standard deviation; C.I., 95% confidence interval for the mean.

Table 1. Ventricular volume (VV) in relation to the brain volume (BV) in healthy dogs <inlinefx>.

The means, standard errors, standard deviations, and 95% confidence intervals for the means of the FA and ADC values for the six tracts were obtained from all nine dogs (**Table 2**) [1].

Tracts	Healthy dogs (n = 9)							
	FA				ADC (10^{-3} mm^2 s^{-1})			
	X	SE	SD	C.I. 95%	X	SE	SD	C.I. 95%
Corticospinal (right)	0.391	0.009	±0.026	(0.371, 0.412)	1.154	0.063	±0.189	(1.009, 1.299)
Corticospinal (left)	0.400	0.006	±0.018	(0.387, 0.414)	1.104	0.055	±0.164	(0.977, 1.230)
Corpus callosum	0.365	0.007	±0.022	(0.348, 0.382)	0.975	0.033	±0.099	(0.899, 1.051)
Cingulum	0.336	0.011	±0.032	(0.311, 0.360)	0.847	0.053	±0.159	(0.725, 0.969)
Fronto-occipital (right)	0.331	0.009	±0.026	(0.311, 0.350)	0.879	0.009	±0.028	(0.858, 0.901)
Fronto-occipital (left)	0.331	0.010	±0.029	(0.308, 0.353)	0.913	0.010	±0.031	(0.888, 0.937)

FA, fractional anisotropy; ADC, apparent diffusion coefficient; X, mean; SE, standard error; SD, standard deviation; C.I., 95% confidence interval for the mean.

Table 2. Fractional anisotropy and apparent diffusion coefficient values of six cerebral white matter tracts in healthy dogs.

Similarities in the FA and ADC values were identified in the nine healthy dogs [1].

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3.6. Discussion

The current study was the first to visually and quantitatively describe the trajectory of cerebral white matter fiber tracts in a group of live dogs using DTT for diagnostic purpose. Diffusion tensor tractography-imaging resolution allowed rapid display and identification of the most representative cerebral white matter fiber tracts in this sample population of nine healthy dogs of varying breeds and genders. This technique described anatomical, geometric, and spatial properties of the fibers. In addition, the conduction properties of the fibers could be estimated through FA and ADC quantification. There was homogeneity and uniformity in the three-dimensional reconstructions in nearly all dogs. Quantification of the FA and ADC values of the most representative tracts was similar in all nine dogs, thus demonstrating the feasibility of the technique and the analysis of the normal appearance of the cerebral white matter (CWM) in dogs in vivo. The analysis of the images in different planes and the three-dimensional reconstructions of the fiber tracts revealed a visual difference in the normal cerebral white matter appearance in one of the nine healthy dogs. This dog showed an altered topography of the corticospinal tract and corpus callosum due to displacement of the fibers. Quantitative assessment of ventricular volume in relation to the brain volume showed that this dog had larger lateral ventricles in relation to the other dogs. Authors believe this was most likely a normal variant because the dog exhibited no clinical neurological signs at the time of imaging. Other studies have shown that some canine species may exhibit a broad range of normal cerebral ventricular sizes, as assessed by neuroimaging, and that cerebral ventricular size is quite variable in a normal dog [1].

The only values quantified in the current study were those specific to the fiber tract and not to the ROIs because our research focused on demonstrating the feasibility of DTT for displaying and the normal appearance of the most representative cerebral white matter fiber tracts of healthy dogs in vivo. The quantification of FA and ADC values, or the exact description of the ROIs, were not used to visualize fiber tracts, as in our experience these values and descriptions can be obtained at different points of the fiber tract trajectories using the colored map. Future studies are needed to develop a method for preparing DTT templates and to reconstruct cerebral white matter pathways in the healthy dog in vivo using an ROI approach. This method is similar to the method used in humans and provides virtual representations of cerebral white matter tracts that are faithful to the classical ex vivo descriptions that include a detailed anatomical study of canines. The preparation of cerebral white matter templates for the healthy dog in vivo will allow investigators to follow the trajectory of the fibers delineating ROIs in DTI for DTT reconstruction. Improved knowledge of anatomy and the development of a template as a guide for the placement of ROIs could be used in future applications such as teaching and guiding virtual dissections of cerebral white matter tracts in healthy dogs in vivo, and comparison with pathological cases where the anatomy is observed distorted by the underlying disease process. Our findings are preliminary and future research will be needed to evaluate the use of DTT in clinical cases. Indeed, the use of this technique as a diagnostic tool is currently limited because templates and standardized FA and ADC values of the cerebral white matter of healthy dogs in vivo (which are prerequisites for the use of this technique in pathological cases) are lacking. Three previous canine DTI studies were conducted ex vivo,

and one was conducted in vivo. In these studies, DTI was used to examine the structure and microstructure of the cerebral white matter but not for diagnostic purposes in canines. The findings of one study supported our study in that they also revealed the presence of association, commissural, and projection fibers in the dog. These data and information are also available in humans, and this allowed us to identify, compare, and reconstruct different fiber tracts in our healthy dogs in vivo. The results of study showed that the DTT reconstructions allowed identification and differentiation of CWM tracts in dogs in vivo, and that these reconstructions were comparable with those obtained in ex vivo canine studies. As new MRI options become increasingly available for daily clinical veterinary practice, novel diffusion techniques such as DTT warrant further exploration. In conclusion, findings from the current study indicated that DTT is a feasible noninvasive technique for in vivo study of CWM fiber tracts in the dog. We believe that the implementation of DTT as a noninvasive diagnostic method will complement conventional MRI, thus allowing investigators to examine the microstructural characteristics of the brain in vivo, and to obtain information on the anatomy, connectivity, and morphology of possible damage to fiber tracts in dogs suffering intracranial pathology or injury. Future research is needed to develop standardized ROI templates for in vivo canine studies and to compare DTT findings with confirmed pathologic findings [1].

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