

Research Paper: Improved human brain tractographs using multi-shell q-ball diffusion magnetic resonance imaging compared with DTI



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ABSTRACT

Introduction: Recently, it has been proven that assuming the Gaussian model in DTI method is inappropriate for propagation in a complex substrate such as human brain tissue. High Angular Resolution Diffusion Imaging (HARDI) (or so called q-ball imaging) is known as a model free method that allows to more accurately detect changes in diffusion with different orientations. In this study, after finding the best angle threshold at the Optic Radiation (OR) level, the length and number of reconstructed nerve fibers in this angle were measured using q-ball imaging and were compared with DTI.

Materials and Method: Tractographs of q-ball images from the human brains of 10 healthy volunteers (30 to 50 years old) were studied using a 3-Tesla scanner. 64 directions of diffusion encoding in two b-values (1000 and 2000 s/mm²), were used for q-ball imaging and in routine b-value of 1000 s/mm² for DTI. The tractographs were compared at the OR level with the tractography based on q-ball and DTI images. The results were analyzed using t-test. The angle threshold for tractography was selected at 45 degrees by comparing the tractographs in 13 angles.

Conclusion: Consequently, the number and length of nerve fibers of OR, measured using the q-ball imaging, were significantly higher than those using the DTI. Finally, the better quality of the tractographs as well as the analyzed quantities, are indicators of larger signal-to-noise ratio in q-ball imaging and indicate that q-ball imaging compared to DTI plays an important role in the development of brain nerve mapping.

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1. Background

While structural MRI such as T1 and T2 weighted imaging provide only an image of the body's anatomy [1], diffusion weighted imaging make it possible to image the microscopic structure of tissue within a voxel by measuring the diffusion coefficient of water molecules in the tissue. In 1990, Mosley et al. [2] concluded that diffusion in neural tissue was related to the orientation of white matter relative to the diffusion gradient; So that the diffusion coefficient in the direction of the nerve fibers is more than this coefficient in the direction perpendicular to the fibers. Diffusion Tensor Imaging (DTI) imagines a three-dimensional ellipse (which is the geometric representation of a quadratic tensor) within each voxel, for different diffusion values measured in at least six directions in three-dimensional space. The diffusion coefficient (D) in this case is displayed as a 33 tensor. A tensor determines diffusion in the brain by three eigenvalues of diffusion ($\lambda_1, \lambda_2, \lambda_3$) that describe diffusion along three vectors. The main eigenvector is parallel to the direction of the main neural pathway of the white matter of the brain in the voxel, and the diffusion in that direction is indicated by λ_1 [3]. DTI parameters, including Fractional Anisotropy (FA), Mean Diffusivity (MD) and diffusion tensor eigenvalues, show accurate information about the microscopic structure of the tissue [4]. One of the most important parameters in diffusion measurement and imaging is the b-value parameter, which depends on the strength (G) and duration of the magnetic gradient (δ and Δ) and is used to prepare the Magnetization for diffusion encoding in DTI or other diffusion imaging sequences.

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)$$

Nerve fiber tractography uses the random motion of water to determine the direction of a set of axonal nerve fibers. In particular, tractography follows the estimated diffusion orientation from one voxel to another in three dimensions and traces the principal pathways of the white matter. DTI tractography has become the standard tool for analyzing the orientation of white matter fibers and their microstructures.

Despite many positive effects of DTI imaging on neuroscience and tractography, its limitations should

not be overlooked. These limitations, which DTI is incapable of describing, include the inability of this method to detect the main direction of diffusion in voxels containing curved and crossing fibers, as well as the non-Gaussian nature of diffusion, especially at b-value > 1000 s/mm² (using stronger gradients for longer periods of time). DTI, assumes that the diffusion of water molecules follows a normal distribution, and this diffusion is described by a tensor, and therefore can only determine one direction of the nerve fibers in each voxel, and prevents accurate diffusion information in the areas of the brain with crossing fibers. The non-Gaussian behavior is more evident in b-value > 1000 s/mm² [5].

To overcome some of the limitations of DTI, several methods have been developed, such as q-space imaging (QSI), known as q-ball imaging, or Diffusion Spectrum Imaging (DSI) [6], to receive and reconstruct the information. In these methods, which are not limited to the assumption of the Gaussian model [6], b values of much larger than 1000 s/mm² with strong gradients and higher number of directions can be used [7].

The fibers of the Optic Radiation (OR) extend from the cells of the lateral geniculate body (LGB), where the nerve fibers of the retinal ganglion cells collide with the nerves coming from the visual cortex, to the visual area in the occipital cortex. The OR contains all the visual fibers of the opposite half of the visual field [8]. Visual pathways are often involved in the pathology of diseases such as MS due to the sensitivity of the optic nerves to optic neuritis. OR is an important part of the brain in MS pathology. In fact, it is probably one of the most common areas in the brain affected by the disease lesions because of its location. For example, while OR have about 1% of the total white matter volume of the brain, it contains about 7-10% of the volume of lesions observed by T2 imaging [9]. Previous studies on MS disease using 1.5 Tesla scanners explain the high value of MRI information obtained from the optic nerve in MS patients. However, routine MR imaging may face some problems and difficulties due to the complexity of the optic nerve and its surrounding structure. The main difficulties are the small size of the Optic Tract (OT); nerve movement; signal from surrounding fat, bone, and cerebrospinal fluid (CSF); and susceptibility effects caused by air in nearby structures [10]. Diffusion tensor imaging is more accurate than conventional imaging in providing

more detailed pathology to determine the degree of damage in each affected area. The quantitative nature of this technique also helps researchers diagnose Normal Appearing White Matter (NAWM) and Normal Appearing Grey Matter (NAGM) [11]

The purpose of this study is to compare two imaging techniques, DTI and q-ball imaging. Initially, healthy human brain tractography was performed in 13 different angles, and by selecting the desired ROI in Optic Radiation and analyzing the reconstructed nerve fibers (tracts) in the tractography in each angle, the best angle threshold for tractography of the OR in q-ball and DTI imaging was found. At the best angle, the tract length and the number of tracts measured using DTI tractographs were compared with those measured using q-ball imaging tractographs.

2. Method

Theory

Q-space and q-ball imaging: The q-ball imaging is one of the q-space imaging (QSI), based on q values instead of b values. Using this imaging method, the diffusion function is measured directly. QSI uses the Fourier relationship between the diffusion signal and the diffusion function to measure the diffusion function directly without considering a specific model for diffusion processing [12, 13]. q-space is a three-dimensional space with coordinates (q_z, q_y, q_x) defined by the diffusion gradients G_x, G_y and G_z . Q and G on each axis are related by the diffusion wave vector q:

$$Y\delta g q=(2\pi)^{-1}$$

In this equation, Y is equal to the desired nuclear gyromagnetic ratio, δ is equal to the diffusion gradient duration and g is equal to the diffusion gradient vector. The value of the q-space signal at each point in the coordinates is modeled by the mean value of the displacement of the molecule in the voxel and the b-value of the diffusion gradient. Because of the relationship between the signal and the mean displacement of the molecule in the voxel, this signal will be an indirect measurement of the tissue structure within the voxel [1].

The diffusion function can be described generally by the diffusion probability density function $P(x, x_0)$ or diffusion propagator. This function describes

the probability for a spin to displace from position x_0 to position x in the diffusion time T. In MR, the observed signal is generated from an average over all spins in the voxel [13]:

$$P(r) = \int p(x, x_0)\rho(x_0)dx_0$$

In this formula, $r=x-x_0$ (relative spin displacement) and $\rho(x)$ is equal to the initial density of the spin. $P(r)$ is the Probability Density Function (PDF) or diffusion function, which describes the average probability of relative displacement r in diffusion time t for a spin, which is related to the received diffusion signal by a Fourier transform:

$$P(r) = \mathcal{F}[E(q)]$$

Equation (4) describes the Fourier transform with respect to the diffusion wave vector q. Although the 3D PDF provides valuable information about the microscopic structure of the tissue, it is best to use the Orientation Distribution Functions (ODF) to obtain a tissue orientation map. The diffusion ODF, $\psi(u)$, is computed as the radial projection of the diffusion function [12]:

$$\psi(u) = \frac{1}{Z} \int_0^\infty P(ru)dr$$

In this equation, Z is a dimensionless constant to normalize the function and u indicates the fiber orientation.

The Q-ball imaging method is based on receiving information from the spherical shell in the diffusion wave vector space. The advantage of this method is that it requires obtaining information from a single spherical shell (a large number of angular measurements with a fixed b-value) instead of a three-dimensional Cartesian grid. Several studies have shown that the Q-ball imaging model includes high b-values (2000-4000 s/mm²) with at least 45 diffusion gradient directions. Although the optimal b-value for estimating multiple orientations of nerve fibers has not been determined, the results show that the quality of information increases with increasing the number of gradient directions [14]. Mathematically, Q-ball imaging uses the Funk-Radon Transform (integration on large spheres in q-space) to reconstruct the diffusion signal to estimate the

ODF. Imagine that the Q-ball sampling points are scattered on the surface of a sphere, in which case the approximate value of ODF (Funk-Radon Transform result) in the north-south direction of the sphere would be equal to the sum of all q-space signals measured from the points on the equator. In general, to calculate the approximate amount of ODF in any desired direction, we must add all the q-space signals from the points on the new equator (equator perpendicular to the desired axis). QBI can describe the orientation of the nerve fibers by finding the maximum ODF diffusion [6, 13]. To improve the ODF obtained by the Q-ball method, the radius of the Q-ball sphere can be increased (increasing the b-value); however, this increase in radius can cause noise in diffusion images or in q-space signals, which can itself cause problems in estimating ODF [7].

In this study, the Multi-Shell Q-ball method is used, which uses several concentric spherical shells with constant b-values to describe the signal changes with low, medium and high b-values [10]. It can also be said that while low-b-value shells provide better SNRs, high-b-value shells show high angular CNRs, which together can better describe complex tissues [12].

Subjects

MR images was obtained with a 3 Tesla Siemens Prisma scanner from 10 adults between 30 and 50 years old (mean age 3 ± 37 years). All participants were healthy volunteers with no history of nervous system disease and had no abnormal MR imaging findings. **Consent has been obtained from each participant in accordance with the regulations of Tarbiat Modares University and the National Brain Mapping Laboratory (Ethics Code: IR.MODARES.REC.1397.144).** Due to the fact that in individuals, the left optic radiation nerve fibers are extracted separately with the neural fibers in the right optic radiation, and each has its own parameters, a total of 10 sets of nerve fibers in the right OR and 10 sets of nerve fibers in the left OR should have been compared with each other, however, due to failure in obtaining acceptable nerve fibers in the right or left OR of some subjects, 9 and 8 sets of nerve fibers in the left and right OR of the healthy subjects were examined and compared, respectively.

MR Imaging

q-ball imaging (HARDI) on the whole brain, is obtained in 3 shells, in the first shell with a b-value of zero and in 5 gradient directions, in the second shell with a b-value of 1000 s/mm^2 in 64 gradient directions and in the third shell with a b-value of 2000 s/mm^2 in 64 gradient directions. TR = 9600 ms, TE = 92 ms, slice thickness 2 mm, spatial resolution $2\times 2\times 2 \text{ mm}$ and FOV 220 mm were selected. Low b-value shell ($b=1000 \text{ s/mm}^2$) was used to perform DTI analysis. Also, T1 structural image was taken of the whole brain of each Volunteer, with parameters TR = 1840 ms, TE = 2.43 ms, slices thickness 1 mm, spatial resolution $1\times 1.1\times 1.1 \text{ mm}$ and FOV equal to 255 mm. q-ball and T1 images were taken from the brains in a protocol for about 25 minutes. The length of multi-shell q-ball imaging was 22 minutes, and T1 imaging was 3 minutes.

Diffusion modeling and tractography

Prior to data analysis, to diffuse geometric distortions due to eddy currents and artifacts due to subject's motion, as well as distortions resulting from Echo Planar Imaging (EPI), all images were sorted, aligned and registered with a $b = 0$ images using the non-rigid method (elastic), based on the studies of Leemans and Jones [15] as well as Irfanoglu et al. [16]. In this method, diffusion gradients were adjusted by proper rotation of b-matrix.

For Q-ball images, the diffusion tensor parameters must be more accurately estimated by considering the non-Gaussian diffusion properties. There are several methods for estimating diffusion tensor. ExploreDTI [17] supports linear, weighted linear, non-linear, and robust methods. Due to the higher accuracy of the robust method in estimating diffusion tensor, in both Q-ball and DTI data, one of the models of this method, REKINDLE, was used to estimate the diffusion tensor. The results of simulations and real data show that REKINDLE is able to detect and delete outliers and reduce computation time, without significantly reducing the accuracy [18].

The general basis of deterministic tractography algorithms is to use the orientation information described by the diffusion tensor. Common orientation information is related to the main eigenvector of the diffusion tensor. A deterministic tractography is generated starting from one or more

“starting points”, usually in white matter, and follows the paths according to the tractography algorithm until the nerve fibers are terminated or cut off. The ExploreDTI program covers two tractography methods based on DTI and CSD (Constrained Spherical Deconvolution), which are based on the studies of Baser [19] and Eurison [20], respectively. DTI-based tractography was used for DTI images of the brains and CSD tractography was used for multi-shell q-ball images.

Angle threshold in tractography is the maximum bending angle allowed for the nerve fiber path. This limitation prevents the reconstruction of pathways of nerve fibers that are obviously anatomically incorrect, by orientation algorithms [21]. The nerve fibers follow the direction of the main eigenvector of the diffusion tensor ellipse, reaching the voxel boundary. After that, these fibers enter the neighboring voxel according to the direction of the main eigenvector in the next voxel to continue the process of the tractography. The angle threshold value is used to determine the termination time of nerve fiber tractography [22]. To obtain the best angle threshold for brain tractography, the angle threshold parameter in the CSD tractography of healthy human brains, were examined from an angle of 10 to 70 degrees (angles 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70 degrees). In this way, by keeping the other parameters involved in the tractography, constant, including the step size (1 mm), and changing the angle threshold, CSD is done in each angle. By drawing the ROI in the desired area, the best angle which completely covers and pictures the target nerve fibers, while preventing anatomical noise, can be achieved. It should be noted that all comparisons between Q-ball and DTI images are made at the best angle threshold.

Although it is possible to select an area and perform tractography in the same area, to avoid possible errors when drawing the ROI, first the tractography on the whole brain was performed and then the desired area was selected and the rest of the nerve fibers outside that ROI were removed. The selected nerve fibers in the ROI were isolated and analyzed. The target area of this study for tractography was the Optic Radiation area, which according to the studies of Wu [23] Bertani [24] and Hofer [25], has been selected in the brains of all the subjects. This is done manually by drawing the desired areas using the ExploreDTI program to draw the best ROI for each of the brains

according to the anatomical differences of each brain.

Statistical analysis

In this study, the parameters obtained from DTI and Q-ball imaging were descriptively analyzed and the results were presented as the mean standard deviation for each group. Kolmogorov-Smirnov test was used to check the normality of the group's distribution. The mean of the studied groups was compared using t-test analysis with 95% confidence level.

3. Results

Extraction of the best angle threshold for tractography: The best angle threshold for tractography was selected based on the criteria of signal-to-noise ratio and covering up the OR tracts. In this research, this angle is an angle that despite the complete coverage and extraction of the desired nerve fibers, OR fibers, do not cause the formation and imaging of nerve fibers that are not related to OR (anatomical noise) or nerve fibers that are anatomically wrong, which are caused due to a very high angle threshold. For example, in Figure (1) the left and right OR nerve fibers of a healthy brain are seen at four angles 10, 20, 45, 70 degrees.

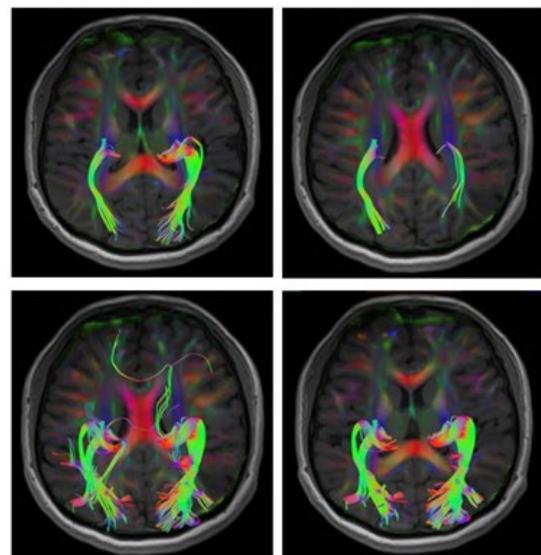


Figure 1. Up-right (10 degree angle) - up-left (20 degree angle) - down-right (45 degree angle) - down-left (70 degree angle)

Considering that in most tractographs of the brain, angles of 45 to 50 degrees were among the angles

from which the resulting nerve fibers were without anatomical noise, the angle of 45 degrees was selected in this study as the best angle threshold for human brain tractography, for both DTI and q-ball imaging.

number of nerve fibers in each subject was compared in left and right OR by DTI and Q-ball imaging methods.

The mean length of nerve fibers in each brain sample was also compared in left and right OR by DTI and q-ball imaging methods.

Number and length of OR nerve fibers: The

Table 1. Mean and standard deviation of number of nerve fibers in right and left OR

Brain's Section	Imaging	Number of Subjects	Average Number of Nerve Fibers	Standard Deviation	P-Value
Left OR	DTI	9	106	46	<0.05
	q-ball	9	161	54	
Right OR	DTI	8	101	46	<0.05
	q-ball	8	207	77	

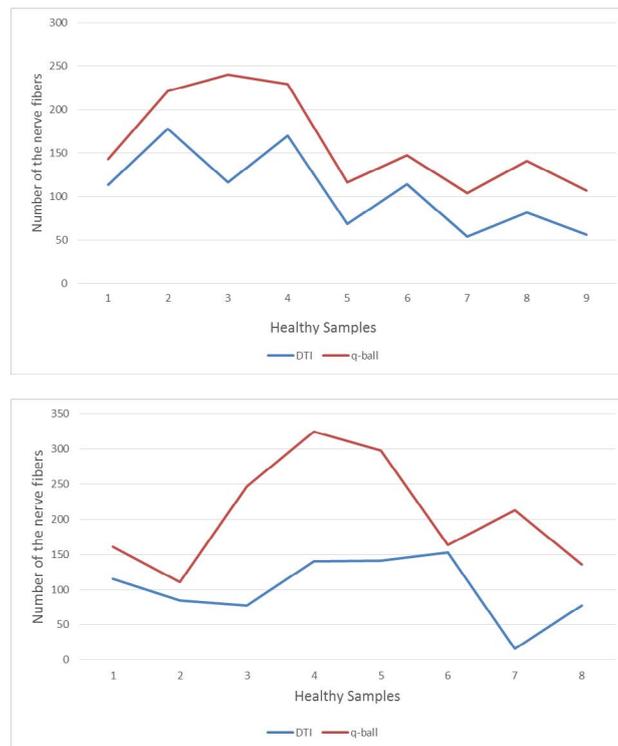


Figure 2. Up: Number of nerve fibers in the left OR of healthy subjects. Down: Number of nerve fibers in the right OR of healthy subjects

Table 2. Mean and standard deviation of nerve fiber length in right and left OR

Brain's Section	Imaging	Number of Subjects	Average Length of Nerve Fibers (mm)	Standard Deviation (mm)	P-Value
Left OR	DTI	9	82.52	4.11	<0.05
	q-ball	9	93.74	5.15	
Right OR	DTI	8	77.99	2.73	<0.05
	q-ball	8	92.34	3.47	

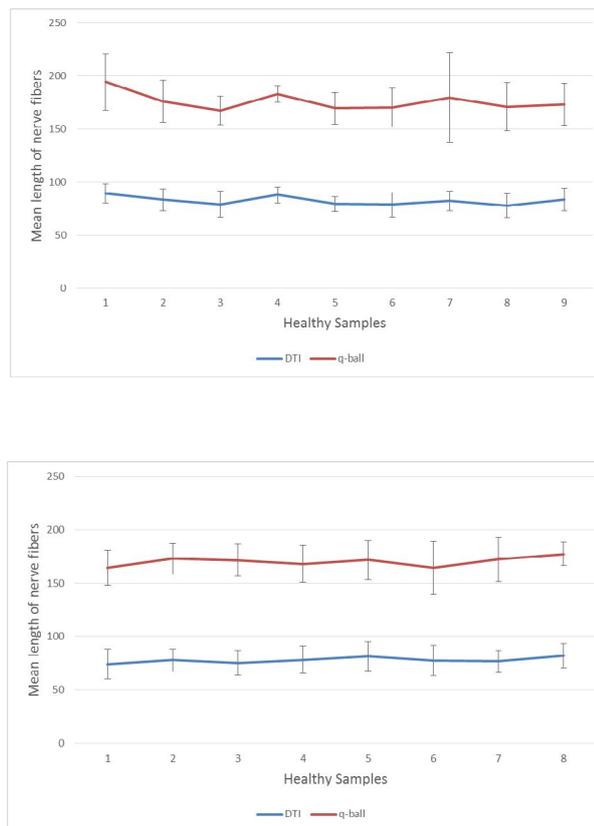


Figure 3. UP: Mean length of nerve fibers in left OR of healthy subjects. **Down:** Mean length of nerve fibers in right OR of healthy subjects

Due to the p-value above 0.05 in the normality test, the obtained results follow the normal distribution and the t-test can be performed. With respect to p-value less than 0.05 in t-test, the mean of the two groups defined in each of the graphs shown in Figures (2) and (3) are statistically different and have a significant differences. As it can be seen in Figures (2) and (3), the number and length of nerve fibers obtained from DTI-based tractography are less than the number and length of nerve fibers obtained from Q-ball based tractography in the right and left OR of each brain.

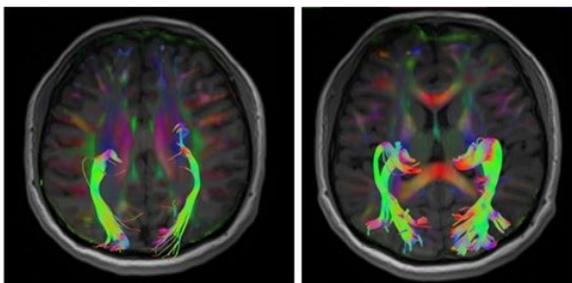


Figure 4. Right: Image of left and right OR nerve fibers reconstructed in a healthy subject by Q-ball method. **Left:** Image of left and right OR nerve fibers reconstructed in a healthy subject by DTI method

Comparison of DTI and q-ball based tractography images:

At the end of this study, tractography images of reconstructed nerve fibers in the Optic Radiation region of the healthy brains, based on DTI and Q-ball imaging methods, were compared.

4. Discussion

DTI is one of the MRI imaging methods used to improve understanding of white matter configuration and the various pathologies that may affect it. Nerve fiber tractography using DTI, is a method which represents the orientation and integrity of white matter nerve fibers in brain. The main direction of diffusion in each voxel can be identified in the diffusion tensor. Nerve fiber tractography increases the accuracy of MRI findings, thereby improving the relevance of this information to clinical findings. Using tractography, the three-dimensional structure of these fibers in the brain, as well as any abnormalities, can be observed directly [26]. Over the past few years, however, it has been proven that it is inappropriate to assume a Gaussian model for

diffusion in a complex substrate such as human brain tissue. One of the conditions in which this model is incapable, is the condition in which there are several directions of the nerve fibers in a single voxel. Therefore, the use of a single nerve fiber distribution tensor model creates ambiguity in areas where several nerve fibers cross, merge, or branch. A new method that allows the researcher to more accurately detect changes in diffusion in different directions is to use High Angular Resolution Diffusion Imaging (HARDI), like the q-ball imaging [27].

It should be noted that although the number of nerve fibers can be measured by tractography, this measurement depends on the amount of angle threshold provided [28]. In this study, by comparing the nerve fibers obtained from the analysis of nerve fibers at each angle in the OR, the best angle threshold was selected to be 45 degrees. As it can be seen in Figure (1), the nerve fibers at the lower angles are not completely reconstructed and many of the Optic Radiation nerve fibers do not appear in the tractography image. At high angles, the depiction of irrelevant and incorrect nerve fibers (anatomical noise) or anatomically incorrect nerve fibers can disrupt the tractography. In the images obtained from the q-ball data, angle 45°, while fully covering the OR nerve fibers, has the least amount of anatomical noise and is therefore selected as the best angle threshold for brain tractography in this study. This choice of angle is consistent with the results of a study by Thomas et al. [21].

In the present study, the number and length of nerve fibers in the Optic Radiation region of healthy brains were compared using the DTI and q-ball imaging at a threshold angle of 45°. As a result of these comparisons, the number of nerve fibers obtained in the left OR of the subjects using the q-ball imaging was 52% higher than the number of nerve fibers obtained in the left OR using the DTI method, and the results had a significant difference with each other (p -value <0.05); Similarly, this value for the right OR of the subjects was 105% and a significant difference was observed in the results (p -value <0.05). Next, the length of nerve fibers obtained in the left OR of the brains using the q-ball method was observed to be 14% longer than the length of the nerve fibers obtained in the left OR of the brains using the DTI method. This parameter for the right OR of healthy subjects was 18%, which in both regions, the results obtained by DTI and q-ball

methods were significantly different from each other (p -value <0.05). As a result, in this study, it has been shown that the number and length of nerve fibers using the q-ball imaging method is greater than the number and length of nerve fibers using the DTI imaging method in each healthy subject. This reduction in the number of nerve fibers reconstructed by the DTI imaging method in the brains is shown in the tractography images in Figure (4). It can be concluded that q-ball imaging, due to its positive effect on the tractography image quality and higher SNR in nerve fibers, reconstructs brain nerve fibers better than DTI imaging and has the potential to better diagnose neurological diseases such as Multiple sclerosis (MS). As clinical applications continue to advance, nerve fiber tractography should play a vital role, not only in identifying the target nerve fibers, but also in identifying the various diseases affecting a particular white matter neuron.

It is noteworthy that in previous researches and their results, multi-shell q-ball imaging method has not been used to compare the parameters of different parts of the brain, such as the OR region, *in vivo*.

5. Conclusion

In this study, it was concluded that by reducing the angle threshold of tractography, it is not possible to completely reconstruct and study the desired nerve fibers. Likewise, at high angle thresholds, tractography will involve anatomical noise (False Positive) or incorrect nerve fibers, which greatly reduces the accuracy of tractography and reconstruction of the desired nerve fibers. After comparing the tractography results of Q-ball images at 13 different angles (from 10 to 70 °) and removing images with high anatomical noise that did not completely cover the OR, the 45 ° angle was considered the best tractography angle threshold in this research. Also, in this study, it was observed that the number and length of nerve fibers obtained from DTI-based tractography and the number and length of nerve fibers obtained from Q-ball-based tractography were statistically different and there were significant differences. The number and length of nerve fibers in left and right Optic Radiation of healthy brains, obtained from DTI-based tractography are less than the number and length of nerve fibers obtained from Q-ball-based tractography. It can be concluded that HARDI-based tractography from the OR in brain is

significantly better than DTI-based tractography and can easily detect complex pathways of white matter at the junctions and within each voxel. Therefore, Q-ball imaging can be an essential component of clinical studies that seek to evaluate the whole white matter by diffusion imaging.

One of the limitations of this study that could potentially affect the results of the tractography is the scan time. In this study, this time lasted 22 minutes which can result in artifacts due to patient motion.

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