Editorial

Uncertainty Assessment of Quantitative Measurements in Medical Imaging: Applications in Cross-Sectional and Longitudinal Diffusion MRI

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Received: 15 October 2019
Accepted: 21 October 2019
DOI: https://doi.org/10.18502/fbt.v6i4.2208
http://FBT.tums.ac.ir

1. Introduction

Medical imaging measurements have been increasingly investigated as imaging biomarkers for detecting physiological and pathological changes. It is critical to evaluate the reliability of the changes in measurements observed in an individual patient for any clinical decision making. The purpose of this article is to review the utility of uncertainty analysis in medical imaging measurements for individual patients undergoing any pathology or medical therapy.

We specifically show how to assess whether the observed alterations in measurements are true changes, i.e. the changes due to medical conditions alone, beyond the uncertainty associated with the imaging, image analysis, or natural physiological occurrences. In order to elaborate the uncertainty concept and the potential applications of uncertainty analysis in the field of medical imaging, we reopen two of our previous articles published in the "journal of Physics in Medicine and Biology" [1], and the "Journal of neurological sciences" [2], respectively. The first study delineates the uncertainty analysis in the context of longitudinal imaging for evaluating the validity of serial measurements for assessing radiation-induced neurotoxicity in patients who had low-grade or benign tumors and were treated by partial brain radiation therapy. The second work intricates such an application for estimation of interhemispheric variation uncertainty to identify the epileptogenic side in the patients with temporal lobe epilepsy in a cross-sectional study.

The analysis of a change in a medical imaging measurement in an individual patient is valuable in the context of individualizing treatments: for example, decreasing radiation dose in a patient who shows high risk for white matter toxicity. Whether an individual patient has a true change cannot be determined from the mean of changes observed in a group of patients. Even though a group of patients has a statistically significant mean change, some individuals in the group may not have true changes. Conversely, observing a statistically insignificant mean change from a group of patients does not imply that there is no individual with a true change. In order to assess an individual change, one must determine how large a change can be considered as a true change. If an 'uncertainty range' can be estimated from test–retest data, an individual patient's change can be compared to this uncertainty range. In other words, the reproducibility of an imaging biomarker must be tested in order to determine whether an observed imaging change in an individual patient is a 'true change', i.e., a

1.1.The Alterations in Imaging Indices

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change beyond the level of uncertainty in the measurement [3].

1.2. Diffusion Measurements in Longitudinal Radiation Therapy Assessments

Previous studies have suggested that a change in Diffusion Tensor Imaging (DTI) index of brain white matter structures following Radiation Therapy (RT) is an indicator of radiation-induced neurotoxicity [1]. They have examined Fractional Anisotropy (FA) as an index of fiber integrity, Mean Diffusivity (MD) as an index of overall diffusivity, Radial Diffusivity (RD) as an index of demyelination, and Axial Diffusivity (AD) as an index of fiber degradation/degeneration [4, 5]. In longitudinal imaging studies, this uncertainty range has been defined as the Repeatability or Reproducibility Coefficient (RC). Several studies have estimated the RC of diffusion indices. The broad range of RC suggests that many factors can influence the RC, including imaging acquisition, data preprocessing, segmentation methods, and characteristics of the structures under study. The estimated RC is essential to determine how reliable a longitudinal individual change is for potential use in clinical decision making.

1.3. Diffusion Measurements in Cross-Sectional Epilepsy Neuroimaging Assessments

DTI has been also investigated as a potential imaging modality for the detection of physiological and pathological changes in white and gray matter structures engaged in an epileptic network. Previous studies have reported the ability of DTI to help identify which temporal lobe is epileptogenic by comparing variations between patients with Mesial Temporal Sclerosis (MTS) and non-epileptic controls [6-8]. However, this necessitates calibration with non-epileptic controls if a different MRI scanner is used. Our prior study has compared the differences between homologous regions in each hemisphere in individual subjects, so that each patient can serve as his or her own control [2]. The cingulum, fornix, and hippocampus are integral components of Papez' circuit. Their bilateral structure, parasagittal location and prominence make them suitable sites for comparative study of the interhemispheric variation of diffusion indices. In the analysis of interhemispheric asymmetry of TLE bilateral structures, an interhemispheric variation of an imaging index in an individual patient must be beyond the minimum detectable value (interhemispheric variation uncertainty; HVU) to be interpreted as a truly significant variation [2, 3].

2. Method and Materials

2.1. Repeatability Coefficient

Let I_{ik} be the index observed value for i^{th} subject and k^{th} replication, $i = 1, 2 \dots, n$, $k = 1, 2 \dots,$ K (in our test and retest dataset, n=12, K = 2) as:

$$I_{ik}/\mu_i = 1 + \varepsilon_{ik} \quad (1)$$

Which relates I_{ik} to its true value μ_i for each subject through a residual relative error ε_{ik} with the within-subject variance $\sigma_w^2 = var(\varepsilon_{ik})$ in normalized ANOVA model. The within and between-subject means of squares (WMS and BMS) with χ^2 distributions of n(K-1) and n-1 degrees of freedom are:

$$WMS = \frac{1}{n(K-1)} \sum_{i=1}^{n} \sum_{k=1}^{k} \left[\frac{I_{ik} - \overline{I_i}}{\overline{I_i}} \right]^2 \quad (2)$$

and

$$BMS = \frac{K}{n-1} \sum_{i=1}^{n} \left[\frac{\overline{I_i} - \overline{I}}{\overline{I}} \right]^2 \quad (3)$$

respectively, where $\overline{I_i}$ is the mean over replications for i^{th} subject, and $\overline{I}$ is the mean over all observations. The within-subject standard deviation can be estimated by $\widehat{\sigma_w^2} = WMS$. Rewriting the Equation (2) for K=2:

$$\widehat{\sigma_w^2} = 1/n \sum_{i=1}^{n} 1/2 \left[\frac{I_{it} - I_{ir}}{(I_{it} + I_{ir})/2} \right]^2 \quad (4)$$

Where t and r denote test and retest, respectively. The RC is given by $RC = 2.77\sigma_w$, which defines the 95% Confidence Interval (CI) of the normalized measurements to determine whether a change in an individual patient is a true change. The 95% Confidence Interval (CI) of the estimated RC is given by:

$$RC_L = 2.77\sqrt{\frac{n.WMS}{\chi^2_{\tilde{n}}(0.975)}}\ , RC_U = 2.77\sqrt{\frac{n.WMS}{\chi^2_{\tilde{n}}(0.025)}}\ , \widehat{RC}\epsilon(RC_L, RC_U) \qquad (5)$$

Assuming there is no change in a structure between test and retest due to disease progression or therapy, any change has to be due to random and/or systematic errors that could have originated from imaging device, image acquisition, patient re-positioning, image processing and analysis, and/or subject-specific natural physiological variations [1].

2.2. True Individual Longitudinal Changes

In the first study [1] , we studied twenty-two patients who had low-grade or benign tumors and were treated by PBRT. The diffusion tensor images in the patients were acquired pre-RT, week 3 during RT, at the end of RT, and 1, 6, and 18 months after RT. We calculated a percentage change ($\Delta I_t\%$) in FA, MD, AD, or RD in a segmented white matter structure of a patient from baseline scan to follow-up scan t (t=3 or 6 weeks during RT, or 1 month, 6 months or 18 months after RT). Considering an interval $(-\delta_c, \delta_c)$ within which there is essentially no change, three possible scenarios could occur for $\Delta I_t\%$. In the first scenario, $\Delta I_t\%$ is confidently considered to have no change if the interval $(\Delta I_t\% - \mathrm{R\,C_L}\ ,\ \Delta I_t\% + \mathrm{RC_U})$ is contained inside the interval $(-\delta_c, \delta_c)$. In the second scenario, an individual patient is considered to have a true change with 95% confidence if the interval $(\Delta I_t\% - \mathrm{R\,C_L}\ ,\ \Delta I_t\% + \mathrm{RC_U})$ lies outside the interval $(-\delta_c, \delta_c)$ and does not contain zero. For a single direction of change, the requirement for a true change is reduced to $\Delta I_t\% \geq R\ C_L$ for a positive change or $\Delta I_t\% < -RC_U$ for a negative change. In the third scenario, if the interval $(\Delta I_t\% - R\ C_L\ ,\ \Delta I_t\% + RC_U)$ and the interval $(-\delta_c, \delta_c)$ overlap but do not contain one another, we are unable to confidently confirm a true change.

2.3.Interhemispheric Variation of an Index

In order to determine whether an interhemispheric variation of a measurable quantity in an individual patient is a true variation (beyond the uncertainty), it should be compared with the HVU measured for that quantity in the specific region of interest [2]. HVU can be estimated by asymmetry analysis of a cohort of non-epileptic subjects who have undergone imaging with the same scanner, under the same imaging conditions and segmentation method, for which no significant asymmetry is expected to be observed. An HVU was estimated for MRI and DTI indices within some brain structures. We then used the HVU levels to define the 95% Confidence Interval (CI) to distinguish true interhemispheric variations for individual TLE patients. In Equations (1) through (4) above, the measurements are acquired within bilateral structures in brain hemispheres (K=2), therefore, a within-subject standard deviation can be estimated by:

$$\widehat{\sigma_w} = \sqrt{WMS} = \sqrt{\frac{1}{2n}\sum_{i=1}^{n}[I_{ir} - I_{il}]^2} \qquad (6)$$

Where r and l denote right and left sides, respectively.

The HVU is given by $2.77\sigma_w$ and is estimated by $2.77\sqrt{WMS}$. The interhemispheric variation is expected to be in the range of –HVU to HVU for 95% of all nonepileptic subjects. Using a previously published formulation [9], (the lower (HVU_L) and the upper (HVU_U) limits of the 95% confidence interval (CI) of the estimated HVU are calculated by:

$$HVU_L = 2.77\sqrt{\frac{n.WMS}{\chi^2_{\tilde{n}}(0.975)}}\ ,\ HVU_U = 2.77\sqrt{\frac{n.WMS}{\chi^2_{\tilde{n}}(0.025)}} \qquad (7)$$

For non-epileptic subjects undergoing the same imaging condition and image processing course, any interhemispheric variation may be attributable to natural physiological occurrences.

2.4.True Individual Interhemispheric Variations

In TLE patients, the true index value for a given involved sub-region in each subject differs between sides. A true individual interhemispheric variation corresponds to $\mu_{i,contra} - \mu_{i,ipsi} \neq 0$. Assuming $\varepsilon_{i,contra}$ and $\varepsilon_{i,ipsi}$ are independent and have the same within-subject standard deviation for all subjects, $\Delta I_{\mathrm{i}} = I_{i,contra} - I_{i,ipsi}$ has a mean, $\mu_{i,contra} - \mu_{i,ipsi}$ and a within-subject variance, $2\sigma_w^2$. Therefore, the 95% CI for $\mu_{i,contra} - \mu_{i,ipsi}$ is $(\Delta I_{\mathrm{i}} - 1.96\sqrt{2\sigma_w^2}\ ,\ \Delta I_{\mathrm{i}} + 1.96\sqrt{2\sigma_w^2})$ or $(\Delta I_{\mathrm{i}} - HVU\ ,\ \Delta I_{\mathrm{i}} + HVU)$. If the 95%

CI does not contain zero and the true value of $dHVU$ is known, a 95% confidence of a true interhemispheric variation exists. In the current estimation scheme for HVU, the effect of a limited number of nonepileptic subjects on the degree of uncertainty around the estimate of HVU is accounted for. A hemisphere variation is conservatively considered to be a true variation with 95% confidence if the interval $(\Delta I_i - HVU_L\ ,\ \Delta I_i + HVU_U)$ does not contain zero [9].

3. Results

3.1. Evaluation of Longitudinal Changes in Diffusion Indices

Using a test–retest diffusion tensor dataset of twelve patients from NBIA database, we estimated the uncertainty in diffusion indices of fornix, cingulum, and corpus callosum. Diffusion indices in different white matter structures showed different uncertainty ranges. The estimated RCs are listed in Table 1. We evaluated the within-subject variance in the segmented structures, from which the estimated RC and their variations come. We compared the within- and between-subject variations using F-statistics. The within-subject variation in the test–retest data was significantly smaller than the between-subject variation, and the test–retest dataset is valid for estimating the RC. The histogram of the percentage changes in diffusion indices suggested a distribution close to normal.

Table 1. Estimated RC% and confidence interval

	Cingulum	Fornix	Corpus Callosum
RC%(FA)	4.3(3.1,7.1)	7.9(5.7,13.1)	6.1(4.3,10.0)
RC%(MD)	2.9(2.1,4.8)	2.2(1.6,3.7)	3.8(2.7,6.3)
RC%(AD)	2.5(1.8,4.1)	2.8(2.0,4.6)	1.9(1.4,3.1)
RC%(RD)	3.4(2.4,5.6)	3.0(2.1,4.9)	5.9(4.3,9.8)
Volume(m^3)	7183±404	1234±99	10666±657

The estimated RC% and its confidence interval $(RC_L\%, RC_U\%)$ for each diffusion index and each structure.

Overall, 23% of the patients treated by RT had FA changes, 44% had MD changes, 50% had AD changes, and 50% had RD changes beyond the 95% CI $(-RC_U,\ RC_L)$ of the estimated RC. In addition, the number of the patients who had changes in diffusion indices beyond the uncertainty range increased over time. As anticipated, the group means reached significance at the later time points when more patients had individual changes beyond the uncertainty. For all the structures under study, the number of the patients who had true FA changes increased from 11% at week 3 during RT, to 18% at the end of RT, 22% at 1 month, 27% at 6 months, and 46% at 18 months after RT, indicating that radiation effects on the diffusion indices became more pronounced over time (See Figure 1. as an illustration).

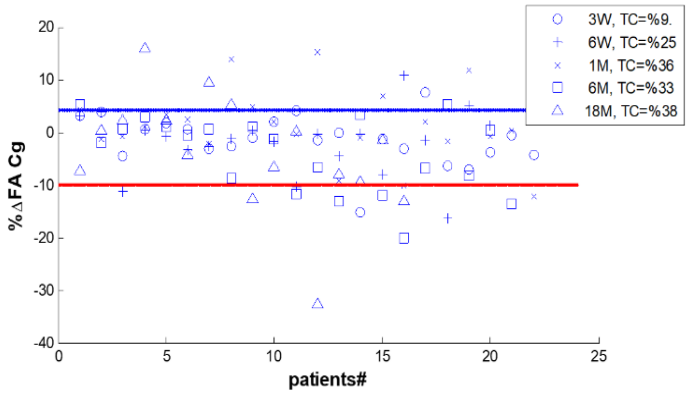

Figure 1. The individual percentage changes in FA in the cingulum in the patients who underwent PBRT. TC indicates the percentage of the patients who had changes beyond the uncertainty. The lines show the estimated RC_U and RC_L (minus upper limit and lower limit of RC), respectively. If a diffusion index percentage change is larger than RC_Lor smaller than RC_U, we consider it a true change

3.2. Individual Analysis of Interhemispheric Variation for FA

Using twenty-three nonepileptic subjects, the HVU and 95% CI (HVU_L, HVU_U) were estimated (Table 2). For each individual of the cohort of TLE patients, a determination was made as to whether an interhemispheric variation of mentioned biomarkers was beyond uncertainty. Almost all interhemispheric variation of indices was beyond the uncertainty for pathology-proven MTS cases. The interhemispheric variation of FA in the posteroinferior cingulum, FA in the fornix crus, the hippocampal MD value, FLAIR intensity, and the volume were beyond the uncertainty for 15, 14, 18, 13, and 16 TLE patients respectively and lateralized them. Consolidating lateralization results of HVU analysis on all mentioned biomarkers by majority voting has detected the epileptogenic side for 19 out of 20 TLE cases with no wrong lateralization (See Figure 2).

Table 2. HVU and its 95% CI (HVU_L, HVU_U) estimated using control nonepileptic subjects for the lateralization biomarkers

Imaging Attributes	N	HVU	HVU_L	HVU_U
Posteroinferior Cingulum FA	23	0.027	0.021	0.037
Crus of Fornix FA	23	0.018	0.014	0.025
Hippocampal MD	20	$3.1 \times 10{-}5$	$2.4 \times 10{-}5$	$4.5 \times 10{-}5$
Hippocampal Volume	45	0.069	0.058	0.087
Hippocampal FLAIR Intensity	25	0.099	0.078	0.137

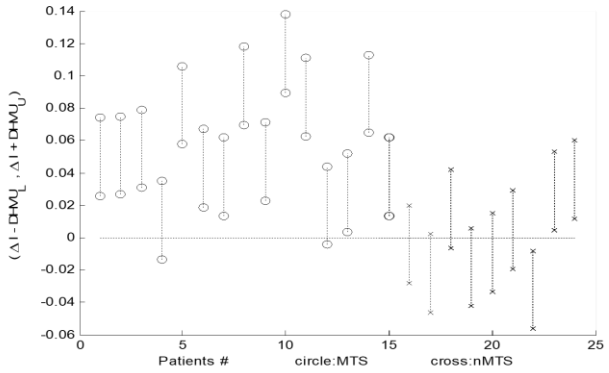

Figure 2. Interhemispheric variation of FA within the cingulum posteroinferior sub-region for individual patients. The interval ($\Delta I - HVU_L$, $\Delta I + HVU_U$) has been depicted for each individual TLE patient with MTS (circles) or without MTS (crosses). An individual patient was considered to have a true hemispheric variation with 95% confidence if this interval did not contain zero

4. Discussion

Several factors can affect the accuracy and confidence of the estimated RC, including systematic errors and random errors. The systematic errors include differences between scanners, diffusion imaging protocols, pre-processing methods, structure segmentation methods, and characteristics of white matter structures. The random errors include scanner hardware noise, patient repositioning error, and idiosyncrasies of subjects. Random effects as a group can be reduced by averaging multiple measurements or increasing the number of subjects. However, each systematic error always creates a measurement bias in the same direction, which affects the exchangeability of measurements obtained from the different scanners. On the other hand, random errors affect the reproducibility of measurements. In order to assess the exchangeability of diffusion indices between different scanners or image acquisition protocols, a same group of subjects should be imaged using different scanners with the same protocols, or different protocols on the same scanner. Statistical analysis of these differences allows us to determine whether the indices can be used interchangeably across platforms and protocols. However, to test reproducibility of the DTI indices, repeated scans have to be performed on the same scanner and using the same protocol. To test both inter exchangeability and reproducibility, repeated measures have to be done in a group of subjects on various scanners, using different protocols, and with the number of the subjects that are justified statistically. This will involve in a large number of repeated scans, which has not been done up to date. However, to gain our understanding of these questions, several studies have probed the problems from various points of view. By testing normal subjects on two different vendor scanners [9], it was found that the diffusion indices were variable by the use of different scanners, inter-scanner variations from a single vendor, poor calibration, the number of subjects in the test and retest data, different image acquisition protocols with different parameters including the Signal to Noise Ratio (SNR) and the number of diffusion gradient directions, and post-processing steps, including segmentation [1, 10-14]. In our work, diffusion index measurements were averaged over many voxels in the extracted structures, reducing the effect of differences in SNR between scanner systems. Also, the longitudinal (repeated) scans for each individual patient were done on the same scanner. Baseline diffusion indices vary across patients due to many reasons, possibly including age and sex. If using diffusion indices themselves to estimate the RC, it would lead to an inaccurate estimation. By normalizing the diffusion indices to their baseline values, we minimized the effects of cross-subject (and to some extent the effect of cross-scanner) variation and made the comparison between structures more significant. The larger structures with greater anisotropy usually have more reliable estimates of RC, because a large number of voxels in the structure leads to a stable mean of diffusion index measures. Low anisotropy can also decrease accuracy in estimating RC, for example in the fornix. Low anisotropy in the fornix also challenged the consistency of the segmented volumes from the test and retest data, as indicated by a low agreement between the

two segmented volumes. The large estimated RC of FA in the fornix is unlikely to be due to the choice of scanner and protocols, and most likely due to the challenges from low anisotropy, small diameter of the fiber bundles and the shape and characteristics of the structure. Co-registration was used to minimize errors caused by the segmentation process; however, the accuracy of image registration can be confounded by subject repositioning, noise, spatial resolution, partial volume averaging, and data interpolation, even without any gross anatomy changes. The fine structure of white matter fibers results in diffusion tensor indices, particularly FA, being highly sensitive to partial volume averaging occurred during data interpolation. Reproducibility of a diffusion index in a small structure or a structure with a large variation in the index could be worse than a large structure, and thereby the estimated RC could be large. This is also reflected in our relatively large RC estimates for the fornix. To decide whether a diffusion index change is a true change, we used the 95% CI of the estimated RC of that index, but not the estimated RC, which is a conservative approach.

Quantitative neuroimaging biomarkers are increasingly used as means of lateralizing TLE in attempts to lessen diagnostic ambiguity and avoid invasive electrographic monitoring approaches. An assessment of interhemispheric variation, applied here to these related limbic structures, is a necessary component in the analysis of imaging attributes to ensure the certainty of a true difference in the individual patient. The introduction of the HVU as a metric in this study provides the means to establish the trueness in outcome for all measures. In turn, this allows comparison of imaging attributes in order to better judge their relative efficacy in lateralizing the ictal onset zone in TLE. The presence of variability in a quantitative imaging index can be due to the imaging system-related or subject-related factors, which make a variation in an index measured in an individual patient difficult to interpret. However, in interhemispheric asymmetry analysis, since the paired bilateral structures undergo the same imaging condition, the variability in the extracted interhemispheric index could be confined to the subject-related factors, including natural physiological occurrences and pathology. In the current study, in order to determine whether the variation can quite purely account for the pathology, the variability for natural physiological occurrences was estimated from a cohort of control, nonepileptic subjects who had undergone imaging with the same scanner and imaging parameters. Subsequently, if the observed interhemispheric variation for an individual patient was beyond the natural physiological occurrences (uncertainty), a true significant pathology-induced variation was determined by a conservative rigor of applying an upper and lower limit of a 95% confidence interval. Comparison of a diffusion index in paired structures with an index mean established in a control group can be misleading when bilateral changes are noted as these may be a consequence of spurious physiological change rather than a marker of epileptogenicity. The variability of an extracted index has been addressed comprehensively in several studies by repeated (i.e., test–retest) measurements. The choice of a subregion of the cingulum where there is little variability in controls and the implementation of the HVU analysis neutralizes the issues of scanner choice and imaging parameters while avoiding the need for co-registration. It is, therefore, restricted to subject-specific and fiber-specific features (i.e., fiber tract size, shape and diffusivity pattern) of the image and, ostensibly, reduces the uncertainty in declaring true FA and MD variation. This study supports the notion that HVU analysis has a role as an application to a battery of quantitative imaging studies that, in concert, may be used to support clinical decision-making in the evaluation of TLE.

5. Conclusion

The goal of this article was to review the concept and the methodology to estimate the uncertainty of longitudinal as well as cross-sectional interhemispheric changes in diffusion indices in white matter structures that may be valuable for assessment of radiation-related neurotoxicity and pathology-related neuroimaging measurements, respectively. We demonstrated the concept of how to apply the estimated the 95% CIs of the RC or HVU to evaluate the observed changes in diffusion indices of the same white matter structures. This framework provides a statistical reference to determine the measurement changes beyond uncertainty in individual patients experiencing physiopathology of any neurological disorder, or undergoing any medical treatment. The concept can be applied to other imaging

modalities and biomarkers in diagnostic and therapeutic assessments.

References

1- M.-R. Nazem-Zadeh, C. H. Chapman, T. S. Lawrence, C. I. Tsien, and Y. Cao, "Uncertainty in assessment of radiation-induced diffusion index changes in individual patients," *Physics in medicine and biology,* vol. 58, no. 12, pp. 4277-4296, 2013.

2- M.-R. Nazem-Zadeh *et al.*, "Lateralization of temporal lobe epilepsy using a novel uncertainty analysis of MR diffusion in hippocampus, cingulum, and fornix, and hippocampal volume and FLAIR intensity," *Journal of the neurological sciences,* vol. 342, no. 1-2, pp. 152-161, 2014.

3- H. X. Barnhart and D. P. Barboriak, "Applications of the repeatability of quantitative imaging biomarkers: a review of statistical analysis of repeat data sets," *Translational oncology,* vol. 2, no. 4, pp. 231-235, 2009.

4- S. K. Song, S. W. Sun, W. K. Ju, S. J. Lin, A. H. Cross, and A. H. Neufeld, "Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia," *Neuroimage,* vol. 20, no. 3, pp. 1714-1722, 2003.

5- C. A. M. Wheeler Kingshott and M. Cercignani, "About "axial" and "radial" diffusivities," *Magnetic Resonance in Medicine,* vol. 61, no. 5, pp. 1255-1260, 2009.

6- M. E. Ahmadi *et al.*, "Side matters: diffusion tensor imaging tractography in left and right temporal lobe epilepsy," *American journal of neuroradiology,* vol. 30, no. 9, pp. 1740-1747, 2009.

7- S. Y. Yoo *et al.*, "Apparent diffusion coefficient value of the hippocampus in patients with hippocampal sclerosis and in healthy volunteers," *American journal of neuroradiology,* vol. 23, no. 5, pp. 809-812, 2002.

8- N. K. Focke, M. Yogarajah, S. B. Bonelli, P. A. Bartlett, M. R. Symms, and J. S. Duncan, "Voxel-based diffusion tensor imaging in patients with mesial temporal lobe epilepsy and hippocampal sclerosis," *Neuroimage,* vol. 40, no. 2, pp. 728-737, 2008.

9- M. Cercignani, R. Bammer, M. P. Sormani, F. Fazekas, and M. Filippi, "Inter-sequence and inter-imaging unit variability of diffusion tensor MR imaging histogram-derived metrics of the brain in healthy volunteers," *American journal of neuroradiology,* vol. 24, no. 4, pp. 638-643, 2003.

10- T. Zhu *et al.*, "Quantification of accuracy and precision of multi-center DTI measurements: a diffusion phantom and human brain study," *Neuroimage,* vol. 56, no. 3, pp. 1398-1411, 2011.

11- J. A. Farrell *et al.*, "Effects of signal-to-noise ratio on the accuracy and reproducibility of diffusion tensor imaging–derived fractional anisotropy, mean diffusivity, and principal eigenvector measurements at 1.5 T," *Journal of Magnetic Resonance Imaging,* vol. 26, no. 3, pp. 756-767, 2007.

12- D. K. Jones, "The effect of gradient sampling schemes on measures derived from diffusion tensor MRI: A Monte Carlo study†," *Magnetic Resonance in Medicine,* vol. 51, no. 4, pp. 807-815, 2004.

13- T. Zhu *et al.*, "Evaluation of measurement uncertainties in human diffusion tensor imaging (DTI)-derived parameters and optimization of clinical DTI protocols with a wild bootstrap analysis," *Journal of Magnetic Resonance Imaging,* vol. 29, no. 2, pp. 422-435, 2009.

14- Z. Nagy, N. Weiskopf, D. C. Alexander, and R. Deichmann, "A method for improving the performance of gradient systems for diffusion-weighted MRI," *Magnetic Resonance in Medicine,* vol. 58, no. 4, pp. 763-768, 2007.