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Comparison of Multi-Fiber Reproducibility of PAS-MRI and Q-ball With Empirical Multiple b-Value HARDI

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Abstract

Crossing fibers are prevalent in human brains and a subject of intense interest for neuroscience. Diffusion tensor imaging (DTI) can resolve tissue orientation but is blind to crossing fibers. Many advanced diffusion-weighted magnetic resolution imaging (MRI) approaches have been presented to extract crossing-fibers from high angular resolution diffusion imaging (HARDI), but the relative sensitivity and specificity of approaches remains unclear. Here, we examine two leading approaches (PAS and q-ball) in the context of a large-scale, single subject reproducibility study. A single healthy individual was scanned 11 times with 96 diffusion weighted directions and 10 reference volumes for each of five b-values (1000, 1500, 2000, 2500, 3000 s/mm²) for a total of 5830 volumes (over the course of three sessions). We examined the reproducibility of the number of fibers per voxel, volume fraction, and crossing-fiber angles. For each method, we determined the minimum resolvable angle for each acquisition. Reproducibility of fiber counts per voxel was generally high (~80% consensus for PAS and ~70% for q-ball), but there was substantial bias between individual repetitions and model estimated with all data (~10% lower consensus for PAS and ~15% lower for q-ball). Both PAS and q-ball predominantly discovered fibers crossing at near 90 degrees, but reproducibility was higher for PAS across most measures. Within voxels with low anisotropy, q-ball finds more intra-voxel structure; meanwhile, PAS resolves multiple fibers at greater than 75 degrees for more voxels. These results can inform researchers when deciding between HARDI approaches or interpreting findings across studies.

Keywords

Q-ball; PAS-MRI; Reproducibility; Crossing Fiber; Angular Error; Minimum Resolvable Angle; HARDI

1. INTRODUCTION

Diffusion tensor imaging (DTI)[1] is widely recognized as a robust method and heavily relied upon for interpreting brain structural connectivity in vivo, but it can only resolve a

dominant single fiber orientation. Advanced diffusion weighted magnetic resonance imaging (MRI), such as Q-ball[2], Persistent Angular Structure (PAS-MRI)[3], Spherical Deconvolution (SD)[4, 5], Diffusion Orientation Transform (DOT)[6], seek to resolve this shortcoming by modeling complex intra-voxel structure. With DTI, empirical reproducibility studies[7] provided concrete information linking observed behavior with theoretical noise sensitivities. Understanding the empirical tradeoffs between these sequences is critical to design of optimal imaging protocol and analysis specification. Yet, to date, comparative analysis of the advanced sequences (commonly known as high angular resolution diffusion imaging - HARDI) has not been performance on large standardized dataset. The overall objective of this work is to address this shortcoming.

Herein, we focus on two methods, Q-ball and PAS-MRI. Q-ball models the voxel wise orientation diffusion function (ODF) by low-order spherical harmonics[8], and is thus able to detect multiple fibers as peaks in diffusion signal in a spherical coordinate system. PAS-MRI more explicitly models the intra-voxel diffusion by a discrete number of fiber compartments[3]. Prior work with Q-ball has shown that it resolves multiple fibers in regions of fractional anisotropy (FA) < 0.4 and detects many voxels with the second direction of diffusion for FA > 0.15 at b-values greater than 1500 s/mm^2 [9]. In [10], Q-ball resolved crossing angles to approximately 45 degrees with lower accuracy at b-values of higher than 4000 s/mm^2 , and it was estimated that lower b-values lead to under estimation in crossing fibers.

Similarly, PAS-MRI has been shown to recover multiple fiber orientations at “low” b-value of 1200 s/mm^2 and has been shown more consistent than q-ball on synthetic MRI data[11]. PAS-MRI was further established as a special case of SD described as maximum entropy spherical deconvolution (MESD) which was shown to be more accurate than traditional SD at the cost of increased computational time[12]. The empirical literature has not yet shown how consistently PAS reproduces the crossing fiber angles.

Briefly, in this study (see Figure 1), we pre-process the data with eddy and topup (FMRIB Software Library (FSL), [13, 14]) for each scan session individually and, then all sessions were registered to the Montreal Neurological Institute (MNI) template in FSL to establish a coordinate system for inter-session analysis. Thereafter, the gold sets were created by concatenating all the single scans per b-value in the acquisition order and HARDI methods were implemented.

2. METHODS

2.1 DW-MRI Data Measurements

A healthy volunteer was scanned for three different sessions each two hours long at 3T (Achieva, Philips Medical Systems, Best, The Netherlands) with a 32 channel head coil on consecutive days. The first two scan sessions consist of four repetitions of 96 gradient directions per the b-values of 1000, 1500, 2000, 2500 and 3000 s/mm^2 . For each shell, a scanner average of 10 minimally weighted reference images (“b0”) was acquired. The last scan session had three repetitions of 96 gradient directions per the same b-values above equivalent to 15 single scans. This data was acquired at the voxel resolution of

2.5mm×2.5mm×2.5mm with a matrix of 96×96 and 38 slices. Briefly, scan parameters were: Multi-Band=2;SENSE=2.2;TR= 2650 ms;TE=94 ms;partial Fourier=0.7. Fold over direction was A-P with a P fat shift. For each set of the 5 diffusion weighted shells, an additional “b0” was acquired with reverse phase encoded volumes (i.e., fold over direction A-P with A fat shift), 3 diffusion weighted directions with a b-value of 1000 s/mm² along the imaging frame cardinal directions, and all other parameters were kept constant.

2.2 Data Pre-processing

The data for each session were corrected for patient movement, eddy current distortion, and susceptibility distortion through topup and eddy [13, 14]. Every diffusion weighted scan in each session had a single b0 (scanner average of ten scans). In addition, each session also had four reverse phase encoded b0 volumes (scanner average of ten scans). All b0s (including reverse phase encoded b0s) in a session were concatenated together and fed as inputs to topup. For eddy, every scan in a session was concatenated and then corrected using the results from topup (note that the acquisition did not have complete reverse phase encoding acquisitions for the diffusion weighted directions). Afterwards, the distortion-corrected b0s from the first session were averaged and registered to a 2.5mm isotropic MNI T2 resample from 0.5mm weighted template using 6 degree of freedom registration with normalized mutual information metric (flirt, [15]). The volumes for the next session were brought to the same space by averaging its b0s together, performing skull stripping with bet [16, 17], and registering it to the averaged b0s in the first session. The same procedure was subsequently done to the last session to bring all three corrected sessions to a common subject-specific MNI space.

All sessions were normalized by the b0 corresponding to the scan to account for amplitude drift. A weighted mean b0 was created from all b0 scans in MNI space by a weighted average of all b0's. Weight has been taken as inverse of the median of all b0 scans in MNI space averaged with the mean of b0's from all sessions. The resulting normalization scan was computed by multiplying the weighted mean b0 to the ratio of diffusion weighted scan (in MNI space) to the b0 (in MNI space).

2.3 Data Segmentation

The data was divided into 11 single scans per b-value each consisting of 96 gradient directions with a single b0. To create the reference standard (“gold model”), we concatenated the 11 single scans in the order of acquisition to create a volume of 1067 gradient directions per b-value. For the analysis a white matter mask was created a structural image using FSL's automated segmentation tool (fast, [15]) and subsequently registered to the diffusion data.

2.4 Q-ball Reconstruction

Q-ball was reconstructed following [2] and using spherical harmonic basis functions [8] using the Camino Diffusion Toolkit[18]. Q-ball estimates the diffusion orientation distribution function (ODF) by approximating it through a Funk-Radon Transform of the diffusion weighted signal. Herein, we use the spherical harmonic order of 8 for Q-ball, as per the guidance in [8].

2.5 RE-PASMRI Reconstruction

PAS was reconstructed from maximum entropy spherical deconvolution [12]. We used the reduced encoding model for the MESD [19]. Similar to Q-ball, PAS estimates the “persistent angular structure” of the diffusion propagator which resembles the DODF from Q-ball. We used a reduced encoding of 16 as per [19] which gives a good trade-off between computation speed and accuracy for the PAS. The gold sets (amalgamated 11 single scans) for the PAS were processed across multiple CPU cores with the data being split at imaging slices.

2.6 Peak Reconstruction

The peak reconstruction of the ODF and the PAS was performed using sfpeaks from Camino which is an implementation for searching the local maxima of the reconstructed PAS and ODF's using Powell's method [3]. Both PAS and Qball were restricted to detecting peaks of (principal direction threshold) greater than one unit of peak strength divided by the mean of all the detected reconstruction functions (PAS/ODF). We used the recommended default parameters of the program sfpeaks. These parameters follow the precedence of [3].

2.7 Metrics: Reproducibility of Number of Peaks

The consensus number of peaks was defined per voxel as the mode number of peaks across the 11 repetitions. The mean and standard deviation of agreement with consensus (1 versus 0 for disagreement) was determined with the white matter mask for each shell. To assess bias, absolute agreement was computed with the mean and standard deviation of agreement with gold standard number of peaks was determined within the white matter mask for each shell.

2.8 Peak Fraction

The consensus peak fraction was defined per voxel as the mean peak fraction for the first 3 peaks across the 11 repetitions. The root mean squared error (RMSE) and bias (mean difference) between each repetition and the gold standard for each shell were computed and averaged over the white matter mask.

2.9 Metrics: Reproducibility of Crossing Fiber Angle

For any case of voxel where two or more peaks were detected, we determine the minimum angle being resolved, $\angle = \operatorname{argmin}_{i,j,k} (\arccos(i,j) \arccos(j,k) \arccos(j,k))$ where peaks are represented as vectors i, j, k . The absolute error per voxel for the crossing fiber angle is defined as $|\angle_{gold} - \angle_{test}|$. We define a crossing fiber *success fraction* as the proportion of voxels which have error less than 20 degrees.

3. RESULTS

3.1 Consistency in Number of Peaks and Peak Strength

The consensus for the number of peaks per voxel is consistent as a function of b-value for both PAS and Q-ball (Table 1). PAS is more consistent than Q-ball for all experiments in Table 1, yet the within white matter mask variance is similar. For both methods, substantial bias is evident between the single repetition and gold standard data in terms of lower

consistency with the gold standard versus with the consensus. PAS exhibits a trend toward lower bias an increasing b-value while q-ball appears to increase. The RMSE of the peak fraction for 11 single scans shows a decreasing trend with increasing b-value for PAS while for Q-ball remains consistent (Table 2). Peak fraction bias decreases with increasing b-values for PAS, but remains consistent for Q-ball.

3.2 Crossing Fiber Angles indexed with FA

There is an increase in the number of crossing fibers voxels detecting in “gold standard” maps increasing b-value (refer Figure 2). For all b-values, PAS resolves crossing fibers in the range of 65 to 90 degrees. At lower b-values, crossing fiber are detected up to an FA of ~ 0.6 , but at b-value of 3000 s/mm^2 , the concentration of voxels with crossing fibers has a FA of < 0.4 . The spatial maps in Figure 2 show qualitative agreement between the gold standard and single repetition, but there are clear spatial patterns of differences. These differences are reflected quantitatively in the bias shown in Tables 1 and 2.

Figure 3 presents a similar analysis for Q-ball. The voxels with crossing fibers largely occur at 70 to 90 degree angles; however, a clear second population crosses at ~ 55 degrees. While crossing fibers are often detected in voxels with FA up to ~ 0.4 , the majority of detected crossing fibers lie in voxels with FA < 0.2 . Notably, number of crossing fibers increases with b-value. Similarly with PAS, the spatial maps for Q-ball show systematic difference in the number of fibers estimated with the gold standard relative to the a single repetition, which is also reflected in Tables 1 and 2.

3.3 Success Fraction and Error

PAS resolves crossing fiber most successfully when the angle is greater than 75 degrees (Figure 4A), which occurs when the difference between gold is minimized (Figure 4B). There is a trend for more accurate crossing fiber detection at high angles for lower b-values, and more accurate low angle crossing for higher b-values. Q-ball exhibits overall lower success fraction than PAS, and has a peak sensitivity for 65–75 degree crossings (Figure 4C). Lower angles crossing are more accurate with Q-ball, but Q-ball shows degrading performance near 90 degree crossing. The highest b-values resulted in the lowest errors for Q-ball.

4. CONCLUSION

This is the first large-scale empirical reproducibility analysis to compare Q-ball at PAS at 3T in vivo. For the acquisition studied, PAS is more reproducible both in terms of number fibers per voxel (Table 1) and the peak fraction (Table 2). However, there is still substantial variability (15% $\sim$ 20%) in terms of consensus for both Q-ball and PAS. It is important to note that Q-ball and PAS detect different aspects of intra-voxel structure within identical data. Note the two-dimensional histograms in Figure 2 and 3 where PAS identifies more fibers in moderate FA voxels, while Q-ball resolves fibers within voxels with low FA. Similarly, PAS MRI is more consistent for crossing fibers at near-right angles while Q-ball appears more consistent for lower angles. A deeper consideration of the validity and

consistency of cross-fiber populations across analysis method is clearly warranted and will be pursued.

Moreover, the study reveals that both Q-ball and PAS exhibit strong biases in estimated fiber fractions with the number of signal averages considered. Specifically, compare the consensus reproducibility versus the gold standard reproducibility in Tables 1 and 2. Qualitatively, the differences can be appreciated in terms of the peak maps in Figures 2 and 3 and seen in the rendering of Figure 5. Visually, the single scan estimates for Q-ball appear consistent with prior expectations of fiber crossing locations; while the face validity differences for PAS are less clear. Deeper consideration of Q-ball and PAS estimation with signal-to-noise-ratio (SNR) and/or number of repetitions is clearly warranted (as has been done for DTI) [7].

In summary, this study provides direct empirical evidence of systematic differences between Q-ball and PAS. Although b-value clearly impacts estimation of fiber structure, the choices in analysis approach (Q-ball versus PAS) and number of scans (single repetition versus gold standard) have a more substantial impact on data interpretation. Additionally, the types of crossing fibers detected by the methods were difference in terms FA, crossing angle, and number of peaks. There is clear opportunity for innovation in data interpretation to improve consistency, minimizing the impact of SNR, and unifying models of intra-voxel structure. In the meantime, PAS would appear to be a pragmatic alternative to Q-ball for detecting intra-voxel structures in voxels with moderate FA.

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Figure 1.

5830 volumes were acquired in 3 sessions that comprised 11 (4/4/3) repetitions of 5 shells, each with 96 diffusion weighted directions and a scanner average of ten b0 images. All data from each session was distortion corrected and the reregistered in MNI space. “Gold standard” data for each shell was created by concatenating all data into a single acquisition, while each empirical acquisition shell was also considered separately. PAS and Q-ball were run on all data and reproducibility measures were computed.

Figure 2.

Results for PAS: (A) Two-dimensional histograms of crossing fiber angles detected with the gold standard at each b-value. (B) FA maps at each b-value computed with DTI for the gold standard. (C) Number of peaks detected for the gold standard. (D) Number of peaks detected for a single repetition.

Figure 3.

Results for Q-ball: (A) Two-dimensional histograms of crossing fiber angles detected with the gold standard at each b-value. (B) FA maps at each b-value computed with DTI for the gold standard. (C) Number of peaks detected for the gold standard. (D) Number of peaks detected for a single repetition.

Figure 4.

(A) Crossing fiber success fraction for PAS and (B) mean error between each repetition and the gold standard for PAS. (C) Crossing fiber success fraction for Q-ball and (D) mean error between each repetition and the gold standard for Q-ball.

Figure 5.

Illustration of the differences in model fit for the gold standard datasets with: (A) PASMRI – 1000 s/mm², (B) Q-ball – 1000 s/mm², (C) PASMRI – 3000 s/mm², and (D) Q-ball – 3000 s/mm².

Table 1

Reproducibility for the Number of Peaks

b-Values s/mm ²	PAS			Q-ball		
	Mean Consensus	Std. Dev. in WM	Abs. Agreement (Gold)	Std. Dev. Of Abs. Agreement in WM (Gold)	Mean Consensus	Std. Dev. in WM Agreement
1000	0.792	0.170	0.678	0.302	0.6834	0.183
1500	0.799	0.168	0.713	0.277	0.691	0.184
2000	0.799	0.169	0.729	0.261	0.681	0.178
2500	0.804	0.166	0.743	0.250	0.669	0.173
3000	0.793	0.167	0.737	0.244	0.652	0.168
						0.475
						0.302

Table 2

Reproducibility for the Peak Fraction

b-Values s/mm^2	PAS			Q-ball		
	RMSE Consensus	Std. Dev. in WM	RMSE Gold	Std. Dev. In WM (Gold)	RMSE Consensus	Std. Dev. in WM (Gold)
1000	0.075	0.032	0.103	0.049	0.128	0.060
1500	0.070	0.031	0.094	0.046	0.124	0.060
2000	0.068	0.030	0.090	0.045	0.126	0.056
2500	0.066	0.030	0.086	0.044	0.125	0.052
3000	0.068	0.030	0.087	0.043	0.126	0.049
						0.215
						0.120
						0.118
						0.114
						0.112
						0.110