Magnetic Resonance in Medicine 59:216–220 (2008)

Diffusion-Weighted Imaging of the Fetal Brain In Vivo

Dong-Hyun Kim,[1,2*] SungWon Chung,[2] Daniel B. Vigneron,[2] A. James Barkovich,[2] and Orit A. Glenn[2]

A method of performing diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) of the fetal brain in utero is proposed. The major difficulty of performing diffusion imaging in utero is the presence of motion. By modifying conventional single-shot spin-echo echo-planar DWI with a short repetition time sequence, a sequence that performs DWI and DTI within a breath-hold of the mother (13 sec and 18 sec, respectively) was devised. T_1 weighting caused by the use of short repetition times is compensated by interspersing diffusion imaging with additional b=0 image acquisitions. In utero fetal brain DWI and DTI were performed using this sequence. Quantitative analysis revealed minimal differences in the obtained apparent diffusion coefficient (ADC; directionally averaged ADC) values when using this sequence. The method can be readily implemented in a clinical setting and is especially useful when scanning mothers who cannot tolerate lengthier breath-holds. Magn Reson Med 59:216–220, 2008. © 2007 Wiley-Liss, Inc.

Key words: fetal brain; MRI; DWI; DTI

Fetal MR brain imaging is proving to be a powerful modality for evaluating the developing fetal brain and is a valuable complement to prenatal ultrasound (1,2). The development of ultrafast imaging techniques has contributed to the increasing clinical utilization of fetal MR imaging (3–5). Other advanced imaging strategies, such as diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI), which offer unique quantitative information about water molecular motion and tissue microstructure, have recently been applied to the human fetus to illustrate changes during development both in vivo (6,7) and on fetal autopsy specimens (8,9). Clinical studies of the fetus using DWI have also been conducted (10,11).

The major difficulty of performing DWI of the fetal brain in utero is the presence of motion. Fetal motion is especially marked during the second trimester and early third trimester, when most clinical fetal MRI is performed. Maternal breathing can also contribute to motion degradation of DWI images since image acquisition requires the mother to hold her breath. Considering the inherent sensitivity of DWI to motion-related artifacts, these effects add to the difficulty of acquiring DWI of the fetal brain. While breath-hold single-shot acquisitions have been predominantly used for fetal DWI, this technique alone cannot provide the robustness needed against unpredictable fetal motion and motion due to maternal breathing. Therefore, the goal of this study was to devise a DWI technique with reduced susceptibility to motion, capable of obtaining trace apparent diffusion coefficient (ADC) maps (D_{av}; averaged ADC), that could be used to image the fetal brain in the clinical setting. In addition, we investigated the possibility of extending the study to acquire DTI.

MATERIALS AND METHODS

Our current clinical fetal DWI protocol uses a multislice single-shot spin-echo EPI (echo-planar imaging) acquisition. As with conventional trace ADC acquisitions, data from three different orthogonal diffusion directions are gathered to calculate rotationally invariant trace ADC maps. In our proposed method this fetal DWI sequence was used but with a shortened TR (repetition time). Reducing the TR allows the scan time to be reduced to a reasonable level where breath-holding is not an issue for the mother. The adverse effect of reducing the TR would be to introduce T_1 weighting in the raw images (b=0 image and DW images) due to incomplete longitudinal magnetization recovery. This shortcoming can be compensated by acquiring an additional b=0 image. The timing of acquiring the DWI dataset would be:

$$b = 0 \rightarrow bx \rightarrow by \rightarrow bz \rightarrow b = 0 \qquad [1]$$

where each acquisition is separated by a short TR. Any dummy acquisitions prior to the first b=0 image are eliminated to reduce the scan time and enforce T_1 weighting starting with the second image. The signal intensity of each of the acquired images can then be modeled as:

$$I(x,y) \rightarrow I(x,y)\cdot w_i(x,y)\cdot(1 - e^{-TR/T1(x,y)}) \rightarrow \text{"} \rightarrow \text{"} \rightarrow I(x,y)\cdot(1 - e^{-TR/T1(x,y)}) \qquad [2]$$

since steady state of the magnetization is achieved after the first b=0 image. This is true when the excitation pulse is 90°. Deviation from this flip angle will result in a delay time of reaching steady state, which is dependent on the T_1 value. With the 90° excitation assumption, all images after the initial b=0 image are weighted by $(1\text{-}e^{-TR/T1(x,y)})$ while the DW images are additionally weighted by $w_i(x,y)$ where i = x,y, or z depending on the particular diffusion weighting. The value of $T_1(x,y)$ can be calculated from the first and final b=0 images and consequently used to compensate the intermediate DW images. Another reason to acquire the b=0 images at the first and last part is to provide a visual guide to determine any amount of motion present during the acquisition. Since these two images have higher signal-to-noise ratio (SNR) compared to diffusion images, the presence of motion can be readily determined.

[1]School of Electrical and Electronic Engineering, Yonsei University, Seoul, Korea.

[2]Department of Radiology, University of California, San Francisco, California.

Grant number: National Institute of Health (NIH) K23NS052506.

*Correspondence to: Dong-hyun Kim, PhD, School of Electrical and Electronic Engineering, Yonsei University, Seoul, Korea. E-mail: donghyunkim@yonsei.ac.kr

Received 30 November 2006; revised 27 September 2007; accepted 1 October 2007.

DOI 10.1002/mrm.21459

Published online 29 November 2007 in Wiley InterScience (www.interscience.wiley.com).

To validate this technique, DWI with short TRs was performed on an adult volunteer. Different TR values (TR = 7, 3, 2, and 1 sec) were used to investigate the effect of TR shortening and examine the ability to compensate for T_1 weighting using an additional b=0 image. Two quantitative metrics were used to evaluate the ADC value changes after compensation from different TRs. Relative SNRs, obtained by dividing the mean signal intensity of a region of interest (ROI) by the standard deviation obtained from background noise, were calculated for the different TR acquisitions. Another quantity, the fractional error, was used to represent the difference between the ADC values measured at each TR with the ADC value obtained from TR = 7 sec:

$$\text{Frac Error}_{TR} = \frac{ADC_{measured} - ADC_{TR=7}}{ADC_{TR=7}} \times 100 \qquad [3]$$

All SNR calculations and fractional error values were obtained from ROI placed in the adult brain and averaged. These included basal ganglia, thalamus, optic radiations, calcarine gray matter, corticospinal tract, parietal and frontal white matter, hippocampus, visual association, and the posterior limb. The fractional error questions the ability to use the ADC values for quantification in the selected ROIs. In addition, we evaluated whether steady state (90° excitation) is achieved after the first excitation by acquiring multiple short TR images with the diffusion gradients turned off and comparing the individual images.

Fourteen fetuses that were 22 weeks of gestation or older were enrolled in this study (average: 26 ± 4 weeks). No sedating agents were administered to the mother or the fetus. Scans were performed on a 1.5T GE (General Electric Healthcare Technologies, Milwaukee, WI) MR scanner with an EXCITE platform using an 8-channel pelvic torso phased array coil. Single-shot fast spin-echo T_2-weighted images were acquired during normal maternal breathing using real-time imaging of the fetus (12). These images were used as localizer scans for the DWI prescription.

DWI was acquired with two different protocols. The default protocol had relatively long TR: 18-sec 3-directional DWI with breath-hold, TR/TE: 4500/80 ms, 32 cm field of view (FOV), 128 × 128, 8–10 slices, 5 mm thickness, 2 mm skip, 167 kHz bandwidth, and b = 600 sec/mm². Our proposed protocol had a shorter TR: 13-sec 3-directional DWI with breath-hold, TR/TE: 2500/80 ms, 32 cm FOV, 128 × 128, 8–10 slices, 5 mm thickness, 2 mm skip, 167 kHz bandwidth, and b = 600 sec/mm². Images were reconstructed with the algorithm mentioned above to compensate for T_1 effects. The correlation of the ADC values from the two protocols was investigated. ROIs were selected from the two T_2-weighted images and the corresponding ADC values were compared. The selected ROIs were similar to those used in the adult brain study. The size of the ROIs chosen was ≈0.5 cm², corresponding to about 8 pixels for both the adult and fetal cases.

We also extended the protocol to study the feasibility of performing DTI. For this method the sequence was further modified with a 2.2-sec TR with six different diffusion directions for DTI analysis. The b=0 images were obtained at the 1st and 5th TR while the six diffusion directions were acquired during the 2nd, 3rd, 4th, 6th, 7th, and 8th TR acquisition. This resulted in an 18-sec total scan time. Different ordering schemes can be used. Tensor analysis was performed after processing the images with the proposed algorithm.

Table 1
Average SNR Loss and Fractional Error for Different TR Values from an Adult Brain

	TR = 7	TR = 3	TR = 2	TR = 1
Relative SNR	1	0.88	0.73	0.52
Fractional error (%)	0	3.89	3.84	5.22

Fractional error can be used as a measure of difference between true and measured ADCs.

RESULTS

Figure 1 shows postprocessed DW images acquired with different TR values in a normal adult brain. The DW images from as short as a 2-sec TR looked similar to the 7-sec TR image, although at a loss in SNR. Quantitative analysis of average SNR loss and fractional error confirmed this observation (Table 1). Compared to the TR = 7 sec image, the SNR loss was ≈25% for TR = 2 sec and 50% for TR = 1 sec. While the SNR loss was severe, the differences in the average fractional error were relatively small regardless of TR value, indicating that ADC quantification does not change significantly when using shorter TR acquisitions. All short TR acquisitions had fractional error values of ≈5%. Images acquired with diffusion gradients turned off to investigate whether steady state is achieved after the first excitation showed that after the first image consequent b=0 images revealed differences that were within the level of noise, confirming our assumption that 90° excitation was achieved.

In Fig. 2, in vivo fetal ADC maps acquired from the default protocol and our proposed method are shown. Note that the default protocol was acquired in 18 sec and the proposed protocol was acquired in 13 sec. The Bland–Altman curve displaying the differences in ADC values for the two methods shows that there was a bias in the two measurements at a value of -86×10^{-6} mm²/s. The stan-

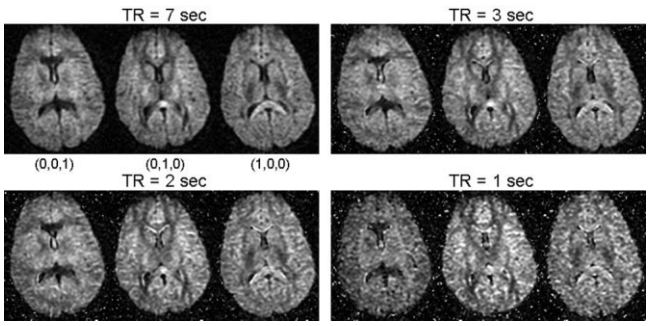

FIG. 1. Three direction DW images for different TR values from a normal adult volunteer (b = 600 s/mm²). The direction of the diffusion gradients is indicated below the TR = 7 sec images. The proposed T_1 compensation method was employed to postprocess the DW images for TR = 3, 2, and 1 sec acquisitions. Average SNR of these images is given in Table 1.

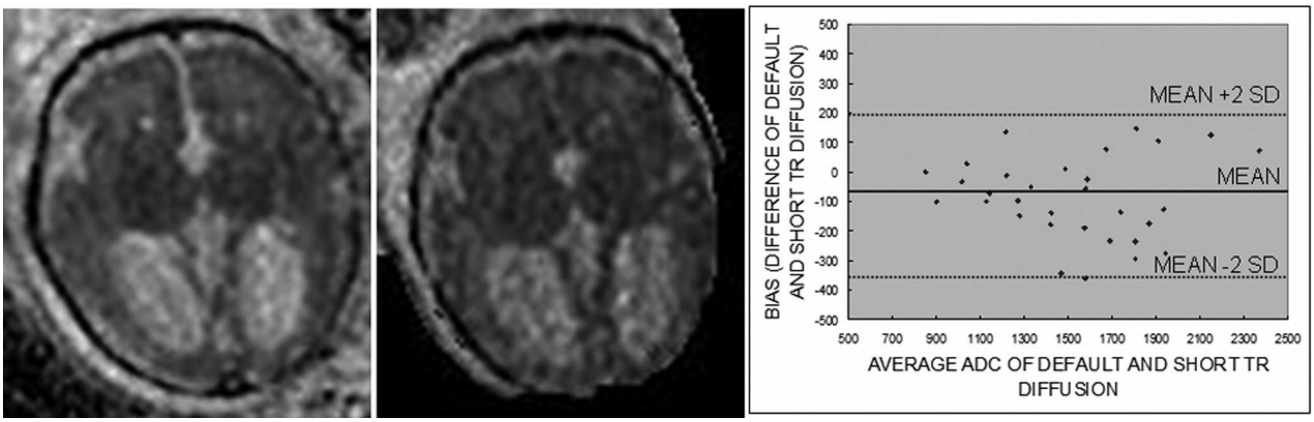

FIG. 2. Fetal ADC maps. (Left) Obtained from the default protocol using 4.5-sec TR and (middle) obtained using our proposed protocol using 2.5-sec TR. The Bland–Altman plot on the right shows the bias (difference of the ADC values obtained from the default and short TR acquisition) for various regions. The mean difference is biased at -86×10^{-6} mm^2/s. The SD (standard deviation) value was 140×10^{-6} mm^2/s. Bias values are within mean $\pm$ 2 SD. Linear regression demonstrated a high correlation ($R^2 = 0.8619$).

dard deviation of differences was 140×10^{-6} mm^2/s. Linear regression revealed a squared correlation coefficient of $R^2 = 0.8619$. The constant offset value is most likely due to the imperfect modeling of the amount of T_1 weighting in the spin-echo-based sequence. For these sequences the amount of T_1 weighting should take into account the 180° pulse effect which results in (13):

$$1 - 2e^{-(TR-\tau)/T1} + e^{-TR/T1} \quad [4]$$

where τ represents the timing between the 90 and 180 pulse. Our less sophisticated model was used here to simplify the calculations.

Finally, Fig. 3 shows results from the proposed DTI experiment. Various tensor-related measurements obtained from a 30-week-old fetus with suspected mild ventriculomegaly are given. Similar to findings by Scifo et al. (14), slight anisotropy can be identified in the genu and splenium of the corpus callosum. The definition of other tensor-related maps can be found in Ref. (15).

DISCUSSION

We have developed a new, faster DWI method of obtaining trace ADC in live human fetuses. The method relies on using conventional fast spin-echo with echo-planar readouts with short TR. By using multiple b=0 images, T_1 weighting can be compensated. The total scan time for obtaining 3-directional DW images was 13 sec, which did not cause any problems in maternal breath-holding for the mother. The reduction in scan time of ≈30% from the default protocol reduces the probability of being susceptible to randomly occurring motion. The approach also lends itself toward applications of in vivo DTI of the fetal brain.

We have also shown that ADC values obtained via this method correlate highly with ADC values obtained with the default method despite the reduced SNR. The average ADC taken from the voxels chosen (≈8 voxels) reduced the deviations, resulting in an SNR of ≈10:1. Taking into account that previous clinical fetal diffusion studies (11,12), although limited in number, have used a similar approach to the default method, our proposed method can be useful in a clinical setting. It is also worth mentioning that the reason we have chosen to compare the DTI values from our method to the default method, instead of reporting and comparing the quantitative values obtained in our study against other studies, is that there is strong age-dependence in these values. In fact, previous studies (8) have targeted an age group different from ours, which can

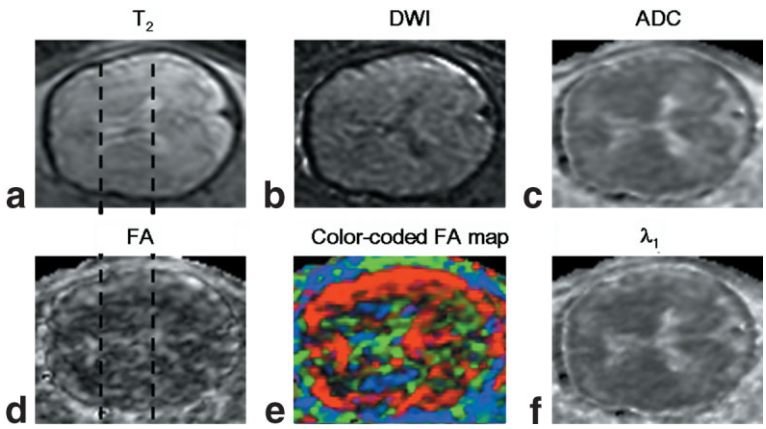

FIG. 3. Diffusion tensor imaging of the fetal brain in vivo. Using a 2.2-sec TR, DTI data was acquired from the fetal brain in 18 sec. The fractional anisotropy map (d) and the color-coded FA map (e) show anisotropy in the genu and splenium of the corpus callosum. A straight line is drawn between the T_2 image and FA map to show the region of anisotropy.

lead to significantly different quantitative values for the fast-developing brain.

By reducing TR, water proton components with shorter T_1 values will have a greater effect on the ADC values. This is due to relative suppression of signal from components with long T_1 values caused by incomplete spin-lattice relaxation at shorter TR. It would be good to have some idea how large the effect would be and what would happen with the ADC values, but measurements of this sort have not been studied well for the fetal brain. The amount of this effect could be another potential explanation of why the ADC values have a constant offset for the short TR acquisitions.

The overall short scan time in itself makes the protocol less susceptible to motion artifacts. As mentioned, compared to our routine clinical 18-sec DWI sequence, the probability of motion being present was reduced. In addition, occasionally we have had instances where the mother cannot tolerate the 18-sec breath-hold. In these situations our protocol definitely serves as a meaningful alternative method. It is worth noting that given these benefits the success rate of these DWI schemes is still unsatisfactory. In our experience, two or three trials were usually necessary before good quality data was acquired.

While our preliminary studies show the feasibility of performing quantitative DWI with reduced TR, another potential benefit of acquiring multiple b=0 images is that it provides a motion-tracking scheme to reduce motion effects. Figure 4 illustrates this point by showing the first and last b=0 images of the DWI sequence. During the short 13-sec DWI scan, it can be seen that the fetus's brain moved slightly upward while rotating in the clockwise direction. While more sporadic and obvious motion effects can be apparent in the DW images with close to zero signal intensity, these minute motions that are likely caused by a very small drift of the fetus are not readily detectable in the DW images themselves. In these cases the motion during the scan can be modeled as an approximate linear motion, providing the possibility for further correction (16). An alternative way would be to target the last b=0 image to the first and align the other diffusion images with interpolated values. The availability of such a scheme could be very useful.

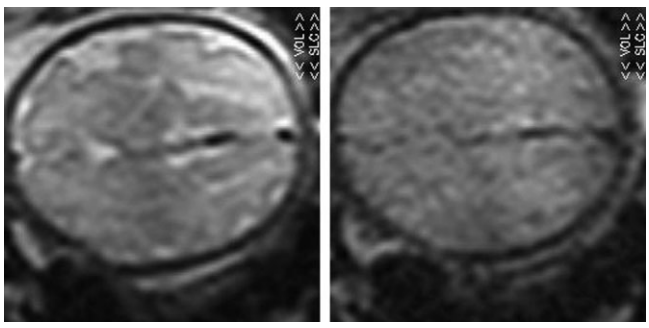

FIG. 4. Motion detected in the first and last b=0 images. Although the last b=0 image is heavily T_1-weighted, the edge structure is maintained. In this example, it can be seen that the fetus moved in two ways during the DWI exam. A gross movement to the upper direction can be seen in addition to a slight rotation clockwise.

In reality, the overall success of in vivo DWI of the fetal brain will be determined by the SNR available in the DWI scans and the ability to overcome motion-related issues. While we have provided a preliminary method to address the motion issues, the need for improving SNR still warrants attention. One questionable concern with our approach would be that the SNR may be lower due to the shortened TR that we are using. While we have shown that this does not cause a significant problem in ADC quantification, it has been shown that noise effects can be sensitive to rotationally invariant indices of diffusion (17). To promote signal intensity, adding a driven equilibrium module can be an effective approach (12). Single-shot isotropic diffusion acquisitions can also be considered an alternative for shortening the scan time (18,19). In this case, issues such as reduced SNR due to the longer echo times and inability to acquire tensor information may be a limiting factor.

Finally, another potential difficulty with fetal brain DWI is the highly unpredictable position of the fetus with respect to the magnet. Because of the variability of the fetal position within the mother, it is unlikely that the fetal brain will be at the magnet's isocenter, leading to gradient nonuniformities in the diffusion images. We have observed offsets of the fetal brain typically in the range of ≈15 cm from the isocenter. Due to the typical small size of the fetal brain and its positioning, the effect on quantitative values may be considerable. Special treatment of this issue would be helpful (20).

CONCLUSION

We have developed a clinically feasible DWI protocol for the fetal brain using a single-shot EPI sequence with short TR and multiple b=0 images. These multiple b=0 images are used to compensate for T_1 weighting due to the shortened TR and also can potentially be used as a motion-tracking scheme. Using this protocol we reduced the scan time for obtaining trace ADC values to 13 sec from our original 18 sec. Quantitative analysis shows that ADC values matched the true ADCs.

REFERENCES

1. Levine D. Obstetric MRI. J Magn Reson Imaging 2006;24:1–15.
2. Glenn OA, Barkovich J. Magnetic resonance imaging of the fetal brain and spine: an increasingly important tool in prenatal diagnosis: part 2. AJNR Am J Neuroradiol 2006;27:1807–1814.
3. Levine D, Barnes PD, Sher S, Semelka RC, Li W, McArdle CR, Worawattanakul S, Edelman RR. Fetal fast MR imaging: reproducibility, technical quality, and conspicuity of anatomy. Radiology 1998;206:549–554.
4. Brugger PC, Stuhr F, Lindner C, Prayer D. Methods of fetal MR: beyond T2-weighted imaging. Eur J Radiol 2006;57:172–181.
5. Chen Q, Levine D. Fast fetal magnetic resonance imaging techniques. Top Magn Reson Imaging 2001;12:67–79.
6. Righini A, Bianchini E, Parazzini C, Gementi P, Ramenghi L, Baldoli C, Nicolini U, Mosca F, Triulzi F. Apparent diffusion coefficient determination in normal fetal brain: a prenatal MR imaging study. AJNR Am J Neuroradiol 2003;24:799–804.
7. Bui T, Daire JL, Chalard F, Zaccaria I, Alberti C, Elmaleh M, Garel C, Luton D, Blanc N, Sebag G. Microstructural development of human brain assessed in utero by diffusion tensor imaging. Pediatr Radiol 2006;36:1133–1140.
8. Gupta RK, Hasan KM, Trivedi R, Pradhan M, Das V, Parikh NA, Narayana PA. Diffusion tensor imaging of the developing human cerebrum. J Neurosci Res 2005;81:172–178.

9. Huang H, Zhang J, Wakana S, Zhang W, Ren T, Richards LJ, Yarowsky P, Donohue P, Graham E, van Zijl PC, Mori S. White and gray matter development in human fetal, newborn and pediatric brains. Neuroimage 2006;33:27–38.
10. Agid R, Lieberman S, Nadjari M, Gomori JM. Prenatal MR diffusion-weighted imaging in a fetus with hemimegalencephaly. Pediatr Radiol 2006;36:138–140.
11. Baldoli C, Righini A, Parazzini C, Scotti G, Triulzi F. Demonstration of acute ischemic lesions in the fetal brain by diffusion magnetic resonance imaging. Ann Neurol 2002;52:243–246.
12. Busse RF, Riederer SJ, Fletcher JG, Bharucha AE, Brandt KR. Interactive fast spin-echo imaging. Magn Reson Med 2000;44:339–348.
13. Lee JN, Riederer SJ. A modified saturation-recovery approximation for multiple spin-echo pulse sequences. Magn Reson Med 1986;3: 132–134.
14. Scifo P, Baldoli C, Righini A, Pontesilli S, Cachia A, Dubois J, Le Bihan D, Scotti G, Fazio F. Diffusion tensor imaging using SENSE in prenatal studies. In: Proc ISMRM, Kyoto, Japan. 2004; p 582.
15. Conturo TE, McKinstry RC, Akbudak E, Robinson BH. Encoding of anisotropic diffusion with tetrahedral gradients: a general mathematical diffusion formalism and experimental results. Magn Reson Med 1996;35:399–412.
16. Norris DG. Implications of bulk motion for diffusion-weighted imaging experiments: effects, mechanisms, and solutions. J Magn Reson Imaging 2001;13:486–495.
17. Bastin ME, Armitage PA, Marshall I. A theoretical study of the effect of experimental noise on the measurement of anisotropy in diffusion imaging. Magn Reson Imaging 1998;16:773–785.
18. Chun T, Ulug AM, van Zijl PC. Single-shot diffusion-weighted trace imaging on a clinical scanner. Magn Reson Med 1998;40:622–628.
19. Song AW, Guo H, Truong TK. Single-shot ADC imaging for fMRI. Magn Reson Med 2007;57:417–422.
20. Bammer R, Markl M, Barnett A, Acar B, Alley MT, Pelc NJ, Glover GH, Moseley ME. Analysis and generalized correction of the effect of spatial gradient field distortions in diffusion-weighted imaging. Magn Reson Med 2003;50:560–569.