Diffusion Tensor Imaging of the Human Kidney: Does Image Registration Permit Scanning Without Respiratory Triggering?

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Purpose: To investigate if image registration of diffusion tensor imaging (DTI) allows omitting respiratory triggering for both transplanted and native kidneys

Materials and Methods: Nine kidney transplant recipients and eight healthy volunteers underwent renal DTI on a 3T scanner with and without respiratory triggering. DTI images were registered using a multimodal nonrigid registration algorithm. Apparent diffusion coefficient (ADC), the contribution of perfusion (F_P), and the fractional anisotropy (FA) were determined. Relative root mean square errors (RMSE) of the fitting and the standard deviations of the derived parameters within the regions of interest (SD_{ROI}) were evaluated as quality criteria.

Results: Registration significantly reduced RMSE in all DTI-derived parameters of triggered and nontriggered measurements in cortex and medulla of both transplanted and native kidneys ($P < 0.05$ for all). In addition, SD_{ROI} values were lower with registration for all 16 parameters in transplanted kidneys (14 of 16 SD_{ROI} values were significantly reduced, $P < 0.04$) and for 15 of 16 parameters in native kidneys (9 of 16 SD_{ROI} values were significantly reduced, $P < 0.05$). Comparing triggered versus nontriggered DTI in transplanted kidneys revealed no significant difference for RMSE ($P > 0.14$) and for SD_{ROI} ($P > 0.13$) of all parameters. In contrast, in native kidneys relative RMSE from triggered scans were significantly lower than those from nontriggered scans ($P < 0.02$), while SD_{ROI} was slightly higher in triggered compared to nontriggered measurements in 15 out of 16 comparisons (significantly for two, $P < 0.05$).

Conclusion: Registration improves the quality of DTI in native and transplanted kidneys. Diffusion parameters in renal allografts can be measured without respiratory triggering. In native kidneys, respiratory triggering appears advantageous.

J. MAGN. RESON. IMAGING 2016;00:000–000.

Diffusion-weighted magnetic resonance imaging (DWI) has been applied frequently for the evaluation of renal function in native[1–3] as well as in transplanted kidneys.[4–6] Its derived quantitative parameter, the apparent diffusion coefficient (ADC) parameter, documents changes like fibrosis or edema. Moreover, DWI may also provide information on concurrent micro-circulation, including capillary perfusion, quantified with the "fraction of the perfusion" (F_P).[7] Diffusion tensor imaging (DTI)[8] yields in addition the fractional anisotropy (FA), providing structural information of the renal tissues.[9–13] However, abdominal DTI is very sensitive to motion artifacts caused by respiration, which reduce the image quality in native kidneys, might cause phase misregistration, and lead to higher variability of diffusion parameters.[14] Therefore, DTI is commonly acquired, with respiratory triggering, at the expense of measurement duration in native kidneys. Performing DTI in transplanted kidneys is less prone to respiratory motion artifacts due to the extraperitoneal allograft position in the iliac fossa. Consequently, DTI has been applied in several studies both with respiration triggering[6,15] and without controlling for respiratory motion[13] in transplanted kidneys. Nevertheless, the

View this article online at wileyonlinelibrary.com. DOI: 10.1002/jmri.25176

Received Nov 3, 2015, Accepted for publication Jan 19, 2016.

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residual motion artifacts may still increase the variability of diffusion parameters in transplanted kidneys. A previous study has shown that performing image registration, based on the method proposed by Lu et al[16] on triggered and nontriggered DTI of native human kidneys significantly reduces motion artifacts and improves signal quality.[17] Despite registration improvements in native kidneys, the results from triggered scans were still better than those without triggering.[17] However, the triggered and nontriggered measurements were matched for number of acquisitions, but not for scan time, i.e. resulting in shorter duration of the nontriggered scans.

The aims of this study were therefore 1) to compare triggered and nontriggered DTI measurements and determine the value of image registration in transplanted kidneys, and 2) to perform nontriggered measurements with the same measurement duration as triggered scans per subject in native kidneys. Our purpose was to determine whether performing registration on nontriggered DTI may allow omitting respiratory triggering for human transplanted and native kidneys.

Materials and Methods

Subjects

The study protocol was approved by the local Ethics Committee and the study registered with ClinicalTrials.gov (NCT00575432). Written informed consent for the MRI procedures was obtained from each subject according to the local Institutional Review Board. Between July 2013 and June 2014, subjects with functioning renal allograft (estimated glomerular filtration rate according to Modification of Diet in Renal Disease-formula[18] higher than 30 mL/min/1.73 m^2) presenting to the nephrology department of our hospital were recruited for this study. Nine subjects (three female, six male, mean age 44.6 years, range 18–66 years) participated in this study. Three subjects were measured twice with the same protocol in the frame of a reproducibility study, thus, a total of 12 measurements were performed. Additionally, eight healthy volunteers (eight male, mean age 23, range 19–26 years) were recruited with no history of any urinary system disease, metabolic abnormality, or hypertension. The volunteers were selected based on personal declaration, excluding potential renal or other dysfunction or specific medication. The subjects were told to eat and drink moderately before the MR examination.

MRI

Imaging was performed on a clinical 3T scanner (Siemens Trio, Healthcare, Erlangen, Germany), using a six-channel array body coil in combination with a spine matrix coil. For acquiring morphological images, all subjects underwent a coronal T_1-weighted FLASH scan (fast low angle shot) and T_2-weighted HASTE (half Fourier acquisition single shot turbo spin echo) sequence. For functional evaluation, a diffusion-weighted single shot echo-planar fat saturated sequence was performed with 10 different b-values between 0 and 700 sec/mm^2: (0, 10, 20, 50, 100, 180, 300, 420, 550, 700 sec/mm^2) in six noncollinear directions. The following parameters were used: TR_{min} = 3300 msec, TE = 57 msec, field of view (FOV) = 30 × 30 cm, 7 coronal slices with a thickness of 5 mm and a gap of 2 mm, parallel imaging (generalized autocalibration partially parallel acquisition, GRAPPA; acceleration factor = 3), matrix size of 192 × 192 pixels for transplanted kidney and matrix size of 128 × 128 pixel for native kidney, acquisition number of 2. Respiratory-triggered DTI was employed with a stretchable elastic belt, wrapped around the abdomen. The second DTI scan was performed without triggering employing the same parameters as for the triggered DTI, except for TR, which was set to TR = 3000 msec in transplanted and TR = 2800 msec in native kidneys. While for transplanted kidneys the number of acquisitions was the same for triggered and nontriggered DTI (resulting in a measurement duration of 6 min fixed for the nontriggered DTI), in native kidneys the measurement duration for the nontriggered DTI was matched to the individually different duration of the triggered DTI, resulting in a higher number of acquisitions of the nontriggered scans. The measurement time was therefore recorded for the respiratory controlled investigations.

Nonrigid Image Registration

The image registration software was more fully described previously.[16,17] In brief, the fusion of two images is driven by an optimization that seeks to maximize the mutual information between the two aligned images. To ensure solvability of the optimization, the problem is cast as maximization of an energy function. The optimization of the energy function is performed using the finite-difference method to compute the gradient of the cost function in an efficient way. The resulting transformation is finally regularized with a Gaussian kernel (σ = 5) to yield a smooth transformation resembling those found in biological processes.

Data Analysis

Diffusion parameters were determined using biexponential fitting to separate diffusion and microcirculation contributions, which yield the perfusion fraction (F_P), pure diffusion (ADC_D),[6] and the signal intensity at b = 0 s/mm^2 (S_0).

$$S_i = S_0 \cdot [F_p \cdot \exp(-b_i \cdot ADC_p) + (1 - F_p) \cdot \exp(-b_i \cdot ADC_D)] \quad (1)$$

DTI analysis of the kidneys was performed using an in-house IDL program (Interactive Data Language, ITT, Boulder, CO). FA values were calculated from ADC values along each of the six directions. Out of the seven slices that were acquired, the three central slice positions were selected for analysis for each case in order to cover most of the kidneys.

Regions of interest (ROIs) were manually placed in the upper pole, middle pole, and lower pole of the medulla and cortex of native and transplanted kidneys by an author (M.S.) with 3 years of experience (maximum 18 ROIs for each kidney) on the coronal T_1-weighted images and simultaneously on the corresponding diffusion images of the three slice positions separately for each subject. The mean individual ROI size of medulla and cortex in transplanted kidney was 0.43 ± 0.12 cm^3 and 0.37 ± 0.08 cm^3, respectively, and in native kidneys was 0.39 ± 0.06 cm^3 and 0.38 ± 0.06 cm^3, respectively.

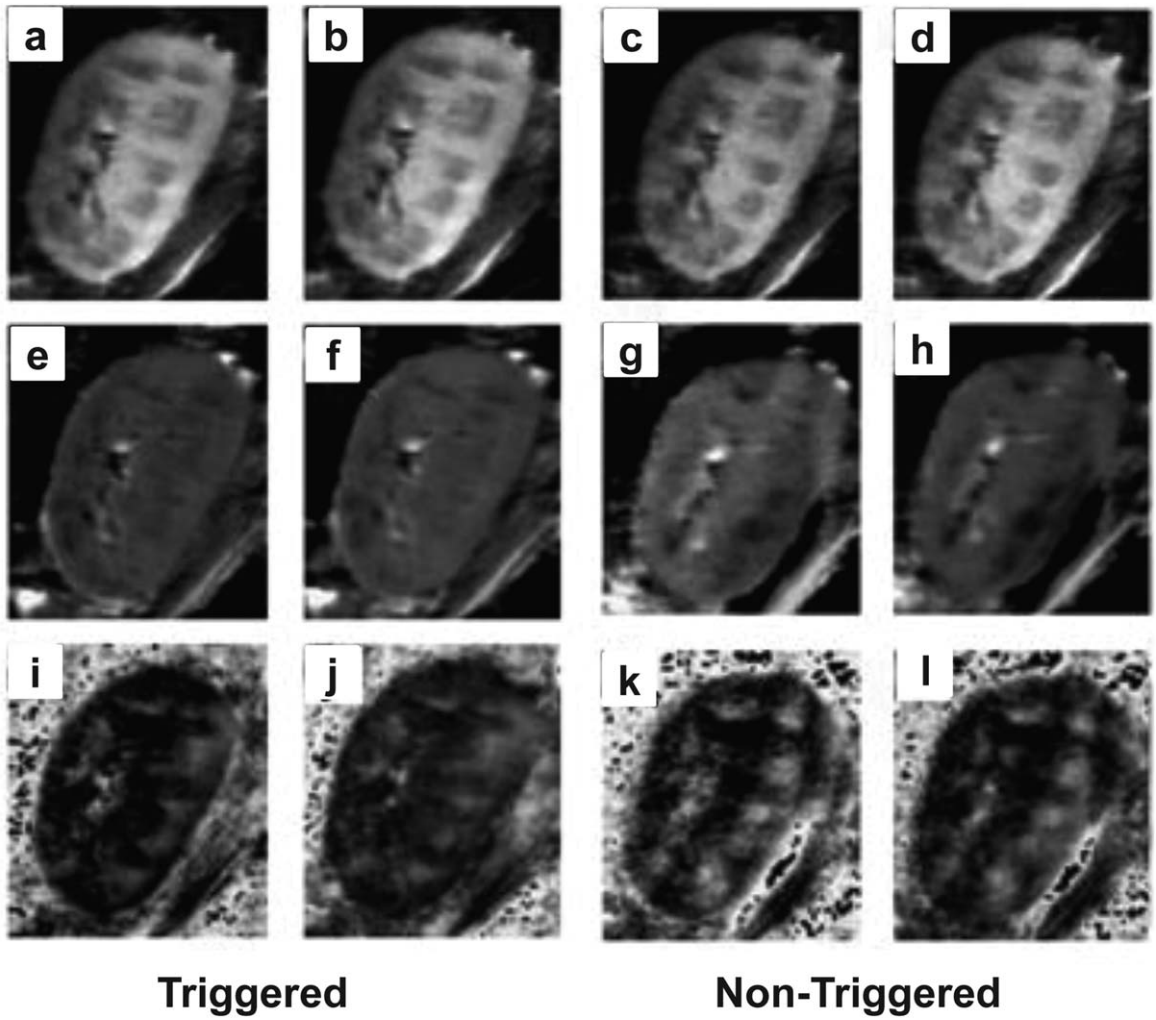

FIGURE 1: In an example of the renal allograft group, the figure compares S_0 (a–d), ADC (e–h), and FA (i–l) maps of original and registered images with and without respiratory triggering (a,e,i: triggered original images; b,f,j: triggered registered images; c,g,k: nontriggered original images; d,h,l: nontriggered registered images).

Statistical Analysis

For comparison of the results with and without registration, and to compare between triggered and nontriggered scans, the root mean square errors (RMSE) of the fitting model and the standard deviations within the regions of interest (SD_{ROI}) from all the pixels within the ROI were evaluated. RMSE and SD_{ROI} were averaged over all ROIs separately in medulla and cortex.

Since RMSE values are scaled to the signal intensity, they are calculated relative to the fitted signal intensity, S_0. The SD_{ROI} of the diffusion parameters S_0, ADC_D, F_B, and FA were also calculated as criteria for stability. This procedure was based on the assumption that the ROIs were placed on areas presenting homogeneous tissue of the medulla and cortex, and differences between variations within ROIs are assumed to be due to motion.

The sample size of both transplanted and native kidney groups was selected on the basis of a power analysis using the RMSE results from a previous DTI registration study on native kidneys.[17]

Paired *t*-tests were applied for group comparisons of RMSE, SD_{ROI}, and DTI parameters between 1) images with and without registration, and 2) triggered and nontriggered scans. In order to prevent type II errors (i.e. failing to detect a difference) one-tailed *t*-tests were performed and no corrections for multiple comparisons applied. The statistical analyses were performed using Microsoft Office Excel 2007 and SPSS v. 18.0 (SPSS, Chicago, IL). $P < 0.05$ was considered significant.

Results

DTI measurements were successfully completed in all subjects. However, one subject with a renal allograft was excluded due to polycystic kidney disease. The average acquisition time of diffusion measurements in transplanted kidneys was 6 minutes (fixed) and 12.6 ± 0.7 minutes in nontriggered and triggered scans, respectively. Similarly, the average diffusion measurement time for the native kidneys group was 10.3 ± 1.8 minutes and 10.9 ± 2.2 minutes in triggered and nontriggered scans, respectively, and were found to be not statistically different ($P = 0.08$). Figures 1 and 2 show examples of S_0 and ADC maps as well as FA maps of triggered and nontriggered scans of allograft and native kidneys, respectively, and calculated from original images and registered images. Visually, the diffusion

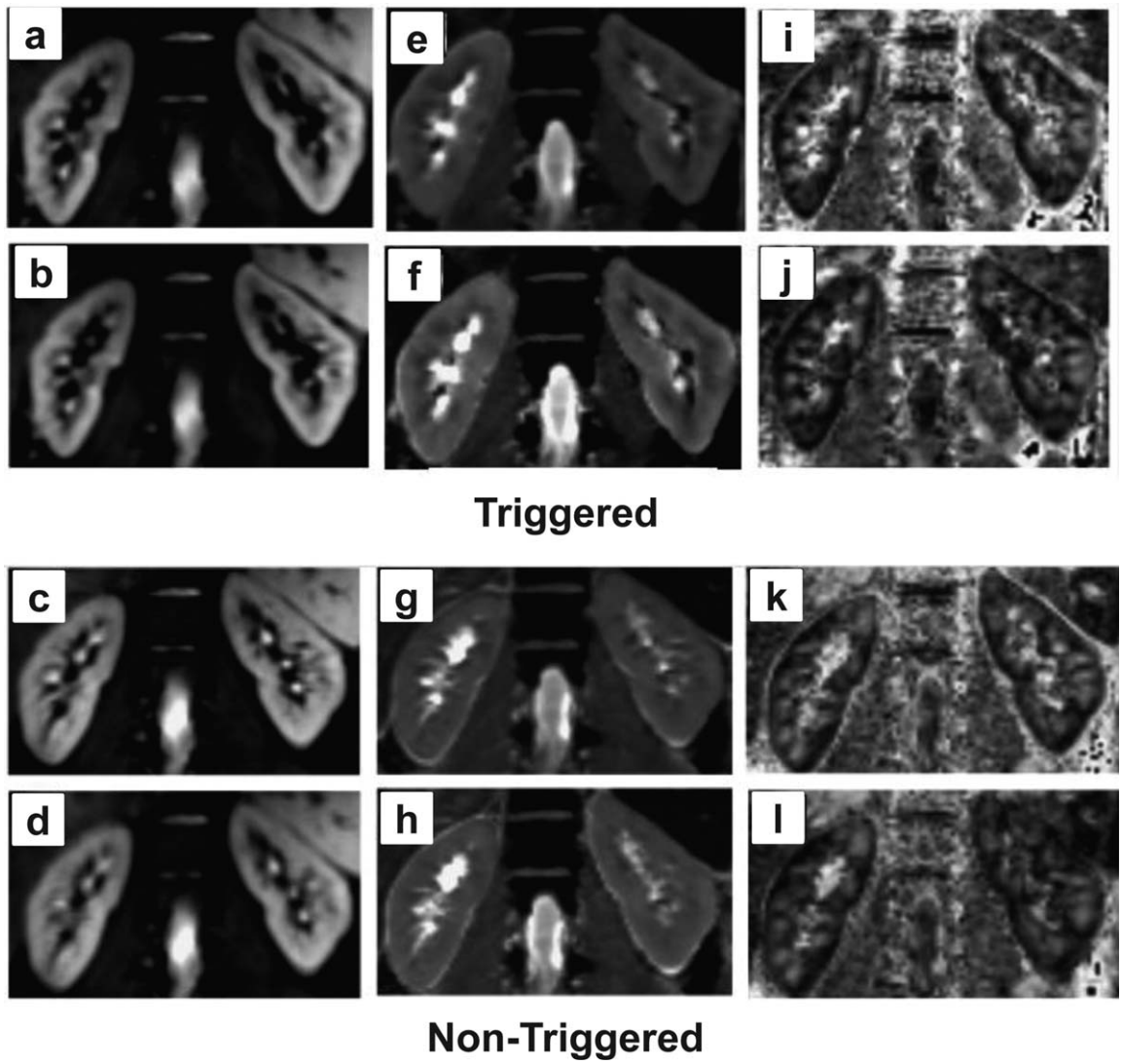

FIGURE 2: In an example of the native kidney group, the figure compares S_0 (a–d), ADC (e–h), and FA maps (i–l) of original and registered images with and without respiratory triggering (a,e,i: triggered original images; b,f,j: triggered registered images; c,g,k: nontriggered original images; d,h,l: nontriggered registered images).

parameter maps did not show a considerable difference between triggered and nontriggered measurements or between those obtained from original and registered images.

Quantitative Results

RMSE AND SD_{ROI} IN RENAL ALLOGRAFTS. A significant RMSE decrease was obtained in the medulla and cortex of triggered measurements ($P < 0.0004$) and nontriggered measurements ($P < 0.01$) after registration in renal allografts employing the same number of averages (Fig. 3). The quantitative results showed that SD_{ROI} of all diffusion parameters, ie, the medullary and cortical SD_{ROI} of S_0, ADC_D, F_B and FA parameters, were reduced after performing registration in both triggered and nontriggered measurements for allograft kidneys (Table 1), and this decrease was significant in 14 out of 16 comparisons ($P < 0.04$, Table 1).

The RMSE of triggered and nontriggered scans in allografts were 2.51 ± 0.55 and 2.86 ± 0.76, respectively, in medulla; and 2.19 ± 0.37 and 2.42 ± 0.61, respectively, in cortex and were not found significantly different between triggered and nontriggered scans with registration ($P > 0.14$, Fig. 3). Likewise, without registration the RMSE in triggered scans was not different than those calculated from nontriggered scans. Additionally, no significant difference was found between triggered and nontriggered scans for SD_{ROI} of all diffusion parameters (four parameters in cortex and medulla in triggered and nontriggered scans).

RMSE AND SD_{ROI} IN NATIVE KIDNEYS. Registration significantly decreased RMSE in triggered scans ($P < 0.04$) and in nontriggered scans ($P < 0.01$). The RMSE reduction due to registration was more pronounced in nontriggered scans than in triggered scans (Fig. 4). The SD_{ROI} of all but one diffusion parameter (S_0 in medulla of nontriggered

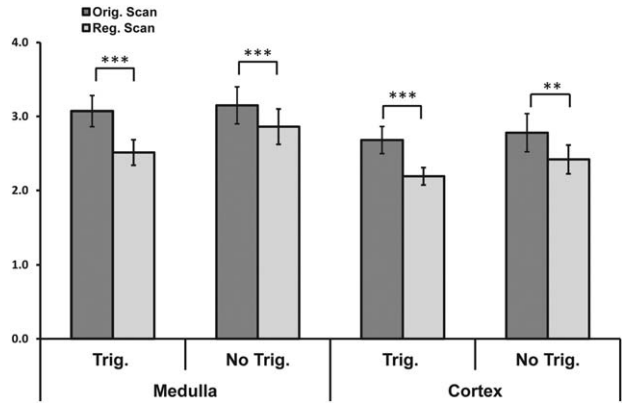

FIGURE 3: Comparison of RMSE of medulla and cortex in allograft kidneys between original and registered measurements for 11 scans with respiratory triggering and without triggering (***$P < 0.001$, **$P < 0.01$). Error bars indicate the standard error of the RMSE mean. No significant difference was found between triggered and nontriggered measurements.

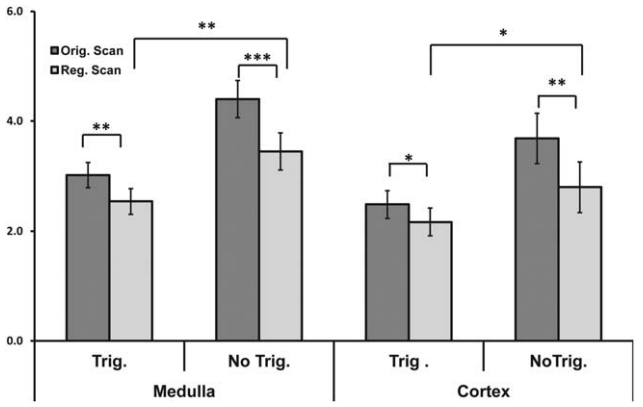

FIGURE 4: Comparison of RMSE of medulla and cortex in native kidneys between original and registered measurements for eight scans with respiratory triggering and without triggering (***$P < 0.001$, **$P < 0.01$, *$P < 0.05$); error bars indicate the standard error of the RMSE mean.

scan) decreased after employing registration (Table 2). The decrease of SD_{ROI} due to registration was found to be significant ($P < 0.05$) in 9 out of the 16 comparisons.

RMSE of triggered scans in both medulla and cortex (2.54 ± 0.36 and 2.17 ± 0.49, respectively) were significantly lower ($P < 0.02$) than those calculated from nontriggered scans (3.45 ± 0.89 and 2.80 ± 0.72, respectively) after registration (Fig. 4). However, SD_{ROI} were slightly higher in 15 out of 16 comparisons in triggered scans compared to nontriggered scans (significantly for two parameters: SD_{ROI} for S_0 in medulla of original images and for ADC_D in cortex of registered images).

COMPARISON OF MEAN VALUES IN RENAL ALLOGRAFT. The mean values of S_0, ADC_D, and F_P parameters were not significantly different between original and corresponding registered images (Table 3). However, FA was significantly different between original and registered images in cortex and medulla of triggered scans (cortex: 0.21 ± 0.05 vs. 0.17 ± 0.04; medulla: 0.25 ± 0.08 vs. 0.21 ± 0.07) and nontriggered scans (cortex: 0.21 ± 0.06 vs. 0.17 ± 0.02; medulla: 0.25 ± 0.05 vs. 0.23 ± 0.05). Comparing mean diffusion parameters for ADC, F_P, and FA between triggered and nontriggered scans showed no significant difference. S_0 was significantly higher in triggered compared to nontriggered measurements ($P < 0.01$), except for cortical S_0 in registered images.

COMPARISON OF MEAN VALUES IN NATIVE KIDNEYS. ADC_D and F_P (except cortical F_P in nontriggered scans) were not significantly different between original and registered images. Nevertheless, a significant decrease ($P < 0.01$) was obtained owing to registration for all FA values, ie, in medulla and cortex for triggered and for nontriggered scans (Table 4).

TABLE 1. Standard Deviations Within the Regions of Interest (SD_{ROI}) of the DTI Parameters in Medulla and Cortex of Triggered and Nontriggered Scans in Renal Allografts

SD_{ROI}	Renal allograft	Relative S_0 [%]	ADC_D [10^{-5} mm^2/s]	F_P [%]	FA
Medulla	Orig. Trig.	9.4	13.9	5.15	0.073
	Reg. Trig.	8.7	11.0	3.98	0.060
	P-values	$P < 0.04$	$P < 0.004$	$P < 0.02$	$P < 0.01$
	Orig. Non. Trig.	8.9	13.6	5.34	0.077
	Reg. Non. Trig.	8.7	11.8	4.43	0.070
	P-values	$P > 0.2$	$P < 0.02$	$P < 0.01$	$P < 0.02$
Cortex	Orig. Trig.	6.3	10.5	4.14	0.056
	Reg. Trig.	5.7	9.2	3.25	0.045
	P-values	$P < 0.02$	$P < 0.02$	$P < 0.02$	$P < 0.001$
	Orig. Non. Trig.	6.9	10.9	4.04	0.060
	Reg. Non. Trig.	5.9	9.40	3.45	0.046
	P-values	$P < 0.01$	$P < 0.02$	$P > 0.06$	$P < 0.003$

P-values compare original versus registered results.

TABLE 2. Standard Deviations Within the Regions of Interest (SD_{ROI}) of the DTI Parameters in Medulla and Cortex of Triggered and Nontriggered Scans in Native Kidney

SD_{ROI}	Native Kidney	Relative S_0 [%]	ADC_D [$10^{-5}mm^2/s$]	F_P [%]	FA
Medulla	Orig. Trig.	11.3	13.9	6.71	0.085
	Reg. Trig.	9.9	11.2	4.56	0.074
	P-values	$P < 0.003$	$P > 0.09$	$P > 0.07$	$P < 0.001$
	Orig. Non. Trig.	9.2	11.5	5.07	0.077
	Reg. Non. Trig.	9.8	10.1	4.33	0.068
	P-values	$P > 0.1$	$P > 0.05$	$P < 0.04$	$P < 0.004$
Cortex	Orig. Trig.	6.5	10.3	4.16	0.063
	Reg. Trig.	6.0	7.8	3.51	0.051
	P-values	$P > 0.07$	$P > 0.06$	$P < 0.05$	$P < 0.002$
	Orig. Non. Trig.	6.3	7.8	3.69	0.056
	Reg. Non. Trig.	6.2	6.8	3.08	0.047
	P-values	$P > 0.4$	$P < 0.03$	$P < 0.02$	$P < 0.003$

P-values compare original versus registered results.

Slight but significant differences were also observed between the mean values of registered triggered and nontriggered scans for ADC_D and FA in cortex and F_P in medulla ($P < 0.05$). S_0 was highly significantly higher in triggered compared to nontriggered measurements in both cortex and medulla ($P < 0.0003$).

DISCUSSION

The results of the current study first show that DTI in transplanted kidneys can be performed shorn of notable quality loss without respiratory triggering especially when performing image registration, thus allowing for faster measurement times. In native kidneys, respiratory triggering appears still slightly advantageous over nontriggered DTI, although at matched measurement times the differences are relatively low. Second, the study demonstrates that performing nonrigid image registration on individual echo planar images (with virtually frozen movement) led to higher signal stability and reduced variations of diffusion parameters in both transplanted and native kidneys.

The RMSE and SD_{ROI} of triggered scans in transplanted kidneys were not significantly different from those calculated in nontriggered scans with and without registration, which is probably due to a lower respiratory motion sensitivity of the allograft position extraperitoneally in the iliac fossa compared to native kidneys. This result thus showed that respiratory triggering can be omitted for DTI in transplanted kidneys, especially when performing image registration to further improve the stability of the parameter estimation.

This is in contrast to native kidneys with less clear results: Although registration improved DTI stability of

TABLE 3. Mean ± SD of All Pixels Within ROIs of the DTI Parameters in Medulla and Cortex of Triggered and Nontriggered Scans With and Without Performing Registration in Renal Allografts

Mean ± SD	Renal allograft	S_0	ADC_D [$10^{-5}mm^2/s$]	F_P [%]	FA
Medulla	Orig. Trig.	3.7 ± 0.1	180 ± 9	7.0 ± 3.7	0.25 ± 0.08
	Reg. Trig.	3.6 ± 0.9	180 ± 7	6.9 ± 3.9	0.21 ± 0.07
	P-values	$P > 0.3$	$P > 0.4$	$P > 0.4$	$P < 0.04$
	Orig. Non. Trig.	3.1 ± 0.8	178 ± 9	7.6 ± 3.5	0.25 ± 0.05
	Reg. Non. Trig.	3.2 ± 0.8	180 ± 9	7.3 ± 3.9	0.23 ± 0.05
	P-values	$P > 0.08$	$P > 0.1$	$P > 0.3$	$P < 0.004$
Cortex	Orig. Trig.	4.3 ± 0.1	183 ± 15	8.3 ± 3.3	0.21 ± 0.05
	Reg. Trig.	4.3 ± 0.1	184 ± 12	8.0 ± 3.7	0.17 ± 0.04
	P-values	$P > 0.4$	$P > 0.3$	$P > 0.4$	$P < 0.002$
	Orig. Non. Trig.	3.7 ± 0.9	180 ± 13	9.9 ± 2.0	0.21 ± 0.06
	Reg. Non. Trig.	3.5 ± 0.9	182 ± 11	9.2 ± 3.1	0.17 ± 0.02
	P-values	$P > 0.1$	$P > 0.2$	$P > 0.1$	$P < 0.02$

P-values compare original versus registered results.

TABLE 4. Mean ± SD of All Pixels Within ROIs of the DTI Parameters in Medulla and Cortex of Triggered and Nontriggered Scans With and Without Applying Registration in Native Kidneys

Mean ± SD	Native Kidney	S_0 [au]	ADC_D [10^{-5} mm^2/s]	F_P [%]	FA
Medulla	Orig. Trig.	4.0 ± 0.4	186 ± 11	7.4 ± 3.4	0.320 ± 0.027
	Reg. Trig.	4.0 ± 0.4	185 ± 10	8.8 ± 2.5	0.291 ± 0.021
	P-values	$P > 0.2$	$P > 0.1$	$P > 0.07$	$P < 0.01$
	Orig. Non. Trig.	3.0 ± 0.3	183 ± 6	7.1 ± 2.2	0.294 ± 0.030
	Reg. Non. Trig.	3.0 ± 0.3	182 ± 7	7.3 ± 2.2	0.267 ± 0.029
	P-values	$P > 0.1$	$P > 0.2$	$P > 0.07$	$P < 0.003$
Cortex	Orig. Trig.	4.7 ± 0.3	196 ± 10	12.1 ± 3.6	0.226 ± 0.017
	Reg. Trig.	4.7 ± 0.4	197 ± 11	11.1 ± 2.8	0.203 ± 0.019
	P-values	$P > 0.2$	$P > 0.2$	$P > 0.09$	$P < 0.003$
	Orig. Non. Trig.	3.7 ± 0.4	194 ± 9	10.3 ± 2.8	0.194 ± 0.019
	Reg. Non. Trig.	3.7 ± 0.3	193 ± 8	11.1 ± 2.4	0.170 ± 0.014
	P-values	$P < 0.02$	$P > 0.2$	$P < 0.04$	$P < 0.001$

P-values compare original versus registered results.

nontriggered scans more than of triggered scans (leading to a smaller RMSE difference between triggered and nontriggered scans), RMSE was still significantly lower in triggered scans, despite matched measurement times. This result confirms and extends our previous findings[17] that similarly reported higher stability of triggered than nontriggered scans, but only for a matched number of acquisitions. In addition, the current results suggest that triggered renal DTI scans are still slightly more stable when nontriggered scans are prolonged. Moreover, if measurement times are matched we conclude that employing DTI scans without respiratory triggering is not advantageous for the patient compared to triggered DTI. However, the lower SD_{ROI} of most parameters of nontriggered scans suggests that the differences between triggered and nontriggered scans become negligible when measurement durations are matched. The lower RMSE (which is reported relative to S_0) in triggered compared to nontriggered scans in native kidneys is due to higher S_0 in triggered scans. This may explain the different results for RMSE and SD_{ROI} in native kidneys. The lower S_0 in nontriggered scans is most likely due to phase dispersion during the acquisition, i.e. individual DTI images are not entirely "frozen." T_1 effects, i.e. higher S_0 intensities in triggered scans due to longer TR, adds in addition to the S_0 difference between triggered and nontriggered scans.

The mean values of ADC_D in the medulla and cortex of triggered and nontriggered scans in the transplanted kidney group are in agreement with the results of previous studies.[4,6] However, FA values in transplanted kidneys are lower than those in a previously published study,[13] which may be due to the different interval time between transplantation and MR examination, differences in glomerular filtration rate of allografts, or the small number of subjects.

The mean values of ADC_D, FA, and F_P of triggered and nontriggered scans in native kidneys were in agreement with the results of a previous study.[17] However, the calculated mean values of F_P are lower than those in previously published articles,[4,10,14] which may be due to shorter echo times or slight processing differences. Some derived diffusion parameters were significantly different between original and registered images in both renal allografts and native kidneys as well as in native kidneys between triggered and nontriggered scans. This suggests that DTI results derived from triggered and nontriggered scans and from original and registered images should not be directly compared, especially in native kidneys.

A limitation of this study is the small number of subjects that may not be sufficient in the native kidney group for a final decision if respiratory triggering is advantageous compared to nontriggering when acquisition times are matched. However, it appears that using shorter acquisitions for nontriggered scans yields lower parameter stability compared to triggered scanning.

In conclusion, the clear improvement due to registration and the small difference between triggered and nontriggered scans in transplanted kidneys suggest that renal allografts can be measured without respiratory triggering, but employing registration to improve stability. However, in native kidneys the triggered scans still show less signal variation than the nontriggered scans.

Acknowledgment

Contract grant sponsor: Swiss National Science Foundation (SNF); contract grant number: 320030-138150
The result of this study has been accepted for an E-poster presentation at the scientific sessions of the ISMRM 22nd Annual Meeting & Exhibition in Milan, Italy 2014.

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