Consensus-based technical recommendations for clinical translation of renal diffusion-weighted MRI

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1. Contributing technical details of protocols or answering surveys;
2. Helping to collect, tabulate and compare protocols and surveys submitted;
3. Helping to develop, organize, and document the online supplementary material (github or equivalent);
4. Regularly taking part in teleconferences or discussions of the panel in order to define a consensus;
5. Other substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work (please specify);
6. Drafting the work;
7. Revising the work critically for important intellectual content;
8. Final approval of the version to be published;

9. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Abstract

Objectives: Standardization is an important milestone in the validation of DWI as an imaging biomarker for renal disease. Here, we propose technical recommendations on three variants of renal DWI and associated MRI biomarkers (ADC, IVIM and DTI) to aid ongoing international efforts on methodological harmonization.

Materials and Methods: Reported DWI biomarkers from 194 prior renal DWI studies were extracted and Pearson correlations between diffusion biomarkers and protocol parameters were computed. Based on the literature review surveys were designed for the consensus-building. Survey data were collected via Delphi consensus process on renal DWI preparation, acquisition, analysis, and reporting. Consensus was defined as ≥ 75% agreement.

Results: Correlations were observed between reported diffusion biomarkers and protocol parameters. Out of 87 survey questions, 57 achieved consensus resolution, while many of the remaining questions were resolved by preference (65-74% agreement). Summary of the literature and survey data, as well as recommendations for the preparation, acquisition, processing and reporting of renal DWI were provided.

Discussion: The consensus-based technical recommendations for renal DWI aim to facilitate inter-site harmonization and increased clinical impact of the technique on a larger scale. We anticipate an iterative process with continuous updating of the recommendations according to progress in the field.

Keywords: biomarker, DWI, ADC, IVIM, DTI

Introduction

Diffusion-weighted (DWI) magnetic resonance imaging (MRI) has been shown to provide differentiated information on the microstructure of kidney tissue. Furthermore, significant efforts have been made to adopt DWI as a MR-biomarker for functional renal imaging [1-6]. However, to successfully translate the research results of renal DWI to clinical practice, there are still some challenges to overcome. Firstly, acquisition protocols vary between research groups and reflect local practice and expertise. Secondly, patient preparation, data post-processing and image analysis are not standardized, with several approaches being used by different research groups. As has been recognized by other consortium efforts [7-9], our motivation behind prioritizing standardization of these processes is the generation of reliable MRI biomarkers that are ready to be broadly utilized in multi-site studies. When achieved, the data generated from standardized study protocols will sufficiently increase the evidence base to determine threshold values for DWI-based parameters, to differentiate between renal pathologies. Histopathological correlation should also continue to be performed to ensure diagnostic validation of the MR biomarkers. With the aim to move towards a standardization and to facilitate the validation of DWI as a renal MRI biomarker, an international, multidisciplinary group of renal imaging researchers with experience and / or ongoing work in renal DWI was recently formed as part of the 'PARENCHIMA' (the European Cooperation in Science and Technology) COST action (www.renalmri.org).

As a first step in this endeavour, Caroli et al. [10] published a review and statement paper reflecting the current state of research to assess diffuse renal pathology by renal DWI. The work summarizes the acquisition protocols used in human renal DWI studies up to August 2017 (172 studies) involving both healthy subjects and patients with renal disease. It highlights the large diversity in

acquisition protocols, patient preparation and image post-processing techniques, as well as the lack of "gold standard" for the measurement of *in vivo* renal DWI. This diversity of acquisition protocols across studies has led to a variability of acquired quantitative renal diffusion parameters, which is summarized in the detailed supplement material of the review [10]. Therefore, a further mission of the PARENCHIMA initiative is building consensus on renal DWI acquisition protocol, patient preparation and post-processing techniques.

In this work, a consensus on recommended acquisition protocol for renal DWI was formed consistent with the consensus-building goals of the Delphi process [11-13]. The design of the surveys for the consensus building was informed by a literature review (extending the prior review until November 2018) that aimed to identify which acquisition parameters had the most impact on DWI measurements. For the development of the recommendations, the three most common variants of renal DWI data used in the literature were considered: 1) monoexponential model with parameter apparent diffusion coefficient (ADC); 2) biexponential ADC or IVIM (intravoxel incoherent motion) model with the parameters water diffusion in the tissue (D), flowing fraction (f) and pseudodiffusion (D*); and 3) diffusion tensor imaging (DTI) with mean diffusivity (MD) and fractional anisotropy (FA). All three variants of renal DWI aim to estimate a diffusion constant of water in tissue. However, in all models this diffusion constant is named differently (ADC, D, and MD). ADC quantification methods considering a non-Gaussian DWI signal behaviour are not covered in these recommendations given their more preliminary stage of investigation and are not deemed as ripe for standardization as the other methods described above. We summarize the three common renal DWI approaches and associated quantification methods below.

Monoexponential ADC

This quantification model for DWI MRI is the most popular due to its simplicity and modest acquisition requirements. The ADC model assumes a uniform Gaussian displacement distribution of the water molecules corresponding to a monoexponential diffusion-weighted signal decay of the MR signal. The computation of the monoexponential ADC is based on the Stejskal-Tanner equation [14]:

$$\frac{S_b}{S_0} = e^{-bADC_{mono}} \quad (1)$$

where S_b is the diffusion-weighted signal intensity, S_0 is the signal intensity without a diffusion weighting (b = 0 s/mm^2), b is the diffusion weighting strength (in s/mm^2), and ADC_{mono} is the apparent diffusion coefficient of water within the observed image voxel.

For renal tissue, the monoexponential model is known to be insufficient to describe the diffusion-weighted signal decay, with IVIM effects occurring at low b-values (<200 s/mm^2) [15] and non-Gaussian effects possibly occurring at high b-values (>800 s/mm^2). However, as a single parameter estimation, the monoexponential model provides relatively robust ADC and requires only moderate signal-to-noise ratio on DWI.

Given the contrast effects mentioned above, the estimated ADC is strongly dependent on the choice of selected b-values [15,16] and no consensus exists with regard to the choice and number of b-values in a renal DWI acquisition protocol. Taking into account Equation (1), a set of minimum two b-values is enough to reach a stable diffusion signal [16,17] for the quantification of ADC. However, most authors prefer to describe the diffusion signal decay more precisely by

including more b-values in the acquisition protocol. Considering possible anisotropic diffusion, it is common practice to measure the b-values in several orthogonal directions during the ADC acquisition [15,16].

Intravoxel incoherent motion (IVIM)

First described by Le Bihan et al. [18] in 1986 the IVIM model is another option to interpret the physiological underpinning of the diffusion signal. Since the initial studies in human subjects by Muller et.al. in 1998 [19] and later by Thoeny et al. in 2006 [20] showing the potential of the IVIM model to interpret diffusion signal in the kidney, this quantification has been demonstrated to improve the representation of the diffusion-weighted signal in renal tissue compared to the ADC_{mono} [21-23].

IVIM considers the diffusion signal originating from two different compartments. One compartment reflects the slow thermal diffusion in the tissue (D), hindered or restricted by local microstructure. The second compartment considers the fast molecule movement associated with incoherent flow in the microvasculature or renal tubules that mimics random water motion assuming that many vessel and tubules orientations are present within the voxel (quantified by the pseudodiffusion, D* and the flowing fraction, *f*).

This method of quantification utilizes a biexponential decay, describing the overall diffusion weighted signal as the sum of the diffusion and flowing components:

$$\frac{S_b}{S_0} = (1 - f)\, e^{-bD} + f e^{-bD^*} \qquad (2)$$

where S_b is the diffusion-weighted signal intensity, S_0 is the signal intensity without a diffusion weighting (b = 0 s/mm^2), b is the diffusion weighting strength (in s/mm^2), D is the water diffusion in the tissue (slow component), D^* is the pseudodiffusion (fast component), and f is the flowing fraction.

To quantify IVIM parameters, a minimum of four b-values are needed to determine all unknown parameters in Equation (2), which typically extends the acquisition time in comparison to the monoexponential ADC. Furthermore, there is no universally accepted algorithm yet to calculate IVIM quantitative parameters. In many studies, a so-called "segmented fitting" or "2-step" approach is used to calculate the IVIM parameters (2), due to its extended stability and faster fitting [24-27]. In the "segmented fitting", a threshold b-value is defined to separate flowing from diffusion effects (microcirculation-induced decay assumed negligible above this threshold). However, although D is more stable in the "segmented fitting", than in others, the estimates of f and D* can be biased depending on threshold choice. More recently, Bayesian probability-based fitting methods have been explored, with or without fixing of the pseudodiffusion coefficient (this has shown higher precision/accuracy, and low inter-subject variability [28]).

Other, more complex, extended IVIM models can be found in the literature that aim to incorporate more characteristics of functioning renal tissue into the signal description. Three compartment models include an additional component taking into account multiple sources of intravoxel incoherent motion, e.g. due to the glomerular flow [29,30], vascular vs. tubular flow, or residual fat signal [31]. Other extended models combine IVIM with diffusion anisotropy for a more comprehensive description of both structural and microcirculation features [32,33]. These models are mentioned here solely to indicate current research frontiers as they require further investigation before they can be pursued in the context of consensus standardization.

Diffusion tensor imaging (DTI)

Measurement of the directional dependence (anisotropy) of apparent diffusion in tissue microstructure provides a marker of that tissue's integrity and thereby of its clinical function. Diffusion tensor imaging (DTI) quantitatively measures and maps the anisotropy imposed on water diffusion by a tissue`s microstructure.

For DTI analysis, diffusion-weighted signals along several diffusion directions are acquired and fit to a 3×3 symmetric tensor model [34,35]. The eigenvalues of this tensor describe the maximal, intermediate, and minimal diffusion values, with eigenvectors reflecting their corresponding orientation. The primary eigenvector, associated with the largest eigenvalue, indicates the orientation of maximal diffusion. Another parameter, called fractional anisotropy (FA) reflects the amount of diffusion directivity in DTI studies (0 = complete isotropy, 1 = complete anisotropy), while mean diffusivity (MD) is a DTI specific ADC equivalent. Several studies have demonstrated that DTI provides powerful biomarkers of diffusion isotropy in the cortex and anisotropy in the renal medulla [15,22,36-43]. This behaviour is consistent with the known structural organization of medullary constituents such as the tubular loops of Henle, collecting ducts, and vascular vasa recta, which have an inward radial pattern towards the renal pelvis.

As with many diffusion biomarkers, FA and MD depend on the number and magnitude of the applied b-values [37,44,41]. As diffusion anisotropy is a key target of DTI, acquisition of multiple diffusion directions (minimally 6) is required for tensor computation. However, while some study of diffusion direction choice in renal DTI has been performed supporting at least 12 directions

[45], determination of an optimal number or choice of b-values and directions for renal DTI, analogous to comprehensive efforts in the brain [28] or muscle [46], has not yet been performed.

Materials and Methods

Literature review and data extraction

In order to justify the motivation for the standardization process, assess the state of the renal DWI literature, and provide input to subsequent recommendations, we summarize reported DWI biomarkers from a wide range of prior renal DWI studies assessing diffuse renal diseases. These efforts build upon reviews and meta-analyses that have aimed to understand the variability of reported renal diffusion biomarkers in the literature [4,15,23].

A systematic review and analysis of the literature (using the same search criteria in PubMed as previously used by Caroli et al. [10], but extending those until November 2018) was carried out. Specifically, papers were categorized according to their protocol and quantification scheme as either ADC (113 studies), DTI (40 studies), or IVIM (41studies). From each paper, we extracted protocol parameters including full b-value ranges, repetition times (TR), echo times (TE), number of gradient directions and field strength. The distribution of b-value ranges was extracted for each DWI model for visualization. Additionally, DWI biomarkers were also extracted for cortex, medulla, and whole kidney (as available in each study), reporting values in healthy adult controls. For each b-value range, the maximum and average b-values were also computed. ADC studies provided ADC values [20,21,42,47-61], DTI studies provided MD and FA values [29,32,33,62-68,45,69-73] and IVIM studies provided D, f and D* values [20,21,28,29,32,42,54,55,69,70,73-80].

Following data extraction, correlations were computed in healthy volunteers only via Pearson correlation coefficients with the following protocol parameters: (1) TR; (2) TE; (3) average b-value; (4) maximum b-value; (5) transverse relaxation factor $T2 = \exp(-TE/T2t)$; (6) $T1 = (1-\exp(-TR/T1t))$, where $T2t = 87$ ms and $T1t = 1147$ ms were taken as representative relaxation times for renal tissue at 3.0 T [81]. After correlation with individual protocol parameters, correlations were computed between diffusion biomarkers and all possible products or ratios of the protocol parameters (52 combinations in all). Correlation coefficients R and significance levels p were derived for each correlation using the Igor Pro 7 software (Wavemetrics, Inc., Lake Oswego, OR USA). Significant correlations were noted both without ($p<0.05$) and with Bonferroni correction for multiple comparisons ($p<0.05/52=0.00096$). Finally, all diffusion biomarkers from healthy volunteers were grouped according to field strength (1.5 T or 3.0 T) and compared for differences with a two-tailed Student's t-test, for which significant differences are indicated for $p<0.05$.

Description of survey process

As described in the accompanying covering letter by Sourbron et al. and in keeping to the 'approximation of a two-step modified Delphi method [82]' for consensus-building, a survey was circulated using a publicly available tool (Google Forms) to a range of renal imaging researchers with experience and / or ongoing activity in renal diffusion imaging. In addition to offering participation to all members of the PARENCHIMA collaboration, every effort was made to invite at least one researcher or corresponding author from each group contributing to the literature as surveyed previously [10]. Two rounds of surveys were circulated over a period of 4 months. Between the first and second circulation and following review of initial results with the ASL, BOLD and T1/T2 panels at a meeting in Aarhus, the list of questions was increased and refined to

avoid ambiguity and increase the likelihood of reaching consensus on as many items as possible. The surveys included questions on: Respondent training, Patient preparation, Image acquisition, Diffusion parameters, Analysis, and Reporting. The full list of questions from the final circulation is provided in the Results section along with summarized results, percentage agreement, no basis and disagreement for all responses, as well as percentage agreement and disagreement without abstentions. Nearly all questions tested level of agreement or disagreement qualitatively. In the first circulation, 5 options were provided (Strongly agree / Agree / Neutral / Disagree / Strongly Disagree). In the second circulation the available responses were simplified and allowed for abstention (Agree / Disagree / I have insufficient experience to make a recommendation). Other questions focused on the preferred field strength or allowed multiple selections to test support of multiple related issues (e.g. reported parameters). Text comments were also collected on sets of questions of similar topics. For both rounds, responses were aggregated following the completion of the survey. The first round survey was issued on 1/11/19, and the second on 3/27/19; both were open for approximately 1 month.

After excluding abstentions, the level of agreement or disagreement as a percentage of all responses was calculated for each question. Responses for which either agreement or disagreement reached 75% or higher were deemed to have achieved consensus. Responses that related to one that has already reached consensus were deemed to have been resolved. For responses with agreement levels between 60% and 75%, a ‘preference’ was indicated but without the full weight of consensus. Similarly, other responses mutually exclusive from a preference or reaching lower levels of agreement on the same topic were deemed to have been resolved by that preference.

Finally, the combination of all of these directly or indirectly resolved questions were considered to generate a set of recommendations.

Results

Literature review

Figure 1 shows the distributions of b-value sampling and diffusion directions from all renal studies considered (control and patient-related). ADC and IVIM studies have featured a continuous range of b-values, while DTI studies have used a sparser selection, consistent with more time devoted to directional sampling. Finally, the majority of ADC and IVIM studies used 3 orthogonal directions for isotropic imaging. Since many of these studies employ inline processing with vendor software, the 3 directions are typically immediately averaged, both for convenience and for enhanced signal-to-noise ratio, to generate approximate 'trace-weighted' images prior to generation of ADC maps. DTI studies used six directions most often, but studies using as many as 30 directions have also been reported. While 6 directions is the bare minimum required for tensor calculation, other supplemental criteria have been suggested; for example, a minimum of 12 directions has been suggested to eliminate orientation bias in tensor results [83]. It should be noted that overall parameter estimation quality depends strongly and nonlinearly on the signal-to-noise ratio (SNR): it is essential that the SNR is considerably higher than a critical SNR. This critical SNR is about 8 for medium and high IVIM perfusion and 50 for the low IVIM perfusion regime [17].

Table 1 shows the results of the diffusion biomarker vs. protocol parameter correlations in healthy volunteers. All correlation results are shown for individual protocol parameters and biomarkers, and additional correlations are shown with protocol parameter combinations that provided higher

correlation coefficients. The primary protocol element correlation with reported diffusion biomarkers is average b-value, which significantly correlated negatively with tissue diffusivity D (Cx (cortex): R = -0.506, p = 0.03; Md (medulla): R = -0.528, p = 0.02) and positively with flow fraction f (Cx: R = 0.687, p = 0.002; Md: R = 0.566, p = 0.01). These correlations may have contributions from partial sampling of the IVIM signal response, with higher b-value ranges providing better estimates of both slow and fast diffusion components. Conversely, if b-values are sampled beyond the appropriate SNR level, Rician noise bias can lower ADC or D values and inflate f values. Similar negative correlation trends ($p < 0.1$) are seen between cortical ADC (R = -0.378, p = 0.08) or cortical MD (R = -0.531, p = 0.05) and maximum b-value. Transverse relaxation effects cause secondary correlations of flowing fraction with echo time TE (R = 0.474, p = 0.055) or equivalently T2 decay factor (R = -0.495, p = 0.04), likely due to reduction of the more rapidly relaxing tissue compartment, as quantified by Lemke et al. [17], and supported by the disparate relaxation times of renal tissue [81] and serum blood [84] or urine [85-87]. Another potential modulator of contrast is diffusion time, which is lengthened at larger echo time, though the role of this parameter in renal tissue has not been conclusively mapped out. Combining b-value and sequence timing factors together showed some amplified correlations, particularly for flow fraction and tissue diffusivity. In some cases, increasing T1 recovery increased flow representation and therefore higher f and ADC. Finally, a combination of relaxation factors and average b-value showed a negative correlation trend (R = -0.463, p = 0.07) with medullary FA, consistent with a modulation in flow effects on diffusion anisotropy. Figure 2 shows example correlations between renal DWI biomarkers in the literature and protocol parameters. As these variations of acquisition protocols and DWI biomarkers should be avoided in the translation of renal DWI to clinical practice, the present manuscript describes ongoing efforts to maximize lessons learned from

existing work to facilitate multi-site consistency through standardized acquisition, analysis, and reporting guidelines.

Table 2 shows summarized diffusion biomarkers in cortex and medulla in healthy volunteers from the literature review, stratified by field strength (1.5 T or 3.0 T). The only cases showing significant differences were IVIM pseudodiffusion (D*) and DTI mean diffusivity (MD) in cortex, both of which were higher at 1.5 T than 3.0 T.

Survey results

The second-round survey included 21 respondents from 21 institutions in 8 different countries on 3 continents. 9 of 21 (43%) were radiologists, while 13/21 (57%) were physicists (11), biomedical engineers (1), or mathematicians (1). 71% of the respondents used renal diffusion for volunteer research, 76% used it for patient research, 38% used it for clinical practice, and 14% used it for clinical trials.

For the second-round survey, among the 87 questions testing levels of agreement, 23 reached consensus agreement and 18 reached consensus disagreement. These results also resolved 16 other questions on the same topics as the "parent" consensus questions. For the remaining questions, if preferences are made for 17 questions, the remaining 13 questions are resolved. The fully aggregated survey responses, as well as text comments provided, are included as supplementary material, with Table 3 summarizing results of agree / disagree questions (with those reaching consensus highlighted). Regarding magnetic field strength, a consensus majority (81%) responded either 1.5 T or 3.0 T as acceptable. Regarding reporting preferences, all suggested acquisition

details (matrix, image orientation, fat suppression mode, averages, slice thickness, resolution, field of view, TR, TE, number and choice of b-values, and number of directions) received consensus support to be reported. Reporting biomarkers in both cortex and medulla was supported by consensus. Regarding processing, motion correction algorithm, processing software, IVIM fit algorithm, and IVIM fit option received consensus support to be reported. Regarding biomarkers' summary statistics, mean, median, and standard deviation values received consensus support to be reported. There are a range of topics that did not reach the level of consensus, including slice thickness, repetition time TR, number of signal averages, breathing mode, separate vs. combined protocols, diffusion gradient waveform, the number and highest b-value employed, number of diffusion directions for DTI, and aspects of ROI prescriptions.

Considering the literature trends, consensus views, preferences, comments and practical aspects surrounding future evidence generation, recommendations are given in Table 4 for ADC, IVIM, and DTI protocols. For many of the issues guiding protocol selection, the survey process provided clear indications of consensus choices (Table 3). For those topics not reaching consensus, we combine lesser-weighted preferences, practical issues, and information from text survey responses to synthesize recommendations. For acquisition, the consensus includes pulse sequences, RF coils, in-plane matrix / resolution, slice coverage, parallel imaging acceleration, fat suppression, echo time, and absence of cardiac gating. Strong preference (62%) was given for > 4 mm slice thickness, though some respondents expressed a desire for lower values when feasible. Strong preference (67% agreement) was also given for a TR=2-4 s. Given some contribution of T1 weighting to parameter variability, we have suggested a standardized repetition time TR = 4 s. Breathing mode did not reach consensus, however strong preference (70%) was given to

respiratory gating and free breathing (66%). Free breathing was noted to be acceptable in cases of renal allograft imaging. We have recommended respiratory gating when available and free breathing with post-hoc unilateral motion correction when not available (which was separately recommended by consensus). Regarding field strength, consensus approval for either 1.5 T or 3.0 T was found (81%), and only minimal differences were observed in the literature (Table 2). The SNR advantage of higher field is balanced by other disadvantages for DWI such as susceptibility-induced image distortion. Correspondingly, either field strength is deemed acceptable and investigators suggested to employ whichever is better equipped with hardware or software elements consistent with recommendations herein.

Discussion

The design of diffusion MRI protocols for renal imaging remains controversial, with some support for separate protocols for each diffusion technique and slightly more support for combined protocols. Similarly, separate protocols for 'standardized' efforts and exploratory research had only 50% support. Since deriving all measures from a combined protocol requires more sophisticated workflows than are universally available and consistent with the goals of generating generalizable evidence, we have thus recommended parsimonious protocols for ADC, IVIM, and DTI studies. As noted below, however, the encoding parameters suggested have commonalities (e.g. b-values) that may allow pooling of analogous biomarkers and consistency with advanced protocols involving combined encoding.

Diffusion weighting (choice of b-values) is a crucial element of diffusion MRI protocols. For ADC studies, consensus was found for more than 2 b-values, including values < 200 sec/mm^2, with

strong preference for a maximum b-value of 800 s/mm^2. For IVIM studies, consensus was found for a number of b-values greater than 6 b-values, with highest preference for more than 8. Finally, for DTI studies, preference was given to more than 2 b-values (61%), with a maximum b-value of 600 s/mm^2 (59%). 6 directions were deemed insufficient for DTI (76%), with a slight preference for more than 12 directions (63%). In addition to these indications from our panel, we may also take guidance from optimization studies on renal DWI sampling [16,17] that emphasized the importance of several key b-value regimes: low (0-200 s/mm^2) intermediate (200 - 400 s/mm^2), and high (600-800 s/mm^2). Finally, we deem it valuable to suggest common encoding parameters between techniques (ADC, IVIM, DTI) where possible to enable reasonable comparison of analogous MRI biomarkers (e.g. ADC and MD) in future datasets. Taking all of this into account, we recommend the following b-value sets (Table 4): for ADC studies, b = 0, 100, 200, 800 s/mm^2, 3 directions; for IVIM studies b = 0, 30, 70, 100, 200, 400, 800 s/mm^2, 3 directions; for DTI studies, b = 0, 200, 800 s/mm^2, 12 or more directions.

Manual ROI placement had consensus support over automatic (e.g. histogram-based) placement, with the unweighted (b = 0) image having consensus support for ROI prescription. Cortical ROIs should be continuous stripes (1 per slice), unless structural abnormalities prevent this, while medullary ROIs should be separate, with three regions sampled (upper, middle, lower poles). Generally, all slices from whole kidney coverage should be sampled with the exception of the 2 outermost slices where region delineation may be unclear.

We acknowledge some limitations in the procedures used to generate recommendations in this work. First, all entries in the literature review were assigned equal weight irrespective of

population size or technological availability. Heterogeneity also exists in the survey process, in which participant elections may have been driven by different priorities and informed by different levels of clinical or technical experience. In addition, while we modeled our approach on the Delphi consensus procedure, its application was adjusted for the purposes of this review and its timeframe. The survey also highlighted other areas of disagreement between the participants. In particular, it was not possible to obtain a consensus on technical questions like the use of segmented echo planar acquisitions, or the advantage of bipolar diffusion gradients. Uncertainty exists also for physiological questions such as the effect of diet on DWI. As some of these issues have already been partly addressed in the literature, the survey indicates that currently available evidence may not be sufficient for conclusive resolution. This report should therefore motivate a significant effort to investigate theses dedicated methodological questions.

Conclusions

The present work has summarized trends in the literature of renal diffusion MRI to date and their correlation with aspects of protocol design. In pursuit of minimizing this inter-study and inter-site variation, for the generation of evidence basis for reliable and high impact of imaging markers for renal disease, and with the guidance of a Delphi-based consensus process of experts in the field, we have generated a set of recommendations for future data collection. These protocols have been chosen to be achievable by any center and enable future pooling of data from multiple centers when equivalent protocols have been employed. We expect that this recommendation process to be an iterative one and ensuing efforts may refine or add to these recommendations. Importantly, these translational efforts do not replace and are not in conflict with ongoing innovation efforts to uncover more specific biomarkers from renal DWI with more advanced methods. Instead, they

reflect a view that commitment of some effort to generating generalizable workflows in parallel will yield tremendous benefits to the field as a whole and increase chances of clinical impact on a larger scale.

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		ADC			D			f			D*			MD			FA		
		R	p	N	R	p	N	R	p	N	R	p	N	R	p	N	R	p	N
Ave b-val	Cx	-0.162	0.47	22	**-0.506**	**0.03**	**18**	**0.687**	**0.002**	**18**	-0.268	0.40	12	-0.147	0.62	14	0.144	0.60	16
	Md	-0.154	0.56	17	**-0.528**	**0.02**	**18**	**0.566**	**0.01**	**18**	-0.319	0.31	12	0.093	0.75	14	-0.296	0.27	16
Max b-val	Cx	*-0.378*	*0.08*	*22*	-0.245	0.33	18	0.285	0.25	18	0.106	0.74	12	*-0.531*	*0.05*	*14*	0.102	0.71	16
	Md	-0.223	0.39	17	-0.260	0.30	18	0.281	0.26	18	0.239	0.46	12	0.161	0.58	14	-0.192	0.45	16
TE	Cx	0.220	0.37	19	0.149	0.57	17	*0.474*	*0.055*	*17*	-0.262	0.44	11	0.036	0.90	14	-0.087	0.75	16
	Md	0.345	0.19	16	0.163	0.53	17	0.150	0.57	17	-0.272	0.42	11	-0.152	0.61	14	0.216	0.42	16
TR	Cx	0.225	0.44	14	-0.270	0.30	17	0.097	0.71	17	0.392	0.23	11	-0.168	0.57	14	0.038	0.89	16
	Md	0.039	0.90	12	-0.186	0.48	17	0.043	0.87	17	0.459	0.16	11	-0.060	0.84	14	-0.292	0.27	16
T2f	Cx	-0.223	0.36	19	-0.151	0.56	17	**-0.495**	**0.04**	**17**	0.249	0.46	11	-0.083	0.78	14	0.102	0.71	16
	Md	-0.378	0.15	16	-0.158	0.55	17	-0.155	0.55	17	0.257	0.45	11	0.127	0.67	14	-0.255	0.34	16
T1f	Cx	-0.016	0.96	14	-0.142	0.59	17	0.171	0.51	17	0.298	0.37	11	-0.268	0.35	14	0.126	0.64	16
	Md	0.110	0.73	12	-0.129	0.62	17	0.018	0.95	17	0.274	0.42	11	-0.116	0.69	14	0.079	0.77	16
Aveb * TE	Cx	0.007	0.98	19	-0.338	0.19	17	**0.713**	**0.001**	**17**	-0.395	0.23	11	-0.168	0.57	14	0.086	0.75	16
	Md	**0.506**	**0.046**	**16**	-0.331	0.20	17	**0.501**	**0.04**	**17**	-0.457	0.16	11	0.001	1.0	14	-0.216	0.42	16
Aveb*T2f	Cx	-0.067	0.78	19	**-0.701**	**0.003**	**17**	*0.435*	*0.08*	*17*	-0.184	0.59	11	-0.106	0.72	14	0.200	0.46	16
	Md	0.107	0.69	16	**-0.741**	**0.001**	**17**	**0.559**	**0.02**	**17**	-0.228	0.50	11	0.167	0.57	14	-0.357	0.18	16
Aveb*T2f/ T1f	Cx	0.262	0.37	14	*-0.479*	*0.05*	*17*	0.223	0.39	17	-0.338	0.31	11	0.141	0.63	14	0.030	0.91	16
	Md	0.175	0.59	12	**-0.503**	**0.04**	**17**	*0.427*	*0.09*	*17*	-0.340	0.31	11	0.253	0.38	14	*-0.463*	*0.07*	*16*
Aveb*T1f/ T2f	Cx	**0.691**	**0.006**	**14**	-0.381	0.13	17	**0.682**	**0.003**	**17**	-0.174	0.61	11	-0.269	0.35	14	0.133	0.63	16
	Md	**0.660**	**0.02**	**12**	-0.369	0.15	17	*0.477*	*0.05*	*17*	-0.240	0.48	11	-0.049	0.87	14	-0.204	0.45	16
Maxb*T1f /T2f	Cx	0.110	0.71	14	-0.155	0.55	17	**0.547**	**0.02**	**17**	0.171	0.62	11	**-0.539**	**0.047**	**14**	0.088	0.75	16
	Md	0.293	0.36	12	-0.150	0.57	17	0.310	0.23	17	0.236	0.48	11	-0.015	0.96	14	-0.163	0.55	16

Table 1 : Correlations between reported renal diffusion metrics in the literature from cortex (Cx) or medulla (Md) regions of healthy volunteer kidneys and the corresponding studies' protocol parameters average b-value (ave b-val), maximum b-value (max b-val), echo time (TE), repetition time (TR), T2-weighting factor (T2f), and T1-weighting factor (T1f) (see text for calculation of relaxation weighting factors). Pearson correlation coefficients R, significance levels from two-sided t-test p, and number of studies contributing N are shown for the following diffusion parameters : apparent diffusion coefficient (ADC), IVIM tissue diffusivity (D), IVIM flow fraction (f), IVIM pseudodiffusivity (D*), DTI mean diffusivity (MD), and DTI fractional anisotropy (FA). Significant correlations ($p<0.05$) are highlighted **in bold**, moderate trends ($p<0.1$) *in italics*.

			ADC	D	f	D*	MD	FA
Cortex	1.5 T	Mean +/- s.d.	2056 ± 285	1966 ± 72	19.9 ± 3.2	50800 ± 13454	2508 ± 86	0.208 ± 0.045
		N	12	7	7	4	4	4
	3.0 T	Mean +/- s.d.	2243 ± 225	1919 ± 229	20.1 ± 8.4	24964 ± 20298	2262 ± 164	0.215 ± 0.043
		N	10	11	11	8	10	12
		p	0.100	0.538	0.944	**0.028**	**0.004**	0.779
Medulla	1.5 T	Mean +/- s.d.	1987 ± 267	1884 ± 76	17.5 ± 5.5	57350± 25505	2348 ± 589	0.425 ± 0.079
		N	8	7	7	4	4	4
	3.0 T	Mean +/- s.d.	2031 ± 227	1796 ± 228	18.0 ± 7.8	29016 ± 19272	2092 ± 162	0.335 ± 0.082
		N	9	11	11	8	10	12
		p	0.721	0.261	0.877	0.110	0.452	0.105

Table 2 : Comparisons between reported renal diffusion metrics in the literature from cortex or medulla regions of healthy volunteer kidneys at different field strengths (1.5 or 3.0 T). Mean and standard deviation values, significance levels from two-sided t-test p, and number of studies contributing N are shown for the following diffusion parameters : apparent diffusion coefficient (ADC), IVIM tissue diffusivity (D), IVIM flow fraction (f), IVIM pseudodiffusivity (D*), DTI mean diffusivity (MD), and DTI fractional anisotropy (FA). Significant field differences ($p<0.05$) are highlighted in bold. ADC, D, D*, and MD values are given in 10^{-6} mm^2/s, f is given in %, and FA is unitless.

	All responses			W/o abstentions		Choice
Question	**% Agree**	**% No basis**	**% Disagree**	**% Agree**	**% Disagree**	
Diet needs to be controlled before the scan	33.3	28.6	38.1	46.7	53.3	
Subject should be scanned in a normal hydration status when clinically appropriate	**76.2**	19.1	4.8	**94.1**	5.9	Agree
Subjects are required to follow a controlled and standardized salt intake before the scan	4.8	42.9	52.4	8.3	**91.7**	**Disagree**
Single-shot echo planar imaging sequence	**100**	0	0	**100**	0	Agree
Multi-shot echo planar imaging sequence	28.6	33.3	38.1	42.9	57.1	
RF body matrix coils	**95.2**	4.8	0	**100**	0	Agree
Axial slice orientation	28.6	4.8	66.7	30	70	Disagree
Coronal slice orientation (consistent with above)	42.9	9.5	47.6	47.4	52.6	
Oblique coronal slice orientation along long kidney axis (consistent with above)	**76.2**	0	23.8	**76.2**	23.8	Agree
Acquired matrix size >128	**85.7**	0	14.3	**85.7**	14.3	Agree
Inplane resolution 2 mm or smaller	19.1	0	**81.0**	19.1	**81.0**	**Disagree**
Inplane resolution between 2 and 3 mm	**90.5**	0	9.5	**90.5**	9.5	Agree
Inplane resolution > 3 mm	4.8	9.5	**85.7**	5.3	**94.7**	**Disagree**
Slice thickness 2 mm or less	0	9.5	**90.5**	0	**100**	**Disagree**
Slice thickness between 2 and 4 mm	57.1	4.8	38.1	60	40	Agree
Slice thickness > 4 mm	61.9	0	38.1	61.9	38.1	Agree
Gap between slices	42.9	4.8	52.4	45	55	
Full kidney slice coverage	**90.5**	0	9.5	**90.5**	9.5	Agree

Parallel imaging acceleration (factor 2)	**95.2**	0	4.8	**95.2**	4.8	Agree
Parallel imaging acceleration (factor > 2) (consistent with above)	19.1	23.81	57.1	25	**75**	**Disagree**
SPAIR fat suppression	61.9	23.8	14.3	**81.3**	18.8	Agree
STIR fat suppression (consistent with above)	9.5	28.6	61.9	13.3	**86.7**	**Disagree**
2000 ms< TR < 4000 ms	66.7	0	33.3	66.7	33.3	Agree
TR > 4000 ms	38.1	4.8	57.1	40	60	Disagree
TE < 100 ms	**95.2**	0	4.8	**95.2**	4.8	Agree
TE minimum allowed by hardware / sequence	**85.7**	9.5	4.8	**94.7**	5.3	Agree
2 signal averages	38.1	4.8	57.1	40	60	Disagree
3 signal averages	66.7	0	33.3	66.7	33.3	Agree
Expiration Breathhold acquisition	9.5	4.8	**85.7**	10	**90**	**Disagree**
Free breathing acquisition (consistent with above)	66.7	0	33.3	66.7	33.3	Agree
Respiratory gated acquisition (consistent with above)	66.7	4.8	28.6	70	30	Agree
Cardiac gating (systole)	0	33.3	66.7	0	**100**	**Disagree**
Cardiac gating (diastole)	4.8	33.3	61.9	7.1	**92.9**	**Disagree**
Separate acquisitions for ADC / IVIM vs. DTI studies in a multiparametric protocol	42.9	9.5	47.6	47.4	52.6	

Separate protocols for multiparametric acquisitions and exploratory renal diffusion MRI research	47.6	4.8	47.6	50	50	
Single protocol to provide all metrics (ADC, DTI, IVIM)	47.6	14.3	38.1	55.6	44.4	
Monopolar diffusion gradients	57.1	19.1	23.8	70.6	29.41	Agere
Twice-refocused Bipolar diffusion gradients	28.6	42.9	28.6	50	50	
DWI sequence with only 2 b-values	14.3	0	**85.7**	14.3	**85.7**	**Disagree**
DWI sequence with more than 2 b-values	**90.5**	0	9.5	**90.5**	9.5	Agree
ADC studies : include low b-values < 200 s/mm2	**85.7**	0	14.3	**85.7**	14.3	Agree
ADC studies : highest b-value 600 s/mm2	19.1	0	**81.0**	19.1	**81.0**	**Disagree**
ADC studies : highest b-value 800 s/mm2 (consistent with above)	61.9	0	38.1	61.9	38.1	Agree
ADC studies : high b-value 1000 s/mm2 (consistent with above)	28.6	4.8	66.7	30	70	Disagree
IVIM studies : 4 b-values	0	9.5	**90.5**	0	**100**	**Disagree**
IVIM studies : 6 b-values	19.1	9.5	**71.4**	21.1	**78.9**	**Disagree**
IVIM studies : 8 b-values	47.6	9.5	42.9	52.6	47.4	
IVIM studies : > 8 b-values	52.4	4.8	42.9	55	45	
DTI studies : 2 b-values	38.1	28.6	33.3	53.3	46.7	
DTI studies: > 2 b-values	38.1	38.1	23.81	61.51	38.5	Agree

DTI studies : highest b-value 400 s/mm2	4.8	28.6	66.7	6.7	**93.3**	**Disagree**
DTI studies : highest b-value 600 s/mm2	47.6	19.1	33.3	58.8	41.2	
DTI studies : highest b-value 800 s/mm2	38.1	23.8	38.1	50	50	
DTI studies : highest b-value 1000 s/mm2	9.5	28.6	61.9	13.3	**86.7**	**Disagree**
DTI studies : 6 directions	19.1	19.1	61.91	23.51	**76.5**	**Disagree**
DTI studies : 12 directions	42.9	28.6	28.6	60	40	Agree
DTI studies : > 12 directions	47.6	23.8	28.6	62.5	37.5	Agree
Post-hoc EPI distortion correction	52.4	38.1	9.5	**84.6**	15.4	Agree
Post-hoc motion correction / registration	**90.5**	9.5	0	**100**	0	Agree
Unilateral motion correction / registration	47.6	38.1	14.3	**76.9**	23.1	Agree
Manual ROI placement	**85.7**	9.5	4.8	**94.7**	5.3	Agree
Manual ROI placement on ADC map	42.9	9.5	47.6	47.4	52.6	
Manual ROI placement on b0	**76.2**	9.5	14.3	**84.2**	15.8	Agree
Manual ROI placement on FA map	42.9	14.3	42.9	50	50	
Manual continuous cortical stripe ROI per slice	47.6	19.1	33.3	58.8	41.2	
Manual Whole medulla ROI per slice	23.8	19.1	57.1	29.4	70.6	Disagree
Manual Whole kidney ROI per slice	33.3	14.3	52.4	38.9	61.1	Disagree
Manual Multiple medulla ROI per slice	**76.2**	9.5	14.3	**84.2**	15.8	Agree
Manual Multiple cortical ROIs per slice	52.4	9.5	38.1	57.9	42.1	
If multiple, Three cortical ROIs per slice	38.1	19.1	42.9	47.1	52.9	

If multiple, Three medulla ROIs per slice	47.6	19.1	33.3	58.8	41.2	
If multiple, >Three cortical ROIs per slice	28.6	14.3	57.1	33.3	66.7	Disagree
If multiple, >Three medullary ROIs per slice	33.3	14.3	52.4	38.9	61.1	Disagree
If multiple slices, 3 slices sampled	52.4	9.5	38.1	57.9	42.1	
If multiple slices, >3 slices sampled	57.1	9.5	33.3	63.2	36.8	Agree
Automatic ROI placement, based on b0 histogram	23.8	38.1	38.1	38.5	61.5	Disagree
Automatic ROI placement, based on ADC histogram	14.3	42.9	42.9	25	**75**	**Disagree**
Automatic ROI placement, based on FA histogram	19.1	42.9	38.1	33.3	66.7	Disagree
Report diffusion biomarkers in cortex	**95.2**	4.8	0	**100**	0	Agree
Report diffusion biomarkers in medulla	**90.5**	9.5	0	**100**	0	Agree
Report diffusion biomarkers in whole kidney	38.1	14.3	47.6	44.4	55.6	
Diffusion units 10^-3 mm2/s	**81.0**	0	19.1	**81.0**	19.1	Agree
Diffusion units 10^-6 mm2/s	28.6	0	71.4	28.6	71.4	Disagree
Diffusion units microns^2/ms	14.3	0	**85.7**	14.3	**85.7**	**Disagree**
Colormap presentation	**76.2**	0	23.8	**76.2**	23.8	Agree
Grayscale map presentation	61.9	0	38.1	61.9	38.1	Agree
Parametric map fusion with anatomic imaging	61.9	9.5	28.6	68.4	31.6	Agree

Table 3 : Summary of survey results on agree / disagree questions. Questions highlighted in bold achieved consensus (>= 75%). The choice on each question (Agree or Disagree) is labelled and color-coded; Green = consensus (>=75%); Orange = preference (>=60%); Red = indeterminate.

Protocol option	Recommendation			Weight
Preparation	**Normal hydration**			
Field strength	**1.5 T or 3.0 T**			
Sequence	**Single shot EPI**			
Orientation	**Oblique coronal**			
Matrix	**>128**			
In-plane resolution	**2-3 mm**			
Slice thickness	>4 mm			
Coverage	**Full kidney**			
Parallel imaging factor	**2**			
Fat suppression	**SPAIR**			
TR (s)	4			
TE (ms)	**Min (< 100)**			
Averages	3			
Breathing mode	Respiratory gated (or free breathing with post-hoc motion correction)			
Cardiac gating	**no**			
Diffusion gradients	Monopolar			
	ADC	IVIM	DTI	
# b-values	4	>6	>2	
Suggested b-values	0,100,200,800	0,30,70,100,200,400,800	0,200,800	
# directions	3	3	12 or more	
Time (min)	2	3.8	5	
Distortion correction	**Recommended**			
Registration	**Recommended, unilateral if possible**			
Image quality control	Recommended			
ROI placement	b=0 image			
Cortical ROI	1 stripe / slice ;> 3 slices			
Medullary ROI	3 samples / slice ;> 3 slices			
Reporting	**Cortex and Medulla**			
Metric statistics reporting	**Mean, Median, Standard deviation, ROI size**			
Diffusion units	**10^{-3} mm^2 / s**			
Map format	Colormap , fused with anatomy if possible			

Table 4: Recommendations for acquisition and processing of renal DWI data. Recommendations in bold are derived from consensus view of the expert panel. Weight of each recommendation is color coded (green = consensus (>=75%) ; orange = preference (>=60%).

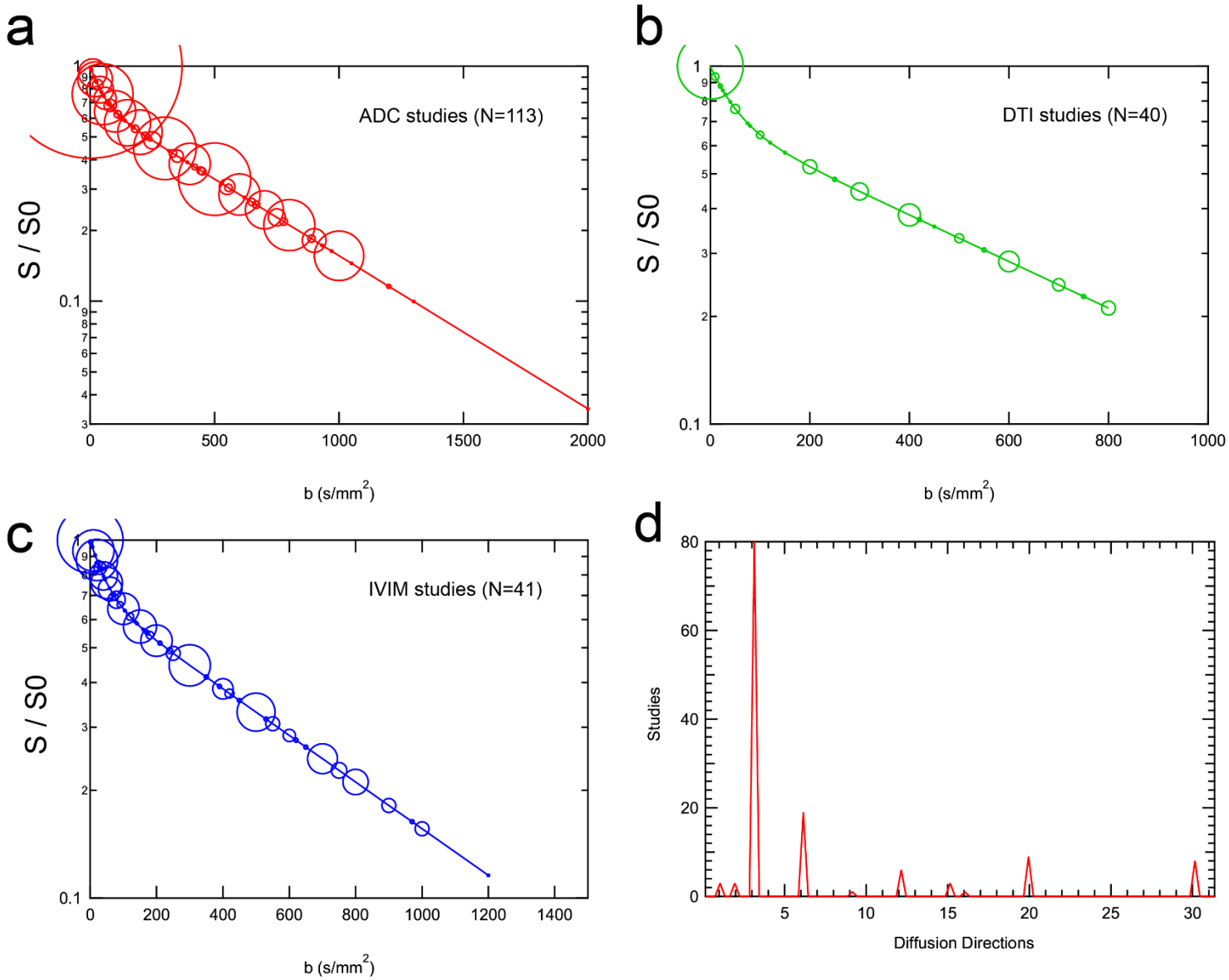

Figure 1 : Distributions of diffusion MRI sampling in renal DWI literature studies. b-value distributions used in studies reporting (a) ADC values, (b) DTI metrics, or (c) IVIM metrics. In the 'bubble' plots, the size of the circle reflects the amount of studies utilizing that b-value. (d) Distribution of diffusion directions employed; ADC and IVIM studies dominantly employed 3 directions, with DTI studies employing more directions.

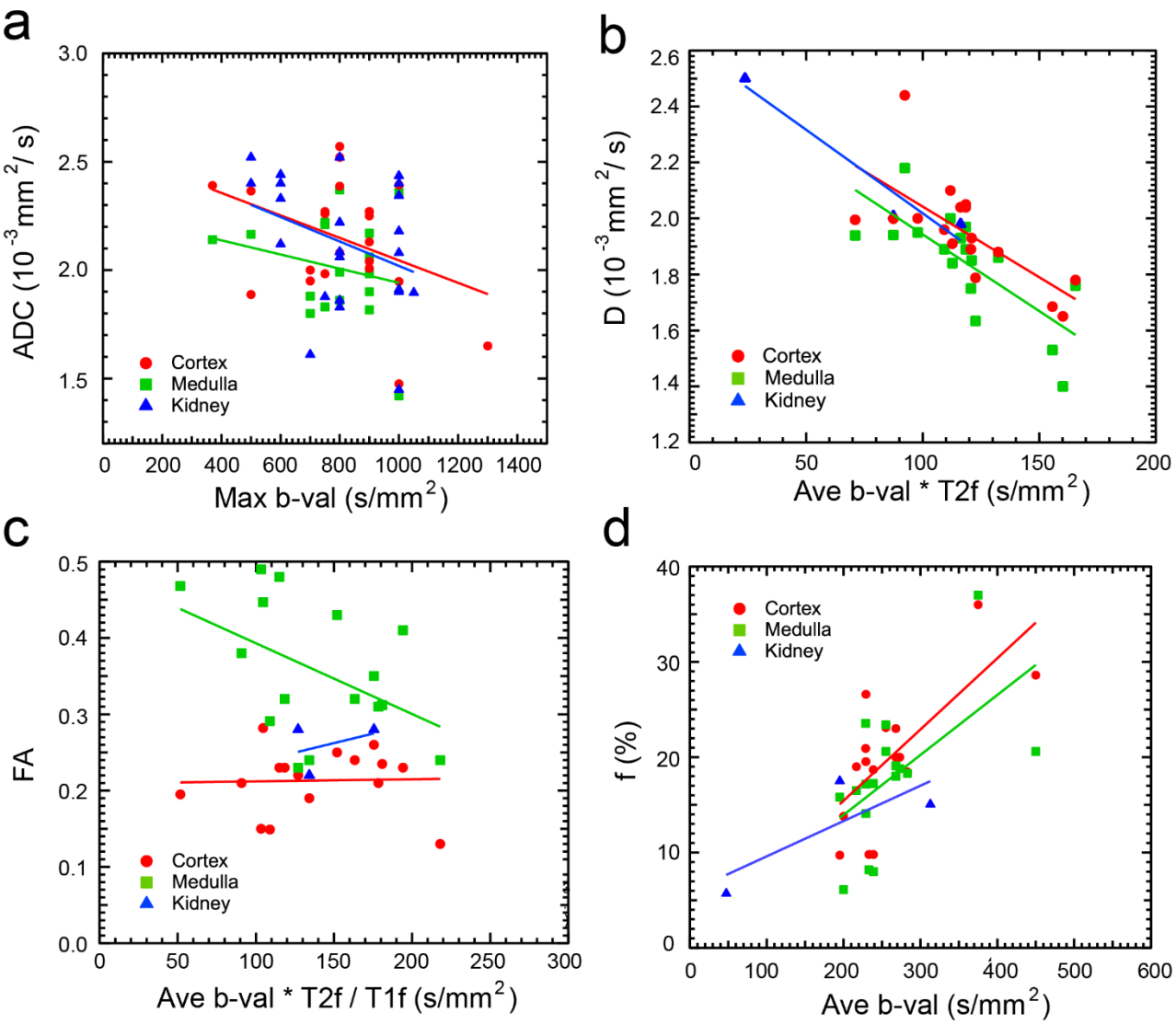

Figure 2: Correlations between renal diffusion MRI metrics and protocol parameters from the literature from cortex, medulla, and whole kidney tissue in healthy adults. (a) ADC, (b) IVIM tissue diffusivity D, (c) DTI fractional anisotropy FA, and (d) IVIM flow fraction f vs. average or maximum b-value with relaxation weighting terms. Inter-study variation can be reduced when desired for larger evidence generation using more standardized protocols.

Comments (diet)

We use it along with other techniques like BOLD and ASL and so we always prefer to use at least 4 hr fasting.

It may help to reduce susceptibility artifacts from bowel gas if subjects avoid large meals, fiber, red meat 24 hrs before scan.

Hydration

Avoiding a high protein diet before the scan and having light meals 24 hours before the examination would be helpful (this would also reduce colonic loading that might interfere with the MRI acquisition).

Not possible in daily routine.

DWI may be frequently performed along with other techniques such as BOLD which will require some standardization of diet/water intake.

Comments (hydration)

Hydration has an influence over diffusion parameters.

Normal hydration level (1 glass water) suggested

Standard hydration should be preferred

This should be guided by eliciting clinical history on the day of the scan - anything between 250 - 500 ml of water would be appropriate if no clinical contra-indications (such as existing oedema, etc).

Comments (salt intake)

Seems difficult to control, would need a very specific list of allowed/forbidden foods and quantities.

This would be difficult to achieve for patients that are not already on a controlled diet and the non-compliance rate would be high (as well as potentially result in failures of patient recruitment).

Comments (k-space readout)

I have always used single-shot EPI

Speed is an issue with multi echo shot EPI

This should be guided by the information available in the current literature that yields best image quality.

Comments (field strength)

Higher distortion in coronal at 3T

3T preferred when available.

Comments (image orientation)

Coronal. Oblique not mandatory but definitely an option in particular if simplifies matching geometry to other MR acquisitions as part of a multiparametric protocol. The TRs are normally long enough to allow full kidney coverage even if doing pure coronal (i.e. no oblique).

As part of multiparametric approach, it makes sense to have all the acquisitions in the true coronal plane.

Axial minimizes distortion, but coronal to scanner or the kidney matches the other sequences in an multiparametric MRI protocol.

Long axis alignment (using anatomic referencing) best chance for standardized regional sampling

Oblique coronal slice orientation along long kidney axis (for native kidneys), axial plane for transplanted kidneys

In-plane motion preferred

Ideally the DWI acquisition should match and be "mapped" to anatomical imaging / other MRI pulse-sequence acquisitions so that renal mpMRI protocols become. reality.

We do axial DWI and coronal DTI. In our experience, for quantitative imaging, straight axial and straight coronal works well with consistency in clinical practice. With oblique, there is potential to automatically increase TE if FOV gets changed due to patient size or if the angle gets steep.

Oblique coronal slice orientation along long kidney axis should be done with two independent slice packages, one aligned to the left and one aligned to the right kidney.

I think would be reasonable to acquire both axial and oblique coronal.

In my opinion all orientations can be used.

Comments (image matrix)

Depends on FOV

agree, with lower than 128, the spatial resolution is too low.

Comments (inplane resolution)

High resolution (2mm or smaller) would increase the acquisition time and the noise; low resolution (>3mm) would be not enough.

SNR is an issue with high inplane resolution.

Comments (slice thickness)

[4-5] mm

Ideally it would be great to have slice thickness between 2 and 4mm, but taking into account the time limitation even 5-6mm could be enough (I vote for saving time using higher slice thickness and use it for acquiring more b values).

Higher SNR, more kidney coverage in fewer slices and less acquisition time.

Large slice helpful for sufficient SNR in advanced protocols.

SNR again an issue.

Slice thickness>4 mm increases SNR

We make every effort to use 3mm in general. although 4 mm has been occasionally used clinically for speed if running out of time.

Comments (slice coverage)

More than 1 slice, e.g. 3 slices.

Comments (parallel imaging)

I have always used factor = 2 - no experience with factors>2

For EPI, parallel imaging will reduce effective TE and potentially reduce artifacts

If sufficient snr eg at 3t

factor>2 makes images noisy with the current acquisition method. perhaps something to reconsider in future, in combination with SMS or CS.

2 or higher

Comments (fat suppression)

Is an option for a spectrally selective method missing? I normally use that at 3T with acceptable results (i.e. the so called FatSat on Siemens)

I have always used SPAIR fat suppression (called ASPIR on GE scanners)

With EPI, fat suppression is essential

Comments (TR)

Collected respiratory triggered

[4-5] s

TR depends also by respiratory triggered acquisition

5100 ms

Comments (TE)

70 ms

Should be guided by hardware capabilities.

as long as it is consistent.

Comments (signal averages)

Depends on no. directions / scan time / bval. If time allows do multiple averages particular at the highest bvals. Can also allow retrospective rejection of corrupted volumes (e.g. dropout)

It's again a matter of acquisition time, as having 2 averages doubles the acquisition time. We prefer to use just 1 average and acquire a higher number of b values

Even more if using free breathing

More signal averages for higher b-values

NSA>3 increases SNR ratio

1

Ideally the acquisition should be good enough to allow good quality data to be acquired from a single acquisition. if absolutely;y necessary 2 signal averages should be the maximum.

Comments (breathing modes)

I would use resp. gating or triggering if scan time allowed.

A breathhold is not feasible for long IVIM acquisitions. Free breathing saves time and is ok for allografts, navigator-gated was shown in a previous study to be better at controlling motion in native kidneys. Co-registration if data is necessary with either, anyway.

For extended advanced protocols, free breathing would be preferred along with image registration; similarly if respiratory gating is not available

free breathing for transplanted kidneys

If patient well-trained and co-operative respiratory gating would be a reasonable option. Expiration breath-hold would prolong the acquisition time for too long (for whole kidney coverage) with the risk of motion artefacts / corrupted data.

FB helpful if possible in future.

Respiratory gated acquisition would be best but often impractical

all three can be used

Comments (cardiac gating)

Never used for DWI

informative for research studies but for multiparametric MR may be time prohibitive

For advanced / research applications only - not enough data available in the area for confident assessment. However, it would make sense, in the future, to have this incorporated.

have not explored the cardiac gating if it makes a difference

Comments (separate vs. combined protocols)

If you combine protocols you save a lot of time

Ideally, there should be a single protocol for all metrics, although it may be more difficult to implement. Protocols for mpMRI and exploratory diffusion research can be different, but the goal should be to integrate the result of the exploratory research into mpMRI.

Single protocol time-efficient but requires specialist processing

if possibile all metrics in a single protocol

Provided that the focus is a DWI / DTI / IVIM acquisition - it is difficult to see how other more advanced imaging sequences could be fitted in in addition to this protocol and anatomical imaging (maybe BOLD / T1 mapping could be "squeezed in").

Preferably one single protocol to provide all metrics for both exploratory DWI reserch, and multiparametric acquisitions

Comments (DWI number of b-values)

I mean 2 non-zero b-values in addition to the b=0 s/mm2 non diffusion-weighted baseline scan (having a relatively simple clinical protocol in mind)

At least 3 b-values samples the exponential curve and provides better ADC values.

For IVIM severla low b-values (below 100) are needed

min. 3 per directions

Comments (ADC low b-value inclusion)

Ok to see the perfusion effect on ADC. Can do IVIM if we want to separate the diffusion effect from perfusion.

allows some sensitivity to flow effects which are typically relevant; helpful to include even if ADC only is collected

for pseudodiffusion

Comments (ADC highest b-value)

limited by gradient hardware

I am happy with highest on the range of [600-800] s/mm2 but having to choose only one for consistency I went with 800 s/mm2

Values above 1000 would need DKI fit of signal.

700-1000

b=800 seems to be sufficient for kidneys. b1000 images look noisy.

Comments (IVIM number of b-values)

Low number of b values makes it impossible to use a segmented fitted approach (which seems to me the best option)

Currently using 9 b-values, have not performed a study to see if fewer can be used.

8 samples should be sufficient once IVIM model has already been selected for use

If one is interrested in the perfusion fraction f solely (not in D*), 6 b-values might suffice.

the more b-values (especially low ones) the better, however problem of time in daily routine

considering possible 3 diff. components including tubuli

Comments (DTI number of b-values)

I mean 2 non-zero b-values in addition to the b=0 s/mm2 non diffusion-weighted baseline scan (having a relatively simple clinical protocol in mind)

I have never performed DTI

a minimal set that would allow comparison of diffusivities from other protocols

Comments (DTI highest b-value)

I am happy with highest on the range of [600-800] s/mm2 but having to choose only one for consistency I went with 800 s/mm2

Comments (DTI number of directions)

Dependent on scan time and number of averages in each direction. I would recommend 12 as a minimum

6 is the minimum, the more the better, with acquisition time as the limitation.

a compromise of time and SNR

6 Directions for the fractional anisotropy, tractography likely requires more.

Comments (image quality control)

Distortion correction would be helpful in some cases but not sure distortion correction tools are mature enough for renal clinical applications so probably would not recommend using it as the default approach. Unilateral motion correction seems mandatory to me if doing rigid registrations as the kidneys do move independently to a significant extent.

Unilateral correction more difficult to be performed

Not sure what is meant by unilateral motion correction: for 1 kidney only?

unilateral correction essential (in free breathing protocol) given independent motion

QA / QC should be implemented at acquisition level in the first instance so that the radiographers are well trained and recognise if an acquisitions needs to be repeated to achieve high quality data.

Comments (map for manual ROIs)

Recommending a method for ROI choice is not trivial. If the cortico-medullary differentiation is still possible (may depend on CKD stage) AND data has been properly acquired and motion-corrected, the FA maps provide a good source of contrast to readily differentiate cortex and medulla. If not, I would resort to drawing in the b0 map.

Rather place ROI on b0 rather than maps, to avoid artifacts.

FA map useful for medulla selection when DTI is available

Why not semi-automatic? I think we are still quite far from automatic ROI placement.

Comments (shape of manual ROIs)

Continuous cortex and multiple medulla ROIs as default. The exception would be if cysts or other structural abnormalities exist which would not allow one to draw a continuous cortical ROI.

Using multiple ROIs rather one large one allows avoidance of artifacts. Cortex and medulla ROI should be separated, as they have different vascularisation and physiological properties. Although there is poor contrast to differentiate Cx from

Med on diffusion, anatomical images can be used as reference.

large ROIs best use of available data

Medulla-wedge shaped, cortical curvilinear

Circles or any other shape as long as they confidently select anatomically-correct parts of the cortex / medulla. Why not use anatomical imaging, well-registered with ethical DWI / ADC / etc, with good cortico-medullary contrast to guide this process?

Shape of the manual ROIs should aline with the anatomicl shape of cortex and medull

Comments (slices for ROI sampling)

More is better but drawing ROIs manually is a laborious process so I'd say sampling from 3 slices not a dealbreaker.

Depends on the slice thickness.

In my case I use 5mm thickness + 1 mm gap; taking 3 slices (central + slice before and after) you already have a representative portion of the cortex and medulla.

For whole kidney I would suggest to remove the first and last slice and take all the others

Comments (automatic ROI placement)

Most automatic methods depend on cortico-medullary differentiation existing. In patients this may be an issue. However as mentioned above where this exists the FA maps provide a good source of contrast.

dangerous - highly affected by artefacts

Automatic ROI placement might become possible using AI methods in the future. Presently, I don't think automatic approaches based on histograms are reliable.

supervised ROI placement is essential. Automatic may be attempted if software allows. Our software doesn't allow automatic yet. we are working on developing an automated version.

Comments (acquisition details reporting)

Other things to report: scanner vendor/model; field strength; fat suppression used (yes or no at least); any physiological triggering/gating if used; bandwidth; echo-spacing; slice gap if used; order of acquisition of slices (sequential/interleaved); if undersampling was used (either partial Fourier and/or parallel imaging). This may sound like a lot, but it is generally hard to replicate protocols from papers if they are not comprehensive.

parallel imaging factor, receiver bandwidth

Maybe all these parameters should be "assembled" as a guide to reviewers and be a "requirement" for future submissions in the field (that could be adopted by journals, such as JMRI / MRM).

Most of these specific acquisition details are quite general, and might be more suited for the general PARENCHIMA paper as discussed in Aarhus.

Comments (processing details reporting)

in addition: ROI used (whole kidney/cortex/medulla vs multiple ROIs, manual vs automatic ROI)

Do not have experience with ivim

Most of these specific postprocessing details are quite general, and might be more suited for the general PARENCHIMA paper as discussed in Aarhus.

Comments (regional metrics reporting)

Like to separate cortex from medulla

As many metrics as possible should be reported - this is the only way in which the best parameters / biomarkers will emerge as potential candidates for clinical translation.

Comments (diffusion units reporting)

microns^2/ms can make the text cleaner but not standard so may still confuse people especially as bvals almost always referred to as s/mm^2

I do not use smaller units, but they may be better as they would highlight differences in ADC or D without having to use many decimals.

Comments (summary statistics reporting)

Elaborate on single-subject vs. group metrics (e.g. stdev)

DWI biomarkers often have non-normal distribution

Partly depends on the distribution of the data

Comments (parametric map presentation)

Grayscale seems to be standard especially for FA, but if using colorscale use perceptually linear ones (not jet!). Fusion can be nice but would not recommend as the default approach.

Maps and maps + anatomy fusions are great for presentation purposes.

fusion challenging given EPI distortion; grayscale most standardizable

This depends on the local preference, looks nice, but no real benefit