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Sensitivity Calibration with a Uniform Magnetization Image to Improve Arterial Spin Labeling Perfusion Quantification

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Abstract

Quantification of perfusion with arterial spin labeling (ASL) MRI requires a calibration of the imaging sensitivity to water throughout the imaged volume. Since this sensitivity is affected by coil loading and other interactions between the subject and the scanner, the sensitivity must be calibrated in the subject at the time of scan. Conventional ASL perfusion quantification assumes a uniform proton density and acquires a proton density reference image to serve as the calibration. This assumption, in the form of an assumed constant brain-blood partition coefficient, incorrectly adds inverse proton density weighting to the perfusion image. Here a sensitivity calibration is proposed by generating a uniform magnetization image whose intensity is highly independent of brain tissue type. It is shown that such a uniform magnetization image can be achieved, and brain tissue perfusion values quantified with the sensitivity calibration agree with those quantified with a proton density image when segmentation of brain tissues is performed and appropriate partition coefficients are assumed. Quantification of brain tissue water density is also demonstrated using this sensitivity calibration. This approach can improve and simplify quantification of ASL perfusion and may have broader applications to measurement of edema and sensitivity calibration for parallel imaging.

Keywords

perfusion imaging; arterial spin labeling; partition coefficient; water density; coil sensitivity

INTRODUCTION

MRI is increasingly used as a research tool in experimental and clinical research studies, so the need for deriving quantitative measures of physiology from MR signal intensities continues to grow. While numerous factors can complicate quantitative imaging, perhaps the most immediate is the difficulty in relating measured signal intensity to the magnetization present within a local region. This difficulty has become more pronounced at high field, where spatial non-uniformity of transmit fields occurs, and with the spatial non-uniformity of receive sensitivity introduced by the widespread use of receive arrays for improved sensitivity and to permit parallel imaging acceleration. Though many quantitative measurements, such as T2 and apparent diffusion coefficients (ADC), can employ ratios between images that do not require absolute sensitivity calibration, other measurable quantities, such as tissue water density and arterial spin labeling (ASL) perfusion, require such calibration to provide absolute measurements.

The requirement of sensitivity calibration for ASL quantification is inherent to the labeling technique itself. ASL uses arterial water as an endogenous tracer for the measurement of perfusion (1). The amount of labeled water that appears some time later in the tissue is a direct indicator of perfusion. Hence quantification of ASL perfusion becomes analogous to measurement of water density. Because a suitable method for sensitivity calibration is not typically available, standard quantification models (1,2) use division of the perfusion image by a proton density weighted image, combined with an assumed constant tissue proton density expressed as a brain-blood partition coefficient λ . Such coil sensitivity calibration using a proton density image will add inverse proton density weighting to the perfusion quantification (3). The quantification error occurs because one approximates the true λ varying throughout the brain with a single constant value. Division by a true coil sensitivity, instead of a proton density reference image, will remove the unnecessary proton density weighting (and the need for brain-blood partition coefficient) and therefore improve ASL perfusion quantification. Since the true proton density differs between normal gray and white matter and even more in pathology, this assumption is a considerable source of error in ASL quantification.

When the coil sensitivity is very uniform, as for transmit receive coils at low field, a measurement of sensitivity in the cerebrospinal fluid (CSF) of the ventricles (4), or potentially a reference phantom, can be used for quantification. Unfortunately this approach is not effective for modern imaging configurations with the nonuniform receive sensitivity of receive coil arrays and the nonuniform transmit field produced at high fields. It has been shown that the coil sensitivity may be estimated on a spatially uniform phantom (5), but it is preferable to measure the coil sensitivity on the same subject to avoid the effects from different loading. Recently a method was reported to map the coil sensitivity in-vivo by minimizing the contrast between gray matter (GM), white matter (WM) and CSF (6) with an optimal combination of TE and TR. Such sensitivity maps have been combined with the CSF calibration approach to quantify ASL perfusion in several studies (7, 8). Here we propose a quick scan to measure the scanner sensitivity by generating a single image with the same magnetization not only for GM, WM and CSF, but also potentially for other pathological tissues. This uniform image, except for coil sensitivity effects, can then be used as a sensitivity map to quantify perfusion or potentially other quantities. The feasibility and accuracy of perfusion measurement using the generated sensitivity map is evaluated.

THEORY

Coil Sensitivity

To measure the coil sensitivity of the brain, a uniform magnetization needs to be created for different brain tissues (gray matter, white matter, and CSF) so that the measured image will be proportional to coil sensitivity. The multiple inversion recovery (MIR) technique (9) has been optimized to achieve uniformly zero magnetization for the purpose of background tissue signal suppression in applications to angiography (10) and perfusion measurement (11). Here we used the MIR technique to prepare a uniform, nonzero magnetization image for all brain tissues.

The magnetization created by the MIR pulses at the imaging time (time 0) is a function of the brain local tissue T1, T2 and WD (10):

$$M(t_{sat}, t_1, \dots, t_n, T_1, T_2, WD, c) = WD \cdot \left(1 + \sum_{i=1}^n (c^i - c^{i-1}) e^{-t_i/T_1} + c^{n+1} e^{-t_{sat}/T_1}\right) \cdot e^{-TE/T_2} \quad [1]$$

where WD is water density, t_{sat} is the time for the application of the starting saturation pulse and subsequently several inversion pulses (with n inversion times $t_1, \dots, t_n$) are applied with

potentially imperfect inversion. c is the cosine of the effective flip angle achieved with the inversion pulse, allowing for the efficiency of inversion, $|c|$, less than one. Our goal is to create a constant target magnetization, V_t , that is independent of WD, T1 and T2. This is, of course, impossible for an arbitrary combination of these parameters. For three tissues, GM, WM and CSF, with known relaxation and water density, the use of a three or more inversion MIR sequence may permit creation of equal magnetization. In order to better accommodate pathology with different relaxation, however, we instead chose to assume a relationship between WD, T1 and T2 derived from literature values. Tissues with pathology may have different relaxation than GM, WM and CSF but the general relationship between T1, T2 and WD tends to be preserved in pathology. By optimizing for a range of tissue water densities, and therefore corresponding T1's and T2's, we make the technique robust to pathological changes in WD.

To a reasonable approximation in most tissues, T1 can be expressed as a function of WD in a power law form (12).

$$\frac{1}{T_1} = \frac{WD}{T_{1CSF}} + \frac{(1-WD)^{\alpha_1}}{\rho_1} \quad [2a]$$

where T_{1CSF} is the T1 of CSF, and α_1 , and ρ_1 are model parameters. It is worth noting that the function always passes through the point (WD_{CSF}, T_{1CSF}) where WD_{CSF} is the water density of CSF, assumed to be 1 g/ml. Though a similar functional form could be employed for T2, we chose to use a different smoother function to approximate the relationship of T2 and WD:

$$T_2 = A_2 \cdot e^{(WD - WD_{WM})/B_2} + C_2 \quad [2b]$$

where WD_{WM} is the water density of white matter, and A_2 , B_2 and C_2 are model parameters. This form tends to give a smoother dependence of T2 on WD than a power law form (see results). The model parameters can be determined by specifying the water densities of gray matter, white matter, and CSF (WD_{GM} , WD_{WM} , WD_{CSF}), T1 and T2 values of gray matter (T_{1GM} , T_{2GM}), white matter (T_{1WM} , T_{2WM}) and CSF (T_{1CSF} , T_{2CSF}).

Once the relationship between WD, T2, and T1 is specified, designing the preparation is an optimization problem. The objective of the optimization is to determine the pulse timings for which the cost function is minimized. We used the simplest cost function, the sum of squared differences (norm 2 distances) between the theoretical magnetization and the target magnetization. The functional form of the optimization problem can be written as:

$$\min_{t_1, \dots, t_n} \left\{ \sum_{T_1=T_{1\min}}^{T_{1\max}} w(T_1) [M(t_{sat}, t_1, \dots, t_n, T_1, T_2, WD, c) - V_t]^2 \right\} \quad [3]$$

with condition $t_{sat} < t_1 < t_2, \dots, t_{n-1} < t_n$

$w(T_1)$ is weight function. $w(T_1) = 1$ means equal weight for all considered T1's. From Eq. [2a], WD can be expressed as a function of T1 since T1 is a monotonic function of WD. T2 can be also expressed as a function of T1 because T2 is a function of WD from Eq. [2b] and WD is a function of T1. The cost function does not depend on T1 due to the summation from $T_{1\min}$ to $T_{1\max}$. Therefore, the cost function of Eq. [3] becomes a function of $t_1, \dots, t_n$ and t_{sat} . For a fixed t_{sat} , the nonlinear optimization problem can be solved for $t_1, \dots, t_n$ (n N), and the average relative deviation can be calculated as

$$Dev(t_{sat}, V_t) = \frac{1}{V_t} \sqrt{\frac{\sum_{T_1=T_{1min}}^{T_{1max}} [M(t_{sat}, t_1, \dots, t_n, T_1, T_2, WD, c) - V_t]^2}{\sum_{T_1=T_{1min}}^{T_{1max}} 1}} \quad [4]$$

The timing of the saturation pulse t_{sat} is constrained by the maximum allowed preparation time (T_{prep}). The optimal t_{sat} (and the corresponding $t_1, \dots, t_n$) for a given T_{prep} was chosen as the value that minimized Dev for all $t_{sat} < T_{prep}$.

Quantification of Perfusion

Perfusion was quantified using the more standard tissue-blood partition coefficient approach. This method divides the difference image by a proton density weighted reference image to calculate flow according to the formula (2,13)

$$f = \lambda \cdot \frac{\Delta S}{S_t^0 g(T_{1a}, T_{1t}, \alpha, \tau, w, \delta)} e^{\left(\frac{T_E}{T_{2l}} - \frac{T_E}{T_{2t}}\right)} \quad [5]$$

where f is the perfusion rate, ΔS is the perfusion difference signal, λ is tissue-to-blood partition coefficient of water, with the value assumed as 0.9 ml of blood/g of tissue, S_t^0 is the fully relaxed equilibrium signal of tissue, T_{2l} is the T2 of the labeled magnetization, T_{2t} is the T2 of tissue, $g(T_{1a}, T_{1t}, \alpha, \tau, w, \delta)$ is a function containing the relaxation (blood T1 relaxation time T_{1a} and tissue T1 relaxation time T_{1t}), labeling (labeling duration τ , postlabeling delay w , labeling efficiency α) and transit time (the time δ that the labeled blood takes to travel from the labeling location to the ROI) related terms.

Perfusion can also be quantified using the sensitivity map (4)

$$f = \frac{\Delta S}{sen(x) \rho \lambda_a g(T_{1a}, T_{1t}, \alpha, \tau, w, \delta)} e^{\frac{T_E}{T_{2l}}} \quad [6]$$

where λ_a is the water density of blood, assumed to be 0.8533 g of water/ml of arterial blood (14). ρ is the tissue density, assumed to be 1.05 g of tissue/ml of tissue (14). The sensitivity map was provided by the uniform reference image.

$$sen(x) = \frac{S_U}{V_t} \quad [7]$$

where S_U is the uniform magnetization image signal. It is worth noting that the sensitivity map is an absolute sensitivity to pure water in unit of signal/(g of water/ml of tissue), not a relative number as commonly referred to in parallel imaging. The symbols used in the optimization and perfusion quantification are listed in Table 1.

METHODS

Two separate imaging protocols were performed. The first protocol was to measure the parameters required for the optimization: c , the cosine of the effective flip angle achieved with the inversion pulse, in Eq. [1] for the inversion pulse, and the T1 and T2 values of brain

tissues. The second protocol used the pulse timings calculated from the simulation to show the feasibility of sensitivity mapping using a uniform magnetization reference image and of using the sensitivity map to improve perfusion quantification on human subjects. All 10 subjects were recruited and studied following a human subjects protocol approved by the institutional review board and all gave written consent prior to participation. All volunteers were imaged on a 3 Tesla HDx (GE Healthcare, Waukesha WI) using an 8 channel head coil receive array and the body coil for transmission.

***In vivo* Measurement of Relaxation and Inversion Efficiency**

Four healthy volunteers were imaged with spin echo echo-planar imaging (EPI) using a 256×128 matrix on a 24-cm field of view and a 5-mm-thick axial slice through the superior part of the lateral ventricles.

To measure the inversion efficiency, two images were acquired with $TR = 3$ s, $TE = 20.7$ ms and 10 averages for each image. Two different preparations were applied for the two images. One preparation was simply a saturation 1.982 s before imaging. The second applied a saturation pulse at 2.0 s and an adiabatic inversion 18 ms before imaging. The timing of the two preparations was intended to measure the signal immediately before and 18 ms after the adiabatic inversion. These two images were used to assess the inversion efficiency of the adiabatic pulse. The saturation pulse consisted of three non-selective 10-ms duration, 12.5-kHz bandwidth quadratic phase saturation pulses, played 17-ms apart with gradient crushing of any transverse magnetization after each pulse. Perfect saturation was assumed for the saturation pulse. The inversion pulse was a spatially non-selective 10-ms duration, $\mu = 4.5$, $\beta = 1250\text{s}^{-1}$ hyperbolic secant (HS) pulse. These pulses are identical to saturation and inversion pulses used in the uniform magnetization preparation sequence.

The second part of the protocol was for relaxation measurement. This was required because of the wide range of T_1 and T_2 values of brain tissues at 3T reported in the literature (15–22). T_1 and T_2 values of gray matter were reported in the range of [1.0 s, 1.82 s] and [0.051 s, 0.11 s] respectively. T_1 and T_2 values of white matter were reported in the range of [0.73 s, 1.11 s] and [0.056, 0.081] respectively. Saturation recovery (SR) preparation was performed to measure the T_1 values with $TR = 13$ s and $TE = 20.7$ ms. The saturation pulse was applied at each of the following times: 26 ms, 250 ms, 500 ms, 750 ms, 1000 ms, 1500 ms, 2000 ms, 4000 ms, 6000 ms, 8000 ms, and 12000 ms before the image acquisition. For T_2 measurement, a spin-echo EPI sequence was used with $TR = 13$ s and TE 's of 123.3 ms (MinFull TE), 160 ms, 240 ms, 320 ms, 400 ms, 640 ms, 960 ms, 1280 ms, 1600 ms, and 2000 ms (max TE allowed).

Analysis of Relaxation and Inversion Efficiency—Regions of Interest (ROIs) for each subject were manually drawn in gray matter, white matter, and CSF on the saturation recovery image with the saturation pulse applied at 12000 ms. To minimize the effect of measured tissue properties on location in the image, we drew regions at four different locations (anterior, posterior, left and right of the image slice). The inversion efficiency of the inversion pulse, T_1 and T_2 values were calculated by averaging over four regions of interests (ROIs) for each anatomic region. The inversion efficiency is defined as the ratio of the signal after the inversion pulse to the signal immediately before the time of inversion pulse after compensating for T_1 relaxation during the time between the inversion pulse and the image acquisition. T_1 values were obtained (23) using a three-parameter nonlinear least square fitting routine to solve equation [8] for S_0 , T_1 and C_n :

$$S(T_{sat}) = \sqrt{(S_0 - S_0 \cdot e^{-(T_{sat}/T_1)})^2 + C_n^2} \quad [8]$$

where C_n is a noise related constant, T_{sat} is the saturation time, S_0 is calibration constant including the water density, the sensitivity of the coils, and the gain of the MR imager. T_2 values were determined (23) using a three-parameter nonlinear least square fitting routine to solve the equation [6] for S_0 , T_2 and C_n :

$$S(TE) = \sqrt{(S_0 \cdot e^{TE/T_2})^2 + C_n^2} \quad [9]$$

Optimization of Pulse Timings for the Uniform Magnetization Reference Image

The measured tissue relaxation values, except T_2 of white matter, were used to determine the relationship between T_1 , T_2 and WD. Optimizations for a number of different white matter T_2 values instead of fixing the measured value was performed due to the complexity of T_2 relaxation in white matter. Prior studies (24–26) have demonstrated that the T_2 decay of white matter is multiple-exponential due to the contribution from different water environments. For sequences with short or intermediate TE, the T_2 value of white matter may see more contribution from the short T_2 components than for the longer TE's used in our T_2 measurement. We calculated optimizations for a range of white matter T_2 's from 35ms to our measured, long TE, white matter T_2 value. The performance from the range of white matter T_2 values was evaluated in the in-vivo application. Because the ventricles were generally small in the chosen slice, quantification of T_1 and T_2 was not very accurate for CSF. Instead, T_1 and T_2 values of 4200 and 2000ms for CSF (27) were taken from the literature. Water densities of gray matter, 0.88 g/ml, and white matter, 0.73g/ml, were also taken from the literature (14) because no standard MR method for measuring water density in the presence of transmit and receive nonuniformity has been established. Water density of CSF was assumed to be 1g/ml.

The parameters α_1, ρ_1 , for the relationship between T_1 and WD were determined analytically from Eq. [2a] with the T_1 and WD values of gray matter, white matter and CSF. For each assumed white matter T_2 value, the unknown parameters A_2 , B_2 , and C_2 were then calculated by the least square fitting of Eq. [2b] based on T_2 and water density values of gray matter, white matter, and CSF.

Inversion efficiencies, $|c|$, of gray matter, white matter and CSF measured from the first protocol were fit to a linear relationship with their T_1 values. The linear function was incorporated in the optimization model shown as Eq. [3].

Optimal timing of the saturation and inversion pulses of the preparation was determined for each assumed T_2 of white matter by minimizing the deviations in magnetization from the target, V_t , over a range of T_1 from $T_{1\text{min}} = 0.6$ s to $T_{1\text{max}} = 4.2$ s. The deviation as a function of T_1 was estimated at 1ms intervals over the range. Optimizations were performed separately for magnetization target values, V_t , of 5%, 10% and 20% of the fully relaxed CSF equilibrium signal. Several different target magnetizations were explored. The three target magnetizations were chosen because the relative deviation from the target value over gray matter, white matter and CSF becomes larger with larger target magnetization. The trend can also be seen in Table 2 and Fig. 2. TE was specified as the minimum TE, 16.7 ms in the spin-echo EPI sequence used for acquisition. The maximum number of inversions, N , was set to 4. The timings for the saturation and inversion pulses were obtained by solving Eq. [3] with a nonlinear optimization procedure with constrained conditions implemented within the IDL programming and visualization environment (ITT Visual Information Solutions, Boulder CO). Several maximum preparation times ($T_{\text{prep}} = 3$ s to 10s in step of 1s) were tested to investigate the effects of the preparation time on the optimization. Because achieving excellent results for at least normal tissue was an important objective, we added additional

weight to the T1 values corresponding to normal GM, WM and CSF. Specifically, the weight function was defined as:

$$w(T1) = \begin{cases} 10^4 & T1 = T_{1GM}, T_{1WM}, T_{1CSF} \\ 1 & \text{else} \end{cases} \quad [10]$$

***In vivo* Measurements of Optimized Uniform Magnetization Images and Perfusion**

Six healthy subjects were studied to show the feasibility of creating a uniform magnetization image and the accuracy of perfusion quantification with the sensitivity map that the uniform magnetization image provides.

First, images prepared with different MIR pulse timings corresponding to different assumed white matter T2's, target magnetization levels and maximum preparation times were acquired with the EPI sequence (TR: 3.75 s; TE: 16.7 ms; matrix: 128 × 128; slice thickness: 5 mm; FOV: 24 cm). Pulse timings were evaluated for assumed T2's of white matter of 35, 40, 45, 50, 55, 60, 65 and 68 ms. Three target magnetization levels were tested in vivo: 5%, 10% and 20% of the fully relaxed CSF magnetization. The maximum preparation time, T_{prep} , was set to 3 s in order to reduce the sequence time. Because the relative deviation decreases with prep time but acquisition time increases with prep time, a trade-off must be made between these competing objectives that depends on the available imaging time and the targeted accuracy of quantification. A proton density weighted image was, also acquired with EPI, to help evaluate the accuracy of the sensitivity maps. The proton density weighted image used the same sequence acquisition parameters as the uniform magnetization prepared sequence, and the sequence used manual prescan in order to keep the same T/R gain as the uniform magnetization image.

Next, an acquisition of ASL perfusion images and a set of uniform magnetization reference images at matched spatial resolution were performed. The reference images were prepared with a particular set of pulse timings optimized for assumed T2 of white matter of 50 ms and signal level of 0.1. This T2 was chosen based on preliminary studies suggesting this assumed T2 produced nearly optimally uniform images with shorter TE's. The image acquisition was a spin-echo EPI with 64 × 64 matrix, 24 cm field of view and 5 mm slice thickness to match the ASL image resolution. The saturation and inversion times were optimized for the slightly different TE (15.6 ms) in the 64 × 64 resolution. The timings of saturation and inversion pulses were optimized to generate uniform magnetization for the first acquired slice. Subsequent slices in the multi-slice acquisition do not demonstrate uniform magnetization due to T1 relaxation. In order to acquire multi-slice uniform magnetization images, the sequence was repeated with a different slice acquisition order for each TR so that each slice occurs as the first slice in one of the TR's. In addition, multi-slice proton density weighted images (TR = 3.75 s) were acquired at the same resolution and slice thickness to serve as a conventional reference image for perfusion quantification.

ASL perfusion images were acquired (TR = 6 s, TE = 15.6 ms) in the same slices as the reference images using pulsed continuous arterial spin labeling (PCASL) (28). PCASL was performed with a train of repeated Hann window shaped RF pulses (pulse duration $\delta = 500$ us, average pulse amplitude $b1_{\text{ave}} = 17$ mG, repetition time of RF pulses $\Delta t = 1.5$ ms) and repeated gradients (maximum gradient $G_{\text{max}} = 0.9$ G/cm and average gradient $G_{\text{ave}} = 0.1$ G/cm). A postlabeling delay of 1.5 s was used to allow enough time for the labeled blood to arrive in the region of interest and a labeling duration of 1.5 s was used. Forty pairs of label and control images were acquired for signal averaging.

Analysis of Optimized Uniform Magnetization Images—Regions of interest (ROIs) were manually drawn on the high resolution, 128x128 matrix size, single-slice proton density weighted image. Three types of regions were drawn for each subject: gray matter, white matter, and CSF. Each region had an area of approximately 20–23 mm². The ROIs were drawn in adjacent regions to minimize signal variations due to coil sensitivity gradients. The average signal for each ROI was measured for all the 128 x128 images, acquired with the preparations optimized for three different target magnetizations, 0.05, 0.1, and 0.2, and for a range of assumed white matter T2 from 35 ms to 68 ms.

Analysis of Water Density—Water densities of gray matter, white matter, and CSF were calculated based on the above ROIs. The water density of each ROI was calculated for each prepared image as the ratio of the ROI signal in the proton density weighted image to the CSF water sensitivity of the prepared image after compensating for T2 decay during the echo time (TE):

$$WD_{ROI} = \frac{PD_{ROI}}{sen_{CSF}} \cdot e^{TE/T_2} \quad [11]$$

where PD_{ROI} is the ROI signal in the proton density weighted image, sen_{CSF} is the CSF water sensitivity of the prepared image. The CSF water sensitivity was defined as the CSF signal in the prepared image divided by the target magnetization:

$$sen_{CSF} = \frac{S_{CSF}}{V_t} \quad [12]$$

where S_{CSF} is the CSF signal in the prepared image.

Quantification of Perfusion—Perfusion was quantified from the ASL difference images using the standard approach and the uniform magnetization approach (Eq. [5] and Eq. [6]). The ASL signal difference was first calculated voxel-by-voxel by the subtraction of the label image from its corresponding control image. The signal difference was averaged after excluding the first two repetitions for which a steady state was not yet reached. g was chosen to be the same simple one-compartment model in both quantification approaches:

$$g(T_{1a}, T_{1t}, \alpha, \tau, w, \delta) = 2\alpha T_{1a} (e^{-w/T_{1a}} - e^{-(\tau+w)/T_{1a}}) \quad (13)$$

where T_{1a} is the T1 relaxation time of blood, T_{1t} is the T1 relaxation time of tissue, α is the labeling efficiency, τ is the labeling duration, w is the post-labeling delay, and δ is arterial transit time. Because g is an identical factor in both approaches, our conclusions should not be affected by the one-compartment assumption.

In both quantification approaches, we assumed T2 of the labeled signal was identical to the tissue T2, though this assumption may be suspect, especially at higher field strength (29).

The T2 assumption removes the $e^{\left(\frac{TE}{T_{2l}} - \frac{TE}{T_{2t}}\right)}$ term of Eq. [5] in the standard approach. With the assumption of identical T2 between labeled signal and tissue, the exponential term $e^{\frac{TE}{T_{2l}}}$ in Eq. [6] can be incorporated into the sensitivity map. If we optimize the preparation for uniform signal at a TE of 0, the appropriate T2 correction factor will already be present in the references image and perfusion quantification will not require a measure of T2. In this study, we did not optimize the preparation for a uniform signal at a TE of 0, because optimizing for the acquired TE creates an image that can be more readily assessed for uniformity.

To facilitate quantitative analysis of GM and WM, multi-slice proton density weighted images were segmented using SPM2 (Wellcome Department of Cognitive Neurology), resulting in probability maps of gray matter, CSF, and white matter. For quantification of GM and WM perfusion, masks were generated by including only those voxels with > 95% probability of being the corresponding tissue type. GM and WM masks were projected onto the ASL perfusion images to calculate the average GM and WM perfusion. The high threshold of 95% was used in order to minimize the partial volume error in the perfusion calculation.

Quantitative perfusion maps were also generated. The high threshold of 95% used for the tissue type masks would not cover the voxels with GM and WM partial volumes. To calculate whole brain perfusion map, a different threshold was used to segment GM and WM. The voxels with values greater than 50% in the gray matter probability map were considered to be GM with T2 value of 69 ms, while the voxels with values less than 50% were considered to be WM with T2 value of 50 ms. GM and WM perfusion maps were calculated separately from Eq. [6], and were added together to form the whole brain perfusion map. If the preparation were optimized to create a uniform magnetization at a TE of 0, no segmentation of GM and WM would be required for quantification of perfusion maps.

RESULTS

In vivo Measurement of Relaxation and Inversion Efficiency

Relaxation measurements were consistent across subjects. Averaged over four subjects, gray matter and white matter T1 values were (mean $\pm$ SD) 1515 ± 48 ms, and 957 ± 19 ms, and T2 values were 69 ± 7 ms and 68 ± 3 ms. Based on the measured T1 values, the model parameters α_1 and ρ_1 were 0.8131 and 395.9024 respectively by solving Eq. [2a] analytically, which yielded a smooth relationship between T1 and WD (Fig. 1a). Based on the measured T2 values, the model parameters A2, B2, and C2 determined by least squares fit of Eq. [2b] were 0.00007877, 0.0159, and 67.9981. The model from Eq. [2b] generated smoother curve between T2 and WD than a power law form (Fig. 1b). The optimization using the smoother function from Eq. [2b] gives optimized pulse timings where the simulated signal has no abrupt change near the T1 of CSF. The measured inversion efficiencies of gray matter, white matter and CSF, 0.91 ± 0.008 , 0.90 ± 0.001 , 0.97 ± 0.013 were fit well to a linear dependence ($R^2 = 0.9998$) on T1's:

$$c(T_1) = -\frac{0.0732}{(T_{1CSF} - T_{1WM})}(T_1 - T_{1WM}) - 0.8995 \quad (14)$$

Optimization of pulse timings for the Uniform Magnetization Reference Image

Numerical optimization of pulse timing successfully achieved uniform magnetization across the range of T1's examined. Figure 2 shows the signal dependence on T1 (Fig. 2a, $T_{prep}=3.0$ s and Fig. 2b $T_{prep}=10.0$ s) at the optimized pulse times for $T_{2WM} = 50$ ms and $V_t = 0.2$, 0.1 and 0.05. The longer preparation time gave more uniform signals across the T1 range. Because of the large weights for GM, WM and CSF (in Eq. [10]), the signal deviation from the target signal level at the T1s of gray matter, white matter and CSF was minimal. This is very important because signal deviation from the target signal level in the uniform reference image will bring the unnecessary tissue-dependent signal weighting and hence affect the accuracy of perfusion quantification. The relative deviation (Eq. [4]) over the targeted T1 range (0.6 s–4.2 s) and over T1s of normal brain (gray matter, white matter and CSF) are

listed in Table 2. The table of relative deviation indicates the smallest signal variation is expected for the pulse times optimized at the target signal level of 0.1 and 0.05.

***In vivo* Measurements of Optimized Reference Images and Perfusion**

***In vivo* Contrast and Its Dependence on Assumed White Matter T2—**

Representative in-vivo images obtained in one volunteer using preparations optimized for three different target magnetizations, 0.05, 0.1, and 0.2, and for a range of assumed white matter T2 from 35 ms to 68 ms are shown in Figure 3. Obvious gray, white matter and CSF contrast is observed with preparations optimized assuming small or large white matter T2 values, but preparations optimized assuming white matter T2 value in the middle of the range, approximately 50 ms, shows nearly equal signal for gray matter, white matter and CSF. The average signals on images prepared with the $T_{2WM} = 50$ ms optimized inversion timing measured within neighboring gray matter, white matter and CSF ROI's from six subjects were 1820 ± 187 , 1782 ± 146 , 1677 ± 129 for $V_t = 0.2$; 836 ± 73 , 829 ± 57 , 833 ± 61 for $V_t = 0.1$ and 410 ± 35 , 384 ± 25 , 417 ± 29 for $V_t = 0.05$. The coefficients of variation among three neighboring tissue types, standard deviation divided by the mean, were $5.34\% \pm 1.98\%$, $2.73\% \pm 1.15\%$, and $5.60\% \pm 2.51\%$ for target magnetizations of 0.2, 0.1 and 0.05. All target magnetizations reached good contrast matches. Paired t-tests of coefficients of variation with two tails were used to determine the differences between the target magnetizations. No significant contrast difference was found ($p=0.88$) between the target magnetization of 0.05 and target magnetization of 0.2. Target magnetization of 0.1 reached the best contrast match ($p=0.009$ compared to target magnetization of 0.2, and $p=0.08$ compared to target magnetization of 0.05) between gray matter, white matter and CSF with preparation optimized assuming T_{2WM} of 50 ms. It is not surprising to see that the contrast with the target magnetization of 0.1 shows the trend (marginal p value of 0.08) of better match than with the target magnetization of 0.05 although the optimization showed similar signal deviations (0.0075 and 0.0077) between them (see Table 2). The relative signal deviation with SNR consideration may explain the difference between the two target signal levels. The relative signal deviation with additional noise considered will be

$\sqrt{0.0075^2 + (\sigma_n/0.1)^2}$ and $\sqrt{0.0077^2 + (\sigma_n/0.05)^2}$ (where σ_n is the standard deviation of noise) at the target magnetization of 0.1 and 0.05. When the value σ_n is comparable with 0.05, the relative signal variation is dominated by the noise term, which makes the better contrast match at the target magnetization of 0.1.

With assumed T_{2WM} of 50 ms, the model parameters A_2 , B_2 , and C_2 in the relationship of T2 and WD (Eq. [2b]) were 0.05856, 0.02593, and 49.9414 respectively. With the assumed T_{2WM} of 50 ms and signal level of 0.1, the obtained optimized timings of saturation and inversion pulses were 3000 ms, 1806.508 ms, 762.788 ms, 125.512 ms, 52 ms respectively for the multi-slice uniform magnetization images.

Water Density Measurements—Water densities of each tissue type, calculated from the images prepared with T_{2WM} assumed to be 50 ms, were averaged over all six subjects for each targeted signal level. The average water densities were listed at different target signal levels for gray matter, white matter and CSF respectively (Table 3). The measured CSF water density was 96%, slightly below the expected value 100%. This underestimation of CSF water density was likely caused by the inclusion of small amounts of tissue signal in the manually drawn CSF region. With a smaller ROI, the CSF water densities were closer to 100%.

Quantification of Perfusion—The multi-slice uniform magnetization images acquired to match the perfusion slices show very good uniformity between gray matter, white matter,

and CSF (Figure 4a), consistent with the results above. Proton density weighted images and perfusion difference images show the expected contrast between tissue types (Figure 4b and 4c).

The perfusion images quantified with the uniform magnetization images are compared to those quantified with proton density images and an assumed uniform partition coefficient, in Figure 5a and Figure 5b. A difference image (Figure 5c), generated by subtracting the perfusion images quantified with the proton density images from those quantified with uniform magnetization images, shows higher gray matter perfusion signal and slightly lower white matter perfusion signal. The perfusion values of gray matter and white matter averaged over six subjects for the two different quantification approaches, listed in Table 4, also showed higher gray matter perfusion and lower white matter perfusion in the images quantified with the uniform magnetization approach. The perfusion contrast ratio between gray matter and white matter can be quantified from Table 4. The perfusion contrast ratio increased from 3.99 (quantified with proton density images) to 4.73 (quantified with the uniform magnetization images). For the perfusion values quantified using proton density images, a uniform whole brain partition coefficient $\lambda=0.9$ ml of blood/g of tissue was assumed. However, the partition coefficient differs between gray and white matter: $\lambda_g=0.98$ ml/g and $\lambda_w=0.82$ ml/g (14). The two different gray and white matter partition coefficients were then used to separately quantify the gray and white matter perfusion values, by multiplying the gray matter perfusion value by λ_g/λ , and multiplying the white matter perfusion by λ_w/λ . The perfusion values with different partition coefficients are also shown in Table 4 for comparison. The gray and white matter perfusion values quantified with the uniform magnetization approach showed statistically significant difference ($p=0.003$ for gray matter, and $p<0.0001$ for white matter) with the perfusion values quantified with the proton density images and a uniform whole brain partition coefficient, but good agreement ($p=0.23$ for gray matter, and $p=0.07$ for white matter) with the perfusion values quantified with the proton density images but using different gray and white matter partition coefficient. The agreement between the quantification results when appropriate partition coefficients are assumed supports the accuracy of the uniform magnetization quantification approach. Moreover, the uniform magnetization quantification approach provides a pixel-by-pixel perfusion map without the need for measuring the partition coefficient map and proton density images.

DISCUSSION

These results support the accuracy and feasibility of the uniform magnetization quantification approach. By producing a uniform magnetization with B1 and B0 insensitive RF pulses, one can obtain a sensitivity map that can be used to quantify perfusion maps without assumptions about the spatial distribution of the partition coefficient.

Previously an approach to achieve a minimum contrast image using a saturation recovery sequence and optimizing TR and TE to minimize contrast was reported (6). This approach can achieve a good contrast match for the chosen tissues, but the deviation from uniformity for tissues with T1's between the selected ones is quite large. The relative deviations (Dev) over GM, WM, and CSF were 0.0365, 0.0435, 0.0590, and 0.0781, while Dev over the T1 range (0.6 s – 4.2 s) were 0.1947, 0.2028, 0.1981, and 0.1843 for target magnetization of 0.07, 0.1, 0.2 and 0.37 (Fig. 6). The minimum Dev over GM, WM and CSF was 0.0365 ($V_t = 0.07$) with the optimal TR and TE approach, which is 4.8 times larger than Dev (0.0075 at the target magnetization of 0.1, see Table 2) with our uniform magnetization approach. With the target magnetization of $V_t=0.37$ (TR=2000 ms, TE= 33ms), a similar magnetization level to that used in the approach with optimal TR and TE, Dev is 0.0781, even 10 times larger than that obtained with our approach. Dev over the T1 range (0.6 s – 4.2 s) is around

0.19 at all the magnetization levels, which is much larger than Dev of 0.0510 with our uniform magnetization approach. Therefore, Our approach is more robust to the variations of tissue properties (T1, T2, WD), both the variations within normal tissue types and the variations between normal and pathological tissues.

It is possible that the absolute signal level of the uniform magnetization image is more vulnerable to sources of error than the uniformity of the image. Acquiring an additional proton density image to verify the signal intensity of CSF, as in Chalela et al. (4) can be used as an additional check on this concern. The effect of the uniform magnetization image on the signal-to-noise ratio of the perfusion measurement must be also considered. Though the uniform magnetization image typically has a much larger signal than the ASL difference image, the noise of the reference image may have a significant effect on quantitative perfusion noise if the ASL difference images are averaged for a much longer time and the target magnetization of the uniform magnetization image is low. The addition of smoothing in the reference image might help further alleviate this concern, however care must be taken to use an edge preserving smoothing filter, to avoid errors near the edge of the brain, and to avoid smoothing kernels comparable in size to the brain or the spacing of any array coils.

While we have emphasized the quantification of perfusion, this technique for measuring the absolute sensitivity of the MRI scanner to water has numerous other potential applications. One such application is the quantification of tissue water density. Water content can be an important indicator of tissue injury and a measure of response to treatment for edema (30). Sensitivity maps could also be used to remove coil dependent sensitivity variation from MRI images and may help improve parallel imaging by providing sensitivity maps relatively free from underlying tissue anatomy and contrast.

Assumed values of T1, T2 and WD of GM, WM, and CSF were used to determine the relationship between WD, T2 and T1. The optimization calculates the optimized parameters (t_{sat} , t_1 , t_2 , t_3 and t_4) using the relationship. The success of the optimization does rely on the relationship between WD, T2, and T1 but not on the particular value of T1 as long as the relationship between parameters is fairly accurate. For applications such as aging and typical pathology, T1 may well be longer, but T2 and WD are also expected to increase, the deviations from the relationship can be expected to be small (31–34). Though our in-vivo evaluation was limited to normal healthy brain tissue, our optimization was constructed to achieve uniformity across a range of tissue T1's so uniform magnetization could be achieved in aging and pathology.

It is likely that deviations from the idealized relationship between WD, T2 and T1 will lead to some deviations from uniformity. Most likely, pathology with abnormal relationship between relaxation rates and WD, such as hemorrhage or melanoma (35), will be the greatest challenge. Evaluation of our strategy in clinical applications remains an important next step. It is important to remember, however, that the standard assumption of a uniform partition coefficient will likely be even more in error for pathology. The sensitivity to the inversion efficiency of the pulses is not particularly strong, depends primarily on T2 of tissue, and should be expected to be similar for different adiabatic pulses and different scanners. T1 and T2 values are tissue properties that depend on the field strength of the MR scanner, so the relationship between relaxation rates and WD needs to be recalculated and the timing of the inversion pulses will have to be re-optimized for different field strengths.

Although the acquisition that we used to acquire the uniform magnetization image is 2D multi-slice EPI sequence, it may be more efficient to acquire the images with 3D acquisition due to the requirement of only one preparation. Future studies combining 3D acquisition with the uniform magnetization approach are planned.

An important remaining uncertainty in quantification of perfusion is related to the T2's of tissue and the ASL signal. Ideally, imaging would be performed with a very short TE, such that T2 should not be a factor. In practice, TE's are large enough that T2 decay must be considered in quantification of perfusion. The standard division by a fully relaxed reference image and assumed partition coefficient quantification method assumes that the T2 decay rate of the ASL signal is the same as tissue. With the uniform magnetization image quantification, there is more flexibility. If we assume the T2 of the ASL signal is unrelated to the tissue T2, then we use a preparation optimized to create a uniform magnetization at the echo time. The decay rate of the ASL signal must be separately estimated and corrected for. If we assume the T2 of tissue and the ASL signal is the same, then it is preferable to optimize the preparation for uniform signal at a TE of 0. Then the effect of tissue T2 decay will be present in the reference image and the quantification will properly correct for this decay.

CONCLUSION

Our results support the feasibility and benefits of ASL perfusion quantification with a sensitivity map based on a uniform magnetization image. Incorporation of this technique does not require much additional imaging and can reduce the errors associated with the use of assumed partition coefficients. Use of this quantification approach should help to improve the increasingly accurate measures of perfusion provided by arterial spin labeling.

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Figure 1.

(a) T1 relaxation time modeled (Eq. [2a]) as a function of water density using the values for T1 in gray matter, 1515 ms, and white matter, 957 ms, measured experimentally; (b) T2 relaxation time modeled as a function of water density using the values for T2 in gray matter, 69 ms, and white matter, 68 ms, measured experimentally. Modeling using Eq. [2b] (dashed line) is smoother than the curve obtained with the power law form (similar to Eq. [2a], solid line). Circles indicate white matter, gray matter and CSF T2 values. The optimization using the smoother function Eq. [2b] gives the preparation at the optimized pulse timings where the simulated signal has no abrupt change near T1 of CSF

Figure 2.

The simulated signal using the optimized inversion times as a function of T1 for T2WM = 50 ms and V_t=0.2, 0.1 and 0.05 (shown as colored lines) at (a) T_{prep} = 3 s; and (b) T_{prep} = 10 s. T1_{min} and T1_{max} used in the optimization were 600 ms and 4200 ms. The simulated signals from gray, white and CSF are also shown.

Figure 3. Typical example of images acquired in a volunteer showing the influence of optimized pulse times with different target signal levels (0.2, 0.1 and 0.05) and different assumed white matter T2.

Figure 4. Representative EPI images with (a) uniform magnetization using the pulse times optimized for $T2WM=50$ ms and $Vt=0.1$, (b) proton density contrast and (c) perfusion difference contrast.

Figure 5. Perfusion images quantified with (a) the conventional method, (b) the uniform magnetization image method; (c) difference images between (b) and (a), the image was multiplied by 10 for better visibility.

Figure 6.

Simulated signal obtained using the optimal TR and TE to achieve a minimum contrast image reported by Wang et al. Though it is possible to achieve fairly similar signal for GM, WM and CSF, large deviations from this signal occur for tissues with other T1's, especially those with T1's longer than GM as can occur in pathology.

Table 1

Symbols used in the optimization and perfusion quantification

Symbol	Description	Unit
t_{sat}	Saturation time	s
$t_1, \dots, t_n$	Inversion times	s
WD	Water density	g/ml
$ c $	Effective of inversion	
V_t	Target magnetization	
α_1, ρ_1	Parameters in the relationship of T1 and WD	
A_2, B_2, C_2	Parameters in the relationship of T2 and WD	
$WD_{\text{GM}}, WD_{\text{WM}}, WD_{\text{CSF}}$	Water density of gray matter, white matter, and CSF	g/ml
$T_{1\text{GM}}, T_{1\text{WM}}, T_{1\text{CSF}}$	T1 of gray matter, white matter, and CSF	s
$T_{2\text{GM}}, T_{2\text{WM}}, T_{2\text{CSF}}$	T2 of gray matter, white matter, and CSF	s
$w(T1)$	Weight as a function of T1	
Dev	Relative deviation from the target magnetization	
λ	Tissue-blood partition coefficient	ml/g
λ_g, λ_w	Gray matter, and white matter partition coefficient	ml/g
ΔM	Perfusion difference signal	
M_t^0	Fully relaxed tissue magnetization	
T_{1t}	T1 of tissue	s
T_{1a}	T1 of arterial blood	s
T_{2l}	T2 of labeled magnetization	s
T_{2t}	T2 of tissue	s
λ_a	Water density of blood	g/ml
ρ	Tissue density	g/ml
S_U	Signal of uniform magnetization image	
f	Perfusion rate	ml/g.s
α	Labeling efficiency	
τ	Labeling duration	s
δ	Arterial transit time	s
$\text{sen}(x), \text{sen}_{\text{CSF}}$	Water sensitivity map, CSF water sensitivity	

Table 2

the average deviation from the targeted signal for the optimized T1 range and T1s of brain regions (GM, WM, and CSF).

relative deviation (Dev)	T _{prep} = 3 s			T _{prep} = 10 s		
	0.2	0.1	0.05	0.2	0.1	0.05
Signal Level V _i						
T1s from 0.6s to 4.2s	0.0554	0.0510	0.0826	0.0309	0.0242	0.0399
T1s of GM, WM and CSF	0.0156	0.0075	0.0077	0.0035	0.0018	0.0028

Table 3

Measured water densities of gray matter, white matter, and CSF at different target signal levels V_t .

Measured water density (g/ml)	Gray matter	White matter	CSF
$V_t = 0.2$	0.88 ± 0.03	0.76 ± 0.05	0.96 ± 0.05
$V_t = 0.1$	0.89 ± 0.01	0.77 ± 0.03	0.96 ± 0.05
$V_t = 0.05$	0.89 ± 0.05	0.77 ± 0.05	0.96 ± 0.05

Table 4

Perfusion values of gray and white matter quantified using different methods.

Perfusion (ml/100g.min)	Gray matter	White matter
quantified with WD and λ	75.83 ± 11.39	18.99 ± 4.55
quantified with WD, λ_g and λ_w	82.57 ± 12.48	17.30 ± 4.15
quantified with uniform images	83.51 ± 13.11	17.64 ± 4.38