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Magnetization transfer using inversion recovery during off-resonance irradiation

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Abstract

Estimation of magnetization transfer (MT) parameters *in vivo* can be compromised by an inability to drive the magnetization to a steady state using allowable levels of radiofrequency (RF) irradiation, due to safety concerns (tissue heating and specific absorption rate (SAR)). Rather than increasing the RF duration or amplitude, here we propose to circumvent the SAR limitation by sampling the formation of the steady state in separate measurements made with the magnetization initially along the $-z$ and $+z$ axis of the laboratory frame, i.e. with or without an on-resonance inversion pulse prior to the off-resonance irradiation. Results from human brain imaging demonstrate that this choice provides a tremendous benefit in the fitting procedure used to estimate MT parameters. The resulting parametric maps are characterized by notably increased tissue specificity as compared to those obtained with the standard MT acquisition in which magnetization is initially along the $+z$ axis only.

Keywords

exchange; solid pool; brain imaging; parametric mapping

INTRODUCTION

The exchange of bulk water protons with the protons contained in the macromolecules generates the so-called magnetization transfer (MT) effect when the “solid” pool is saturated by placing a continuous-wave (CW) radiofrequency (RF) pulse several kHz off resonance from water [1]. By progressively incrementing the duration of the off-resonance pulse, the T_1 of water in the presence of saturation (T_{1sat}) and the steady-state (SS) magnetization (M_{ss}) can be estimated. In addition, the forward exchange rate from the solid to the free pool, k_f , can be calculated as $(1-M_{ss}/M_0)/T_{1sat}$. This expression for k_f is valid when complete saturation of the solid pool is achieved, and in the absence of off-resonance

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artifacts. Attempts to provide a quantitative description of the MT effect in the case of incomplete saturation and in the presence of off-resonance artifacts led to the introduction of an analytical description of the two-pool model (for review, see [2]), whereas more extended and realistic models can even involve more than two pools of exchanging spins [3,4].

The MT effect is an attractive MR imaging modality for clinical applications, because the interaction of bulk water protons with the protons contained in the macromolecules can ultimately provide information about tissue integrity. However, the detection of the MT effect in clinical practice is usually limited to the measurement of a qualitative MT ratio (MTR), which is the result of the combination of several fundamental quantities, and is dependent on the acquisition parameters [5]. Likely due to this limitation, controversial results about MTR differences have been reported in literature, for instance in the brains of schizophrenic patients as compared to control subjects [6–9]. In multiple sclerosis, weak correlations of MTR with disability parameters have also been found [10]. On the other hand, the acquisition and processing MT protocols for obtaining quantitative MT parametric maps, which are based on the two-site exchange model [11], are generally not straightforward in clinical MRI practice, and provide parametric maps with limited tissue contrast and specificity.

The basic source of instability in the fitting procedure of T_{1sat} and M_{ss} originates from the impossibility of using MT pulses that are long enough to achieve the steady state, due to safety limitations imposed by the specific absorption rate (SAR) of RF power deposition. To circumvent this limitation, here we suggest a novel protocol for the acquisition of MT *in vivo*. The method is easy to implement, as it relies on classical CW MT measurements, with the difference that two consecutive sets of measurements are acquired with the magnetization initially along the $-z$ or $+z$ axis, i.e. with or without an on-resonance inversion prior to the off-resonance irradiation (Fig. 1). Whereas the usage of inversion recovery approaches have been suggested to measure MT effects ([12,13] and reference therein), the implementation of an on-resonance inversion pulse prior to the off-resonance irradiation has not been exploited so far. *In vivo* results from the human brain are reported to demonstrate the efficacy of the proposed approach.

METHODS

Five healthy subjects (35 average years old) were investigated on a 90-cm-bore 4 T magnet (OMT, Inc., Oxon, UK) with Varian UNITY^{INOVA} console (Varian Inc., Palo Alto, CA). A TEM volume coil [14] was used for signal transmission and reception from the human brain. Images were acquired using fast spin-echo readout, $TR=9-10$ s (depending on the coil loading), number of echoes = 16, $TE=0.073$ s, matrix 256×256 , $FOV=25.6 \times 25.6$ cm² and slice thickness=4 mm. The MT experiment used a 6 kHz off-resonance CW-pulse with incremental duration (0.0, 0.3, 0.6, 0.9, 1.2 s) and $\omega_1^{max}/(2\pi) = 0.15$ kHz, applied prior to the imaging readout. Separate measurements were performed with the magnetization initially along the $+z$ or $-z$ axis, i.e. without or with initial global inversion achieved by an adiabatic full passage pulse of the hyperbolic secant family (pulse length = 6ms, $\omega_1^{max}/(2\pi) = 1.2$ kHz, bandwidth ~ 3.3 kHz). With this choice of parameters, the duration of the MT protocol was ~ 25 min. First order shim terms were manually adjusted using the global, unlocalized water signal, typically reaching a water line-width $\sim 20-30$ Hz. Data were collected from an axial (transverse) section at the level of the corpus callosum, for optimal visualization of grey and white matter structures. The RF power delivered to the coil was limited to a safe operating range using the hardware monitoring module of the Varian console. In addition, the RF power output over the full range of settings used in these experiments was measured with an oscilloscope connected to the coil port. From these measured values, the average RF power delivered to the coil was computed by integration of

all RF pulses in the sequence, and SAR was estimated assuming a tissue load of 3 kg in the volume coil. When using the longest pulse, the estimated SAR was always below the Food and Drug Administration limit of 3 W/kg averaged over the head for 10 min (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072686.htm>).

Estimation of MT parameters

The parameters T_{1sat} and M_{ss} were calculated on a pixel-by-pixel basis from the time-course of signal intensity (SI) using a non-linear regression algorithm with the following functions:

$$SI(t) = M_0 e^{-t/T_{1sat}} + M_{ss} (1 - e^{-t/T_{1sat}}) \quad (1)$$

$$SI(t) = -M_0 e^{-t/T_{1sat}} + M_{ss} (1 - e^{-t/T_{1sat}}) \quad (2)$$

where M_0 is the fully relaxed magnetization in the absence of RF, and t is duration of the CW pulse. Eq. (1) and Eq. (2) apply when magnetization is first placed in the positive or negative hemispheres of the laboratory frame, respectively. Note that the *in vivo* system is generally characterized by multiple pools of protons (for instance, characterizing white and grey matter), which could invalidate the simple description based on mono-exponential functions provided by Eqs. 1 and 2. However, the mono-exponential approximation seems a reasonable choice for parametric maps which are generated on a pixel-by-pixel basis. In addition, the presence of the on-resonance inversion pulse prior to the CW irradiation might slightly modify the conditions of saturation of the solid pool as compared to the case of Eq. 1, especially at short saturation times. Whenever the effect of the inversion pulse is inconsequential as compared to the effect of the subsequent off-resonance irradiation for saturating the solid pool, there is no conceptual difference between Eq. 1 and 2. In this case, the magnetization of the observed free water pool either decays or recovers in presence of the off-resonance irradiation to the same steady state value, with same relaxation time T_{1sat} .

Here, we compared the robustness of the parametric maps (T_{1sat} and M_{ss}/M_0) obtained a) when fitting Eq. (1) only to the data acquired from the positive hemisphere (standard approach), or b) when fitting Eq. (2) only to the data acquired from the negative hemisphere, or c) when fitting Eq. (1) and Eq. (2) simultaneously to the data acquired from both positive and negative hemispheres (i.e., our approach). The fitting routines were developed with Matlab 7.2 (The Mathworks, Inc). Robustness of the parametric maps were evaluated by estimating the coefficient of variations of T_{1sat} and M_{ss}/M_0 in regions of interest (ROIs) placed in the white matter (WM) and grey matter (GM) within the same subject, along with the mean and standard deviations among different subjects.

RESULTS and DISCUSSION

As shown in Fig. 2, the SI of the water tends to approach a SS value (M_{ss}) in the presence of off-resonance CW irradiation. Notably, the time constant which characterizes how fast the SS is reached (i.e., T_{1sat}), along with the value of the SS itself, does not appear to depend on the initial orientation of magnetization ($\mathbf{M}$), i.e. whether $\mathbf{M}$ is initially aligned along $+z$ or $-z$ (Fig. 2 and Table 1). This finding inherently confirms that, under the experimental conditions used, the presence of the on-resonance inversion pulse can be neglected as compared to the subsequent CW irradiation in terms of saturating the solid pool. Notably, by

using Bloch simulations, it can be demonstrated that the magnetization of spins with $T_2 \sim 10 \mu\text{s}$ and $T_1 = 1 \text{ s}$ (general assumptions for macromolecular relaxation parameters [12]) is already zero at the end of the inversion pulse used in this study. This means that the duration of the inversion pulse should be added to the total duration of the saturation time of the solid pool in Eq. 2. On the other hand, a CW irradiation with $\omega_1^{\text{max}}/(2\pi) = 0.15 \text{ kHz}$ needs to be longer than only $\sim 15 \text{ ms}$ to completely saturate the macromolecular spins. Since the minimum CW irradiation time used in this study (300ms) was much longer than 15ms, and was also much longer than the duration of the inversion pulse (6 ms), the complete saturation of the macromolecular pool was always achieved, while the presence of the initial on-resonance inversion could be neglected in subsequent calculations. The fitting results also confirm that Eqs. 1 and 2, which utilize mono-exponential rather than multi-exponential functions, are a reasonable representation of the observed SI time evolution. Overall, the same $T_{1\text{sat}}$ satisfactorily describes both the decay and recovery to the same steady state value of magnetization, while the resulting fitted curves well describe the time-course of the SI at all investigated saturation times.

Extracting $T_{1\text{sat}}$ and M_{ss} from the experimental data implies the solution of 3-parameter fitting based on Eq. (1) and/or Eq. (2). Due to SAR limitations in humans, the most problematic parameter to fit is M_{ss} , as impractical CW irradiations on the order of a few seconds are in principle required to reliably determine the value of M_{ss} . In addition, the presence of a SS value different from the noise level has a detrimental effect on $T_{1\text{sat}}$ fitting, since it reduces the dynamic range of the SI decay. As a result of these limitations, when sampling SI with a standard MT acquisition with incremental CW irradiation up to 1.2 s, both $T_{1\text{sat}}$ and M_{ss}/M_0 parametric maps are of poor quality and are characterized by the presence of many “holes” (Fig. 2, first row). The quality of the parametric maps drastically improves when fitting the data with the inversion pulse prior to the CW irradiation (Fig. 2, second row). This improvement occurs despite of the fact that the number of data points was the same as in the “standard” acquisition. The reason for this improvement is the ~ 3 -fold increase of the dynamic range of the SI variations. Indeed, whereas in the previous case magnetization decays from M_0 to $M_{\text{ss}} \sim 0.5 M_0$ (i.e. 50% dynamic range), in the present case M_0 recovers from $-M_0$ to $M_{\text{ss}} \sim 0.5 M_0$ (i.e., 150% dynamic range), thus largely facilitating the fitting of $T_{1\text{sat}}$ and M_{ss} . The choice of using the complete data set acquired from both positive and negative hemispheres brings about a further tremendous benefit in terms of reliability of the fitting of $T_{1\text{sat}}$ and M_{ss}/M_0 (Fig. 2, third row), resulting in parametric maps with notably increased tissue specificity as compared to the classical MT acquisition performed from the positive hemisphere only. Note that part of this additional improvement originates from doubling the number of data points. Accordingly, the coefficient of variations of $T_{1\text{sat}}$ and M_{ss}/M_0 calculated from regions of WM and GM are several folds smaller whenever global inversion is applied prior to the CW irradiation (Table 1). The standard deviations of the parameters within different subjects substantially decreases as well, thus leading to a possibility of increased statistical power for those studies which are designed to compare different conditions and/or populations of subjects. Finally, the MTR maps obtained with or without the initial inversion pulse are both affected by the same $T_{1\text{sat}}$ s, but the inversion-recovery-like-acquisition inherently enhances the $T_{1\text{sat}}$ -weighting, which results in increased WM/GM contrast (Fig. 3).

When the magnetization exchange rate is calculated as $k_f = (1 - M_{\text{ss}}/M_0)/T_{1\text{sat}}$, the obtained values are in the range of 1 s^{-1} (Fig. 4). These results are in agreement with previously published estimates of k_f [15], despite the limitations that are intrinsic in the simplified model of exchange phenomena underlying such calculation. In this context, the quantitative estimate of k_f needs to be appreciated as an average magnetization exchange rate, rather than in terms of an accurate estimate of the forward exchange rate from one specific pool of protons to another.

In order to further increase the reliability of the parametric mapping, other independent acquisitions can in principle be performed with any initial orientation of the magnetization. The significant limitation of this approach, however, is the long acquisition time. Therefore, the details of the acquisition protocol needs to be fine-tuned to the time limitations of the specific study of interest. Whereas we have shown that optimal parametric maps were obtained with a full data set of images acquired consecutively from the positive and negative hemisphere, reasonable compromises can be reached using subsets of data (for instance, the data from the negative hemisphere only, Fig. 2). Also, whereas the present study was performed by using CW off-resonance irradiation, any train of saturation pulses can be equally employed. Finally, sampling the SS formation from the negative hemisphere is anticipated to provide similar benefits to experiments based on chemical exchange saturation transfer (CEST), as these methodologies are conceptually similar to the MT approach.

In conclusion, we have demonstrated that the formation of the SS in MT experiments in vivo can be reliably sampled by changing the initial orientation of magnetization, rather than increasing the duration of the off-resonance irradiation, and thus can circumvent SAR limitations.

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Abbreviations used in the text

CW	continuous-wave
RF	radiofrequency
GM	grey matter
MT	magnetization transfer
MTR	magnetization transfer ratio
ROI	region of interest
SAR	specific absorption rate
SI	signal intensity
T_p	pulse duration
WM	white matter

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Figure 1.

Pulse sequence for the described MT protocol. The frequency of the MT pulse is 6 kHz off-resonance, and the peak amplitude ($\gamma B_1/2\pi$) is 150 Hz for human studies. The dashed squares indicate incremental durations of the MT pulse, which is applied immediately prior to the excitation pulse of the imaging module. The MT measurement is performed twice, with and without an on-resonance inversion pulse prior to the off-resonance irradiation, with no time delay. The time between the inversion pulse and the excitation pulse of the imaging module is determined by the duration of the MT pulse, thus leading to inversion recovery that occurs entirely in presence of the off-resonance irradiation. In this study, the imaging module consisted of a fast SE readout with 90° excitation, while the MT pulse consisted of CW irradiation. However, other types of imaging readout are possible, as well as other pulsed approaches can be implemented instead of CW irradiation to achieve the off-resonance saturation.

Figure 2.

Parametric maps of T_{1sat} and M_{ss}/M_0 obtained with three different protocols from one representative subject. First row: results obtained when using only the data set with $\mathbf{M}$ initially along $+z$; second row: results obtained when using only the data set with $\mathbf{M}$ initially along $-z$; third row: results obtained when using the full data set with $\mathbf{M}$ initially along $+z$ and then along $-z$. The plots on the left show a representative example of the time course of the measured SI from a voxel located in the white matter (circles) as a function of the duration of the CW pulse; the solid lines indicate the results of the fitting with Eqs. (1–2).

Figure 3.

Representative maps of MTR obtained as MCW/M_0 , where MCW is magnetization in correspondence of a CW-pulse duration of 600 ms, when M is initially along +z (left) or -z (right). The MTRs calculated from two ROIs placed in the WM and GM are (0.65 ± 0.02) and (0.76 ± 0.02) , respectively, when M is initially along +z, whereas they are (0.07 ± 0.003) and (0.23 ± 0.02) when M is initially along -z, (average $\pm$ s.d., $n=5$).

Figure 4.

Map of the magnetization exchange rate k_f , calculated as $(1-M_{ss}/M_0)/T_{1sat}$, obtained from the same subject shown in Fig. 2. The estimated parameters M_{ss}/M_0 and T_{1sat} used for the calculation are those obtained from fitting the full data set, with $\mathbf{M}$ initially along $+z$ and then along $-z$.

TABLE 1

ROI-based analysis of parametric maps obtained when using the data set with M initially in the positive hemisphere (method “+z”), or in the negative hemisphere (method “-z”), or both positive and negative hemispheres (method “+z & -z”), n=5.

White Matter				
Parameter	Method	Mean	SD	Average intra-ROI coefficient of variation
T_{1sat} (s)	+z	0.75	0.12	28%
	-z	0.55	0.02	7%
	+z & -z	0.58	0.01	4%
M_{ss}/M_0	+z	0.40	0.03	17%
	-z	0.44	0.03	10%
	+z & -z	0.47	0.02	3%
Grey Matter				
Parameter	Method	Mean	SD	Average intra-ROI coefficient of variation
T_{1sat} (s)	+z	1.20	0.41	53%
	-z	0.77	0.06	17%
	+z & -z	0.92	0.08	11%
M_{ss}/M_0	+z	0.40	0.07	46%
	-z	0.39	0.10	34%
	+z & -z	0.53	0.02	6%