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Concurrent saturation transfer contrast in *in vivo* brain by a uniform magnetization transfer MRI

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Abstract

The development of chemical exchange saturation transfer (CEST) and magnetization transfer (MT) contrast in MRI have enabled the enhanced detection of metabolites and biomarkers *in vivo*. In brain MRI, the separation between CEST and MT contrast has been particularly difficult due to overlaps in the frequency responses of the contrast mechanisms. We demonstrate here that MT and CEST contrast can be separated in the brain by the so-called uniform-MT (uMT) technique, thus opening the door to addressing long-standing ambiguities in this field. These methods could be useful for keeping track of important endogenous metabolites and for providing an improved understanding of neurological and neurodegenerative disorders. Examples are shown from white and gray matter regions in healthy volunteers and patients with multiple sclerosis, which demonstrated that the MT effects in the brain were asymmetric and that the uMT method could make them uniform.

Keywords

MRI; chemical exchange saturation transfer; magnetization transfer; multiple sclerosis

Introduction

Magnetic resonance imaging (MRI) offers a number of contrast mechanisms to noninvasively visualize the anatomical structures, physiological conditions, and functional activities of the human body. Saturation transfer (ST) provides a family of powerful and flexible contrast mechanisms, including magnetization transfer (MT) (Henkelman et al., 2001) and chemical exchange saturation transfer (CEST) (van Zijl and Yadav, 1022; Liu et al., 2013; Vinogradov et al., 2013; Kogan et al., 2013), to probe biomarkers, physiologically active molecules, and macromolecules in tissues and organs. Since the ST family shares a

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common practical procedure, in which off-resonance pre-saturation irradiation modulates the MRI signal (Vinogradov et al., 2013), those contrast mechanisms often interfere with one another, while their differentiation is highly important. For example, CEST contrast is usually produced when the pre-saturation irradiation is applied around a specific frequency offset, while MT contrast can be achieved over a broader range of frequency offsets. MT is also known to exhibit asymmetries with respect to the water resonance, which often prevents a conventional symmetry analysis from disentangling it from CEST contrast. Recently, it has been demonstrated that certain MT effects can be made uniform and that it is possible to separate such MT effects from the estimation of CEST effects (Lee et al., 2012; Lee et al., 2013). This so-called uniform-MT (uMT) strategy is based on the finding that the uniform and efficient saturation of a strongly coupled proton spin pool can be achieved, regardless of the frequency offsets of the off-resonance pre-saturation irradiation, by irradiating the pool simultaneously at more than one frequency position (Lee et al., 2011).

In the brain, it has been well known that white matter and gray matter provide considerable MT effects (van Zijl and Yadav, 2011; Henkelman et al., 1993; Stanisz et al., 2005), and MT contrast has become a routine technique, especially for the characterization of white matter diseases, such as multiple sclerosis (MS) (Grossman et al., 1994; Ge, 2006; Filippi and Mocca, 2007; Ceccarelli et al., 2012). Recently, several endogenous CEST contrast mechanisms have been established in the brain, which can be useful for detecting metabolites such as myo-inositol (Haris et al., 2011), creatine (Kogan et al., 2013), and glutamate (Cai et al., 2012), and accessing pH values through the so-called amide proton transfer (APT) mechanism (Zhou et al., 2003). Such methods have the potential for diagnosing and monitoring neurological and psychiatric disorders. On the other hand, there have so far been no conclusive studies that could quantify the interferences between the MT and CEST contrast mechanisms, although considerable uncertainties have frequently been reported in CEST measurements, including ‘negative’ CEST (Vinogradov et al., 2013; Zhou et al., 2003). Here, we also show that several CEST contrast mechanisms in the brain may be buried under the MT effects from white matter and gray matter and that the uMT technique can reveal those intrinsic CEST effects from the background MT effects.

Methods

Uniform-MT method

Recently, it has been demonstrated that certain proton systems can be completely saturated, regardless of the frequency positions of the saturating RF irradiation, when such systems are irradiated simultaneously at more than one frequency position (Lee et al., 2011). If this complete saturation can be attained within a time scale much shorter than the time scale of the MT phenomena, the induced MT effects do not depend much on the frequency positions of the pre-saturating RF irradiation. This method is called uMT (Lee et al., 2013). Based on this uMT technique, a scheme to isolate genuine CEST effects from asymmetric MT effects has been devised by using the pre-saturating RF irradiation with two frequency components (Lee et al., 2012; Lee et al., 2013): First, the separation between two frequency positions of the pre-saturating RF irradiation is fixed, which can be easily implemented through the cosine modulation of the RF shape used for the pre-saturating RF irradiation. The cosine

modulation makes two copies of the original RF shape around the irradiation frequency, separated by twice the modulation frequency. In this study, the modulation frequency was chosen to be 1500 Hz or 5 ppm at 7 T, which is large enough to avoid any simultaneous saturation of multiple CEST and NOE sites as well as any MT pools with their spectral ranges larger than the modulation frequency could be completely saturated (Figure 1a). Second, the water signals are acquired against the frequency offsets of the pre-saturating RF irradiation, which is cosine modulated, hence the actual frequency positions are the frequency offset plus and minus the modulation frequency. After dividing by the water signal measured without the pre-saturating RF irradiation, the water signals against the frequency offsets consist of a Z-spectrum with two dips near at the positive and negative modulation frequencies, from which genuine CEST effects as well as a new type of MT contrast can be estimated (Figure 1b). In addition, the frequency positions of two dips can be used to construct a B_0 map since those dips should appear at the positive and negative modulation frequencies if there is no frequency shift due to the spatial variation of the B_0 field.

MRI human subjects

After approval from the Institutional Review Board of the New York University Medical Center and signed informed consent, the brains of five healthy volunteers (four male and one female, mean age 35.6 ± 5.7 years) and two MS patients (all male, mean age 36.0 ± 1.4 years) were investigated.

MRI hardware

The MRI experiments were performed on a 7T whole-body Siemens scanner (Siemens, Erlangen, Germany). For the in-vivo experiments, a volume-transmit, 24-element receive head coil array (Nova Medical, Boston, MA) was used. For the phantom experiments, a 28-element knee coil array (Quality Electrodynamics, Mayfield Village, OH) was used.

MRI experiments

The study protocol consisted of a localizer, uMT CEST acquisition (Lee et al., 2012; Lee et al., 2013), conventional CEST acquisition, and WASSR acquisition (Kim et al., 2009). For the signal acquisition, a segmented GRE acquisition with centric phase encoding order was used. For the GRE sequence, flip angle = 15° , TR = 24 ms, TE = 3.5 ms, dwell time = 15 μ s, slice thickness = 5 mm, matrix size = 192×192 . The field of view (FOV) was 200 mm $\times$ 200 mm except for two healthy volunteers, with whom the FOV's were 250 mm $\times$ 250 mm and 170 mm $\times$ 170 mm. Each signal acquisition covered 96 k -space lines, so two signal acquisitions were performed for each image. For the off-resonance pre-saturation irradiation, a train of 10 Gaussian pulses and a train of 10 cosine-modulated Gaussian pulses were used in the conventional and uMT CEST experiments, respectively. Each pulse was 100 ms long, followed by a delay of 100 μ s, and the frequency offsets for the pre-saturation irradiation was varied from -2500 Hz to 2500 Hz with a step size of 100 Hz. Their nominal flip angles were 1440° ($B_{1,\text{rms}} = 1.4 \mu\text{T}$) for the Gaussian pulses and 2880° ($B_{1,\text{rms}} = 1.9 \mu\text{T}$) for the cosine-modulated Gaussian pulses, respectively. The Gaussian pulse can perturb a spin within a frequency range between -50 Hz and +50 Hz from its frequency offset, and the

cosine-modulated Gaussian pulse can affect a spin within the frequency ranges between -1550 Hz and -1450 Hz and between 1450 Hz and 1550 Hz from its frequency offset. The modulation frequency for the cosine-modulated Gaussian pulse was 1500 Hz. For the WASSR acquisition, a train of two 100 ms-long 180° Gaussian pulses with an inter-pulse delay of 100 μ s, were used as the off-resonance pre-saturation irradiation, and the frequency offset was varied from -500 Hz to 500 Hz with a step size of 20 Hz.

Data analysis

All the image reconstruction and data processing were performed using MATLAB (Release 2012b, The Mathworks Inc., Natick, MA). Each image was reconstructed by taking the square root of the sum of squares of the signals from the individual coils in the array. From all the WASSR, conventional CEST, and uMT CEST acquisitions, the Z spectra were reconstructed pixel-wise and interpolated at every 1 Hz by using a cubic spline interpolation. Each interpolated Z spectrum from the WASSR acquisition has one minimum, which was taken as a B_0 value. This WASSR B_0 value was used to shift the interpolated Z spectrum of the corresponding pixel from the conventional CEST acquisition. For the uMT CEST acquisitions, each interpolated Z spectrum is supposed to have two minima around ± 1500 Hz. The average of the frequency positions of these two minima was taken as a B_0 value, which was used to shift the interpolated Z spectrum. After dividing each shifted Z spectrum by the signal intensity of the corresponding pixel from a reference image, which was collected without any off-resonance pre-saturation irradiation, MTR_{asym} values at each pixel were estimated by subtracting the values of the shifted Z spectrum at the positive offsets from the values at the corresponding negative offsets. For the uMT CEST acquisition, the MTR_{asym} values were negated, and the frequency offset was replaced with $(1500 - \delta)$ Hz, where δ was the original frequency offset ($0 \leq \delta \leq 1500$). The MT contrast maps were obtained by evaluating MTR at the zero frequency offset for the uMT CEST acquisition and at the frequency offsets -1500 Hz and $+1500$ Hz for the conventional CEST acquisition, respectively. Based on the MTR values from the uMT CEST acquisition, the pixels were segmented into higher ($> 35 \sim 40\%$), intermediate, and lower ($< 25\%$) MT regions. The MTR values separating MT regions were chosen manually for each subject.

Results

The conventional and uMT CEST MRI experiments were performed on the brains of five healthy volunteers and two multiple sclerosis (MS) patients. The reference image was acquired without the off-resonance pre-saturation irradiation (Fig. 2a) and used as the reference for the data processing. From the uMT CEST MRI experiment, MT contrast (Fig. 2b) can be evaluated as the magnetization transfer ratio (MTR) (Henkelman et al., 2001), which is a ratio of the signal decrease due to MT to the reference signal, at the zero frequency offset, when the off-resonance pre-saturation irradiation has two irradiation components at $\pm f_m$ simultaneously (Fig. 2i). Based on these MTR values, we segmented the brain images into regions with higher, intermediate, and lower MT, which have been reported to correlate with regions of white matter, gray matter, and cerebrospinal fluid (CSF), respectively (Grossman et al., 1994).

Corresponding to this MT contrast from the uMT CEST experiment or uMT contrast, two MT contrast maps can be obtained from the conventional CEST MRI experiment, in which the pre-saturation irradiation is applied at the frequency offset $-f_m$ (Fig. 2c) or $+f_m$ (Fig. 2d). The MTR values at $-f_m$ were higher by 4 – 8% than those at $+f_m$ (See the topmost image of the column ‘1500’ in Fig. 3, which shows the difference), which manifested the asymmetric MT effect in the brain (Hua et al., 2007). The uMT contrast was stronger by 9 – 16% in the higher MT segment and 8 – 13% in the intermediate MT segment. Similar trends were observed in the images from all subjects (Supplementary Fig. 1).

For the MS patients, T_2 -weighted images were acquired to identify lesions (Ge, 2006; Ceccarelli, 2012). It has been known that MS lesions lead to longer T_2 and reduced MT effects, possibly as a result of demyelination (Stanisz et al., 1999). The same MS lesions could be recognized in the uMT contrast map (Fig. 2f and Supplementary Fig. 2) but it was not easy to identify them in the conventional MT contrast maps (Figs. 2g-2h).

The MTR values measured at two frequency offsets that are symmetric around the water signal are usually compared (images in the rows labeled as ‘Before’ in Fig. 3) to remove the contribution due to the direct saturation of the water signal and to produce ‘positive’ CEST contrast (Guivel-Scharen et al., 1998). This MTR asymmetry (MTR_{asym}) value can be sensitive to the frequency shift of the water signal, which may cause imperfect cancellation of the direct saturation effects. With the help of a frequency-shift or B_0 map and interpolation, the cancellation can be improved in evaluating the MTR_{asym} values (images in the rows labeled as ‘After’ in Fig. 3) (Kim et al., 2009). This so-called B_0 correction generally lowered the MTR_{asym} values along the frequency offsets but did not change the MTR_{asym} contrast much when the frequency offset was larger than 800 Hz (Fig. 3). Regardless of the B_0 correction, the MTR_{asym} values at the frequency offsets larger than 800 Hz were ‘negative’ with the conventional method while almost ‘null’ with the uMT method (Fig. 3), which can be explained in terms of asymmetric MT effects becoming uniform by the uMT method. On all the human subjects, we obtained the same results that the B_0 correction improves the MTR_{asym} contrast at the lower frequency offsets and that the MTR_{asym} values at the larger frequency offsets were negative with the conventional method while almost null with the uMT method (Supplementary Figs. 3-6).

The B_0 -corrected data were grouped according to the pixel-wise MTR values from the uMT method to produce the box plots of Z spectra and MTR_{asym} curves for the segments with the higher and intermediate MTR values (Fig. 4 and Supplementary Figs. 7-10). The signal intensities in the higher-MTR segment (Fig. 4a) were smaller than those in the intermediate-MTR segment (Fig. 4b), as expected. The box plots of Z spectra from the conventional method (the black boxes in Figs. 4a-4b and Supplementary Figs. 7-8) manifested that the signal intensities at the far negative frequency offsets were smaller than those at the corresponding positive frequency offsets, which indicates asymmetric MT effects and can be clearly seen in the box plots of the MTR_{asym} curves (the black boxes in Figs. 4c-4d and Supplementary Figs. 9-10). The box plots of Z spectra from the uMT method (the red boxes in Figs. 4a-4b and Supplementary Figs. 7-8) had two direct saturation dips at $\pm f_m$ and displayed flatter signal intensities around the zero frequency offset in the Z spectra, which

indicate the good achievement of uMT and lead to zero baselines in the MTR_{asym} curves (the red boxes in Figs. 4c-4d and Supplementary Figs. 9-10).

The averaged MTR_{asym} values at the larger frequency offsets, where CEST effects are not typically expected, clearly revealed the difference between the conventional and uMT methods (Fig. 5). Over the human subjects, the uMT method consistently produced much smaller asymmetric MT effects, by a factor of 8 to 30 on average, compared with the conventional method. Even the variations in the averaged MTR_{asym} values were smaller by a factor of 1.2 to 5.5 in the uMT method. Notice that the MT effects are more asymmetric in the higher-MTR segments than in the intermediate-MTR segments. The higher-MTR segments may contain most of the white matter, in which it has been known that myelin water produces large MT effects (Stanisz et al., 1999).

Discussion

In order to produce the same amount of CEST effects, the radio frequency (RF) power of the off-resonance pre-saturation irradiation was doubled in the uMT method compared to the conventional method, which may be one of the reasons why the MTR values produced by the uMT method (Figs. 2b and 2f) were higher than the corresponding MTR values from the conventional method (Figs. 2c-2d and 2g-2h). When the RF power of the off-resonance pre-saturation irradiation was matched, the MTR values generated by the two methods became similar (Supplementary Fig. 11). However, the two MTR contrast maps looked distinctly different, exhibiting asymmetric MT effects, and MS lesions were recognizable more easily with the uMT contrast map (Fig. 6).

Compared to the traditional MT methodology (Henkelman et al., 2001), the pre-saturation irradiation used in this work was applied at the smaller frequency offset (1500 Hz vs. 8 kHz) with an order of magnitude weaker RF power (1.9 μT vs. 15.7 μT). The weaker RF power ensured that the contribution of the direct water saturation to the uMT contrast may not be significant in spite of the smaller frequency offset, which is still large enough to expect that any ST effects other than MT would not contribute much to the uMT contrast. MT contrast has been used to probe proton species in different environments, such as white matter and gray matter, and to monitor the changes in such environments, for example, the demyelination and remyelination of MS lesions (Ge 2006; Filippi and Motta, 2007; Ceccarelli et al., 2012). Hence, the MT contrast from the uMT method can be expected to be useful for such applications, probably with improved performance.

The removal of the influence of MT effects from MTR_{asym} provides in principle the opportunity to measure more accurately metabolites' CEST contrast in the brain. While another ST mechanism, the nuclear Overhauser effect (NOE), may contribute to the MTR_{asym} contrast (Ling et al., 2008), many metabolites in the brain collectively contribute to CEST effects. For example, efforts to target a specific endogenous metabolite through CEST effects, such as MICEST (Haris et al., 2011) for *myo*-inositol, CrCEST (Kogan et al., 2013) for creatine, and GluCEST (Cai et al., 2012) for glutamate, or to record a particular transfer mechanism such as amide proton transfer (APT) (Zhou et al., 2003) due to backbones of proteins and peptides have been reported. While our experimental parameters

might not be optimized for any specific contrast, each contrast could be evaluated according to the frequency offset (Supplementary Fig. 12). There were marked differences between those CEST contrasts via the conventional and uMT methods, and the CEST contrasts from the uMT method seemed more consistent because they were mostly nonnegative. For example, conventional GluCEST and APT contrasts were negative in most of the images (Supplementary Fig. 12). For reference, we also provide conventional CEST measurements from phantom solutions, made of typical metabolites found in brain (Provencher, 1993), to illustrate the frequency responses of individual metabolites (Supplementary Fig. 13). For example, *myo*-inositol could be detected mainly through MICEST, but the converse would not be true: creatine and glutamate produce sizable contributions to MICEST. Notice that the B_0 correction on the phantom solutions also affected CEST contrasts at the lower frequency offsets.

The pixels with the MTR values less than 20% likely correspond to CSF, the signal from which is known to have very long lifetime. The duration of the off-resonance pre-saturation irradiation used in this report might not be long enough to cause the saturation of the water protons in those pixels, so they were excluded from the analysis using Z spectra and MTR_{asym} curves.

The reasons for the distributions in the box plots of Z spectra and MTR_{asym} curves (Fig. 4 and Supplementary Figs. 7-10) are the spatial variations in the physical and chemical parameters in tissues, such as concentration, pH, and chemical exchange rates, and the imperfections of experimental conditions, for example, the non-uniformity in the RF field produced by a coil array. Although there are many correction methods for the non-uniformity during the signal acquisition (Belaroussi et al., 2006), the correction for the off-resonance pre-saturation irradiation has not yet been fully established (Liu et al., 2013; Vinogradov et al., 2013; Sun et al., 2007; Singh et al., 2012). The information to correct the non-uniformity of the RF field could be obtained through the measurements varying the duration and RF power of the off-resonance pre-saturation irradiation (McMahon et al., 2006) or by the use of some non-conventional metrics (Sun, 2011; Zaiß and Bachert, 2013). On the other hand, the non-uniformity of the RF field may be reduced by using parallel transmission (Fujita, 2007; Katscher and Börnert, 2006). The parallel transmission can also help to reduce the specific absorption rate (SAR) during the pre-saturation RF irradiation (Homann et al., 2011). With the uMT method, the SAR limits the range of the duration and RF power of the off-resonance pre-saturation irradiation, but this limitation appears to be outweighed by the fact that it reveals contrast that would be invisible otherwise.

Higher B_0 field is beneficial to the differentiation of CEST sites because the chemical shifts of CEST sites are proportional to the B_0 field. On the other hand, the spectral range of MT pools are determined mostly by the residual dipolar couplings between the constituting proton spins and may not depend much on the B_0 field. With the uMT method, the distance between two frequency components of the pre-saturation RF irradiation is supposed to be large enough not to simultaneously irradiate multiple CEST and NOE sites, but small enough to completely saturate MT pools. This work demonstrated that it was possible to make MT effects uniform at 7 T. This finding implies that the uMT method would work well at the B_0 field lower than 7 T. At lower fields, the SAR limit is less severe and field

inhomogeneity artifacts are easier to correct, but the CEST measurement may suffer from the smaller frequency separation between CEST sites, especially for those sites that are very close to the water resonance.

Conclusions

We show here that the CEST effects from some metabolites in the brain may not be observed cleanly due to superimposed MT effects in conventional CEST measurements. In this report, we demonstrate that such CEST and MT effects can be disentangled and measured separately by the uMT method. Specifically, determining whether a given MTR asymmetry should be assigned to genuine CEST effects or MT effects is a major step towards the goal of reliably tracking metabolites or pathological tissue transformations in the brain. Furthermore, the presented method provides a tool for measuring MT contrast in a more robust way than the conventional approach. As a particular example, we also show that MS lesions are visualized cleaner by uMT than by conventional MT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- The MT effects from white matter and gray matter are asymmetric.
- Several CEST contrast mechanisms in the brain may be buried under the MT effects.
- The uMT technique can separate genuine CEST effects from the background MT effects.
- The uMT technique also measures MT contrast in a more robust way.

Figure 1.

Schematics of the uMT technique. (a) The frequency positions of the pre-saturation RF irradiation in the uMT method, relative to the spectral ranges of water and CEST, NOE, and MT pools. The distance between two frequency components is fixed ($2f_m$), and the water signal is measured against the middle of the two frequency positions. (b) A typical Z-spectrum obtained with the uMT method. 'CEST' and 'MT' respectively indicate the estimation of the CEST and MT contrast on the Z-spectrum.

Figure 2.

MRI images from the brain of a healthy volunteer and a MS patient. (a) A reference image and (b-d) MT contrast maps from a healthy volunteer. $MTR = 1 - (M_{z,sat}/M_0)$, where $M_{z,sat}$ and M_0 are respectively the signals with and without the saturating RF irradiation. (e) A T₂-weighted image and (f-h) MT contrast maps from a MS patient. (i) The frequency offsets for the saturating RF irradiations were $\pm f_m$ (b,f) with the uMT method, $-f_m$ (c,g) or $+f_m$ (d,h) with the conventional MT method. In this study, f_m was 1500 Hz. The MT contrast maps are color-coded and overlaid on their respective reference images. For the MS patient, possible lesions are indicated by arrows (e-h).

Figure 3.

MTR_{asymp} maps at the frequency offsets from 0 Hz to 1500 Hz. (a) MTR_{asymp} maps from a healthy volunteer. (b) MTR_{asymp} maps from a MS patient. 'Conv' and 'uMT' mean the conventional and uMT methods, respectively. 'Before' and 'After' indicate before and after applying B₀ correction to the images, respectively.

Figure 4.

Z spectra and MTR_{asym} curves from a healthy volunteer's brain. (a-b) Box plots of Z spectra from the segments with (a) higher and (b) intermediate MTR values. (c-d) Box plots of MTR_{asym} curves from the segments with (c) higher and (d) intermediate MTR values. The black and red boxes represent the data from the conventional and uMT methods, respectively.

Figure 5.

Comparison of the asymmetric MT effects over the human subjects. (a) Box plots of the averaged MTR_{asy} values on the higher-MTR segments. (b) Box plots of the averaged MTR_{asy} values on the intermediate-MTR segments. The thin diamond and thick rectangular boxes represent the data from the conventional and uMT method, respectively. The MTR_{asy} values were averaged over the frequency offsets from 4 ppm to 5 ppm, where any CEST effects are not normally occurring. The subjects from 1 to 5 are the healthy volunteers, and the others the MS patients.

Figure 6.

MRI images from a MS patient's brain, magnified around MS lesions. (a) A T₂-weighted image with circles indicating possible lesions. (b-d) MT contrast maps with the pre-saturation irradiation applied at (b) $\pm f_m$, (c) $-f_m$, and (d) $+f_m$. (e,f) MT contrast maps with the conventional method when the RF power of the pre-saturation irradiation was matched to the uMT method. The pre-saturation irradiation was applied at (e) $-f_m$ and (f) $+f_m$.