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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 has 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.

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) (Kogan et al., 2013; Liu et al., 2013; Vinogradov et al., 2013; van Zijl and Yadav, 2011), to probe biomarkers, physiologically active molecules, and macromolecules in tissues and organs. Since the ST family shares a 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, 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 (Henkelman et al., 1993; Stanisz et al., 2005; van Zijl and Yadav, 2011), and MT contrast has become a routine technique, especially for the characterization of white matter diseases, such as multiple sclerosis (MS) (Ceccarelli et al., 2012; Filippi and Rocca, 2007; Ge, 2006; Grossman et al., 1994). 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., 2014), 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.

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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, 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 (Fig. 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 the positive and negative modulation frequencies, from which genuine CEST effects as well as a new type of MT contrast can be estimated (Fig. 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.

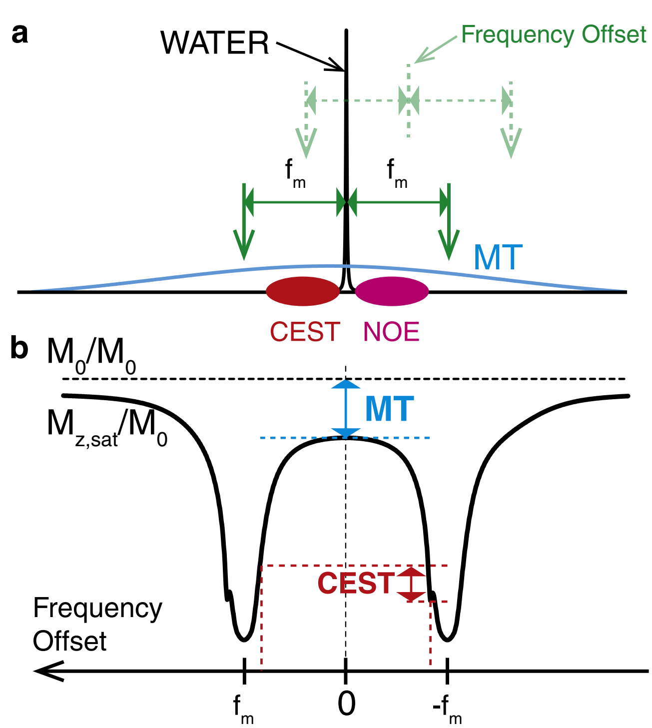

Fig. 1. Schematics of the uMT technique. (a) The frequency positions of the pre-saturation RF irradiation in the uMT method, relative to the spectral ranges of water and CEST, NOE, and MT pools. The distance between two frequency components is fixed ($2f_m$), and the water signal is measured against 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.

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 males 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 7 T 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, 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 μs, slice thickness = 5 mm, and matrix size = 192 × 192. The field of view (FOV) was 200 mm × 200 mm except for two healthy volunteers, with whom the FOVs were 250 mm × 250 mm and 170 mm × 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 μs, 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° ($B_{1,rms}$ = 1.4 μT) for the Gaussian pulses and 2880° ($B_{1,rms}$ = 1.9 μT) 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 μs, was 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