Published in final edited form as:

Magn Reson Med. 2016 January ; 75(1): 88–96. doi:10.1002/mrm.25990.

Magnetization-Transfer Contrast (MTC) Suppressed Imaging of Amide Proton Transfer (APT) and Relayed NOE (rNOE) CEST Effects in the Human Brain at 7T

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Abstract

Purpose—To use the Variable Delay Multi-Pulse (VDMP) CEST approach to obtain clean Amide Proton Transfer (APT) and relayed Nuclear Overhauser (rNOE) Chemical Exchange Saturation Transfer (CEST) images in human brain by suppressing the conventional magnetization transfer contrast (MTC) and reducing the direct water saturation (DS) contribution.

Methods—The VDMP CEST scheme consists of a train of RF pulses with a specific mixing time. The CEST signal with respect to the mixing time shows distinguishable characteristics for protons with different exchange rates. Exchange rate filtered CEST images are generated by subtracting images acquired at two mixing times at which the MTC signals are equal, while the APT and rNOE-CEST signals differ. Since the subtraction is done at the same frequency offset for each voxel and the CEST signals are broad, no B_0 correction is needed.

Results—MTC-suppressed APT and rNOE-CEST images of human brain were obtained using the VDMP method. The APT-CEST data shows hyper-intensity in gray matter versus white matter while the rNOE-CEST images show negligible contrast between gray and white matter.

Conclusion—The VDMP approach provides a simple and rapid way of recording MTC-suppressed APT-CEST and rNOE-CEST images without a need for B_0 field correction.

Keywords

Chemical Exchange Saturation Transfer (CEST); magnetization transfer contrast (MTC); Variable Delay Multi-Pulse (VDMP); relayed NOE (rNOE); amide proton transfer (APT)

INTRODUCTION

Chemical exchange saturation transfer (CEST) MRI provides an alternative contrast mechanism to relaxation contrast based imaging (1). Amide proton transfer (APT) is one of

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the most studied and widely utilized mechanisms in CEST imaging due to the abundance of mobile proteins and peptides in tissue. The APT signal appears around 3.5 ppm downfield from water and it has been shown to be useful in grading tumors, separating tumor recurrence from treatment necrosis and detecting early effects of treatment (2,3), as well as monitoring pH effects during early ischemia (4–8). Recently, Nuclear Overhauser enhancement (NOE) effects at about 0–5 ppm upfield from the water signal have been observed in CEST studies (9). This is thought to be due to a two-step relayed NOE process (rNOE) that consists of an initial intramolecular dipolar coupling between aliphatic protons and exchangeable protons, followed by a chemical exchange process to water (10,11). In rNOE-CEST, the intra-molecular NOE is the rate-determining step due to its much lower transfer rate compared to chemical exchange (12,13).

CEST effects are usually detected using continuous-wave irradiation or a train of frequency selective pulses to saturate the exchangeable spins. However, such saturation scheme also generates magnetization transfer contrast (MTC) due to the saturation of semisolid macromolecular protons (14,15) as well as direct saturation (DS) of bulk water protons. Depending on the B_1 field used, these two confounding effects may be much larger than the CEST signals, which are typically a few percent of the water signal. The most common way of suppressing these two confounds is acquiring an image at the opposite frequency of the CEST signal with respect to the water resonance, and then subtracting the two images to yield the magnetization transfer ratio asymmetry (MTR_{asym}) (16,17). This works well for DS, which is symmetric around the water resonance, but not for the MTC effect, which is known to be asymmetric with respect to the water frequency (18,19). Furthermore, APT and rNOE essentially resonate at opposite sides of the water frequency, and therefore become mixed when performing an asymmetry analysis (20,21).

Several techniques have been developed to overcome the problems associated with MTR_{asym} . These methods include line-shape fitting (22–25), alternating-Phase Irradiation (ZAPI) (26), saturation with frequency alternating RF irradiation (SAFARI) (27), chemical exchange rotation transfer (CERT) (28), Length and Offset VARIation of Saturation (LOVARS) (29), and the uniform-MT (uMT) approach (30). Recently, a Variable Delay Multi-Pulse (VDMP) approach was proposed (31), in which low power saturation or excitation pulses were applied as a T2 filter to reduce the MTC interference to the CEST signal. However, similar to some other pulsed-CEST techniques, the original proposed VDMP approach focused on maximizing the CEST contrast rather than minimizing MTC. In the current study, we propose an improved VDMP approach that can suppress the MTC contribution while still allowing the application of high power saturation or excitation pulses. In this approach, two images at a single saturation frequency are acquired. The first image is acquired at a short mixing time and a second image is acquired with a mixing time specifically chosen for the MTC intensity being equal to that at the short mixing time. By taking the difference between the two images, the MTC effect is removed. Here we use this approach to generate MTC-suppressed APT and rNOE images in vivo in the human brain at 7T.

METHODS

MR Pulse Sequence

The VDMP sequence appears similar to the conventional pulsed-CEST (2,32) or pulsed-MT (33), i. e. a train of selective saturation pulses with inter-pulse delays followed by image acquisition. The inter-pulse delay (time between the end of a saturation pulse to the start of the next saturation pulse) is defined as the mixing time (τ_{mix}). The CEST signal of slow-exchanging protons (e.g., amides) increases initially as a function of τ_{mix} since these labeled spins require a longer time to exchange with water. After reaching a maximal value, the CEST signal will then decay as a function of τ_{mix} due to water T1 relaxation. The characteristic buildup and decay curves can be used as an exchange rate filter to remove MTC. Two images will be acquired with two different mixing times: $\tau_{\text{mix}} = 0$ ($S_1, \tau_{\text{mix}} = 0$), and τ_{null} ($S_2, \tau_{\text{mix}} = t$), for which the MTC intensity is equal. Therefore, MTC can be removed when taking the difference of the two images. The resultant CEST signal is called the VDMP difference, which is defined as the normalized VDMP signal intensity difference between the two images:

$$\Delta \text{VDMP} = S_{1, \tau_{\text{mix}}=t1} - S_{2, \tau_{\text{mix}}=t2} \quad [1]$$

In the current paper we generally use $t1 = 0$ ms, but in principle, one can apply any pair of mixing times ($t1, t2$) for which CEST contrast is sufficient while the MTC effect cancels.

Theoretical Simulations

CEST buildup curves with respect to mixing time for a range of typical exchange rates were simulated to illustrate the principles outlined. Simulations were performed using custom written scripts in Matlab (Release 2012a, The Mathworks, Inc, Natick, MA, USA) by numerically solving the Bloch-McConnell equations using a two-pool model at 7T. 16 saturation pulses at 3.5 ppm, each with duration of 20 ms and peak B_1 of 1.5 μT were applied. The water T1 and T2 were assumed to be 2 s and 60 ms respectively. The mixing time was incremented with 3 ms steps from 0 to 150 ms. Exchanging protons with exchange rates ranging from 0 to 10^4 Hz were modeled and their CEST signal intensity was plotted as a function of τ_{mix} . All intensities were normalized to the first data point ($\tau_{\text{mix}} = 0$ ms), i. e. corresponding to a normalized CEST signal intensity $S(\tau_{\text{mix}})/S(\tau_{\text{mix}}=0)$. Because the CEST signal intensity is proportional to the exchangeable proton fraction, the normalized CEST signal with respect to $\tau_{\text{mix}} = 0$ ms is independent of the concentration of exchanging protons. The VDMP difference ratio was simulated as a function of exchange rate. Two pairs of Z-spectra of pure water with different T1 were simulated using the same two mixing times to show the effect of T1w relaxation on DS cancellation.

Factors such as MTC exchange rate (k_{MTC}), MTC pool size ratio (PSR) and apparent water longitudinal relaxation times (T1w) may affect the nulling condition of MTC or the APT/rNOE contrast. Therefore we also performed simulations for a three-pool model (water, MTC pool and exchanging proton pool) in which the signal intensity (S/S_0) of APT and MTC were simulated as a function of mixing time and PSR_{MTC} (5% to 15%) for $k_{\text{MTC}} = 60$ Hz and $T1_w = 1.5$ s; as a function mixing time and T1w (1.3 s to 1.8 s, $k_{\text{MTC}} = 60$ Hz, PSR_{MTC}

= 9%); and as a function of mixing time and k_{MTC} (52 Hz to 68 Hz) for $\text{PSR}_{\text{MTC}} = 9\%$ and $T1_w = 1.5$ s.

In vitro Study

An egg white phantom was used to demonstrate the signal change of APT-CEST and rNOE-CEST signals as a function of mixing time at room temperature. The MRI scans were acquired using a Philips Achieva 7T system (Philips Healthcare, Best, The Netherlands) equipped with a dual transmit head coil operating in quadrature mode and a 32 channel phased array receiver (Nova Medical Inc, Wilmington, MA). The phantom was made from a carton of household grade egg whites (Target Food, Inc.). The egg white was used without further preparation. Imaging parameters: 16 sinc-gauss RF saturation pulses, each of 20 ms duration and maximum B_1 of 3.4 μT ; single-shot turbo gradient echo with TR (between each echo in the readout)/TE/FA = 5 ms/1.48 ms/30°. A single slice of 6 mm thickness across a FOV of 230×230mm² with 3×3 mm² in plane resolution was acquired; k-space was sampled with a centric ordering. The SENSE acceleration factor was 2 (AP). The frequency of the saturation pulse was swept from −20 to 20 ppm at a step size of 1 ppm, except in the range of −4 to 4 ppm, where a 0.5 ppm step size was used. The experiment time for each irradiation frequency was 4.2 s. Z -spectra at 8 mixing times ranging from 0 to 140 ms were acquired.

Human Study

All studies were conducted under the approval of the institutional review board (IRB) of the Johns Hopkins University School of Medicine. Five healthy volunteers participated in the study, and all provided informed consent. The imaging parameters used for the human subjects were the same as for the egg white phantom. The maximum SAR was 24%, which occurred when the mixing time was 0 ms. Statistics were performed using the Student's *t* test.

RESULTS

Simulations

In Figure 1a, simulations of the normalized VDMP signal (color scale) as a function of τ_{mix} for different exchange rates are presented (Notice that the axis representing exchange rate has a logarithmic scale). Protons with slow and fast exchange rates exhibit very different buildup characteristics. For slow-exchanging protons, the normalized VDMP signal builds up initially, and then decays at longer mixing time. The mixing time required to reach the maximal signal depends on the exchange rate. As a consequence, the CEST signal null time (τ_{null}), i. e. the mixing time at which the VDMP-CEST signal is identical to that at $\tau_{\text{mix}} = 0$ ms, is much longer for slow-exchanging protons. In contrast, there is no build-up process for fast-exchanging protons (>500 Hz). The CEST signal decays with increasing mixing time. Figure 1b shows the behavior of the normalized VDMP signal as a function of mixing time for the exchange rate of several typical types of exchanging protons in vivo. When the MTC signal reaches the null time, the rNOE and APT signals are still positive. Figure 1c shows the VDMP difference ratio as a function of exchange rate at $\tau_{\text{mix}} = 80$ ms, at which MTC signal ratio reaches unity. It is evidence that this MTC-suppressed VDMP-CEST is most

sensitive for protons with exchange rates of 10 – 70 Hz. For fast-exchanging protons (~1000Hz), the VDMP difference ratio becomes negative. Water direct saturation varies slightly with respect to the mixing time due to the water T1 relaxation as simulated in Figure 1d.

MTC pool size ratio (PSR) itself affects the MTC effect, but does not alter the null time and CEST contrast (Figures 2a and b). However, the observed T1w, which can be affected by the PSR (34), has some effect on MTC null time (Fig. 2d) and, as well described before, on the CEST contrast (Fig. 2c). Difference in exchange rate within the MTC pool will also affect the null time but not the CEST contrast (Figures 2e and f). The mixing time at which MTC is nulled increases with slower MTC exchange rate and longer T1 of water.

In vitro

Egg white is primarily composed of approximately 90% water, 10% proteins and a small amount of metabolites. It shares many similarities with human brain tissue except the MTC effect is weak due to the lack of a large semi-solid protein/lipid network. The VDMP Z-spectra of the egg white phantom as a function of mixing time are shown in Figure 3a. Figure 3b provides a zoomed in view of the Z-spectra, showing clear saturation effects at each side of the direct water saturation, corresponding to APT around 3.5ppm and rNOE CEST effects upfield from water. The normalized VDMP difference spectra obtained by subtracting the Z-spectra acquired at longer mixing time from those at zero mixing time are plotted in Figure 3c. Both rNOE-CEST and the APT effects build up with increasing mixing time, and show positive contrast in the difference spectra as shown in Figure 3d. At more than 40 ms, the APT-CEST starts to decay comparing to the difference spectrum at $\tau_{\text{mix}} = 20$ ms, while the rNOE-CEST signal reaches a maximum at $\tau_{\text{mix}} = 100$ ms and still shows little decay for $\tau_{\text{mix}} > 100$ ms.

In vivo human brain

The null time for the MTC pool of human brain was optimized by acquiring a series of VDMP Z-spectra with different mixing times. The imaging slice is shown in Figure 4a. When plotting the MTC signal intensity at 8.0 ppm from water as a function of mixing time, it can be seen that the MTC signal at 100 ms is indistinguishable from that at 0 ms (Figure 4b). The VDMP Z-spectra and the corresponding VDMP difference spectra of the whole slice at several mixing times are plotted in Figures 4c and 4d. Strong MTC signal components are present between -15 ppm and 15 ppm in the VDMP difference spectra at $\tau_{\text{mix}} = 40$ and 60 ms. The MTC contribution becomes negligible when the mixing time is around 100 ms.

A typical MTC-weighted image (at offset 8 ppm) acquired by the VDMP sequence with 0 ms mixing time is shown in Figure 5a. The MTC weighted image clearly distinguishes the gray matter (GM) and white matter (WM). Therefore, we used it to generate a mask to separate these two tissue types. The resulting VDMP Z-spectra of WM and GM are presented in Figure 5b. The GM and WM have very different MTC intensities, around 4% in WM and 2% in GM at 20 ppm (5% and 2% at -20ppm, respectively) and 10% in WM and 5% in GM at 8 ppm (13% and 6% at -8pp, respectively, Figure 5b) When applying the

VDMP difference, the MTC contributions in both GM and WM are canceled as seen in Figures 5c, d and there is negligible residual signal at high offset frequencies in the spectra (Figure 5d) and the difference image at 8 ppm (Figure 5c).

After confirming that MTC interference could be removed using a mixing time of 100 ms, APT and rNOE maps were generated at offsets of 3.5 and -3.5 ppm, respectively. These are displayed in Figures 6a and 6b, respectively. The APT-CEST signal is relatively weak (less than 2%), with clear hyper-intensity in gray matter compared to white matter. The rNOE-CEST signal has higher amplitude VDMP, close to 5%, and appears iso-intense across the brain. Statistics over 5 volunteers (Figure 6c) indicates that the APT signal is significantly different between GM and WM ($p < 0.05$), while the rNOE signal difference between WM and GM is not significant.

DISCUSSION

Using an optimized VDMP scheme, we obtained APT/rNOE-CEST images of human brain with MTC suppression and some minimal DS interference. The VDMP pulse sequence functions as a magnetization transfer rate filter when varying the mixing time while keeping the number of pulses constant. It provides a simple way of acquiring APT/rNOE-CEST images on clinical scanners with low SAR and excellent reduction of MTC and DS signal contributions.

Given a fixed saturation pulse number and width, the CEST/MT signal difference measured by the VDMP sequence depends on the mixing time. During the pulses, both slow- and fast-exchanging protons are labeled. However, the CEST buildup curves as a function of mixing time differ greatly for slow-exchanging and fast-exchanging protons. For fast-exchanging protons, the saturated spins fully exchange with water protons during the saturation pulse, and no additional increase in saturation takes place during the mixing time. Therefore, for these protons, the signal intensity change as a function of mixing time becomes independent of the exchange rate and decays due to the relaxation time constant T_1 (Figure 1b). On the contrary, for slow-exchanging protons, the saturated spins take longer time to fully exchange with water and saturation transfer still continues during the mixing time, causing the CEST signal to increase. At very long mixing time the signal gain from the exchange cannot compensate for the signal loss due to T_1 relaxation. As a result, the CEST signal from slow-exchanging protons would eventually decay with respect to the mixing time at a rate that depends on T_1 (Figure 1b). We exploit the VDMP signal buildup pattern for slow-exchanging protons to suppress the MTC effect, which can be done because the exchange rate of protons from the MTC pool to water protons is around 40–60 Hz (35,36), which is higher than the typical exchange rates of amide (29 Hz) (4,37) and aliphatic protons (17 Hz) (36). Note that the exchange rate of MTC pool is a population-averaged value between the slow-exchanging protons in myelin lipids and proteins, and the fast-exchanging protons such as the amine and hydroxyl groups in these compounds. Therefore, when measuring the apparent exchange rate of the MTC pool, the result will depend on the number of pulses and the saturation power applied in the Pulsed-CEST/MT. Also notice that in most of the MTC literature, the exchange rate listed is that from water to the semisolid and thus much smaller in a ratio dominated by the ratio of the free and bound proton pool.

Water DS can be greatly suppressed by subtracting the two images acquired with two mixing times, which was confirmed from the similar water DS signals at two difference mixing times (Figure. 1d) and in the egg white phantom. However, the DS cancelation is not perfect and caution thus needs to be taken into account when studying exchange at frequencies very close to water, such as for the hydroxyl protons. The residual DS did not affect the current study appreciably since the APT and rNOE resonances were sufficiently far from water. Fast-exchanging protons will contribute a small negative VDMP signal as shown by the simulations in Figure 1c. For this reason, some negative signals in the VDMP difference Z-spectra on human brain between 0 – 1 ppm (Fig. 4d) can probably be attributed to fast-exchanging hydroxyl protons. It is unlikely that this signal difference resulted from a resonance shift due to RF heating since the same result was found when reversing the order of frequency offsets (Data not shown. Amine protons, which typically exchange with rates larger than 1000 Hz (38), can produce negative VDMP signal around 2 ppm, which can potentially affect the APT signal. However, as the simulations predicted, the effect should be minimal for such fast exchange rates under the current experimental conditions.

Three-pool Bloch simulation showed that the mixing time for MTC signal cancellation depends on the k_{MTC} and apparent T1w (Figure. 2) but not on PSR. The nulling time is longer with low MTC exchange rate, while the time reduces with short T1w. The observed CEST contrast is dependent on T1w as seen from Fig. 2C and well known from previous literature (16,37). Thus, suppression of MTC in vivo may not be perfect over an inhomogeneous organ as k_{MTC} and apparent T1w may differ between different tissue compartments.

The VDMP spectra from the egg white phantom clearly show the signals from amide protons (0 – 5 ppm) and aliphatic protons (–5 – 0 ppm) (Figures 3b and 3c). The frequency range is consistent with NMR studies of mobile proteins (39). The difference spectra thus give a good impression of the build up and decay behavior to be expected for APT/rNOE-CEST. Since the amide protons exchange faster than rNOE process, the APT signal reaches a maximum at around 20 to 40 ms mixing time, much faster than the signal from rNOE. When increasing the mixing time to 100 ms, the APT signal decreases from 4.5 % to 3 % while the rNOE signal only changes slightly (Figure 3d). The VDMP difference spectra also show that there are strong peaks in the range of 0–3 ppm, which are even higher than the main amide proton signal. This signal possibly originates from relayed NOEs from the aromatic protein protons and slowly exchanging side-chain amide protons. The water direct saturation differences depend only slightly on mixing time, which is consistent with the simulation in Figure 1d.

In the human brain, the APT signal is significantly lower than in egg white. As expected, the VDMP Z-spectra in gray and white matter showed very different MTC intensities, but we were able to accomplish MTC cancellation in both compartments, which we attribute to an accidental coincidence of k_{MTC} and T1w being sufficiently similar in gray and white matter. Figures 5a and 5c illustrate that, at 8 ppm, it is possible to reduce the MTC difference between the gray and white matter from more than 10% to a negligible residual. The resulting clean APT/rNOE-CEST images in Figure 6 show some interesting features. The APT map has higher signal intensity in gray matter than in white matter, presumably as a

result of higher content of mobile proteins. This observation is consistent with APT and rNOE-CEST map of mouse brain reported by Jin *et al* (40). The WM/GM contrast is different from the APT images recorded by other pulse-CEST sequences such as ZAPI, SAFARI and uMT methods. We speculate that this is due to some residual MTC contrast in these methods.. The exchange rate of amide protons is around 29 Hz, which is relatively close to the exchange rate of MTC, around 40– 60 Hz. When MTC reaches the nulling mixing time, the APT has already started to decay. Therefore, the APT signal measured by the current scheme is only a few percent, and depends on the mixing time. Nevertheless, the APT map obtained this way reflects the true APT weighting with strongly reduced MTC and DS confounds. Interestingly, on the other hand, while the absolute intensity of the rNOE-CEST map was much stronger than for APT, the difference between gray and white matter was not significant for the current saturation scheme. This result indicates that the mobile macromolecules that contribute to the rNOE signal distribute equally in both WM and GM compartments. This result is very gratifying in view of recent spectroscopy data showing that the mobile macromolecules contributing to the MRS baseline have comparable concentration between WM and GM (41). Earlier work by our group had already shown that, at very low B_1 , the rNOE Z-spectral features resemble those in the mobile macromolecule (MM) baseline in MRS (11). The mobile macromolecule content in the healthy human brain tissue may be altered during disease processes such as cancer and multiple sclerosis (42,43). Such physiological changes can now potentially be monitored by the VDMP method without significant MTC interference. However, caution is needed because the null time may change under pathological conditions, i. e. in the presence of lesions, due to changes in k_{MTC} and $T1w$. Then, a single null time may not enough to remove the MTC pool completely from normal and pathological tissue. The current method still can be applied by recording images with several mixing times to find the null times for different tissues.

7 T human studies can be severely hampered by B_0 and B_1 inhomogeneity. Our current study demonstrates that the VDMP difference approach is relatively insensitive to B_0 inhomogeneity since it avoids the use of MTR asymmetry analysis. The B_0 field inhomogeneity is at most 30–100 Hz over the whole brain (~ 0.10 – 0.3 ppm). Since the saturation lines for exchangeable protons are relatively broad compared to the B_0 field inhomogeneity, they have a relatively uniform intensity in regions around ± 3.5 ppm (see Z-spectra in Figures 4c and 5a). While B_1 inhomogeneity will affect the magnitude of the saturation, it does not affect the exchange filtering, as this depends only on the mixing time. The MTC and DS signals will cancel even if voxels experience different B_1 . B_1 inhomogeneity would show a pattern of intensity changes symmetric to the image center and this is not visible in Figs. 6a and b, which demonstrates that the current method is immune to B_1 inhomogeneity. In this study, one volunteer was tested to find the optimal mixing time (100 ms) and two full Z-spectra were acquired at 0 and 100 ms for all the other volunteers to check the residual MTC. Once a VDMP protocol is established for a certain organ, only two images with the established mixing times for MTC and DS removal are necessary to obtain APT or rNOE-CEST, respectively. The DS and MTC are suppressed by subtracting the two images, and no asymmetry analysis is needed. Therefore, the APT/rNOE-CEST can be performed rapidly, and have great potential to be incorporated as part of a clinical exam.

The VDMP difference technique is applicable at 3 T MRI as well. However, while offering better B_0 and B_1 homogeneity, an increased challenge is that direct water saturation is significantly higher as the frequency difference with water in Herz is reduced by more than 50%. For an individual Z-spectrum, the direct water saturation can in principle be corrected by using the “inverse metric” of Z-spectra approach. (21) However to apply this principle in the VDMP technique needs to be investigated and demonstrated experimentally. Practically, a weaker saturation pulse still needs to be applied to reduce its impact on the t_{null} . We are currently in the process of optimization this method at 3T. In the current study, single slice images were acquired as a demonstration. 3D whole brain APT/rNOE-CEST should be well possible using the current VDMP method considering its short acquisition time.

CONCLUSION

We report a two-scan VMDP method that can suppress direct saturation (DS) and conventional magnetization transfer contrast (MTC) by taking the difference between images acquired at two different mixing times. When tested on healthy human brains, the MTC for white matter was suppressed from more than 10% at 8 ppm to negligible values. With a clean background without MTC, clean APT and rNOE maps were obtained. Interestingly, the APT showed hyper-intensity in the gray matter, while the rNOE map was iso-intense between GM and WM. Since the reported method does not require asymmetry analysis, it is robust against B_0 field inhomogeneity, and eliminates the need for acquiring a full Z-spectrum. The signal suppression is also B_1 insensitive because it depends only on the mixing time. These advantages could facilitate fast translation of CEST imaging from research into clinical scans.

Acknowledgments

Grant support from NIH: R01EB015032, P50CA103175, and P41 EB015909.

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Figure 1.

Bloch simulations: (a) Effects of mixing time and exchange rate (log plot) on the normalized CEST signal intensity $S(\tau_{\text{mix}})/S(\tau_{\text{mix}}=0)$ (color scale) for the VDMP sequence; (b) Projections of the VDMP-CEST signal ratio from Figure 1a as a function of mixing time for four exchange rates corresponding approximately to typical rNOE (16 Hz), APT (29 Hz), MTC (60 Hz) and fast exchange (1000 Hz); (c) VDMP as a function of exchange rate at $\tau_{\text{mix}} = 80$ ms; (d) Z-spectra showing water direct saturation at 0 and 80 ms mixing time and VDMP with water T1 relaxation times of 1.5 s and 2.5 s, respectively.

Figure 2.

Three-pool Bloch simulations of APT-CEST (a,c,d) and MTC signal (b,d,f) as a function of mixing time and PSR_{MTC} for $T1w = 1.5$ s, $k_{\text{MTC}} = 60$ Hz (a,b); as a function of mixing time and apparent water $T1$ for $k_{\text{MTC}} = 60$ Hz, $\text{PSR}_{\text{MTC}}=9\%$ (c,d); as a function of mixing time and MTC exchange rate for $T1w = 1.5$ s, $\text{PSR}_{\text{MTC}}=9\%$ (e,f).

Figure 3.

(a) VDMP Z-spectra of an egg white phantom as a function of mixing time; (b) Zoomed-in view of (a); (c) VDMP difference spectra as a function of mixing time; (d) VDMP as a function of mixing time for APT and rNOE.

Figure 4.

(a) Image slice of choice; (b) VDMP Z-spectral signal intensity at 8 ppm (dominated by MTC) as a function of mixing time; (c) Z-spectra resulting from summation over all voxels within a brain slice and (d) the corresponding VDMP difference spectra as a function of mixing time.

Figure 5.

(a) MTC map at 8 ppm using a VDMP sequence with 0 ms mixing time; (b) Z-spectra of white matter (WM) and gray matter (GM) acquired using $\tau_{\text{mix}} = 0$ ms and 100 ms; (c) Residual MTC map at 8 ppm after subtracting the two images acquired with 100 ms and 0 ms mixing times; (d) The corresponding VDMP difference spectra for WM and GM.

Figure 6.

VDMP images of (a) APT and (b) rNOE calculated at 3.5 and -3.5 ppm respectively with mixing times of 0 ms and 100 ms; (c) Average APT and rNOE VDMP difference signal intensities in WM and GM over 5 volunteers. Error bar denotes the standard deviation.