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Communication

Is there any difference in Amide and NOE CEST effects between white and gray matter at 7 T?

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ABSTRACT

Measurement of Chemical Exchange Saturation Transfer (CEST) is providing tissue physiology dependent contrast, e.g. by looking at Amide and NOE (Nuclear Overhauser Enhancement) effects. CEST is unique in providing quantitative metabolite information at high imaging resolution. However, direct comparison of Amide and NOE effects between different tissues may result in wrong conclusions on the metabolite concentration due to the additional contributors to the observed CEST contrast, such as water content (WC) and water T_1 relaxation (T_{1w}). For instance, there are multiple contradictory reports in the literature on Amide and NOE effects in white matter (WM) and gray matter (GM) at 7 T. This study shows that at 7 T, tissue water T_1 relaxation is a stronger contributor to CEST contrasts than WC. After water T_1 correction, there was no difference in Amide effects between WM and GM, whereas WM/GM contrast was enhanced for NOE effects.

1. Introduction

Chemical Exchange Saturation Transfer (CEST) is a relatively new imaging technique based on indirect detection of low concentration metabolites through the water signal [1]. Two most studied CEST effects are Amide-CEST and relayed Nuclear Overhauser Enhancement (NOE) [2–5]. Ever since its introduction in 2000 [6], CEST has found diverse applications in metabolic imaging of glutamate [7], glucose [8], glycogen [9], creatine [10], myo-inositol [11], and glycosaminoglycans [12]. Also, Amide-CEST has been extensively used in the clinic for glioma grading [13–15], therapy response monitoring [16,17], and differentiation of radiation necrosis from the actual tumor [18].

However, despite all those applications, the knowledge on the origin of CEST contrast has lagged behind. In consequence, there are contradictory reports on distribution of Amide- and NOE-CEST effects between white matter (WM) and gray matter (GM) in the healthy human brain at 7 T. For instance, Dula et al. [19] used traditional asymmetry analysis (MTR_{asym}) to measure Amide-CEST and reported enhanced contrast in WM versus GM. Jones et al. [20] also used MTR_{asym} as a measure of Amide-CEST but did not find any difference between WM and GM. Nor did the Lorentzian fit method reveal any difference in Amide-CEST between WM and GM [21]. In contrary to the previous studies, Liu et al. [22] reported elevated Amide-CEST in GM compared to WM, by fitting four-pool Bloch-McConnell equations [23] to the experimental CEST (or Z-) spectra. Interesting to note that due to multiple CEST sequences and CEST effect extraction techniques, there are contradicting reports from the same group: no WM/GM contrast in [20,21] and hyperintensity in GM versus WM in [24] for Amide-CEST; hyperintensity in WM versus GM in [3,4] and negligible WM/GM contrast in [24] for NOE. The aim of the current study was to unravel the controversy outlined above, which is crucial for robust application of CEST-MRI in a clinical setting.

2. Methods

2.1. Numerical simulations

Four-pool (water, Amide-CEST, Nuclear Overhauser Enhancement-NOE and Magnetization Transfer-MT) Bloch-McConnell equations were solved numerically [25] at a B_1 of 1 μT assuming the following pool parameters [26]: (1) water

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(T_2 = 55 ms); (2) Amide-CEST (T_1/T_2 = 1 s/10 ms, exchange rate 50 Hz, pool size 0.13%, chemical shift 3.5 ppm); (3) NOE (T_1/T_2 = 1 s/0.3 ms, pool size 3%, exchange rate 10 Hz, chemical shift −3.5 ppm); and (4) MT (T_1/T_2 = 1 s/10 μs, pool size 3%, exchange rate 50 Hz, chemical shift −2.4 ppm). The T_1 values of all pools except water were fixed to 1 s, as suggested previously [27]. The water T_1 (T_{1w}) and water content (WC) were varied from 1 s to 2 s and from 50% to 100%, respectively.

Two methods to quantify Amide and NOE CEST effects were used in the simulations. The first method is the pool difference method:

$$Amide = M_z(3.5\ \text{ppm},M_A = 0)/M_0 - M_z(3.5\ \text{ppm},M_A = 1)/M_0 \quad (1)$$

where *Amide* is the effect size of cytosolic amides, $M_z(\Delta\omega, M_A)$ is the signal in the Z-spectrum at $\Delta\omega$, M_0 is the steady-state signal at 300 ppm and M_A is the amplitude of the Amide-CEST compartment (M_A = 0 and M_A = 1 without and with Amide pool, respectively). An equivalent equation applies to NOE at $\Delta\omega$ = −3.5 ppm.

The second method is the modification of the first, using the inverse metrics for T_{1w} relaxation compensation [28,29]:

$$AREX_{Amide} = \left[\frac{1}{M_z(3.5\ \text{ppm},M_b = 1)/M_0} - \frac{1}{M_z(3.5\ \text{ppm},M_b = 0)/M_0}\right] \Big/ T1w \quad (2)$$

where AREX represents a T_{1w} relaxation compensated Amide signal. An equivalent equation applies to NOE at $\Delta\omega$ = −3.5 ppm.

2.2. Data acquisition

The study was approved by the local ethics committee of the University Medical Center Utrecht and all of volunteers gave informed consent. All experiments were performed on a 7 T Achieva whole-body MR system (Philips Healthcare, Cleveland, OH, USA) using a quadrature transmit coil in combination with a 32-channel-receive head coil (Nova Medical, Wilmington, MA, USA). Five healthy subjects were scanned using a modified 3D interleaved CEST sequence [30]: saturation prepulse (a single RF-spoiled 25 ms sinc-gauss pulse followed by a 50 mT/m spoiler of 10 ms) interleaved with a sagittal, segmented EPI readout, (EPI factor 13 with a binomial RF pulse for water only excitation, TR/TE/FA = 65 ms/5.1 ms/15°, center of k-space weighted acquisition). The FOV was 217 × 217 × 185 mm^3 and the voxel size was 2 mm isotropic with SENSE factor 2 (anterior-posterior) and 2.8 (left-right). The total scan time was 5 min 11 s Third-order shims were applied to improve the homogeneity of the magnetic field across the whole brain.

Z-spectra were sampled at 37 offsets from −5.4 to 5.4 ppm (normalization offsets at ±100 kHz) with varying B_1 levels (0.2–1.0 μT with steps of 0.2 μT). B_1 is expressed as a continuous wave power equivalent. A B_1 map was acquired based on a dual TR sequence [31] and subsequently scaled to reflect the ratio between actual B_1^+ and nominal B_1^+. A T_1-weighted anatomical scan was used to create masks of white matter (WM) and gray matter (GM). A high-resolution T_1 map was obtained using the method in [32].

2.3. Data processing

Co-registration and segmentation (using a threshold of 0.9) were done in FSL (FMRIB v6.0, UK, FLIRT [33,34]). Amide and NOE effects in WM and GM were quantified as whole-brain averaged using the corresponding masks and the three-point method [5]. Before the averaging, each spectrum in the ROI was B_0-corrected pixel-wise by estimating the minimum of CEST spectrum (spline interpolated to a resolution of 1 Hz) and shifting the whole z-spectrum accordingly [35]. The three-point method is an approximation since it assumes a linear baseline [5], and hence the effects are termed Amide* (Eqs. (3) and (4), without and with T_{1w} relaxation compensation [28,29], respectively) and NOE* (Eqs. (5) and (6), without and with T_{1w} relaxation compensation [28,29], respectively). Both the three-point and AREX methods are based on an assumption that CEST effects can be isolated from MT and direct water saturation effect. A Student *t*-test was performed to compare the WM and GM results at a significance level of p = 0.05. Simulations and further image processing and analysis were done using MATLAB (The Mathworks Inc., USA).

$$Amide^* = \left(\frac{\text{Mz}(3.0\ \text{ppm}) + \text{Mz}(4.0\ \text{ppm})}{2}\right) - \text{Mz}(3.5\ \text{ppm}) \quad (3)$$

$$AREX^*_{Amide} = \left[\frac{1}{\text{Mz}(3.5\ \text{ppm})} - \frac{1}{\left(\frac{\text{Mz}(3.0\ \text{ppm})+\text{Mz}(4.0\ \text{ppm})}{2}\right)}\right] \Big/ T1w \quad (4)$$

$$NOE^* = \left(\frac{\text{Mz}(-5.0\ \text{ppm}) + \text{Mz}(-2.0\ \text{ppm})}{2}\right) - \text{Mz}(-3.5\ \text{ppm}) \quad (5)$$

$$AREX^*_{NOE} = \left[\frac{1}{\text{Mz}(-3.5\ \text{ppm})} - \frac{1}{\left(\frac{\text{Mz}(-5.0\ \text{ppm})+\text{Mz}(-2.0\ \text{ppm})}{2}\right)}\right] \Big/ T1w \quad (6)$$

3. Results

Representative WM and GM masks, T_1 and B_1 maps for an axial slice through the brain of a healthy volunteer are shown in Fig. 1.

3.1. Bloch-McConnell simulations

To characterize the influence of T_{1w} and WC on Amide and NOE effects, four-pool Bloch-McConnell simulations were performed. In Fig. 2, two different metrics of Amide (Amide and $AREX_{Amide}$, without and with T_{1w} relaxation compensation, respectively) and NOE

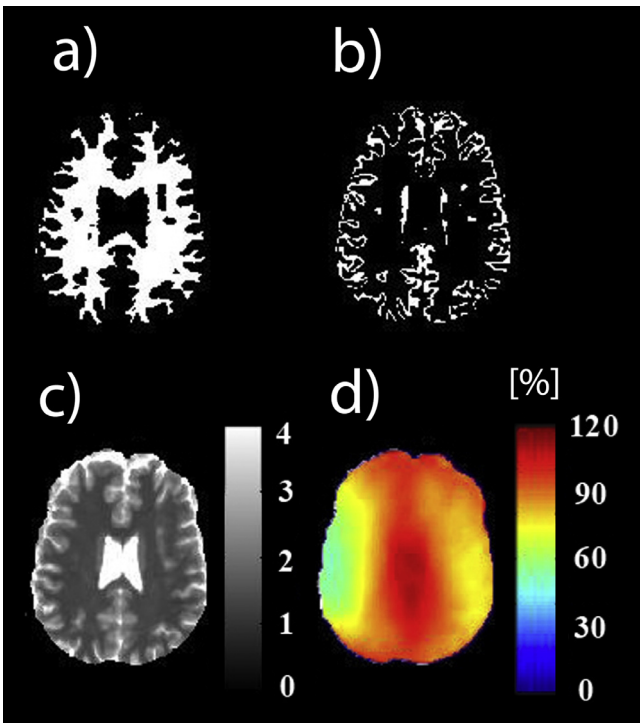

Fig. 1. An axial slice from the brain of a healthy volunteer for (a) WM mask, (b) GM mask, (c) T_1 map and (d) B_1 map.