On the distribution of pure Amide Proton Transfer and pure Nuclear Overhauser Enhancement signals in gray and white matter in the human brain at 7T

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Abstract. Chemical exchange saturation transfer (CEST) is capable of generating tissue physiology dependent contrast, e.g. metabolite level, by looking at APT (amide proton transfer) and NOE (nuclear overhauser enhancement) signals [1]. Therefore, CEST has the potential to be an important pathology biomarker. However, direct comparison of APT and NOE signals between normal and pathological tissue may result in artificial conclusions due to confounding effects on APT and NOE, such as magnetization transfer (MT), direct water saturation (DS), water T_1 relaxation (T_{1w}) and water content (WC). This study performed in the healthy human brain shows, that after correcting for T_{1w} (using an acquired T_1map) and WC in the MT/DS free APT and NOE signals, there is no significant difference in signal between white matter (WM) and grey matter (GM) for APT, whereas the WM/GM contrast is enhanced for NOE.

Methods. All experiments were performed on a 7T Achieva MR system (Philips, Best, the Netherlands) using a quadrature transmit coil in combination with a 32-channel-receive head coil (NOVA medical). A 3D interleaved CEST sequence [2] was modified with the following parameters: sagittal acquisition with segmented EPI readout (EPI factor of 13) using a binomial RF pulse for fat suppression, SENSE factor 2 (AP) and 2.8 (RL), saturation prepulse 25ms (bandwidth 85Hz) followed by a spoiler of 10ms, TR/TE/FA=65ms/5.1ms/15°, FOV 217x217x185 mm^3, reconstructed voxel size 2mm), time per volume 8.2s, total scan time 5min11s. CEST data were acquired (k-space center-weighted) at 37 offsets from -5.4 to 5.4 ppm (normalization offsets at ± 100kHz) with varying B_1 levels (0.2-1.0μT with steps of 0.2μT). B_1 is expressed as a continuous wave power equivalent (CWPE). A B_1map was acquired based on a dual TR sequence [3]. A T_1-weighted anatomical scan (3D TFE, TR/TE/FA= 5.5ms/2.0ms/6°, voxel size 1mm) was used for co-registration of the CEST data and T_1map (obtained using the method in [4]), which also was used to create partial volume masks of WM and GM. Both co-registration and segmentation were done in FSL (FMRIB v6.0, UK). All data analysis and simulations were done in MATLAB®.

Simulations. The average concentrations of APT and NOE pools in the human brain were estimated from a four-pool model by means of comparison between simulated and experimental data (data not shown), assuming exchange rates of 30Hz and 4Hz for APT and NOE, respectively. Four-pool simulations were done to estimate the effects of T_{1w} and WC on APT (**Fig. 1 A**) on NOE (**Fig. 1 B**) using 3-point method for APT and NOE extraction [6]. According to our simulations (data not shown), 3-point method derived APT and NOE are slightly underestimated but free of MT and DS effects. The T_{1w} effect was corrected as suggested by Zaiss et al [7]. Effect of WC was corrected by multiplying T_{1w} corrected APT and NOE signals with their corresponding water fractions. MT/DS free APT and NOE, corrected for T_{1w}/WC effects are defined as pure APT and pure NOE, respectively.

Experimental data. Whole brain WM and GM binary masks (obtained from their partial volume masks using a threshold factor of 0.8) were used to compute their corresponding average CEST spectra at varying B_1 levels. Average APT and NOE signals in WM and GM were calculated using 3-point method [6] Average APT and NOE signals in WM and GM at each B_1 level were pooled together from 5 healthy volunteers for statistics (**Fig. 2 A**). The T_{1w} effect on APT and NOE was corrected as suggested by Zaiss et al [7] with a linear B_1 correction using an acquired B_1map. Effect of water content was corrected by multiplying T_{1w} corrected APT and NOE signals in WM and GM with their corresponding water fractions (assuming water fractions of 70% for WM and 80% for GM [8]). Data from **Fig. 2A** corrected for T_{1w} and WC effects are shown in **Fig. 2 B**.

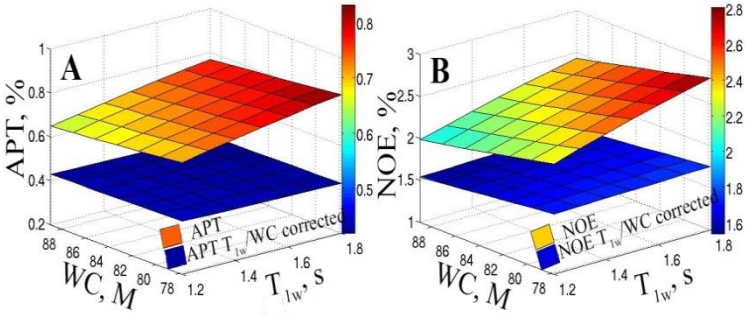

Fig. 1. *Simulated dependencies for 3-point method derived APT (A) and NOE (B) as a function of water T_1 (T_{1w}) and water content (WC). Skewed and flat planes for non-corrected and T_{1w}/WC corrected data, respectively. Simulations were done at 0.8 μT. using a 4 pool model with parameters being average between WM and GM: 1.H2O (T_2 40ms), 2.APT (T_1 1s, T_2 10ms, 62mM, 30Hz), 3.MT (T_1 1s, T_2 15μs, 8.34M, 4Hz) [5] and 4. NOE (T_1 1s, T_2 2.5ms, 1.5M, 4Hz). Super-lorentzian lineshape was assumed for MT. The skewed planes in (A) and (B) are offset by 0.2% and 0.5%, respectively, for clear visualization.*

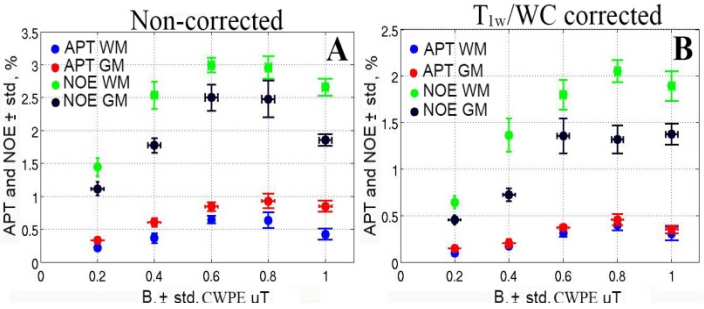

Fig. 2. *Experimental results for 5 healthy volunteers, non-corrected (A) and T_{1w}/WC corrected APT and NOE (B). Horizontal and vertical error bars represent standard deviation for APT/NOE and B_1 level, respectively.*

Results and discussion. As shown in the **Fig. 1**, pure APT and pure NOE can be obtained after correction of MT/DS free APT and NOE for T_{1w} and WC effects. A similar correction algorithm was applied to experimental data (**Fig. 2**). Clear, comparison of non-corrected and corrected APT signal in WM and GM reveals that the APT contrast between WM and GM comes from the T_{1w} and WC effects. Thus, in contrary to multiple reports [9], where APT and NOE were contaminated with the effects of the water pool parameters, we show that after correction of MT/DS free APT and NOE signals for T_1w and WC, there is no significant difference in pure APT between WM and GM, while pure NOE is significantly higher in WM. Average APT pool (assuming exchange rate 30Hz) in WM and GM was estimated to be 62±8 mM and average NOE pool (assuming exchange rate 4Hz) was estimated to be 1780±100 mM and 1230±100 mM in WM and GM, respectively.

References. [1] Zhou J et al. NatureMed. 2011. [2] Jones CK et al. MRM 2012. [3] Yarnykh VL. MRM. 2007. [4] Ordidge RJ et al. MRM. 1990. [5] Ramani A et al. MRM. 2002. [6] Zu Z et al. MRM 2013. [7]. Zaiss M et al NMRBiomed 2014. [8] Heiko N et al. NeuroImage. 2006. [9] Liu D et al. MRM. 2013.

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