Imaging of Endogenous CEST Agents in the Human Brain using Frequency Labeled Exchange (FLEX) Transfer

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TARGET AUDIENCE: Researchers and Clinicians interested in chemical exchange saturation transfer (CEST) and/or imaging endogenous mobile proteins, peptides or metabolites containing rapidly exchanging protons in vivo.

PURPOSE: CEST contrast agents are a powerful tool for studying physiology because they are sensitive to processes such as changes in pH, temperature, and protein or metabolite concentration. Recently, a new technique for labeling exchanging protons was proposed which offers some advantages over the CEST method. This method, dubbed frequency labeled exchange (FLEX) transfer labels exchanging protons with their chemical shift evolution instead of saturation. This is accomplished using a pair of excitation pulses after which this magnetic label is stored as longitudinal proton magnetization and transferred to the water pool to be indirectly detected by measuring the water signal intensity. Analogous to CEST, a series of such label-transfer modules (LTMs) is applied prior to detection to enhance the transfer effect on the water signal.

Using excitation pulses for magnetic labeling as opposed to saturation (i.e., CEST) enables FLEX to label exchanging protons more rapidly and avoids interference from conventional magnetization effects (MT) in tissue.[1,2] Additionally, FLEX data can be analyzed using time domain analysis, which can easily separate out different components in the FLEX signal without need for asymmetry analysis. To date, the results of FLEX studies have only been published from experiments carried out on phantoms using high-resolution NMR spectrometers or animal MRI scanners. The series of excitation pulses used for FLEX experiments poses several challenges for human vivo studies including B_1 inhomogeneity of the excitation pulses over a large field of view, duty cycle limitations, and specific absorption rate (SAR) limits. Here, we present FLEX results from human brain acquired using a 3 T human MRI scanner.

METHODS: The FLEX method has been described in detail elsewhere.[1-3] FLEX MRI images were acquired for five healthy human volunteers using a 2 s preparation period followed by a single-shot EPI readout (TR/TE = 8 s/13 ms) with a 10 mm slice across a field of view of 200 × 200 mm^2 with 3 × 3 mm^2 in-plane resolution. The FLEX preparation consisted of 100 LTMs, each LTM was 20 ms in duration and consisting of a pair of 1 ms excitation pulses (amplitude = 5.9 μT) applied 968 Hz (7.6 ppm) away from the water resonance. The delay between these excitation pulses (t_{evol}) was varied between 0.3 to 10.1 ms in steps of 0.2 ms. This gave a total scan time of approximately 14 minutes for FLEX experiments when both the sine and cosine components of the FLEX signal were collected (2 x 52 = 104 acquisitions). The SAR value calculated by the scanner software was 17%.

RESULTS: Figure 1 shows FLEX time domain signals and spectra from the grey and white matter of a single volunteer (note: grey matter data may include contributions from CSF). Comparing the results, FLEX pulses cause the bulk water signal to drop to ~50% in white matter (a) and ~60% in gray matter (d). The FLEX time domain signal (shown in Figs. 1b,e) can be obtained by subtracting the baseline (red line in Fig. 1a,d) from the experimental data. The FLEX signal can also be visualized in the frequency domain by Fourier transforming the time domain signal (Figs. 1c,f). The amplitude of the FLEX signal (proton transfer ratio or PTR) from endogenous CEST agents can be plotted for each voxel to generate a FLEX PTR map (Fig. 2).

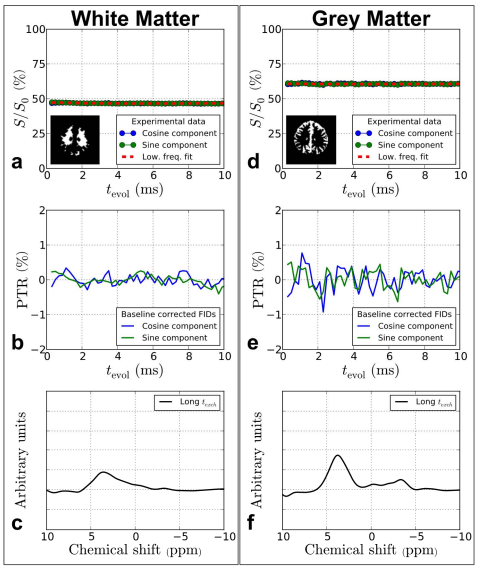

Fig. 1. FLEX data from a single human volunteer

DISCUSSION: The greater drop in the bulk water signal in white matter compared to gray matter is due to conventional MTC induced by the FLEX labeling pulses. However the effect of the bulk water can be separated from the FLEX solute data by subtracting the baseline The decay of the FLEX data (Figs. 1b,e), which is attributed to the solute water exchange rate (k_{sw}) + $1/T_{2s}^*$, is ~400 s^{-1}. This indicates that the FLEX signal is composed of rapidly exchanging protons as $1/T_2$* is expected to be on the order of tens of Hz. The components of the composite signal in the spectra (Figs. 1c,f) therefore most likely are fast amides and amines of mobile proteins and abundant metabolites, which typically exchange at that rate. In the PTR map, which is free of interference from the large water signal and conventional MT, the signal is generally higher in grey matter/CSF compared to white matter.

CONCLUSIONS: The first human in vivo results from FLEX MRI experiments are presented. FLEX MRI in the human brain preferentially detects more rapidly exchanging amide/amine protons compared to traditional CEST experiments, thereby changing the information content of the exchangeable proton spectrum. This has the potential to open up different types of endogenous applications as well as more easy detection of rapidly exchanging protons in diaCEST agents or fast exchanging units such as water molecules in paraCEST agents without interference of conventional MTC.

REFERENCES: 1. Yadav et al., Magn Reson Med 2012; 68:1048-1055. 2. Lin et al., Magn Reson Med 2012; 67:906-911. 3. Friedman et al., J Am Chem Soc 2010; 132: 1813-1815. Funding: NIH grants R01EB015032, P50CA103175 and P41 EB015909

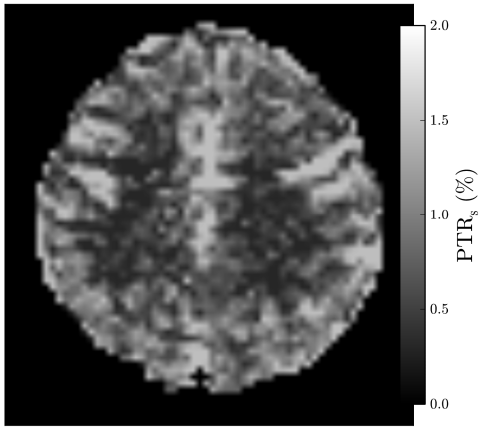

Fig. 2. FLEX proton transfer ratio map