Imaging of Regional Distribution of Brain Glutamate with GluCEST MRI

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Introduction: Glutamate (Glu) is the major excitatory neurotransmitters in the brain, and is likely involved in nearly all signal processing functions of the central nervous system (CNS) as well as being altered in many CNS diseases, such as Alzheimer's, Multiple sclerosis. In addition to its role as the predominant excitatory neurotransmitter in the brain, glutamate also serves as a metabolic intermediate in the brain. Proton magnetic resonance spectroscopy (^{1}H-MRS) can detect several neurotransmitter signature groups (-CH_2) using a variety of techniques. However, ^{1}H-MRS techniques require long acquisition times and have poor spatial resolution. The CEST effect from amide and hydroxyl protons from different molecules have previously been exploited [1-3]. Based on Glu amine proton exchange saturation transfer (GluCEST) effect, recently, we demonstrated the feasibility of mapping relative changes in Glu concentration as well as pH *in vivo* [4]. GluCEST provides markedly increased spatial and temporal resolution than ^{1}H-MRS. In the current study, brain regional variation of GluCEST is investigated and compared to existing MRS and positron emission tomography (PET) studies.

Methods: The study was conducted under an approved Institutional Review Board (IRB) protocol. Seven normal male volunteers (n=7, 18-67 years old) were scanned at a Siemens whole body 7T scanner using a 32-channel volume RF coil. Multi-slice GluCEST maps of human brains were acquired using the following imaging parameters: number of average=2, slice thickness = 5 mm, GRE flip angle=10°, GRE readout TR = 5.5 ms, TE = 2.6 ms, field of view = 240 × 240 mm^2, matrix size = 192 × 192, with a saturation pulse at B_{1rms} of 155 Hz (3.6 μT) for 1 s duration and single shot readout every 16 s. Raw CEST images were acquired at varying saturation offset frequencies ranging from -2 to +4 p.p.m. with a 0.25 p.p.m. increment. To remove field inhomogeneities induced artifacts, B_1 and B_0 maps are acquired for GluCEST map reconstruction at +3ppm as previously described [4, 5].

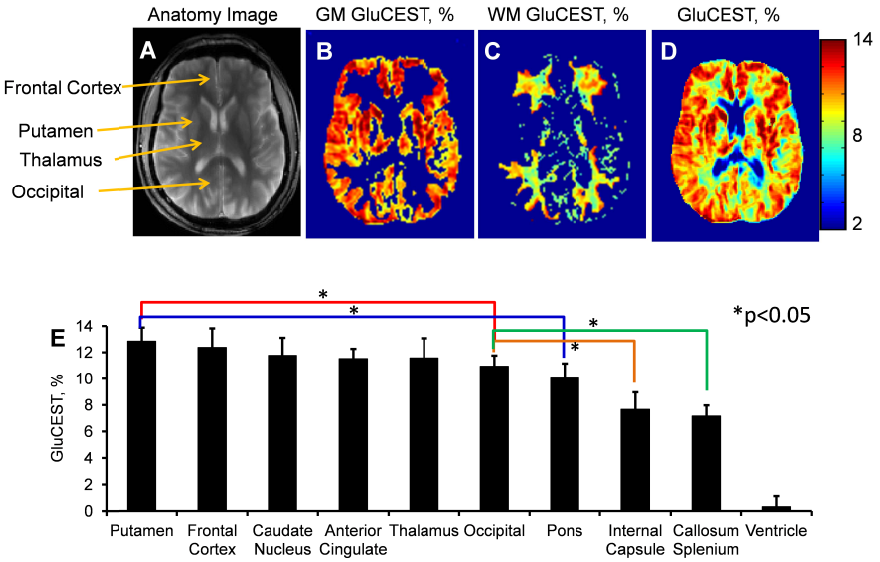

Figure 1. A representative axial brain MR image (A) and the corresponding segmented GM, WM and entire GluCEST maps (B-D). The slight difference of CEST contrast between same tissues of left and right hemispheres may be due to brain positioning asymmetry. Regional variation of averaged (n=7) GluCEST contrast is shown in E.

Results: The observed GluCEST is about 60% higher in gray matter (GM), such as putamen and occipital lobe than in white matter (WM) regions such as, internal capsule and callosum splenium (Figure 1). This is consistent with the reported ^{1}H-MRS results [6]. The GluCEST regional distribution (Figure 1.E) also reflects the known regional variation of physiological concentrations of glutamate quantified by ^{1}H-MRS [6]. GluCEST in putamen is significantly higher than that in occipital gray matter ($p<0.05$) and in all the other white matter regions. GluCEST map shows a similar distribution pattern compared to PET map of the metabotropic Glu receptor subtype 5 (mGluR5), although with much higher resolution (<10mm^3 (GluCEST) *vs.* ~200 mm^3 (PET)) [7]. No obvious age dependence is found probably due to the limited sample size.

Conclusion: We demonstrated the feasibility of mapping GluCEST *in vivo* with a spatial resolution <10 mm^3. The regional variation of Glu depicted by this high-resolution GluCEST maps is consistent with the previously published ^{1}HMRS as well as PET studies.

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