A novel single-voxel ^{1}H-MRS sequence for single-shot detection of brain glycine

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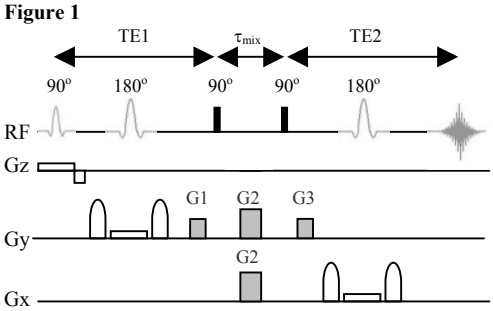
Introduction: Glycine (Gly) serves as an essential coagonist for the glutamatergic N-methyl D-aspartate (NMDA) receptor subtype. NMDA receptor hypofunction is implicated in brain disorders including schizophrenia (1) and several therapeutic agents are under development to treat this disorder (e.g. Gly transport inhibitors). We recently developed a non-invasive method capable of monitoring cerebral Gly levels in response to such therapeutics involving ^{1}H-MRS echo time (TE)-averaging. That method acquires several TEs which when averaged result in suppression of *J*-coupled mI resonances thereby enhancing singlet Gly-detection sensitivity (2). However, sampling of multiple TEs requires long measurement times. Thus, the method is susceptible to patient motion. Accordingly, we developed a novel single-shot method capable of suppressing mI with high efficiency whilst retaining the Gly resonance.

The sequence is shown schematically in figure 1, and is analogous to the double-quantum filtered (DQF) ^{1}H-MRS editing sequences typically used for the detection of *J*-coupled species such as GABA (3). However, the novel sequence uses two broadband hard 90° RF pulses for coherence transfer and the coherence transfer pathway (CTP)-selection gradient integral ratios is set to G1:G2:G3 = 1:1.5:1 ensuring filtration of the CTP (**p** = 0,+1,-1,0,+1,-1). The sequence effectively is a single- and zero-quantum filter (SZQF). In this abstract, we describe implementation of this sequence for mI suppression and Gly enhancement both in phantoms and *in vivo*. The sequence initially was tested in phantoms and individual sequence timings were empirically adjusted to maximize attenuation of mI resonances at 3.52 ppm. SZQF ^{1}H-MR spectra subsequently were acquired from phantoms containing Gly and mI concentrations typically found *in vivo.* Preliminary *in vivo* data were acquired from two healthy volunteers.

Figure 1



Methods: All measurements were performed on a 4.0 T Varian Unity/INOVA whole body MRI/MRS scanner (Palo Alto, CA) with a transverse electromagnetic (TEM) resonator head coil used for radiofrequency (RF) transmission and reception. Shinnar-Le Roux (4) optimized RF pulses were used for slice-selection and standard rectangular RF pulses of 250 ns duration were used for non-selective excitation. All data were acquired from 8-ml voxels. *In Vitro* Measurements: We initially acquired a series of SZQF ^{1}H-MR spectra from a voxel positioned at the center of a spherical phantom (300-ml) containing mI (8 mM), creatine (Cr; 10 mM) and chelated gadolinium (~0.5 mM, 0.1% v/v Omniscan). The optimal sequence timings were determined as follows: TE1 = 59.0 ms, τ_{mix} = 39.0 ms, TE2 = 22.5 ms using a TR = 2000 ms and NEX = 128. An identical measurement was performed on a second phantom containing Gly (1 mM) with the same quantity of Cr and gadolinium. Subsequently, Gly (1 mM equivalent) was added to the mI phantom and a third SZQF ^{1}H-MR spectrum was acquired from the modified phantom. *In Vivo* Measurement: The optimized sequence was used to acquire datsets from the occipital cortex of healthy controls (two males, mean age: 24.5 years) to demonstrate *in vivo* feasibility. Data Processing: Raw data were processed using FELIX 2002 (Accelrys Inc., San Diego, CA) by zero-filling to 4096 complex points, application of an exponential filter (line broadening 2 Hz), fast Fourier transformation (FFT) and phase correction. Signal assignments were based on previously reported chemical shift values (5) and all spectra were chemical shift referenced to the Cr methyl resonance at 3.0 ppm.

Results: Figures 2(a) and (b) display the SZQF ^{1}H-MR spectra recorded from the Gly+Cr and mI+Cr phantoms, respectively. Figure 2(c) shows the corresponding spectrum obtained from the Gly+mI+Cr phantom. All three ^{1}H-MR spectra presented in figure 2 are presented using identical 1D scaling and show the characteristic methyl and methylene singlet resonances of Cr at 3.0 and 3.9 ppm, respectively. Figure 2(a) shows an additional peak at 3.55 ppm, which corresponds to the Gly methylene resonance. Figure 2(b) shows a mI resonance at 4.05 ppm and a group of strongly attenuated mI peaks between 3.45 and 3.65 ppm. In addition to the Cr singlet peaks, figure 2(c) shows additional resonances attributable to the Gly singlet and to the attenuated mI resonances.

Figure 2

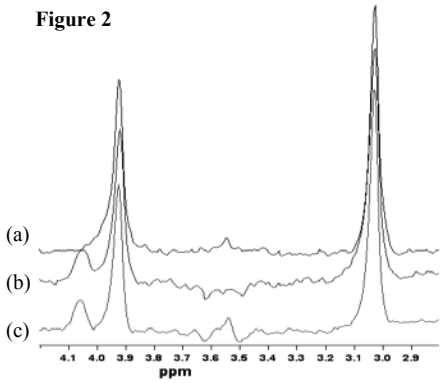


Figure 3

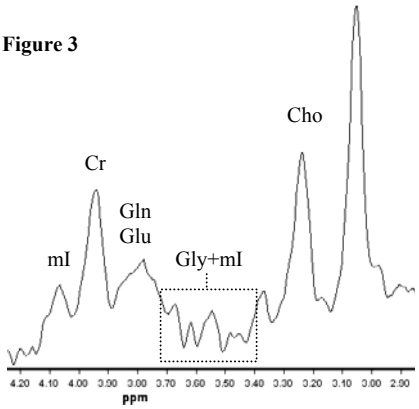


Figure 3 shows a preliminary SZQF ^{1}H-MR spectrum recorded *in vivo* from the occipital cortex one of our volunteers. Peaks observed can be assigned to Cr (3.0 and 3.9 ppm) and to the methyl proton peak of choline (Cho) at 3.2 ppm. The downfield mI peak also is seen at 4.05 ppm and a group of peaks between 3.7 and 3.9 ppm are likely to be attributable to glutamate (Glu) and glutamine (Gln). Importantly, the complex signature of mI resonances and Gly peak is observed in the *in vivo* spectrum. For both *in vivo* spectra, we measured the integrals for the Gly+mI peaks and for the Cr 3.0 ppm peak. The mean (±SD) Gly+mI:Cr ratio was calculated as $0.1505 \pm 4.95 \times 10^{-3}$.

Discussion: The SZQF ^{1}H-MRS sequence we describe was designed to selectively highlight the Gly singlet peak by attenuating the *J*-coupled mI peaks in a single-shot. In phantoms, we found that the SZQF sequence suppressed mI resonances near 3.52 ppm by about 98% when compared to data obtained with conventional PRESS ^{1}H-MRS methodology (TE = 30ms; data not shown). This provides a mI suppression factor comparable to that obtained using TE-averaged ^{1}H-MRS (2). In addition, these phantom measurements demonstrate the applicability of the SZQF sequence for Gly detection with a potential fourfold reduction in measurement time compared to our TE-averaging approach (2). Further, the *in vivo* data closely match *in vitro* findings. Together, these data warrant additional *in vivo* SZQF ^{1}H-MR studies to establish test-retest reliability of this sequence.

References: [1]Olney JW, *et al*. JPsychiatry Res 1999;33(6)523-533; [2]Prescot AP, *et al*., Magn Reson Med, 2005:Accepted for publication; [3]Keltner J, *et al*., Magn Reson Med 1997;37(3):366-371; [4]Shinnar M, *et al*., Magn Reson Med 1989;12(1):81-87; [5]Govindaraju V, *et al*., NMR Biomed 2000;13(3):129-153.

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