In Vivo Glycine Detection with TE-Averaged ^{1}H-MRS

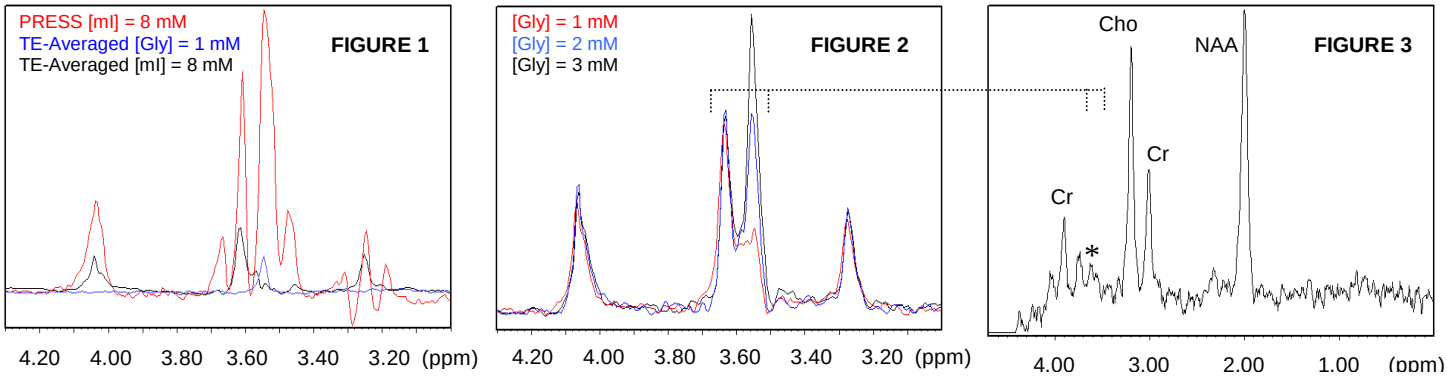
A. P. Prescot[1], B. D. Frederick[1], Y. Ke[1], J. Brown[2], L. Wang[2], M. J. Kaufman[1], P. F. Renshaw[1]

[1]Brain Imaging Center, McLean Hospital, Belmont, MA, United States, [2]Translational Medicine and Technology, GlaxoSmithKline, Greenford, London, United Kingdom

Introduction Glycine (Gly) is an important inhibitory amino acid neurotransmitter in brain but also participates as a co-transmitter in excitatory N-Methyl-D-Aspartate (NMDA) receptor signaling (**1**). Its brain concentration is ~1 mmol/kg (**2**). A number of brain disorders appear to be related to NMDA receptor dysfunction including substance abuse (**3**), schizophrenia (**4,5**), and anxiety disorders (**6**). Though proton magnetic resonance spectroscopy (^{1}H MRS) can detect Gly, its 3.55 ppm resonance overlaps with myo-inositol (mI) resonances. This complicates use of standard ^{1}H MRS techniques for identifying in vivo Gly except in Gly-excess conditions such as nonketotic hyperglycinemia (**7**). However, Gly quantification in the non-excess conditions noted above remains extremely challenging. Accordingly, we developed a more sensitive ^{1}H MRS methodology based on echo time (TE)-averaging, which involves the acquisition and averaging of multiple TEs (**8**). This technique exploits the fact that the strongly *J*-coupled mI resonances surrounding the Gly singlet are subject to destructive interference between successive TEs, leaving the uncoupled Gly resonance relatively unchanged. In this abstract, we present phantom data using mI and Gly concentrations mimicking those found in vivo (**2**) to demonstrate the advantage of this technique. In addition, we present preliminary feasibility data applying this method in vivo in a healthy human subject.

Methods All data were acquired on a Varian/Unity INOVA 4 T whole-body MR system using a standard quadrature head coil for RF transmission and signal reception. A PRESS sequence was modified to enable TE-averaging (TE=30–284 ms,128 increments, TR=2000 ms, NEX=2). Global water suppression was achieved using the WET suppression sequence (**9**). *In vitro* Measurements: The TE-averaging sequence was initially used to acquire a spectrum from an 8 cc voxel positioned at the center of a spherical phantom (300-ml) containing mI (8 mM) and chelated gadolinium (~0.5 mM, 0.1 % v/v Omniscan). An identical measurement was performed on a second phantom containing Gly (1 mM) with the same quantity of gadolinium. Reference ^{1}H-MR spectra were recorded from both phantoms using a standard PRESS sequence (TR=2000 ms, TE = 30 ms, NEX = 64). Subsequently, Gly was added to the mI phantom in three steps to provide Gly concentrations of 1, 2 and 3 mM, and TE-averaged spectra were acquired from the modified phantom following each addition. *In vivo* Measurement: A TE-averaged dataset was acquired from the pons of a healthy 22 year-old woman to demonstrate the feasibility of the technique *in vivo*. The pons region was selected due to the relatively high Gly concentration within the brainstem (**10**). The voxel size for this measurement was 3.4 cc. Data Processing: Data were processed using FELIX 2002 (Accelrys, San Diego, CA) by averaging the 128 TEs, application of a exponential filter (line broadening = 2 Hz), fast Fourier transform (FFT) and manual phase correction. Signal assignments were based on previously reported chemical shift values (**2**) and all spectra were referenced to the downfield mI resonance at 4.05 ppm.

Results and Discussion Figure 1 shows a conventional PRESS ^{1}H-MR spectrum recorded from the mI phantom overlaid with TE-averaged data recorded from the mI and Gly phantoms (see color coding). Vertical scaling was identical for the 3 spectra shown. The TE-averaging method significantly attenuates the four strongly *J*-coupled mI resonances with the peak centered at 3.53 ppm showing severe signal cancellation. By contrast, the uncoupled Gly methylene proton resonance (centered at 3.55 ppm) exhibits less signal attenuation. The maximum amplitude of the Gly resonance was approximately 70% of the corresponding peak observed in the standard PRESS ^{1}H-MR spectrum (Gly PRESS data not shown). Figure 2 shows TE-averaged ^{1}H-MR spectra recorded from the three mI + Gly mixture phantoms with identical vertical scaling. These data clearly demonstrate how the Gly 3.55 ppm singlet resonance amplitude increases with increasing concentration (see color coding). Figure 3 displays a TE-averaged ^{1}H-MR spectrum recorded *in vivo* from the pons of our volunteer. The peaks between 3.5–3.7 ppm (labeled * in figure 3 and bracketed in figures 2 and 3) correspond to mI and Gly. The mI/Gly peak ratios shown in figure 2 suggest that the in vivo Gly concentration may fall between 1.0 and 1.5 mM, which is consistent with literature values (**2**).



Conclusions and Future Work TE-Averaging methodology significantly attenuates the strongly *J*-coupled resonances of mI thereby providing a novel and sensitive means for non-invasively measuring brain Gly concentration *in vivo*. We are currently acquiring TE-averaged ^{1}H-MR spectra from a larger subject cohort and are exploring several quantification strategies for assessing TE-averaged data.

References

1 Kleckner, N.W, Dingledine, R. Science 241:835-7, 1998.
2 Govindaraju, V. et al.. NMR Biomed. 13:129-53, 2000.
3 Bisaga, A., Popik, P. Drug Alcohol Depend. 59:1-15, 2000.
4 Olney, J.W, Farber, N.B. Arch. Gen. Psychiatry 52:998-1007, 1995.
5 Coyle, J.T. Harvard Rev. Psychiatry 3:241-53, 1996.
6 Gorman, J.M. J. Clin. Psychiatry 64 Suppl. 3:28-35, 2003.
7 Huisman, T.A. et al. Eur. Radiol. 12:858-61, 2002.
8 Bolan, P.J. et al. Magn. Reson. Med. 48:215-222, 2002.
9 Ogg, R.J. et al. J. Magn. Reson. 104:1-10, 1994.
10 Schell, M.J. et al. J. Neurosci. 17:1604-15, 1999.

Acknowledgements

This work was supported by NIH grants DA015116, DA009448, DA014178, DA019378, DA014013, DA017324 and by GlaxoSmithKline.