Measurement of Glutathione (GSH) Using A Standard STEAM Sequence with Optimized (TE, TM) Parameters: Spectral Simulation, Phantom, and Human Experiments at 3T

S. Yang[1], and Y. Yang[1]

[1]Neuroimaging Research Branch, National Institute on Drug Abuse, NIH, Baltimore, MD, United States

Introduction

Glutathione, in its primary reduced form (i.e., GSH), is a major antioxidant in the central nervous system. Because the proton resonances of all three (glycine, cysteine, and glutamate) moieties of GSH overlap with other metabolites [1], it is difficult to measure GSH using unedited magnetic resonance spectroscopy (MRS). Therefore, spectral editing, such as J-difference editing [2] or multiple quantum filtering [3-4], has been primarily employed to measure GSH, in which the CH_2 proton resonances of the cysteine moiety of GSH at 2.95 ppm are chosen as the target resonances and need to be distinguished from the prominent singlet resonance of creatine (Cr) at 3.02 ppm. A recent report [5] suggested an alternative strategy of using a standard STEAM sequence with optimized (TE, TM) parameters to simplify the C4 proton resonance of the glutamate (Glu) moiety of GSH (glu-GSH) at 2.54 ppm into a pseudo-singlet while suppressing the overlapping proton resonances of other metabolites: *N*-acetylaspartate (NAA), glutamine (Gln), and aspartate (Asp) around 2.54 ppm. However, after carefully evaluating the proton resonances residing around 2.54 ppm, we found that *N*-Acetylaspartylglutamate (NAAG) is another metabolite that has proton resonances overlapping with the glu-GSH resonance around 2.54 ppm and that the NAAG resonance at 2.54 ppm cannot be efficiently suppressed using the "optimized" (TE, TM) parameters reported in [5]. Therefore in this study, we extended the original (TE, TM) optimization by including NAAG as an additional overlapping metabolites and pinned down optimized (TE, TM) parameters for resolved measurement of GSH at 3T. Phantom and human experiments were conducted for verification.

Methods

Spectral Simulation. The responses of five metabolites (glu-GSH, NAA, NAAG, Gln, and Asp) to a STEAM sequence were simulated using the GAMMA library [6] throughout the two-dimensional (TE, TM) parameter space in a range of 0 to 200 ms for TE and a range of 0 to 140 ms for TM, with a step size of 1 ms in both parameters. The chemical shifts and coupling constants were taken from the literature [1]. The spectral simulation methods for simulation of RF pulses and spoiler gradients have been introduced in the previous report [5] and are omitted here for simplicity.

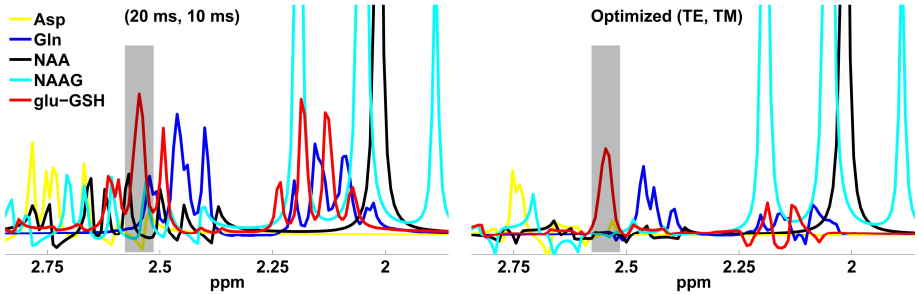

Fig.1. Simulated STEAM spectra of Asp, Gln, NAA, NAAG, and glu-GSH at (TE, TM) = (20 ms, 10 ms) and optimized (TE, TM) = (73 ms, 72 ms), with a 5-Hz line broadening. The shaded bars indicate the region of the central peak of target C4 pseudo-triplet proton resonance of glu-GSH at 2.54 ppm.

Optimization of (TE, TM) Parameters. The C4 proton resonance of glu-GSH at 2.54 ppm is chosen as the target resonance. The major overlapping resonances are the multiplet proton resonances of NAA around 2.48 ppm, NAAG around 2.52 ppm, Gln around 2.45 ppm, and Asp around 2.65 ppm. The left column of Fig. 1 shows the simulated STEAM spectra of Asp, Gln, NAA, NAAG, and glu-GSH at typical short-echo (TE, TM) = (20 ms, 10 ms), with a 5-Hz line broadening. The shaded bars indicate the region of the central peak of the target C4 pseudo-triplet proton resonance of glu-GSH. Extensive spectral overlap is clearly shown around 2.54 ppm. To distinguish the target glu-GSH resonance from the overlapping resonances, one strategy is to suppress the overlapping resonances while maintaining the target glu-GSH resonance as intense as possible. As such, an index or cost function for the (TE, TM) optimization was designed as $\boldsymbol{F} = \boldsymbol{C}_{GSH}[[\boldsymbol{b}]^2/([\boldsymbol{a}]+[\boldsymbol{c}])]-\boldsymbol{C}_{Asp}\boldsymbol{A}_{Asp}-\boldsymbol{C}_{Gln}\boldsymbol{A}_{Gln}-\boldsymbol{C}_{NAA}\boldsymbol{A}_{NAA}-\boldsymbol{C}_{NAAG}\boldsymbol{A}_{NAAG}$, where $\boldsymbol{C}$ is the concentration weighting factor (according to the literature [1,7], $\boldsymbol{C}_{GSH}$:$\boldsymbol{C}_{Asp}$:$\boldsymbol{C}_{Gln}$:$\boldsymbol{C}_{NAA}$:$\boldsymbol{C}_{NAAG}$ =2:1.5:4:7.5:2.5), $\boldsymbol{A}$ is the peak area of Asp, Gln, NAA, or NAAG in the region of the target glu-GSH resonance. Because the target glu-GSH resonance cover a relatively large region of 2.43-2.65 ppm, it is not feasible to suppress all the overlapping metabolite resonances in that target resonance region. So we designed the first item in the index to turn the target pseudo-triplet resonance into a pseudo-singlet, thus reducing the target spectral region at least by a half, as illustrated in Fig. 2. In the first item, [$\boldsymbol{b}$] is the peak area of the central peak of target pseudo-triplet resonance of glu-GSH, [$\boldsymbol{a}$] and [$\boldsymbol{c}$] are the peak areas of the two outer-wings of the pseudo-triplet. The index $\boldsymbol{F}$ should be maximized at the optimized (TE, TM) parameters, which requires: 1) maintaining the central peak of the target C4 proton resonance of glu-GSH at 2.54 ppm while suppressing the outer-wings to effectively reduce the target spectral region; and 2) suppressing the overlapping resonances of Asp, Gln, NAA, and NAAG around 2.54 ppm.

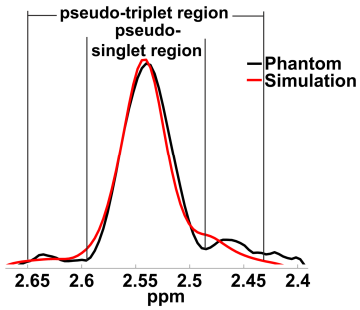

Fig.2. STEAM spectra (around 2.54 ppm) of GSH from phantom (black) and simulation (red) at the optimized (TE, TM) = (72 ms,73 ms). The spectrum from phantom was smoothed with a 5-Hz line broadening and the simulated spectrum was also smoothed to match the line width of the phantom spectrum.

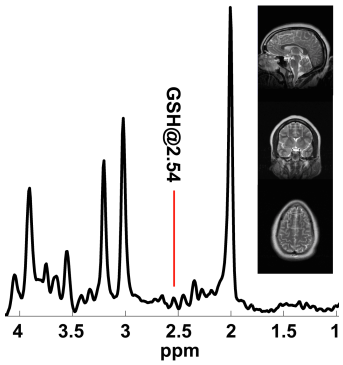

Fig.3. Representative STEAM spectrum from the frontal lobe of a human subject, acquired using the optimized (TE, TM) = (73 ms, 72 ms) at 3T. The resolved GSH resonance at 2.54 ppm was marked with a red line.

Phantom and Human Experiments. Phantom and human experiments were conducted on a Siemens Allegra 3T human scanner with a standard STEAM sequence. The sequence parameters were TR=2 s, bandwidth=2 kHz, sampling points=2048, voxel size=20×20×20 mm^3 (phantom) or 40×40×25 mm^3 (frontal lobe), NEX = 256. The phantom contained 50 mM GSH in a buffered solution (pH 7.2).

Results and Discussion

A contour diagram of the index $\boldsymbol{F}$ was generated in the (TE, TM) parameter space, similar with that in the previous report [5]. However, the maximum index is different after considering NAAG in the optimization, which resides at (TE, TM) = (73 ms, 72 ms). The right column of Fig. 1 shows the simulated STEAM spectra at (73 ms, 72 ms). Compared to the spectrum at (20 ms, 10 ms), the target GSH resonance at the optimum (TE, TM) is resolved from the overlapping metabolite resonances. Fig. 2 shows STEAM spectra (around 2.54 ppm) of GSH from phantom (black) and simulation (red) at the optimized (TE, TM) = (73 ms, 72 ms). As being expected, the target pseudo-triplet resonance of GSH at the optimum (TE, TM) is simplified to a pseudo-singlet, thus reducing the target spectral region at least by a half for efficient suppression of the overlapping resonances. Fig. 3 shows a representative STEAM spectrum from the frontal lobe of a human subject, acquired using the optimized (TE, TM) parameters. The resolved GSH resonance at 2.54 ppm provides a potential to improve the quantification of GSH levels. Correspondingly, an optimized quantification algorithm for reliably quantifying small peaks in a limited spectral region will be of great help for this application.

References 1. Govindaraju V et al., NMR Biomed 2000;13:129-153. 2. Terpstra M et al., MRM 2003;50:19-23. 3. Trabesinger AH et al., MRM 2001;45:708-710. 4. Zhao T et al., MRM 2006; 55:676-680. 5. Yang S et al., ISMRM 2008, 1639. 6. Smith SA et al., JMR 1994;106A:75-105. 7. Edden RAE et al., MRM 2007;57:977-982.