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Echo-time optimization for J-difference editing of glutathione at 3T

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Abstract

Purpose—To investigate the echo-time-dependence of J-difference editing of glutathione and to determine the optimal echo time (TE) for in vivo measurements at 3T.

Methods—Spatially resolved density-matrix simulations and phantom experiments were performed at a range of TEs to establish the spatial and TE modulation of glutathione signals in editing-on, editing-off and difference spectra at 3T. In vivo data were acquired in five healthy subjects to compare TE 68 ms and TE 120 ms. At the longer TE, high-bandwidth, frequency-modulated slice-selective refocusing pulses was also compared with conventional amplitude-modulated pulses.

Results—Simulations and relaxation-corrected phantom experiments suggest that the maximum edited signal occurs at TE 160 ms, ignoring transverse relaxation. Considering in vivo T_2 relaxation times of 67–89 ms, the optimal in vivo TE is estimated to be 120 ms. In vivo measurements showed that this TE gave 15% more signal than TE 68 ms. A further gain of 57% resulted from using improved slice-selective refocusing pulses.

Conclusion—J-difference editing of glutathione using TE 120 ms delivers increased signal due to improved editing efficiency that more than offsets T_2 losses. The additional echo time also allows for use of improved slice-selective refocusing pulses, which results in additional signal gains.

Keywords

brain; edited MRS; glutathione; GSH; echo time

Introduction

Glutathione (GSH) is the brain's main antioxidant and is primarily located in astrocytes (1, 2). Impairment of GSH antioxidant function, associated with oxidative stress, has been implicated in the pathophysiology of several psychiatric and neurodegenerative disorders including schizophrenia (1, 3-5), bipolar disorder (6-8), and Parkinson's disease (9-11). GSH is present in brain tissue at millimolar levels (12) and can therefore be detected non-invasively in vivo by proton magnetic resonance spectroscopy (^1H -MRS). Like other metabolites with coupled spin systems, the spectrum of GSH has several broad low-amplitude signals, none of which are fully resolved from other compounds in the in vivo spectrum. Quantification of GSH is therefore challenging, and while it can be estimated from 'LCModel fitting' of conventional high field MRS (13), more frequently spectral-editing approaches are used, either based on multiple-quantum filtering (14, 15) or J-difference editing (3, 16, 17). In recent times, the J-difference method has become the more commonly used editing approach for GSH.

As shown in Figure 1, glutathione is a tripeptide of glutamate, cysteine, and glycine. The cysteine moiety forms an ABX spin system, with signals at 2.93, 2.97, and 4.56 ppm (18). In J-difference editing of GSH, the editing pulse is applied at 4.56 ppm, and an edited signal is observed at ~ 2.95 ppm. The optimal echo time (TE) used for editing depends on the target molecule. In theory, ignoring relaxation, triplet-like signals should be edited at a TE of $1/2J$ (where J is the scalar coupling constant; for a typical 3-bond proton-proton coupling constant of 7 Hz, $1/2J \approx 70$ ms), while doublet-like signals should be edited at $1/J$ (≈ 140 ms) to maximize the edited signal. Approximating GSH as a simple A_2X spin system suggests the longer TE (140 ms) would be optimal. However, strong coupling effects make this prediction uncertain.

As a result, a large range of echo times, from 68 ms to 131 ms has been reported as optimal for in vivo J-difference editing of GSH. Terpstra *et al.*, who pioneered the measurement, reported that TE 68 ms is optimal based on phantom measurements made at 4T; this echo time continues to be used in vivo at 4T and 3T (19-23). Echo times of 80 ms and 94 ms have also been used at 3T (3, 24). One study proposed a TE of 131 ms based on phantom data and density operator simulations at 3T to maximize the edited GSH signal and minimize spectral interference from the co-edited N-acetyl-aspartate (NAA) signal (25); this echo time has been used in vivo at 3T (26).

This wide range of parameters is perhaps surprising, in contrast to GABA, for example, for which an echo time of 68 ms has been consistently used since editing was first reported (27). The aim of this study therefore was to systematically investigate the TE-dependence of the edited GSH signal, taking into account both the effects of scalar couplings and T_2 relaxation, using a combination of density-matrix simulations, and phantom and in vivo experiments.

Methods

Simulations

Density-matrix simulations were performed for a B_0 field strength of 3T using MATLAB-based software and literature values (18) for GSH chemical shifts and coupling constants. The excitation pulses were assumed to be an ideal rotation around the x-axis with a flip angle of 90° . Note that there was no need to perform a full spatial simulation of the excitation pulse, since this does not effect the evolution of spin-spin couplings, and would only serve to make the simulations more time-consuming. The MEGA-PRESS pulse sequence (28) was simulated using 20 ms sinc-Gaussian editing pulses with a bandwidth of 75 Hz and slice-selective refocusing pulses with a bandwidth of 1300 Hz and a duration of 6.91 ms ('GTST' pulses) (29, 30) for a nominal voxel size of $3\text{ cm} \times 3\text{ cm}$, in the dimensions defined by these pulses. The spin-system evolution was simulated for all positions on a 19×19 two-dimensional array spanning $3.6\text{ cm} \times 3.6\text{ cm}$ to examine spatial effects across a range that extends beyond the limits of the $3\text{ cm} \times 3\text{ cm}$ nominally excited region. The simulations are performed over a larger dimension than the nominal voxel size in order to capture the actual slice selection profile of the refocusing pulses used, and the effects of chemical shift displacement. This spatial simulation approach has been described in detail previously (31). Such spatially resolved simulations are important, as the time-evolution of coupled spin systems is spatially inhomogeneous (31-36). The shape of the spectrum that is acquired experimentally is the sum over the whole voxel and representative simulations must therefore capture this spatial inhomogeneity. At each position, a 2048-point free induction decay was simulated with 2 kHz spectral width, apodized with a 2.5-Hertz exponential filter, zero-filled to 8192 datapoints, and Fourier transformed.

Simulations were performed at TEs from 70 ms to 240 ms in 10 ms increments. The duration of the first slice-selective spin echo (TE1) was 13.4 ms, with the second spin echo adjusted to make up the remainder of TE. For each TE, spatially resolved spectra were integrated between 2.71 ppm and 3.19 ppm and summed to represent the signal from the whole (simulated) voxel.

Phantom experiments

A one-liter phantom of 50 mM GSH in phosphate-buffered saline with a pH of 7.0 was prepared. A Philips Achieva 3T scanner was used, with body coil transmit and a 8-channel head coil for receive.

J-difference editing experiments were performed at TEs from 70 ms to 240 ms in 10 ms increments using the MEGA-PRESS pulse sequence. TE1 was fixed at 13.4 ms and TE2 was changed to vary the total TE, as in the simulations. 2048 datapoints were acquired at a spectral width of 2000 Hz and a TR of 2s. The slice-selective refocusing bandwidth was 1300 Hz (GTST pulses; limiting B_1 field $13.5\text{ }\mu\text{T}$; duration 6.91 ms) (29, 30). In editing ON acquisitions, a 20 ms editing pulse with a bandwidth of 75 Hz was applied at 4.56 ppm, and at 8 ppm in the OFF acquisitions. Spectra were processed with 3 Hz exponential line broadening and zero-filling to 8192 datapoints. A linear baseline correction was applied to the resulting spectra and the edited GSH peak at 2.95 ppm was integrated.

When inferring optimal in vivo acquisition parameters from phantom data, one major issue is estimating the effects of transverse (T_2) relaxation. The function $S_p(TE)$ that describes the signal intensity of phantom experiments is T_2 -weighted according to a time constant $T_{2,phantom}$ that will be substantially longer than (but not negligible with respect to) the time constant in vivo $T_{2,iv}$. Thus the in vivo response function $S_{iv}(TE)$ can be predicted according to:

$$S_{iv}(TE) = S_p(TE) \exp(-TE/T_{2,iv}) \exp(TE/T_{2,phantom}) \quad [1]$$

Although the $T_{2,iv}$ of GSH at 3T has not been reported to date as far as we are aware, it has been measured as 67 ms at 4T (37). T_2 is expected to be approximately inversely proportional to B_0 , which would give an estimated value of 89 ms at 3T. The in vivo T_2 of GABA at 3T has previously been measured as 88 ms (38), in good agreement with that estimate. GABA has a coupled spin system similar to GSH, but is a somewhat smaller molecule, so it might be expected that the T_2 of GSH would be slightly shorter than that of GABA. Therefore, using Equation 1, the predicted in vivo GSH signal as a function of TE was calculated for these upper and lower limits for $T_{2,iv}$, 67 ms and 89 ms. The phantom T_2 was assumed to be 260 ms, based upon previous measurements for a similar GABA phantom at 3T (38).

In vivo experiments

Five healthy volunteers (two female, age 31 ± 8 years) gave informed written consent with local Institutional Review Board approval. For each subject, edited measurements were performed at TEs of 68 ms and 120 ms. For the shorter TE measurement, slice-selective refocusing was achieved using the same “GTST” pulses (29, 30) also used for the phantom TE series (bandwidth 1300 Hz). For the longer TE, two measurements were made either using GTST refocusing pulses or the longer-duration frequency-modulated refocusing pulses “fmref07” (bandwidth 2200 Hz; (29, 39)). Measurements were made in a $(3.6 \text{ cm})^3$ midline parietal region using VAPOR water suppression (40). Other parameters matched the phantom experiments with the exception that TE1 was increased to 26.6 ms in measurements using fmref07 refocusing pulses. For the in vivo data, the Gannet program (41, 42) was used to frequency-and-phase-correct individual transients using the signal of the NAA peak. Time-averaged time-domain data were then loaded into the program csx3 (43), and the signal at ~ 2.95 ppm in the difference spectrum was integrated after a linear baseline correction with 3 Hz line broadening.

Results

Two-dimensional spatial simulations at TE 120 ms are shown in Figure 2a for the GTST refocusing pulses with a bandwidth of 1300 Hz. In the vertical dimension, corresponding to the direction of the first refocusing pulse (shorter TE1 duration), no significant spatial dependency of the multiplet signal is seen. However, in the horizontal dimension corresponding to the second refocusing pulse, there are two distinct regions, which have been color-coded green and red. In the green areas, the OFF multiplets are negative as

desired, whereas they are positive in the red areas. ON multiplets are positive, as expected, in all regions. The difference between these two, labeled DIFF, gives positive signal in the green region and no signal in the red region. This spatial heterogeneity in editing sensitivity has previously been described for GABA (31). Red regions are those where the GSH cysteine-beta spins (~2.95 ppm) undergo the second slice-selective refocusing pulse, but the cysteine-alpha spins (4.56 ppm) do not. At a slice-selective bandwidth of 1300 Hz, this accounts for 16% of the voxel, reducing to 9% for a slice-selective bandwidth of 2200 Hz.

Figure 2B shows the variation in the 2.95 ppm GSH multiplet as a function of TE. Since the spectra are homogeneous across the spatial dimension defined by the first refocusing pulse, this figure only shows the horizontal dimension. While the OFF spectra across most of the voxel (green) modulate with TE, as a result of coupling evolution, multiplets in the red region do not. In the ON spectra, evolution of the alpha-beta couplings is refocused throughout the voxel, giving a similar multiplet form at all TEs. However, there is some modulation due to evolution of the geminal (beta-beta) strong coupling (Figure 1). The difference spectra show TE-dependence of the size and shape of the positive signal in green regions, and a uniform loss of signal in red regions.

Figure 3a shows simulations of the TE-modulation of the 2.95 ppm multiplet after integration over the whole voxel, and Figure 3b shows the integral of those spectra. The ON multiplets are positive with subtle TE-modulation (blue). The OFF multiplets vary more strongly with TE (red). The difference between the two results in spectra with net positive signal, that peaks at TE 160-170 ms.

Figure 4 shows the same information (the TE-dependence of the spectra) for the phantom. Figure 4a shows multiplets that are in good qualitative agreement with the simulations of Figure 3a. Figure 4b shows the TE-dependence of the integrals, which again agree well with the simulations. The difference curve from Figure 4b can be corrected to remove the moderate T_2 -weighting that occurs in a phantom, assuming a phantom T_2 of 260 ms. This curve is shown in Figure 4c as $T_2=\infty$, and is maximal at TE 160 ms. Reintroducing T_2 relaxation to simulate the in vivo case (and normalizing each curve to a maximum value of 1), the maximum signal intensity shifts to TE 120 ms for T_2 values of 67 ms and 89 ms.

Figure 5a shows representative DIFF spectra from one subject in vivo. It can be seen that the signal amplitude at TE 120 ms with higher-bandwidth refocusing pulses is significantly larger than the signal at a TE of 120 ms and 68 ms with lower-bandwidth refocusing pulses. Figure 5b shows the average GSH integral from all five subjects for each scan normalized by the total of each subject. The average DIFF GSH signal is 15% larger at TE 120 ms than at TE 68 ms. The integral is 57% larger at TE 120 ms using high-bandwidth refocusing pulses than using amplitude-modulated pulses.

Discussion

In vivo detection of glutathione is challenging, owing to the low concentration of GSH, its coupled spin system, and heavily overlapped spectrum. The determination of optimal acquisition parameters for GSH editing is important for multiple reasons: improved SNR can

deliver better measurement reproducibility, shorter scan times, or reduced measurement volumes; additionally, establishing standardized acquisition parameters makes comparisons between different studies more meaningful. In this work, simulations and phantom experiments were used to establish the TE-dependence of GSH editing efficiency and predict that in vivo measurements at TE 120 ms should give improved SNR values over that at TE 68 ms. In vivo measurements supported this, and demonstrated a further benefit of the longer TE, namely that it allows the use of improved slice-selective refocusing pulses.

The glutathione cysteine spin system in the editing experiment can be treated as an ABX system, with signals at 4.56 ppm, 2.97 ppm and 2.93 ppm corresponding to the cysteine alpha and beta protons respectively (Figure 1). Spatially resolved simulations of the spin system reveal substantial spatial heterogeneity in the coupling evolution, as a result of the chemical shift displacement between slice-selective refocusing bands for the alpha and beta spins. Integrating across the voxel, coupling evolution is represented in the OFF integrals by an approximately cosinusoidal function with a period of ~330 ms, reflecting the two alpha-beta couplings of 5 and 7 Hz. These couplings are refocused in the ON experiment, whose curve shows some residual modulation due to evolution of the 14 Hz beta-beta strong coupling, which is not refocused by the editing pulses.

Spatial inhomogeneity of coupling evolution during PRESS acquisitions have been widely discussed in the literature, with regard to lactate (29, 32, 33, 44), and glutamate (33, 34). The OFF scan of MEGA-PRESS is essentially a PRESS acquisition, and inherits these issues, while they impact the ON scans much less strongly, as has been discussed for GABA (20, 31). To our knowledge, there has been little prior work investigating spatial effects in the detection of GSH, by editing or otherwise. There is good qualitative agreement between the simulations and the phantom experiments in both the form of multiplets and the envelope of TE-modulation. The major discrepancy between the simulations and the phantom acquisitions is the omission of T_2 relaxation from the simulations. T_2 relaxation biases the signal curves towards shorter TEs. When this T_2 bias is removed from the phantom data ($T_2=\infty$ curve), the TE-dependence of editing substantially agrees with the simulations. Applying estimated in vivo T_2 biases, the optimal TE shifts to 120 ms. Compared to the commonly used value of 68 ms, these phantom data suggest that 120 ms has a significant theoretical advantage (of 55% if T_2 is 89 ms, or 42% if T_2 is 67 ms).

The in vivo data also show that the TE of 120 ms gives more signal than 68 ms. However, this increase is much less than the phantom data suggested. One possible explanation is that the in vivo T_2 is shorter than 67 ms. An alternative explanation arises from the different lineshapes of the edited signal at the two TEs. At the shorter TE, the multiplet has negative outer lobes, as shown in Figures 3a and 4a; this might lead to misidentification of the baseline when quantifying in vivo data, considering the signal as a positive signal within a baseline well. Indeed, when phantom data are integrated incorrectly in this way, the shorter TE appears less disadvantageous; the marginal benefit of 120 ms is 0-20% as opposed to 42-55%. The in vivo benefit of a TE of 120 ms over 68 ms, measured to be 15%, lies within this range.

The in vivo data show that the clearest benefit of the longer TE is that it can accommodate better slice-selective RF pulses. The frequency-modulated refocusing pulses give more signal due both to the higher bandwidth and the more rectangular slice profile. Considering the simplistic two-compartment (red-green) model, increasing the refocusing bandwidth from 1.3 kHz to 2.2 kHz is expected to deliver 8% more signal due to reduced size of the red compartment. A secondary benefit of using higher-bandwidth pulses is reduction of the chemical shift displacement artifact, leading to improved localization of the full spectrum. The majority of the 57% signal increase arises due to the improved slice profile with flatter passband response within the slice and improved excitation of signal up to the edges of the voxel (calculated as 45.5% from the water reference integral ratios). These benefits occur twice over as two dimensions of the voxel are defined by slice-selective refocusing pulses.

GSH phantom TE series have been presented previously in the literature, with conflicting reports. Our findings are in agreement with one of those two reports (25) which shows that a TE of 130 ms gives more phantom signal than 110 ms or 150 ms. Other papers reported a maximum edited signal at TE 68 ms in phantoms (16,45). While it is difficult to reconcile this finding with the data and simulations reported here, it should be remembered that the response of the GSH spin system depends on a number of factors, including the transmitter B_1 level, slice-selective pulse waveforms, bandwidth, and timing of the editing pulses. Some implementations of the MEGA-PRESS sequence may not always maintain the temporal spacing of the editing pulses at TE/2, which is the optimum setting required to remove J-modulation from the ON spectra. One further point raised in reference 25 is that it is appropriate to consider not just the optimal GSH signal but also the baseline impact of the co-edited NAA signal at 2.7 ppm. As seen in figure 5, this NAA spectral shape also changes strongly as a function of both TE and the bandwidth of the slice-selective refocusing pulses used.

In conclusion, a comprehensive study of J-difference editing of glutathione at a range of echo times has been presented. Approximating the in vivo T_2 of GSH, simulations and phantom experiments suggest an optimal in vivo echo time of 120 ms. This longer echo time is shown in vivo to be an improvement over the commonly used TE of 68 ms. Although the margin of improvement is less than expected based on phantom experiments, the further benefit of using improved refocusing pulses of longer duration is substantial.

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Fig. 1.

Structure of glutathione (GSH). GSH is a tripeptide of glycine (Gly), cysteine and glutamate (Glu). The glutamate moiety is attached through its side-chain carboxylate (denoted Glu'). Editing pulses are applied to the cysteine alpha proton at 4.56 ppm. The observed signal originates from the beta protons at 2.93 ppm and 2.97 ppm. Arrows represent scalar (J-) couplings.

Fig. 2. Spatial simulations of the GSH multiplet at 2.95 ppm using GTST slice-selective refocusing pulses for the MEGA-PRESS sequence with (ON) and without (OFF) editing pulses applied at 4.65 ppm; the difference spectrum (DIFF = ON – OFF) is also shown. Regions in which coupling evolves as desired and produces a negative signal in the OFF spectrum are colored green, while regions where couplings are refocused in the OFF spectrum are colored red. (a) Two-dimensional spatial simulations for an echo time of 120 ms. (b) One-dimensional spatial simulations at a range of echo times from 70 ms to 240 ms.

Fig. 3.

Simulations of GSH as a function of TE. The spatial simulations from Figure 2 were summed over the whole voxel at a range of echo times. (a) GSH multiplets plotted between 2.71 ppm and 3.19 ppm. (b) GSH integral curves. Note that in (a), the ON multiplet varies subtly with echo time, which is reflected in its corresponding integral in (b). The DIFF lineshape obtains its peak integral at an echo time of 160–170 ms, and has negative outer lobes at lower echo times (as seen in a).

Fig. 4.

Phantom experiments at a range of echo times. (a) GSH multiplets plotted between 2.71 ppm and 3.19 ppm. (b) GSH integral curves. (c) normalized integral curves removing phantom T_2 effects (' $T_2 = \infty$ '), and simulating in vivo relaxation with T_2 values of 67 ms and 89 ms respectively (estimated to be the likely lower and upper limits of the in vivo GSH T_2 relaxation time at 3T, respectively). Note that the experiments were performed in increments of 10 ms; if TE was sampled more finely, it's likely that the optimum TE would be slightly different for TE 67 and 89 ms.

Fig. 5.

In vivo experiments using three different sets of parameters: an echo time of 68 ms with 1300 Hz refocusing bandwidth (green); an echo time of 120 ms with 1300 hz refocusing bandwidth (blue); and an echo time of 120 ms with 2200 Hz refocusing bandwidth (red). Representative spectra from one subject are shown in (a) for each of the different parameter sets. GSH integrals (2.95 ppm) normalized by the sum of the integrals from each subject averaged across all five subjects are shown in (b). Note that the aspartyl resonance of NAA (2.4-2.8 ppm) also varies strongly as a function of TE and slice-selective refocusing pulse bandwidth.