Glutathione measurement using short-TE ^{1}H MRS at 3T: accuracy and precision assessment

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Introduction Glutathione (GSH) is the major intracellular non-protein thiol and plays an important role in protecting cells against oxidative stress. Disorders in GSH metabolism are implicated in the pathophysiology of psychiatric and neurodegenerative diseases[1]. Due to unresolved GSH resonances resulting from strong spectral overlapping, measurements of GSH in human brain have been mainly done using editing schemes at long TE[2]. Although editing approaches provide resolved measurement of GSH, several downsides remain[3]. As an alternative approach, short-TE MRS methods have been employed to detect GSH[4]. The largest benefit of short-TE MRS is the feasibility of measuring an abundant number of metabolites simultaneously. However, due to the spectral overlap, GSH resonances are hardly resolved and quantification was commonly achieved by deconvolution methods. In the previous study, GSH values obtained using both MEGA-PRESS and short-TE STEAM methods were demonstrated to be comparable[2], however, the accuracy and precision of GSH measurements using short-TE MRS methods still remain to be addressed, which is unfeasible without knowing the ground truth of GSH levels in the brain. Therefore, the aim of this study was to evaluate the accuracy and precision of GSH measurements at 3T with short-TE MRS and LCModel[5] under various experimental conditions using synthesized spectra with known metabolite concentrations.

Methods ***^{1}H MR Spectral synthesis*** Spectral simulation based on density matrix formalism was performed in Matlab using the following experimental parameters: B_0 = 3T, spin-echo excitation with ideal RF pulses, TE = 6 ms, spectral width = 2 kHz, number of points = 2048. 20 simulated metabolites spectra using published concentrations[6] and experimental measured macromolecule baseline spectra were combined to create synthesized ^{1}H MR spectra. FWHM of resonances was varied from 3-12Hz (1Hz/step) and SNR of the spectra was set from 25-250 (25/step) by adding random noise. At each FWHM and SNR combination, 300 spectra were created with different GSH concentrations ranging from 0.5-1.5 µmol/g to mimic intersubject and pathophysiological differences.

Accuracy and precision evaluation To evaluate the accuracy of the measurement, the mean error of the measurement was calculated as below:

$$Mean\ Error(\%) = \left(\sum_{i=1}^{300}\left(\frac{[GSH]_o - [GSH]_i}{[GSH]_i}\right)\times 100\right)/300$$

where $[GSH]_i$ is the input known GSH concentration for synthesized spectra, $[GSH]_o$ is the output GSH concentration from LCModel. The precision of the measurement was evaluated by calculating the variability of the measurement using the residual standard deviation of the linear regression for output GSH concentrations and input GSH concentrations, and then divided by the mean of the input values.

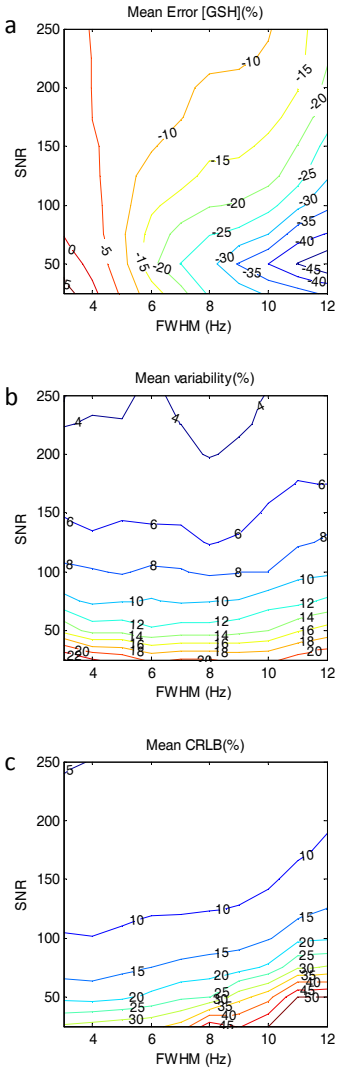

Figure 1. Illustrations of mean GSH measurement error(a), variability(b), and CRLB(c) as a function of SNR and FWHM.

Results and Discussion In general, an underestimation of GSH concentrations was observed using the short TE MRS and the measurement accuracy was found to depend on the experimental conditions (Fig.1a). With an excellent linewidth (3Hz), the mean error approached zero and was insensitive to SNR (Fig.1a). The flat residual baselines and identical macromolecule baselines for different SNR values in Fig.2a suggest that with the excellent linewidth the residual baseline can be correctly estimated regardless of SNR. With the increase of the linewidth, the mean error starts to vary with SNR (Fig.1a), which is ascribed to the influence of the variability on estimated residual baselines (Fig.2b). The higher the SNR, the less sensitive the mean error is to the linewidth. At high SNR condition (250) the mean error of GSH quantification is less than -10% across a large range of linewidths (3-10Hz). Common application studies, based on case-control comparisons, require comparative measures and thus do not suffer significantly from a systematic underestimation. Considering the common experimental linewidth achieved at 3T, i.e. 5-7Hz, the relative mean error is expected to be less than 10%. This relative error decreases with the increase of SNR, e.g. at SNR=200, this relative error is only 2% for a linewidth of 5-7Hz. If high SNR is not available, linewidth and SNR should be matched between groups.

The precision of the measurement is largely influenced by SNR (Fig. 1b). When SNR is above 80, less than 10% of experimental variability can be achieved regardless of the linewidth. The Cramér–Rao lower bound (CRLB) decreases with the increase of SNR in general while it increases steadily in the broad linewidth range (Fig. 1c). It is expected to drop below 20% with a common linewidth of 5-7Hz when SNR is larger than 65.

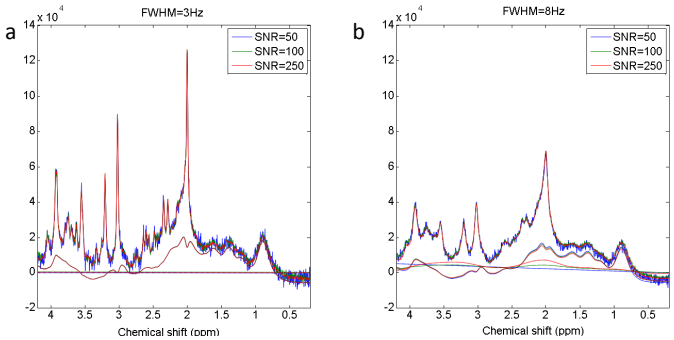

Figure 2. Synthesized ^{1}H spectra, macromolecule baselines and residual baselines under condition of (a) fixed FWHM = 3Hz and different SNRs and (b) fixed FWHM = 8Hz and different SNRs.

Conclusion

We conclude that GSH concentrations can be measured with high precision using short-TE MRS methods at 3T when SNR is sufficient. GSH changes can also be accurately measured if experimental conditions, i.e. spectral linewidth and SNR, are carefully matched between groups.

References [1] Gysin et al., Proc Natl Acad Sci USA, 104(42), 2007; [2] Terpstra et al., MAGMA, 18(5), 2005; [3] Harris et al., Magn. Reson. Med., 72(4), 2014. [4] Mekle et al., Magn. Reson. Med., 61(6), 2009; [5] Provencher et al., Magn. Reson. Med., 30(6), 1993. [6] Govindaraju et al., NMR Biomed,13, 2000.**Acknowledgements** Supported by Centre d'Imagerie BioMédicale (CIBM) of the UNIL, UNIGE, HUG, CHUV, EPFL and the Leenaards and Jeantet Foundations.