Glutathione cannot be quantified reliably from short echo PRESS spectra

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Target Audience: MR Spectroscopists, Researchers in: Aging and dementia, Psychiatric studies

Purpose: Glutathione (GSH) is an important intracellular antioxidant in the brain. Studies have shown that neurodegenerative diseases can alter GSH concentration; hence its quantification has been a great matter of interest. Magnetic resonance spectroscopy (MRS) has been used to measure brain GSH. However its low concentration and overlap with other metabolite signals have made its correct measurement challenging. To overcome these problems J-difference edited ^{1}H MRS pulse sequences such as MEGA-PRESS, have been introduced to measure GSH [1]. There have also been reports of GSH quantifications using short echo PRESS pulse sequences [2][3]. In the MEGA-PRESS spectra the GSH signal is visually detectable which will provide accuracy and reproducibility of GSH concentration measurements and quantification. However, in the short echo PRESS spectra the GSH signal is not visually detectable and the quantification is based on the assumption that the GSH signal lies in the spectra.The aim of this study is to evaluate the reliability of GSH quantification using short echo PRESS pulse sequences and comparing it with MEGA-PRESS.

Methods:

Phantom study: Two identical phantom solutions (P1 and P2) were prepared in a phosphate buffer containing brain metabolites: NAA, Cr, Cho, Glu, Gln, Myo-Ins, Asp and GABA with the average physiological concentration of a normal brain [4]. An average physiological concentration of GSH (~1mM) was only added to one of the phantoms (P2). Short echo PRESS ^{1}H MR spectra (TE=35ms, TR=2000ms, 64 averages, 2 dynamics, voxel size=3×3×3cm^3) and MEGA-PRESS spectra (TE=130ms, TR=2000ms, 64 averages, 2 dynamics, voxel size=3×3×3cm^3) were acquired from both phantoms on a 3T Philips *Achieva* scanner. Spectra were fitted in jMRUI (V 5.1) using the QUEST algorithm [5] with metabolite basis sets simulated for the appropriate sequence timings using NMR SCOPE. The basis set used for the quantification of both phantoms included NAA, Cr, Cho, Glu, Gln, Myo-Ins, Asp, GABA and GSH.

Human Study: Spectra were acquired from 7 healthy volunteers (2M, 5F) on the above scanner. A 4.5×2.5×2.5 cm^3 voxel was placed in the left anterior cingulate cortex (ACC). Short echo PRESS (TE=35ms, TR=2000ms, 64 averages, 4 dynamics) and MEGA-PRESS spectra (TE=130ms, TR=2000ms, 64 averages, 4 dynamics) were acquired from the voxel. The PRESS spectra were fitted using jMRUI (V 5.1), the QUEST algorithm with 11 metabolite basis sets simulated for the appropriate sequence timings using NMR SCOPE. The GSH, NAA and Cr in the MEGA-PRESS spectra were quantified using AMARES [6]. Concentrations were corrected for the proportion of cerebrospinal fluid in the voxel based on segmentation of T_1-weighted images.

Results: Phantom study: The GSH concentrations measured from the PRESS spectra using jMRUI were not significantly different ($p<0.95$) in the two phantoms (P1=1.19 mmol/l, P2=1.05 mmol/l), despite one not containing any GSH (GSH true concentration in P1=0 mmol/l, P2=1.012 mmol/l). The Cramer Rao Lower Bounds (CRLB) of the GSH quantified in both phantoms was below 18% (CRLB P1=13.48%, CRLB P2=17.77%). In contrast, from the MEGA-PRESS acquisitions it was clear that phantom 1 did not contain GSH, as no resonance from GSH appeared in its edited spectrum (**Fig. 1**) and the concentration calculated was P1=0 mmol/l, P2=1.2 mmol/l.

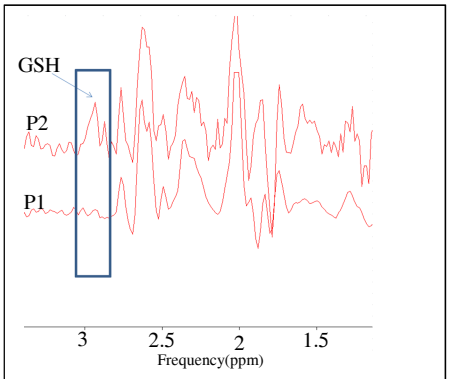

Fig. 1. P1 and P2 MEGA-PRESS spectra. P1 does not contain any GSH and no GSH resonance appeared in the spectra. P2 contains GSH, and the GSH peak can be seen in the spectra.

Human Study: The GSH signal can be clearly identified in the MEGA-PRESS spectra (**Fig. 2**), while in the PRESS spectra no particular peak can be assigned to GSH. GSH concentration calculated from the MEGA-PRESS spectra was 0.7±0.16 mmol/kg wet weight while from the PRESS spectra a significantly different value ($p<0.0005$), 2.0±0.42 mmol/kg wet weight was calculated.

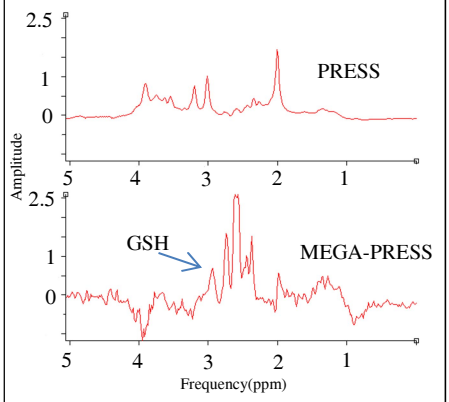

Fig 2. GSH signal can be identified in the MEGA-PRESS spectra of a healthy volunteer while in the PRESS signal no specific peak can be assigned to GSH.

Discussion: In the phantom experiment, when quantifying the PRESS spectra, it is clear that including GSH in the basis set returns a similar concentration for the anti-oxidant, whether it is present in the sample or not. This undermines the contention that physiological levels of GSH can be measured with short echo PRESS. Certainly if GSH is reduced under certain conditions, this would not be detectable using short echo PRESS and jMRUI. We note that in a phantom study of GSH measurement using short echo and LCModel [2] that the LCModel also returned a physiological concentration of GSH when none was present in the phantom. In the human study, the concentration calculated from the MEGA-PRESS and PRESS spectra were significantly different. Considering also the phantom data, it is difficult to have confidence in the PRESS result as it relies entirely on the model fit being able to extract a minor component which cannot be identified directly.

Conclusion: Due to the uncertainties in GSH quantification raised by the phantom and human study, normal physiological concentrations of GSH cannot be reliably quantified using short echo PRESS at 3T, whereas in MEGA-PRESS the GSH signal is visually detectable and more accurate quantification can be performed.

Acknowledgment: European Commission-TRANSACT-FP7; UK-Medical Research Council; NIHR/WT Clinical research facility for support of scanning

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