Detection of Glutathione with High Precision in the Anterior Cingulate Using Short TE ^{1}H MRS at 3T

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Introduction

The redox regulator and antioxidant glutathione (GSH) plays an important role in the pathophysiology of schizophrenia (1). Previous studies using ^{1}H MRS to non-invasively measure GSH levels in human brain focused on the richly innervated areas of the prefrontal cortex (2) or the anterior cingulate (3). Detection of GSH is difficult due to overlapping resonances, while, on the other hand, sufficiently high precision is required to allow distinction between natural variability, pathology, and treatment effects. Recently, the spin echo full intensity acquired localized (SPECIAL) MRS technique was proposed (4), and its application to human brain yielded reliable quantification of several metabolites (5). Thus, the aim of this study was to acquire short TE single volume spectra using SPECIAL to quantify GSH and other metabolites of interest in the context of schizophrenia with high precision in the anterior cingulate of human brain at 3T.

Methods

Scans were performed on a 3T Trio system (Siemens Medical Solutions, Erlangen, Germany) using a TEM volume coil (6). First- and second-order shims were adjusted using FAST(EST)MAP (7). ^{1}H single volume spectra were acquired for N = 4 volunteers using the SPECIAL technique. Results were quantitatively analyzed using LCModel (8).

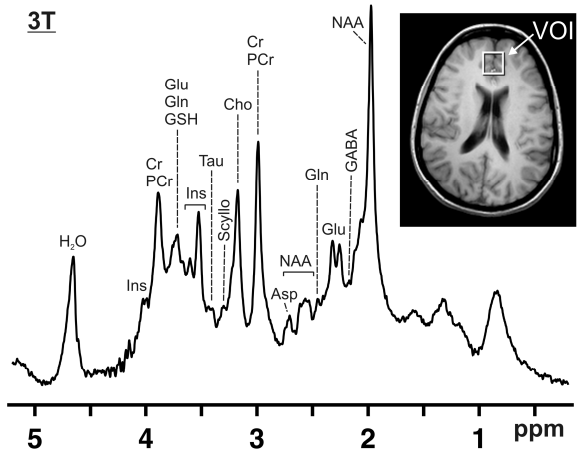

Fig. 1. ^{1}H spectra from the frontal lobe of a human volunteer acquired with the SPECIAL sequence. VOI=20x20x25 mm^3, TR/TE=4000/6, spectral width=2kHz, 148 scans; Data processing consisted of zero-filling up to 8-k data points, 1 Hz Gaussian weighting of the FID, Fourier transformation, and phase correction. Inset: transverse T_1-weighted gradient echo image with the location of the VOI.

Results

Localized shimming resulted in water linewidths of 6.6 ± 0.4 Hz, and metabolite linewidths were estimated as 4.7 ± 0.9 Hz with usually one second-order shim setting at maximum. Excellent spectral quality was reproducibly obtained for all volunteers (Fig. 1). No lipid contaminations and no degradation due to motion were observed. Cramer-Rao lower bounds (CRLBs) from LCModel quantification for GSH ranged from 7-11% with a mean of 9% indicating high precision. Fourteen additional metabolites were quantified with CRLBs below 20% (Table 1), including glutamate (Glu), glutamine (Gln), and γ-aminobutric acid (GABA) that are of interest in the study of schizophrenia.

Table 1. Metabolite quantification of ^{1}H spectra. Absolute concentrations and Cramer-Rao lower bounds (CRLBs) are given as mean values plus standard deviations. For calculating absolute concentrations, the water signal from the VOI was used as reference.

Metabolite	Conc. (mmol/kg)	CRLB (%)
Asp	3.1 ± 0.4	10 ± 1.5
Cr	5.4 ± 0.9	7 ± 1.4
GABA	2.3 ± 0.3	15 ± 2.4
Gln	2.7 ± 0.6	13 ± 1.7
Glu	10.1 ± 0.1	4 ± 0.6
GSH	**1.5 ± 0.3**	**9 ± 1.7**
Ins	5.3 ± 1.1	6 ± 2.4
NAA	10.1 ± 0.4	3 ± 0.5
Scyllo	0.4 ± 0.1	16 ± 6.2
PE	3.0 ± 0.3	10 ± 1.5
GPC+PCho	1.6 ± 0.3	4 ± 0.5
NAA+NAAG	10.4 ± 0.6	2 ± 0.5
Ins+Gly	6.2 ± 0.8	3 ± 0.5
Cr+PCr	7.3 ± 0.7	3 ± 0.6
Glu+Gln	12.8 ± 0.6	4 ± 0.5

Discussion

The spin echo-based SPECIAL sequence provides an almost twofold increased sensitivity compared to STEAM (4). This allowed the determination of GSH with high precision as part of a neurochemical profile of in total fifteen metabolites that were reliably quantified in the anterior cingulate on a clinical platform at 3T. The resulting concentration of GSH was in excellent agreement with a previous study at 4T (3), while scan time was reduced by almost a factor of two and a larger number of metabolites quantified. In addition, the size of the VOI was smaller than in previous studies (e.g. (2)) at field strengths $B_0 \leq 3$T. It is concluded that the precision of detection of GSH using ^{1}H MRS was sufficiently high for clinical applications related to schizophrenia, e.g. treatment monitoring of patients after administration of therapeutic agents.

References and Acknowledgements (1) R. Gysin et al., Proc Natl Acad Sci USA, 104(42), 16621-16626, 2007; (2) K.Q. Do et al., Eur J Neuroscience, 12(10), 3721-3728, 2000; (3) M. Terpstra et al., MAGMA, 18(5), 276-282, 2005; (4) V. Mlynarik et al., MRM, 56(5), 965-970, 2006; (5) R. Mekle et al., MAGMA, 21(Suppl. 1), 214, 2008; (6) J.T. Vaughan et al, MRM, 32(2), 206-218, 1994; (7) R. Gruetter, MRM, 43(2), 319-323. 2000; (8) S.W. Provencher et al., MRM, 30(6), 672-679, 1993.

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