Fast Absolute Quantitation Using FID Echo Planar Chemical Shift Imaging (FID EP-CSI)

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Introduction: Absolute quantitation (AQ) of metabolite concentrations is a well-studied problem in NMR. Approaches to AQ include replace-and-match method, principle of reciprocity, external phantom reference, and tissue water as an internal reference – each with its own advantages and disadvantages [1]. These AQ methods have been extensively applied to brain spectroscopy using single-voxel (SV) spatial localization techniques [2-4], and there is now some general agreement between various groups concerning metabolite concentrations and peak assignments of the major resonances in the *in vivo* proton spectrum.

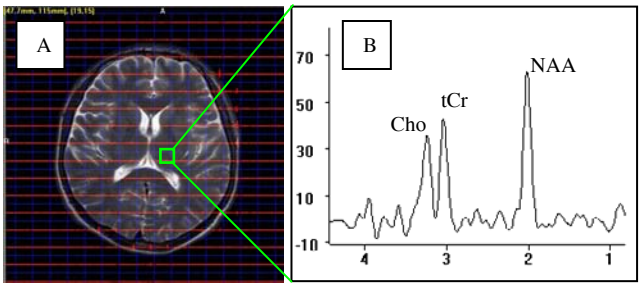
However, SV localizations are limited by lack of spatial information concerning distribution of metabolites over an inhomogeneous region. In contrast, chemical shift imaging (CSI) has significant advantages in terms of spatially mapping the distribution of metabolites [5]. Despite these advantages, there have been few reports of AQ proton CSI of the human brain [6], as one of the main deterrents of standard CSI in a typically busy clinical hospital setting is the long acquisition times required. For example, if internal tissue water is used as an AQ reference, it may require an unacceptably long time to record an unsuppressed water CSI acquisition, in addition to the water-suppressed metabolite measurement.

Our objective is to demonstrate use of FID Echo planar Chemical Shift Imaging (FID EP-CSI) as a fast and accurate means to obtain a regional map of absolute concentrations of brain metabolites. To our knowledge, this is the first work using FID EP-CSI for AQ. Compared to spin-echo EP-CSI acquisitions [7], FID acquisitions minimize J-coupling, removes need for T2 decay correction since TE is effectively zero, thereby reducing potential error in AQ calculations caused by inaccurate T2 measurements. To validate our sequence, internal tissue-water was used as an AQ standard [2-4]. *In vitro* validation experiments with known phantom concentrations show accuracy within 3% of actual values, while *in vivo* AQ measurements of NAA, TotCr, and Cho in the thalamus were found to be 12.6 ± 0.4, 8.3 ± 0.3, 2.5 ± 0.2 (mM, mean ± SD), respectively, in good agreement with previous standard 2D-CSI studies. For 16x16 spatial resolution, TR = 1500ms, and number of signal averages (NSA) = 1, combined acquisition time of both water-suppressed and unsuppressed spectra required for AQ calculations was 56s, compared to a 13min exam using conventional phase encoded CSI with identical resolution and TR, making AQ with FID EP-CSI a feasible option for routine use in clinical diagnosis.

Material and Methods: Experiments were performed on a 3T Philips Achieva scanner (R 1.7.1, Philips Medical Systems, Best, The Netherlands). A 16x16 matrix with 1024 spectral samples, 2048 gradient echoes (1024 even echoes, 1024 odd echoes), 250mm FOV, and 10mm slice thickness and EP-CSI readouts immediately following (delay = 0.5ms) a slice-selective RF pulse are the scan parameters that were common to *in vitro* and *in vivo* experiments. CHESS (ref) pulses were used for all water suppression acquisitions. Phantom for *in vitro* validation of AQ accuracy consisted of a 60mm diameter, 120mm tall cylindrical bottle containing 0.1% methanol solution in water (56mM). For *in vitro* acquisitions, TR = 1500ms and NSA = 1 for both water-suppressed and unsuppressed acquisitions. *In vivo* measurements were acquired in the thalamus (gray matter) of the brain in 3 healthy volunteers, with 3 different acquisitions per subject TR = 1500, 2500, 3500ms in order to determine reproducibility of AQ calculations, and additional outer volume suppression (8 regional suppression technique (REST) slabs) was used for fat suppression; *in vivo* water spectra were acquired with NSA = 1, and water-suppressed spectra with NSA = 8 to ensure sufficient SNR for accurate AQ. Reconstruction was performed on even and odd echoes by shifting each sampled point to a common temporal origin using Matlab (Mathworks, Natick, MA, USA). This scheme causes the effective sampling interval for the spectra to be twice the echo time (after reconstruction the effective spectral dwell time = 0.74ms). Metabolite peak integration, baseline correction, additional offline water suppression and Gaussian filtering (2-5Hz) were applied using 3D*i*CSI, an interactive software package developed in-house [8].

$$[M] = \frac{N_W}{N_M}\frac{S_M}{S_W}\cdot 10^{(G_M-G_W)/20}\cdot\frac{1-\exp(-TR/T1_W)}{1-\exp(-TR/T1_M)}\cdot[W]$$

Absolute concentrations of metabolite [M] using internal tissue-water reference [W] were calculated using the following equation. N_M is the number of protons in the corresponding metabolite peak M: $N_W = 2$, $N_{methyl} = 3$, $N_{NAA} = 3$, $N_{tCr} = 3$, $N_{Cho} = 9$. S_M and S_W denote the signal (area under peak) of metabolite M and water reference W. G_M and G_W are gain attenuations applied by the system to water-suppressed and water-unsuppressed acquisitions, respectively. Internal gray-matter water concentration reference [W] = 0.84·55.6M = 46.9M [9]. For *in vitro* T1 corrections, T1 for phantom solution was measured using a standard IR sequence, yielding $T1_{methyl} = 3.2$s, $T1_W = 1.9$s. For *in vivo* corrections, T1 values of brain metabolites at 3T were taken from [10] as $T1_{NAA} = 1.47$s, $T1_{tCr} = 1.46$s, $T1_{Cho} = 1.3$s, $T1_W = 1.4$s.



Source	NAA	Tot Cr	Cho
Subject 1	12.2 ± 1.5	8.06 ± 1.6	2.71 ± 0.8
Subject 2	13.0 ± 2.2	8.62 ± 0.3	2.27 ± 0.2
Subject 3	12.5 ± 1.2	8.2 ± 0.6	2.37 ± 0.1
Average	12.6 ± 0.4	8.3 ± 0.3	2.5 ± 0.2
Soher et al. [6]	10.8 ± 2.8	7.9 ± 2.5	2.5 ± 0.8

Table: Comparison of AQ concentrations in current work vs. literature values. Units are in mM, mean ± SD. N = 3 for each subject in current work, N = 16 for [6].

Figure A: T2-weighted reference image for 2D FID EP-CSI planning, including thalamus.

Figure B: Sample spectra from voxel located in thalamus region, after postprocessing.

Results: *In vitro* AQ measurements (N = 4) on the 56mM methanol phantom = 54.3 ± 0.6 (mM, mean ± SD), showing accuracy to within 3% of actual values. For each subject, the small SD's reflect the reproducibility of AQ measurements. *In vivo* measurement are also in close agreement with literature values reported by [6] in the thalamus, measured using conventional spin-echo 2D-CSI.

Conclusion: Conventional CSI is very time consuming due to the large number of phase-encodes – requiring N^2 TR's to achieve an NxN spatial resolution. EP-CSI readouts are not purely spectroscopic but are acquired with a rapidly switching encoding gradient, enabling the acquisition of both spectral and spatial information in one dimension simultaneously [11]. Phase encoding is then only required for the remaining spatial dimension(s), resulting in an acquisition of only N TR's for NxN resolution, and hence a square-root reduction in the scan time. With a TR = 1500ms, 16x16 spatial resolution, NSA = 1, acquisition time = 28s. For AQ using an internal tissue-water reference, two acquisitions – water spectra and water-suppressed spectra – are required, resulting in a total acquisition time of 56s. I*n vivo* datasets were acquired with NSA = 1 for water spectra and NSA = 8 for improved metabolite spectra SNR, with total scan time 3 min 44s. This is in contrast to standard CSI, where an equivalent acquisition would require ~13min for the first case, and ~1hr the latter. The fast acquisition of FID EP-CSI, coupled with its demonstrated accuracy, makes it a feasible option for routine use in clinical diagnosis with AQ. While we are using internal tissue-water as a reference for AQ, the FID EP-CSI acquisition is also readily interchangeable with other AQ techniques, yielding the same time advantages.

Most implementations of EP-CSI have focused on using spin-echo EP-CSI readouts in the acquisitions [7]. To our knowledge, this is the first use of FID EP-CSI for AQ purposes. Since TE = 0, correction for T2 decay is not required in AQ calculations, thereby reducing error in AQ calculations caused by inaccurate T2 measurements. Rapid acquisition time also minimizes potential measurement errors due to motion artifact.

References: [1] Jansen J et al., Radiology, 240(2):318-332, 2006. [2] Christiansen P et al., MRI, 11:107-118, 1993. [3] Barker PB et al., NMR Biomed, 6:89-94, 1993. [4] Kreis R et al., JMR B, 102:9-19, 1993. [5] Brown TR et al., Proc Natl Acad Sci USA 79:3523-6, 1982. [6] Soher BJ et al., MRM, 35:356-363, 1996. [7] Posse S et al., MRM, 37:858-865, 1997. [8] Zhao Q et al., Proc ISMRM 2465, 2005. [9] Diem K, Lentner C. Documenta Geigy: Scientific Tables, p. 519. Ciba-Geigy Limited, Basle, 1970. [10] Mlynarik V et al., NMR Biomed, 14:325-331, 2001. [11] Mansfield P, MRM, 1:370-386, 1984.