Absolute Quantification of Brain Metabolites in Small MRS Voxels

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Introduction: Magnetic resonance spectroscopy (MRS) enables noninvasive insight into the in vivo human metabolism making the technique a promising candidate to improve diagnoses of brain lesions in the clinical routine and for neuroscientific research. However, main challenges applying the method are: 1.) in order to get region specific results small voxel sizes should be used, which reduces the achievable signal to noise ratio (SNR) and 2.) absolute quantification is difficult, because the standard method to achieve absolute concentrations, internal water referencing [1], might fail due to a change of the water concentration in lesions or with age.

The aim of this investigation was to enable measurements of mM metabolite concentrations in small but clinically and neurophysiologically relevant regions. For this purpose, non-water suppressed MRS via the metabolite cycling technique [2,3] (MC) was used enabling frequency and phase alignment of individual FIDs prior averaging using the high SNR of the water peak. This allows for constructive averaging which increases the resulting SNR and reduces the line width of the spectra. But the water peak obtained by MC is not reliable for quantification, since it might be slightly altered by the influence of the applied inversion pulse. Therefore the MC technique was combined with the calibration method ERETIC [4] to enable absolute quantification. ERETIC is not affected by the MC inversion pulse. Additionally it is independent of the disease state of the investigated tissue.

Methods: With the approval of the local ethics committee, non-water suppressed PRESS localization via the MC technique was performed in 6 healthy volunteers. For comparison water suppressed spectra (WS) were acquired, using VAPOR. The settings for both methods were as follows: 3 T Achieva, Philips Healthcare, Best, TE/TR = 33/2500 ms, 512 averages/volunteer, 2000 Hz band width. MRS spectra were obtained from the left occipital cortex (OCC; voxel size = 17.8x11.2x8.6 mm). Inner-volume suppression was applied to avoid chemical shift displacement and render localization volumes consistent across all metabolites of interest. The obtained spectra were fitted with LCModel [5] using simulated metabolite basis sets as in reference [3]. The fitted resonance areas were corrected for relaxation attenuation and for partial volume effects due to CSF. Tissue segmentation was performed on a T1-weigthed 3D image using SPM8. Absolute concentrations expressed in mMol per liter (mM) were determined by using the internal water as described by Gasparovic et al. [6] and with ERETIC. The concentration of the internal water was estimated from the voxel composition and assuming the relative densities of MR-visible water in GM, WM, and CSF as 0.78, 0.65, and 0.97. In case of WS additional 16 non-water suppressed scans were acquired for internal water referencing. With ERETIC the areas of the metabolite resonances are compared to an externally generated NMR like signal, that is inductively coupled into the receive coil and recorded together with the metabolite signal. In order to determine absolute concentrations of total N-acetyl aspartate (tNAA), creatine (Cre) and choline (Cho) in vivo, the ERETIC signal was calibrated in vitro using a phantom with physiological brain metabolite levels. Relaxation time and temperature differences between the in vivo and in vitro measurements were corrected.

Results and Discussion: Considering the small voxel size, the spectral quality, indicated in Figure 1, is sufficient. Cramér-Rao lower bound (CRLBs) are slightly lower for MC compared to the WS spectra: tNAA (CRLBs (MC/WS) 5 /5.8), Cre (5.5/8.1) and Cho (13/18), which may be a result from the frequency alignment and phase correction prior to averaging. The presence of the ERETIC signal does not influence the quality and post-processing of the MC and WS spectra as can be seen in Figure 1. In Figure 2 the metabolite concentrations obtained for the MC and WS spectra using internal water versus ERETIC as reference standard are summarized. For the WS spectra, the concentrations of the metabolites are similar for both reference standards. The concentrations from the MC spectra are in good accordance to the ones obtained from both WS measurements when ERETIC is used, but overestimated when the water peak is used as reference. This may be due to partial inversion of the water peak flanks.

With the segmentation data a mean concentration of the internal water of 40.1 M (coefficient of variation (CV) 2%) is determined in the measured voxel, almost confirmed by the ERETIC based result of 38.4 M (CV 5 %) averaged over all MC and WS scans. The difference may be explained by errors in the estimation of the water densities and the relaxation times of water in different tissue types. The higher CV for ERETIC can possibly explained by inter subject variations in the achieved B_1^+ field, which ERETIC does not account for. ***In conclusion*** the combination of MC with ERETIC allows to measure mM metabolite concentrations reliably in small MRS voxels in the human brain.

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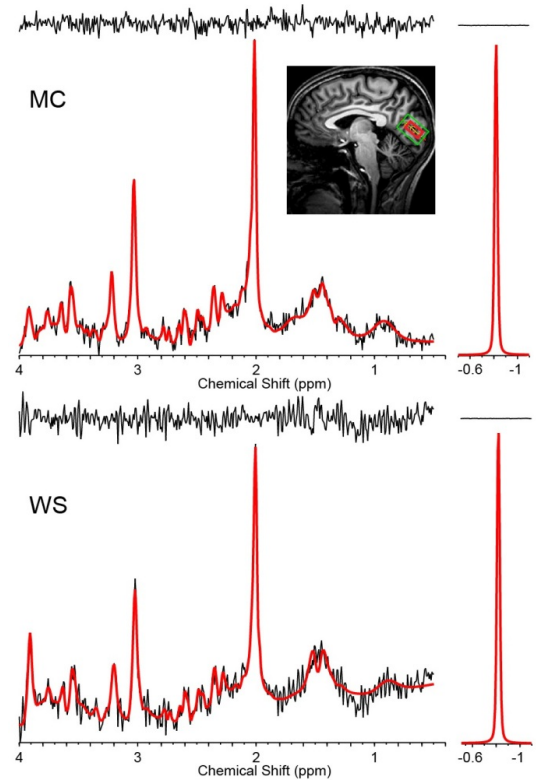
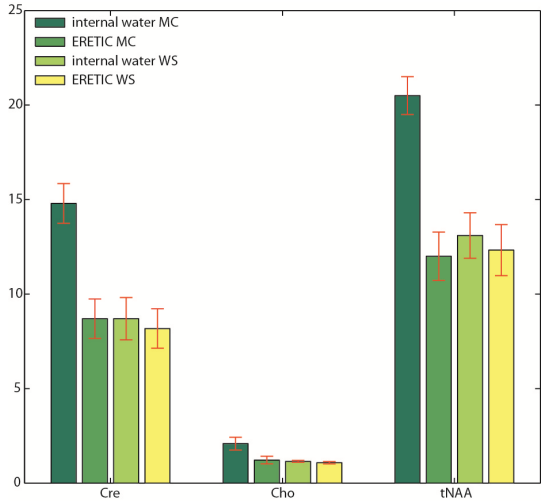


[Figure 1] Here spectra acquired with MC (above) and with WS in the same volunteer are shown with the ERETIC peak at -0.8 ppm. The red line indicates the LCModel fit, the underlying black line indicates the measured signal. Above each spectrum, the residuum is shown.



[Figure 2] Metabolite concentrations in mM measured in spectra with (WS) and without water suppression (MC). Results obtained with ERETIC as reference are compared to results obtained with internal water referencing.