In vitro and *in vivo* validation of absolute quantitation of brain proton MR spectra (^{1}H-MRS) with respect to heterogeneous tissue compositions

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PURPORSE: Brain ^{1}H-MRS permits *in vivo* detection of biochemical changes in numerous neuropathologic conditions, including cancer, multiple sclerosis or psychiatric diseases [1,2]. Absolute quantitation of metabolite concentrations (C_M in mM) allows parameter independent comparison of results obtained with variable measurement settings (B_0, *TE, TR*) [3]. A commonly used approach is based on multiplying the ratio of metabolite and water signals (I_M/I_W) acquired in the same MRS voxel with tissue water concentration (C_W). However, since the metabolites and brain tissue water have different T_1 and T_2 relaxation times and occupy different volume fractions (α) in grey matter (GM), white matter (WM) and cerebral spinal fluid (CSF) [4], this approach should take into account tissue volume fractions (f_{GM}, f_{WM}, f_{CSF}) in a MRS voxel as well as signal attenuations ($R=e^{-TE/T2}\cdot(1-e^{-TR/T1})$):

$$C_M = \frac{I_M}{I_W}\cdot\frac{f_{GM}\cdot R_W^{GM}\cdot\alpha_{GM} + f_{WM}\cdot R_W^{WM}\cdot\alpha_{WM} + f_{CSF}\cdot R_W^{CSF}\cdot\alpha_{CSF}}{f_{GM}\cdot R_M^{GM} + f_{WM}\cdot R_M^{WM}}\cdot C_W \qquad (Eq.\ 1)$$

The aim of the present work was to validate this approach by means of phantom measurements in voxels with heterogenous metabolite and water concentrations as well as with *in vivo* ^{1}H-MRS data acquired in the insular cortex (*IC*) of healthy controls with various repetition times and different voxel volumes.

MATERIAL AND METHODS: All MR measurements were performed with a whole-body 3 T MR scanner (Magnetom Trio, Siemens, Germany). A circular polarized head coil (Biomedical Rapid, Germany) was used for the *in vitro* study, whereas the 12 channel *receive only* head matrix coil was used for the *in vivo* examinations. All MRS data was acquired with a PRESS sequence (TE 30 ms, manual shim) in voxels which were selected by means of T_1-weighted 3D MRI data acquired prior to MRS (MP-RAGE TR/TE/TI 2300/3.03/900 ms; 192 sagittal 1 mm slices, $FOV_{AP\times FH}$: 256×256 mm²). The phantom consisted of four plastic chambers (33×33×54 mm³) with aqueous N-acetyl aspartate solutions (NAA). Free water volume fractions were varied by adding D_2O. As illustrated in *Fig. 1,* the adjusted water and NAA concentrations simulated compositions in WM (C_{NAA}/C_W: 50/33300 mM), GM (C_{NAA}/C_W: 25/44400 mM) and CSF (C_{NAA}/C_W: 0/55500 mM). Eight single voxel MRS scans (V: 3.5 ml) with (NEX 32) and without (NEX 16) water suppression were performed with different voxel positions to investigate the change of NAA concentration by crossing from the WM into the GM chamber while simultaneously varying the CSF fraction (see *Fig. 1*). The *in vivo* study comprised measurements of metabolite (NEX 128) and water (NEX 16) ^{1}H-MR spectra in the *IC* of two healthy control groups (*GI*, *GII*), each consisting of five persons (25±3 years). Voxel volumes (V) as well as repetitions times (TR) for water and metabolite spectra measurements were varied between both groups (V_{GI}/V_{GII} 2.5/3 ml; $TR_{M,GI}/TR_{M,GII}$ 5/2 s; $TR_{W,GI}/TR_{W,GII}$ 10/2 s). For all *in vitro* and *in vivo* spectra I_M and I_W were quantitated with the LCModel [5]. MP-RAGE data was first segmented in WM-, GM- and CSF-compartments, then automatically co-registrated with the MRS voxel positions and finally used for estimation of relative WM, GM and CSF volume fractions (f_{GM}, f_{WM}, f_{CSF}). Whereas the *in vitro* metabolites and water T_1- and T_2-values were estimated from additional measurements (NAA_{WM} T_1/T_2 = 1.68/0.99 s, NAA_{GM} T_1/T_2 = 1.62/1.2 s; H_2O_{WM} T_1/T_2 = 4.14/2.5 s; H_2O_{GM} T_1/T_2 = 3.22/2.46 s, H_2O_{CSF} T_1/T_2 = 2.94/2.03 s), the corresponding *in vivo* values were adapted from literature [6-7]. *In vitro* NAA concentrations as well as *in vivo* concentrations of NAA, creatine (Cr) and total choline (tCho) were determined using *Eq. 1* with an assumed free water concentration C_W = 55555 mM. *In vitro* NAA concentrations were additionally estimated assuming MRS voxels containing only WM or GM. For the *in vivo* data these additional calculations were performed while assuming homogeneous GM voxels.

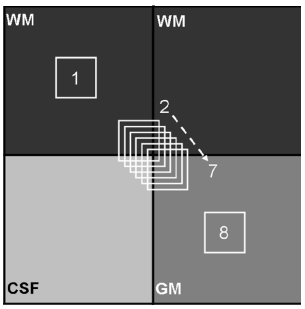

Fig. 1: *Water intensities within the WM, GM and CSF phantom chambers together with selected positions of 8 MRS voxels.*

RESULTS: Changes of *in vitro* NAA concentrations, calculated by assuming heterogeneous (green line) and homogenous (orange and magenta lines) tissue compositions within the selected voxels, are shown in *Fig. 2*. As can be seen from the figure NAA concentrations determined by taking into account the partial GM, WM and CSF volumes (green line) are in good agreement (max. error 3.9%) with the values calculated by using the nominally adjusted NAA concentrations (black line). Contrary, NAA concentrations estimated without correction of partial volume effects are underestimated (max. error: 40.5%), especially for voxels containing CSF solution. *Fig. 3* shows *in vivo* distributions of NAA, Cr and tCho concentrations for both volunteer groups (*GI*: blue boxes; *GII*: green boxes) with (dashed lines) and without (full lines) taking into account the heterogeneous tissue composition within the MRS voxels (*GI*: WM/GM/CSF = 33±7/62±4/6±4%; *GII*: WM/GM/CSF = 22±13/66±10/12±6%). As indicated by the smaller distances between the lower and upper percentiles, corrected *in vivo* NAA and Cr concentrations are distributed with less scatter (max. variation: 8.2% for *GI* and *GII* with uncorrected data; max. variation: 3.9% for *GI* and *GII* with corrected data). The variation of tCho concentrations remained nearly the same before (max. 9.0%) and after application of the partial volume correction (max. 8.9%).

DISCUSION: This study presents a validation of a method to correct estimated metabolite concentrations for heterogeneously composed MRS voxels. Results of both *in vitro* and *in vivo* studies demonstrate the importance of considering tissue composition, especially to account for the partial volume effects of CSF, which contains only water with vanishing metabolic contributions. As assessed in the present work partial volume effects of CSF led to substantial underestimation of metabolite concentrations (max. 40.5% *in vitro* / max. 8% *in vivo*) (see *Fig. 2* and *Fig. 3*).

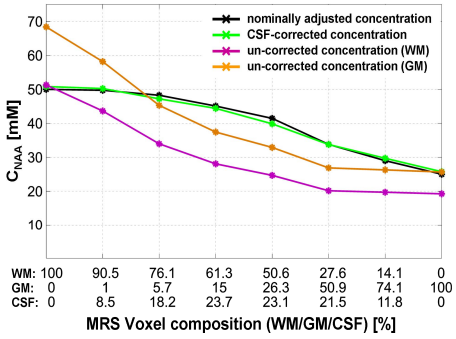

Fig. 2: *In vitro NAA concentrations estimated from differently composed MRS voxels. Values were estimated by taking into account the heterogeneous voxel composition (green) as well as by assuming homogeneous voxels consisting of GM (orange) or WM (violet). The black line represents the nominally adjusted NAA concentrations.*

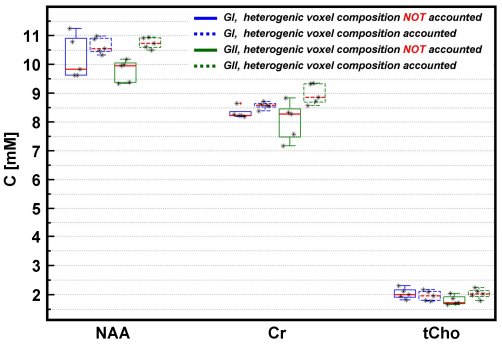

Fig. 3: *In vivo NAA, Cr and tCho concentrations for both control groups (blue: GI; green: GII) considering homogeneous (full) and heterogeneous (dashed) MRS voxels. Red lines in the boxes represent median values, whereas the upper and lower box limits correspond to the 75th and 25th percentile, respectively.*

REFERENCES: [1] Mullins EM. *Neuroimag. Clin. N. Am. 2006*; 16: 605-18. [2] Mason JF et al. *NMR Biomed. 2006*; 19: 690-701. [3] Jansen JFA et al. *Radiology 2006*; 240(2): 318-32. [4] Ernst T et al, *J. Magn. Reson. 1993*; B 102: 1-8. [5] Provencher SW, *Magn. Reson. Med. 1993*; 30: 672-9. [6] Mlynárik V et al. *NMR Biomed. 2001*; 14: 325-331. [7] Deistung A et al. *Magn. Reson. Med. 2008*; 60: 1155-1168.