TEST-RETEST QUANTITATION OF ABSOLUTE METABOLITE CONCENTRATIONS WITH PARTIAL VOLUME CORRECTION USING DIFFERENT SEGMENTATION METHODS

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Target Audience: Clinicians and scientists employing magnetic resonance spectroscopy.

Purpose: The quantitation of absolute metabolite concentrations via Magnetic Resonance Spectroscopy using water as an internal concentration standard, requires the accurate determination of the compartmentation within the localized region of interest. Previous work has shown that different segmentation approaches yield different estimates of metabolite levels in grey matter [1]. In this study, we sought to investigate the test-retest reliability of absolute metabolite quantitation using two commonly used segmentation algorithms.

Methods: ***Acquisition.*** Anatomical and MR spectroscopic data from 12 healthy controls (1 female, age range: 23-50) was acquired on a 3T Siemens MAGNETOM Verio Scanner using a 32 channel phased-array coil. T1-weighted images were acquired using an MP2RAGE sequence with the parameters: TR=5s, TE=3.93ms, FOV=192mm, 256x256 acquisition matrix, 1.0x1.0x1.0mm voxel dimensions. 1H MRS spectra from two regions of interest were obtained with a point-resolved-spectroscopy (PRESS) sequence with the following parameters: TE= 30ms, TR=3000ms, 80 water suppressed and 16 water-unsuppressed averages. A 25x16x16 mm^3 cortical voxel was prescribed on the Anterior Mid-Cingulate Cortex (ACC) with the center of the voxel projecting to the genu of the corpu collosum, and an orientation that is parallel to the hippocampal axis. A 28x16x16 mm^3 subcortical voxel was localized on the thalamus while maximizing the amount of grey matter within the voxel. Regions of interest were shimmed automatically with the FASTESTMAP Sequence [2,3] . The inbuilt AutoAlignHead Siemens sequence was used to align the geometry of the voxel to a standard. On the retest scan, the voxels were automatically localized using the saved voxel geometry information from the first scan. ***Voxel Registration.*** Averaged spectra were exported from the scanner as Raw Data Format (.rda) files. To register the MRS voxel onto the antomical image, the transformation matrix of the MRS voxel was first calculated from the rda file header. A binary mask representing the limits of the MRS voxel was then constructed to map the voxel onto the anatomical image [4]. ***Segmentation.*** SPM12 New Segment and Freesurfer (version 5.3.0) were used to segment the brain into different tissue compartments. Freesurfer grey matter, white matter and CSF tissue classes were extracted from the segmentation-generated tissue labels. GM, WM and CSF tissue fractions were then calculated within the registered SVS voxel from the segmentation outputs. ***Absolute Metabolite Quantitation.*** Scanner-averaged frequency domain spectra were analyzed with LCModel [5], which implements a fully automated quantitation algorithm which does not account for partial volume effects. Inclusion criteria for good quality spectra were SNR higher than 15, an FWHM lower than 12Hz, and Cramer Rao lower bounds lower than 20%. Compartmentation within the MRS voxel was considered for the quantitation of absolute metabolite concentrations by applying equation (1) while ignoring relaxation effects of metabolites since they have similar T1/T2 times in GM and WM and areapproximately accounted for by LCModel [1]. Absolute metabolite concentrations were calculated using tissue fraction percentages generated using SPM and Freesurfer.

$$C_M = \frac{I_M}{I_W} \cdot \frac{2}{N_M^{1H}} \cdot C_W^0 \cdot \frac{f_{GM} \cdot R_W^{GM} \cdot \alpha_{GM} + f_{WM} \cdot R_W^{WM} \cdot \alpha_{WM} + f_{CSF} \cdot R_W^{CSF} \cdot \alpha_{CSF}}{f_{GM} \cdot R_M^{GM} + f_{WM} \cdot R_M^{WM}} \quad \textbf{e.q. (1)}$$

Results and Discussion: ***Voxel Registration and Segmentation:*** The reliability of the automatic MRS voxel re-localization method was assessed using the Sørensen–Dice metric which yielded mean ± standard deviation values of 0.78 ± 0.10 for the ACC voxel and 0.71 ± 0.28 for the Thalamic voxel. Anatomical image segmentation using SPM and Freesurfer yielded results that were significantly different between the two algorithms. Mean values of grey matter, (GM), white matter (WM) and corticospinal fluid (CSF) fractions within the two SVS voxel are illustrated in table 1. Within the same package, the segmentation algorithms exhibited high reliability across scanning time-points as the estimates for the tissue classes within the MRS voxel did not reached significance using a two sided paired t-test. Comparing the values between segmentation algorithms, results exhibited discrepancies of more than 20%. SPM's segmentation of the ACC voxel yielded CSF fractions that were 20% higher than Freesurfer's, while in the thalamic voxel, the opposite effect was observed, as Freesurfer's CSF tissue fractions were more than 30% higher than SPM's. Given that a criterion for localizing the thalamic voxel was to maximize the amount of grey matter, Freesurfer's results demonstrate better estimates based on visual inspection, as the amount of white matter with SPM segmentation was significantly high (Figure 1). ***Absolute Metabolite Quantitation.*** As a result of peak resonance overlaps at 3T, five metabolite concentrations were considered as reliable: tNAA (NAA + NAAG), tCre (Cr + pCr), tCho (Cho + pCho), mI, Glx(Glu + Gln). Means and SDs of uncorrected and partial volume corrected metabolite spectra are presented in table 2. Overall, Freesurfer yielded higher estimates of absolute metabolite concentrations when compared to SPM. Pairwise absolute percentage differences were then calculated for uncorrected, Freesurfer-corrected and SPM-corrected metabolite concentrations. The averaged standard deviations of absolute percentage difference were consistently lower for Freesurfer-corrected concentrations for the ACC voxel. No general trend was observed for the thalamic voxel.

Table 1 Test-retest tissue fraction estimates of SPM and Freesurfer

Fraction	Scan A: SPM	Scan B: SPM2	Scan A: FS	Scan B: FS
ACC_{GM}	74.5% ± 3.0%	72.9% ± 3.1%	47.3% ± 4.4%	47.3% ± 4.4%
ACC_{WM}	11.9% ± 2.5%	11.9% ± 2.6%	19.5% ± 2.9%	19.5% ± 2.9%
ACC_{CSF}	13.6% ± 4.0%	15.2% ± 4.0%	33.1% ± 5.0%	33.1% ± 5.0%
THA_{GM}	54.2% ± 3.4%	48.0% ± 1.3%	85.8% ± 4.2%	80.3% ± 2.1 %
THA_{WM}	38.5% ± 4.2%	39.3% ± 15.3%	3.9% ± 1.8%	3.9 % ± 4.2 %
THA_{CSF}	7.3% ± 2.9%	12.7% ± 15.3%	10.3% ± 3.3%	15.3% ± 15.6%

Metabolite	Uncorrected(mM)	SPM	Freesurfer
ACC - tNAA	7.1± 0.5	8.2 ± 0.5	10.6 ± 0.9
ACC - tCre	5.7± 0.3	6.7 ± 0.4	8.6 ±0.8
ACC - tCho	1.6 ± 0.1	1.8 ± 0.2	2.3 ± 0.3
ACC - Glx	9.1± 0.5	10.6 ±0.7	13.5 ± 1.3
ACC - mI	4.3± 0.3	5.1 ± 0.4	6.5 ± 0.7
THA- tNAA	7.1 ± 0.44	7.9 ±1.4	8.7± 1.7
THA- tCre	5.9 ± 0.26	6.4 ±1.0	7.0 ±1.3
THA- tCho	1.6 ± 0.10	1.8 ± 0.4	2.0± 0.5
THA- Glx	8.48 ± 0.6	9.4 ± 1.9	10.4 ±2.3
THA- mI	3.7 ±0.3	4.1 ± 0.9	4.6 ± 1.1

Table 2. Uncorrected and corrected metabolite concentrations.

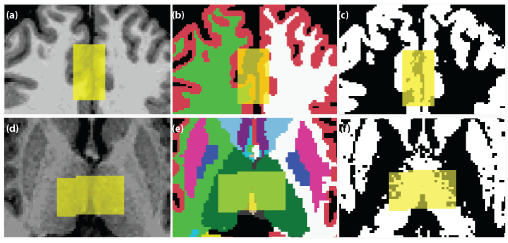

Figure 1. Masks illustrating voxel positioning superimposed over (a/d) T1w images, (b/e) Freesurfer and (c/f) SPM GM segmentations.

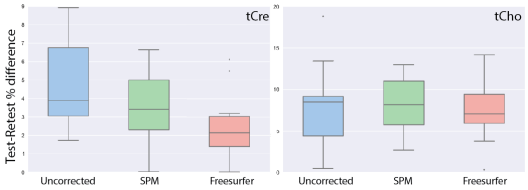

Figure 2. Box plots of percentage differences for corrected and uncorrected data for tCre and tCho.

Conclusion: In summary, our observations suggest that partial volume correction may help improve absolute metabolite concentration estimates, though there are substantial differences between the segmentation algorithms of SPM and Freesurfer in cortical and subcortical regions, which are reflected in the correction of metabolite concentrations. Careful consideration of which package to use for estimating compartmentation within different MRS regions of interest is recommended.

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