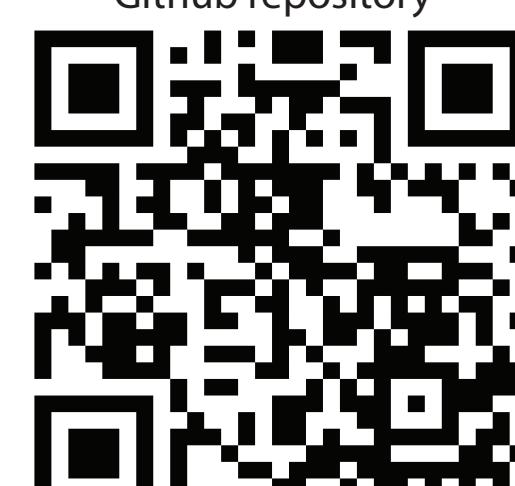


# Test-Retest reliability of 1H-MRS absolute metabolite quantitation with partial volume correction using different segmentation methods

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## Introduction

- The use of water as an internal concentration standard, is a feasible and common techniques for accurate 1H-MRS metabolite quantitation.
- Large spectroscopic voxels commonly contain a mixture of grey and white matter (GM, WM) and cerebrospinal fluid (CSF).
- Metabolite signals only arise from GM and WM.
- GM and WM compartments have different water concentrations [1] and exhibit different T1/T2 relaxation-time constants for metabolites and water [2,3].
- Compartmentation can be taken into account for absolute quantitation (eg. Equation 2).
- Previous work has shown that different segmentation approaches yield different estimates of corrected metabolite concentrations [4].
- In this study, we investigate the reproducibility of absolute metabolite quantitation with internal water referencing while taking partial volume effects into account.
- We test the effects of different segmentation strategies on the reproducibility of metabolite quantitation in cortical and subcortical regions with varied tissue fraction content.

## Methods

### Data Acquisition

#### Dataset 1

- Subjects:** 10 healthy controls (age = 28.3±2.3).
- System:** 3T MAGNETOM Trio (Siemens, Erlangen, Germany).
- MPRAGE:** TR=1s, TE=2.7ms, FOV=192mm, 256x256 acq. matrix, 1.0mm<sup>3</sup>.
- 1H-MRS:** Frontal White matter Voxel (WM). PRESS TE=30ms, TR=5000ms, 3.0mL, 128 supp averages, 16 unsupp acq, 8-channel head coil.

#### Dataset 2

- Subjects:** 20 healthy controls (age = 38.9±11.4).
- System:** 3T MAGNETOM Verio (Siemens, Erlangen, Germany).
- MP2RAGE:** TR=5s, TE=3.93ms, FOV=192mm, 256x256 acq. matrix, 1.0mm<sup>3</sup>.
- 1H-MRS: Anterior Cingulate Cortex (ACC):** PRESS TE=30ms, TR=3000ms, 6.4 mL, 80 supp acq., 16 unsupp acq., FASTESTMAP shimming [5,6], AutoAlignHead repositioning [7], 32-channel head coil.
- 1H-MRS: Bilateral Thalamus (THA):** PRESS TE=30ms, TR=3000ms, 7.2 mL, 80 supp acq., 16 unsupp acq., FASTESTMAP shimming, AutoAlignHead repositioning.

### Voxel Registration

- MRS voxel was mapped onto anatomical space by calculating the transformation matrix from the Siemens Raw Data Format (RDA) file header.
- Voxel overlap was calculated via the Sørensen–Dice coefficient (DC, equation 1).

$$DC = \frac{2|A \cap B|}{|A|+|B|} \quad (1)$$

### Tissue Fraction Extraction

- Three different Segmentation algorithms were tested: SPM12 NewSegment, FSL FAST, Freesurfer (FSU).
- GM, WM, CSF tissue percentages were calculated within the limits of the MRS binary mask. Probabilistic maps were binned to make tissue concentrations add up to 100%.

### Absolute metabolite quantitation

- Method 1: LC-Model quantitation [8].
- Method 2: LC-Model quantitation correction with partial volume correction (Equations 2-3) [9-11]. Relaxation effects were ignored since metabolites have similar T1/T2 times in GM, WM and are approximately accounted for in LC-Model.

$$C_{Met} = \frac{I_{Met}}{I_{H2O}} \cdot \frac{2}{N_{Met}^{1/H}} \cdot C_{H2O}^0 \cdot \frac{f_{GM} \cdot R_{H2O} \cdot \alpha_{GM} + f_{WM} \cdot R_{H2O} \cdot \alpha_{WM} + f_{CSF} \cdot R_{H2O} \cdot \alpha_{CSF}}{f_{GM} \cdot R_{GM} + f_{WM} \cdot R_{WM}} \quad (2)$$

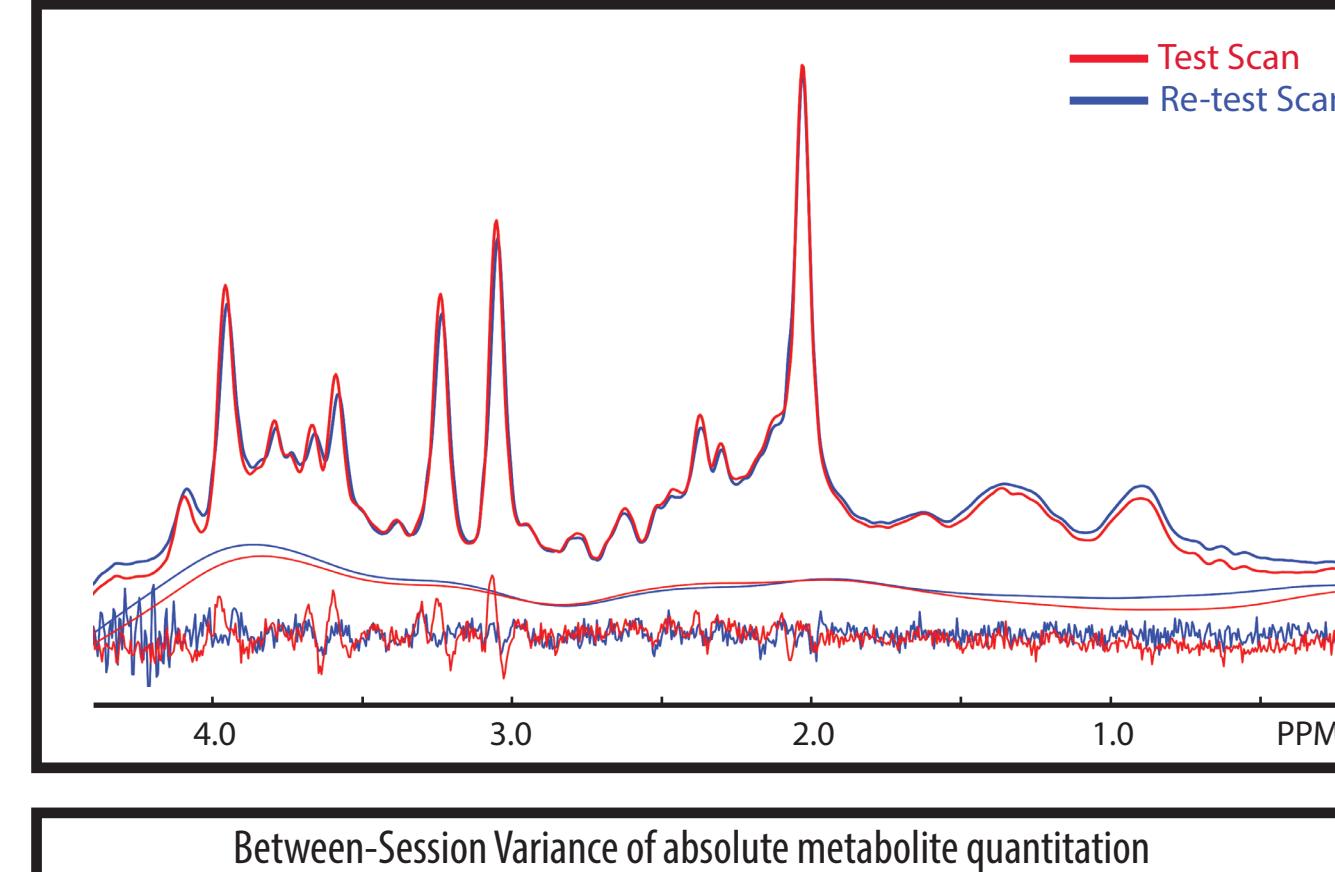
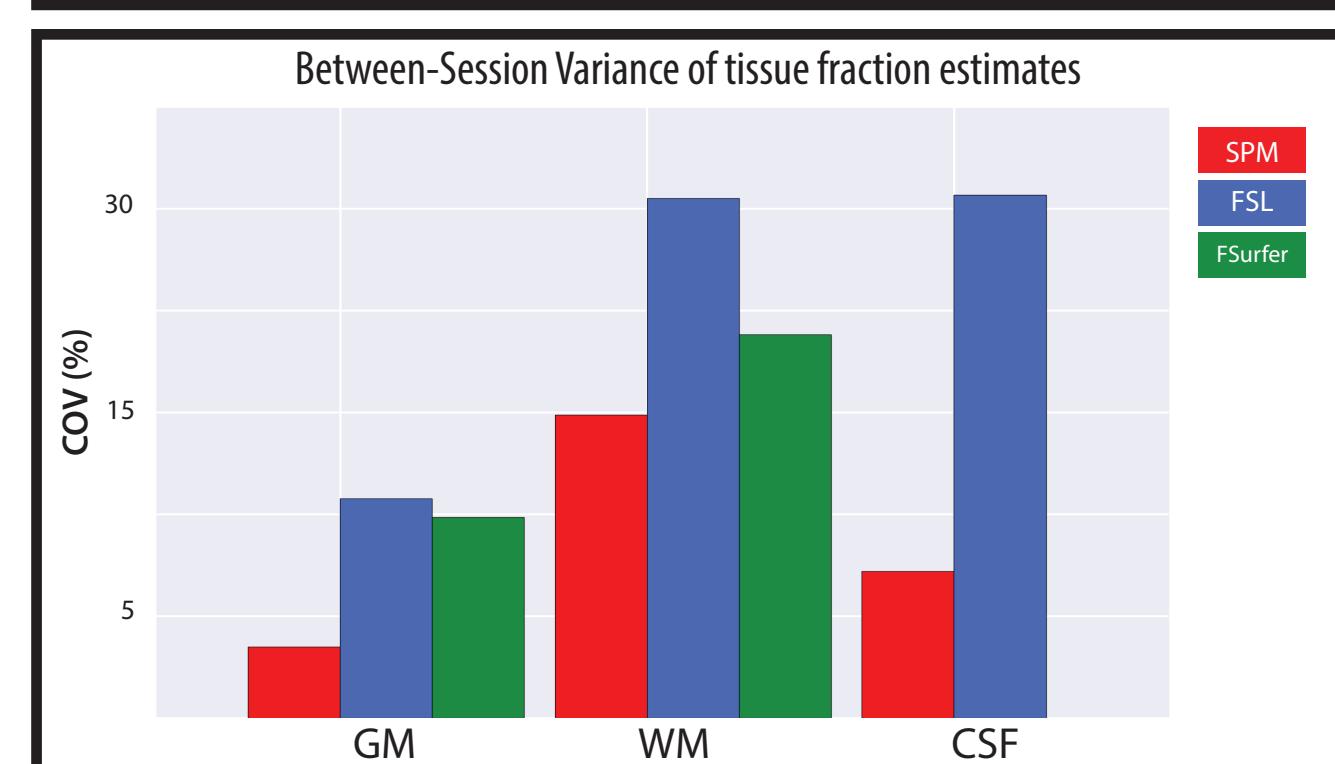
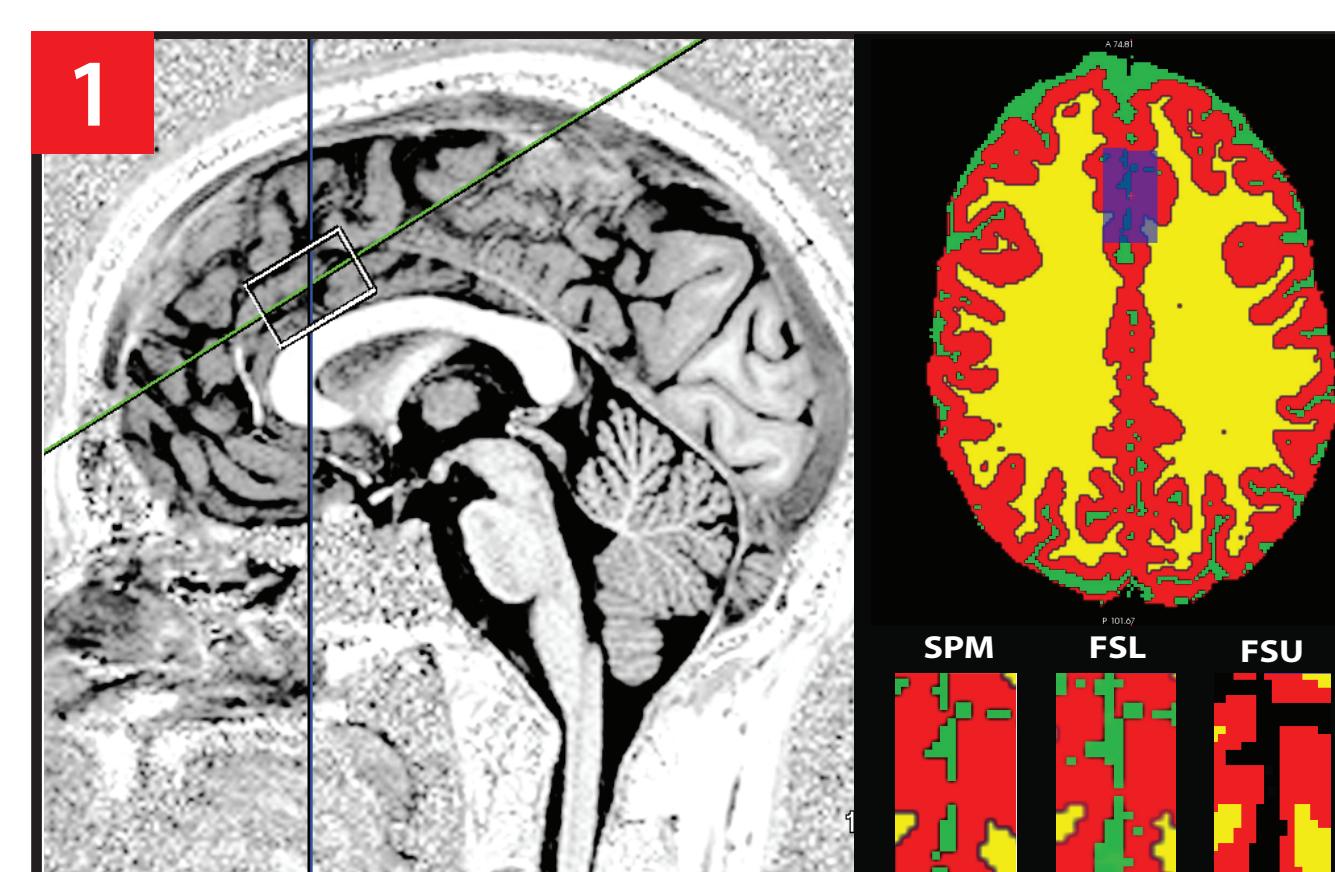
$$R(TR, TE) = (1 - e^{-\frac{TR}{T1}}) \cdot e^{-\frac{TE}{T2}} \quad (3)$$

$$\alpha_{GM} = 0.81 ; \alpha_{WM} = 0.71 ; \alpha_{CSF} = 1.0$$

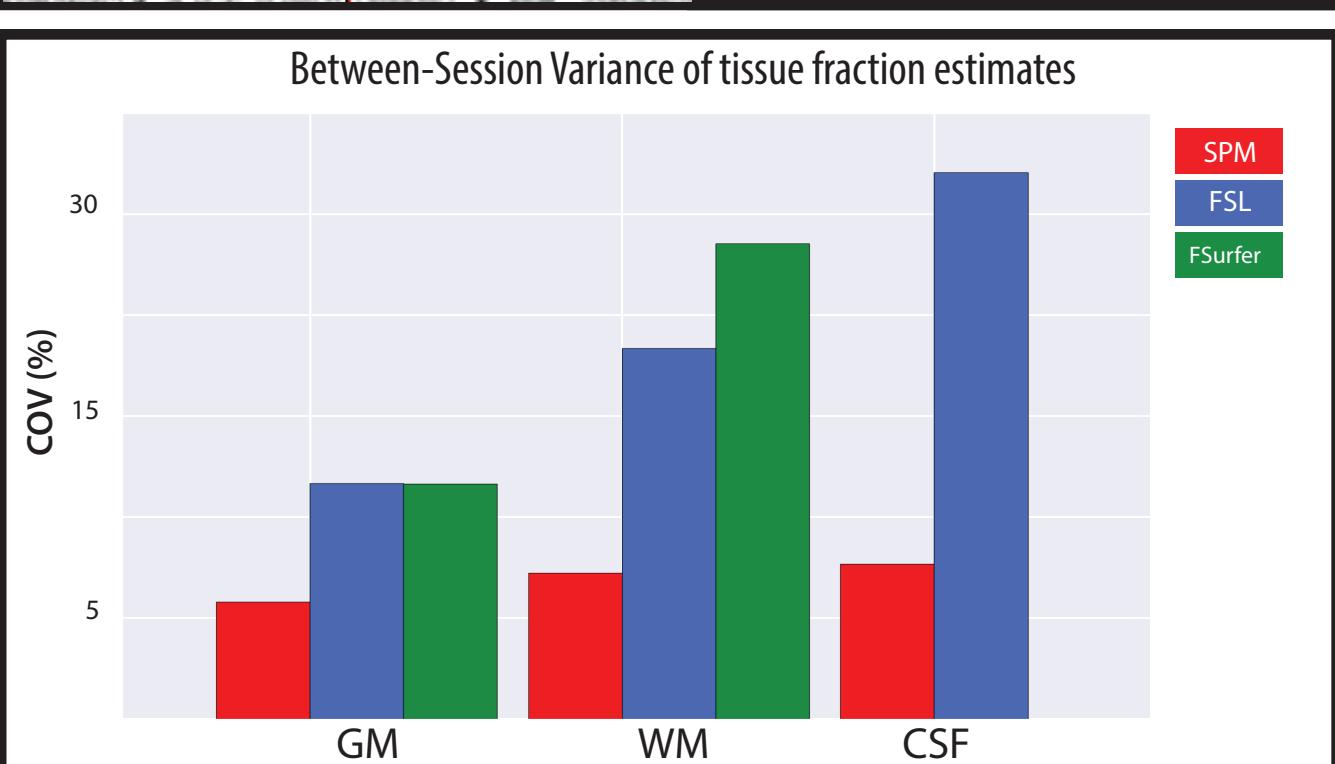
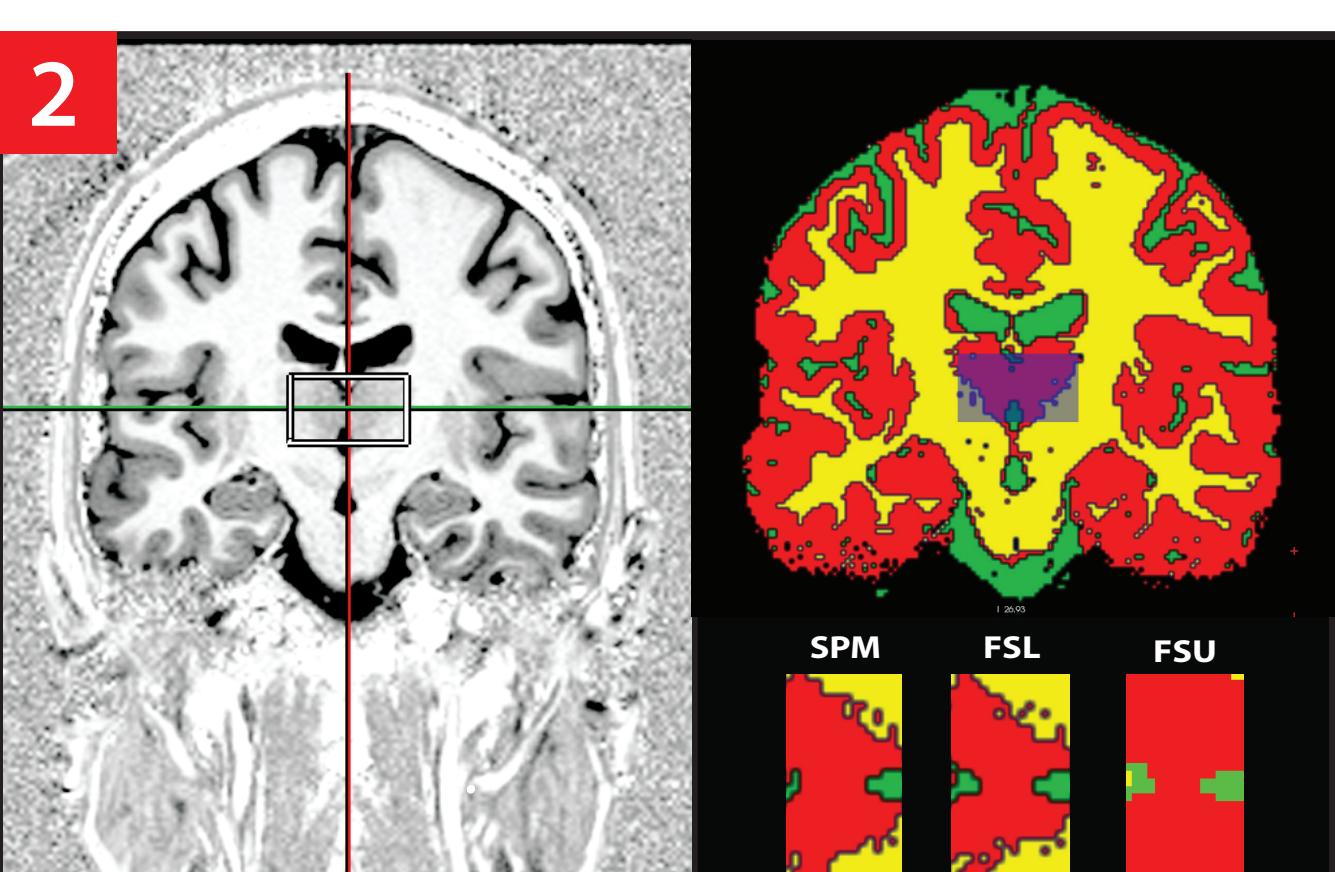
### Statistical Analysis

- Test-retest reliability was assessed by calculating the coefficient of variation for tissue fraction and absolute metabolite estimates (COV = SD/Mean).

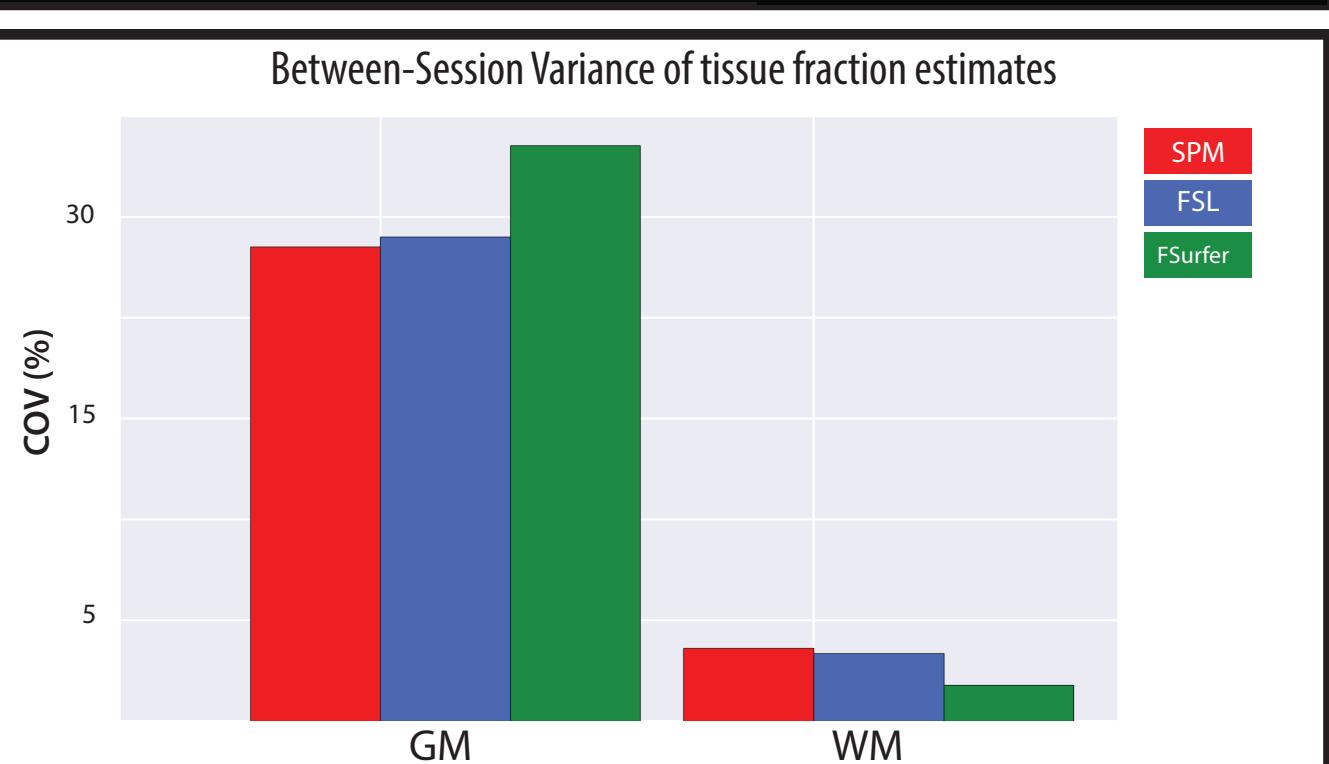
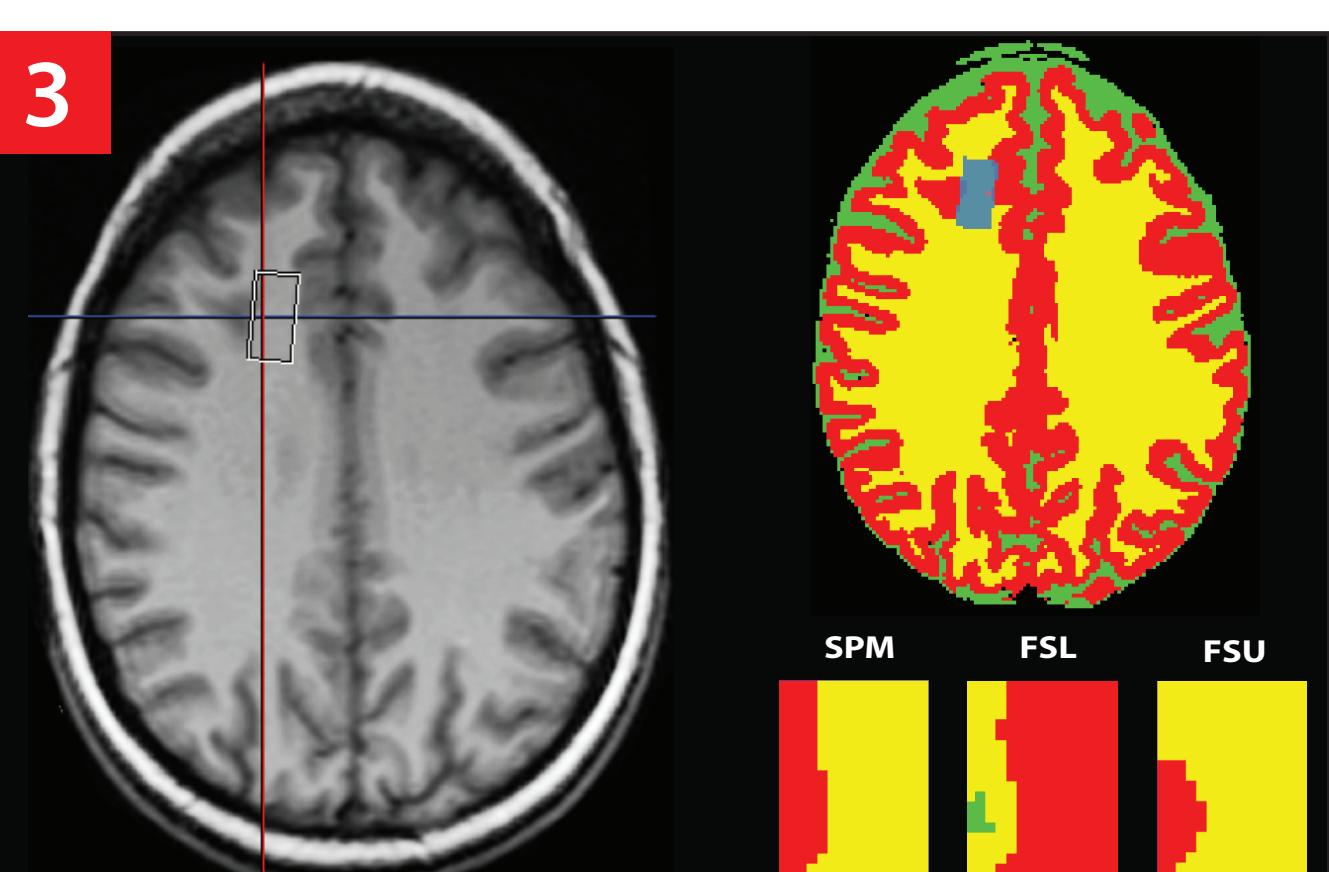
## Results



**Figure 1.** Test-retest reproducibility of voxel localization, tissue fraction estimation, quantitation correction for the ACC Voxel.



**Figure 2.** Test-retest reproducibility of voxel localization, tissue fraction estimation, quantitation correction for the THA Voxel.



**Figure 3.** Test-retest reproducibility of voxel localization, tissue fraction estimation, quantitation correction for the WM Voxel.

### Re-localization Accuracy

- The relocalization procedure yielded Dice coefficients Means and SDs of 0.76 ± 0.14 for the ACC voxel, 0.81 ± 0.13 for the THA voxel, 0.12 ± 0.14 WM voxel.

### Segmentation Consistency

- No significant differences were observed in tissue fraction estimates between sessions using the three algorithms.
- SPM & FSL estimates were similar, however, Freesurfer GM estimates were significantly different (20-30% lower in the ACC and 30-40% higher in the THA, 5-10% lower WM).
- SPM exhibited the highest consistency (lowest COV%) in tissue fraction estimates between sessions.

### LC-Model Quantitation

- Five metabolite concentrations were considered reliable: tNAA (NAA +NAAG), tCre (Cr + pCr), tCho (Cho + pCho), mI, Glx(Glu + Gln).
- No significant differences were observed between scans for LC-Model and tissue fraction corrected metabolite concentrations.
- Mean COV% were lower than 10% for all reliable metabolites.

### Quantitation Correction

- Correction with SPM tissue estimates exhibited the highest reliability between-sessions (lowest COV%) for different anatomical sequences and different voxels.
- Quantitation correction with SPM decreased between-session variance for Glu/tCho in the thalamic voxel. Increases in variance for other metabolites in different regions were slight and non-significant.

## Discussion

- In this study, we examined the reliability of 1H MRS absolute metabolite quantitation with partial volume correction.
- We observed that sophisticated and commonly used segmentation algorithms yield different regional estimates of tissue fractions.
- We report that SPM yields the highest consistency in partial volume estimation between-sessions.
- Although consistency does not imply validity, we observed that quantitation correction with SPM tissue fraction estimates yields the lowest between-

session variance across different groups, voxels and anatomical sequences.

- In comparison with LC-Model quantitation, we report a decrease in variance for key metabolites estimates when considering SPM tissue fractions.
- To interrogate changes of relevant metabolites in the longitudinal setting in psychiatric or neurological disorders, we recommend correction for 1H-MRS partial volume effects, which can be achieved with MRI T1-weighted based segmentations.

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