Comparison of Different CSF Correction Methods in a MRS Study of Depressed Psychiatric Patients

J. D. Port[1], I. Hancu[2], H. A. Edmonson[1], Z. Bao[3], and M. A. Frye[4]

[1]Radiology, Mayo Clinic, Rochester, MN, United States, [2]GE Global Research Center, Niskayuna, NY, United States, [3]Information Services, Mayo Clinic, Rochester, MN, United States, [4]Psychiatry, Mayo Clinic, Rochester, MN, United States

Introduction: MR spectroscopy is a potentially valuable tool that has been used extensively to study psychiatric diseases. However, there has been much debate in the literature about the best way to perform CSF corrections on spectroscopic data. Since CSF has no significant metabolite levels, any CSF sampled within the MRS voxel "dilutes out" (i.e., artifactually lowers) the measured tissue metabolite levels. Traditionally, metabolite ratios (usually to Cr) have been used to correct for the variable amounts of CSF sampled in voxels of different patients. Newer techniques (1-3) use anatomical images (T1-weighted, T2-weighted, etc) to measure the amount of CSF in a voxel and correct for the CSF fraction mathematically. It is unclear which method is the best, as each has its limitations. We recently performed an MRS study of depressed psychiatric patients (4), and found several significant metabolic differences in the dorsolateral prefrontal and midline anterior cingulate cortex of depressed patients relative to normal controls. We reanalyzed this data, performing CSF correction using ratios, T1-weighted anatomical images, and T2-weighted anatomical images. We hypothesized that one of these CSF correction methods would minimize the p-values between comparisons of MRS data from patients versus normal controls, and therefore this method of CSF correction could be considered "the best."

Methods: This human subjects study was performed with Institutional Review Board approval (06-006659). A total of 37 depressed patients with underlying bipolar disorder or major depressive disorder and 12 normal controls were scanned using a 3T MRI scanner with a receive-only 8-channel head coil and body transmit. Two voxels were sampled in each subject: a 2x2x2cm voxel centered on the left dorsolateral prefrontal cortex (LDLPFC), and a 2x2x1cm "flat" voxel centered on the pregenual midline anterior cingulate cortex (MACC). Two MRS techniques were scanned for each voxel, a standard PRESS sequence (TR=2000ms, TE=30ms, num acq=128 for the LDLPFC voxel, 256 for the MACC voxel), and a 2D-J averaged sequence (5) (TR=2000ms, TE=35-195ms in 16 steps, num avg=8 for the LDLPFC voxel, 16 for the MACC voxel). T1-weighted anatomical images of the whole brain were acquired using a sagittal 3D MP-RAGE sequence (TR=3000ms, TE=minimum full, TI=900ms, FA=8deg, 256x256, FOV=260mm, slice=1.2mm); bright-fluid anatomical images, referred to as "T2-data", of the whole brain were acquired using a sagittal 3D Fiesta sequence (TR=7ms, TE=minimum full, FA=70deg, 256x256, FOV=260mm, slice=1.2mm). Spectra were processed with LCModel (6) using a vendor-supplied basis set for the PRESS sequence and a custom basis set supplied by Dr. Hancu for the 2DJ sequence. Spectra were visually inspected, and those with artifacts were discarded; thus not all subjects were used in this current analysis. The fraction of CSF was computed separately for each voxel location using each anatomical dataset. Briefly, the T1-data were intensity-corrected using N3 (7), and the non-brain tissues eliminated using a tissue mask computed by SPM. Brain images were then registered to the ICBM Tissue Probabilistic Atlases in SPM, and segmented using a 4-class process into gray matter, white matter, CSF, and other. Segmentation data were then remapped back into subject space, and the fraction of CSF (FCSF) computed as FCSF = VoxCSF / (VoxGM + VoxWM + VoxCSF + VoxOther). T2-data were thresholded into two intensity classes using Otsu's method, and the FCSF computed as FCSF = VoxCSF / (VoxCSF + VoxBrain). Metabolite concentrations were CSF-corrected using each of the FCSF measures using [M]Corr = [M]Measured * 1/(1-FCSF). Statistical analysis was performed only on metabolites with LCModel CRLB <= 20%. A standard t-test was used to compare corrected metabolite levels between patients and normal controls, patients with bipolar disorder (BPD) versus major depressive disorder (MDD), and patients with melancholic versus atypical depression. An ROC analysis was performed to compare the three CSF correction techniques.

	Melancholic	Atypical	p	AUC	χ^2	p
LDLPFC 2DJ Glu	n=22	n=13				
/Cr	1.0±0.1	1.2±0.2	**0.004**	0.79		
CSF T1	46.5±5.2	58.1±13.9	**0.015**	0.75	2.44	*0.294*
CSF T2	48.8±5.5	60.5±15.3	**0.023**	0.73		
	Depressed	Control	p	AUC	χ^2	p
LDLPFC PRESS NAAG	n=16	n=7				
/Cr	0.4±0.1	0.3±0.1	**0.021**	0.81		
CSF T1	2.2±0.8	1.6±0.3	**0.015**	0.83	0.08	*0.962*
CSF T2	2.3±0.8	1.7±0.3	**0.015**	0.83		
	Depressed	Control	p	AUC	χ^2	p
MACC 2DJ Glu	n=28	n=8				
/Cr	1.2±0.2	1.0±0.2	**0.007**	0.82		
CSF T1	128.3±23.6	105.6±20.5	**0.017**	0.78	0.78	*0.677*
CSF T2	121.2±20.4	98.6±19.4	**0.011**	0.80		
	BPD	MDD	p	AUC	χ^2	p
MACC 2DJ Cho	N=15	n=19				
/Cr	0.4±0.0	0.4±0.0	0.986	0.50		
CSF T1	39.9±6.7	44.5±5.3	**0.044**	0.71	5.09	*0.079*
CSF T2	38.4±5.8	41.5±4.3	**0.037**	0.71		

Results: No significant differences in raw, T1-corrected or T2-corrected Cr levels were found for any of the three comparisons. Statistically significantly (bold) decreased LDLPFC 2DJ Glu levels were found in melancholic versus non-melancholic depressed patients (Table), while significantly increased MACC 2DF Glu levels and LDLPFC PRESS NAAG levels were found in depressed patients versus normal controls. In general, all three CSF correction methods yielded significant results for most statistical comparisons. Interestingly, significantly increased MACC 2DJ Cho levels were found in major depression versus bipolar disorder using T1- and T2-corrected metabolites, but not using ratios. Five comparisons had a significant finding using only one of the three CSF-correction techniques (not shown). ROC analysis showed similar areas under the ROC curves (AUC), with no single CSF-correction technique better than any other (italics).

Discussion: It is generally believed that anatomically-based CSF-correction techniques are superior, as they provide "absolute" metabolite concentrations rather than ratios (which are challenging to interpret if both the numerator and denominator of the ratio vary). However, if one can prove that the metabolite value used in the denominator is stable, ratios may actually improve statistical sensitivity relative to anatomically-based CSF correction methods.

References: 1) MRM 35:356-63, 1996; 2) MRM 44:401-11, 2000; 3) MRM 48:555-8, 2002; 4) Biol Psychiatry 2009 Apr; 65(8 Suppl S):134S; 5) MRM 53:777-82, 2005; 6) MRM 30:672-9, 1993; 7) IEEE Transactions on Medical Imaging 17:87-97, 1998.