A Fully Automated and Robust Method of Extracting CSI voxels from Precise Anatomical Locations: An Application to a Longitudinal ^{31}P MRS Study

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Purpose: One of the difficulties associated with longitudinal ^{1}H or ^{31}P MRS studies using a multi-voxel acquisition approach is ensuring consistency in voxel placement in specific anatomical regions of interest within same subjects at multiple time point measurements as well as between subjects. However, any ^{1}H or ^{31}P MRS acquisition methods involving phase encoding for localization such as the chemical shift imaging (CSI) sequence has the advantage of re-shifting the voxel grid after the data has been collected in order to best optimize voxel placement in specific regions of interests. This is accomplished by applying a phase shift in the k-space domain prior to the Fourier Transformation of the data to the spatial domain. Consistent voxel placement in specific anatomical locations is critical in minimizing variability in partial volume effects within and between subjects, which helps to produce a more robust and reliable outcome leading to optimal sensitivity in detecting biochemical differences. In this study, we propose a novel method, which is 100% fully automated, to systematically place voxels in pre-defined anatomical locations followed by extraction of MRS signals from those voxels for quantification. The processing pipeline steps are presented and applied to an existing longitudinal data set using a 3D whole brain ^{31}P MRS acquisition protocol.

Methods: Our coregistration scheme required a volumetric T_1-weighted image set that was acquired during the same session as the multi-voxel CSI acquisition, such that both sets of data shared the same scanner reference frame from which the orientation vectors were derived (i.e., the reference frame of the MRI matches that of the CSI). This must be acquired at each time point of interest, as all subsequent T_1-weighted volumes will be coregistered to the orientation corresponding to the CSI and volumetric T_1-weighted set acquired at the first time point (B1). To standardize the voxel placements, specific anatomical locations [or regions of interests (ROI's)] are pre-defined using a high-resolution standard reference brain (A) such as the MNI brain. The coordinates representing the center of these anatomical locations expressed in cartesian coordinates (i.e., in pixel or millimeter units) are then mapped/transformed in subject or CSI space. Once the ROI locations are mapped in the subject or CSI space, the appropriate transformation was applied to grid shift a voxel to these locations and the MRS signal was then extracted. In greater detail, the steps include the following: Using FSL FLIRT[1], we determined the transformation matrix ($M_{A\rightarrow B1}$) required to coregister the standard reference brain onto subject brain B1. $M_{A\rightarrow B1}$ is then used to establish the the new center coordinates needed to localize our ROIs within the subject space. Coregistering subsequent time points (Bn) onto B1 requires a similar transformation matrix for matching Bn onto B1 ($M_{Bn\rightarrow B1}$), as determined by applying FLIRT to the respective T_1-weighted images. The inverse of $M_{Bn\rightarrow B1}$ (i.e., $M_{B1\rightarrow Bn}$) was then applied to the ROI center coordinates in B1 space to determine their new coordinates in Bn space. All the new ROI center coordinates are then used to calculate the nearest CSI voxels corresponding to the ROIs and the shift values necessary to bring the center of the nearest CSI voxel to match that of the ROI. These shift values are determined for each individual ROI followed by extraction of the MRS signal from the ROI using in-house Matlab (Mathworks, Natick, NA) scripts. The extracted MRS signal was then quantified using a spectral fitting method such as LCModel or fitMAN. The entire process is automatized by using unix shell scripts, essentially requiring only inputs indicating desired ROI and corresponding atlas as well as the file path of B1.

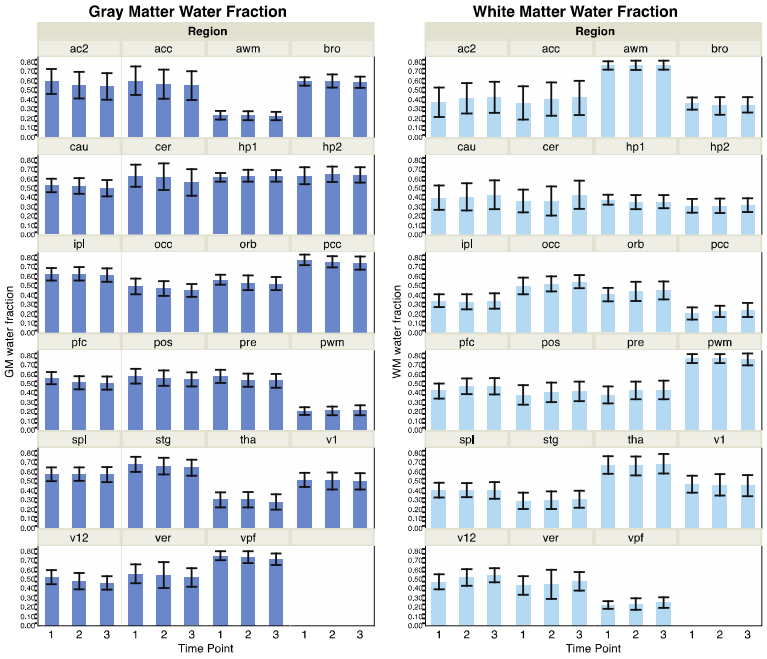

Figure 1. Mean gray and white matter fractions of each individual regions of interest based on FSL FAST segmentation. Error bars indicate standard deviation. There is high consistency in voxel composition across multiple subjects over time indicating reliable voxel placement. The ROI abbreviations include dorsal ACC (ac2), ACC (acc), frontal WM (awm), inferior frontal gyrus (bro), striatum (cau), cerebellum (cer), hippocampus (hp1), posterior hippocampus (hp2), inferior parietal (ipl), occipital lobe (occ), medial orbital (orb), posterior CC (pcc), DLPFC (pfc), post-central gyrus (pos), pre-central gyrus (pre), posterior WM (pwm), superior parietal (spl), superior temporal gyrus (stg), thalamus (tha), occipital ventral and posterior (v1), occipital - calcarine fissure (v12), vermis (ver) and ventrolateral pfc (vpf).

Results: One approach to verify the consistency of our voxel placement was to compare relative tissue compositions [i.e., gray and white matter fractions (GM and WM) and CSF] within our various ROI's. FSL FAST[2] was used to segment the T_1-weighted images. If ROI regions are coregistered correctly, we would expect relative compositions of GM, WM and CSF to be similar from subject to subject as well as across the various time points. Our analysis was performed on 32 healthy control subjects, 24 of which have data collected from 3 different time points with the remainder (N = 8) only having data from 2 time points. Overall, there is excellent agreement within a region across multiple time points (Figure 1), indicating consistent placement of voxels to the desired ROI (Figure 2). A repeated measures generalized linear model analysis of our data with either GM, WM, or CSF fraction as the dependent variable and with region, time point, subject, and time-by-ROI interaction as main effects, yielded non-significant time-by-ROI interactions (p = 0.47, p = 0.51, p = 0.47 for GM, WM, and CSF respectively), as would be expected if consistent coregistration had been performed.

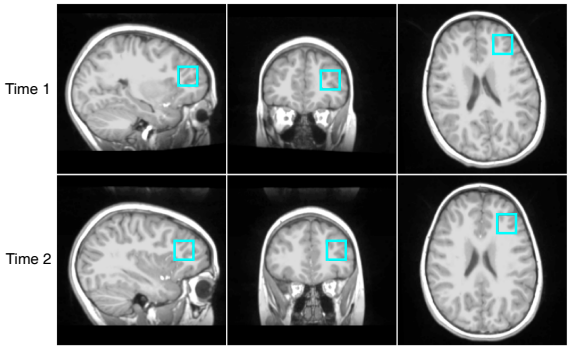

Figure 2. Coregistration of CSI voxel location in data collected at two different time points. Blue boxes indicates voxel location as calculated from their corresponding ROI centers. Overall, there is excellent agreement in voxel placement between the two time points.

Conclusion: Our method of using same-session volumetric $T1_1$-weighted images to determine the precise shift needed to extract the desired voxel at an intended ROI is highly efficient and provides excellent consistency in voxel placement and extraction for longitudinal MRS studies. This pipeline is extremely useful for those interested in longitudinal MRS studies and would be compatible with both 3D and 2D CSI techniques, although coregistration for 2D CSI data sets would be expected to be slightly less robust due to the limitation of being able to shift only along the in-plane axes.

1. Jenkinson, M., Bannister, P., Brady, M. & Smith, S. *NeuroImage* **17,** 825–841 (2002).
2. Zhang, Y., Brady, M. & Smith, S. *IEEE Trans Med Imaging* **20,** 45–57 (2001).