

Correlation of MR Relaxation Parameters with Tissue Macromolecular Composition

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INTRODUCTION

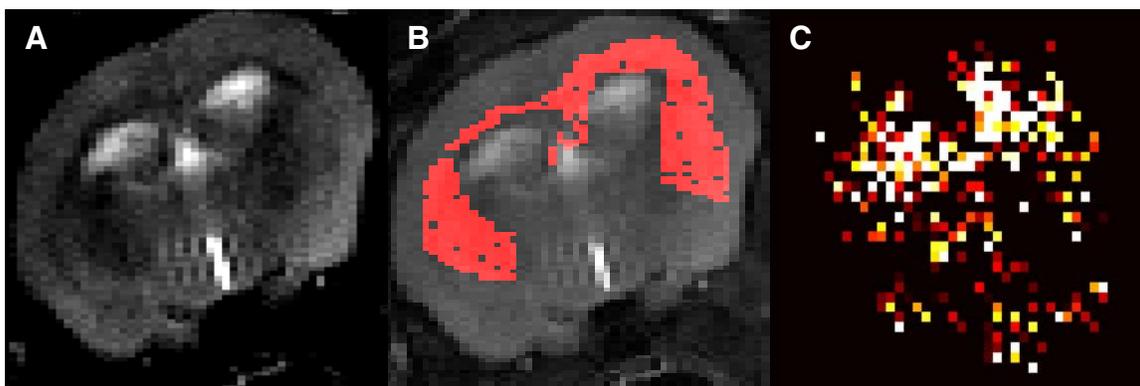
The quantitative values of tissue NMR parameters, such as relaxation rates, are directly related to tissue biomolecular composition, and variations of these account for much of the useful contrast available from MRI. Previous correlations between quantitative chemical analyses and in vivo imaging data have relied on measurements using tissue samples, homogenates, or histological slices stained for specific features. Such studies however do not permit precise comparisons between spatially heterogeneous variations on a voxel by voxel basis. We have therefore developed methods to compare quantitative MR imaging data with imaging matrix assisted laser desorption/ionization mass spectrometry (MALDI-MS). The latter permits the measurement of the distribution of constituent macromolecules at all locations within an excised slice at a spatial resolution comparable to in vivo MRI. From these spectra images can be produced representing the distribution of each peak or region of the mass spectra. A key step in the correlation of these data is accurate realignment of the MALDI-MS and MRI data sets. We have developed methods based on mutual information algorithms to provide this coregistration. We present a demonstration of the success of these developments in which quantitative maps of relaxation parameters have been spatially coregistered to the MALDI-MS images formed by integrating spectra corresponding to the myelin ion peak within slices of a mouse brain.

MATERIALS AND METHODS

C57/BL6 mice were acquired from Jackson Labs (Bar Harbor, ME, USA), and all experiments were performed with the approval of the local IACUC. All MR images were acquired with a Varian 9.4T INOVA 21cm bore MR scanner (Palo Alto, CA, USA). Gradient echo images (TR=150 ms, TE=2.4 ms, $\alpha=40^\circ$, 256×256, FOV=25.6×25.6 mm², THK=1 mm.) were acquired at nine flip angles (10, 20, 30, 40, 50, 60, 70, 80, and 90°). Spin-echo images (TR=4000, 256×128, zero-filled to 256×256) were acquired for the same slices at four different echo times (12, 30, 48, and 66 ms). Finally, a 3D gradient echo (TR=25 ms, TE=2.3 ms, $\alpha=15^\circ$, 256×256×128, FOV=25.6×25.6×12.8 mm³) was acquired for anatomical coregistration. Parametric maps of T₁ and T₂ were calculated from the MR images using software written in Matlab (Natick, MA, USA). After sacrifice, the mouse was decapitated, and its head frozen in a block of ice and sectioned into 20µm thick slices with a Leica CM3600 cryomicrotome (Vienna, Austria). Photographs were taken of every other slice with a Canon 20D digital camera (Tokyo, Japan) and Quantaray 70-300 mm macro lens which were mounted to the microtome on an adjustable gantry. Sections near the corpus callosum were transferred to gold-plated slides and analyzed in a MALDI mass spectrometer in imaging mode at 200 µm lateral resolution. From the mass spectra, images corresponding to the integrated peaks between *m/z* 14243 and 14538 (previously identified as myelin base protein) were produced. These were then coregistered to the MRI data using rigid-body registration methods.

RESULTS

Panel A shows a T₂-weighted image of a slice through mouse brain for anatomical reference. A 3D scatter plot (not shown) of the T₁, T₂, and integrated myelin mass peak revealed that the highest concentration of myelin was contained in pixels covering a narrow range of T₁ and T₂. Panel B shows the pixels in the same slice that fall within the range of T₁ (950-1050 ms) and T₂ (36-40 ms) chosen from the scatter plot. Panel C shows the coregistered MS myelin image.



DISCUSSION

The range of apparent T₁ and T₂ extracted from the parametric maps is in reasonable agreement with values expected for white matter at 9.4T. These pixels are spatially correlated with the myelin distribution mapped by MALDI-MS, and correspond to the white matter in the MR images. To our knowledge, this is the first time mass spectral data acquired on a voxel-by-voxel basis has been used to correlate macromolecular content with MR relaxation parameters in tissue. Although this study was conducted prospectively using the well-characterized dependence of T₁ and T₂ on myelin content, current and future studies will further develop this technique by employing statistical methods to evaluate additional empirical correlations between proteomic content and appropriate MR parameters.