Validation of MRI Mn Concentration Mapping in the Rat Brain

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Target Audience

This work will be of interest to researchers planning MRI studies using Mn^{2+}, and possibly other paramagnetic ions, as a contrast agent in the brain of small animals.

Purpose

Mn^{2+} is used as a contrast agent in MRI, which increases the R1 relaxation rate, roughly proportional to its concentration, and accumulates in regions of neuronal activity[1]. Mn imaging studies generally report R1-weighted signal changes or probability maps[2,3] of likely locations of Mn accumulation. Region-of-interested (ROI) averaged relaxation rate changes have been reported[4], and converted to Mn^{2+} concentration using a calibration factor, without details of the Mn^{2+} distribution. We have previously reported initial results of Mn imaging in the rat brain with MRI relaxation rate changes, and with positron emission tomography (PET) and autoradiography (AR)[5]. In this work, we validate the use of relaxation rate changes to estimate Mn^{2+} concentration in the brain of live rats at a per-voxel level. This technique offers potential much greater experimental power than ROI-averaged or probabilistic results, and should facilitate study activation-induced Mn uptake by revealing variation in its strength and distribution in response to varying strength and type of stimuli, which cannot be assessed with previous methods.

Methods

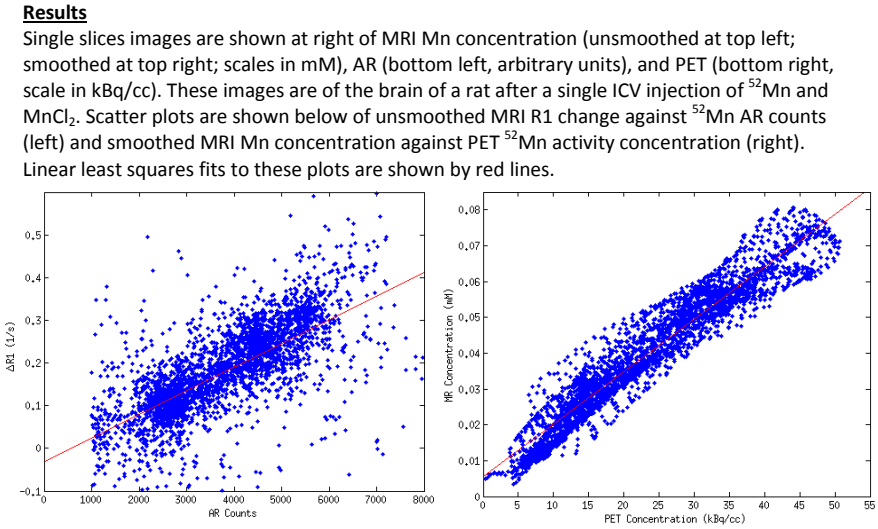
^{52}Mn was produced by irradiating natural Cr foil with 12.5 MeV protons ($^{52}Cr(p,n)^{52}Mn$)[6]. Mn was separated from Cr by column chromatography and redissolved in phosphate-buffered saline. Additional non-radioactive $MnCl_2$ was added to provide MR contrast. Healthy Sprague-Dawley rats received single injections: direct intracerebroventricular (ICV) (30 µl, 0.2 µmol Mn, 282 kBq ^{52}Mn) by stereotaxic surgery. MRI R1 maps were acquired at baseline and post-injection with a 7 T small animal MR system (Bruker, Germany) using a sagittal multi-slice FLASH-based Look-Locker sequence[7] (Parameters: TR=10 s, TE=3 ms, inter-excitation time=150 ms, 40 images per inversion, excitation angle=20 deg, matrix size 128x72, FOV=4x2.25 cm^2, slice thickness 625 µm, 17 slices, and acquisition time 12 min.) PET data was acquired on a Focus 120 small animal microPET system (Siemens, Germany) with a 450-600 keV energy window, and reconstructed by filtered back projection with cascade, scatter, and attenuation corrections, into single frame images with 0.433x0.433x0.796 mm^3 voxels. Autoradiographs (AR) were acquired by slicing frozen brain tissue into 20 µm segments onto slides and placing against radiosensitive phosphor screens for 3 days. Screens were read on a storage phosphor system (Cyclone), producing images with 43.2 µm pixels. A Mn concentration to R1 change calibration constant was measured by non-imaging inversion recovery on prepared Mn solutions in saline.

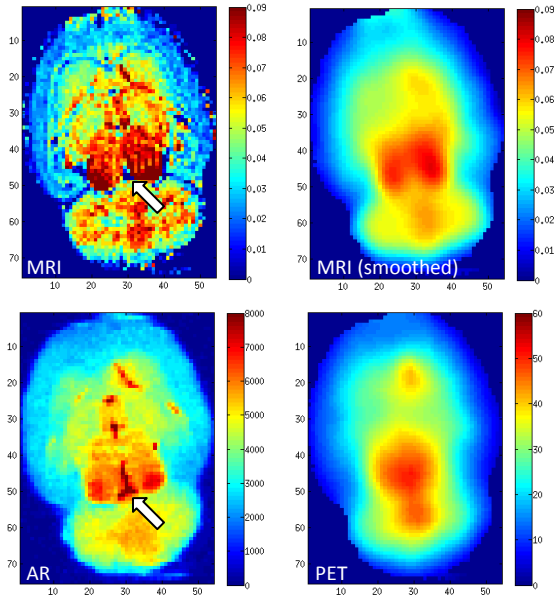
Analysis

MRI R1 maps were coregistered and subtracted to produce maps of R1 change, and converted to concentration using the calibration constant 4.2 $mM^{-1}s^{-1}$. AR slice images and PET images were coregistered to the MR image. The MR concentration image was smoothed with a 2 mm FWHM Gaussian kernel convolution to match the PET image spatial resolution. Scatter plots of unsmoothed MR against AR, and smoothed MR against PET concentration were fit with linear least squares models.

Results

Single slices images are shown at right of MRI Mn concentration (unsmoothed at top left; smoothed at top right; scales in mM), AR (bottom left, arbitrary units), and PET (bottom right, scale in kBq/cc). These images are of the brain of a rat after a single ICV injection of ^{52}Mn and $MnCl_2$. Scatter plots are shown below of unsmoothed MRI R1 change against ^{52}Mn AR counts (left) and smoothed MRI Mn concentration against PET ^{52}Mn activity concentration (right). Linear least squares fits to these plots are shown by red lines.





The MRI vs. AR plot fit has R^2 of 0.458, and was highly statistically significant ($p << 0.0001$ of null hypotheses of 0 slope or 0 intercept). The smoothed MRI vs. PET fit has R^2 of 0.912 and slope 0.001465 (mmol/l)/(kBq/cc) and intercept 0.0055 (mmol/l). This slope is 13% different from the expected slope of 0.00129 (mmol/l)/(kBq/cc) given what was injected and accounting for radioactive decay at the time of imaging. Mn distributions are qualitatively similar between modalities, although localized discrepancies are evident in the ventricles (marked with white arrows in unsmoothed MRI and AR images at right).

Conclusion

Excellent quantitative agreement is seen between MRI-derived relaxation rate change or Mn concentration, and PET and AR concentrations in images of the same animals. This validates the use of MR relaxation rate change to measure Mn accumulation in the rat brain. Mn concentration mapping with MRI is a potentially useful tool to improve the experimental power of Mn-uptake imaging to assess neuronal activation.

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