Dynamic Manganese-Enhanced MRI after Transient Focal Ischemia in Rats

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Introduction: Manganese enhanced MRI (MEMRI) has been used previously to map brain activation during somatosensory activation, injection of excitotoxic compounds, and during acute stroke (1-5). Since manganese enters the cells through voltage gated calcium channels, changes in calcium flux, for example with increased or decreased synaptic activity, result in changes in the rate of uptake of exogenous manganese, and hence in local tissue relaxation rates. During acute stroke for example, anoxic depolarization leads to increased calcium accumulation and hence increased manganese uptake (5). However in the chronic phase, there is likely reduced calcium flux due to extensive neuronal death in the infarct region. In the present study we aim to show that serial, minimally invasive MEMRI can map the changes in local brain activity in chronic stroke. Previous work in this field has generally involved arterial mannitol injection to transiently open the blood brain barrier (BBB) in order to supply i.v. manganese directly to the brain. Such preparations are generally acute. In this study we have used intrathecal injection of $MnCl_2$ into the CSF space via the cisterna magna, to provide uniform distribution of manganese ions throughout the brain without disrupting the BBB.

Methods: 8 Male Sprague-Dawley rats (250-300 g) were use for the study. Animals were allowed to breath freely under Isoflurane anesthesia (1-2% in O2/Air). In 4 animals, 50µl of 25mM $MnCl_2$ solution was injected over 30 seconds directly into the cisterna magna using a Hamilton syringe with 1-inch needle, while the other 4 animals were controls. 12 hours after the injection, all rats were subjected to 60 minutes of middle cerebral artery occlusion (MCAO). A 4.7T (GE Omega) MRI system was used to acquire multislice inversion recovery (IR) and multi-echo (ME) spin-echo EPI images to map longitudinal and transverse relaxation rates (R_1, R_2) over 8 days after MCAO. ΔR_1 was computed by subtracting the R_1 values at each post stroke time point to the R_1 value immediately before the stroke procedure. High resolution T_1-weighted images and EPI diffusion tensor images were also acquired. To better visualize the spatial variation of the $MnCl_2$ "transit", the serial R_1 maps were co-registered and parameterized by pixel-by-pixel fitting of the R_1 curves to a 5^{th} order polynomial function, from which the maximum, "peak" R_1 value, and "time-to-peak" were extracted and mapped.

Results: Animals exhibited variable uptake curves, however they all showed the same trend. Calculation of relative R_1 (ΔR_1) greatly reduced apparent variability. While the normal side showed continuous uptake of manganese until around 3 days after injection, the stroke area had reduced manganese concentration for the first 2 days and gradually recovered to the normal curve (Fig. 1,3). The fitted R_1 peak maps in one animal (Fig 2) indicate reduced Mn uptake in much the same regions that show DWI hyperintensity following stroke, however the extent of the area of decreased uptake appears slightly larger then the diffusion lesion. Early R_1 decrease in the stroke region was also seen in the control animals and is likely due to edema. Subsequent R_1 increase in the stroke area may be due to delayed Mn uptake as a result of gliosis and macrophage activity.

Conclusion: Dynamic minimally invasive MEMRI with intrathecal injection is capable of detecting decreased brain activity due to infarction after transient ischemia. This approach may allow for long term survival studies of altered brain activity in various disease models such as transient stroke, epilepsy, brain tumor, AD etc.

References: (1) Lin et al. MRM 1997;38:378 (2) Duong et al. MRM 2000;43:383 (3) Van der Linden et al. Neuroscience 2002;112:467 (4) Aoki et al. 2002;48:927 (5) Aoki et al. MRM 2003;50:7.

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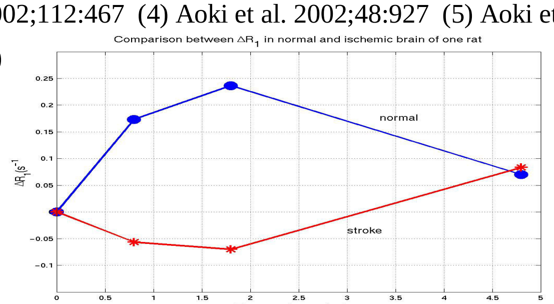
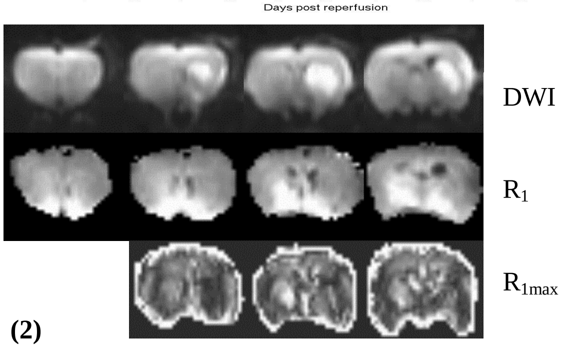


Figure 1: (left) Normal and ischemic ΔR_1 in striatum of one animal.
Figure 2: (lower left) diffusion weighted and R_1 images compared to fitted R1 peak maps.



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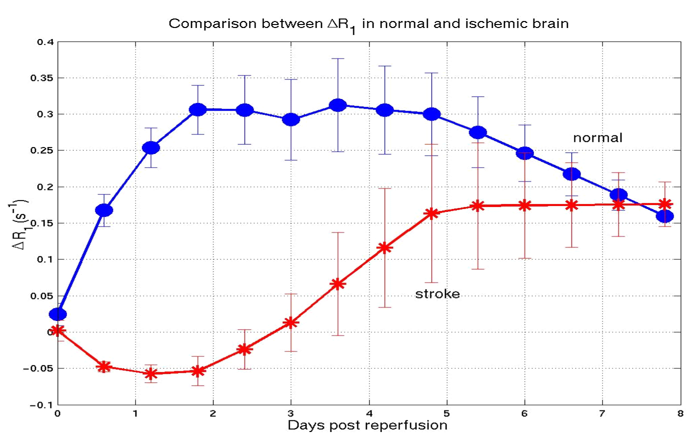

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