Manganese-enhanced MRI of rat brain using manganese-releasing alginate beads
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Introduction
Manganese-enhanced MRI (MEMRI) is a versatile technique for imaging of the central nervous system. Tissue manganese reduces T₁ and improves tissue contrast. For detection of laminar architecture in the brain, high concentrations of manganese in tissue are needed. However, systemic administration of high doses of MnCl₂ is neurotoxic due to the initial high blood concentration. This could be managed with slow release preparations of Mn²⁺. A candidate for slow release is alginate beads which can be given different gelling properties by altering the composition and arrangement of the monomers in the polymer chains and by selecting different divalent ions. The aim of the present study was to evaluate manganese-enhancement in brain tissue after systemic administration of manganese (Mn⁷⁺) releasing alginate beads.

Materials and Methods
Alginate gel beads: Manganese Alginic gel gel beads (diameter ~400 microns) were formed by dripping a 1.8% (w/v) solution of high-M alginic (from Macrocystis pyrifera, 40% G) into solutions containing 100mM MnCl₂ 40; n=5); Mn²⁺-containing alginate gel beads (MnAlg40; n=5) 2; Mn³⁺-containing alginate gel beads (MnAlg120; n=3). MnCl₂ 40mM/kg (MnAlg120; n=4).

Manganese-enhanced MRI
TT Bruker Biospec 70/20 AS with BGA-12 400mTm gradients. Coronal T₁ maps were obtained with a Rapid Acquisition with Relaxation Enhancement with Variable Repetition Time (RARE/VR) sequence Effective TE = 12.5ms; TR = 225/300/500/ 800/1600/3000/6000/15000ms; RARE factor = 4 and FOV = 4x3.5cm. The acquisition matrix was 200x175 giving a resolution of 200x200µm². T₁ maps were obtained 6 hours (h), 24h, 3 days (d), 6d and 10d after intraperitoneal MnCl₂ injection.

Data analysis: The mean relaxation (R₁) maps. Differences in mean R₁ between groups in each region at the different time-points were tested using ANOVA with post-hoc LSD test.

Results
Although there was a trend towards higher R₁ effect with MnCl₂ 40 than MnAlg40, no significant differences were detected in cortex. In thalamus and striatum, MnCl₂ 40 gave temporary higher R₁ at day 3 and 6 than MnAlg40, but no differences were found on day 10 after injection. This effect may be related to a more continuous release of manganese from the beads, resulting in a more steady influx of manganese into the cerebral tissue.

In conclusion, manganese releasing alginate beads provide good manganese-enhancement with reduction in T₁, comparable to that of MnCl₂ in the rat brain. Higher manganese dose with resultant higher R₁ after 10 days could be administered with alginate beads without apparent toxic effects. This may be a good alternative to repeated or continuous injections of MnCl₂.

References:
¹Thuen et al. (2008), Manganese-enhanced MRI of the rat visual pathway: Acute neural toxicity, contrast enhancement, axon resolution, axonal transport, and clearance of Mn²⁺. JMRI, 28: 855–865
²March et al. (2006). Effect of Ca²⁺, Ba²⁺ and Sr²⁺ on alginate microbeads. Biomacromolecules 7(5): 1471-1480

Figures:
Figure 1: Figure shows the temporal development of R₁ in cortex (A), thalamus (B) and Striatum (C) for rats injected with either 40mg/kg MnCl₂ (MnCl₂ 40), Manganese Alginic gel beads at a dose of 40mg/kg (MnAlg40) and 120mg/kg (MnAlg120). # p < 0.05 MnAlg40 vs MnCl₂ 40; * p < 0.05 MnAlg120 vs MnCl₂ 40; § p < 0.05 MnAlg40 vs MnAlg120.

Figure 2: Figure shows T₁-maps with ROI in striatum (A; dotted line), cortex (B; dashed line) and thalamus (B; solid line)