Manganese-enhanced MRI reveals laminar structures in the rat retina

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Introduction Manganese (Mn) is a calcium analog and an MR contrast agent. Mn enhancement in tissues is highly dependent on cell types, cell density, baseline and evoked neural activity, synaptic transport of Mn, and regional vascular permeability to Mn. Mn-enhanced MRI had been used to study brain function (1), fiber tract tracing (2), and neuroarchitecture (3).

The retina is composed of three highly structured cell layers: an outer photoreceptor layer, a middle bipolar cell layer, and an inner ganglion cell layer. It is nourished by the retinal and choroidal vasculatures [5] located on either side of the retina. The retinal vasculature exists primarily within the ganglion cell layer, but does project a deep planar capillary bed into the bipolar cell layer. The choroidal vasculature does not exist within any retinal layer, but rather is located directly beneath the photoreceptor layer, sandwiched between the retinal pigment epithelium and the sclera.

The goal of this study was to explore the use of Mn-enhanced anatomical MRI to visualize different tissue layers in the rat retina under anesthetized and awake conditions. It is hypothesized that Mn-enhanced MRI could be used to resolve different tissue layers in the retina under basal conditions. Gd-DTPA contrast-enhanced MRI was also used to visualize vascular layer and for overlaying Mn-enhanced MRI on the same animals to confirm layer assignments.

Methods Two groups of male Sprague Dawley rats were imaged. In Group I (n = 6), pre-Mn images was acquired and $MnCl_2$ was administered intravenously (120 mM, 0.3 mL) over 1-2 min followed by MRI while the animals were under 1.5% isoflurane anesthesia under relatively dark condition. In Group II (n = 4), $MnCl_2$ (120 mM, 0.3 mL) was administered intravenously over 1-2 min under 1.5% isoflurane anesthesia and the animals were allowed to wake up immediately under ambient light in his home cage for ~30-45 mins. The animals were then anesthetized for MRI. Imaging was performed at ~2 hrs after Mn injection. In addition, Gd-DTPA was also administered to help tissue layer assignments at ~2.5-3 hrs post Mn injection. End-tidal CO2, O_2 saturation, heart rate, respiration rate, and rectal temperature was monitored and regulated.

MRI was performed on a 4.7T/40cm Bruker scanner using a custom-made single-loop coil (0.8 cm) for the left eye for improved sensitivity and reduced FOV. T_1-weighted imaging was acquired with FLASH acquisition, TR = 100 ms, TE = 4 ms, slice thickness = 0.8 mm, FOV = 8 mm x 8 mm, matrix = 128 x 128 (62 µm x 62 µm), and 16 or 32 averages.

Results and Discussion Before Mn injection (Figure 1, Group I), three laminar structures were observed (green arrows), consistent with previous findings [6]. These assignments were validated previously using histology [6] and they are: i) The inner strip was assigned to be the ganglion and bipolar cell layer and the embedded retinal vasculature. ii) The middle strip was assigned to be the photoreceptor layer. iii) The outer strip was assigned to be the choroidal vascular layer. Following 1 hr after Mn injection, enhancement was observed primarily in the inner (retinal vascular layer) and the outer (choroidal vascular layer) strips, with the outer strip being significantly more enhanced than the inner strip (Fig. 1). Some enhancement was seen in the middle layer after 2-3 hrs post Mn injection (Fig. 1).

Figure 2 shows the results of Group II in which the animal was awake and exposed to ambient light (Group II had better SNR than Group I but does not alter the conclusions). Multiple laminar structures were observed (green arrows). Roughly equal enhancement was observed in both the inner and outer strips, in contrast to the anesthetized condition of Group I. These results suggest that activity dependent difference due to being awake and exposed to ambient light.

To further corroborate the classification of different retinal tissue strips by MRI, Gd-DTPA was administered at ~ 2.5-3 hrs after Mn injection (group II). T_1-weighted images of the retina after Gd-DTPA administration showed marked enhancement of the anterior segment of the eye due to the high permeability of the ciliary body **(Fig. 2).** Extra-ocular enhancement was also observed (red dash arrows). Strips showed Gd-DTPA T_1-weighted enhancements co-localized with the strips enhanced by Mn, suggesting that Mn is largely accumulated in the vasculatures and/or photoreceptor does not significantly accumulate Mn under these experimental conditions. Further investigation is warranted.

Conclusion This study demonstrates a novel application of Mn-enhanced MRI. Mn-enhanced MRI can be used to resolve laminar structures in the retina. The enhancement differences between awake + absence of light and anesthesia + dark was substantial, with the inner layer being particularly more enhanced in the awake conditions. Mn enhanced thus offer a unique means to investigate structure and function of the retina with laminar specificity, which may be altered in retinal diseases.

References: [1] Lin et al, MRM (1997). [2] Pautler et al, MRM 2002. [3] Aoki et al, Neuroimage 2004. [4] Duong et al, IOVS (2002), ISMRM (2002). [5] Sharma et al, in Alder's Physiology of the Eye 1992. [6] Cheng et al, ISMRM 2006, submitted. **Acknowledgement:** Funded by the Whitaker Foundation and the NEI/NIH.

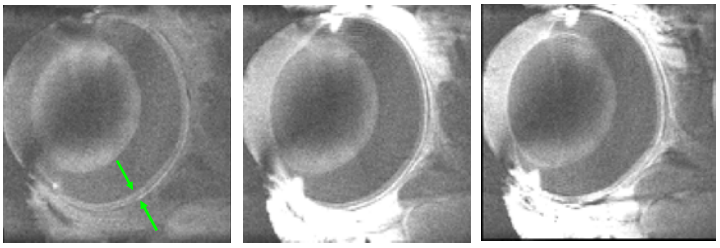

Figure 1.

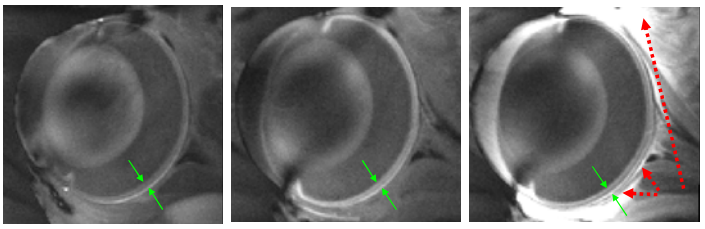

Figure 2