Manganese-enhanced MRI of Bilateral Retinas in Rat: Flickering White Light versus Dark

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INTRODUCTION: Manganese is a contrast agent typically introduced into the body through the infusion of a $MnCl_2$ solution. The agent lowers the T1 and T2 relaxation times around water. The Mn^{2+} ion is a Ca^{2+} analog that can enter the cell via voltage gated ion channels. This makes its passage into excitable cells like neurons and myocytes possible. Although Mn^{2+} can accumulate in most tissues, it is shown that in certain tissues there is an increase in accumulation where there is increased cellular activity. The goal of this study was to show that the exposure of the eye to light and dark will differentially affect the accumulation of Mn2+ within the different layers [1] by using T1-weighted MRI at 39x39µm.

METHODS: Sprague Dawley rats (n=3,250-300g) were anesthetized with urethane (1.5 mg/kg, i.p), mechanically ventilated, paralyzed with pancuronium bromide (4 mg/kg first dose, 4 mg/kg/hr, i.p). MRI was performed on a Bruker 7T pharmascan with 30 G/cm gradient and a custom 1.6 cm(I.D.) circular surface coil, placed on top of rat head, directly over eyes. A light blocking eye patch was taped over the right eye. A custom made fiber-optic light stimulation device was placed in front of left eye with 10 Hz flickering achromatic light at a luminance level of 374 cd/m^2 with a 50% duty cycle. Manganese chloride ($MnCl_2{\cdot}4H_20$) was infused via tail vein for 1 hr at a rate of 2ml/hr at a concentration of 44 mg/kg. Manganese was administered at the onset of MRI acquisition. Left eye visual stimulation started 45 minutes after onset of manganese infusion and was stimulated 60 seconds off, 60 seconds on for 1hr.

Images were acquired with axial orientation using FLASH with FOV= 24 x 8 mm, TR= 250, TE= 7.0ms, matrix= 533 x 177, 3 slices, slice thickness = 0.7 mm, 10 averages, with a resolution of 39x39µm. Each time point consisted of 15 min scan, after 135 minute time point, a 39 x 39µm image was acquired for display purposes(FOV= 24 x 8mm, TR=250ms, TE= 7.7ms, matrix 610 x 205, 3 slices, slice thickness= 0.7mm, 20 averages (30 min acquisition). Data was analyzed using a custom program to linearize the retina [2] to extract changes from the inner and outer retina.

RESULTS\DISCUSSION: Figure 1 shows a typical MRI at 39x39 µm following MnCl2 injection. Also shown are the two bright layers located on either side of the retina, designated as the inner and out retina. **Figure 2** shows the normalized pixel intensity of outer retina for left (light exposure) and right (dark exposure) eye for 3 animals. Dark exposure showed higher signal intensity than light exposure in the outer retina. This correlates well with the notion that in darkness the photoreceptors depolarize and there is an increase in cGMP-gated ion channel demand which leads to greater uptake of manganese in the outer retina [3], whereas in light the photoreceptors hyperpolarize (in marked contrast to the brain).

Figure 3 shows the normalized pixel intensity of inner retina. Light exposure showed higher signal intensity than dark exposure in the inner retina, in contrast to the outer retina. When the inner retina is stimulated with light, it increases neural activity and thus increases accumulation of manganese in the inner retina.

The novelty of this approach includes in-magnet Mn infusion and visual stimulation, and the use of a single-surface coil to image both eyes simultaneously where one eye is stimulated by light and other eye is kept in the dark under the same setting. Both eyes should receive the same Mn. This approach allows us to detect differential layer-specific changes in function and physiology in the retina associated with visual stimulation, potentially opening up new avenues for retinal research.

REFERENCE [1] Silva et al., NMR Biomed 2004, 17:532. [2] Cheng et al, PNAS 2006, 103:17525. [3] Burkowitz et al., IOVS 2006, 47:2668

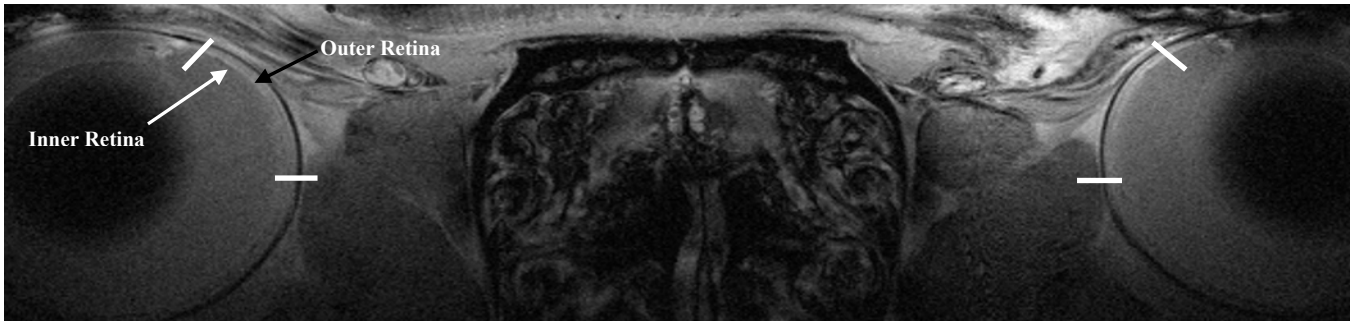

Figure 1. MRI at 39 x 39µm image taken after 135 min time point. The outer retina is indicated by black arrow, the inner retina is indicated by white arrow. Region used for intensity profile analysis is located between white bars. Signal intensity profiles were taken in the direction from sclera to the vitreous.

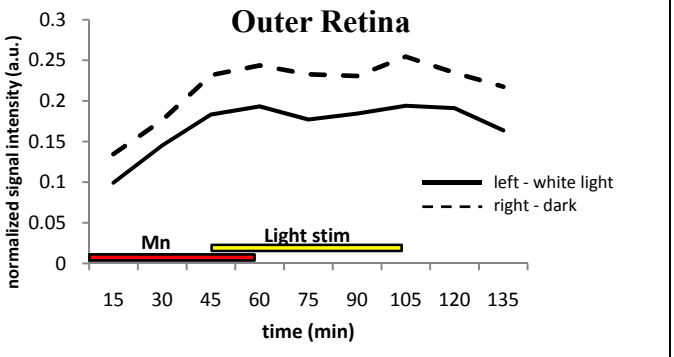

Figure 1. Normalized signal intensity change of outer retina. Colored bars represent duration of manganese infusion (red, 0-60 min) and Visual stimulation (yellow, 45-105 min, left eye only).

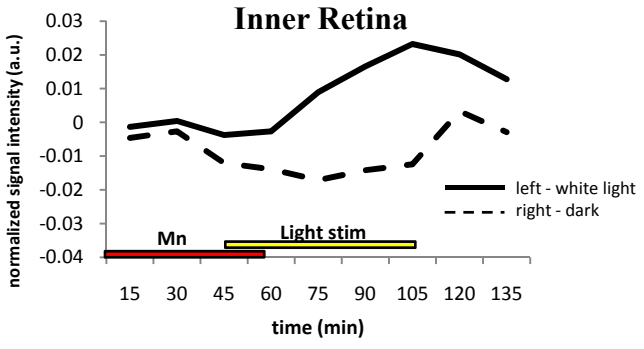

Figure 2. Normalized signal intensity change of inner retina. Colored bars represent duration of manganese infusion (red, 0-60 min) and Visual stimulation (yellow, 45-105 min, left eye only).