Contrast-Enhanced MRI of the Human Retina

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INTRODUCTION MR imaging of the human retina is challenging because the thin structure of the retina requires very high spatial resolution, the orbital region has high magnetic susceptibility, and constant eye movement in unanesthetized humans may cause significant motion artifacts. Our previous study demonstrated the feasibility of achieving laminar-specific anatomical MRI of the human retina albeit with unvalidated layer assignments[1]. The purpose of this study was two-folded: 1) to develop methods to improve fixation stability and to evaluate the eye fixation stability using an independent eye-tracking device; and 2) to corroborate the MRI layer classification by using contrast-enhanced MRI with the administration of a blood-pool Gd-based contrast agent Gadobutrol. High-resolution laminar specific T1-weighted gradient echo and balanced Steady-State Free Procession (bSSFP) were acquired before and after Gadobutrol injection. Due to the known blood-retina barrier and the impermeability of retinal pigment epithelium to Gadobutrol, we predict that only the two vascularized layers bounding the retina will be enhanced, but not the avascular layer of photoreceptors in between.

METHODS Eye-fixation stability tests were performed on four subjects with the same setup as MRI studies but outside the scanner room. The corneal position was noninvasively digitized at 240 Hz with 0.1° angular resolution using an eye tracker (ETL-500; ISCAN Inc., Woburn, MA). Subjects were instructed to maintain stable eye fixation on a target and blink immediately after MRI data acquisition sound cues (via playback of recorded MRI scanner sounds). Angular displacements were converted to linear displacement at the posterior retina (1° =291μm), and standard deviation (SD) of the horizontal and vertical displacements were computed and plotted as a function of time. MRI studies were performed on four subjects using a 3T Philips Achieva scanner equipped with 80 mT/m gradient system. A custom-made, receive-only eye coil with 6 cm in diameter was used. The same strategy of alternative fixations and blinks was employed with the actual scanner sounds as a cue. Anatomical scans utilized a 2-dimensional (2D) axial T1-w gradient echo sequence with 6 s acquisition (i.e. fixation) time and 4 s pause (i.e. blinks) time, and repeated for 30 times leading to a total 5 mins per scan. Other parameters were TR/TE=20/2.2 ms, FA = 20, FOV = 30*75 mm, matrix = 252*313, resolution = 0.12*0.24*2.00 mm. On one subject, Gd-based contrast agent Gadobutrol (Gadovist®, Bayer HealthCare Pharmaceuticals) at 1 mmol/ml concentration was intravenously injected at a dose of 0.1 mmol/kg and dose rate of 0.1 ml/s, followed by another 3 mins post-contrast T1-w scan. A 2D bSSFP sequence with the same resolution as the T1-w sequence and 12 repetitions (2 mins per scan) was performed before and after Gadobutrol injection. All time-series images were co-registrated and automated profile analysis was performed to align the retina and calculate the layer thickness of the retina using custom-written code in Matlab®.

RESULTS Eye-tracking displacements of the vertical and horizontal eye movement using the eye-fixation protocol with cued blinks are shown in **Figure 1A**. The large regular vertical deflections were eye blinks, where the closed eyelids resulted in a loss of tracking. After the blinks were removed (**Figure 1B**), the displacements were within the range of -150 μm to +150 μm. The group-averaged temporal SDs of the horizontal and vertical displacements at the posterior retina were, respectively, 78±51 and 130±51 μm (mean ± SD, four subjects). T1-w MRI revealed three alternative bright, dark and bright layers of the retina at the posterior pole (**Figure 2A**). Contrast-enhanced MRI showed marked signal increases in the inner and outer layers (**Figure 2B**, blue arrows), as well as the surrounding muscles. No enhancement was observed in the middle layer, vitreous or fat tissue as expected. The subtraction of post-contrast image from pre-contrast image showed enhancements on either side of the retina, with the outer layer being more enhanced and thicker than the inner layer (**Figure 2C**). bSSFP sequence was explored to improve SNR efficiency and thus reduce the scan time. Similar to T1-w images, three alternating bright, dark and bright layers were observed on the bSSFP images before Gadobutrol injection, and the two bounding layers were enhanced after Gadobutrol injection (data not shown). From the vitreous to the sclera, the group-averaged inner, middle and outer layer thicknesses were 119±13, 201±13 and 329±53 μm for T1-w image, and were 282±83, 259±37 and 351±80 μm for bSSFP image (mean ± SD, four subjects).

DISCUSSION and CONCLUSIONS Eye fixation with cued blinks can achieve stability of the retina within 100 μm, adequate for the MRI spatial resolution herein. MRI robustly detected the laminar structure of the retina at a clinical 3T scanner free of motion artifacts. Contrast-enhanced MRI corroborated the layer assignments by selectively enhancing the vascularized layers. Therefore, the MRI "inner" layer corresponds to include the vascularized ganglion cells and inner nuclear layer, the MRI "middle" layer corresponds to include the avascular photoreceptor cells layer, and the MRI "outer" layer corresponds to include the choroid. In addition, the "outer" layer was more enhanced than the "inner" layer suggested that the choroidal vasculature has higher blood flow and blood volume than the embedded retinal vasculature, consistent with established differences between these two vasculatures[2]. The contrast enhancement and laminar assignments herein are in good agreement with previous MRI studies in anesthetized baboon[3], cats[4] and rats[5]. Future studies will aim to improve spatial resolution by using phase-array coils and higher field, improve fixation stability, and to explore applications in retinal diseases such as diabetic retinopathy where retinal thicknesses and vascular permeability may change.

References: 1) Peng, Q et al, ISMRM 2010, p688. 2) Bill A. Circulation in the eye, in Handbook of Physiology: Cardiovascular System, Vol IV. The American Physiological Society, 1984. 3) Zhang Y. et al, MRM 2011;66:546–554. 4) Shen Q et al, JMRI 2006;23(4):465-472. 5) Cheng H et al. PNAS 2006;103:17525-17530.

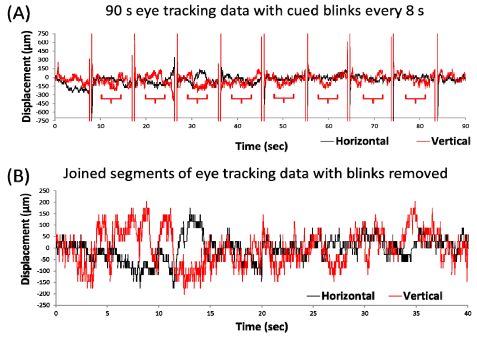

Figure 1 (A): Time course of the eye movement displacement over time from one representative subject. **(B)** The joined segments of the eye-tracking data with blinks were removed.

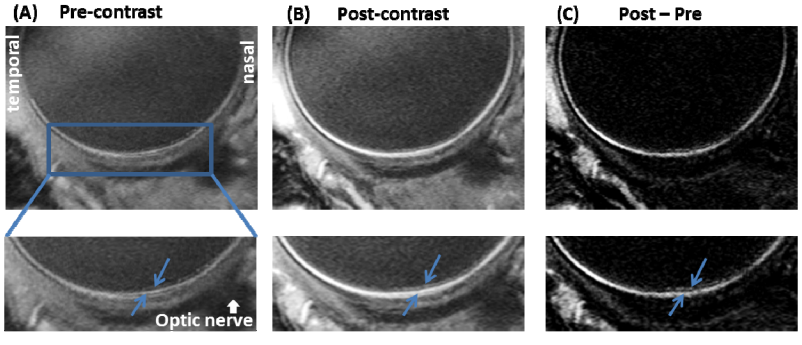

Figure 2 T1-w images before **(A)** and after **(B)** Gadobutrol injection, and the difference between post- and pre-enhancement shown in **(C)**. Enlarged images of the posterior part of the retina revealed laminar structure of the retina with either side of the retina being enhanced.