ANATOMICAL, BOLD, BLOOD FLOW MRI OF NON-HUMAN PRIMATE (BABOON) RETINA

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INTRODUCTION Advances in MRI technologies have made it possible to achieve multi-layer resolution of the thin retina of only 276 micron thick [1]. In rodent models, layer-specific resolution of anatomical, blood flow (BF) and functional MRI has been reported [2-5]. Translation of retinal MRI applications from rodents to humans has two major challenges: *i)* hardware that limited spatial resolution and signal-to-noise ratio on clinical MRI scanners, and *ii)* eye movement in unanesthetized humans. As a first step toward translation, we investigated the feasibility of multimodal retinal MRI on anesthetized/paralyzed large non-human primate (NHP) (baboon) using a standard clinical 3.0 Tesla MRI scanner. Baboon was chosen because it has large eyes and the retina of baboon, compared to rodent, is evolutionally closer to that of human, likely better recapitulates human retinal diseases. Anesthesia and paralysis were used to exclude movement artifacts, such that we could focus on evaluating hardware feasibility, pulse sequence protocols and parameters for high-resolution multimodal MRI of the retinas on a clinical scanner. These multimodal MRI protocols included anatomical MRI, basal BF MRI, BOLD fMRI of hyperoxic inhalation and BF fMRI of hypercapnic inhalation. This study presents a novel approach to visualize anatomical, physiological (BOLD and BF) and functional MRI of the retinas of large NHPs on a clinical scanner, and this serves as a first step toward translation. This approach has the potential to complement existing retinal imaging techniques.

METHODS Survival studies were performed on normal female baboons (10-20kg, N = 7). Animals were anesthetized with 0.8~1.0% isoflurane, mechanically ventilated, and paralyzed with vecuronium (0.1mg/kg). End-tidal CO_2, O_2 saturation, heart rate, respiration rate, and rectal temperature were monitored continuously and maintained within normal physiological ranges. At the end of the MRI study, neostigmine (0.5-2 mg) was administered to reverse paralytic effects. BF MRI was also measured on a post-mortem animal (N = 1) to verify that BF contrast was free of artifacts.

MRI was performed on a Siemens 3T TIM TRIO using a small receive-only surface coil (4 cm) and the body transmit coil. A Single slice transecting the optic nerve head was acquired. **Anatomical MRI** was acquired using FLASH with TR/TE/FA=50ms/3ms/50°, BW=16 kHz, FOV=29×29mm, and spatial resolution =0.1×0.2×2.0 mm^3. Gd-DTPA (0.2-0.3 mmol/kg) was intravenously infused over a few mins and MRI measurements were made before and immediately after Gd-DTPA injection, the total scan was 15 mins. **BOLD MRI** was acquired using pass-band bSSFP technique [6] with TR/TE/FA=8ms/4ms/40°, BW=36 kHz, FOV=50×50mm, spatial resolution = 0.3×0.6×2.0 mm^3, and temporal resolution = 4s, 10mins each trial. **BF MRI** was acquired using pseudo-continuous ASL using echo-planar imaging [7] with TR/TE=3500ms/16ms, FOV = 128×128 mm, spatial resolution = 2×2×2 mm^3, labeling duration = 2.1 sec, post-labeling delay = 700 ms, and 12 contiguous slices, 7 mins each trial. **Histology:** Four eyes from two different female baboons (both 19 years old, 14 and 18.5 kg) were enucleated and immersion fixed in 10% neutral buffered formalin and subjected to H&E stain. Thicknesses were analyzed.

RESULTS AND DISCUSSION Anatomical MRI detected three alternating bright-dark-bright bands (**Figure 1**). The hyperintense inner strip nearest to the vitreous was enhanced by an intravascular contrast agent, likely included the inner neural layers and the embedded retinal vessels. The hypointense middle strip showed no contrast enhancement, likely included the avascular photoreceptor layer. The hyperintense outer strip showed contrast enhancement, likely corresponded to the vascularized choroid. In the posterior retina, the total thickness including the choroid was 557±91μm (±SD) by MRI, which is thicker than that by the histology (326±10μm, P<0.05). It could arise from collapse of choroidal vessels and tissue shrinkage during histology procedure, difference in regions analyzed for two methods, and/or partial volume effect in MRI. BOLD fMRI of oxygen inhalation relative to air increased 6.5±1.4% (**Figure 2**). Note that the slow rise and fall of the temporal responses are due to the large dead volume of the mechanical ventilator. Basal BF was 83±30mL/100g/min, and hypercapnia increased BF by 25±9% (P<0.05, paired t test) (**Figure 3**). By comparison, gray and white matter basal BF values in the brain were smaller but their percent changes were larger likely because of dividing by the smaller denominators.

CONCLUSION This study reports a proof-of-concept that anatomical MRI, hyperoxia-induced BOLD fMRI changes, quantitative basal blood flow and hypercapnia-induced blood-flow fMRI changes in the retina of anesthetized baboon can be imaged using a clinical 3.0 Tesla scanner. These findings offer encouraging data to explore human applications. Translating high-resolution anatomical, blood flow and functional MRI to image the unanesthetized human retina could have important applications. Irrespective of whether these approaches can be translated to humans, this approach can be utilized to study retinal diseases and to test novel therapeutic strategies in the retinas of large non-human primates, which likely better model human retinal diseases. Future studies will focus on improving spatial resolution to visualize different layers of the retina.

REFERENCE 1) A. Bill, Handbook of physiology Part 2, Microcirculation, Renkin, Michel, Eds. 1984. 2) Cheng et al. PNAS 2006, 103, 17525. 3) Nair et al. ISMRM 2007. 4) Li et al. IOVS 2009, 50: 1824. 5) Muir and Duong, NMR in Biomedicine 2010. 6) Lee et al, MRM 2008, 59:1099. 7) Wu et al, MRM 2007, 58:1020. Supported by EIA 0940104N, and CTSA imaging supplement UL1RR025767.

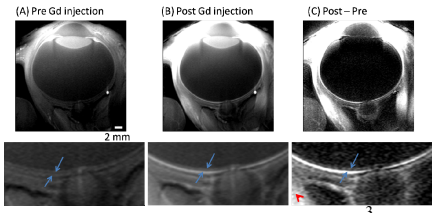

Figure 1. Anatomical MRI at 0.1×0.2×2.0 mm^3 from a normal baboon **(A)** before, **(B)** after Gd-DTPA and **(C)** the subtracted image. Three distinct bright-dark-bright bands are evident.

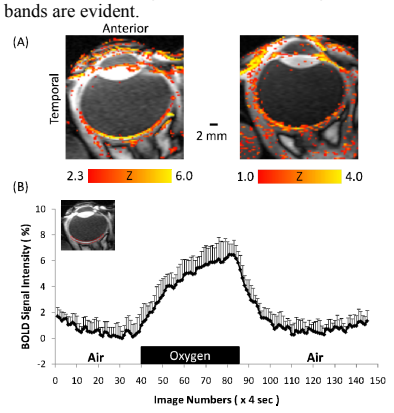

Figure 2. (A) BOLD fMRI activation map at 0.3×0.6×2.0 mm^3 of O_2 inhalation from 2 baboons, and **(B)** the averaged time course of O_2 versus air inhalation (error bar indicates SD).

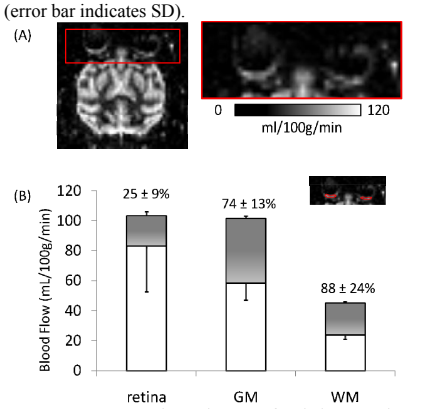

Figure 3. (A) Basal BF image of a baboon retina at 2×2×2 mm^3. **(B)** Basal blood flow and hypercapnia-induced blood-flow changes (shaded regions) of the retina, gray and white matter (GM and WM) (±SD).