Laminar-specific BOLD Functional MRI of the Human Retina to Hyperoxia Inhalation

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INTRODUCTION The human retina is nourished by two separate circulations, retinal and choroidal circulations. While BOLD fMRI has been extensively applied to study the coupling of blood flow, oxygenation and metabolism in the brain, similar studies in the retina are sparse due to: i) the thin retina requires very high spatial resolution, ii) the large magnetic susceptibility variation in the orbital region precludes the use of conventional gradient echo planar imaging, and iii) the potential eye movement in the awake humans. We previously reported the feasibility of performing BOLD fMRI in the human retina associated with hyperoxia but without laminar resolution[1]. This study reports marked improved spatial resolution and eye-fixation stability to achieve laminar-specific BOLD fMRI responses from the retinal and choroidal circulations in the human retina. BOLD fMRI utilizes a pass-band bSSFP (balanced Steady-State Free Procession) sequence with a reversed partial Fourier readout to increase the effective TE while maintain the same TR. bSSFP has high SNR per unit time, reduces signal drop off and distortion, and is sensitive to BOLD signal changes[2]. Hyperoxia (100% Oxygen) inhalation was employed to modulate the hemodynamic responses from the retinal and choroidal vasculatures.

METHODS MRI was performed on 4 healthy volunteers with 1 to 2 repeated measurements made on each subject on 1 to 3 separate visits. A strategy with alternation of fixations (during data acquisition which has gradient sound) and blinks (during silence period) via MRI sound cues was established to obtain retinal MRI with minimal motion artifacts. MRI studies were performed on a 3T Philips Achieva with a custom-made surface coil as a receiver. BOLD fMRI utilized a 2D bSSFP sequence with repetition cycle between inversion pulses of 6s and inversion delay of 2 s. The inversion recovery pre-pulses were applied to suppress otherwise bright vitreous signal. Partial Fourier with reversed readout (i.e., center k-space data were acquired later) was implemented to achieve a large TE/TR ratio to enhance BOLD sensitivity. Other MRI parameters were: TR = 15 ms, TE = 12 ms, FA= 35º, FOV = 70x100 mm (spatial resolution of 150x450x3000 μm^3). The higher resolution direction was placed along the anterior-posterior direction to minimize partial volume effect caused by retinal curvature. BOLD fMRI to hyperoxia was acquired during which subject breathed 2 mins air, 1.5 min pure oxygen and 2 mins air. Automated profile analysis[3] was performed to align the retina and calculate BOLD %-changes along the length of the retina. Statistics was performed with one-way ANOVA and Turkey's multiple comparison tests.

RESULTS bSSFP off-resonance bands artifacts in the human retina were often observed as expected but they are temporally stable (**Figure 1A**). High-order shimming was prescribed to minimize and avoid banding artifact appeared around the posterior part of the retina (**Figure 1B**). bSSFP fMRI clearly showed the laminar structure of the posterior retina with three alternative bright-dark-bright layers, while the adjacent vitreous and sclera appeared relatively dark (**Figure 1C**). The temporal standard deviation of the bSSFP signal at the posterior retina was 2.5% over a 6-minutes period, indicative of its temporal stability. Hyperoxia induced a significant increase in bSSFP signal along the length of the retina (**Figure 1D**). In addition, the bSSFP signal %-changes profile showed higher changes on the outer layer compared to inner layer **(Figure 1E**). The group averaged bSSFP %-changes associated with hyperoxia were 2.3±2.6% for the inner layer (P>0.05 compared to air), 5.3±1.1% for the middle layer (P<0.001) and 4.9±1.5% for the outer layer (P=0.002) (mean ± SD, N=7 sessions from 4 subjects). bSSFP %-changes in the middle and outer layers were significantly larger than that of the inner layer (P<0.05).

DISCUSSIONS bSSFP fMRI demonstrates three layers of the retina/choroid complex, with the inner layer corresponding to the inner neural retina where retinal circulation exists, and the outer layer corresponding to the vascularized choroid[3], made possible by eye fixation protocol and bSSFP acquisition. bSSFP BOLD sensitivity was further improved by using reversed partial-Fourier readout which increased the effective TE while maintain the temporal resolution. Similar to the brain, hyperoxia increased BOLD signal of the retina as a result of increasing oxygen saturation mostly in the capillaries and venules. As expected, BOLD responses largely co-localized to the retinal and choroidal vascular layers. The middle avascular layer showed BOLD signal changes which was likely due to partial volume effects from both sides. Improved spatial resolution should address this issue. Hyperoxia induced vasoconstriction of the retinal blood vessels but not in the choroid[4]. In addition, blood flow and vascular density in the choroid is significantly higher than that in the retinal vasculature, which should translate to a higher BOLD response in the choroid. We expected that BOLD response of hyperoxia in the choroidal vasculature to be larger than in the retinal vasculature (as observed). Our result is consistent with a previous study in the rat retina[5].

CLOCULISONS This study demonstrates high-resolution, laminar-specific BOLD responses to hyperoxia in the unanesthetized human retina for the first time. The bSSFP sequence provides laminar resolution and strong BOLD sensitivity without signal drop-off and image distortion. Laminar-specific, depth-resolved BOLD fMRI offers a way to probe retinal oxygenation changes in healthy and diseased states, and complements existing retinal imaging techniques. Future studies will aim at further improving spatial resolution and applying to retinal diseases such as diabetic retinopathy.

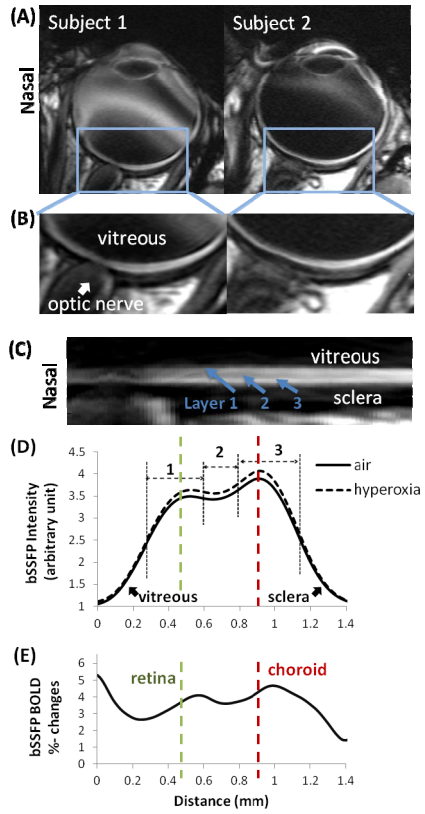

Figure 1 (A) Two representative inversion-recovery bSSFP images from two subjects. **(B)** Enlarged images of posterior retinas. **(C)** Linearized posterior retina showed three distinct layers of the retina/choroid complex between vitreous and sclera. **(D)** bSSFP signal profiles across the retinal thickness during air (solid line) and hyperoxia (dash line) from one representative scan. 1: inner layer. 2: middle layer. 3: outer layer in MRI, with layer 1 corresponding to the inner neural retina and its embedded retinal vasculature and layer 3 corresponding to the choroid. **(E)** Corresponding BOLD %-changes profile across the retinal thickness.

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