fMRI of the human retina associated with oxygen inhalation

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INTRODUCTION Except optical coherence tomography which provides anatomical but not physiological data, existing retinal imaging techniques lack depth resolution and rely on optical transparency which could be hampered by media opacity (*e.g.*, cataracts and vitreous hemorrhages). Although MRI has comparatively lower spatial resolution, it offers depth-resolved, and often time quantitative, physiological parameters. With improvement of MRI technologies over the past decade, high resolution MRI of the retina is becoming feasible. Anatomical laminar resolution [1,2], relaxation and diffusion time constants [3], and blood flow MRI [4], BOLD fMRI of physiological [1] and visual stimuli [5] have been reported in animal models. Similar applications in the human retinas remain challenging because the eye is near air-tissue interface, high spatial resolution is needed to image the thin retina, clinical gradients are less powerful compared to animal scanner, and there is potential eye movement.

In this study, we explored the feasibility of performing fMRI associated with oxygen challenge in normal in vivo human retinas. fMRI utilized an inversion-recovery balanced steady state precession (IR-bSSFP) sequence. Inversion recovery contrast was used to suppress vitreous signal to minimize partial volume effect. bSSFP was used to achieve high spatiotemporal resolution to minimize image distortion and signal drop out in the region of high magnetic susceptibility of the eye.

METHODS Experiments were performed on 3 normal human volunteers with 2 or 3 repeated measurements made on each subject. Subjects were asked to blink if needed right after the data readout train (which generated distinct sounds as cue) but otherwise fixated on a point during MRI. MRI studies were performed on a 3T Philips Achieva. A custom-made circular eye coil of 6 cm in diameter was used. fMRI utilized a 2D IR-bSSFP sequence with a TFE shot cycle between inversion pulses TS=3000 ms and TI=1200ms, TR/TE/FA=12ms/6ms/40º, and readout bandwidth = 6.4 kHz. The spatial resolution was 1.6x2x4mm and the temporal resolution per image was 3 s. O2 challenge included 3 inhalation epochs of (30 s air and 30 s O2), followed by another 30 s of air. Corregistration was performed as needed. To avoid bias from potential "correlation" noise, fMRI time courses were obtained from ROI of a posterior part of the retina. Percent changes were tabulated at 80% of maximum fMRI signal changes.

RESULTS Conventional gradient-echo EPI BOLD fMRI yielded significant susceptibility artifacts and signal drop out because the retina is located close to air-tissue interface (data not shown). bSSFP acquisition overcame these limitations. Fixation and blinking protocol yielded reasonably stable images. The use of custom-made surface coil markedly improved SNR compared to volume coil (data not shown), making it possible to achieve reasonably high spatiotemporal resolution.

Figure 1A shows two representative IR-bSSFP images and "activation" maps from oxygen challenge for two repeated scans from one subject. Inversion-recovery contrast suppressed the otherwise strong vitreous signals, improved delineation of the retina and minimized partial volume effect by the vitreous. Activated pixels are highly localized to retinas with no significant number of activated pixels in the anterior chamber, lens and vitreous. Activated pixels were also observed in muscle surrounding the retina and the optic nerve, as expected. **Figure 1B** shows the corresponding fMRI time courses associated with O2 challenge using ROI analysis. Robust fMRI responses were observed. The average fMRI signal change from the ROI analysis was 2.2 ± 0.5% (n = 8 repeated trials from 3 subjects).

DISCUSSION This study demonstrates a novel fMRI application to detect changes associated with oxygen challenge in the in vivo human retinas at reasonably high spatiotemporal resolution. This was made possible by choosing the optimal surface coil, the appropriate imaging protocol, optimizing imaging parameters, minimizing eye movement as well as image co-registration. Additional improvements will be needed and are expected. The conservative fMRI percent change was 2.2 ± 0.5% from a large part of retina. This finding is consistent with a BOLD fMRI study in rat retina associated with oxygen challenge (1) Although the bSSFP signal source remains unclear, it is believed that bSSFP yields T_2 BOLD at short TE/TR and T_2* BOLD at long TE/TR (5). bSSFP fMRI parameters herein were designed to be sensitive to oxygenation change and indeed appeared to be sensitive to oxygenation change. Many retinal diseases are known to affect oxygenation in the retina including retinal ischemia, diabetic retinopathy and retinal degeneration. Given the general lack of depth-resolved physiological imaging techniques for the retina, the ability to perform fMRI associated with physiological and functional stimulations may have important applications, especially if higher spatiotemporal resolution can be achieved. Future studies will aim at improving spatial resolution and to image visual stimulations.

In conclusion, we demonstrate, for the first time, the feasibility of performing fMRI on the in vivo human retina associated with oxygen challenge. We are hopeful that with continuing advances in MRI technologies, much improvement in spatiotemporal resolution is expected. This approach – along with other existing MRI techniques – has the potential to provide depth-resolved, multiple clinically relevant data to facilitate diagnosis of human retinal diseases. Retinal MRI could also open up new avenues of retinal research and complement existing retinal imaging modalities.

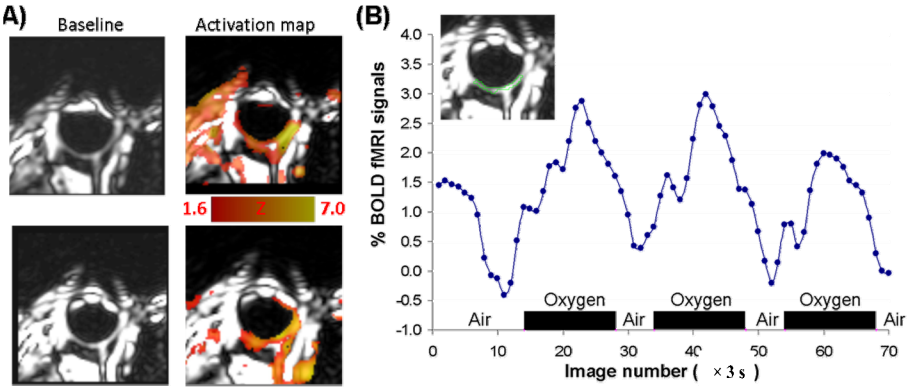

Figure 1. (A) IR-bSSFP images with inversion recovery suppression of the vitreous and the fMRI activation maps associated with O2 challenge from two repeated scans. (B) The corresponding BOLD fMRI time course from an ROI (inset) of a large part of the retina to avoid correlation bias.

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