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Magnetic Resonance Imaging of the Retina: from mice to men

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Abstract

This mini-review provides an overview of MRI applications to study rodent, cat, non-human primate and human retinas. These techniques include T₁- and T₂-weighted anatomical, diffusion, blood flow, blood volume, blood-oxygenation level dependent (BOLD), manganese-enhanced, physiological and functional MRI. Applications to study the retinas in diabetic retinopathy, glaucoma, and retinal degeneration are also reviewed. MRI offers some unique advantages compared to existing imaging techniques and has the potential to further our understanding of physiology and function in healthy and diseased retinas.

Keywords

BOLD; choroid; blood flow; blood volume; contrast-enhanced MRI; manganese-enhanced MRI; diabetic retinopathy; glaucoma; retinal degeneration; age-related macular degeneration; ocular imaging; optical imaging; eye motion; BOLD fMRI; visual stimulation

Retinal anatomy and physiology

Diabetic retinopathy, glaucoma, and age-related macular degeneration are the leading causes of blindness affecting the retina. The neural retina (~200µm thick) consists of 8 major layers: the ganglion cell layer, inner plexiform layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, inner segments, outer segments, and the retinal pigment epithelium (1).

The retina is nourished by two separate circulations (1, 2): the retinal and the choroidal vessels. The retinal vessels are localized in the ganglion cell layer with retinal capillaries projected down into the inner nuclear and inner plexiform layers. The choroidal vasculature is located outside the neural retina between the retinal pigment epithelium and the sclera. The avascular layer (~100µm) in between the retinal and choroid layers consists of the outer plexiform layer, outer nuclear retina, inner and outer photoreceptor segments. Retinal blood vessels have tight-gap junctions, constituting the blood-retinal barrier similar to the blood-brain barrier. By contrast, the choroidal vessels are porous, relying on the retinal pigment epithelium to act as a barrier. Basal retinal and choroidal blood flow, and their responses to stimuli differ substantially from each other (1). The arterio-venous oxygen saturation difference of the retinal circulation is similar to the brain (~50%) but that of the choroidal circulation is very small (3–5%). Moreover, the choroid is innervated by the autonomic system but the retina is not (2, 3).

Anatomical MRI

Ex vivo MRI can visualize most of the anatomical retinal layers (4) mentioned above. In live animals, protocols to achieve optimal animal preparation, anesthesia and post-processing motion corrections have been detailed (5, 6). *In vivo* anatomical MRI of the rodent retinas resolves multiple (3 to 5) anatomical layers based on T_1 (7–10), T_2 (7–10), diffusion (7,9,10), and balanced-steady-state free precession (bSSFP) (11) contrasts with an in-plane spatial resolution up to $20 \times 20 \mu\text{m}$. A representative anatomical MRI with and without Gd-DTPA (gadolinium diethylenetriaminepentacetate) from a cat eye showed three layers on pre-contrast MRI. Post-contrast MRI and the difference image delineate the retinal and choroidal vascular layers, and the avascular in-between because the retinal vessels and the retinal pigment epithelium are impermeable to Gd-DTPA. The ciliary bodies are permeable to Gd-DTPA, and thus the anterior chamber is enhanced. With bSSFP acquisition, remarkable resolution and contrast among different retinal layers can be obtained without using an exogenous contrast agent (Figure 1A) (11).

T_1 , T_2 and apparent diffusion coefficients of the neural retina are similar to those of the brain but those of the choroid are higher (7–10). Moreover, there are diffusion anisotropy differences among different layers of the retina (7,9,10). The thickness of the neural retina ranges from 200 to $300 \mu\text{m}$ across different species and it has been reported in mouse (10,11), rat (8), cat (7), baboon (12), and human (13) by MRI. The thicknesses of the neural retinal and choroid are also dependent on location, with central retina being thicker than peripheral retina. The choroid layer thickness ranged from $90 \mu\text{m}$ in rodents (8) to $600 \mu\text{m}$ in humans (13) by MRI.

Blood-flow MRI

Arterial spin-labeling MRI can resolve two distinct blood-flow layers in the retina, separated by a region with little or no blood-flow signal (Figure 1B, $42 \times 42 \times 42 \mu\text{m}$) (14–17). The “outer” layer corresponding to the choroid has very high blood flow, 7.7 mL/g/min in rodents under isoflurane anesthesia (14–17), resulting in low oxygen extraction fraction and small arterio-venous oxygen saturation difference. The “inner” layer corresponding to the retinal vasculature has much lower blood flow, 1.3 mL/g/min (14–16), similar to cerebral blood flow of 1 mL/g/min (18). The avascular layer shows no blood-flow signal, albeit some partial volume effect.

Functional MRI (fMRI)

Layer-specific fMRI of hypercapnia ($5\% \text{CO}_2$), hyperoxia, carbogen ($5\% \text{CO}_2 + 95\% \text{O}_2$), hypoxia ($10\% \text{O}_2$) inhalation, and visual stimuli using BOLD (19,20), blood-volume (21,22), and/or bSSFP (11) contrasts have been reported. Blood-flow fMRI responses to pharmacological challenge have also been reported (23). Many of these studies show the retinal and choroidal vessels respond to various “stimuli” differently.

For example, in hyperoxia, BOLD increase was larger in the outer choroid layer ($12 \pm 2\%$) than the inner retinal layer ($7 \pm 2\%$, $P < 0.01$) in rats (8). This is because *retinal* blood vessels are known to constrict during hyperoxia, which reduces blood flow and attenuates BOLD signal increase (24). In contrast, *choroidal* blood vessels constrict to a smaller extent during hyperoxia, leading to a larger BOLD increase in the choroidal layer. In hypercapnia, BOLD increase in the inner “layer” ($10 \pm 2\%$, $P < 0.01$) was substantially larger than the outer layer ($1.6 \pm 1\%$) (8). This is likely because hypercapnia has smaller vasodilatory effect on *choroidal* vessels and/or the oxygen extraction in the choroid is small (24). These differential layer-specific BOLD responses are consistent with published literature using oxygen electrodes (24).

Mild hypoxia (10% O₂) decreases BOLD signal but the magnitude changes are different with $-12\pm 2\%$ in the inner (retinal) layer and $-30\pm 3\%$ in the outer (choroid) layer (11).

Contrast-enhanced MRI

Anatomical MRI studies of the retina using contrast agents have been reported including those employing manganese-enhanced (4,25) and chromium-enhanced (26) MRI. The retinal and choroidal vascular layers and their respective blood barriers can be visualized by using Gd-DTPA (7,8) as described above.

Blood volume index can be measured by using the blood-pool contrast agent, monocrystalline iron oxide nanoparticles (MION). Blood-volume fMRI responses to hypercapnia and hyperoxia show differential responses between the retinal and choroidal layers (21). Blood-volume fMRI has been used to evaluate retinal and choroidal responses in rats at graded luminance, frequency, and wavelength of flickering light (22) (Figure 1C). In the retinal vasculature, increasing luminance increases fMRI signals, red light gives weaker response compared to blue and green, and 10Hz flicker gives maximal fMRI signals, as expected. The choroidal vascular response is weak and does not depend on flicker parameters, suggesting differential neurovascular coupling between the two vascular layers. Together, these findings offer a mean to probe the unique hemodynamic regulations in the eye.

Layer-specific fMRI of light and dark adaptation has been reported using manganese-enhanced (27,28) and diffusion (29) MRI contrasts. Vascular diameter and vessel intensity changes due to hyperoxia and carbogen inhalation can be detected on angiographic images without contrast agent (30).

Other contrasts

3D angiography ($42\times 42\times 84\mu\text{m}$) without and with contrast agent is capable of visualizing arterial and venous vessels in rats at $42\times 42\times 84\mu\text{m}$ (30), providing remarkable details of vessels in the eye and the choriocapillaris. Relative pO₂ (ΔpO_2) associated with carbogen inhalation in the vitreous next to the retina has been reported by T₁-weighted MRI in which dissolved molecular oxygen acts as the endogenous contrast agent (31). This approach has also been used to map quantitative pO₂ distribution in the human vitreous (32).

Retinal disease applications

MRI has been applied to study retinal diseases. Blood flow MRI of diabetic retinopathy (15), retinal degeneration (16,17) and glaucoma (33) in animal models show early blood-flow changes before retinal thickness changes by anatomical MRI. BOLD fMRI showed reduced responses to hyperoxia and hypercapnia in an animal model of retinal degeneration (8). These data show that these retinal diseases affect the two vasculatures differently at different stages. Manganese-enhanced MRI shows early abnormality in ion regulation in diabetic retinopathy (34), retinopathy of prematurity (35), glaucoma (36,37), and retinal degeneration (25,38,39). Permeability changes using contrast-enhanced MRI (40) and ΔpO_2 MRI (41) have been reported in diabetic retinopathy in rats.

Human applications

High-resolution anatomical, BOLD and blood-flow MRI on a human 3T clinical scanner is feasible on anesthetized baboon retinas where motion can be eliminated (12). The challenges in MRI application of the human retinas are eye motion and limited spatial resolution due to weaker magnetic field gradients. Eye fixation to a target with cued blinks every 4–8 s is

comfortable and minimizes motion artifacts (13,42). A small eye radiofrequency coil, tailored pulse sequences and parameters can be used to improve signal-to-noise ratio (13). Anatomical (13,43), blood-flow (44,45) and BOLD (46) MRI applications to the human retina on 3T (Siemens and Phillips) clinical scanners are feasible with eye fixation and cued blink, albeit lacking layer resolution to date except for anatomical MRI. BOLD fMRI can detect hemodynamic changes in the retina due to hypercapnia and hyperoxia (46). Blood-flow fMRI can detect changes due to hypercapnia (44), hypercarbia (47) and isometric exercise (48). Figure 2A shows a representative basal blood-flow MRI, where blood flow is highest at the posterior pole of the retina (i.e., the macula) and a small indentation at the optic nerve head is apparent. Figure 2B shows the BOLD fMRI responses to hyperoxia of the human retina, delineating robust responses with large percent changes (due to inversion recovery suppression of the vitreous signal). In patients with retinitis pigmentosa, retinchoroidal blood flow is reduced and the extent of blood-flow reduction is correlated with electroretinography (49). Permeability changes using contrast-enhanced MRI (50) and ΔpO_2 changes (42) have been reported in humans with diabetic retinopathy.

Limitations and challenges

The major disadvantages of retinal MRI are its higher cost and lower spatiotemporal resolution compared to optical imaging techniques. The major advantages of MRI are its ability to image physiological and functional parameters and depth resolution. MRI is not competitive compared to optical coherence tomography (51) for measuring layer thickness because optical coherence tomography offers far better spatiotemporal resolution although MRI could provide some useful anatomical contrasts to study retinal diseases.

MRI offers some competitive advantages in measuring blood flow over existing retinal imaging techniques, such as laser speckle imaging (52,53), laser Doppler velocimetry and flowmetry (54), which generally provide a qualitative index of blood flow, limiting cross-subject comparison. Doppler optical coherence tomography has the potential to measure blood flow with substantial depth resolution but remains an active area of research (55). The use of optically based imaging techniques to probe functional responses of the retina is sparse (55). fMRI by comparison offers a unique means to probe “evoked” changes in the retina in a layer-specific manner, offering some competitive advantages over optical imaging techniques. As such, blood flow and functional MRI hold promise in providing competitive and valuable information compared to existing optically based imaging techniques.

The challenges and thus opportunities for further research in retinal MRI applications include the needs to improve: i) spatiotemporal resolution, ii) routine 3D coverage, iii) novel contrasts to better visualize retinal layers, iv) eye fixation stability, v) further applications to preclinical and clinical retinal diseases, such as testing of therapeutic interventions, early detection and characterization of disease physiological processes. These advances can be facilitated by general improvement in MRI hardware including field gradient capability, preamplifiers, detectors, image acquisition speed (i.e., faster sequences and parallel imaging), and eye fixation stability.

MRI has the potential to be used in clinical settings although routine screening will likely be limited due to relatively high cost and low throughput at this time. It is reasonable to expect that MRI costs will decrease over time. That said, identifying patients at high risk of developing retinal diseases early and implementing of preventive measures should be cost effective considering the morbidity and economic burden of blindness from these diseases.

Conclusions

MRI can detect layer-specific anatomy, blood-flow, physiological and functional MRI, offering the potential to further advance our understanding of retinal physiology and function in health and diseased states. MRI has the potential to exert a sustained positive impact in retinal disease research by enabling objective early detection, longitudinal disease staging, and monitoring of interventions via detecting hemodynamic dysregulation in the retina with depth resolution. There remain many challenges before routine clinical retinal MRI applications become feasible.

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Figure 1.

(A) In vivo bSSFP MRI of the mouse retina at $45 \times 45 \times 500 \mu\text{m}$. Contrasts among different retinal layers are observed without exogenous contrast agents. Adapted from (11). (B) Layer-specific blood-flow image and blood-flow profile from a live mouse under 1.1% isoflurane and a dead mouse in the same setting (same animal) at $42 \times 42 \times 400 \mu\text{m}$. Blood flow was acquired using continuous arterial spin labeling with a separate labeling coil at the neck position. chBF – choroid blood flow, rBF – retinal blood flow. Adapted from (14). (C) Layer-specific blood-volume (MION) weighted images and fMRI responses to graded luminance, flicker frequency and wavelength (color) at $60 \times 60 \times 1000 \mu\text{m}$ nominal resolution (mean $\pm$ SEM, $N=7$). Adapted from (22).

Figure 2.

(A) Blood-flow MRI of a human retina acquired using pseudo-continuous arterial spin labeling at $0.5 \times 0.8 \times 8$ mm ($N=1$). Adapted from (44). (B) BOLD fMRI map and time course of the human retina associated with oxygen versus air inhalation at $1.6 \times 2 \times 4$ mm ($N=1$). Inversion pulses were used to suppress the otherwise strong vitreous signal. Adapted from (46).