Published in final edited form as:

Br J Ophthalmol. 2009 May ; 93(5): 603–609. doi:10.1136/bjo.2007.136101.

Projection OCT fundus imaging for visualising outer retinal pathology in non-exudative age-related macular degeneration

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Abstract

Aims—To demonstrate ultrahigh-resolution, three-dimensional optical coherence tomography (3D-OCT) and projection OCT fundus imaging for enhanced visualisation of outer retinal pathology in non-exudative age-related macular degeneration (AMD).

Methods—A high-speed, 3.5 μm resolution OCT prototype instrument was developed for the ophthalmic clinic. Eighty-three patients with non-exudative AMD were imaged. Projection OCT fundus images were generated from 3D-OCT data by selectively summing different retinal depth levels. Results were compared with standard ophthalmic examination, including fundus photography and fluorescein angiography, when indicated.

Results—Projection OCT fundus imaging enhanced the visualisation of outer retinal pathology in non-exudative AMD. Different types of drusen exhibited distinct features in projection OCT images. Photoreceptor disruption was indicated by loss of the photoreceptor inner/outer segment (IS/OS) boundary and external limiting membrane (ELM). RPE atrophy can be assessed using choroid-level projection OCT images.

Conclusions—Projection OCT fundus imaging facilitates rapid interpretation of large 3D-OCT data sets. Projection OCT enhances contrast and visualises outer retinal pathology not visible with standard fundus imaging or OCT fundus imaging. Projection OCT fundus images enable registration with standard ophthalmic diagnostics and cross-sectional OCT images. Outer retinal alterations can be assessed and drusen morphology, photoreceptor impairment and pigmentary abnormalities identified.

Age-related macular degeneration (AMD) is a leading cause of blindness. The majority of patients have the non-exudative form, where drusen and retinal pigment epithelium (RPE) abnormalities correspond to the early stage of the disease and may cause decreased visual acuity. Optical coherence tomography (OCT) can visualise retinal pathology in AMD.¹

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Competing interests: JSS: Carl Zeiss Meditec, Heidelberg Engineering, Optovue—compensation. JSD: Carl Zeiss Meditec, Optovue—affiliation. JGF receives royalties from intellectual property owned by MIT and licensed to Carl Zeiss Meditec and Lightlabs Imaging, and is on the scientific advisory board of and has stock options in Optovue.

Ethics approval: Ethics approval was provided by the institutional review boards of Tufts Medical Center and MIT.

Patient consent: Obtained.

Investigations of dry AMD have been published using standard, ~10 μm axial resolution^{2,3} and ultrahigh, ~3 μm resolution⁴ OCT. Recent advances enable high-speed OCT using spectral/Fourier domain detection.^{5–7} High-speed imaging enables acquisition of three-dimensional OCT (3D-OCT) data.^{8–14}

3D-OCT data sets are large, requiring analysis of numerous cross-sectional images to identify subtle structural changes. Since non-exudative AMD develops in the outer retina, visualisation methods which rapidly identify outer retinal pathology are needed. To compare OCT with standard diagnostics, it is helpful to display 3D-OCT data en face. En face OCT imaging, using fast transverse scanning to obtain images at a single depth, has been demonstrated.^{15,16} Axial summation of 3D-OCT data generates en face fundus images that enable precise registration of cross-sectional images to fundus features.^{9,12,17,18} RPE “shadowgrams” obtained from 3D-OCT data can visualise retinal vasculature.¹⁷

In this study, we demonstrate projection OCT fundus imaging for visualising 3D-OCT data. Projection OCT generates en face fundus images, which can be correlated with fundus photography and fluorescein angiography (FA). This technique selectively displays specific depth ranges in the retina, thus enhancing the contrast of retinal structure alterations. Projection OCT fundus imaging enhances visualisation of outer retinal pathology in non-exudative AMD by allowing focal changes to be quickly localised and corresponding cross-sectional OCT images to be selected for examination.

MATERIALS AND METHODS

Studies were performed with a custom-built research OCT instrument developed at MIT and used at the New England Eye Center. Study data were collected between 2004 and 2007. Our spectral/Fourier domain instrument achieved an axial image resolution of 3.5 μm with an acquisition speed of 24 000 axial scans/s. Commercial spectral/Fourier domain instruments have 5–7 μm image resolutions and comparable acquisition speeds. Our instrument uses a compact, multiplexed superluminescent diode light source (Superlum) with a ~95 nm bandwidth at ~840 nm wavelength, imaging with 750 μW incident power, which is consistent with the American National Standards Institute (ANSI) safe exposure. The transverse image resolution was ~15–20 μm . 3D-OCT data were obtained in ~4 s using a raster scan covering a 6×6 mm² macular region. A total of 180 horizontal, cross-sectional images (B-scans) separated by ~33 μm were acquired. Each B-scan had 500 transverse pixels (A-scans) separated by ~12 μm , and each A-scan had 1024 points.

One hundred and sixty-one subjects with AMD were imaged at the New England Eye Center, Tufts Medical Center. Eighty-three subjects were diagnosed with non-exudative AMD on standard ophthalmic examination. Data from these cases were reviewed, and different drusen morphology and pigmentary anomalies were identified. Four cases representative of these findings are presented in order to compare projection OCT fundus imaging with conventional imaging methods. The study protocol was approved by the institutional review boards of Tufts Medical Center and MIT. Written informed consent was obtained and the study conducted in accordance with Health Insurance Portability and Accountability Act (HIPAA).

To enable the registration of OCT images with standard diagnostics, OCT fundus images were generated by axial summation of the 3D-OCT data^{9,10,12,17,18} (fig 1B,C). However, features characteristic of dry AMD develop principally in the outer retina and can be difficult to visualise in OCT fundus images. Thus, projection OCT fundus images were used to display specific depths of the retina.

To construct projection OCT fundus images, an outer retinal reference contour is generated by identifying the RPE using edge-detection algorithms¹⁹ and using iterative fourth-order polynomial curve fitting. The images in the 3D data set were aligned by these curve fits (fig 1A,D). The outer RPE boundary (basal side of the RPE) served as a reference for selecting different levels of the retina that were summed and displayed as en face fundus images. In cases with small RPE detachments, this outer retinal reference contour corresponds to the Bruch membrane, which is anterior to the choriocapillaris. The different projection levels used were (fig 1D):

- choroidal level: corresponding to the choroid;
- retinal pigment epithelium (RPE) level: corresponding to the normal position of the RPE;
- photoreceptor outer segment (PR OS) level: corresponding to the normal position of the photoreceptor outer segments and photoreceptor inner/outer segment (IS/OS) junction;
- outer nuclear layer (ONL) level: overlapping the normal position of the photoreceptor inner segments (IS) and ONL.

The positions of these levels were selected according to average thickness values of corresponding anatomical layers, which was previously assessed in normal subjects.²⁰ Levels displayed in projection OCT fundus imaging are parallel to the outer retinal contour, but they do not necessarily strictly follow the boundaries of anatomical retinal layers. Projection OCT fundus images are created by axially summing or projecting the signal from selected levels (fig 1E). Examples of images are presented in fig 1F—I. The grey-scale images display the backscattered light within the depth range. Brighter areas indicate increased scattering or light penetration, while dark areas indicate decreased scattering or shadowing by overlying structures.

RESULTS

Clinical findings characteristic of non-exudative AMD include hard, soft, distinct and indistinct (confluent) drusen and pigmentary abnormalities such as pigment accumulation, migration or RPE depigmentation. Representative features including: basal laminar drusen, predominantly hard drusen, predominantly soft drusen, soft confluent drusen and pigmentary anomalies were compared. Four representative cases of these findings are presented here. Other examples, including predominantly soft drusen, are not presented due to space constraints.

Case 1: basal laminar drusen

A 57-year-old white male had basal laminar drusen in his right eye with a visual acuity of 20/25 OD. Small, yellowish spots scattered in the macula are visible on fundus photography (fig 2A). FA (fig 2B) shows numerous, well-demarcated, sharp, focal spots of hyperfluorescence. These findings are not visible on OCT fundus images (fig 2C), where the entire axial signal is summed. However, a cross-sectional OCT image from the 3D-OCT data set reveals distinct drusen (fig 2D) as darkened areas under the slightly elevated RPE. The photoreceptor IS/OS junction and ELM have a rippled appearance. The photoreceptor IS/OS junction is mostly continuous but occasionally disrupted by sharply demarcated deposits (fig 2D, arrow 1). There is no evidence of PR OS layer thinning. Focal areas of increased light penetration into the choroid (fig 2D, arrows 2, 3) occur below some drusen, thus suggesting increased RPE transparency and pigmentary changes.

The ripples in the photoreceptor IS/OS junction can be visualised in the ONL level image (fig 2E) as small, bright areas where the IS/OS junction is displaced from its normal position. The

PR OS level image (fig 2F) shows minimal changes with basal laminar drusen. The drusen are hyper-reflective and extend into the OS level, but they also elevate the PR OS layer, which displaces the hyper-reflective IS/OS junction outside the OS level image. Therefore, the net reflectivity change within the PR OS level from this type of drusen is very small. The RPE level image (fig 2G) shows drusen as a characteristic pattern of dark spots, thus indicating RPE elevation from its normal position. The choroid level projection OCT image (fig 2H) shows focal areas of light penetration through the RPE.

Case 2: predominantly hard drusen

A 71-year-old white male had predominantly hard drusen in both eyes with a visual acuity of 20/25 OD and 20/30 OS. Hard drusen are visible as small, well-demarcated spots in the fundus photograph OS (fig 3A) but are not visualised in OCT fundus images (fig 3B). The OCT cross-sectional images show clustered deposits (fig 3C), forming larger areas of RPE detachment. The clusters are irregularly shaped but not highly elevated. The Bruch membrane is visible underneath the RPE elevations. A region of photoreceptor atrophy is visible (fig 3D, white bracket).

The ONL level image (fig 3E) shows elevations of the outer retinal complex (RPE and the photoreceptor layer) as bright areas. In contrast to the previous case, these elevations are higher and visible over a significant fraction of the macula. The PR OS level image (fig 3F) displays the highest RPE elevations as small, hyporeflexive, regular spots. The larger dark area indicated by a bracket in fig 3F corresponds to the region free from drusen, which is consistent with the cross-sectional image (fig 3D). This dark area results from decreased light scattering at the photoreceptor IS/OS junction, thus suggesting photoreceptor impairment. The RPE level image (fig 3G) shows clusters of drusen as large dark areas with irregular shapes.

Case 3: soft confluent drusen

A 69-year-old female had large, soft confluent drusen OS (fig 4A) with a visual acuity of 20/40. The cross-sectional OCT image (fig 4C) reveals weakly scattering deposits forming “dome-like” RPE elevations. The RPE between the drusen is detached from the Bruch membrane, thus indicating confluence of deposits. The photoreceptor IS/OS junction and ELM are absent above the large RPE elevations, thus indicating photoreceptor impairment. A hyper-reflective feature visible in the ONL produces shadowing in deeper layers (arrow 1) that is consistent with the pigmentary changes in the fundus photograph. OCT cross-sectional images show drusen morphology complementary to the findings on the colour fundus image (fig 4A) and the OCT fundus image (fig 4B).

In the ONL level image, highly elevated drusen are visible in (fig 4D) as bright areas with white borders, which correspond to the intersection of the RPE elevations with the ONL level. In the PR OS level image (fig 4E) regular, darkened areas of deposits are surrounded by hyper-reflective bands representing intersection of the elevated RPE with the PR OS level. In the RPE level image (fig 4F), the dark areas corresponding to RPE elevation are merged due to drusen confluence. The choroidal level image (fig 4G) shows vasculature. The increased choroidal visibility could be related to pigmentary characteristics of the fundus as well as to AMD. Focal dark spots visible in all projection OCT fundus images (eg, arrow 1 in fig 4D, F) correlate with pigmentary changes in the fundus photograph and pigment migration or accumulation in cross-sectional OCT images.

Case 4: pigmentary abnormalities

An 83-year-old white female had dry AMD in both eyes with a visual acuity of 20/30 OU. The red-free photograph (fig 5A) and late-phase FA (fig 5B) show RPE atrophy, pigment clumping

and drusen. In the OCT fundus image (fig 5C) hyper-reflective areas are visible, but it is unclear which layers produce this hyper-reflectivity.

A series of cross-sectional OCT images indicates pigmentary abnormalities. Figure 5D reveals an area of RPE and photoreceptor layer disruption. A hyperscattering feature visible in the ONL in fig 5D (arrow 1) may indicate inner retinal changes and atrophy of the ONL. Increased choroidal light penetration in fig 5D—F suggests RPE depigmentation and atrophy (arrow 2). Focal hyperscattering features seen in fig 5F,G correspond to pigment accumulation (arrow 3) or are present in the ONL, thus suggesting pigment migration (arrow 4).

The ONL level image (fig 5H) visualises elevations of the outer retinal complex as bright regions. Focal hyperscattering features indicate pigment migration. Dark areas in the PR OS level image (fig 5I), corresponding to regions free from drusen in the ONL level, indicate disruptions in the photoreceptor layer (bracket). Hyperscattering regions in the choroidal level projection OCT image (fig 5K) indicate RPE atrophy.

DISCUSSION

Ultrahigh resolution 3D-OCT visualises microstructural changes in the outer retina in non-exudative AMD that are not visible on standard clinical examination. However, 3D-OCT data sets are large, the sequential analysis of cross-sectional images is impractical, and the overall assessment of the macula can be time-consuming. Projection OCT fundus imaging enables the rapid assessment of outer retinal pathology and provides an en face view for direct comparison with standard diagnostics. Projection OCT enables areas of focal pathology to be identified and corresponding cross-sectional OCT images to be selected that are precisely registered to the fundus. The interpretation of projection OCT fundus images is established by correlation with cross-sectional OCT images and clinical findings. Results show that clinical findings characteristic of non-exudative AMD have distinct signatures in projection OCT fundus images.

The AREDS study²¹ established a scale for classifying RPE abnormalities and drusen using colour fundus photography, which is now the standard for the assessment of AMD. The pathology scatters and/or absorbs white light, and differences in colour provide information about the pathology. However, colour fundus imaging does not provide direct information about the depth-resolved, cross-sectional structure of lesions or structural photoreceptor integrity. Conventional OCT fundus imaging integrates the entire axial signal, thereby providing a fundus image analogous to scanning laser ophthalmoscopy. However, imaging is performed at infrared wavelengths, and OCT fundus images have reduced contrast when compared with colour fundus photography. Projection OCT imaging enhances the contrast of retinal pathology by displaying selected retinal depth levels and rejecting unwanted light.

Projection OCT is complementary to standard fundus imaging methods and enables visualisation of outer retinal features, which can be difficult to see using colour fundus photography or OCT fundus imaging. Projection OCT fundus imaging visualises drusen, the extent of photoreceptor disruption, and pigmentary changes or RPE atrophy. RPE atrophy is indicated by abnormalities in the choroid level images from increased RPE light penetration. The RPE level image shows disruptions in the normal RPE position and can detect the presence of drusen and their area. Focal pigment accumulation is identified by shadowing of posterior structures and then visualised in RPE level images as dark spots. Abnormalities in PR OS level images indicate disruption of the photoreceptor IS and OS boundary and confluent drusen.⁴ Abnormalities in the ONL projection image indicate a more pronounced pathology with significant drusen elevation. These results show that features visualised in projection OCT fundus images can be related to specific alternations in outer retinal morphology.

Projection OCT fundus imaging is complementary to segmentation and retinal thickness mapping. Projection OCT imaging shows alterations of normal retinal morphology rather than specific anatomical layers. The identification of retinal layers requires segmentation algorithms to identify boundaries. Automated segmentation of retinal thickness and nerve fibre layer thickness are powerful techniques to assess macular oedema and glaucoma.^{22 23} Segmentation of the ganglion cell complex was also demonstrated.²⁴ Using ultrahigh-resolution spectral/Fourier domain OCT, it is possible to identify the photoreceptor IS/OS boundary as well as detailed outer retinal features.^{20 25} However, automatic segmentation is challenging when retinal pathology disrupts the normal contrast and continuity of the retina, and it can produce errors. The difficulty of automatic segmentation can be appreciated from the OCT images in figs 2, 3. While ultrahigh-resolution OCT shows unprecedented detail, it is more sensitive to pathology than lower-resolution OCT, thereby making automatic segmentation of fine retinal layers difficult. Small errors in determining retinal layers can produce large quantitative measurement errors, because they are integrated over large fundus areas. Projection OCT fundus imaging has the advantage of requiring only a single segmentation step, rather than a detailed identification of multiple retinal layer boundaries, and is therefore more robust than other quantitative OCT methods.

En face imaging relies upon high data-acquisition rates, since each pixel in the en face image requires one axial scan. The technology in this study had an acquisition speed of 24 000 axial scans/s, thus acquiring a 3D-OCT data set in ~4 s. This is too long to prevent ocular motion in some patients. Recently, new technology has become available that reduces acquisition time to ~1 s. With the availability of higher imaging speeds, we believe that en face visualisation methods such as projection OCT will become increasingly important. Additional controlled longitudinal studies are needed and should help to identify markers of early disease and disease progression.

Acknowledgments

Funding: National Institute of Health contracts R01-EY11289-23, R01-EY13178-09, R01-EY013516-06, P30-EY08098 and P30-EY13078; National Science Foundation contract BES-0522845; Air Force Office of Scientific Research, Medical Free Electron Laser Program contracts FA9550-07-1-0101 and FA9550-07-1-0014; The Eye and Ear Foundation (Pittsburgh), Massachusetts Lions Eye Research Fund; unrestricted grants from Research to Prevent Blindness and Medical Student Eye Research Fellowship.

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Figure 1.

Generation of both OCT fundus images and projection OCT fundus images in a normal eye. (A) Approximation of the outer retinal contour with fourth-order polynomial curve fit (red line). (B) Generation of an OCT fundus image by axial summation of the 3-D data set. (C) Example of an OCT fundus image. (D) Cross-sectional OCT image after the flattening procedure; vertical bars indicate selection of projection OCT levels; inset: enlarged outer retinal complex with marked projection levels. (E) Generation of a projection OCT fundus image by axial summation of signal at the RPE level (yellow arrows). (F—I) Projection OCT fundus images: outer nuclear layer level (G), photoreceptor outer segments level (H), RPE level (F) and choroidal level (I). Image sizes are 6 mm×6 mm. ONL, outer nuclear layer; PR OS; photoreceptor outer segment; RPE, retinal pigment epithelium.

Figure 2.

Basal laminar drusen. (A) Colour fundus photograph. (B) Fluorescein angiograph (1:19.6). (C) Optical coherence tomography (OCT) fundus image. (D) Cross-sectional OCT image extracted from the 3-D data set. Arrows: 1, disruption of the photoreceptor inner/outer segment junction; 2, 3, focal increased light penetration into the choroid. (E—H) Projection OCT fundus at the levels shown in (D). The location of the cross-sectional OCT image (D) is shown as a line on the projection OCT fundus images. Image sizes are 6 mm×6 mm. ELM, external limiting membrane; IS/OS, photoreceptor inner/outer segment junction; ONL, outer nuclear layer; PR OS; photoreceptor outer segment; RPE, retinal pigment epithelium.

Figure 3.

Predominantly hard drusen. (A) Colour fundus photograph. (B) OCT fundus image. (C, D) Example cross-sectional OCT images extracted from the 3-D data set. (E—H) Projection OCT fundus images. Brackets in (D) and (F) indicate an area of photoreceptor layer disruption. The locations of cross-sectional OCT images (C—D) are shown as lines on the projection OCT fundus images. Image sizes are 6 mm×6 mm. BM, Bruch membrane; ELM, external limiting membrane; IS/OS, photoreceptor inner/outer segment junction; ONL, outer nuclear layer; PR OS, photoreceptor outer segment; RPE, retinal pigment epithelium.

Figure 4.

Soft, confluent drusen. (A) Colour fundus photograph. Arrows 1 and 2 indicate pigmentary changes. (B) OCT fundus image. (C) Example cross-sectional OCT image extracted from the 3-D data set. Arrow 1 shows pigment migration, and arrow 2 shows pigment accumulation. (D—G) Projection OCT fundus image at the levels shown in (C). The location of the cross-sectional OCT image (C) is shown as a line on the projection OCT fundus images. Image sizes are 6 mm×6 mm. BM, Bruch membrane; ELM, external limiting membrane; IS/OS, photoreceptor inner/outer segment junction; ONL, outer nuclear layer; PR OS; photoreceptor outer segment; RPE, retinal pigment epithelium.

Figure 5.

Pigmentary abnormalities. (A) Red-free photograph. (B) Fluorescein angiograph. (C) OCT fundus image. (D–G) Cross-sectional OCT fundus images extracted from the 3-D data set. Arrow 1 shows a hyper-reflective feature in the outer nuclear layer, arrow 2 shows increased light scattering into the choroid, arrow 3 shows pigment accumulation, and arrow 4 shows pigment migration. (H–K) Projection OCT fundus images at the depth levels shown in (D). The locations of cross-sectional OCT images (D–G) are shown as lines on the projection OCT fundus images. Image sizes are 6 mm×6 mm. BM, Bruch membrane; ELM, external limiting membrane; IS/OS, photoreceptor inner/outer segment junction; ONL, outer nuclear layer; PR OS; photoreceptor outer segment; RPE, retinal pigment epithelium.