Extended Abstract
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Eye 2018: Visible light OCT-based quantitative imaging of lipofuscin in the retinal pigment epithelium

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Abstract

We developed a technology to provide simultaneous VIS-OCT and AF of the retina and a reference standard target at the intermediate retinal imaging plane with a single broadband visible light source. Then both OCT and AF images are made from the same group of photons the OCT probe light capabilities attenuation by the same ocular layers. The technology is able to eliminate the variable pre-RPE attenuation factor in AF imaging using the concurrently acquired VIS-OCT image. To quantitatively bridge the OCT and AF detection schemes thus eliminate the effects of illumination power and detector sensitivity, a normal reference target with known reflectivity and fluorescence efficacy was implemented into the system. Using the standard reference, similar to the one used by Deloris AF and reflectance signals are normalized to a known reference value that is independent of the exposure power and detection gain.

Introduction:
Lipofuscin, a by-product of the visual cycle of photoreceptors, is the major source of the fundus auto fluorescence (FAF) in the Retinal Pigment Epithelium (RPE). The lipofuscin accumulates with aging and in certain pathological disorders and is thus a biomarker for degenerative retinal diseases. Therefore, the quantification of lipofuscin is important in the diagnosis, progression monitoring, and treatment evaluation. Lipofuscin quantification is challenging because the light is attenuated by the media anterior to the RPE which is subject to inter-individual and intra-individual differences. Further, various illumination power and detection sensitivity of different imaging systems can also affect the readings of the detected FAF.
FAF imaging has been used in ophthalmology clinics for many years. For example, hyper auto fluorescence is positively linked with the development of AMD and Stargardt's macular dystrophy. In the case of geographic atrophy (GA), the late stage of dry AMD, advanced RPE alterations exhibit clinically recognizable patterns of hyper auto fluorescence, which is positively correlated with the rate of GA progression and can be evaluated semi-automatically with newly advanced software by non-expert graders.
However, the currently available technologies are not capable to measure standardized FAF intensity. The measured FAF signal by the currently available technologies could be affected by the excitation light intensity, detector sensitivity, and gain of the instrument used.

In addition, and importantly, signals are attenuated by the ocular tissues anterior to the RPE, especially by the lens, and the attenuation cannot be measured directly. The ocular properties of tissues anterior to the RPE could be significantly different among individuals, and it changes over time in the same person. Thus, it is difficult to compare images obtained by the currently available technologies from the same person over time, or from different individuals, which hinders the clinical usefulness of FAF images. It is a challenge to obtain the absolute intensity of FAF.

Methods:
Imaging system:
The system consists of two spectral-domain OCTs in the NIR and visible spectrum, respectively. The NIR-OCT is used only for alignment to reduce visible light exposure and avoid additional bleaching effects to the fluorophores. The VIS-OCT consists of a supercontinuum laser (SC, model: EXB-6, SuperK EXTREME, NKT Photonics, Denmark) with a variable band-pass filter (selected center wavelength: 480 nm, bandwidth: 30 nm). The output VIS light is coupled into the source arm of a single-mode optical fiber-based Michelson interferometer. The NIR-OCT uses a superluminescent diode as the light source (SLD-37-HP, center wavelength: 840 nm, bandwidth: 50 nm, Superlum, Russia). The NIR light is coupled to another fiber-based Michelson interferometer after passing through an optical-fiber isolator. After exiting the optical fibers in the sample arms, both the NIR and VIS light are collimated and combined by two dichroic mirrors (DM1: DMLP505, Thorlabs, and DM2: NT43-955, Edmund Optics). The combined light beam is scanned and delivered to the eye by a combination of a relay lens (L1, f = 75 mm, achromatic) and an ocular lens (L2, Volk lens, 60D).

Results:
In the phantom experiments, we first investigated the influence of detector sensitivity of the system on the AF signal detection. The fluorescent intensities were measured at different detector gains (by varying the detector control voltage) to verify the capability of the technique for cancelling the effects of detector sensitivity. The averaged FAF signals measured from the model eye and signals from the reference fluorescent target (RAF) were plotted against the OD values of the ND filters. At a given gain, the logarithm of the fluorescent signals from the master reference in the model eye linearly decreases with the OD values of the ND filters at a slope of −2, which agrees with the round-trip attenuation of light through the ND filter and the listed transmission data of the

ND filters. The signals from the standard fluorescent reference target are independent of the attenuation of the ND filters and remain constant. The measured signal intensities of FAF and RAF decreased with the PMT control voltage accordingly.

Discussion:

We have demonstrated that the VIS-OCT based multimodal imaging technology is capable to obtain both OCT reflectance and AF images simultaneously. The intensities of the OCT reflectance from the RPE can serve as an internal reference to compensate signal attenuation by ocular tissues anterior to the RPE, including melanin in the RPE cells. The OCT and fluorescence signal intensities from the two reference standards placed in the intermediate retinal imaging plane can be used to not only eliminate the effects of light source fluctuation and detector sensitivity for OCT and AF imaging but also quantify the FAF signal to a value that is proportional to the absolute concentration of lipofuscin.

Conclusion:

We have developed a new multimodal imaging system with two reference targets placed in the intermediate retinal imaging plane for quantitative imaging of RPE lipofuscin. The system employs a single light source to acquire AF and VIS-OCT images of the retina
simultaneously. Since the same group of photons is responsible for both AF and OCT imaging, the OCT image intensities can be used to compensate signal attenuation by media anterior to the RPE, including melanin in RPE cells.

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