Optical coherence tomography: beware of optical illusions

Kok, P.H.B.

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General Introduction
LOOK INSIDE THE EYE

Contrary to many other medical specialists, ophthalmologists have the privilege to “look inside” the organ of their specialism in a noninvasive manner. Using an ophthalmoscope the interior of the eye (retina) can be examined by means of a beam of light. This examination is called funduscop[y. It is now more than 150 years since Hermann von Helmholtz’s ‘revolutionizing discovery’ of the ophthalmoscope in 1851.⁷ A more recent revolutionizing imaging technique of the retina is Optical Coherence Tomography. In 1995, OCT was introduced in ophthalmology for in-vivo imaging of the human retina. OCT can be considered an optical analogue of ultrasonography. It is a noninvasive, fast diagnostic technique. Especially in diseases of the macula, vitreoretinal interface and also in glaucoma OCT has become a very useful tool. With axial resolution in the 5–7 μm range, it provides close to an in vivo “optical biopsy” of the retina, see Figure 1.²⁻¹⁰

BEWARE OF OPTICAL ILLUSIONS

Optical illusions are false visual perceptions of the external environment. For example, the arrows on the cover of this thesis don’t seem to be of identical length, but in reality they are. Optical illusions should be distinguished from hallucinations. A hallucination is an observation, in which the stimulus from the outside world is missing. Optical illusions disappear with eye closure; hallucinations usually do not. Many optical illusions have an ocular basis. Diseases of the central part of the retina, which is called the macula, can cause optical illusions like perceived image shrinking (micropsia),
perceptual distortion (metamorphopsia) or scotoma’s. Nowadays when a patient visits an ophthalmologist with this kind of illusions, his or her ophthalmologist will almost certainly perform imaging of the macula using OCT.

In this thesis, I will demonstrate that optical illusions also occur in OCT images. The image quality and interpretation of OCT therefore needs critical evaluation. The aim of this thesis is to investigate misinterpretation of OCT scans and measurements due to loss of image quality. Furthermore, the clinical interpretation of OCT retinal (layer) thickness measurements is demonstrated in two ophthalmological diseases.

**OPTICAL COHERENCE TOMOGRAPHY**

OCT uses low coherence interferometry of light. Image formation depends on differences in optical backscattering properties of the tissue under investigation.

OCT technology has become a diagnostic imaging modality with a wide spectrum of clinical applications in medical practice, including the gastrointestinal tract, pancreatico-biliary ductal system, cardiology and this “optical biopsy” has high potential in epithelial tumor diagnosis (i.e. kidney cancer, bladder cancer, and premalignant vulvar intraepithelial neoplasia). \(^{(11)}\)

A basic OCT system is based on the principle of a Michelson-interferometer. The setup consist of a broad band light source sending light into the interferometer, where the light is split in two arms; 50% is sent to the reference arm and 50% to the sample arm (also other ratios are being used). In time domain OCT (TD-OCT) the depth information of the retina is acquired as a sequence of samples, over time, which makes this technique relatively slow as compared to the spectral domain OCT (SD-OCT) using Fourier domain transformation for the depth information. TD-OCT systems, commercially available as Stratus OCT (Carl Zeiss Meditec, Inc, Dublin, CA) featured scan rates of 400 A-scans per second with an axial resolution of 8–10 μm in tissue. In 2006, the first commercially available SD-OCT system was introduced. This technique achieves scan rates of 20 000–52 000 A-scans per second and a resolution of 5–7 μm in tissue. \(^{(12,13)}\) In clinical practice TD-OCT has been overtaken by SD-OCT because of its major advances in imaging speed, sensitivity and image resolution. See Figures 2 and 3.

**IMAGE QUALITY**

In the first versions of OCT software (StratusOCT; Carl Zeiss Meditec, Dublin, CA), the only parameter to objectively evaluate the quality of acquired images was the signal-to-noise ratio (SNR). The SNR takes into account the single a-scan that demonstrates the strongest signal and does not account for the distribution of the signal strength throughout the scan image. In later versions, the quality of the obtained OCT images is automatically reported by the software of the TD-OCT (StratusOCT) as a metric, based on the originally used SNR, called signal strength (SS). The software of the different
FIGURE 2. Schematic of a setup for TD-OCT (A) and SD-OCT (B). A: Light from a broad band light source is split in a reference arm and sample arm by using a beam splitter. The optical path length of the reference arm can be changed to match the optical path length in the sample arm. The reflected light of both arms is recombined and directed to a photodiode where the light interferes, i.e. when the optical paths of both arms match within one coherence length. B: a schematic representation of a SD-OCT setup. Here, in contrast to TD-OCT, the reference mirror is fixed and the depth information is encoded in the spectrally resolved interferences fringes detected with a spectrometer.

SD-OCT systems each provide their own image quality parameter (IQP). These IQP’s differ in name and scale. Due to their proprietary nature, manufacturers do not further specify these parameters.

OCT image quality is influenced by opacities in the optical path, therefore opacities (in particular cataract) and OCT image quality is a well studied subject. These studies investigated macular image changes after cataract surgery and the influence of cataract on the SNR, showing a significant increase in signal quality after cataract removal.
In the eye, optical imaging can be described by means of the so-called point spread function (PSF). The PSF is the light distribution on the retina of a point of light that is focused on the retina. Whereas the ideal PSF would be a small point, the true PSF is spread out. Even in a healthy eye, the beam of light is spread out slightly, but cataract introduces more profound changes. Opacification of the lens causes refractive irregularities in the optical pathway, degrading the quality of retinal imaging. Refractive disturbances, for example lower and higher order aberrations, affect the central peak of the PSF, causing spreading over angles of around 0.1°. Irregular particles in the ocular system of small extent (in the order of 10 µm) cause very different effects. They cause scattering of light and affect the skirts of the PSF, causing light spreading over angles larger than 1°. This light is usually called straylight. Apart from refractive type disturbances and scattering type disturbances, a third type of disturbance can be distinguished. Light is lost due to both absorption in the media and also, for a minor part, due to reflection.

**OPTICAL DENSITY FILTERS**

Optical disturbances can be approached using their three main effects; light attenuation, refractive aberrations and straylight. In this thesis these effects were simulated with artificial filters (Figure 4) in order to model a comparable range of optical density values as those observed in cataract patients [10]. The three effects and corresponding filters are: (1) light attenuation, simulated with absorptive (Schott, Mainz, Germany; n=3) and reflective (Balzers, Balzers, Liechtenstein; n=8) filters; (2) refractive aberrations, simulated with defocusing lenses (n=6) because no physical models are as yet available that mimic the aberrations of cataracts; and (3) light scattering/straylight, mimicked using scattering filters (n=7) that were discussed earlier as potential models for the light scattering characteristics of cataracts. The

**FIGURE 3.** Spectral domain OCT (SD-OCT) image of the macula, indicated are the retinal layers that can be distinguished. ILM=internal limiting membrane. NFL=nerve fiber layer. GCL=ganglion cell layer. IPL=inner plexiform layer. INL=inner nuclear layer. OPL=outer plexiform layer. ONL=outer nuclear layer. ELM=external limiting membrane. IS/OS=junction between the inner and outer segments of the photoreceptors. OPR=Outer segments photoreceptors/RPE complex. RPE=retinal pigment epithelium. Macular Inner Retinal Layer (mIRL)=NFL+GCL+IPL.
strength of all types of filters was expressed in optical density. This optical density was determined for the 830 nm central wavelength of the used OCT system (OD$_{λ=830}$).

In chapter 2 a model (using optical density filters) for the effect of disturbances in the optical media on the OCT image quality is discussed. In chapter 3 and 4 of this thesis the effort is discussed to assess and quantify the influence of disturbances in the optical media on the SD-OCT thickness measurements of the peripapillary RNFL (pRNFL) and the macular inner retinal layer (mIRL), consisting of the RNFL, ganglion cell layer (GCL) and inner plexiform layer (IPL), see Figure 3. These measurements are useful in the diagnosis and follow-up of glaucoma (see 1.5). Optical density filters are used to model a comparable range of optical density values as those observed in cataract patients. The ultimate goal is to correct OCT layer thickness measurements affected by a lower image quality.

In chapter 5 the varying effects of optical density filters, as standardised disturbances of the signal on OCT scan quality assessment is investigated, comparing four SD-OCT devices.

**GLAUCOMA**

OCT has become an important instrument in the diagnosis of glaucoma. Previous studies have shown that OCT measured RNFL thickness can be used to differentiate between normal and glaucomatous eyes.\(^{24-28}\) Glaucoma causes characteristic structural damage to retinal ganglion cells and their axons, which results in a decrease in visual function in the form of visual field loss. When glaucoma is detected at an early stage, loss of vision can in theory be prevented. Both structural and functional measures are important in the diagnosis and follow-up of glaucoma. Although evidence remains controversial, it is thought that structural damage precedes functional damage.\(^{29,30}\) In glaucoma there is a loss of retinal ganglion cells and thinning of the RNFL. Currently, peripapillary RNFL (pRNFL) thickness measurements (Figure 5) are used as an objective measurement of glaucomatous damage, and for detecting early glaucoma and progression in the management of patients with glaucoma. More recently the macular inner retinal layer (mIRL) thickness, consisting of the RNFL, ganglion cell layer (GCL) and inner plexiform layer (IPL), see Figure 3, has also shown to be a good diagnostic parameter for early glaucoma.\(^{31}\) It has shown high reproducibility, good diagnostic performance and has the advantage of a central fixation. Both pRNFL and mIRL thickness measurements represent loss caused by damage to the RGC axons in the optic nerve head in glaucoma. Preperimetric detection of glaucoma (before the stage of visual field loss) might allow for patients to be treated at an earlier stage of the disease.

As cataract and glaucoma often coexist in the same eye, cataract can be a confounding factor in the diagnosis and follow-up of glaucoma patients. As both pRNFL and mIRL thickness measured with SD-OCT are important for early detection of glaucoma and detection of progression, it is of interest to know the exact influence of media opacities on both thickness measurements.
INTERPRETATION OF RETINAL OCT

With OCT, it became possible to image the human retina longitudinally in-vivo and to measure the retinal thickness with high accuracy. Multiple retinal layers are distinguishable in these OCT images. Fully automated algorithms have been published for the segmentation of retinal OCT scans that are capable of detecting seven to nine surface boundaries in the retina, based on differences in refractive index resulting in differences in the scattering of laser light.\(^{32,33}\) A damaged ganglion cell layer in the retina is expected to be most pronounced pericentrally in the macula, so changes in the ganglion cells due to disease are most pronounced in this area of the retina. In two ophthalmologic conditions OCT measured pericentral retinal thickness is an important topic of research for this thesis, namely amblyopia (chapter 6) and diabetic retinopathy (chapter 7).

AMBYLOPIA

Amblyopia is defined as a unilateral or bilateral decrease of visual acuity caused by pattern vision deprivation or abnormal binocular interaction during the critical period of visual development, and for which no optical or organic origin can be detected.\(^{34,35}\) Despite much research, the pathophysiology of amblyopia has still not been fully understood. Although the visual cortex is said to be the primary site of amblyopia,
involvement of processes in the retina in amblyopia is increasingly being investigated. Because of contradicting outcomes over the years, retinal involvement as a cause of amblyopia has remained a controversial subject.

Retinal thickness in healthy eyes is determined by several factors, including age, sex, and axial length. Relatively greater axial length in healthy subjects has been shown to be significantly correlated with a thin retina and RNFL. Because amblyopic eyes tend to be hypermetropic, axial length can be a confounder in studies measuring retinal thickness in these patients. Chapter 6 investigated the relationship between axial length and pericentral retinal thickness in the amblyopic and fellow eyes of children with amblyopia compared to healthy children.

**DIABETIC RETINOPATHY**

In diabetes mellitus, retinal vasculopathy and retinal neurodegeneration occur, but it is unknown whether they share a common pathophysiology or are causally related. Diabetic retinal neuropathy could be a secondary result of vascular damage, itself the result of hyperglycemia, leading to increased permeability and occlusion of the retinal microvasculature and subsequent neuronal loss. In this scenario diabetic vasculopathy would be observed preceding the retinal neuropathy. An alternative hypothesis is that diabetes primarily affects the neuroretina, and that this secondarily compromises vascular integrity by an unknown mechanism, in which case diabetic vasculopathy is preceded by diabetic retinal neuropathy. Vasculopathy and neuropathy may also be independent sequelae of the diabetic state. As discussed in chapter 7, a decreased total retinal thickness, most pronounced in the pericentral area, is attributed to a selective loss of thickness in the inner retinal layers in type 1 diabetic patients with no or minimal diabetic retinopathy. This indicates that diabetes has an early neurodegenerative effect on the retina that occurs even though the vascular component of diabetic retinopathy remains minimal. A possible direct causal role of neurodegeneration in the development of diabetic vasculopathy should be the subject of future studies.

**FIGURE 5.** Peripapillary retinal nerve fiber layer (pRNFL) OCT scan. N=nasal, I=inferior, T=temporal, S=superior.
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