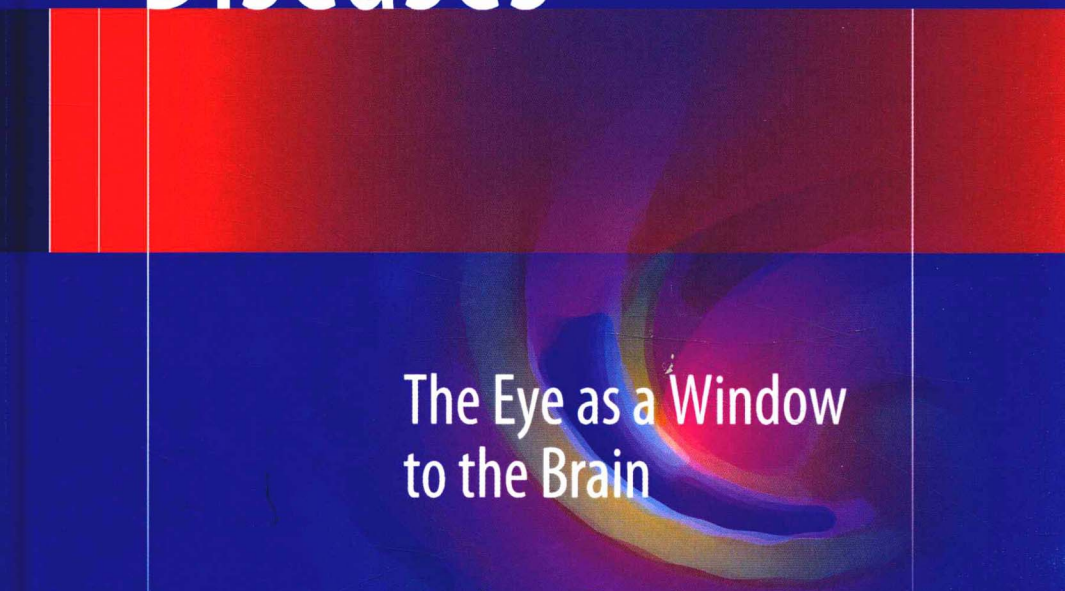
OCT in Central Nervous System Diseases



The Eye as a Window to the Brain

Andrzej Grzybowski
Piero Barboni *Editors*

Springer

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Editors
Andrzej Grzybowski
Professor of Ophthalmology
Head of Ophthalmology Department
Poznan City Hospital
Poznan
Poland

Chair of Department of Ophthalmology
University of Warmia and Mazury
Olsztyn
Poland

Piero Barboni
Studio Oculistico d'Azeglio
Bologna
Italy

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Contents

Chapter 1
Introduction: Retina Imaging – Past and Present

Andrzej Grzybowski and Piero Barboni

Abstract The retina raised the interest of scientists since the 4th century BC, when the Greek anatomist Herophilos, known as the Father of Anatomy, described it for the first time. It was not until the 18th century that scientists started to visualize the retina in the living animal and, later on, in the human eye. The histology of the retina was investigated in the 19th century and by the end of the 20th it was believed that its histological and functional characteristics were largely known. However new and somehow surprising information continues to be collected also in current days. One example is the discovery of Melanopsin-Containing Retinal Ganglion Cells (RCGs), which represent a novel class of photoreceptors. Optical coherence tomography (OCT) has been one of the most significant innovations in ophthalmology and has enabled us to improve our knowledge about specific cells and structures of the retina, such as the RCGs and the retinal nerve fiber layer (RNFL). Since the retina and optic nerve originate from the diencephalon, OCT measurements of both RCGs and RNFL have been shown to be sensitive parameters to investigate different diseases of the central nervous system.

The retina is a mysterious structure. The first use of the term comes, as to our present knowledge, from Herophilos (335–280 or 255 BC), Greek anatomist, who was of founders Greek school in Alexandria. He used two different words, arachnoeides and amfiblesteroides, for retina. For many years, both meanings were related to casting net, and retiform, a word which the modern "retina" is derived. However, as it was nicely shown recently, there might be another explanation of

A. Grzybowski, MD, PhD, MBA (✉)
Professor of Ophthalmology, Head of Ophthalmology Department, Poznan City Hospital, Poznan, Poland

Chair of Department of Ophthalmology, University of Warmia and Mazury, Olsztyn, Poland
e-mail: ae.grzybowski@gmail.com

P. Barboni
University of Bologna, Bologna, Italy

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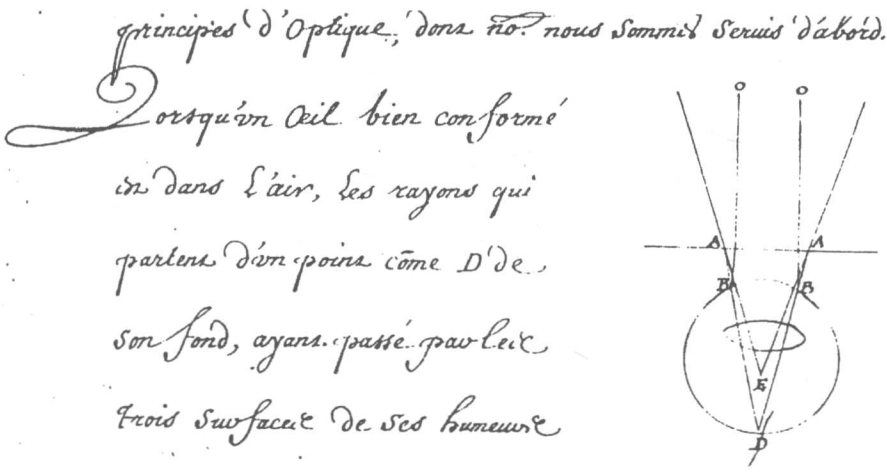
these original terms [1]. Amfiblesteroides meant at that time also anything that is thrown around and encircling walls. For many years it was believed, however, that the lens, not retina is the reception organ of the eye responsible for vision and there was even no agreement as to whether the eye emanated light (extramission theory) or received it (intromission theory) [2, 3]. Leonardo da Vinci (1452–1519) and Johannes Kepler (1571–1630) questioned the role of the lens in light reception. Felix Plater (1536–1614), attributed that role to the retina, what was further experimentally supported by Christopher Scheiner (1575–1650) who, by removing part of the sclera and choroids, was able to notice the reversed picture projected onto the bottom of the eye [3–6].

For the next two centuries, it was disputable weather retina or choroid was a precise structure responsible for vision reception [7]. This was finally settled by Herman von Helmholtz (1821–1894), who also constructed and popularized the first ophthalmoscope in 1851 [8]. This revolutionized the development of retinology.

The first visualization of the eye fundus of the living animal, however, was conducted by Jean Mery (1654–1718) in 1704 (Fig. 1.1). By plunging the head of a cat in water, Mery was able to observe the retinal vessels, the optic nerve head and the choroid [9]. This was later confirmed by Adolf Kussmaul in 1845 [10], Johann Nepomuk Czermak in 1851 [11] and Adolf Ernst Coccius in 1852, who introduced a water-box named 'orthoscope", to neutralize the corneal curvature [12, 13]. It was, however, Johannes Purkinje (1787–1869) in 1823 who described the basics of ophthalmoscopy based on his observations living animal and human eye [14]. One of the pioneers in the use of ophthalmoscopy for the diagnosis of central nervous system disorders was Xavier Galezowski (1832–1907), who published one of early textbooks on this subject and coined a term of cerebroscopy for this examination [15] (Fig. 1.2).

The microscopical structure of the retina was described in the 19th century, and by the end of the 20th century it was believed that its histological and functional characteristics was largely recognized. Then, the discovery of intrinsically photosensitive ganglion cells, a novel class of retinal photoreceptors, which express melanopsin, are sensitive to short-wavelength blue light and project throughout the brain, have presented a completely unknown area of retina-brain possible interactions [16, 17]. It is quite clear today that other cellular components of the retina, namely amacrine cells, bipolar cells and microglial cells, although somehow neglected in the past, play important functions both in physiology and pathology of the retina. For example, it was recently proposed that microglia might accelerate damage wrought by retinitis pigmentosa and that they might provide a target for entirely new therapeutic strategies [18].

One of the major developments in recent years in retinal imaging was the introduction of optical coherence tomography (OCT). OCT was firstly reported by Huang et al. in 1991 [19]. In vivo studies were first reported in 1993 [20, 21], and in 1995 imaging of the normal retina [22] and macular pathology [23] was presented. OCT delivers high-resolution cross-sectional or 3-dimensional images of the retinal and choroid structures, which are generated by an optical beam scanned across the


principes d'Optique, dont nous nous sommes servis d'abord.

Lorsqu'un œil bien conformé

est dans l'air, les rayons qui

partent d'un point comme D de

son fond, ayant passé par les

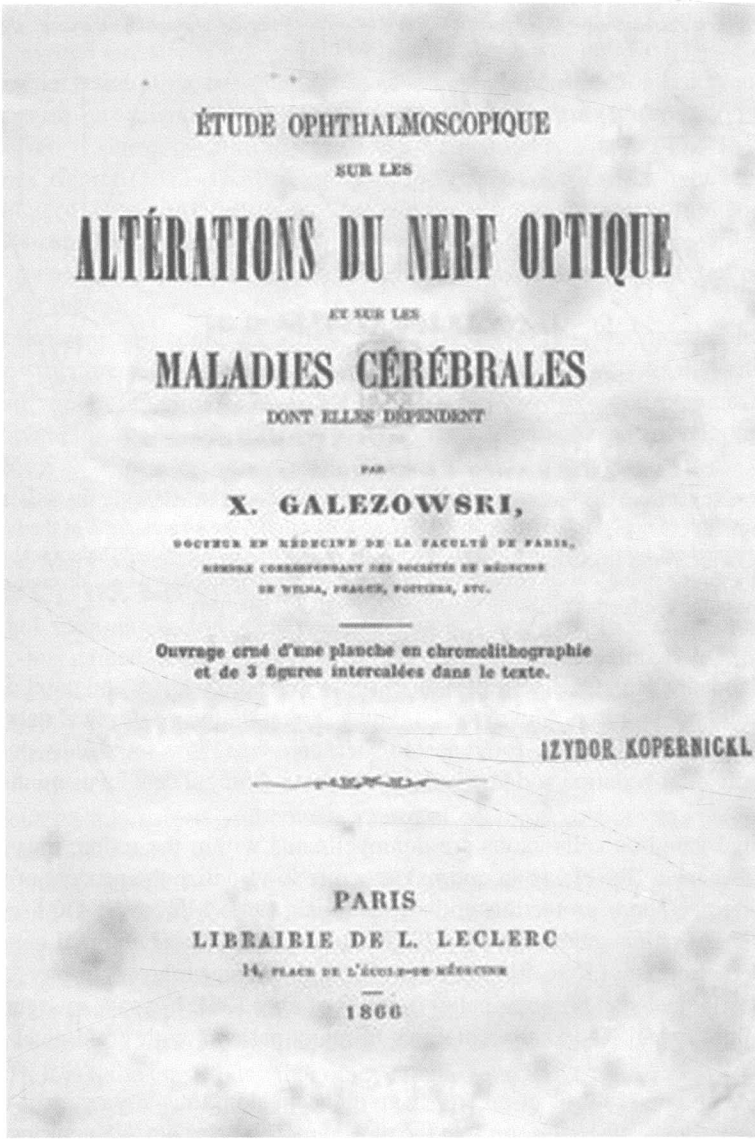
trois surfaces de ses humeurs

Fig. 1.1 Extract from the Proceedings of the Royal Academy of Sciences for the year 1709 — Session of 20th March 1709. By this diagram, La Hire explains the visualization of the fundus of the submerged cat by the fact that the surface of the water having abolished the corneal dioptric power, the rays coming out of the eye would no longer be parallel, but would diverge and that would make the eye fundus visible to the observer (Source: Heitz [9])

retina (and choroid). OCT testing is quick, easy and noninvasive, and pupil dilation is typically not required. Moreover, OCT yields quantitative anatomical data and is related with low variation for repeated measurements, low intra-individual and inter-individual variation and low variability across different centers using the same device.

Retinal ganglion cells axons are nonmyelinated within the retina, thus retinal nerve fiber layer (RNFL) is an optimal structure to visualize the process of neurodegeneration, neuro-protection and neuro-repair [24]. Moreover, OCT enables evaluation of retinal ganglion cells (RGC). For example, it was reported in patients with MS a dropout of RGC in 79 % of eyes and inner nuclear layer atrophy (including amacrine cells and bipolar cells) in 40 % of eyes [25]. It was also argued that OCT might reveal RNFL abnormalities in many patients with no clinical symptoms [26].

Retina and optic nerve originates from diencephalon, thus are a part of central nervous system (CNS). RGC present the typical morphology of CNS neurons. Optic nerve, like all fiber tracts in CNS, is covered with myelin and is unsheathed in all three meningeal layers. Insult to the optic nerve, similar to CNS, lead to retrograde and anterograde degeneration of damaged axons [27]. Because of these many similarities, it has not been very surprising that many CNS diseases can be also detected on the retina level. They include multiple sclerosis, Alzheimer disease, Parkinson disease, and many others. Moreover, it was shown that there are some common degenerative mechanisms between Alzheimer disease and eye diseases, like glaucoma and age-related macular degeneration [28]. Thus, the aim of this book is to present and review all aspects of OCT retina studies in CNS diseases.


ÉTUDE OPHTHALMOSCOPIQUE

SUR LES

ALTÉRATIONS DU NERF OPTIQUE

ET SUR LES

MALADIES CÉRÉBRALES

DONT ELLES DÉPENDENT

PAR

X. GALEZOWSKI,

DOCTEUR EN MÉDECINE DE LA FACULTÉ DE PARIS,

MEMBRE CORRESPONDANT DES SOCIÉTÉS DE MÉDECINE

DE WILNA, POSNANIE, POITIERS, ETC.

Ouvrage orné d'une planche en chromolithographie
et de 3 figures intercalées dans le texte.

IZYDOR KOPERNICKI

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LIBRAIRIE DE L. LECLERC

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1866

Fig. 1.2 Cover page of the book "Etude ophtalmoscopique sur les altérations du nerf optique et les maladies cérébrales dont elles dépenden " (By Xavery Gałęzowski, Paris, 1866)

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Chapter 2
OCT Technique – Past, Present and Future

Tigran Kostanyan, Gadi Wollstein, and Joel S. Schuman

Abstract Optical coherence tomography (OCT) has become the cornerstone technology in clinical and research imaging in the past two decades. OCT performs in vivo, real-time, noncontact scanning and provides cross-sectional and volumetric images with a resolution approaching that of histology. The technology is used in various medical disciplines, but it is still most profoundly used in the field of ophthalmology where it was initially applied. OCT is continuously evolving with newly developed applications.

This chapter will describe the basic principles of OCT techniques, its history, current status, and major ophthalmic applications and research that will determine the future of the technology.

Keywords Time domain (TD-) OCT • Spectral domain (SD-) OCT • Swept source (SS-) OCT • Polarization sensitive (PS-) OCT • Adaptive optics (AO) • OCT blood flow

Abbreviations

OCT	Optical coherence tomography
RNFL	Retinal nerve fiber layer
TD	Time-domain

T. Kostanyan, MD
Department of Ophthalmology, University of Pittsburgh School of Medicine, UPMC Eye Center, Eye and Ear Institute, Ophthalmology and Visual Science Research Center, Pittsburgh, PA 15213, USA

G. Wollstein, MD • J.S. Schuman, MD (✉)
Department of Ophthalmology, University of Pittsburgh School of Medicine, UPMC Eye Center, Eye and Ear Institute, Ophthalmology and Visual Science Research Center, Pittsburgh, PA 15213, USA

Department of Bioengineering, Swanson School of Engineering, University of Pittsburgh, Pittsburgh, PA 15213, USA
e-mail: schumanjs@upmc.edu

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SD	Spectral domain
FD	Fourier domain
SS	Swept source
AO	Adaptive optics
PS	Polarization sensitive
2D	Two-dimensional
3D	Three-dimensional
CCD	Charge-coupled device
ONH	Optic nerve head
ILM	Internal limiting membrane
IS	Inner segment
OS	Outer segment
RPE	Retinal pigment epithelium
LC	Lamina cribrosa
RGC	Retinal ganglion cell
IPL	Inner plexiform layer
GCC	Ganglion cell complex
EDI	Enhanced depth imaging

2.1 Introduction

Optical coherence tomography (OCT) is a diagnostic imaging technology that has gained a leading position in research and clinical practice due to its ability to obtain noncontact, in vivo, high-resolution, micron-scale images of tissue structures. OCT makes *in situ* imaging of tissue microstructure possible with a resolution approaching that of light microscopy histology without the need for tissue excision and processing, referred to as *optical biopsy* [1].

The technology uses the principle of low-coherence interferometry, which was originally applied to ophthalmology for in vivo measurements of the axial length of the eye [2]. OCT has been used to visualize various types of biological tissue [1, 3–9], but it is most profoundly used in ophthalmology due to the almost perfect optical accessibility of the eye.

At the time of introduction, the technology was used to acquire in vivo cross-sectional images of the anterior segment [10], as well as retinal pathologies such as macular edema, epiretinal membranes, macular holes, macular detachment, and idiopathic central serous chorioretinopathy [11]. Optic disc and retinal nerve fiber layer (RNFL) measurements were obtained with OCT shortly afterward [12–14].

OCT has evolved significantly, with improvements in both imaging method and image analysis. The evolution of OCT began with the time domain (TD) technique, followed by spectral domain (SD) and later newer iterations with faster scanning aquisition speeds [15–17] and higher axial resolution [18, 19].

This chapter will describe the basic principles of OCT techniques, its history, current status, and major ophthalmic applications and research that will determine the future of the technology.

2.2 Basic Principles

OCT provides cross-sectional and volumetric images of areas of interest by acquiring either the echo time delay or frequency information of back-reflected light. Differences in the optical properties of biological tissues allow the recognition of layered structures. The speed of light makes it impossible to analyze the acquired information directly, since it would be in the order of femtoseconds, thus OCT systems use the optical technique known as *interferometry*. Low-coherence interferometry enables analysis of this information and the creation of a depth-resolved reflectivity profile (A-scan) of the scanned tissue by matching the light profiles from the scanning and reference arms.

Utilization of light provides OCT technology the ability to obtain images in a non-contact fashion and to achieve resolutions of 1–15 μm, which is one to two orders of magnitude finer than other conventional clinical imaging technologies such as ultrasound, computerized tomography, or magnetic resonance. Light is highly absorbed or scattered in most biological tissues, and therefore the use of this technology is limited only to locations that are optically accessible or that can be imaged using devices such as endoscopes or catheters.

OCT technique can be classified into two major groups: TD and Fourier (or frequency) domain (FD). FD can be further classified into spectral-domain (SD) and swept-source (SS) techniques. In TD-OCT, a broad-bandwidth laser or a low-coherence superluminescent diode light source projects light that is then divided into two arms by a partially reflecting mirror (beam splitter). In the first arm light is projected toward the sampling location, while in the second arm light is projected toward a moving reference mirror at a known position. The backscattered light from both sites travel back to a detector and recombine to form an interference pattern, which is sensed by the interferometer. The interference is only observed when both the sample and the reference arm light beams travel the same distance [12]. Changing the position of the reference mirror allows the machine to sequentially acquire information from different depths in the tissue sample. A cross-sectional image, also known as a B-scan, is generated by performing fast, subsequent axial scans (A-scans) at different transverse positions. Each axial scan represents the echo time delay of back-reflected light from the tissue and gives a profile of the tissue's dimensions along the optical beam. The scanning speed of TD-OCT technology is limited to 400 axial scans/sec, due to the maximal oscillating speed of the reference mirror [20].

SD-OCT is similar in principle, but the data acquisition varies slightly, yet fundamentally, from TD-OCT. The main difference of this iteration is the use of light frequency information instead of time delay data to determine the spatial location of reflected light. SD technology utilizes the Fourier transformation of the reflected light frequencies to encode distances within tissue microstructure [21]. Instead of a moving reference mirror, the mirror is stationary and the interference signal is split into its frequency components using a diffraction grating. The signal is simultaneously detected by a charge-coupled device (CCD). The CCD has an array of photodetectors that are each sensitive to a range of specific frequencies [22, 23].

SD technology allows the acquisition of information from all points along each A-scan simultaneously, substantially increasing scan speed to the range of ~25,000–

75,000 axial scans/sec in the commercially available systems [24, 25] and up to 20.8 million axial scans/sec in research devices [16]. The substantial increase in scanning speed allows for the acquisition of three-dimensional (3D) data sets, which is done by combining rapidly acquired subsequent cross-sectional scans. The wide bandwidth of the light source also enables a substantial enhancement in axial resolution up to 1 μm [26, 27] and an improved signal-to-noise ratio [28].

SS-OCT is a form of Fourier domain technology that uses a single tunable laser that sweeps through different frequencies to rapidly cover the entire broad spectrum. The reflectance of the light from the scanned area is captured by a photodetector, which is much faster than the CCD camera used in SD-OCT technology [17, 29]. This allows the SS technology to further enhance the scanning speed up to 400,000 axial scans/sec. Another important advantage of this iteration of OCT technology is the absence of the depth dependent signal drop-off observed with SD-OCT technology [30]. Most SS-OCT devices operate with light sources centered at around 1030 μm (compared with 840 μm in the commercially available TD- and SD-OCT), which reduces the axial resolution to approximately 8 μm but allows for better penetration of the tissue. The combination of improved tissue penetration and reduced signal attenuation allow detailed scanning of structures such as the choroid and the lamina cribrosa inside the optic nerve head. The major characteristics of these three different OCT techniques are presented in Table 2.1.

The key technological parameters that are typically used to characterize OCT technology are the wavelength of the light source, axial or longitudinal resolution,

Table 2.1 Comparison of TD-, SD-, and SS-OCT technologies

Technology	Light source	Ophthalmic device commercially available	Primary advantages	Primary disadvantages
TD-OCT	Relatively narrow band width	Yes	Intensity information acquired in time domain; no complex conjugate image	Moving reference mirror required, limiting acquisition rate
SD-OCT	Broadband width	Yes	No moving reference mirror required; higher resolution than TD-OCT; high scanning speed and axial resolution can be attained	Noticeable signal drop-off with depth
SS-OCT	Narrow band, swept through broad range	Yes	No moving reference mirror required; very high scanning speeds can be attained; minimal signal drop-off with depth	Most ophthalmic systems are operating at longer wave lengths ($\lambda = 1–1.3$ μm) with lower axial resolution than SD-OCT but with improved penetration into structures

lateral or transverse resolution, scanning speed, and imaging depth. The wavelength is inversely related to the axial resolution of the acquired images, with longer wavelength providing lower resolution compared with shorter wavelength.

Axial resolution determines the smallest distance along the axial direction where two adjacent points are discernable, and it is related to the bandwidth or the coherence-length of the source. In posterior segment eye imaging, the light should travel through transparent media, which mostly contains water that absorbs infrared radiation. This limits the technology to the use of light sources of only certain wavelength. Current commercial OCT devices achieve axial resolutions up to 4 μm, and research systems achieve up to ~ 1–2 μm [19].

Transverse resolution is independent of the coherence properties of the light source, and is determined by the spot size, which is limited by the optics of the scanned system. As such, the transverse resolution of OCT among the different generations is within a range of 15–20 μm. Improving the transverse resolution requires the correction of the optical aberrations of the eyes using technologies such as adaptive optics.

Scanning speed is dictated by mechanical constrains such as the maximal oscillating rate of the reference arm (TD-OCT) and the sensitivity of the detector to the back-reflected light. As scanning speed increases, the time the detector remains in the same location is shorter, thus reducing the light that can be detected in each location. Since the power of the projected light is limited in order to be within safety limits, faster scans require a more sensitive detector that can function with a lower level of light.

The imaging depth in TD technology is given by the reference arm's range of movement, while in SD technology it is related to the center wavelength. Longer wavelengths provide increased imaging depth [31, 32], but the use of longer wavelengths for imaging depth improvement is limited by the increased optical absorption of water [33].

2.3 The Past

OCT technology was first described by Huang and colleagues in 1991 [34]. The authors scanned human retinas and atherosclerotic plaques ex vivo with a prototype device using infrared light at a ~ 800-nm wavelength. The axial resolution of cross-sectional images of the retina, optic nerve, and coronary artery wall was 15 μm, which allowed the visualization of some retinal layers, optic nerve head structures, and the composition of the coronary artery. In vivo retinal scanning was conducted using a prototype device based on a slit-lamp biomicroscope that was modified to provide a view of the fundus while scanning with OCT. The development of scan patterns that enabled the acquisition of reproducible measurements [35] led to the use of the technology in clinical practice.

The first commercially available OCT, called OCT 1000, was marketed in 1996 by Zeiss (Dublin, CA). The technology went through two iterations, resulting in OCT 2000 in the year 2000 and then OCT three (Stratus OCT), which became commercially available in 2002. The Stratus OCT had an axial resolution of ~10 μm, a

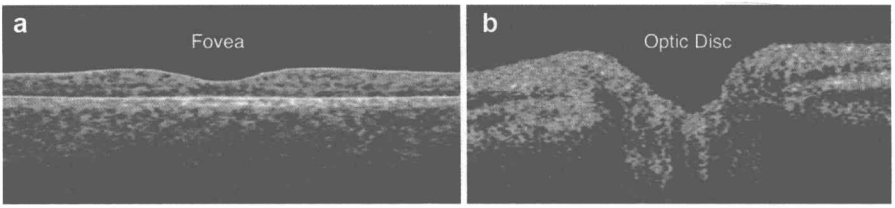

Fig. 2.1 OCT image of a healthy fovea (**a**) and optic disc (**b**). Images were obtained using TD technology and have an axial resolution of ~10 μm

transverse resolution of 20 μm, and a scan speed of 400 axial scans/sec [1, 12]. The typical cross-sectional scan was composed of 128–512 axial scans, comprising an image area of 4–6 mm.

Due to its ability to obtain quantitative and reproducible measurements of the macula [36, 37], retinal nerve fiber layer thickness [35, 38], and optic nerve head [39, 40], TD-OCT technology became the gold standard in-vivo clinical imaging device for posterior segment pathologies in a relatively short period of time. Figure 2.1 shows an example of a cross-sectional scan of the macula and the ONH of a healthy eye obtained with TD technology (Stratus OCT).

The most routine scan patterns used with TD-OCT were a scan comprises of six equally spaced radial scans through the macula (6 mm diameter) and optic nerve (4 mm) and a circular scan with a diameter of 3.4 mm centered on the optic nerve head (ONH). Using automated segmentation, the macular thickness (internal limiting membrane (ILM) to the photoreceptor inner segment-outer segment (IS–OS) junction) can be quantified from the macular scan pattern, and the retinal nerve fiber layer (RNFL) thickness measurements can be quantified from the circumpapillary scan. Cup area, disc area, cup diameter, disc diameter, and rim area are provided after the software detects the ONH margin, allowing quantification of the ONH.

Several improvements in OCT hardware have been introduced since the first commercial TD-OCT system became available. Better axial resolution [26, 27] and increased scanning speed [22, 41] are the two main advancements that were incorporated into the commercial systems. Ultra-high resolution OCT retinal imaging that used specially designed broadband light sources was introduced in 2001 [42]. This OCT device had an axial resolution of ~3 μm, which was markedly better than the 10 μm axial resolution provided by the commercial devices at that time [42, 43]. Further improvements in OCT technology lead to the introduction of SD-OCT (discussed in detail in the next section) which had a faster scanning speed and better resolution than TD-OCT. This can be easily appreciated by comparing Figs. 2.1 and 2.2, in which the same healthy eye was scanned with TD- and SD-OCT, respectively.

In addition to acquiring tissue structural information, OCT has been incorporated into multimodal imaging systems that provide further insight into the functional characteristics of tissue [44–50].