Venturing Into the No-man’s Land of the Retina in Parkinson’s Disease

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ABSTRACT: The development of optical coherence tomography (OCT) has led to increasing interest in the retina in Parkinson’s disease (PD). The retina is a multilayered tissue: looking into the eye from the outside, these layers comprise the nerve fiber layer (NFL); the ganglion cell layer (GCL); the inner plexiform layer (IPL), which contains the interconnecting plexus, including tyrosine hydroxylase-positive (dopaminergic) fibers of amacrine cells; the inner nuclear layer; and several outer retinal layers. Commercial spectral-domain OCT has a specific program for detecting peripapillary NFL defects and a different macular program for diabetic retinopathy. Specific programs for PD are not commercially available. Taking all studies together, it seems that macular programs have a higher diagnostic yield than NFL programs, but the numbers of studies and examined patients are relatively small. It is not certain that all retinal thinning in PD is due to dopaminergic neuronal loss. When applying OCT, the where (region of interest) and the what of the focus of automated programs must be considered. With these caveats, one could take advantage of the power of OCT for looking in-depth into the terra incognita of individual retinal layers at the fovea and perhaps at other appropriate retinal locations.

Key Words: Parkinson’s disease; optical coherence tomography; macula; foveola; retinal nerve fiber layer

Introduction to Optical Coherence Tomography

Over the last decade, a search for easily available, inexpensive, noninvasive markers for the diagnosis and the quantification of progression and response to therapy in Parkinson’s disease (PD) has markedly accelerated. Besides the brain, current interest also focuses on imaging of the retina. Over decades of research, electrophysiological and psychophysical evidence has accumulated on the retinopathy of PD.1 The evidence was strengthened by studies in animal models. However, in vivo human morphological evidence has only recently emerged. This was made possible by the development of a new imaging modality called optical coherence tomography (OCT).2

Galileo named the microscope he used to examine biological tissues “occhiolino” (little eye).3 However, it took over 200 years before microscopic imaging was applied to the eye itself. The development of the ophthalmoscope (from around 1850) allowed clinicians to diagnose ailments that could be seen on the surface of the retina of the eye itself (Fig. 1).4 Ophthalmoscopic evaluation became standard in ophthalmology and also in neurology. Dr. William Cumming in 18465 at the Royal London Ophthalmic Hospital wrote, ‘Every eye could be made luminous if the axis from a source of illumination directed towards a person’s eye and the line of vision of the observer were coincident.” When one looks through the ophthalmoscope, the illuminated surface reflects light; and, depending on differences in the tissue composition and density, the light creates signals in the observer’s retina that ultimately are coded by the brain as an image. Using ophthalmoscopy, spatial contrast differences in
luminance are detected in neighboring areas of the retina. What is examined through the lens of the ophthalmoscope is restricted to what is visible on the surface of the retina: the capillaries and the retinal axons of the optic nerve (the nerve fiber layer [NFL]) coursing from the central-most retinal area, to the foveola, to the optic disc (papilla). Occasionally, when the retina is thinned, the back layer of the pigment epithelium can be observed through the other neural layers.1,7,8 Pathology of the retina is observed in forms of vascular changes (attenuation, dilatation, aneurysmal, and neovascular), lipid exudates, and hemorrhages. However, the retina is a multilayered neural tissue. The layers of the retina, from the outside looking into the eye, are the NFL; the ganglion cell layer (GCL); the inner plexiform layer (IPL), which contains a rich network of fibers; the inner nuclear layer (INL); the outer plexiform layer (OPL); the outer nuclear layer (ONL); the photoreceptors; and the pigment epithelium (Fig. 2).8 The IPL also contains a plexus of tyrosine hydroxylase-positive (dopaminergic) fibers of amacrine cells and other processes.

Individual retinal layers largely remained unseen by ophthalmoscopy, and the layers interposed between the photoreceptors and the ganglion cells were a terra incognita for clinical diagnosis. As a result, for diseases that could selectively affect vulnerable neuronal types located in different layers below the surface in the retina, clinical ophthalmoscopy was unrewarding. What we knew of the pathological processes that target different neurons, dendrites, and axons in layers of the retina emerged from scarce postmortem studies.10

However, in the last decades, imaging techniques found their way into in vivo human retinal studies. One of these, optical coherence tomography (OCT), was introduced in 1991 by Huang and colleagues.11 OCT allows a penetrating look into all retinal layers. An infrared light is shone into the eye, and the ingoing beam gets reflected differently at different retinal layers. The principle of this type of imaging is not unlike that of magnetic resonance imaging and ultrasound imaging. The reflected light energy is quantified in small voxels. Differences in refraction properties are sensed by the instrument, the depth from which they are reflected is quantified, and the differences are color coded and reconstructed as boundaries between neural layers of the retina.12,13

OCT in PD

Commercial spectral-domain OCT with higher spatial and temporal resolution than time-domain OCT14 comes with specific programs for detecting glaucomatous damage and with a different macular program for diabetic retinopathy. Programs specifically geared for detecting PD are not commercially available.

Most OCT studies in PD concentrated on the quantification of the NFL (Table 1). This approach is common in glaucoma. Other studies focused on the macula (Table 2). The macula includes the smaller area of the fovea. In this review, first, macula and NFL studies are considered separately. Some studies also compared their diagnostic yield. A few studies also correlated OCT yield and disease severity with OCT results and visual impairment.

In 2004, Inzelberg et al.15 first reported that the NFL was thinned in PD compared with controls. Since then, several (albeit not all) studies that also used newer, higher resolution (spectral-domain) OCT equipment have confirmed the original report of NFL thinning. Macular quantification appears to have a higher diagnostic yield than NFL quantification, as summarized below. Some studies subdivided the retina into four segments and compared the diagnostic yield for each.

For detecting diabetic maculopathy, commercial OCT programs quantify the volume of retinal tissue...
centered on the fovea, which is not included in the peripapillary NFL program for glaucoma. We summarize the diagnostic yield in different quadrants both for the peripapillary NFL thickness and for the macula. The rationale for a subdivision is rarely stated; however, we know that the optic nerve axonal layer from the foveal area into the optic disc area is not homogenous because of the papillomacular bundle (Fig. 3). OCT equipment automatically divides the 5-mm-diameter macular surface into three concentric areas using the so-called early treatment diabetic neuropathy study protocol. Finally, by obtaining depth values in a foveola-centered matrix, both distance and direction can be quantified.5,30,32,33

Peripapillary Retinal NFL

Thinned retinal NFL (RNFL) thickness was compared between patients with PD and controls in several studies,16,17,22–29 but not in all studies (Table 1).18–21 It is noteworthy that Archibald et al.19 attributed their negative results to the advanced age of their patients (both PD and controls) compared with other studies and the advanced disease in their patients with PD. However, aged controls may also have undetected ophthalmological pathology. Incomplete detailed ophthalmological assessments of the control group may affect normative values. In addition, there are sensitivity differences between OCT equipment, for instance, between Cirrus (Carl Zeiss Meditec, Jena, Germany) and Spectralis (Heidelberg Engineering, Inc., Carlsbad, CA, USA).22,28

Another cause of negative results may be selecting both eyes in patients with PD. Shrier et al.5 reported an interocular asymmetry in PD patients’ retinas. La Morgia et al.27 reported that RNFL thinning was more evident in the eye contralateral to the most affected body side. Cubo et al.31 reported a thinner fovea in the eye contralateral to the tremor-dominant side of the body in patients with PD. By selecting eyes randomly, one runs the risk of diluting diagnostic yield. Both eyes need to be studied.

### Four NFL Quadrants

The inferior and temporal15; superior, temporal, and inferior33; temporal15–17; and superior and nasal15 quadrants are reported as most affected in PD. Apparently, the temporal region is the most commonly identified (Table 1).

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#### TABLE 1. Investigations of retinal nerve fiber layer: PD and control comparison

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients size (no. of eyes)</th>
<th>Equipment</th>
<th>Results of comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inzelberg et al., 200415</td>
<td>PD, 10 (10); HC, 10 (10)</td>
<td>NM</td>
<td>PD had</td>
</tr>
<tr>
<td>Attinas et al., 200816</td>
<td>PD, 17 (34); HC, 11 (22)</td>
<td>Zeiss 3000 unit</td>
<td>PD had</td>
</tr>
<tr>
<td>Moschos et al., 201017</td>
<td>PD, 16 (32); HC, 20 (40)</td>
<td>Stratus</td>
<td>No mean RNFL thickness difference,</td>
</tr>
<tr>
<td>Aaker et al., 201018</td>
<td>PD, 9 (18); HC, 9 (16)</td>
<td>Spectralis</td>
<td>No RNFL thickness difference</td>
</tr>
<tr>
<td>Archibald et al., 201119</td>
<td>PD, 34 (66); HC, 18 (35)</td>
<td>Stratus</td>
<td>No RNFL thickness difference</td>
</tr>
<tr>
<td>Taitroni et al., 201220</td>
<td>PD, 24 (24); HC, 24 (24)</td>
<td>Stratus</td>
<td>No RNFL thickness difference</td>
</tr>
<tr>
<td>Albrecht et al., 201221</td>
<td>PD, 40 (80); HC, 35 (70)</td>
<td>Spectralis</td>
<td>No RNFL thickness difference</td>
</tr>
<tr>
<td>Garcia-Martin et al., 201222</td>
<td>PD, 75; HC, 75</td>
<td>Spectralis</td>
<td>PD had</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spectralis more sensitive</td>
</tr>
<tr>
<td>Rohani et al., 201223</td>
<td>PD, 27 (54); HC, 27 (50)</td>
<td>TOPCON 3D OCT</td>
<td>PD had</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>inf and nasal quads more in aki-</td>
</tr>
<tr>
<td>Kirbas et al., 201324</td>
<td>PD, 42 (84); HC, 40 (80)</td>
<td>Cirrus</td>
<td>PD had</td>
</tr>
<tr>
<td>Garcia-Martin et al. 201325</td>
<td>PD, 46 (46); HC, 33 (33)</td>
<td>Cirrus and Spectralis</td>
<td>PD had</td>
</tr>
<tr>
<td>Sen et al., 201326</td>
<td>PD, 35; HC, 11</td>
<td>NM</td>
<td>PD had</td>
</tr>
<tr>
<td>La Morgia et al., 201327</td>
<td>PD, 43 (86); HC, 86 (86)</td>
<td>Stratus</td>
<td>No mean RNFL thickness difference,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satue et al., 201328</td>
<td>PD, 100; HC, 100</td>
<td>Cirrus and Spectralis</td>
<td>PD had</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moreno-Ramos et al., 20129</td>
<td>PD, 10; HC, 10</td>
<td>NM</td>
<td>PD with dementia had</td>
</tr>
</tbody>
</table>

*More sensitive equipment.*

PD, Parkinson’s disease; HC, healthy controls; NM, not mentioned in the abstract; |, significant decrease in thickness; RNFL, retinal nerve fiber layer; inf, inferior quadrant; temp, temporal quadrant; quad, quadrant; sup, superior quadrant; 3D, three-dimensional; OCT, optical coherence tomography; inferotemp, infero- temporal; supratemp, supratemporal.
The Macula in PD

Altintas et al. observed thinning in the superior inner retina and in the temporal, nasal, and inferior outer retina. Hajee et al. observed thinning in the superior and inferior parts of the inner retinal layer (IRL) and in the central 5-mm quadrant of the macula and observed no change in the outer retinal layer.

Rather than averaging IRL thickness over an extended region, Adam et al. reported a thinner IRL in an annular zone at a distance of 1.00 to 1.75 mm from the foveal pit. The maximum thickness difference was 17 μm, and the average difference was 12 microns. Those authors suggested that loss of dopaminergic amacrine cells may not be the only cause of IRL thinning in PD.

Compared with full (inner and outer) retinal thickness (roughly 300 microns), a 12-micron difference is a paltry 4%. However, comparing the thickness of approximately 80 microns of the inner retina at a distance of 1.5 mm, a 12-micron tissue loss in the affected layer is approximately 15%, suggesting considerable damage. By specifying the region of interest, 78% of eyes in patients with PD were discriminated as true-positives.

Foveolar center thickness mostly represents the thickness of the photoreceptors, whereas the inner layers only slowly emerge on the slope of the pit. Spund et al. identified thinning on the slope of the

TABLE 2. Investigations of macular thickness: PD and control comparison

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients (no. of eyes)</th>
<th>Equipment</th>
<th>Main results of the comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altinas et al., 200816</td>
<td>PD, 17 (34); HC, 11 (22)</td>
<td>Zeiss 3000 unit</td>
<td>PD had ↓sup IRL; ↓temp, nasal, inf ORL; no foveal difference</td>
</tr>
<tr>
<td>Hajee et al., 200930</td>
<td>PD, 24 (45); HC, 17 (31)</td>
<td>RTVue100</td>
<td>PD had ↓IRL in sup and inf quads; no change in ORL</td>
</tr>
<tr>
<td>Aaker et al., 201018</td>
<td>PD, 9 (18); HC, 9 (16)</td>
<td>Spectralis</td>
<td>No difference in IRL thickness; compared with published normal values, PD had ↓ORL sup; ↑ORL nasal; ↑IRL inf quad</td>
</tr>
<tr>
<td>Cubo et al., 201031</td>
<td>PD, 9 (18); HC, 9 (18)</td>
<td>OCT3 Zeiss</td>
<td>PD had ↓fovea; thinner fovea in the contralateral eye to tremor dominant side</td>
</tr>
<tr>
<td>Archibald et al., 201119</td>
<td>PD, 34 (63); HC, 19 (33)</td>
<td>Stratus</td>
<td>No difference in foveal thickness or macular volume</td>
</tr>
<tr>
<td>Albrecht et al., 201221</td>
<td>PD, 40 (80); HC, 35 (70)</td>
<td>Spectralis</td>
<td>PD had ↓INL, especially in temp quad; no difference in other layers</td>
</tr>
<tr>
<td>Shrier et al., 20125</td>
<td>PD, 23 (26); HC, 18 (36)</td>
<td>RTVue100</td>
<td>PD had ↓macular volume at 0.5-0.75 mm from the foveola; IOA in IRL</td>
</tr>
<tr>
<td>Adam et al., 201332</td>
<td>PD, 14 (28); HC, 14 (28)</td>
<td>RTVue100</td>
<td>PD had ↓IRL at radial distances (1-1.75 mm) from the foveola, especially sup quad</td>
</tr>
<tr>
<td>Spund et al., 201333</td>
<td>PD, 30 (50); HC, 27 (50)</td>
<td>RTVue100</td>
<td>PD had ↓IRL at 1-2 mm distances from the foveola</td>
</tr>
<tr>
<td>Garcia-Martin et al., 201325</td>
<td>PD, 46 (46); HC, 33 (33)</td>
<td>Cirrus and Spectralis</td>
<td>PD had ↓fovea, IRL all quads; ↑inf ORL (Cirrus); ↑sup, nasal ORL (Spectralis)</td>
</tr>
<tr>
<td>Satue et al., 201328</td>
<td>PD, 100; HC, 100</td>
<td>Cirrus and Spectralis</td>
<td>PD had ↓mean macular, fovea, ORL inf quad</td>
</tr>
<tr>
<td>Lee et al., 201334</td>
<td>PD, 56; HC, 30</td>
<td>OPKO and OTI Spectral</td>
<td>PD had ↓parafoveal INL, no difference in other layers</td>
</tr>
</tbody>
</table>

PD, Parkinson's disease; HC, healthy controls; ↓, significant decrease in thickness; sup, superior quadrant; IRL, inner retinal layer; temp, temporal quadrant; inf, inferior quadrant; ORL, outer retinal layer; ↑, significant increase in thickness; quad, quadrant; INL, inner nuclear layer; IOA, interocular asymmetry.
foveal pit. Hence, quantifying thinning at a certain perifoveolar distance allowed Spund et al.\textsuperscript{33} to identify the IPL with a fair amount of security. Dopaminergic amacrine neurons are located at the border between the INL and the IPL. The resolution of OCT is about 5 microns, which is insufficient for identifying diverse cell types. Nevertheless, the results reported by Spund et al.\textsuperscript{33} account for the potential pathology of dopaminergic amacrine neurons and their processes.

Decreased macular thickness or volume loss was reported\textsuperscript{5,21,25,28,31,34} mostly because of IRL thinning,\textsuperscript{16,21,30,32–34} because it was demonstrated that the outer retina was not thinned in PD.\textsuperscript{21,30,32,34} Macular thinning was not found in two studies.\textsuperscript{18,19}

### Functional Correlates of Inner Foveal Thinning in PD

The fovea is a tiny area of the retina, but it is easily seen in histological preparations and on OCT images: it is a pit with raised edges. Its thickness and volume change sharply with distance from the fovea. In the center of the pit is the highest density of photoreceptors and neuronal machinery, which is most sensitive to spatial contrast and color differences. Foveal photoreceptors interconnect through the layers of the retina under the modulating effect of diverse types of neurons to the ganglion cells, and they connect to the brain via the NFL.\textsuperscript{35,36} The visual loss in PD is most often demonstrated for contrast sensitivity and color vision, which rely on foveal neuronal processing.\textsuperscript{1,32} Should these deficits originate in the retina, then reduced macular volume should detect differences between PD eyes and control eyes. Total macular volume, as calculated by OCT equipment programs, includes both the inner and outer retina. However, in the foveal center, there is little inner retinal tissue, and the outer retina is unaffected in PD.\textsuperscript{33} Hence, detecting macular volume loss in PD is difficult. Nevertheless, some OCT studies did find a loss of macular volume by restricting the analysis to an annular zone surrounding the foveola where both inner and outer retina participate in total thickness.\textsuperscript{19}

### Comparing the Diagnostic Yield in Four Quadrants of the Peripapillary NFL and Macula

#### RNFL

More than two-thirds of studies (11 of 15) revealed a significant thinning of the RNFL in patients with PD.\textsuperscript{15–17,22–29} Two studies reported thinning in all quadrants,\textsuperscript{22,23} eight of 11 studies reported a mostly thinned temporal RNFL,\textsuperscript{15,17,22–25,27,28} and two studies reported thinning only in this quadrant.\textsuperscript{22,25} Nasal thinning was detected in only three studies.\textsuperscript{16,22,23}

#### Macula

The center of the pit mostly contains photoreceptors. The contribution of the IRL to thickness rapidly increases with distance from the foveola. Most studies did not observe any decrease in thickness of the very center of the foveal segment in PD.\textsuperscript{16,19,21} The IRL starts appearing on the slope of the pit at about 0.75 mm away from the center.\textsuperscript{5,32} The GCL, IPL, and INL constitute the IRL, which is reported as thinned in most studies.\textsuperscript{21,25,30,32–34} Therefore, focusing specifically on the macular IRL may be diagnostically helpful. A recent segmentation method quantifies all retinal layers\textsuperscript{2} but has not been used clinically. Studies subdivide the thickness in nasal, temporal, superior, and inferior segments and quantify retinal thickness in these “pies” by calculating the averages in segments; however, this calculation misses the effect of radial distance from the foveola.

One method relies on quantifying thickness in small voxels that cover a cube ≤ 5 mm, specifying radial distances from the foveola in steps of 0.25 mm.\textsuperscript{5,32,33} This method of defining thickness at different distances from the fovea increases diagnostic yield.

The parafoveal area 1 to 2 mm from the foveola may be the most probable region affected by PD.\textsuperscript{32–34} The parafoveal superior and inferior quadrants\textsuperscript{16,30,32} and the temporal quadrant\textsuperscript{21} of the macula are thinnest in PD.

### OCT and PD Severity

Altintas et al.\textsuperscript{16} reported a correlation between IRL thickness and disease severity in PD according to the Unified Parkinson’s Disease Rating Scale (UPDRS). Garcia-Martin et al.\textsuperscript{23} reported a negative correlation of the NFL and full macular volume with the Hoehn and Yahr (H&Y) scale and a positive correlation with the Schwab and England Activities of Daily Living Scale (SE-ADL); and they proposed that foveal thickness may predict PD severity, quality of life, and lower SE-ADL scores.

Moreno-Ramos et al.\textsuperscript{29} reported a correlation \((P < 0.001)\) between RNFL thickness and scores on the Mini-Mental State Examination (MMSE) and the Mattis Dementia Rating Scale in dementia associated with PD. Lee et al.\textsuperscript{34} reported a thinner RNFL in patients who had PD with hallucinations. Garcia-Martin and colleagues\textsuperscript{22} reported no significant correlation between average RNFL thickness and MMSE scores in patients with PD. La Morgia et al.\textsuperscript{27} did not find a correlation between clinical parameters, including age at onset, disease duration, UPDRS motor score, stage of disease, and RNFL measurements.
Hajee et al.\textsuperscript{30} observed no difference in IRL thickness between treated and untreated patients, and Inzelberg et al.\textsuperscript{13} reported that RNFL thinning was not correlated with disease duration. Cubo et al.\textsuperscript{37} observed a severely thinned RNFL in patients who H\&Y stage 2 or greater PD compared with patients who had H\&Y stage 1 PD; however, no correlation was observed between RNFL thickness and age, disease duration, nonmotor symptoms, or Scopa motor scores. Most of those studies did not compare individual layers and/or segments with other measures.

**OCT and Vision**

The NFL, as mentioned above, represents the axons of the ganglion cells, which are the output neurons of the retina. Its thickness loss is often observed in optic neuropathies, such as glaucoma, ischemic optic neuropathy, and retrobulbar neuritis of multiple sclerosis.\textsuperscript{38–41} The OCT results fit in with a body of evidence of retinal involvement, which is revealed by decreased pattern electroretinography (ERG) responses in PD. The ERG pattern is abolished after optic nerve section.\textsuperscript{17,42}

In four of 15 studies,\textsuperscript{18–21} changes in peripapillary NFL thickness were observed in patients with PD. In addition, neither the ganglion cells (which give rise to the pattern ERG) nor their axons are dopaminergic. Dopaminergic amacrine cells are located at the interface of the INL and the IPL.\textsuperscript{1,2}

However, the ERG pattern in PD is specifically affected, and levodopa-responsive ERG alterations have been demonstrated in animal (including monkey) models of PD.\textsuperscript{43} In PD itself, a correlation between foveal thinning and an attenuation of the multifocal electroretinogram has been observed. Moschos et al.\textsuperscript{17} correlated multifocal ERG (mfERG) in the central retina in PD with OCT thinning. The mfERG technique provides a large array of stimulus elements, typically in a 20- to 30-degree field, and reflects both outer and inner retinal responses. However, it is the foveal inner retina that dominates the peak of the mf ERG response in the fovea.\textsuperscript{44}

When comparing central contrast sensitivity and OCT, Adam et al.\textsuperscript{32} reported that contrast sensitivity inversely correlates with IPL thickness. The correlation is evident in healthy controls. However, in PD, although the retina is thinned and the contrast sensitivity is attenuated, the individual correlation is weak. A remarkable correlation of retinal thinning with visual hallucinations was recently demonstrated by Lee et al.\textsuperscript{34}

Visual hallucinations are not uncommon in PD. Their presence has been attributed to dopaminergic therapy, the presence of Lewy body disease, metabolic causes, and many other possible cerebral causes. Some studies emphasize the role of impaired cortical processing in the extrastriate, frontal, and temporal cortices.\textsuperscript{45} However, over the last 10 years, some studies have emphasized that impaired visual input may be the necessary (albeit not sufficient) condition for visual hallucinations,\textsuperscript{46} known as the Charles Bonnet syndrome, for instance in patients with maculopathy.\textsuperscript{46} Diederich and colleagues suggest that visual hallucination should be considered as a dysregulation of the gating and filtering of external perception and internal image production.\textsuperscript{47}

**In Vivo Histology of the Retina in PD**

Some of the OCT studies by Hajee et al.\textsuperscript{30} and others, including the study by Lee et al.,\textsuperscript{34} emphasize the power of OCT to make the ophthalmoscopically invisible layers of the retina visible and quantifiable. There is resistance to this interpretation by some, because the images are created and not real. However, recreating histology from data is also fundamental to conventional microscopic imaging.

When light waves travel through a medium other than a vacuum, interaction with the medium causes the wave amplitude and phase to change in a manner dependent on properties of the medium. Changes in amplitude (brightness) arise from the scattering and absorption of light, which is often wavelength-dependent and may give rise to colors. A density difference creates retinal signals in the eye, and they are ultimately coded by the microscopists’ brain as an image.\textsuperscript{11} There is no photographic image corresponding to the examined tissue transmitted from the retina of the microscopist to his brain. The fact that reflected light signals, when appropriately coded by our retina and brain, represent real tissue is well exemplified by phase-contrast microscopy (Frits Zernike, the Nobel prize [physics] in 1953).\textsuperscript{13,48} Phase-contrast microscopy is an optical microscopy technique that converts phase shifts in light passing through a transparent specimen to brightness changes in the image. Phase shifts themselves are invisible, but they become visible when represented as brightness variations if appropriately coded with signals to which our eye is sensitive.\textsuperscript{49} However, phase-contrast microscopy has not been applied to clinical diagnosis. In that sense, OCT represents the next development in coding the invisible changes at refractive surfaces into layers of the retina.\textsuperscript{50}

Beyond its clinical practicality, OCT appears attractive because it may directly assess cellular damage in PD. Some comparative studies suggest the specificity of OCT in PD\textsuperscript{5,15–18,22–34} but this is not sufficiently established. Although the identification of diverse amacrine and other retinal cells is not yet possible, it has potential for development in the foreseeable future.
future. We are entering a new territory in research in neurodegenerative disorders by applying OCT.

Quantifying the layers of the retina in PD raises the hope of developing a useful in vivo marker for the disease. OCT is inexpensive and widely available. It is a noninvasive test that may take up only a few minutes per eye. For establishing OCT as a true biomarker of PD, however, we need to establish whether retinal thinning parallels disease progression. The available data are contradictory; however, for seeking such a correlation, one should focus on a particular retinal layer. We also know little about the effects of dopaminergic therapy on retinal thinning. Does dopaminergic therapy influence specific retinal layers in PD?

Conclusions

As most imaging studies do, OCT yields masses of data. What the studies by Hajee et al., Spund et al., and now Lee et al. show is that, when applying OCT, the where (region of interest) and the what of the focus of automated programs must be considered. With these caveats, one could take advantage of the power of OCT for looking in-depth into the terra incognita of individual retinal layers at the fovea and perhaps at other appropriate retinal locations.

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