Integrity of Foveal Cones in Early Age-related Macular Degeneration

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Abstract

In this article, we highlight a method that probes the directional sensitivity of cones, in particular those in the fovea. Directional sensitivity is a unique property of cones, i.e. it is not shared by any other retinal element, and can be taken as a measure of the health of cones. In a group of healthy subjects, the directional reflection was 1.78%. In early age-related macular degeneration (AMD), despite a healthy-looking fovea, the mean directional reflection was 0.92%; in late AMD, the figure decreased further to 0.86%. These findings point to a malfunctioning of the outer segments. In addition, the method yields an estimate of the optical density of macular pigment. In early AMD, the macular pigment did not differ from normal; this finding did not point to a protecting role of macular pigment in AMD.

Keywords

Cones, age-related macular degeneration, Stiles-Crawford effect, macular pigment, fundus reflection, optical density

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Of our large visual field only a small fraction – located in the fovea – is used for acute vision. This highly specialised part of the retina contains virtually no other elements than tightly packed cone photoreceptors. Initially, small parts of the peripheral visual field are affected in diseases such as age-related macular degeneration (AMD), but ultimately the foveal cones can become damaged, and as a consequence visual acuity deteriorates.

In principle, clinicians are interested in methods that specifically probe the condition of these crucial foveal photoreceptors. Visual acuity itself is such a test; however, this relevant measure is subjective and involves the whole visual chain from photoreceptor to brain. With objective methods, such as the light-adapted electroretinogram, a more specific cone-sensitive parameter is available for use, but cells other than cones significantly contribute to the signal. Moreover, solely probing the foveal cones to the exclusion of the overwhelming signal from the peripheral cones requires rather complex techniques.

In the last decade, the diagnostic arsenal for the ophthalmologist was extended with optical coherence tomography (OCT). This technique was a great step forward in obtaining detailed information about the different retinal layers, including that of the foveal cones. For the first time, oedema, subretinal fluid and macular holes clearly showed up in optical images. With the advent of the new-generation spectral OCTs, even the inner and outer segments of the photoreceptors could be distinguished. However, the OCT has its limitations too: even if the retinal layers appear normal on OCT, they may exhibit functional defecits.

In this article, we highlight a method that exclusively probes the condition of cones, in particular those in the fovea. The method exploits a property of the cones – directional sensitivity – that is not shared by any other retinal element. We will describe how this property can be utilised to quantitatively assess the integrity of the foveal cones in retinal diseases, in particular in AMD; a more extensive report has appeared elsewhere.[1]

Stiles-Crawford Effect

In 1933, the visual scientists Stiles and Crawford discovered that a ray of light entering the eye near the edge of the pupil is perceived to be less bright than when entering through the middle of the pupil. This was termed the psychophysical Stiles-Crawford (SC) effect. The SC effect also has an optical equivalent: the light reflected back from the cones is specifically directed towards the middle of the pupil.

Measuring this reflected light is not trivial because only about 1% of the incoming light is returned. *Figure 1* depicts the profile of light (550nm) illuminating a 1.5º spot on the fovea and leaving the eye through a dilated pupil. There is always a background of non-directional light – in absolute terms about 0.5% of the incoming light. A bell-like light distribution (a Gauss curve) is located on top of that with an amplitude of a further 0.5%. Thus, the light reflected back from the foveal cones has two components – non-directional and directional – and the ratio between the two depends on the wavelength. The non-directional light originates in the deeper retinal layers: it has travelled beyond the cones, through the retinal pigment epithelium, and is scattered back from the choroid and sclera. However, the directional light is returned directly from the outer segments of the cones. Such light shows, for instance, no influence of absorption by blood or melanin because these substances are located behind the photoreceptor layer.

Some time ago, it was found that the cause of the directional sensitivity and reflectivity of the cones lies in their particular cone-like shape. The more slender rod photoreceptors do not possess this property. In pathology, cones can become malformed, their outer segments can become shorter or their numbers may be reduced. All this may be so subtle that it is not visible on OCT images, but it causes the SC effect to become less prominent. The profile of the reflected light in the pupil plane is flat in completely disorientated cones. When the amplitude of the Gauss-like profile in the pupil is determined, this provides a quantitative measure of the SC effect known as the directionality. This is a sensitive and specific test of the integrity of the foveal cones.

Foveal Reflection Analyser

Using the SC effect for clinical purposes is not a new procedure; however, an adequate apparatus to do so quickly and reliably was previously unavailable. We recently built a device, the Foveal Reflection Analyser, that measures the light reflected from the fovea in a slit across the dilated pupil of patients;[2] from this reflectance profile the directionality is determined. The new apparatus has an important additional feature: it derives the spectral composition of the light reflected from the fovea. An example of a spectral profile ranging from the deep blue (400nm) to the infrared (950nm) is shown in *Figure 2*. Reflection is extremely low at short wavelengths (less than 0.01%) because the eye lens strongly absorbs short-wavelength light. Around 460nm, the macular pigment causes a reduction in reflection. At long wavelengths, reflection is highest (about 10%) because all ocular absorbers (blood, melanin) are transparent. That is why the fundus looks red. The data are analysed by an ingenious model that takes advantage of the known spectral properties of the ocular pigments.[2] It yields quantitative estimates of the optical densities of these pigments. The apparatus is fast; obtaining the data displayed in *Figure 1* takes about one second. Consequently, the investigator quickly obtains a wealth of data: a measurement of directionality

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(health of cones), the density of the lens (age- and health-dependent, e.g. increased in diabetes), the macular pigment (health-dependent?), melanin and blood. We continue to explore its clinical significance.

Directionality in Early Age-related Macular Degeneration

We were interested in the possible impact of AMD on the optical properties of the foveal cones. In particular, we wanted to know what happened in the early stages of AMD when there are few, if any, visual symptoms. Hence, we measured directionality in 45 eyes with early AMD (combining stages 2 and 3 of the International Classification System) and 11 eyes with late AMD (stage 4). In early

Figure 1: Spatial Profile of 550nm Light Reflected from the Fovea, Measured in a Slit Across the Pupil

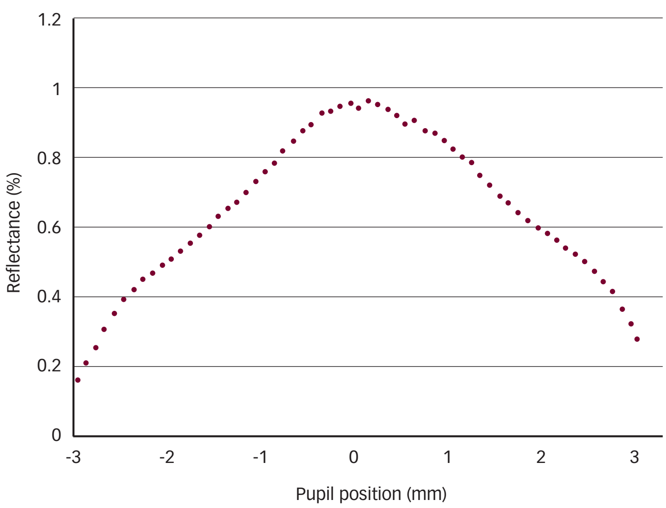
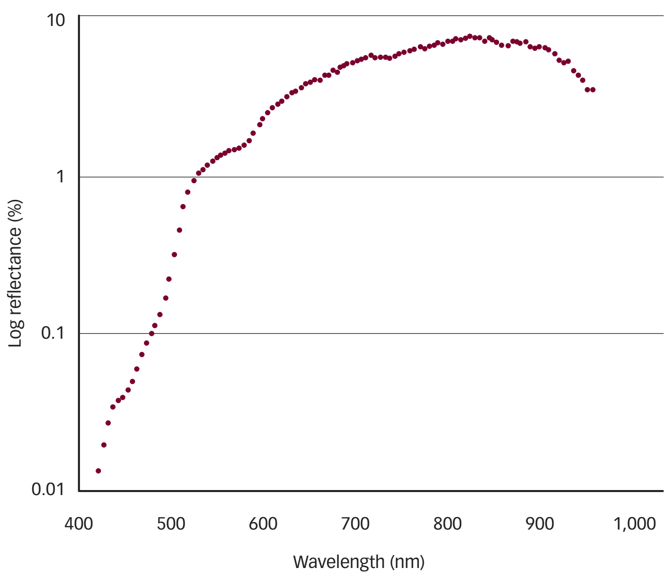


Figure 2: Spectral Composition of an Incoming Beam of White Light Reflected by the Fovea



AMD, mean directionality dropped from a healthy 1.78% (mean of 57 subjects) to 0.92% ($p<0.01$). In late AMD, a further reduction to 0.86 was observed, but the difference from early AMD was not significant. Additional spectral analysis of the reflected light yielded estimates of the amount of ocular absorbers. Lens density was normal in all stages of AMD. Macular pigment was normal in early AMD, but in late AMD it was lower.

Interpretation

In early AMD with soft indistinct or reticular drusen with or without retinal pigment epithelial (RPE) changes or soft distinct drusen with RPE changes, the directionality of the foveal cones has already deteriorated. This may be caused by a distortion of the orderly alliance of the foveal cones, or by a decrease in the total number of cones. It is also possible that the number of photopigment-containing invaginations in the outer segments of the cone, which supposedly play a role in the guided reflection, has decreased in AMD. Literature findings indicate that in early AMD the foveal cone mosaic is surprisingly similar to that of age-matched controls, and the total number of foveal cones is also normal.[3] Thus, a combination of shortened outer segments with, in cases of large drusen, cone disarray is the probable cause of the decline in directionality in early AMD. Malfunctioning of the underlying retinal pigment epithelium is probably the basis for this.

Macular Pigment

As a fringe benefit of this study on directionality, spectral analysis showed that in early AMD the amount of macular pigment was not different from normal. Earlier findings demonstrated that there is no age effect either. These are interesting findings in light of the messages from industry suggesting that taking supplements containing lutein or zeaxanthin is helpful in preventing eye disease. Indeed, lutein and zeaxanthin are the constituents of macular pigment, and ingestion generally increases their optical density in the retina.[4] However, in this study at least there proved to be no relationship between the amount of macular pigment and the prevalence of early AMD. That macular pigment was low in late AMD seems not very surprising. The foveal cones are heavily damaged and thus the number of binding sites of macular pigment is probably reduced. Much is still unknown about the function of macular pigment. Whether a high optical density of macular pigment helps to prevent AMD or other eye diseases is one of the unanswered questions.

Conclusion

Probing the unique property of the directionality of the cone photoreceptors increases our insight into their integrity in the various stages of retinal diseases. In AMD, directionality is reduced at an early stage, pointing to malfunction of the outer segments. The additional feature of spectral analysis of the reflected light adds information about what happens to ocular absorbers in retinal disease. The amount of macular pigment seems rather robust. ■

Dirk van Norren recently retired as a (part-time) Professor in Ophthalmic Physics in the Department of Ophthalmology at University Medical Centre Utrecht. A few years earlier he retired from his main occupation: Director of the TNO Human Factors Institute in Soesterberg in The Netherlands; prior to this position he was Director of the National Aerospace Medical Center in Soesterberg in The Netherlands.

Martijn Kanis is an intern in ophthalmology at University Medical Centre Utrecht, where he recently completed his PhD research. He defended his thesis in September 2008. Before that he studied medicine at Antwerp University, Belgium.

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Editor's Recommendations

Directional and Nondirectional Spectral Reflection from the Human Fovea

van de Kraats J, van Norren D, *J Biomed Opt*, 2008;13(2):024010.

A model of the directional and non-directional reflection spectrum of the human fovea is developed, incorporating reflectors, absorbers and a wavelength-dependent optical Stiles-Crawford effect (OSCE).

Data from 102 healthy subjects between 18 and 75 years of age obtained with the fundus reflection analyser (FRA), an imaging spectrograph that measures the directional reflection profile of the human fovea in the pupil plane from 400 to 950nm, were analysed. Subgroups of young (<40 years of age) and old (>50 years of age) observers were defined. The mean results of the young group defined a template for directionality versus wavelength. For the whole group, mean reflection at 550nm from the cones was 2.12%, from the retinal pigment epithelium 0.56% and from the choroid 7.92%. Lens density, cone disc reflection and blood layer thickness showed significant trends versus age.

The model for the first time simultaneously describes the spectra of the directional and non-directional reflection of the human fovea. Rayleigh scatter losses of the media and in pre-retinal layers were assumed to be zero in the non-directional pathway. The mean density of the macular pigment of a subgroup (53 subjects, 19–75 years of age) correlated significantly with independent data from reflectance and autoflourescence images obtained by scanning laser ophthalmoscope (SLO) and data from flicker photometry. ■

Optical Density of the Aging Human Ocular Media in the Visible and the UV

van de Kraats J, van Norren D, *J Opt Soc Am A Opt Image Sci Vis*, 2007;24(7):1842–57.

The authors analysed the literature on the absorption in the young and aging human eye media. Five templates were derived to provide an adequate description of the spectra from 300 to 700nm for the lens, cornea, aqueous and vitreous.

Two templates were found in all media. They stand for Rayleigh scatter and the absorbance of tryptophan. Three additional templates for the lens represent absorbance in kynurenine derivatives, such as 3-hydroxykynurenine glucoside (3HKG), and absorbance in two substances found at older age. Except for Rayleigh scatter, all templates have a Gaussian shape.

Ageing-trend functions were derived that show a linear slope on an age-squared scale. The result can be used to correct for media losses in visual perception tasks, in fundus reflectometry and in studies on light damage. ■