Scotoma Simulation in Healthy Subjects

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SIGNIFICANCE: This article shows a successful concept for simulating central scotoma, which is associated with age-related macular degeneration (AMD), in healthy subjects by an induced dark spot at the retina using occlusive contact lenses. The new concept includes a control mechanism to adjust the scotoma size through controlling pupil size without medication. Therefore, a miniaturized full-field adaptation device was used.

PURPOSE: The aim of this study was to design a novel concept to simulate AMD scotoma in healthy subjects using occlusive contact lenses.

METHODS: To define an optimal set of lens parameters, we constructed an optical model and considered both the anatomical pupil diameter and the opaque central zone diameter of the contact lens. To adjust the scotoma size, we built a miniaturized full-field adaptation device. We demonstrate the validity of this novel concept by functional measurements of visual fields using automated threshold perimetry. Finally, we conducted a perception study including two tasks, consisting of pictograms and letters. The stimuli were presented at different eccentricities and magnifications.

RESULTS: The visual fields of all 10 volunteers exhibited absolute scotomas. The loss of contrast sensitivity ranged within 27 and 36 dB ($P < .05$), and the scotoma localizations were nearly centered to the macula (mean variation, 2.0 ± 4.8° horizontally; 3.5 ± 4.7° vertically). The eccentric perception of letters showed the largest numbers of correctly identified stimuli. The perception of pictograms showed significantly reduced numbers ($P < .0001$) and revealed a dependency on magnification. The results suggest that best perception is possible for magnified stimuli near the scotoma.

Conclusions: We demonstrated that the creation of an absolute simulated AMD scotoma is possible using occlusive contact lenses combined with a miniaturized full-field adaptation device.

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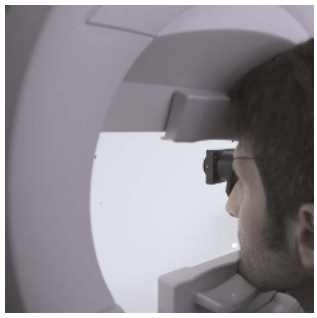

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Age-related macular degeneration is one of the major causes of blindness in Europe and North America and is associated with low vision. According to the World Health Organization, age-related macular degeneration is the third most common cause of visual impairment worldwide. Macular degeneration is also considered the principal source of visual deficiency in developed countries.[1,2] It affects mainly people older than 50 years and is becoming a major public health problem worldwide. As a result, age-related macular degeneration patients suffer from severe disruption to everyday tasks such as reading, driving, and face recognition.[3,4]

Age-related macular degeneration is closely related to the loss of photoreceptors in the macula of the ocular fundus and eliminates the normal retinal input to a large area of the visual cortex. However, there is strong evidence that stimuli presented in the periphery activate regions of the cortex that would normally be responsive only to central visual stimuli.[5,6] In this context, people with macular degeneration can adopt a new eccentric retinal locus (preferred retinal locus) for fixation.[7] Unfortunately, it is very difficult to identify an optimal preferred retinal locus for each patient. For example, some patients choose a retinal locus within the age-related macular degeneration zone, which provides only slight or no visual improvement. For this reason, current vision rehabilitation approaches aim to relocate the retinal images away from the scotoma toward the peripheral retina and/or to adjust their size. There are spectacle-based vision aids with or without prism relocation, implantable vision aids such as telescopic or prismatic intraocular lens concepts, head-worn electronic devices, and also handheld and table top electronic and nonelectronic devices.[8–10] Some strategies include not only the eyes but also a new understanding of functional compensation related to cortical plasticity effects.[11,12] However, the leading question remains: What is the best approach to attain the maximum visual ability for age-related macular degeneration patients?

It would be highly desirable to have a model for age-related macular degeneration in healthy volunteers that is easy to apply and allows the detailed investigation of different approaches to attain maximum visual ability.

In this article, we present a novel concept for simulating age-related macular degeneration scotoma in healthy subjects with an induced dark spot at the retina using occlusive contact lenses with an opaque central zone. For the first time, the concept includes a control mechanism to adjust the scotoma size, using a miniaturized full-field adaptation device. We demonstrate the validity of this novel concept by presenting spectroradiometric measurements of optical contact lens transmissions and functional measurements

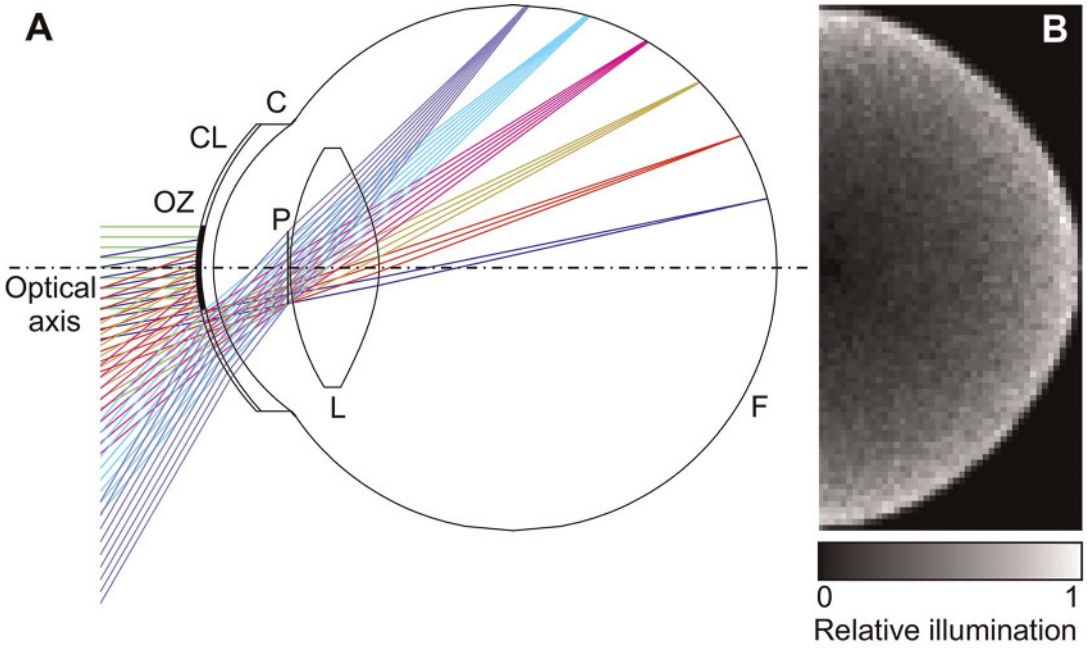

FIGURE 1. (A) Optical model in Zemax OpticStudio. It consists of the contact lens (CL) with an opaque central zone (OZ) and all components of the schematic eye including the cornea (C), the anatomical pupil (P), the eye lens (L), and the fundus (F). (B) Relative illumination at the retina (half field) caused by an occlusive contact lens.

of visual fields. Finally, we conduct a study including 10 volunteers to evaluate differences in the eccentric perception of stimuli.

METHODS

Subjects

We studied 10 (7 males, 3 females) randomly selected healthy volunteers (age, 27 to 43 years). All subjects were free of ocular diseases and had visual acuities between 0.8 and 1.0. Defocus and astigmatism were measured using an autorefractor (CX 1000; Rodenstock Instruments, Erlangen, Germany) and ranged from –4.00 to +0.25 D. We also used the refractor to determine the keratometer value. The mean corneal radius varied from 7.73 to 8.25 mm. None of the volunteers had a history of neurological or psychiatric disorders, and none was taking any medication or drugs. The macular integrity was tested using microperimetry (MAIA; CenterVue SpA, Padova, Italy) and revealed no irregularities (mean integrity index, 6.0 ± 5.5 on a scale from 0 to 100). The standard automated microperimetry revealed mean retina sensitivities of 29.9 ± 0.9 dB. After receiving an explanation of the purpose and the details of the study, all subjects gave their written informed

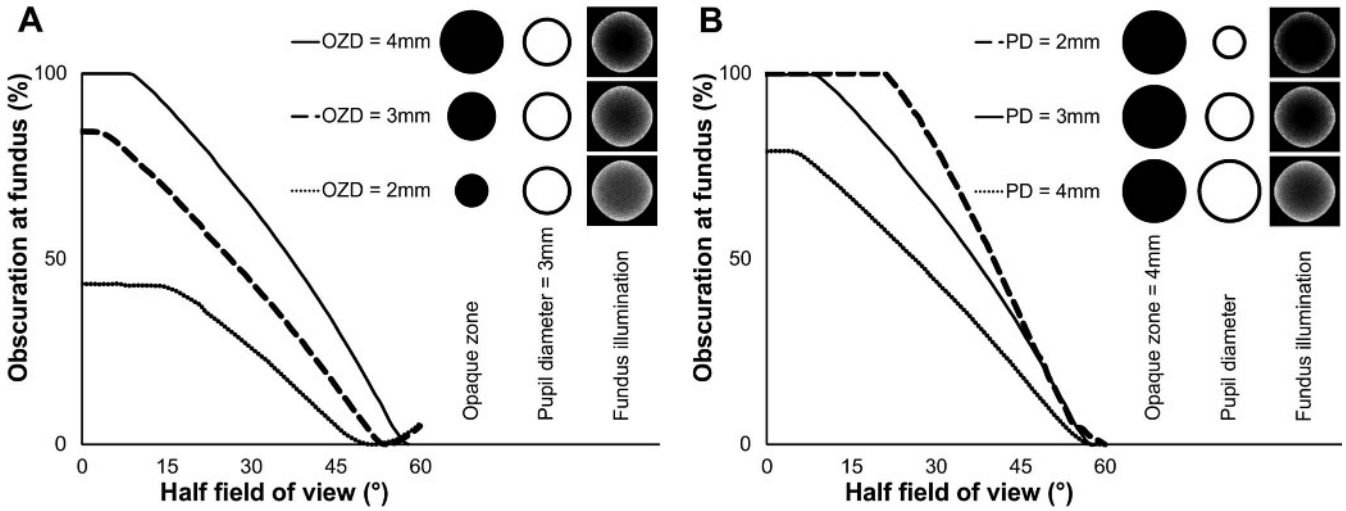

FIGURE 2. (A) Scotoma obscuration as a function of the opaque central zone diameter (OZD) (OZD, 4 mm solid line; OZD, 3 mm dashed line; OZD, 2 mm dotted line). (B) Scotoma obscuration as a function of the pupil diameter (PD) (PD, 4 mm dotted line; PD, 3 mm solid line; PD, 2 mm dashed line). The proportions of OZD and PD as well as the relative illumination at the retina are depicted next to the curves.

TABLE 1. Parameters of the contact lens type used

Parameter	Contact lens FASP iris
Material composition	Methyl methacrylate + silicon + fluorine
Total diameter (mm)	11.9
Central radius	Individually fitted to volunteer
Vertex power	Individually fitted to volunteer
Numeric eccentricity	0.60
Opaque central zone diameter (mm)	4.5
Optical density	<3
Stabilization of orientation	Prism ballast at 270°
Shore D hardness	77
Specific gravity (g/cm^3)	1.155
Refractive index	1.433
Oxygen permeability/DK value	125

consent before participation in the study. Data and information from the subjects were anonymized before analysis. All experiments were conducted in accordance with the Declaration of Helsinki. Approval for the study was obtained from the ethics committee of the Friedrich Schiller University of Jena.

Scotoma Simulation Concept

To define an optimal set of lens parameters including lens transmission, radius, and the aperture and position of the opaque central zone, we designed a model using optical modeling software (OpticStudio 15 SP1, July 30, 2015; Zemax LLC, Kirkland, WA). As model, we used a sequential eye model ("Eye_retinal image.zmx," Radiant Zemax Knowledge Base) including the glass catalog "eye.agf." Our model consists of the contact lens and all components of the chosen sequential eye model. We added the contact lens directly in front of the cornea, with the ability to adjust the size, position, and transmission of the opaque central area. The field of view was set to 120°. To consider spectrally different Lambertian light sources, the OpticStudio Wavelength Editor was used in terms of different wavelengths and its weights. The transmission of the opaque central zone of the contact lens and the lamp emission spectrum (based on the light conditions during the study, see Methods – Perception Study) were measured using an array spectrometer (CAS140-CT; Instrument Systems GmbH, Munich, Germany) and added to the model. The anatomical pupil was set as the system stop, and its diameter was changed according to Baer's formula using luminance as the input parameter.[13] Accommodation was considered by setting the front and the back radius of the crystalline lens as variables. The entire optical model is depicted schematically in Fig. 1. For realistic ray tracing, the nonsequential mode in OpticStudio was used. Optimization was performed using the default merit function.

The model revealed a strong scotoma dependency on the pupil diameter, which in turn is influenced by the applied luminance. Moreover, the scotoma size depends on the opaque central zone diameter. Fig. 2 demonstrates the dependency of the scotoma obscuration on three different diameters of the opaque central zone (Fig. 2A) and the pupil (Fig. 2B). Based on these simulations, lens parameters could be defined. In consultation with two lens manufacturers (Falco Linsen AG, Tägerwilen, Switzerland; Ultravision CLPL, Leighton Buzzard, UK) and after performing spectroradiometric transmission measurements (see Results – Spectroradiometric Measurements), a specific type of lens (FASP iris: O-EXTREM ICE; Falco Linsen AG) was selected. The central radius and the spherical aberrations were fitted individually for each volunteer. Table 1 provides an overview of the parameter set of the lens type used.

Because scotoma obscuration depends on the anatomical pupil diameter, adaptation and control of the pupil diameter are required. Consequently, we constructed a miniaturized full-field adaptation device (Fig. 3). We used a tube 15 mm in length (Microbenchsystem; Qioptiq Photonics GmbH & Co. KG, Göttingen, Germany) and including two hemispheres (Lambertian material with a diameter of 32 mm) at a distance of 10 mm. A nearly homogenous illuminated field was achieved by mounting a light-emitting diode (NSDW570GS-K1; NICHIA, Oka Tokushima, Japan) between the hemispheres. We applied current control to establish the luminance.

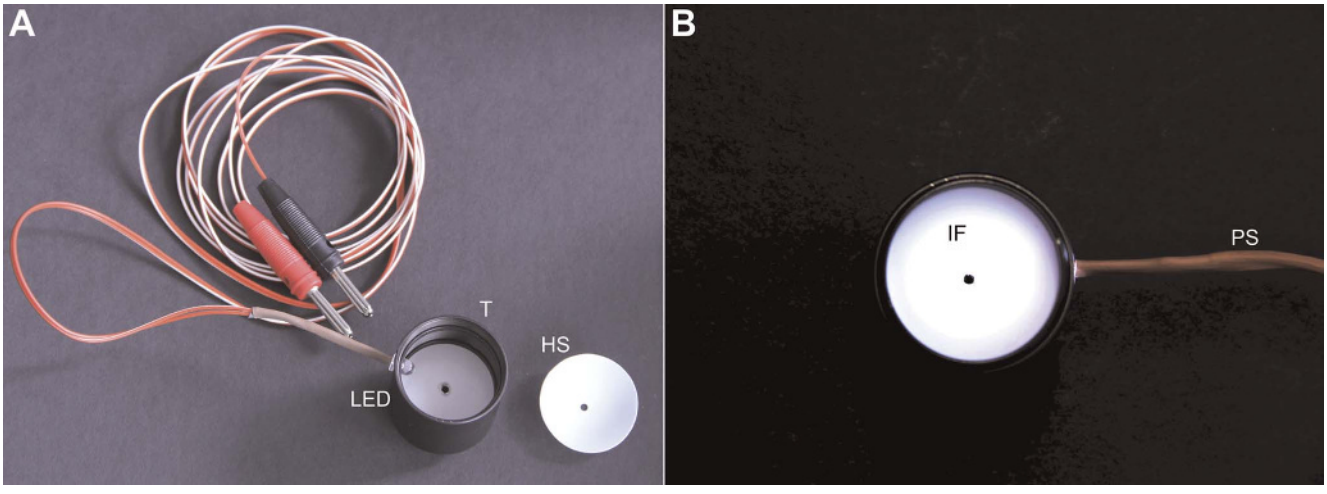

FIGURE 3. (A) Miniaturized full-field adaptation device used with the non–lens-covered eye. The upper half sphere (HS) is removed to show the location of the light-emitting diode (LED) in the tube (T). (B) Nearly homogenous illuminated field (IF) induced by the Lambertian sphere and the LED. The power supply cable (PS) is on the right side.

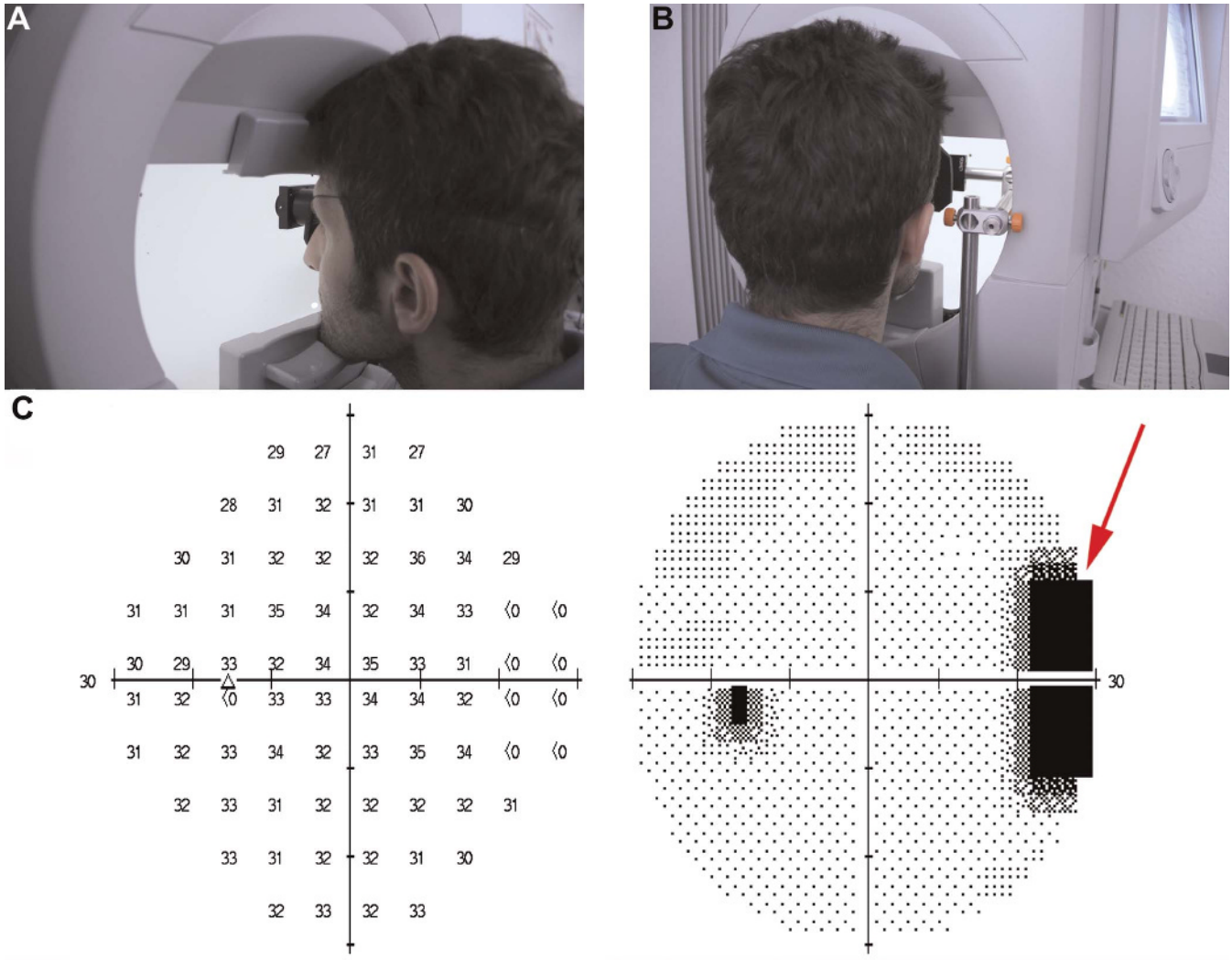

FIGURE 4. (A, B) Miniaturized full-field adaptation device applied to the perimeter (Humphrey Field Analyzer II). (C) Single field analysis of the left eye without any contact lens. The red arrow indicates the restricted visual field caused by the adaptation device. The dark spot in the left hemisphere indicates the papilla.

For additional fixation tasks (sections 2.3 and 2.4), holes with a diameter of 1 mm were made through the poles of both hemispheres. The holes create a very limited viewing angle of about 1°. By aligning the adaptation device and its field of view to an external fixation target, only this target can be perceived when looking through the holes. The device was exclusively used with the non–lens-covered eye. Because of the anatomical and physiological connections between both eyes, the light adaptation of the non–lens-covered eye induced pupil diameter adaptation of the lens-covered eye.[14]

Functional Measurements

The perceived scotoma at the retina was validated using a perimeter (Humphrey Field Analyzer II, Carl Zeiss Meditec AG, Jena, Germany) in combination with the 30-2 SITA (Swedish interactive thresholding algorithm, developed for the Humphrey perimeter) standard automated perimetry (76 test points extending 30° temporally, nasally, superiorly, and inferiorly).[15] Therefore, we covered the left eye of each volunteer with the individually fitted contact lens. Because of the opaque central zone of the lens, the perimeter fixation task was conducted using the right eye, applying the miniaturized full-field adaptation device to the perimeter (Figs. 4A, B). The holed hemispheres led to a highly reduced viewing angle of 1° with the perimeter fixation point in the center and without recognition of any test points. For the lens-covered eye, the adaptation device restricted the visual field nasally (Fig. 4C). Considering the limited spatial resolution of the perimeter, we reduced the pupil diameter to 3.0 mm, inducing scotoma obscuration of approximately ±12.5°.

Perception Study

This study was also performed using the miniaturized full-field adaptation device and the individually fitted contact lenses. For a simulated age-related macular degeneration scotoma of approximately ±7.5°, we adapted the pupil diameter to 3.5 mm.[16] The stimuli were displayed on a 52-inch (LE-52F9BD; Samsung Corp., Seoul, South Korea) liquid crystal display. To standardize the luminance conditions of the perception study, we constructed a red-

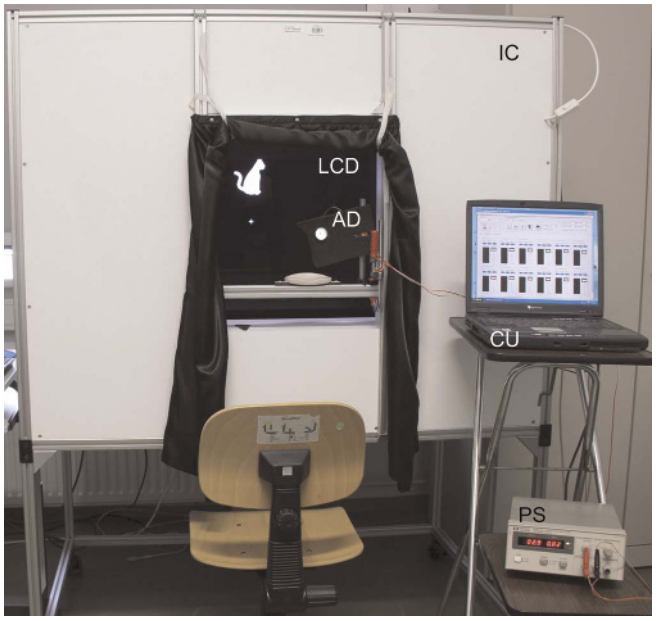

FIGURE 5. Illumination chamber (IC) with liquid crystal display (LCD) on the rear side and miniaturized full-field adaptation device (AD) and its power supply (PS) in the front. The digitally addressable lighting interface is connected to the control unit (CU). One of the pictograms (cat) and the fixation point (underneath the cat) are visible on the LCD screen.

green-blue-white fluorescent tube system illumination chamber (130 × 80 × 100 cm) using Lambertian surface material (Fig. 5). The fluorescent tube system was controlled by a digitally addressable lighting interface (DLI-4 DIN-230; feno GmbH, Oberhaching, Germany) and was adjusted to 15 cd/m^2 (55 lux).

The study included two perception tasks consisting of 10 randomly selected two-dimensional pictograms and 10 randomly selected letters (Fig. 6). Considering the controversially discussed vision rehabilitation approaches using prism spectacles, for each task, the stimuli were presented at different eccentricities (10 and 20°, superiorly) and different angular magnifications (3× and 5×) in a random order. This procedure led to four stimulus groups (10°/3×, 10°/5×, 20°/3×, 20°/5×) for both the pictograms and the letters. The magnification referred to the typical letter size of a newspaper. Then, at the near point distance of 250 mm, the viewing angle is 30 arc minutes (angular magnification, 1×). The miniaturized adaptation device and the liquid crystal display were applied to the illumination chamber. We used a fixation point centered at the display to keep the eccentric stimulus positions stable. Each stimulus was presented for 2 seconds, followed by a completely black image. The volunteer was required to identify the viewed pictogram or letter.

To analyze the differences among the group means, we performed analysis of variance. The Kolmogorov-Smirnov test was used to assess the normality of the distributions. The equality of variances was tested using Levene test. For groups that did not meet the normality assumption, we used the Kruskal-Wallis test. After the main effect analysis, a post hoc probing (homogeneity of variances, Tukey test; inhomogeneity of variances, Games Howell test) of interactions between the groups was performed.

RESULTS

Spectroradiometric Measurements

Fig. 7A shows the optical density of the opaque central zone of various contact lenses. The selected lens (FASP iris: O-EXTREM ICE; Falco Linsen AG) is depicted in Fig. 7B.

The four analyzed lenses clearly differ in their transmission curves. The lens from Ultravision CLPL is transparent to infrared light and has reduced optical densities (<2.5) for the visible spectrum above 620 nm. Between 400 and 600 nm exists a distinct wavelength-dependent characteristic. In contrast, lenses F1, F2, and F3 are characterized by flatter density curves with a nearly non-selective curve for lens F1. In addition, F1 reveals the highest optical density values of approximately 3.5.

Functional Measurements

Fig. 8 shows the functional measurements of 10 volunteers using 30-2 SITA standard automated perimetry. The left eyes were covered with the individually fitted contact lens.

The functional measurements reveal absolute scotomas in all 10 visual fields. The loss of contrast sensitivity at the scotoma center was between 27 and 36 dB ($P < .05$) with a mean of 34.8 ± 2.8 dB (compared with the age-corrected normal values of the Humphrey database). The scotoma localizations are approximately centered with respect to the macula position, with variation by a mean of 2.0 ± 4.8° in the horizontal and 3.5 ± 4.7° in the vertical direction (referring to the maximum total deviation point). All grayscale maps exhibit nasally restricted visual fields caused by the adaptation device (see Methods – Functional Measurements).

Perception Study

Fig. 9 shows the number of correctly identified stimuli for each volunteer for the different eccentricities and magnifications while wearing the contact lenses producing the scotoma.

The eccentric perception of letters shows a larger number of correctly identified stimuli than the pictograms. The 20°/3× group has the lowest perception rate for letters, whereas the remaining groups are similar to each other with a mean of correctly identified stimuli between 9.4 and 9.6 (standard deviation ranging from

FIGURE 6. The randomly selected pictograms (upper two rows) and letters (lower two rows). Graphic and cultural aspects of the pictograms were taken into account, considering the work of Spinillo.[17] Complexity of the pictograms is higher than the complexity of the letters.

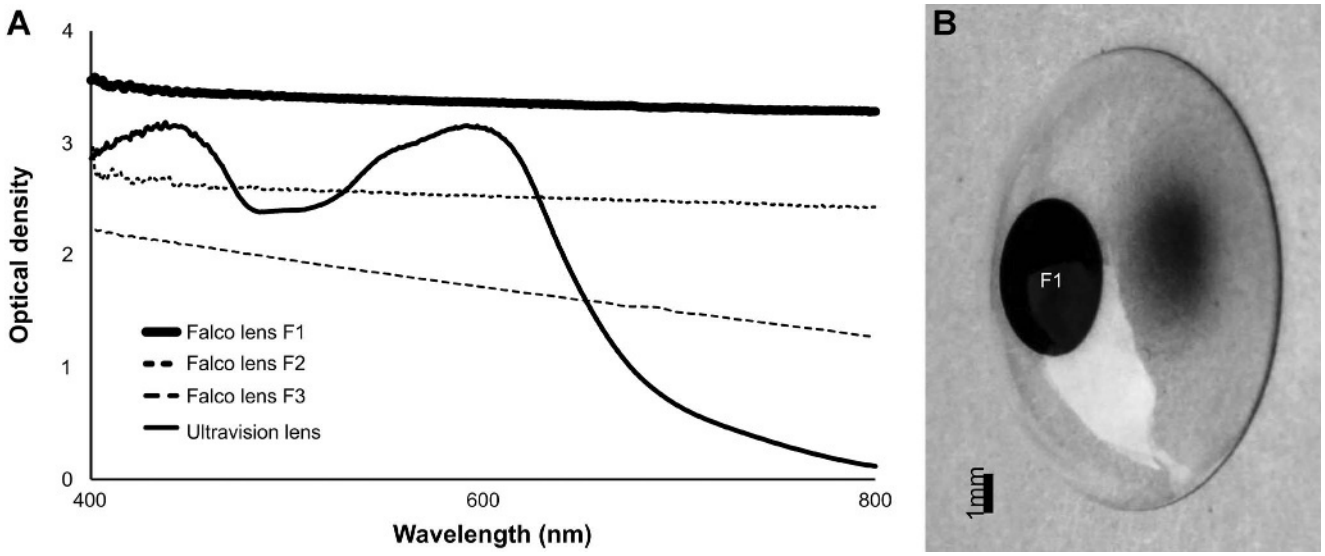

FIGURE 7. (A) Opaque central zone optical density of various contact lenses. We analyzed one lens from Ultravision CLPL (Ultravision lens) and three lenses from Falco Linsen AG (Falco lens F1, Falco lens F2, Falco lens F3). (B) The selected lens type (FASP iris: O-EXTREM ICE) with its corresponding opaque zone optical density of F1.

0.7 to 1.0). In comparison with the letters, the eccentric identification of pictograms has significantly lower numbers ($P < .0001$) and reveals a dependency on magnification (for 10° eccentricity, $P < .001$; for 20° eccentricity, $P < .05$). The highest perception rate (7.8 ± 1.8) is demonstrated for the 10°/5× group. All mean values and standard deviations of correctly identified stimuli are summarized in Table 2. The differences among all groups are significant for the pictograms ($P = .001$) and for the letters ($P = .01$). Table 2 also includes the P values of the post hoc test groups.

DISCUSSION

To the best of our knowledge, this article presents the first successful concept for simulating age-related macular degeneration scotoma in healthy subjects by an induced dark spot at the retina using occlusive contact lenses. The new concept includes a control mechanism to adjust the scotoma size using a miniaturized full-field adaptation device. It offers the possibility of age-related macular degeneration research without patient selection bias and without the need for artificial video-based scotomas.

In recent years, the spectrum of vision rehabilitation approaches has become much wider. Magnification with electronic and nonelectronic aids, head-worn devices, and/or the use of eccentric fixation seem to be helpful techniques in patients with central scotomas.[9,10,18] Several groups have investigated the effectiveness of different rehabilitation methods and devices. These studies have produced variable results, generating some controversy. Verezen et al.[19] found that patients with dense central scotomas are most likely to benefit from eccentric viewing spectacles. Markowitz[20] reviewed the principles of low-vision rehabilitation and noted that residual visual functions can also be improved by the use of eccentric image relocation caused by prisms. Another study, in contrast, reported that prism spectacles are no more effective than conventional spectacles.[21] Many authors conclude that such contradictory results may be owing to patient selection bias.[10,22,23] Virgili et al.[10] even suggest that it would be necessary to investigate which patient characteristics predict performance with different rehabilitation devices. To overcome this problem, we developed a concept for simulating age-related macular degeneration scotoma in healthy subjects, which offers the opportunity to adjust the scotoma size.

The presented concept is based on an occlusive contact lens with an opaque central zone and includes, for the first time, a miniaturized full-field adaptation device. In 2009, Czoski-Murray et al.[24] used custom-made contact lenses to simulate the visual impairment associated with age-related macular degeneration. To address different scotomas, Czoski-Murray et al.[24] used three sizes of central opaque black dots to reproduce three vision states. However, the authors did not design an optical model for calculating the scotoma size and did not perform any functional measurement of visual fields. To standardize the effect of the contact lenses, pilocarpine eye drops were instilled, constricting the pupil. A possible disadvantage of this concept may lie in the adverse effects of pilocarpine, which induces a myopic shift and leads to refraction errors.[25,26] Butt et al.[27] were also concerned over the validity of the Czoski-Murray approach. They measured the effect of opaque contact lenses manufactured by Ultravision CLPL on five healthy volunteers using microperimetry. Their optical model did not include the anatomical pupil, and pilocarpine was not used. The study revealed a median loss of contrast sensitivity of 8.3 dB. The authors concluded that the contact lens does not create any area of absolute scotoma and does not accurately simulate the effects of advanced age-related macular degeneration.[27] In contrast, we designed an optical model, comprising the anatomical pupil and the contact lens (Fig. 1). Our model revealed that a scotoma is a function of both the pupil diameter and the opaque central zone diameter. Our results thus agree with Czoski-Murray et al.[24] in that it is necessary to standardize the scotoma considering the pupil. To avoid any medication bias and to adjust the scotoma size, we constructed a miniaturized full-field adaptation device (Fig. 3). Because of its higher optical density (>3 dB) as well as the nonselective transmission curve (between 400 and 800 nm), the contact lens F1 from Falco Linsen AG, unlike the lens from Ultravision CLPL (Fig. 4), creates an absolute scotoma perceived by the wearer. We validated the scotoma using

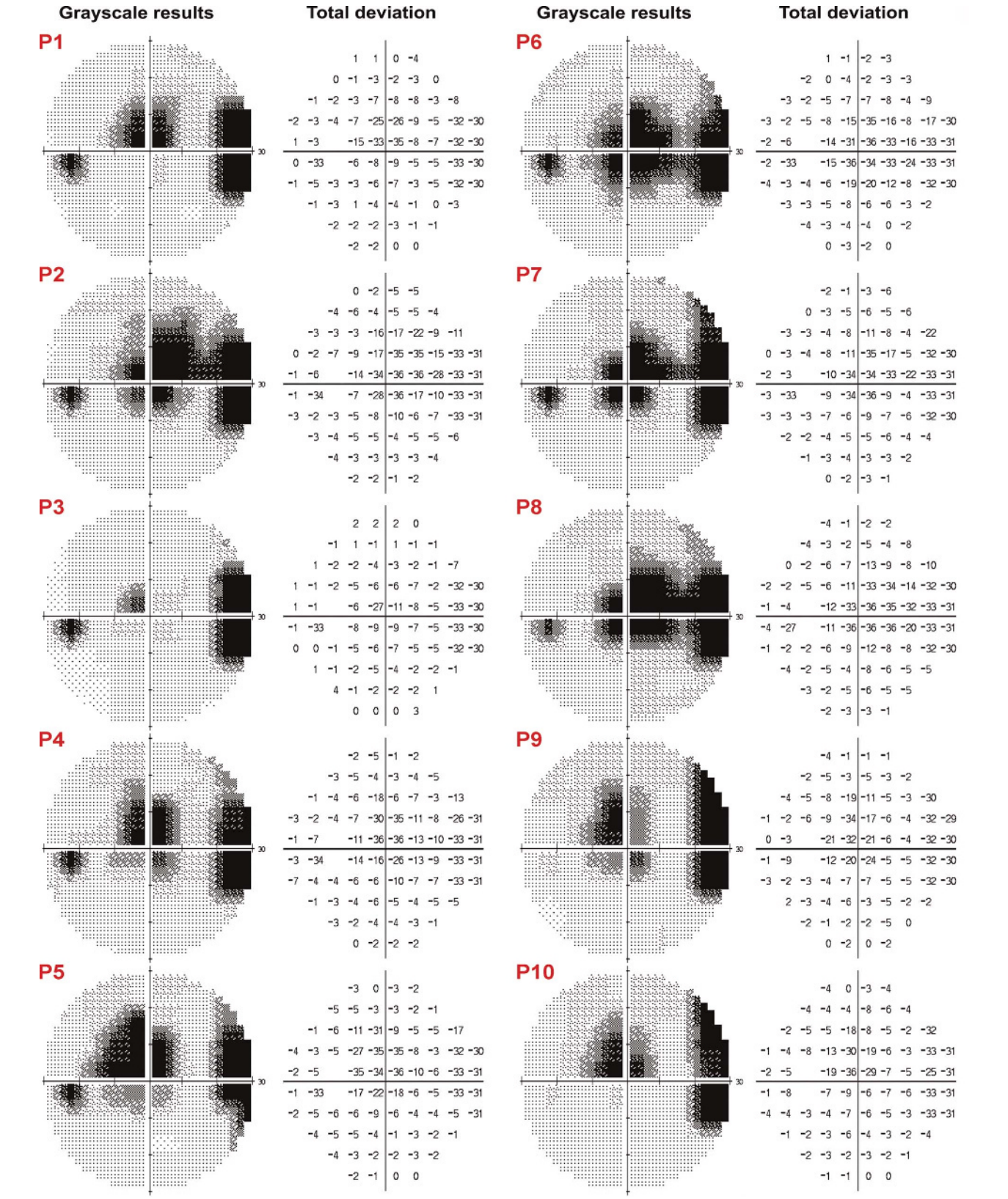

FIGURE 8. Functional measurements of 10 volunteers (grouped into two rows) using 30-2 SITA standard automated perimetry. For each volunteer, grayscale results (left side) and total deviations (right side) are depicted. The numeric total deviation values represent the differences in decibels between the volunteer's test results and the age-corrected normal values at each tested point.

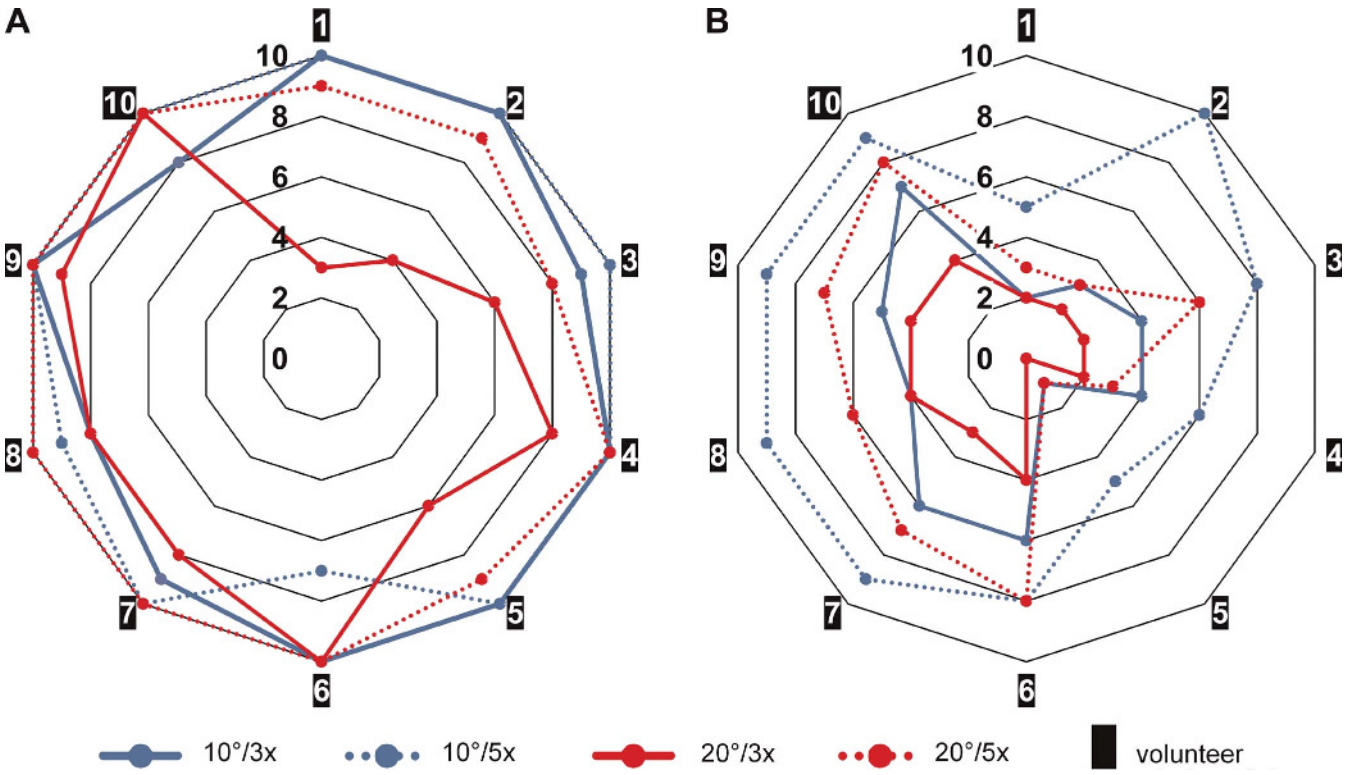

FIGURE 9. Correctly identified stimuli for each volunteer (black rectangle with number) for the different eccentricities (10° blue, 20° red) and the different magnifications (3× solid lines, 5× dotted lines). (A) Perception of the different letters. (B) Perception of the different pictograms.

30-2 SITA standard automated perimetry and found a loss of contrast sensitivity ranging between 27 and 36 dB ($P < .05$) with a mean of 34.8 ± 2.8 dB, which is considerably higher than the value reported by Butt et al.[27] (8.3 dB).

For feasibility reasons, we conducted a perception study with a simulated age-related macular degeneration scotoma of ±7.5° including two tasks, consisting of 10 randomly selected pictograms and 10 randomly selected letters (Fig. 6). For each task, the stimuli were presented at different eccentricities (10 and 20°, superiorly) and different angular magnifications (3× and 5×). Ten volunteers were required to identify the viewed pictogram or letter. In accordance with the work of Spinillo,[17] we checked the syntactic and semantic aspects of the pictograms to ensure that there would be no volunteer demand to interpret several elements in an integrated manner. We found that the eccentric perception of letters showed the largest numbers of correctly identified stimuli (Fig. 9). In

TABLE 2. Mean values and standard deviations (n = 10) of correctly identified stimuli

Mean of correctly named stimuli	Letters		Pictograms	
	3x	5x	3x	5x
10°	9.4 ± 0.8	9.6 ± 1.0	4.2 ± 1.9	7.8 ± 1.8
20°	7.2 ± 2.4	9.5 ± 0.7	2.7 ± 1.3	5.2 ± 2.5

The P values of the different post hoc test groups are ****$P < .0001$, ***$P < .001$, **$P < .01$, and *$P < .05$.

comparison, the perception rate of pictograms showed significant reduced numbers ($P < .0001$) and a dependency on magnification (for 10° eccentricity, $P < .001$; for 20° eccentricity, $P < .05$). Research groups in the field of retinal processing are in absolute agreement with these results. The limited perception at smaller magnifications and/or higher eccentricities relates to the fact that the convergence of cone photoreceptors upon a single ganglion cell increases in the periphery.[28–30] The lower identification rate of pictograms follows the hypothesis that perception efficiency is inversely proportional to complexity (Fig. 6). In addition, letters are overlearned elements of language and very familiar objects with distinctive shapes. The ability to recognize familiar letters is highly developed in visual system.[31] The results of the study also suggest that the best perception is possible for magnified stimuli near the scotoma.

The presented results demonstrate that the creation of an absolute simulated age-related macular degeneration scotoma is possible using occlusive contact lenses combined with a miniaturized full-field adaptation device. Our new concept is suitable for avoiding patient selection bias as well as the impact of different population characteristics on further scotoma studies. The fact that age-related macular degeneration patients in addition often suffer from blurred and distorted vision required different simulation strategies in the future (e.g., blurry or highly aberrative contact lenses). A further application field could be the teaching of early age-related macular degeneration patients considering optimal preferred retinal locus positions.

To determine more learning and practice effects when using the miniaturized full-field adaptation device, further investigations are needed. Experiments involving multiple sessions and repeatable measurements are carried out next.

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