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RETINAL DISORDERS

Parafoveal letter recognition at reduced contrast in normal aging and in patients with risk factors for AMD

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Abstract
Background Patients with early age-related maculopathy (ARM) do not necessarily show obvious morphological signs or functional impairment. Many have good visual acuity, yet complain of decreased visual performance. The aim of this study was to investigate the aging effects on performance of parafoveal letter recognition at reduced contrast, and defects caused by early ARM and normal fellow eyes of patients with unilateral age-related macular degeneration (nfAMD).

Methods Testing of the central visual field (8° radius) was performed by the Macular Mapping Test (MMT) using recognition of letters in 40 parafoveal target locations at four contrast levels (5, 10, 25 and 100%). Effects of aging were investigated in 64 healthy subjects aged 23 to 76 years (CTRL). In addition, 39 eyes (minimum visual acuity of 0.63;20/30) from 39 patients with either no visible signs of ARM, while the fellow eye had advanced age-related macular degeneration (nfAMD; n=12), or early signs of ARM (eARM; n=27) were examined. Performance was expressed summarily as a "field score" (FS).
Results Performance in the MMT begins to decline linearly with age in normal subjects from the age of 50 and 54 years on, at 5% and 10% contrast respectively. The differentiation between patients and CTRLs was enhanced if FS at 5% was analyzed along with FS at 10% contrast. In 8/12 patients from group nfAMD and in 18/27 from group eARM, the FS was statistically significantly lower than in the CTRL group in at least one of the lower contrast levels.
Conclusion Using parafoveal test locations, a recognition task and diminished contrast increases the chance of early detection of functional defects due to eARM or nfAMD and can differentiate them from those due to aging alone.

Keywords Aging · Age-related maculopathy · Age-related macular degeneration · Retina · Macular function · Parafoveal function · Contrast sensitivity · Letter recognition

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Introduction

The late stage of age-related macular degeneration (AMD) is the leading cause of vision loss in individuals over

50 years of age in industrialized countries [1, 2]. This condition is characterized by geographic atrophy of the retinal pigment epithelium (RPE) or presence of subretinal neovascular membranes with choroidal neovascularization (CNV) [3].

According to the international classification and grading system [3], eyes with early age-related maculopathy (eARM) show drusen (>63 µm) and/or hyper- or hypopigmentation of the RPE. Despite normal or only slightly reduced visual acuity, retinal alterations found in eARM [4, 5] and those due to normal aging [6–9] may disrupt metabolic exchange between the choroid and photoreceptors, which has been related to compromised photoreceptor function and cell death [10].

Epidemiologic studies suggest that characteristics of drusen and RPE defects in ARM are risk factors for the development of late AMD [11, 12]. On the other hand, longitudinal studies have shown that only a portion of the patients (10%–15%) with ARM acquire AMD over a 5- to 10-year period [12, 13]. In fact, late AMD can develop in eyes without any early fundus signs [14].

Furthermore, it has been shown that fellow eyes from patients with unilateral AMD are at elevated risk of developing AMD [15], with cumulative incidence rates of CNV lesions in fellow eyes of patients with unilateral CNV of 22% and 37% at 2- and 4-year follow-up respectively [16–18]. Thus, visible fundus characteristics alone are not enough to define clinical features of early ARM. Moreover, it has been shown that good visual acuity does not reliably indicate that there is no development of macular disorders. The disease process can start in the near periphery and not affect foveal vision at all, thus leading to a "ring scotoma" [19–21] that cannot be detected by a test of foveal vision.

Therefore, there is a need to identify additional markers of disease status that can increase and complement our present understanding of the disease and improve the sensitivity of screening programs.

Functional examinations have been proposed as a strategy for providing insights into eARM, for example in its pathogenesis [22], or predictability of CNV development [23] (for a review see Hogg & Chakravarthy, 2006 [24], or Lovie-Kitchin, 2005 [25]).

Patients with eARM may show impairments of parafoveal function [26–29], report difficulties in near vision tasks [30] and, according to our pilot study, show performance deficits in letter recognition in the parafoveal visual field [31]. Hence, sensitivity and reliability of testing visual function in these patients may be improved by the inclusion of parafoveal targets. In this study, we aim to test to what degree letter recognition at reduced contrast in the parafoveal area is altered due to the normal aging process, in eARM and in still normal fellow eyes of patients with unilateral AMD (nfAMD).

Material & methods

Subjects

Normal volunteers Sixty-four normally sighted subjects with an age range of 23 to 76 years participated. In each subject, only the eye with the better acuity was tested—all had 1.0 decimal (20/20 Snellen or 0.0 LogMAR) or better in both eyes. If visual acuities were symmetric, the dominant eye was determined by a peephole test and chosen for examination.

Patients Thirty-nine patients from the Centre for Ophthalmology in Tübingen, Germany (n=29), and Turku, Finland (n=10), participated in this study. Their age range was 55 to 76 years and the tested eyes (one eye per patient) had a minimum visual acuity of 0.63 decimal (20/32) or 0.2 LogMAR (median=1.0; range: 0.63 to 1.60 decimal).

All subjects gave their informed consent, and the examinations were conducted in accordance with the tenets of the Declaration of Helsinki.

Patients were divided into two groups:

- **nfAMD** (n=12): no visible signs of ARM in the tested eye (few hard indistinct drusen <63 µm were permitted, no RPE pigmentary alterations), but with unilateral late AMD (geographic atrophy or choroidal neovascularization) in the fellow eye;
- **eARM** (n=27): presence of early signs of ARM. This group was further divided into two sub-groups, according to the international classification system for ARM [3]:
- **eARM$_1$** (n=13): presence of drusen <125 µm and no RPE alteration, (five fellow eyes with late AMD, six with eARM, and two normal);
- **eARM$_2$** (n=14): presence of drusen >125 µm and/or hypo- and/or hyperpigmentation of the RPE, (eight fellow eyes with AMD, three with eARM, and three normal).

Exclusion criteria were significant media opacities or any other eye diseases, i.e. diabetic retinopathy or glaucoma.

Macular Mapping Test (MMT)

The Macular Mapping Test (MMT by MMTest®, San Francisco, CA, USA) provides psychophysical assessment of parafoveal function [31, 32]. It is a computer-based procedure that presents single letters tachistoscopically on a field of 8° radius on a computer monitor. We found in previous studies that the MMT can be administered by anyone with only basic computer skills. It performs a quick assessment of macular vision (approximately

3 minutes per run) without the use of special equipment [32] and, when comparable, shows good correspondence with perimetric data [33]. Like perimetry, it measures visual function topographically, but unlike perimetry, the task requires not only stimulus detection, but also letter recognition.

Procedure A background pattern resembling a wagon wheel (luminance=164 cd/cm^2) was used to stabilize the patient's gaze (Fig. 1a). A black circle with 0.5° radius and a 18 minarc central aperture was used as the fixation mark. The viewing distance was 73.2 cm and patients were individually corrected for their refractive error and presbyopia. The central display area was calibrated to span 18° diameter of the visual field. In 41 locations, positioned at the center and on concentric rings of 1°, 2°, 4°, 6° and 8° eccentricity (Fig. 1b), randomly chosen Sloan letters were presented one at a time for 250 ms to minimize saccades towards the stimulus. The letters appeared black or grey on white to achieve four contrast levels (100, 25, 10, and 5% - calculated according to Michelson's formula). Their size was supra-threshold and additionally scaled by eccentricity in the visual field [34, 35]. This was considered sufficient to neutralize eccentricity as a variable, since it has been found that the spatial-frequency characteristics of letter identification are "fundamentally identical between central and peripheral vision" [36]. At the end of the test, data were displayed as topographical maps indicating the response to each target. Accordingly, three possible scores were given: 0—not detected (black symbol); 0.5—detected but not recognized (grey symbol); or 1—letter recognized (white symbol) (Fig. 1b).

Field Score To characterize overall performance level, a "field score" (FS) was calculated as the cumulative sum of all response scores, with a maximum of 41 points.

Statistical analysis

To determine the normal reference limits of the FS, we defined a model that explains the age dependency of FS variability.

Values were first subjected to a log odds transformation ($\log odds = \log\left(\frac{p}{1-p}\right)$), to stabilize the variance of the FS observed in the normally sighted subjects over the age range. To avoid a zero value, we added 0.5, and then divided them by 42 to prevent the occurrence of the value 1. This ensures that all values are included in the analysis [37].

The following model was fitted to the log odds values according to the standard least square method (JMP® 7.0.2; SAS Inc.): up to a critical age A the log odds values are constant equal to a parameter b, which represents the mean FS for younger subjects, and for ages higher than A, the log odds values decrease linearly with slope m (equation 1).

$$\begin{cases} age < A \Rightarrow b \\ age \geq A \Rightarrow b + m(age - A). \end{cases} \quad (1)$$

The standard deviation (SD) of the residuals allows determining the 95% reference intervals across the whole age range for healthy volunteers (mean±1.96 * residuals SD).

To simplify the model for all data, the slopes m were set equal to the mean slope of -0.1 per year for all contrast levels, because the estimated m of the different contrasts showed statistically non-significant variation. Finally, values were retransformed and are shown as FS values. Parameters were compared by a z-test based on the standard errors of the estimates.

Results

As in a previous study [32], each test run took, on average, about 3 minutes (180.3±65 s SD).

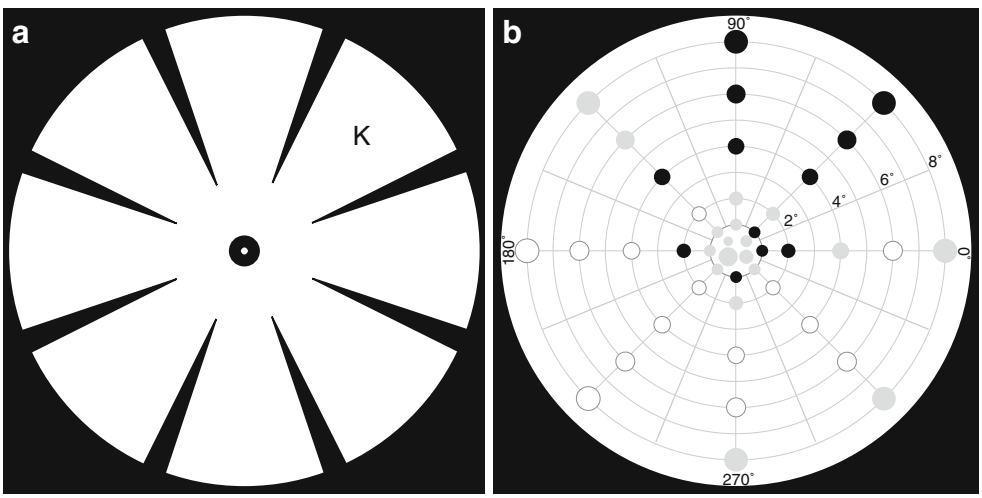

Fig. 1 (**a**) The wagon-wheel background with a central fixation mark and the stimulus, a Sloan letter. (**b**) An example of a recording of a complete trial block with one of the three possible symbols at each location: *black*—not detected, *grey*—detected but not recognized, *white*—letter recognized. Maximal stimulus eccentricity was 8°

Normal aging effects

Applying the log-odds transformation allowed stabilization of data variability in the entire age range, and consequently the estimation of parameters *b* (mean FS for younger subjects) and *A* (age at the beginning of the FS linear decline) for the four contrast levels. The model was fitted with the transformed values (Fig. 2; insets) and parameter *b* was later retransformed into the FS (Fig. 2).

For 100% contrast, parameter b=39.9 (95% confidence interval (CI) 39.7 to 40.2) and A=63.0 years (95% CI from 60.0 to 68.1 years); they were not significantly different from parameters found at 25% contrast, b=40.3 (95% CI 40.1 to 40.5); and A=59.5 years (95% CI 56.4 to 62.3 years) (p=0.21 and 0.80 respectively). This indicates that if contrast is reduced to 25%, normal subjects over the whole age range are able to achieve the same letter recognition performance measured at 100% contrast (Fig. 2).

On the other hand, aging effects on letter recognition could be detected at the lower contrasts. At 10% performance was significantly reduced compared to 100% and 25% contrasts: in younger subjects, b=39.5 (95% CI from

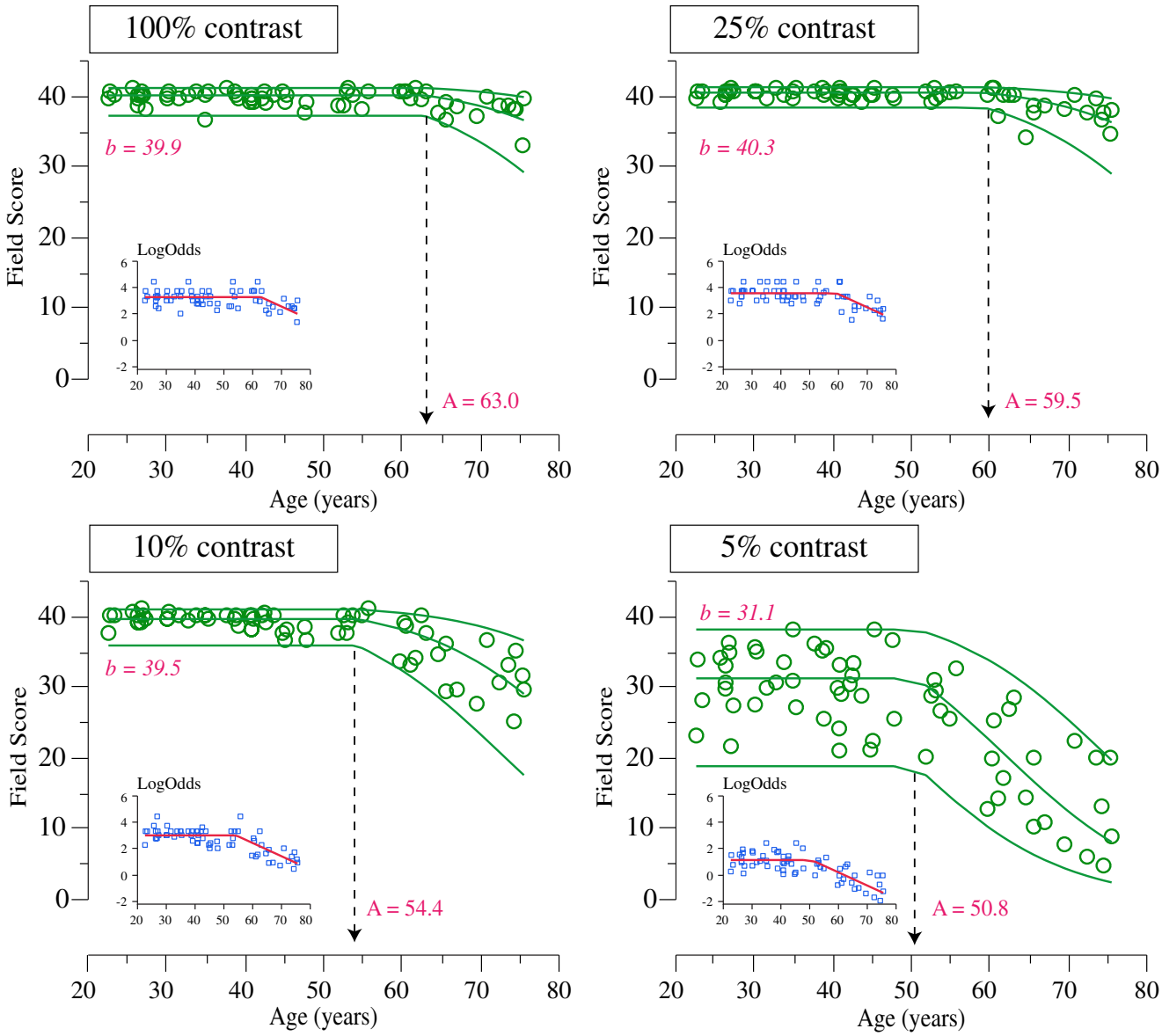

Fig. 2 Plots show the distribution of field scores (FS) achieved by normally sighted subjects (*green circles*) versus age at four contrast levels. *Green lines* are the upper 95% confidence limit, mean, and lower 95% confidence limit respectively. *Vertical lines* indicate the age at the beginning of the FS linear decline (parameter A). The *insets* in each plot show the relationship between the log-odds transformed values (*blue squares*) and age; the *red line* is the model's best fit (see Methods—Statistical analysis). Note that subjects have a constant FS (parameter b) up to an age "A", and from A on, they show a linear decline with equal slope at all contrast levels. Parameters A and b (see equation 1) are given for all contrasts

37.6 to 39.8; p=0.0064); and FS decline begins at younger ages than at 100% and 25% contrast: A=54.4 years (95% CI from 50.9 to 56.9 years; p=0.021). At 5% contrast, the test became more difficult even for very young subjects compared with all other contrast levels: b=31.1(95% CI from 29.2 to 32.7), and A=50.8 years (95% CI from 47.5 to 54.9 years) (Fig. 2). The difference between parameter A found at 10% and 5% contrasts was not statistically significant (p=0.2116).

Results from patients

The distribution of patients' performances, and the 95% reference range across age calculated for the normally sighted subjects between 55 and 76 years, is shown in Fig. 3. If the FS was above the lower limit of the reference interval, the patient's performance was rated as "normal". If the performance was below the lower limit, the result was considered pathological.

Only few patients had FS values considered pathological at contrasts 100% (seven patients) and 25% (12 patients), but considering performances at contrasts 5% and 10%, a total of 26 patients (67%) had scores below the lower reference limit. Table 1 shows the number of patients with FS values considered as "normal" (above the 95% reference limit), or "pathological" (below the limit), and the combination between FS found with 10% and 5% contrasts.

For sub-group eARM$_1$, 8/13 patients had FSs below the normal range at 5% or at 10% contrasts, (four had AMD in the fellow eye; three of them had a visual acuity of 0.8 and the other five of 1.0).

In the sub-group classified as eARM$_2$, 10/14 patients performed below the normal range (seven had AMD in the fellow eye; in two of them visual acuity was 0.63 decimal (20/32), one had 0.8 decimal (20/25), and in the other seven patients it was 1.0 decimal (20/20).

In the group of patients with no signs of ARM in the tested eye and unilateral AMD in the fellow eye (group

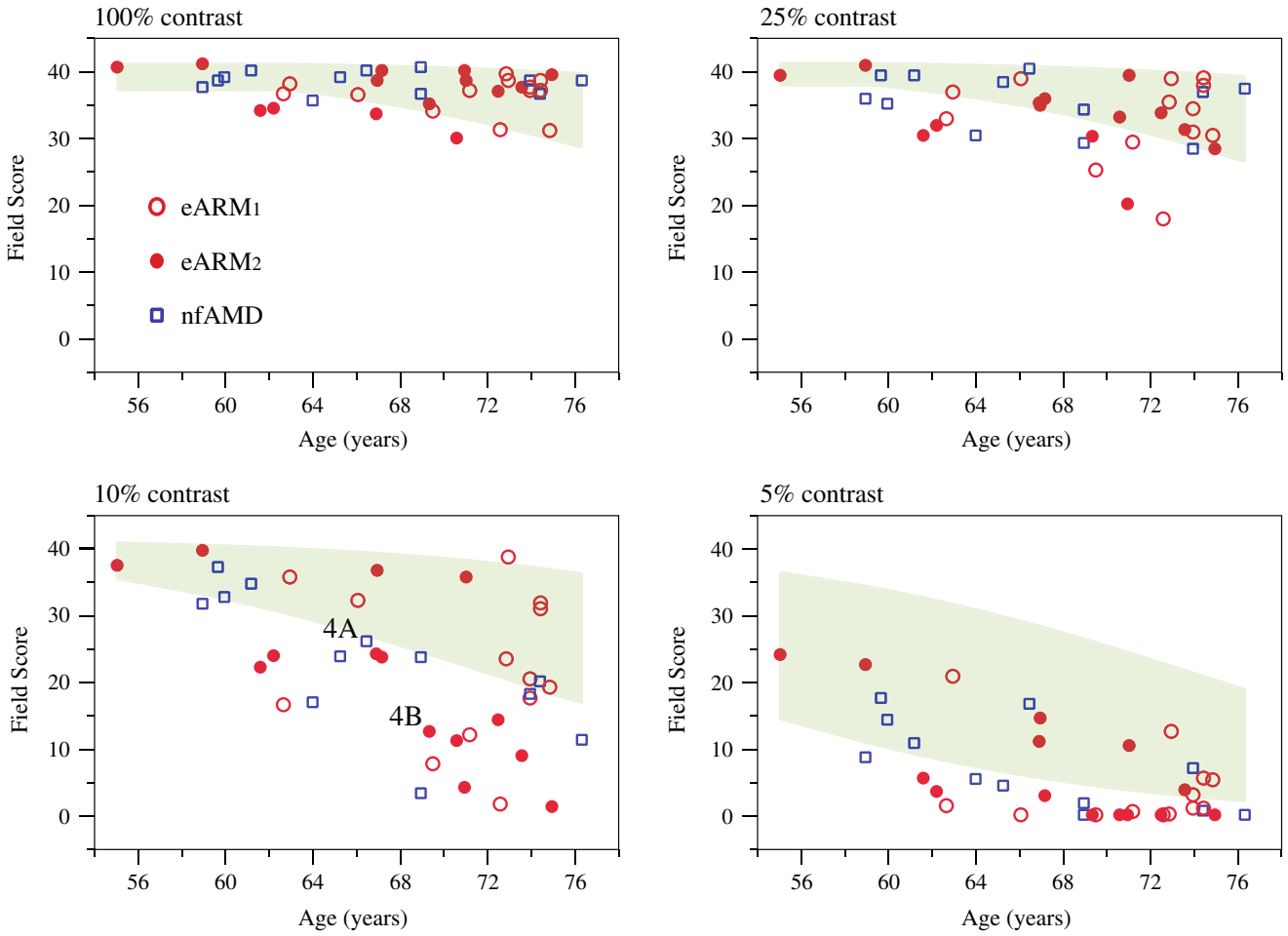

Fig. 3 The patients' field scores (FS) at four contrast levels as a function of age. The *green areas* illustrate the 95% confidence interval of expected values in normally sighted subjects. Individual FS of the eARM$_1$ patients (n=13) tested in this study are shown as *unfilled red circles*, the eARM$_2$ patients (n=14) are shown as *filled red circles*, and normal eyes from patients with advanced unilateral AMD are shown as *blue squares*; nfAMD (n=12). Labels "*4A*" and "*4B*" indicate the patients shown in Fig. 4

Table 1 Number of patients' FS considered pathological (below the 95% lower reference limit), when test was performed at 5 and 10% contrasts

Sub-Group	Fellow eye	Below lower limit only at 5% contrast	Below lower limit only at 10% contrast	Below lower limit at 5% and 10% contrast	Below lower limit at 5% or 10% contrast
eARM$_1$	AMD (n=5)	4	3	3	4
	ARM (n=6)	3	1	1	3
	Normal (n=2)	1	1	1	1
eARM$_2$	AMD (n=8)	6	7	6	7
	ARM (n=3)	2	2	2	2
	Normal (n=3)	0	1	0	1
nfAMD	- (n=12)	7	7	6	8

nfAMD), eight out of 12 patients showed performance below the normal range at lower contrasts. Of these, two eyes had a visual acuity of 0.8, and the other six eyes of 1.0 or better.

Figure 4A presents the morphologically asymptomatic eye of a nfAMD patient who was considered pathological based on FS performance. These results indicate that the eyes that are at higher risk of developing AMD, often show lower parafoveal letter recognition performance at reduced contrast, even before they have morphological signs of ARM or reduced visual acuity.

Figure 4B presents an example of an eARM$_2$ patient who had a pathological FS based on MMT performance at 10% contrast. This example illustrates that including testing at diminished contrast levels in the near periphery yields results that cannot be achieved by visual acuity measurements alone.

Discussion

There is strong evidence that tests of low-contrast foveal vision are predictors of subsequent visual acuity loss in patients older than 52 years [38], and that testing foveal contrast sensitivity (CS) is a sensitive tool for the detection of early deficits [39] and tracking progression [40] in macular disease. In contrast, Stangos et al. [41] found that the degree of CS loss is not a prognostic indicator of neovascular maculopathy. Furthermore, Hyvärinen and colleagues [42] demonstrated the phenomenon of "hidden vision" in patients with ARM or optic nerve atrophy who may have greatly reduced visual acuity and yet normal or nearly normal CS at low spatial frequencies, and moderately good CS at intermediate spatial frequencies. The limitation of these studies lies in the fact that only foveal vision was tested to assess CS.

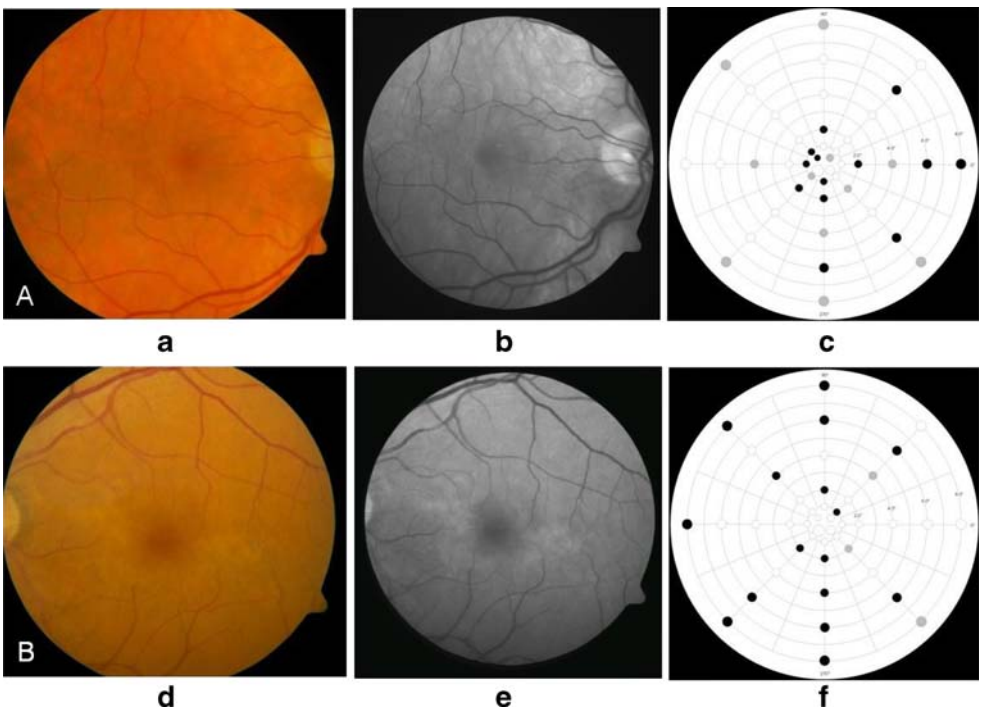

Fig. 4 **A** A case of nfAMD (age: 67 years) with normal funduscopic appearance in the color picture of the right eye (*a*) and in the red-free photograph (*b*). The fellow eye showed a fibrotic choroidal neovascularization (CNV); VA=1.0. (*c*) The losses are found more in the parafoveal than in the foveal area, although there is also one point with no detection and one with detection but incorrect recognition of the letter in the center (*c*) FS=26 (10% contrast). **B** A case of early ARM (group eARM$_2$; age: 70 years, VA=1.0): Funduscopic examination revealed confluent drusen and areas of RPE hypo-pigmentation in the color picture of the left eye (*d*) and in the red-free photograph (*e*); FS=13 at 10% contrast (*f*)

On the other hand, it has been reported that the earliest manifestations of ARM can be found parafoveally, so that low-contrast visual acuity is not sufficient to detect early damage caused by ARM [26, 43–47]. Hence, it is reasonable to assume that mapping vision performance at diminished contrast in the entire central visual field (8° radius) would provide valuable additional information for detection of beginning macular vision loss. In fact, our current results show that ARM can cause significant vision losses in the parafoveal visual field, while visual acuity remains normal.

In addition, if the experimental paradigm requires not only detection, as in perimetry, but discrimination of stimuli, the task gets harder and perceptual thresholds increase, in accordance with previous reports [48–50].

In the present study, the MMT scores for the control group at 5% and 10% contrast begin to decline with age, which was expected due to diminished CS in elderly normally sighted subjects [51]. The measurements reported here show that this decline is more pronounced in patients with the early signs of ARM. This is why the FS values from such patients at diminished contrast fall below the 95% confidence limit of the age function for healthy control subjects. To take advantage of this sensitive indicator, but to keep experimental strain to a minimum, we recommend that measurements with the MMT at 10% contrast be supplemented by an additional test run at 5% contrast to differentiate between loss due to age alone and loss due to impending ARM. The advantage of this procedure lies in the fact that two test runs take only approximately 6 minutes (see results and [32]).

As in a previous pilot study using the MMT [31], our results show that at 100% contrast, patients with ARM have similar scores as normal subjects. However, at reduced contrast, 67% of the patients' FSs fall below the normal 95% reference limit at 5% or 10% contrast, which could be expected based on previous findings [31, 39]. This "detection rate" does not seem to be influenced by the size of drusen or RPE pigmentation shifts, since detection rates in the $eARM_1$ and $eARM_2$ groups were similar.

We showed that eyes from patients with no signs of ARM in the tested eyes but AMD in their fellow eye often have lower MMT performance than healthy age-matched subjects. Accordingly, patients from group $eARM_2$ often have lower performance if their fellow eye*s* have AMD. However, in agreement with findings using other functional examinations [29], the presence of AMD in fellow eyes of patients from group $eARM_1$ is apparently not related to the functional losses found in the examined eye.

In trying to explain our findings, the interpretation of the results may be limited by the relatively small sample. Nevertheless, it cannot be ruled out that functional impairments related to the presence of AMD in the fellow eye might be highlighted in larger samples of ARM patients, regardless of their fundus characteristics. In this case, a follow-up study including a larger number of patients would be suitable to confirm the predictive value of the observed changes, and to formally estimate the sensitivity and specificity of the test.

In summary, sensitivity of visual function testing can be expected to improve by the inclusion of three factors: diminished contrast, the parafoveal field and a discrimination task. We anticipate that future research will provide improved therapies for ARM, so that early detection and timely intervention will be of increasing importance. Hence, having a tool that allows easy screening for early signs of beginning ARM as well as subtle monitoring will improve the prognosis for patients who are at risk.

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