Determinants of Reading Performance in Eyes with Foveal Sparing Geographic Atrophy

Moritz Lindner[1,2,3]; Maximilian Pfau[1]; Joanna Czauderna[1], Lukas Goerdt[1], Steffen Schmitz-Valckenberg[1]; Frank G. Holz[1]; Monika Fleckenstein[1]

[1] Department of Ophthalmology, University of Bonn, Bonn, Germany.

[2] The Nuffield Laboratory of Ophthalmology, Sleep and Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom

[3] Oxford Eye Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Running head: Reading Performance in Foveal Sparing GA

Key words: Geographic atrophy, foveal sparing, age-related macular degeneration, AMD, visual function

Number of words: *4760*

Number of figures *4*

Correspondence:

Prof. Monika Fleckenstein, MD

Department of Ophthalmology, University of Bonn

Ernst-Abbe-Str. 2

53127 Bonn, Germany

Tel.: +49 228 287 15647

Fax: +44 228 287 11470

e-mail: Monika.Fleckenstein@ukb.uni-bonn.de

Financial support:

This study was supported by the German Research Foundation (DFG), Grant No FL658/4-1 and FL658/4-2 to MF and LI2846/1-1 to ML; and the BONFOR GEROK Program, Faculty of Medicine, University of Bonn, Grant No O-137.0022 and O-137.0025 to MP and Genentech Inc., San Francisco, CA, USA. ML is the Knoop Junior Research Fellow at St. Cross College, Oxford, UK. The sponsor or funding organization had no role in the design or conduct of this research.

Abstract

Purpose: To identify anatomic determinants of reading performance in eyes with foveal sparing geographic atrophy (GA).

Design: Prospectively recruited, cross-sectional study: SIGHT (NCT02332343, http://clinicaltrials.gov).

Participants: Patients with foveal sparing GA secondary to age-related macular degeneration.

Methods: Monocular best corrected visual acuity and reading acuity together with reading speed were assessed using Radner charts. Fundus autofluorescence, near-infrared reflectance and spectral-domain optical coherence tomography images were acquired using a Spectralis HRA+OCT or HRA+OCT2 device (Heidelberg Engineering, Heidelberg, Germany). The Minimal Required Reading Rectangle (M3R), a rectangle, sized 19 letters x 2.4 lines in the smallest readable print size of an individual eye was computed and projected into annotated retinal imaging data. The status of the M3R was determined as either "free of atrophy" or "involved into the atrophic process" and the impact on reading was assessed.

Main Outcome Measures: Radner reading score [logRAD] and reading speed [words per minute (wpm)].

Results: A total of 45 eyes (31 patients, 30 female, mean age 76.14 years [64.17 to 89.22 years]) were included. Median BCVA was 0.20[inter-quartile range – IQR: 0.10-0.40] logMAR (Snellen equivalent: 20/32[IQR: 20/25-20/50]). Reading score was 0.52[IQR: 0.30-1.4] logRAD and maximum reading speed was 141.19[IQR: 105.52-164.62] wpm. In 27 eyes the M3R was involved in the atrophic process. This was associated with a significant worsening in Radner score (1.21 [IQR: 0.46-1.40] logRAD vs 0.31[IQR: 0.20-0.51] logRAD, $p<0.001$) and reading speed (110.84 [IQR: 90.0-131.92] wpm vs 162.34[IQR: 137.51-176.66] wpm, $p=0.002$). Eyes where the M3R was non-atrophic additionally showed an increase in reading speed with decreasing print size (peak increase: +73.08 [IQR: 27.43-86.64] wpm compared to the largest test sentence).

Conclusion: The results indicate that a defined area on the retina that can be assessed by retinal imaging is required for unhindered reading in patients with foveal sparing GA. The findings highlight that smaller test sentences can be read faster by patients with this AMD subphenotype. Our results allow predicting reading impairment based on imaging parameters in clinical routine and may support establishing anatomic surrogate endpoints in

clinical trials. Furthermore, the findings could be used to facilitate the adjustment of magnifying reading aids.

Introduction

Geographic atrophy (GA) represents the late-stage of dry age-related macular degeneration (AMD).[1-5] GA is present in 3.5 % of people over 75 years [6, 7] and becomes the predominant type of late AMD in the population of 85 years and older.[8] In industrial countries, late stage neovascular or dry AMD is the leading cause of legal blindness in the elderly and is associated with significant socioeconomic burden.[9-11] While various pathways have been proposed to be involved in the atrophic disease phenotype, the exact underlying pathophysiological mechanisms are incompletely understood. [5]

Typically, patches of GA initially occur in the parafoveal retina. With spread over time, multifocal atrophic areas coalesce, and new atrophic areas may occur. On clinical examination, the fovea may remain uninvolved from outer retinal atrophy until late in the course of the disease. This phenomenon is referred to as “foveal sparing”.[4, 12-14] With the advent of confocal scanning laser ophthalmoscopy (cSLO) fundus autofluorescence (FAF) imaging, it is now possible to accurately and reproducibly quantify GA areas. [15, 16] Recent advances employing combined analysis of FAF and near-infrared reflectance images or green wavelength autofluorescence further improved the accuracy of this technique to delineate atrophy borders even in close proximity to the fovea.[17, 18]

GA areas are associated with a corresponding absolute scotoma. [19] In macular diseases, assessment of visual impairment and quantification of disease progression strongly relies on best corrected visual acuity (BCVA). This is not only the case in clinical routine, but also in the context of clinical trials. However, we could recently demonstrate that the relation between visual acuity and the disease severity as assessed by anatomic markers is poor, particularly in eyes with ‘foveal sparing’ GA. [20] Moreover, in pivotal works by Janet Sunness and coworkers it has been shown that patients with ‘foveal sparing’ are particularly impaired in their reading performance, and may be so despite preserved central visual acuity.[21, 22] This phenomenon can be easily understood if one imagines that a single sentence read by a patient will likely hide within parafoveal atrophic areas in part, while a single letter will still fit into the preserved foveal region (Fig 1 A). Despite these relevant observations, the exact relationship between parafoveal atrophic regions and impaired reading performance is still not understood. This, however, would be important for predicting reading impairment of an individual patient in clinical practice and for adjusting magnifying reading aids. Importantly it would also allow for better alignment of functional and anatomic endpoints in clinical trials. In this regard, precise understanding of structure-function relationships is not only of relevance for a consistent interpretation of trial data. It is also an essential perquisite to enable regulatory agencies to accept anatomic markers as surrogate endpoints in clinical trials.

Herein, we investigate and quantify the spatial relationship between atrophic areas and reading impairment in patients with 'foveal sparing' GA. We can demonstrate that the status of a defined area, termed Minimal Required Reading Rectangle (M3R) is predictive for reading acuity and reading speed.

Methods

Ethics statement

The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board and the Ethics Committee of the Medical Faculty at the Rheinische Friedrich-Wilhelms-Universität Bonn, Germany. Informed consent was obtained from each patient after explanation of the nature and possible consequences of the study.

Patients

All subjects presented in this study were prospectively recruited in the SIGHT study (NCT02332343, http://clinicaltrials.gov) a longitudinal, natural history study in patients with GA secondary to AMD. The general inclusion and exclusion criteria are listed in Table 1 and the corresponding CONSORT chart is provided in Supplement Figure 1. For inclusion into the current analysis a 'foveal sparing' GA [17, 23] surrounding the residual foveal island by at least 270° (assessed by superimposing a virtual pie chart stencil) had to be present. For a detailed definition of the term 'foveal sparing' in context of GA see [17]. Of note, the term 'foveal sparing' does not exclude eyes were the foveal pit was partially atrophic.

Data acquisition and image analysis

Best corrected visual acuity (BCVA) was determined with Early Treatment Diabetic Retinopathy Study (ETDRS) charts on a quasi-logarithmic ordinal scale after performing manual refraction for each eye individually. [24] Monocular reading acuity was assessed using Radner reading charts in German language. Radner reading charts represent a highly validated [25-29] and standardized set of reading test charts made as similar as possible with regard to number of words, word length, number of syllables, and lexical and syntactical complexity.[25] The design principles of the test sentences additionally parallel those of the ETDRS optotypes and show a similar logarithmic size progression, allowing for direct comparison between the BCVA and the Radner test results. Tests were performed as previously described by Radner et al.. [28] In brief, reading charts were presented at a distance of 40 cm, refractive errors as determined above were corrected and presbyopia was compensated with a near addition of 2.5 D. Each test sentence was presented to the participants independently, starting with the largest. The time the participant needed to voice-read the sentence was recorded. The test was terminated if the participant did not manage to read the sentence within 20s, which corresponds to 40 wpm, the minimal acceptable rate for spot-reading. [30] Reading acuity (size of the smallest test sentence read) and reading speed (shortest time needed to read any of the presented sentences) were used for analysis. Eye that could not read the largest line of the Radner charts were assigned a logRAD score of 1.4 and were excluded from the analyses regarding reading speed as indicated. Additionally, an extended variant of the test was performed in a subset of subjects. In these subjects, the test was not terminated if the subject needed > 20s to read a sentence. Rather, the task was repeated with the next smaller test sentence until the smallest sentence was reached, reflecting the previous observation that eyes with foveal-sparing scotomas may only be able to read small print size [21].

Before fundus examination, the pupil of the study eye was dilated with 1% tropicamide eye drops. FAF, near-infrared reflectance (NIR) and spectral-domain optical coherence tomography (SD-OCT) images were acquired using Spectralis HRA+OCT or HRA+OCT2 device (Heidelberg Engineering, Heidelberg, Germany). FAF images were acquired with an excitation wavelength of 488 nm and an emission spectrum of 500 - 700 nm. NIR images were obtained at 820 nm wavelength. The field of view was set to 30° x 30° with a minimal resolution of 768 x 768 pixels and was centered on the fovea. SD-OCT volume scans centered on the fovea were performed with the same device. Multiple SD-OCT scans were averaged (up to 100 single images) by making advantage of the Automatic Real Time (ART)-mode to improve the signal-to-noise ratio.

Measurement of atrophic areas and foveal sparing area were performed as previously described. [17] FAF images with superimposed region outlines were saved to file. The SD-OCT scan crossing the foveola was identified; herein the foveal pit was marked. This mark was instantly transferred to the NIR guidance image by the manufacturer's viewing software. SD-OCT and NIR guidance image were stored to file. Further image analysis was realized using custom-built programs based on FIJI/ImageJ [31] and Matlab 2017b (The Mathworks inc, Natick, USA) and performing three tasks: 1) Registration of NIR/SD-OCT guidance images on FAF images; 2) transferring the location of the foveola as outlined by SD-OCT to FAF images; 3) and computation of the Largest Free Reading Rectangle (LFRR, see below and Figure 2 A).

The Reading Rectangles

Psychophysical tests in healthy individuals realized by McConkie and Rayner have identified that a perceptual span of 19 letters in length allows for unhindered reading. [29, 30,32] Subsequently, based on this work and the observations from Aulhorn et al. [33] Trauzettel-

Klosinski described a perceptual span oval, an area extending from 2° nasal to 5° temporal and 1° superior to 1° inferior) as critical area for reading in patients with hemifield defects [34-37]. This corresponds to the perceptual span 19 letters in width by McConkie and Rayner and consequently ~2.4 lines in height. AMD patients usually have structural alterations in the central macula that affect visual acuity and thereby their ability to recognize letters in a normal text size. Therefore, unhindered reading would require a text or letter size that is at least as tall as the test characters corresponding to the eye's BCVA. Thus, we herein use the term Reading Rectangle to refer to a 19 letters x 2.4 lines rectangular area on the retina. The actual dimensions of this area are determined by the underlying sample letter size, e.g. the size of an optotype read on the ETDRS charts. The size of the Reading Rectangle can therefore be expressed in logMAR equivalents. In brief, conversion was performed taking into account the design principles and size progression of the ETDRS optotypes[38], the standard spacing between two lines (29% of letter height, the mean letter width adjusted for the frequency of the individual characters in German language, [39] the sentence structure and the font type used in Radner charts [28]. In more detail, this corresponds to the following steps:

- Obtaining the size of optotype projected onto the retina by its logMAR value on the ETDRS chart:
  - 10^(logMAR value) = Minimum Angle of Resolution. *Unit Conversion.*
  - 5x Minimum Angle of Resolution = Optotype height on retina (in minarc). *Rationale: The design principles of ETDRS optotypes, where each optotype is five times as high as the Minimum Angle of Resolution it measures).* [38]
  - Optotype height on retina (in minarc) / 60 = **Optotype height on retina (in degree)**. *Unit Conversion.*
- Conversion of optotype height to full text line height.
  - Optotype height on retina / (1-0.29) = **text line height on retina**. *Rationale: Above and below each printed letter, there is a free space, visually separating one line from another. Its height is characteristic for an individual font type and is 29% in case of "Arial", which is used in the Radner charts.* [28]
- Obtaining average letter width
  - Optotype height on retina * 0.44 = **Letter width on retina** (in degrees); With Average height to width ratio = 0.44. *Rationale: height to width ratios differ for each letter (and the resp. font type). An average ratio can be calculated taking into account the frequency of the individual characters as well as the frequency of capital letters in the respective language (here: German)* [40] *and the design characteristics of the font type.*
- Obtaining size of Reading Rectangle on retina

- Optotype width on retina * 19 = **Reading Rectangle width on retina**.
  Rationale: Perceptual span width (see above).
- Text line height on retina * 2.4 = **Reading Rectangle height on retina**.
  Rationale: Perceptual span height (see above).

This calculation can be performed into both directions, i.e. starting with a Reading Rectangle of a defined size (e.g. the largest rectangle that fits into the spared fovea of a patient [see point 1 below]), or starting with a given letter/optotype size (for instance, the smallest optotype a patient could read [see point 2 below]). Thus, based on this concept, two characteristic Reading Rectangles can be obtained for each eye:

1) The Largest Free Reading Rectangle (LFRR) is the largest rectangle fitting inside the area of foveal sparing without overlapping with adjacent atrophic areas (Fig 1, B+D). This was computationally extracted from FAF images using a custom algorithm programmed in Matlab R2017b. Its size determines the size of the largest print, whereof 19 letters x 2.4 lines fit into the spared fovea and thus hypothetically the largest print where unhindered reading is possible. The LFRR did not necessarily have to include the foveola or parts of it. A rectangle was chosen instead of the oval suggested by Trauzettel-Klosinsky [41] as the oval was originally conceptualized based on neuro-ophthalmologic patients exhibiting hemifield defects with semi oval-shaped "macular sparing".

2) The Minimal Required Reading Rectangle (M3R), which is the 19 letters x 2.4 lines Reading Rectangle corresponding to the size of the best corrected visual acuity. The M3R can either be uninvolved by any atrophic process (M3R<LFRR, see Fig 1 B+C) or it can overlap (partially or fully) with areas of atrophy (M3R>LFRR, see Fig 1 D+E). The status of the M3R indicates if a rectangle, sized 19 letters x 2.4 lines in the smallest readable print size, is free of atrophy. In other words, the M3R is the area on the central retina, which hypothetically needs to be free of atrophy in order to allow unhindered reading.

Figure 2 provides a diagram illustrating how LFRR and M3R are obtained, and examples of cases where the M3R is, and, respectively, is not, free of atrophy are shown in Fig 1 B-E. A glossary of these terms is also given in Table 2.

Statistical analysis

Data were compiled in a spreadsheet application and analyzed using R Version 3.4.4. [21] Differences between groups were tested using an unpaired t-test performing Welsh correction in case of unequal variances. Differences in proportions were assessed using Pearson's Chi-square. Where correlation analyses were performed, Pearson's correlation coefficient was employed. All univariate statistics are performed on eye-level, unless stated differently. A linear mixed effect model with reading speed as outcome was used to account for potential interactions between atrophic involvement of the M3R and the status of the fovea. The model considered the hierarchical structure of the data (i.e. eye nested in patients). Data presented in this study are given as median with the corresponding inter-quartile range (IQR). Mixed model results and the data in Fig 3 A are given as mean ± standard error.

Results

A total of 45 eyes (31 patients, 16 female) with foveal sparing GA were included in the study. Mean age of patients was 76.5 years (range 64.2 to 89.2 years). Median GA size was 10.03 [IQR: 7.20 – 16.95] mm² (no data available for one eye, where the atrophy border exceeded the image frame). Despite the foveal sparing shape of atrophy, the foveola itself was at least partially atrophic in 29 eyes (64.4%). The size of the spared fovea could be quantified in all but four eyes and was 0.98 [IQR: 0.55 – 1.46] mm².

Median BCVA at the day of examination was 0.20 [IQR: 0.10 – 0.40] logMAR (Snellen equivalent: 20/32 [IQR: 20/25 – 20/40]) while median Radner reading score was notably worse with a median of 0.52 [IQR: 0.30 – 1.4] logRAD. Herein, 17 eyes were included that were not able to read the largest line of the Radner chart (Radner score: 1.4 logRAD). Correlation between BCVA and Radner score was overall modest (Pearson's r = 0.62 [95%CI: 0.41 – 0.77], p<0.001). Maximum reading speed was 141.19 [IQR: 105.52 – 164.62] wpm and showed a weak correlation with BCVA (Pearson's r = -0.51 [95%CI: -0.74 – -0.17], p=0.006).

In a next step, the influence of the status of the M3R on reading acuity and reading speed was determined. The Radner score was significantly worse in eyes where the M3R was involved in the atrophic process (exemplary case presented in Fig 1 E) as compared to eyes where the M3R was intact (1.21 [IQR: 0.46-1.40] logRAD, n=27 vs 0.31 [IQR: 0.20-0.51] logRAD, n=18, p<0.001, Fig 3 A). Reading speed was also significantly lower in eyes where the M3R was involved in the atrophic process as compared to eyes with intact M3R (110.84 [IQR: 90.0-131.92] wpm, n=12 vs 162.34 [IQR: 137.51-176.66] wpm, n=16, p=0.002, Fig 3 B). Notably, for 17 eyes, no value for reading speed was obtained as patients did not manage to read the largest test sentence on the Radner charts. Of these, 15 eyes presented with a M3R involved in the atrophic process (p=0.003).

To confirm that these observations were not biased by repeated measurements within patients (i.e. inter-eye correlation) or other covariates, in particular the involvement of the foveola into the atrophic process, we created a mixed model encompassing both, the status of the M3R and the foveola as fixed effects. While the status of the M3R remained significant ([effect size ± standard error] -42.33 ± 12.71 wpm, p=0.013), the status of the foveola did not significantly interact with reading speed (slope = 2.39 ± 12.29 wpm, p=0.85).

To further analyze the reading performance of patients with foveal sparing GA, we slightly modified the Radner protocol for a subset of patients (n=21): While usually the test was terminated once a participant had failed to read the test phrase in the given 20s interval, the test would now simply continue with the next smaller sentence. As shown in Fig 4 A, patients managed on average to read smaller test sentences faster than the largest presented test sentences. Only in a single eye (Fig 4 B, eye #37), the largest test sentence was also the one read fastest. In 5 eyes that could not read the largest test sentence at all, smaller sentences could be read within the 20s-time limit (Fig 4 B, eyes #16, #27, #35, #42, #46). On average, the fastest sentence read was 27.43 [IQR: 12.30 – 73.08] wpm faster than the largest test sentence. Notably, this observation was pronounced in those eyes, where the M3R was intact (Fig 4 A, blue line, +73.08 [IQR: 27.43 – 86.64] wpm, n=9), while in eyes where the M3R was affected by atrophy, the gain in reading speed with decreasing letter size was minimal (Fig 4 A, red line, +13.85 [IQR: 0.00 – 47.35] wpm, n=12, p=0.03). Consistent with the results obtained with the unmodified test protocol, the maximum reading speed was severely reduced in eyes where the M3R was affected by atrophy.

In an explorative approach, we evaluated the reading speed curves obtained for each individual eye (Fig 4 B). The falling shoulder of the reading speed curve was usually in the range of the individual eye's BCVA. Thus, the reading speed most notably decreased once the print size approached the size of the BCVA optotypes (best exemplified in Fig 4 B, eye #1 and #10). On the other hand, the LFRR is expected to determine the size of the largest print where unhindered reading is possible for an individual eye. Therefore, a sharp decrease of reading speed would be expected for test sentences of print sizes larger than an individual eyes LFRR. However, there was no obvious association between the LFRR and the rising shoulder of the curve (e.g., see eye #16, where the raise in reading speed occurs at print sizes way larger than predicted by the LFRR). Contemplating eyes, where the M3R was affected by atrophy, 4 eyes (ID 36 – 39) obtained relatively high values for reading speed of > 100 wpm. Reviewing the retinal imaging data from these eyes revealed that in all these cases the atrophy did not entirely encircle the fovea but left a small bridge towards the left, i.e. into reading direction.

Discussion

In this study we could quantify the spatial relationship between areas of geographic atrophy and reading performance. We particularly showed that integrity of a rectangular area confined to the spared fovea, termed Minimal Required Reading Rectangle (M3R), determines if high reading acuity and reading speed can be achieved in an individual eye. Remarkably, while involvement of the foveola in the atrophic process has been shown to be the key determinant of visual acuity in GA,[42] we herein demonstrated that for reading, not the status of the foveola but rather that of the M3R is of relevance. The M3R also facilitates identification of patients exhibiting a “paradoxical” increase in reading performance with smaller print which will become of importance for patient-tailored low-vision rehabilitation.

Knowledge on the M3R in an individual patient may be important in many ways. It may serve as a tool to predict the reading performance of an individual and, thereby, estimate functional impairment in daily life. As the status of the M3R in an individual eye can be graded by assessing only the BCVA and a minimal retinal imaging dataset this will save time as compared to performing a full reading test in first place. The M3R could therefore be employed as a screening tool for high-volume clinics.

In terms of low-vision rehabilitation, rapid serial visual presentation (RSVP) – i.e. projection of single words to facilitate reading without saccades – has been previously shown to improve reading speed in patients with dense central scotomas. [43] Since RSVP essentially minimizes the required reading angle, patients with foveal sparing may be expected to show even greater benefit from RSVP based on the data shown herein. This warrants further investigation. Novel Smartphone or Tablet RSVP applications have been designed to accelerate reading in healthy individuals (e.g. https://www.spreeder.com/) and could be adopted to support reading in patients with foveal sparing. The optimal size and number of the projected words would again be derived from the M3R and the LFRR. Finally, the M3R in conjunction with the Largest Free Reading Rectangle (LFRR) – that is expected to correspond to the largest print size where unhindered reading is possible – would allow predicting the optimal strength for magnifying reading aids with higher precision. Likewise, this might even spot light on the potential to help patients with good visual acuity and a small residual foveal island by de-magnifying reading aids.

In this context, an important observation made herein is also the increase in reading speed with decreasing letter size as seen in several eyes (Fig 4). This phenomenon has previously been described by Sunness et al. in a limited number of patients.[21, 22] We could now confirm that this effect is present to some extent in basically every GA eye with foveal sparing. In extreme cases the first, largest, test sentence could not be read, while a smaller sentence were read at a reasonable speed. In the present dataset, this was more likely to occur if the M3R was not affected by atrophy. This finding is not only of relevance when adjusting magnifying vision aids. It is also of interest when planning clinical trials where Radner reading charts or comparable tests [44] are used for testing reading speed as a secondary endpoint. If the protocol requires terminating the test once a sentence is not read within a defined interval of time – instead of going on the next smaller sentence – this might result in 'faulty' poor reading scores in those patients. Awareness of this phenomenon may reduce discrepancy between functional and anatomic trial outcome measures.

Worth mentioning, it has previously been observed that eyes with foveal sparing scotomas may also show an increase in reading speed with increasing letter size, resulting in a bimodal reading speed curve, with one peak at small print sizes (where the read text fits into the LFRR) and one at very large print sizes (where the text can be read using areas of the retina peripheral to the atrophy) [22]. Such bimodal reading curves did not become apparent in the present dataset as print sizes larger than 2.54 deg were not tested. However, in patients that only achieved a poor reading speed when testing print sizes fitting into the LFRR it is important to consider a potential bimodality of the reading speed curve and test if a better reading speed can be obtained with very large print size.

Anatomic outcome measures are particularly attractive in clinical trials on macular disorders as these are usually faster to obtain and – more importantly – less dependent on the examiner and the cooperation of the patient. However, regulatory authorities require a high degree of validation against functional outcome measures to accept anatomical markers as primary endpoints in interventional trials. The present data on M3R and LFRR represent an important next step in this validation process.

Notably, while the present findings suggest that the M3R can be used to align reading performance as a functional endpoint with anatomic endpoints in clinical trials, the present data are not sufficient to establish the M3R itself as an endpoint for clinical trials. Larger trial cohorts confirming the present findings and describing the course of the M3R over time as well as a direct validation against quality of life assessment tools will be required.

In the present study, we employ an imaging dataset consisting of a cross-foveal OCT, a confocal 488nm FAF image and a near-infrared reflectance image to assess the status of the M3R. Obviously, a 512 nm FAF image could likely substitute the combination of 488 nm FAF image and a near-infrared reflectance [18] and use of dense *en-face* OCT scans alone could even enable the implementation of fully automated algorithms further facilitating the use of M3R in clinical routine.

The M3R turned out to be an effective tool to predict reading performance of an eye based on retinal imaging data. The LFRR, which in turn should predict the maximum print size legible, seemed to be less accurate, as several patients obtained high values for reading speed even for print sizes larger than those predicted by the LFRR (Fig 4 B). This may have several possible explanations: either, for large print sizes the participants of this study were able to use areas of non-atrophic retina outside the fovea to read (i.e. areas not within the spared fovea, but beyond the ring of GA). This extrafoveal reading is commonly observed among patients with central atrophy and has been previously studied in a cohort of patients with central atrophy without foveal sparing, though employing slightly larger print sizes. [30, 37] Another possible explanation may be that the rectangular 19-letters-x-2.4-lines-shape of the LFRR is not ideal. In particular the evidence underlying the height of the LFRR, and likewise the perceptual span oval [41] is relatively indirect. Our observation that in some eyes which had a thin bridge of intact retina between sparing and surrounding retina in reading direction seemed to have a beneficial effect on reading performance is in line with the concept that a reading rectangle less than 2.4 lines in height might still be sufficient. To overcome the resulting limitation of the present work we plan to use a machine learning approach to find the optimum shape of the reading rectangle. This will require significantly larger cohorts and graphics processor-based algorithms.

Of note, only monocular reading performance were analyzed in this study. We did not assess if the M3R would also make a good predictor for binocular reading, e.g. in patients with bilateral foveal sparing GA. Monocular and binocular reading speed are similar in normally sighted individuals. [45, 46] There is also no significant binocular gain in patients with central scotomoas compared to their better eye. [47] Therefore, we may predict that for unhindered binocular reading a non-atrophic M3R in one eye may be sufficient. However, occlusion of one eye has been shown to increase saccade length [45], which might suggest that the relative width of an optimal M3R for binocular reading could have slightly different dimensions (shorter) than for monocular reading.

Several limitations need to be considered. Reading speed may be correlated with the educational level of a test person. For Radner charts a difference of 40 wpm has been observed between students and apprentices. [27] We did not systematically assess the educational background of our participants. However, the effect of the M3R on reading speed as measured in this study was slightly higher (110.84 [IQR: 90.0-131.92] wpm vs 162.34 [IQR: 137.51-176.66] wpm, p=0.002, Fig 3 B) than the observed difference between students and apprentices in another study. [27] It is therefore unlikely that an educational difference between the eyes of patients with and without a (partially) atrophic M3R would have significantly biased the present observations. We also did not assess reading comprehension of longer texts in this study, which is potentially a more meaningful measure for every day reading tasks and only modestly correlates with the results of short sentence reading tests. [48] However, a recent study in patients with AMD could show that, compared to controls, short sentence reading speed and reading comprehension are likewise impaired. [49] Regardless if a reading speed or comprehension test is used to assess reading performance, there is generally little validation of these tests against established quality of life questionnaires. The

Radner test is validated against the NEI-VFQ (at least for patients with hemifield defects), which was an important reason for us to use this test. [29]

In conclusion, we demonstrated that the integrity of a defined rectangular area on the central retina determines reading performance in eyes with foveal sparing GA. The results allow to better estimate the functional impairment of an individual patient, to predict the need of magnifying or de-magnifying reading aids and align reading performance as a functional endpoint with anatomic endpoints in clinical trials.

Figures

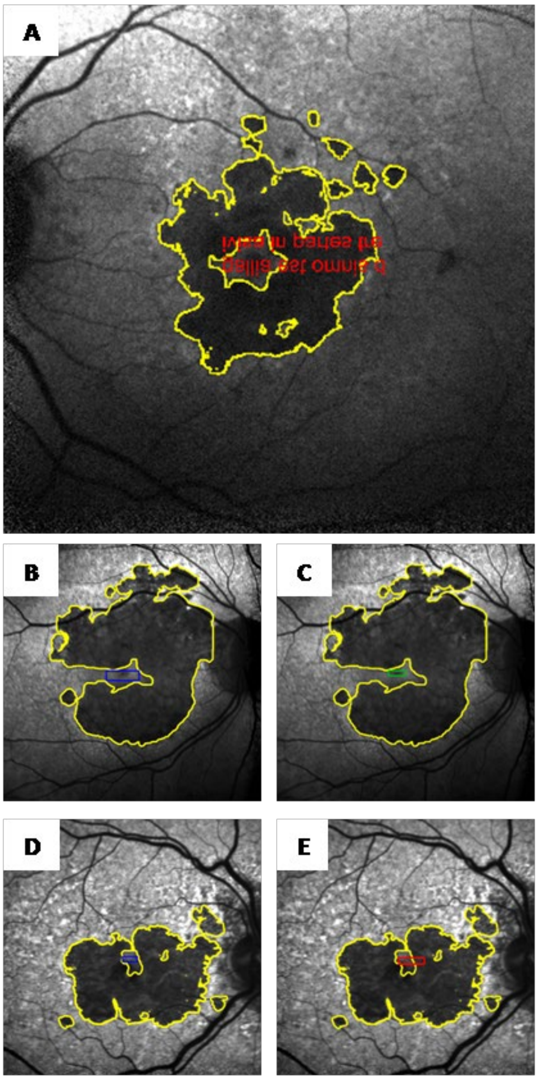

Fig. 1: Fundus autofluorescence images of three representative eyes with the area of Geographic Atrophy outlined in yellow. A) A sample sentence containing 19 characters x two lines in a print size corresponding to 1 logMAR (Snellen equivalent 20/200; this size is chosen for illustration purposes only) projected onto the central retina. The eye shown in B and C has a BCVA of 0.1 logMAR (Snellen equivalent 20/25). B) The Largest Free Reading Rectangle (LFRR) is outlined in blue. C) The Minimal Required Reading Rectangle (M3R, outlined in green) fits into the spared fovea (i.e. M3R < LFRR for this eye). This eye has a good Radner score of 0.2 logRAD and a high maximum reading speed of 164 wpm. The eye shown in D and E has an only slightly lower BCVA of 0.3 logMAR (Snellen equivalent 20/40). D) The LFRR (outlined in blue) is smaller than that of the eye in B and C.

E) The M3R (outlined in red) does not fit into the spared fovea. This eye has a poor Radner score of 1.2 logRAD and a low maximum reading speed is 80 wpm.

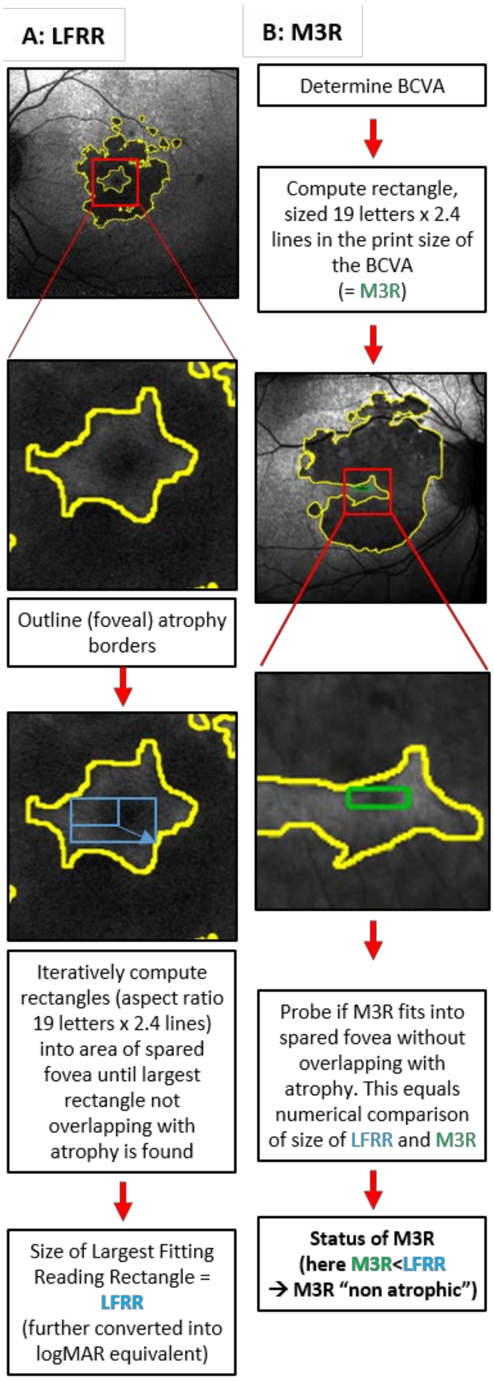

Fig 2: Flowchart illustrating the computation of (A) the Largest Fitting Reading Rectangle (LFRR) and (B) the Minimal Required Reading Rectangle (M3R). See section "Methods, The Reading Rectangles" for a more detailed explanation of how the reading rectangles were obtained.

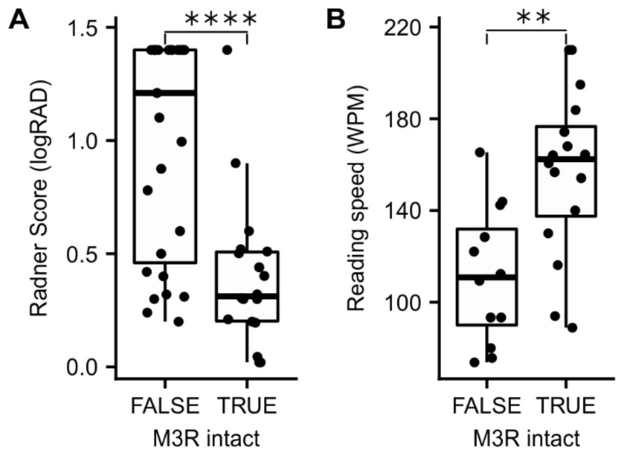

Fig. 3: Radner score (A) and reading speed (B) in eyes with Geographic Atrophy and Foveal Sparing. Eyes with a non-atrophic Minimal Required Reading Rectangle (M3R – right columns) exhibit better Radner scores and faster reading speeds compared with eyes where the M3R is atrophic (left columns).

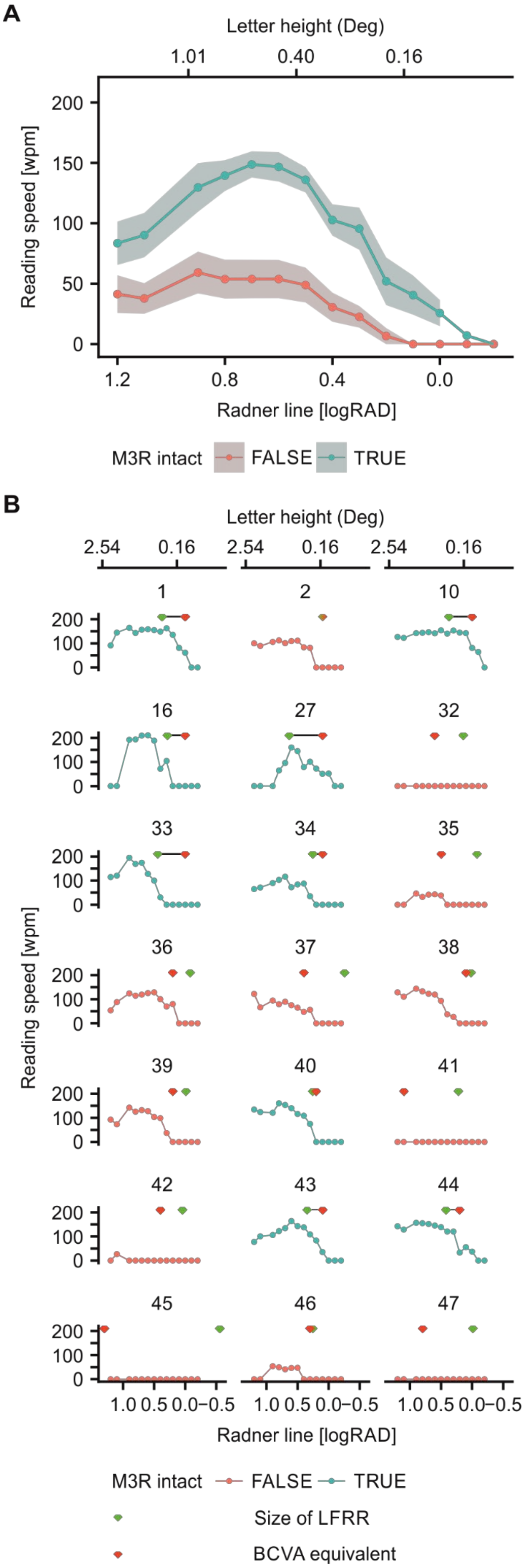
A
Letter height (Deg)
1.01
0.40
0.16
Reading speed [wpm]
200
150
100
50
0
1.2
0.8
0.4
0.0
Radner line [logRAD]
M3R intact
FALSE
TRUE
B
Letter height (Deg)
2.54
0.16
1
2
10
16
27
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
Reading speed [wpm]
1.0 0.5 0.0 −0.5
Radner line [logRAD]
M3R intact
FALSE
TRUE
Size of LFRR
BCVA equivalent

Fig. 4: Reading speed as a function of letter size as obtained with the modified Radner reading test protocol. A: Mean ± Standard Error of the 21 eyes included into this sub-analysis. B: Traces of individual eyes. Eyes with a non-atrophic Minimal Required Reading Rectangle (M3R) are depicted in blue, others in light red. The small markers in B indicate the eye's Best corrected visual acuity (BCVA, dark red) and the size of the Largest Free Reading Rectangle (LFRR) – converted into logMAR equivalents (green). Numbers above the individual traces are eye-IDs. See section "The Reading Rectangles" in methods for further details on how logMAR equivalents were calculated.

Tables

Table 1: Inclusion and exclusion criteria of the SIGHT study

Inclusion criteria	Exclusion criteria
• Men and women, any race, aged 55 years or older • The study eye must have a contiguous well-demarcated area of GA either in a complete ring around the spared fovea or in a horseshoe pattern or single atrophic spots surrounding the intact fovea with a total atrophy size of ≤ 7 DA • BCVA: 35 letters (1 logMAR / 20/200 Snellen equivalent) or better • The partner eye may have any stage of AMD (drusen ≥ 63 µm, GA or CNV). There are no restrictions on the size of the GA if present or on BCVA. This eye may have a history of anti-VEGF treatment • The study eye must have clear ocular media and adequate pupillary dilation to permit good quality images including fundus autofluorescence (FAF), SD-OCT and colour fundus photography as assessed by the investigator • If both eyes meet the criteria to be study eyes each eye will be included	• Presence or history of CNV in the study eye • Ocular disease in the study eye that may confound assessment of the retina (e.g., diabetic retinopathy, uveitis) • Cataract surgery or ocular surgery in the study eye within 30 days prior to the visit • Current or previous participation in clinical studies investigating drugs, medical devices or supplements within 30 days prior to enrolment in the study • Previous or concomitant therapy to treat AMD (investigational or FDA approved); oral supplements of vitamins and minerals are permitted • Known medical history of allergic reactions or sensitivity to fluorescein dye which in the investigator's opinion is clinically relevant

Table 2: Definitions of reading rectangles as used in this study

Reading Rectangle	Any 19 letters x 2.4 lines rectangle, whose actual dimensions can be described a function of the underlying sample text size in logMAR.
The Largest Free Reading Rectangle (LFRR)	The largest Reading Rectangle fitting inside the area of foveal sparing with no atrophy included.
Minimal Required Reading Rectangle (M3R)	A Reading Rectangle in size of the Best Corrected Visual Acuity measured in the individual eye.

References

1. Gass JD. Drusen and disciform macular detachment and degeneration. Arch Ophthalmol 1973;90:206-17.

2. Blair CJ. Geographic atrophy of the retinal pigment epithelium. A manifestation of senile macular degeneration. Arch Ophthalmol 1975;93:19-25.

3. Schatz H, McDonald HR. Atrophic macular degeneration. Rate of spread of geographic atrophy and visual loss. Ophthalmology 1989;96:1541-51.

4. Sunness JS. The natural history of geographic atrophy, the advanced atrophic form of age-related macular degeneration. Mol Vis 1999;5:25.

5. Lim LS, Mitchell P, Seddon JM, et al. Age-related macular degeneration. Lancet 2012;379:1728-38.

6. Klein R, Klein BE, Franke T. The relationship of cardiovascular disease and its risk factors to age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology 1993;100:406-14.

7. Vingerling JR, Dielemans I, Hofman A, et al. The prevalence of age-related maculopathy in the Rotterdam Study. Ophthalmology 1995;102:205-10.

8. Klein R, Klein BE, Knudtson MD, et al. Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. Ophthalmology 2007;114:253-62.

9. Congdon N, O'Colmain B, Klaver CC, et al. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol 2004;122:477-85.

10. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ 2004;82:844-51.

11. Chakravarthy U, Bailey CC, Johnston RL, et al. Characterizing Disease Burden and Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration. Ophthalmology 2018.

12. Sunness JS, Gonzalez-Baron J, Applegate CA, et al. Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. Ophthalmology 1999;106:1768-79.

13. Sarks JP, Sarks SH, Killingsworth MC. Evolution of geographic atrophy of the retinal pigment epithelium. Eye (Lond) 1988;2 (Pt 5):552-77.

14. Lindner M, Bezatis A, Czauderna J, et al. Choroidal Thickness in Geographic Atrophy secondary to Age- Related Macular Degeneration. Invest Ophthalmol Vis Sci 2015;56:875-82.

15. Delori FC, Dorey CK, Staurenghi G, et al. In vivo fluorescence of the ocular fundus exhibits retinal pigment epithelium lipofuscin characteristics. Invest Ophthalmol Vis Sci 1995;36:718-29.

16. von Ruckmann A, Fitzke FW, Bird AC. Distribution of fundus autofluorescence with a scanning laser ophthalmoscope. Br J Ophthalmol 1995;79:407-12.

17. Lindner M, Boker A, Mauschitz MM, et al. Directional Kinetics of Geographic Atrophy Progression in Age-Related Macular Degeneration with Foveal Sparing. Ophthalmology 2015;122:1356-65.

18. Pfau M, Goerdt L, Schmitz-Valckenberg S, et al. Green-Light Autofluorescence Versus Combined Blue-Light Autofluorescence and Near-Infrared Reflectance Imaging in Geographic Atrophy Secondary to Age-Related Macular Degeneration. Invest Ophthalmol Vis Sci 2017;58:BIO121-BIO30.

19. Pilotto E, Guidolin F, Convento E, et al. Fundus autofluorescence and microperimetry in progressing geographic atrophy secondary to age-related macular degeneration. Br J Ophthalmol 2013;97:622-6.

20. Lindner M, Nadal J, Mauschitz MM, et al. Combined Fundus Autofluorescence and Near Infrared Reflectance as Prognostic Biomarkers for Visual Acuity in Foveal-Sparing Geographic Atrophy. Invest Ophthalmol Vis Sci 2017;58:BIO61-BIO7.

21. Sunness JS. Reading newsprint but not headlines: pitfalls in measuring visual acuity and color vision in patients with bullseye maculopathy and other macular scotomas. Retinal cases & brief reports 2008;2:83-4.

22. Sunness JS, Rubin GS, Zuckerbrod A, Applegate CA. Foveal-Sparing Scotomas in Advanced Dry Age-Related Macular Degeneration. J Vis Impair Blind 2008;102:600-10.

23. Lambertus S, Lindner M, Bax NM, et al. Progression of Late-Onset Stargardt Disease. Invest Ophthalmol Vis Sci 2016;57:5186-91.

24. Ferris FL, 3rd, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol 1982;94:91-6.

25. Radner W, Diendorfer G. English sentence optotypes for measuring reading acuity and speed--the English version of the Radner Reading Charts. Graefes Arch Clin Exp Ophthalmol 2014;252:1297-303.

26. Stifter E, Konig F, Lang T, et al. Reliability of a standardized reading chart system: variance component analysis, test-retest and inter-chart reliability. Graefes Arch Clin Exp Ophthalmol 2004;242:31-9.

27. Radner W, Obermayer W, Richter-Mueksch S, et al. The validity and reliability of short German sentences for measuring reading speed. Graefes Arch Clin Exp Ophthalmol 2002;240:461-7.

28. Radner W, Willinger U, Obermayer W, et al. [A new reading chart for simultaneous determination of reading vision and reading speed]. Klin Monbl Augenheilkd 1998;213:174-81.

29. Gall C, Wagenbreth C, Sgorzaly S, et al. Parafoveal vision impairments and their influence on reading performance and self-evaluated reading abilities. Graefes Arch Clin Exp Ophthalmol 2010;248:863-75.

30. Whittaker SG, Lovie-Kitchin J. Visual requirements for reading. Optom Vis Sci 1993;70:54-65.

31. Schindelin J, Arganda-Carreras I, Frise E, et al. Fiji: an open-source platform for biological-image analysis. Nat Methods 2012;9:676-82.

32. Rayner K. The perceptual span and peripheral cues in reading. Cognitive Psychology 1975;7:65-81.

33. Aulhorn E. Über Fixationsbreite und Fixationsfrequenz beim Lesen gerichteter Konturen. Pflüger's Archiv für die gesamte Physiologie des Menschen und der Tiere 1953;257:318-28.

34. Trauzettel-Klosinski S. Rehabilitation for visual disorders. J Neuroophthalmol 2010;30:73-84.

35. Trauzettel-klosinski S. Eccentric fixation with hemianopic field defects: A valuable strategy to improve reading ability and an indication of cortical plasticity. Neuro-Ophthalmology 1997;18:117-31.

36. Trauzettel-Klosinski S, Reinhard J. The vertical field border in hemianopia and its significance for fixation and reading. Invest Ophthalmol Vis Sci 1998;39:2177-86.

37. Trauzettel-Klosinski S, Teschner C, Tornow R-P, Zrenner E. Reading strategies in normal subjects and in patients with macular scotoma-assessedby two new methods of registration. Neuro-Ophthalmology 1994;14:15-30.

38. Bailey IL, Lovie-Kitchin JE. Visual acuity testing. From the laboratory to the clinic. Vision Res 2013;90:2-9.

39. Beutelspacher A. Kryptologie : eine Einführung in die Wissenschaft vom Verschlüsseln2005; 156.

40. Beutelspacher A. Kryptologie : eine Einführung in die Wissenschaft vom Verschlüsseln, Verbergen und Verheimlichen ; ohne alle Geheimniskrämerei, aber nicht ohne hinterlistigen Schalk, dargestellt zum Nutzen und Ergötzen des allgemeinen Publikums, 7., verb. Aufl. ed. Wiesbaden: Vieweg, 2005.

41. Trauzettel-Klosinski S, Brendler K. Eye movements in reading with hemianopic field defects: the significance of clinical parameters. Graefes Arch Clin Exp Ophthalmol 1998;236:91-102.

42. Schmitz-Valckenberg S, Nadal J, Fimmers R, et al. Modeling Visual Acuity in Geographic Atrophy Secondary to Age-Related Macular Degeneration. Ophthalmologica 2016;235:215-24.

43. Rubin GS, Turano K. Low vision reading with sequential word presentation. Vision Res 1994;34:1723-33.

44. Radner W. [Ophthalmologic reading charts : Part 2: Current logarithmically scaled reading charts]. Ophthalmologe 2016;113:1029-35.

45. Johansson J, Pansell T, Ygge J, Seimyr GO. Monocular and binocular reading performance in subjects with normal binocular vision. Clin Exp Optom 2014;97:341-8.

46. Sheedy JE, Bailey IL, Buri M, Bass E. Binocular vs. monocular task performance. Am J Optom Physiol Opt 1986;63:839-46.

47. Kabanarou SA, Rubin GS. Reading with central scotomas: is there a binocular gain? Optom Vis Sci 2006;83:789-96.

48. Ramulu PY, Swenor BK, Jefferys JL, Rubin GS. Description and validation of a test to evaluate sustained silent reading. Invest Ophthalmol Vis Sci 2013;54:673-80.

49. Varadaraj V, Lesche S, Ramulu PY, Swenor BK. Reading Speed and Reading Comprehension in Age-related Macular Degeneration. Am J Ophthalmol 2018;186:138-43.