Wet versus Dry Age-Related Macular Degeneration in Patients with Central Field Loss: Different Effects on Maximum Reading Speed

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Purpose. To describe new, efficient predictors of maximum reading speed (MRS) in age-related macular degeneration (AMD) patients with central field loss. Type of AMD (wet versus dry) was scrutinized, because this factor seems to offer a promising model of differential visual adaptation induced by different temporal courses of disease progression.

Methods. Linear mixed-effects (LME) analyses were performed on a dataset initially collected to assess the effect of interline spacing on MRS. MRS was measured with MNread-like French sentences in 89 eyes (64 dry and 25 wet) of 61 patients with AMD. Microperimetry examination was performed on each eye. The eyes were included only if they had a dense macular scotoma including the fovea, to ensure that patients used eccentric viewing.

Results. Analyses show the unique contributions—after adjustment for the effects of other factors—of three new factors: (1) MRS was higher for wet than for dry AMD eyes; (2) an advantage of similar amplitude was found for phakic eyes compared with pseudophakic eyes; and (3) MRS decreased when distance between fixation preferred retinal locus (PRL) and fovea increased. In addition, the instantaneous slope of the relationship between scotoma area and MRS was much shallower than reported in two other studies.

Conclusions. The four effects improve the ability to predict MRS reliably for AMD patients. The wet/dry difference is a major finding that may result from the different time courses of the two types of disease, thus involving different types of visuomotor and attentional adaptation processes. (*Invest Ophthalmol Vis Sci.* 2011;52:2417–2424) DOI:10.1167/iovs.09-5056

It is still very unclear how to predict everyday visual functional performance, especially reading performance, for low-vision patients with age-related macular degeneration (AMD). An important seminal study showed that standard clinical factors such as acuity were poor predictors of the maximum reading speed (MRS) achieved by low-vision patients.[1] While this study showed that central field loss is a key predictor of poor reading performance, it also showed that future studies of performance with central field loss should clarify "what features of scotomas—size, shape, etc.—predict poor reading."[1] Since then, important studies in this direction have been performed to better characterize the relationship between some clinical factors and MRS.[2–5]

First of all, it has been shown that the size of absolute macular scotoma in AMD patients is a much better predictor of MRS than is acuity and other standard clinical predictors.[6,7] The predictive power of these results is limited, however, by the relatively small range of scotoma sizes investigated. Similarly, an early study that also showed this correlation cannot be used for predictive purposes, as it included only eight AMD eyes.[8] Although scotoma size is recognized as a good predictor of current reading performance, it is not a good predictor of future reading performance in AMD patients tested on two occasions separated by 3 to 12 months.[9] A second good predictor of MRS is the gaze stability measured during fixation of a static target.[10] Finally, one factor that has received considerable interest is the preferred retinal locus (PRL) used during fixation of a static target.[11] (The fixation PRL should not be confused with the PRL, or the set of PRLs, used during reading.) However, the consensus in clinical studies is that the location of the fixation PRL relative to the scotoma is not a statistically significant factor in determining the reading rate of patients with central field loss.[5,12,13]

Surprisingly, only a few studies have been conducted in an attempt to investigate the relationship between the type of AMD and important functional measures such as MRS. Late AMD is characterized by wet (exudative) and dry (geographic atrophy [GA]) forms.[14,15] Most patients with severe visual loss have the wet form,[16] a finding that may explain why this type of AMD is usually considered as "worse" than the dry form. Although a recent study found that the wet/dry factor was not a statistically significant predictor of future fluent reading speed,[9] there are reasons to suspect that wet and dry AMDs should induce different patterns of reading performance at a given time. The major relevant difference for our purpose is that wet AMD develops very rapidly due to choroidal neovascularization, whereas dry AMD has a much slower progression. Wet AMD is also characterized by distortion of the retina and by the presence of fluid, hemorrhage, and scarring. It is likely that these different temporal scales of disease progression induce very different adaptation processes.

The role of adaptation during a disease such as AMD is so crucial[2] that it may explain the variability in functional performance among patients much better than some acknowledged clinical factors. Experimental control of adaptation, however,

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is notoriously difficult. As the wet/dry dichotomy may constitute a good way of indirectly manipulating the adaptation factor, we focused the present work on the relationship between the wet/dry factor and MRS. We used a dataset initially collected and analyzed to investigate the influence of interline spacing and visual crowding on MRS in low-vision patients with central field loss.[17] The major finding is a clear-cut advantage in MRS for wet AMD eyes.

METHODS

The present work is based on a set of data (minus eight Stargardt eyes) initially used in Calabrese et al.,[17] where the methods are presented in detail.

Eyes

All eyes retained in the present work for statistical analyses had a dense macular scotoma that included the foveal area (see the Microperimetry section). Both eyes of each patient were tested whenever possible. When a single eye per patient was retained, it was always the better eye.

Inclusion and Exclusion Criteria

The patients had a confirmed diagnosis of AMD from an ophthalmologist. They all had binocular scotomas and no other significant disease except for lens status. Those with a history of neurologic disease or cognitive impairment were not included. Patients were recruited over a 3-year period (2006–2008) from referrals to the Low Vision Clinic at the La Timone Hospital (Marseille, France). The research was conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants before testing.

Microperimetry

Microperimetry[18] was performed with a commercially available instrument (MP-1; Nidek Technologies, Padova, Italy). Examinations were run on dilated eyes, and the nontested eye was patched. A fundus photograph was taken after the perimetry examinations. For the default setting, red crosshairs (2–4°) were projected in the middle of the viewing area, and the participants were asked to look at this stimulus at all times. Before starting the examination, the operator checked that the patient was able to maintain fixation with a PRL. Then, the operator selected a high-contrast reference area on the fundus image, generally near the optic disc, to be used for automated tracking, thus triggering the start of the examination. When the scotoma was large and the PRL was in the temporal hemiretina (MP1 field of view, 45°), the experimenter slowly moved the fixation target away from the center to induce gradual displacements of the patient's eye (while maintaining the initially established fixation PRL) until the optic disc was visible on the fundus image.

The first examination was static perimetry with Goldmann V stimuli displayed for 200 ms. The semiautomated module was used, in which the operator defined a polygonal area surrounding the scotoma. The experimenter could adjust the number of stimuli tested within the polygonal area. The decision of increasing or decreasing this predefined number depended on several key characteristics of the patients (ability to sit steadily and to maintain attention, fatigability, and cooperation). The initial intensity of the stimuli was determined by an automatic search of the optimal values for four points uniformly distributed across the pattern (pretest option). A 4-2 threshold strategy was then used. The static map allowed us to detect the presence of an extrafoveal island of spared vision within the macular scotoma.

The second examination was kinetic microperimetry (eight outward directions) performed with Goldmann V stimuli at maximum intensity. The center of the radiating trajectories was set as close as possible to the macula center. The same isopter was estimated three or four times (with the same stimulus intensity), providing automatic measures of the scotoma area (in square degrees). Perimetry data were registered by color fundus photography offline. The area of the scotoma was measured as the average of the three or four measures obtained in the kinetic examination. These measures were often unreliable when an extrafoveal island of spared vision lay within the macular scotoma (as detected in the static map)—that is, when the kinetic border "stopped" at the location of the island. In this case, the scotoma area was measured by hand with geometric approximations from the static microperimetry map (the scale in degrees was provided by the superimposed polar grid). The border between seeing and nonseeing points was set close to the seeing points.

The patient's fovea location was estimated as the point with horizontal and vertical coordinates relative to the optic disc, which were, respectively, 15.5° and −1.5°. These values were based on our measurements averaged across healthy control eyes and were in close agreement with previous measures with the MP-1 microperimeter (Nidek Technologies).[19,20]

Analyzing the microperimetry results allowed us to select only eyes with a dense scotoma that covered the fovea and thus ensured that these eyes relied on eccentric viewing.

Independent Variables

For the set of eyes selected at the previous stage, microperimetry maps, as well as additional information available from the system software, were used to extract the following factors: size of scotoma (in square degrees), shape of scotoma (circular, vertical, or horizontal ellipse), distance (in degrees) between the fovea and the fixation PRL,[19,20] presence or absence of an extrafoveal island of functional vision (16 eyes with an island), fixation stability (percentage of fixations within a 4°-diameter circle during the static perimetry examination), and quadrant (upper, lower, left, or right, with respect to scotoma in the visual field) of the fixation PRL (missing data for three eyes that fixated with an extrafoveal island).

Additional continuous factors considered in the analyses were decimal ETDRS acuity, time since diagnosis in months (missing data for six eyes), number of rehabilitation sessions performed in the low-vision clinic, and the age of the patient. A discrete factor (0 or 1) indicated whether each eye was the better one to take into account associated differential performance.[21,22] When acuity was the same in both eyes, the better eye was defined as the one having the smallest scotoma size.

We also included a two-level factor indicating whether eyes were phakic (42 eyes) or pseudophakic (47 eyes). For phakic eyes, lens opacity was graded by ophthalmologists on a 5-level scale (from 0, no cataract, to 5, most severe opacity) inspired by the Lens Opacities Classification II system.[23] All phakic eyes in our study had a grade below or equal to 2 (grades 0, 1, and 2 were obtained by 14, 18, and 10 eyes, respectively).

As there were missing data for two factors (fixation PRL quadrant and time since diagnosis), the total number of data points in any statistical analysis varied with the presence or absence of each of these factors in the model.

Dependent Variable: MRS

Reading speed was measured by asking the patients to read aloud single meaningful sentences in French displayed on a 21-in. monitor (1152 × 864 pixels). Viewing distance was 40 cm by default but could be reduced to 30 or 20 cm for patients with low acuity. Reading was monocular and an appropriate correction for near vision, corresponding to the viewing distance, was added over distance prescription.

Each sentence was created by following MNread principles.[24] The sentences were displayed over three lines centered on the screen and left–right justified. The experimenter triggered the presentation of each sentence by pressing a button and then pressed the same button to indicate that the patient had finished reading the sentence.

Interline spacing and print size, defined as the vertical angular size of the lowercase letter x (x height), were varied. Three different interline spacings per eye were tested: the standard spacing (1X = 2.6

Table 1. Number of Patients for Each Combination of Disease (Wet versus Dry) and Eye Status (Better versus Worse)

	Better Eye		
	Wet	Dry	Total
Two eyes (worse eye)			
Wet	4	4	
Dry	3	17	
Total			28
One eye (always the better eye)	10	23	33
Grand total			61

times x-height), twice the standard spacing (2X), and 0.79X the standard.

The examination started with the sentences presented at the largest print size available (2.63° at 40 cm, 1.5 logMar, 20/630 reduced Snellen fraction): three sentences corresponding to the three interline spacings were successively presented. Another sequence of three sentences was then displayed with a smaller print size (step, 0.1 logMar). The print size was decreased until the patient could read only a few words per sentence.

Response time for each sentence was transformed into words per minute (wpm) and corrected for the number of words misread. An exponential function of the form (reading speed = R_{max} + $k2$ × exp{[(−1/τ) × print size]} was fit to the data as a function of print size for each interline spacing, where $k2$ is the distance between R_{max} and the y-intercept, and τ is the time constant of the exponential function. Maximum reading speed was defined either as the saturation level R_{max} or as the highest observed reading speed when critical print size (i.e., calculated print size corresponding to 90% of R_{max}) was larger than the largest print size used. This latter case usually occurred when the number of data points for each interline spacing was small.

In sum, three MRS values (one for each interline spacing) were collected for each eye. This set of three repeated measures is one factor that justified the use of a mixed-effects analysis rather than multiple regression.

Statistical Analysis

The statistical analysis is based on a linear mixed-effects (LME) model specifying patients and eyes as random factors (eyes are nested within patients). The advantage of using such a model when analyzing multilevel data with repeated measurements has been extensively documented.[25–32] It has also been successfully used in recent studies on AMD.[33,34]

We used the LME program (NLME package[32] in the R system for statistical computing[35] and the GGPLOT2 R package for graphs. Likelihood-ratio tests were used to evaluate the significance of terms in the random-effects structure. We fitted different nested models in which only the random-effects structure was changed, and we compared the different models with likelihood-ratio tests. This was performed with the ANOVA program in the NLME package. The significance of fixed effects in the model was assessed with conditional *F*-tests still using the ANOVA program in the NLME package.[32] Assumptions underlying the models were visually checked with diagnostic plots of residuals.

For ease of interpretation and to reduce multicollinearity, we centered the interline-spacing regressor on the standard interline (1X), whereas the other continuous regressors were centered around their respective means. The fixation stability factor was transformed from proportions (p) to arcsin($\sqrt{[p]}$). Outlier points (i.e., outside the 1.5 × interquartile range) of the continuous regressors were not included in the analyses.

In the initial part of the analysis, the mutual relationships between all the continuous variables (i.e., the dependent variable MRS and the independent variables), were visually inspected with superimposed loess smoothers to check for linearity. The relationships were overall more linear when the MRS was log transformed (log refers to the natural log in the present work). The latter transformation was also chosen for convenience, because a linear model on the logarithmic scale corresponds to a multiplicative model on the original scale. Thus, estimates of coefficients, if small enough, can be directly interpreted as proportional differences.

Results

Applying the selection criteria described in previous sections provided data for 89 eyes (64 dry and 25 wet) of 61 patients. As already emphasized, all the eyes had a dense macular scotoma covering the fovea.

Patient frequency was conditioned on eye status (better versus worse) and eye disease (wet versus dry) is displayed in Table 1. Of the 25 eyes with wet AMD, 20 had scars without fluid or hemorrhage and 5 had hemorrhage. Six of these eyes underwent laser photocoagulation, 17 underwent photodynamic therapy (including 5 of the eyes with prior laser photocoagulation), and 7 had anti-VEGF treatments. Choroidal neovascularization status was established from microperimetry and OCT (Stratus OCT 3000; Carl Zeiss Meditec, Inc.). MRS is plotted for each data point as a function of eye status (better versus worse) and eye disease (wet versus dry) in Figure 1.

The 0-order correlation coefficients between all relevant continuous factors are presented in the correlation matrix shown in Figure 2. Only one measurement per eye (the one for the single interline spacing) was included in these correlations. Descriptive statistics of these factors for the wet and the dry AMD eyes are shown in Table 2: the first major result is a higher MRS for the wet group compared to the dry group (see also Fig. 1).

Inspection of Table 2 suggests that the wet/dry difference in MRS may have been induced by differences in some continuous factors. Notably, number of rehabilitation sessions and fixation stability were on average higher in the wet group. To

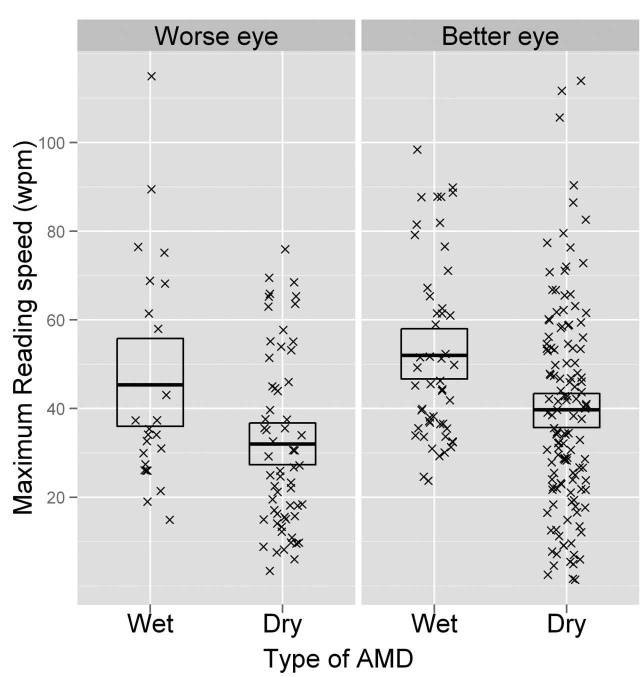

Figure 1. For all data points (+), MRS is displayed as a function of eye status (better versus worse) and eye disease (wet versus dry AMD). Individual data points are horizontally jittered to avoid superimposition. Boxes represent mean MRS (*middle thick line*) and standard errors for each group.

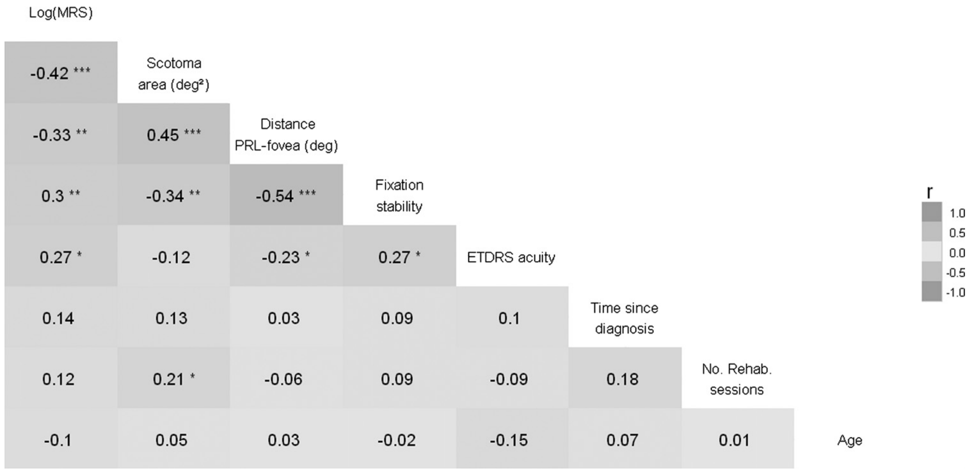

FIGURE 2. The 0-order correlation matrix of log(MRS) and independent variables. Only one measure per eye was included. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

assess whether the wet/dry difference in MRS can be explained by one of these covariates, we performed a first mixed-effects analysis (model 1) with these factors, and the discrete wet/dry factor was included.

The random structure providing the best fit was the following: (1) no random intercept for the eye-within-patient effect; (2) random intercept and random scotoma area slope for the patient effect; and (3) no correlation between intercept and slope for the patient effect.

The results of the fixed effects of the first mixed-effects model are displayed in Table 3. The intercept estimate represents average log(MRS) for the wet AMD group when the continuous factors are at their mean value (as they have been centered around their mean) and the discrete factors at their reference value. This corresponds to an average MRS of ~39 words/min (exp[3.658]). Multiplying this number by 0.74 (i.e., exp[−0.296]) gives the average MRS for the dry group: ~29 words/min. This decrease in MRS is highly significant ($P = 0.009$). Therefore, the dry/wet difference in MRS speed is a genuine difference that cannot be accounted for by a concomitant difference in one of the factors measured in our work.

As shown in our previous work,[17] the scotoma area, the distance between the fixation PRL and fovea and the interline spacing are also significant effects. Although the other continuous factor estimates show effects with signs that are in keeping with established relationships and/or with the 0-order correlations displayed in Figure 2 (for instance, increased fixation stability elicits higher MRS), none of these factors was found to be significant.

We then performed an exploratory analysis by adding the better eye, phakic, island, scotoma shape, and PRL factors to the previous analysis. Most important, adjusting for these factors did not affect the wet/dry difference in MRS. In addition, we found that only one of these discrete factors (the phakic factor) was a significant predictor of MRS. Finally, interaction effects between the wet/dry factor and any of these factors were not significant.

For predictive purposes, the results of previous analyses are summarized in a parsimonious model including only the significant effects (Table 4, model 2). It can notably be seen that MRS for phakic eyes was 40% higher (exp[0.338]) than for pseudophakic eyes. To our knowledge, this effect has never been reported. The significant wet/dry difference was preserved when the same mixed-effects analysis was performed (minus the phakic factor) for the group of phakic eyes (estimate: −0.34, $t_{(1,90)} = -2.9$; $P = 0.004$) and for the group of pseudophakic eyes (estimate: −0.41, $t_{(1,105)} = -2.3$, $P = 0.02$). For phakic eyes, there was no significant 0-order correlation between lens opacity grades and MRS, presumably because lens opacity grades never exceeded 2. For pseudophakic eyes, we could collect the interval between cataract surgery and AMD diagnosis date for 31 eyes: 71% of these eyes had surgery before AMD diagnosis (median interval, 3.5 years before AMD diagnosis). There was no significant 0-order correlation between this interval and MRS. Finally, we note that the phakic factor had no effect on visual acuity as estimated with a mixed-effects model including only the phakic factor. This result is consistent with the well-known finding that visual acuity does not correlate well with performance of daily life activities such as reading.[1]

Although the preceding analyses did not show an interaction between the wet/dry and better eye factors, we reran model 2, this time including only the better eye of each patient, to show the robustness of the effects. The results of this analysis were similar to those displayed in Table 4. The

TABLE 2. Descriptive Statistics for Reading Speed and Continuous Factors for Dry and Wet AMD Groups

	Median (1st–3rd Quartile)		Mean (Min–Max)	
	Dry	**Wet**	**Dry**	**Wet**
Maximum reading speed, words/min	34 (21–53)	43 (34–64)	37 (1–114)	50 (15–115)
Scotoma area, deg^2	99 (61–209)	147 (70–202)	137 (4–402)	161 (7–403)
ETDRS acuity, decimal	0.1 (0.05–0.16)	0.1 (0.06–0.16)	0.1 (0.02–0.5)	0.1 (0.03–0.25)
Distance PRL-fovea, deg	9.2 (5.6–12)	8.4 (6–13)	9.1 (1–20.4)	9.5 (2–19.2)
Time since diagnosis, mo	46 (34–76)	52 (29–66)	62 (6–192)	60 (12–210)
Fixation stability, % within 4°	52 (42–77)	72 (46–87)	58 (15–97)	66 (26–97)
Rehabilitation sessions, *n*	2 (0–12)	10 (2–27)	10 (0–80)	17 (0–78)
Age, y	82 (76–87)	81 (76–85)	80 (55–94)	80 (59–93)

Table 3. Model 1: Results for the Fixed Effects (249 Data Points)

	Estimate	SE	*df*	*t*	*P*
Intercept	3.658	0.106	184	34.5	<0.0001
Dry	−0.296	0.111	184	−2.7	0.009
Scotoma area	−0.002	0.001	184	−2.7	0.008
PRL fovea distance	−0.030	0.014	184	−2.0	0.043
Fixation stability	0.117	0.239	184	0.5	0.623
ETDRS	0.140	0.525	184	0.3	0.790
Time since diagnosis	0.002	0.002	184	1.3	0.213
Rehab sessions, *n*	0.002	0.004	184	0.5	0.605
Age	−0.001	0.009	55	−0.1	0.900
Interline spacing	0.198	0.040	184	4.9	<0.0001

The intercept indicates log(MRS) for wet AMD group (reference level) when all other factors are null (here, when at their mean level). Shown are estimated coefficients of the factors (Estimate), their SE, and results of statistical analyses for each fixed effect (*df*), *t* and *P*). Note that in a linear model with a log-transformed dependent variable, the estimated coefficients represent proportional differences on the original scale of the dependent variable. For instance, the −0.296 estimate in the "dry" row indicates that the dry group's MRS is 0.74: exp(−0.296) times the wet group's MRS (intercept).

P-values were logically larger (as there were only 183 data points instead of 267) but still significant (the PRL fovea distance factor was only marginally significant; $P = 0.08$).

The fits of the effect of scotoma size on MRS in model 2 are shown in Figure 3 for the wet (solid black line) and dry (solid gray line) groups (with MRS displayed on its original scale). Increasing the scotoma area by 1 deg^2 decreases MRS by a factor of 1.002. For comparison purposes, this figure also presents the results obtained in three studies that investigated the 0-order correlation between MRS and scotoma size with much smaller data sets than in our work. The dotted and dashed lines respectively correspond to the fitted curves displayed in Ergun et al.[6] and Sunness et al.[7] Triangles represent the eight data points from AMD eyes displayed (with no fitted curve) in Cummings et al.[8] For the wet group, it should be noted that there are more data points above than below the fitted curve. This pattern is not unusual in multiple regression analyses,[29] and the results here are mainly from the asymmetric marginal distribution of the PRL-to-fovea distance factor.

Discussion

We studied the relationship between MRS and different clinical factors for 89 AMD eyes (61 patients). Static and kinetic microperimetry maps (obtained with MP-1; Nidek Technologies), were used to assess the scotomas' characteristics. Most important, these maps allowed us to control so that all eyes kept in the analysis had a dense scotoma with an area that included the fovea. Reading thus systematically involved eccentric vision.

Our major result is a significantly larger MRS for wet than for dry AMD eyes. This difference was maintained even when adjustment was made for the factors that seemed to confer some advantage to the wet group. For instance, even though wet AMD eyes have a higher fixation stability than dry AMD eyes (Table 2), partialing out this factor does not reduce the difference in MRS. Similarly, including the categorical factors collected in our study does not reduce the amplitude of this difference. A model in which only significant effects were included (model 2, Table 4) indicated a relative decrease by a factor of approximately 30%. These results clearly show that reading performance is more efficient for wet than for dry AMD eyes, a difference that we are not able to account for by any of the discrete or continuous factors measured in our study.

Using a mixed-effects analysis, rather than independent 0-order correlations, allowed us to identify the clinical factors that were good predictors of MRS when all other factors are kept constant. Our study shows that, in addition to the wet/dry dichotomy, three clinical factors were good predictors of MRS: scotoma area, distance between fixation PRL and fovea, and pseudophakia. To our knowledge, the unique contributions of the last two factors have never been acknowledged. Decreasing the PRL-to-fovea distance by 1° increases MRS by approximately 4%. This effect shows that, for any constant scotoma size, using a fixation PRL with an eccentricity as small as possible induces benefits during a reading task. This relationship suggests that the PRL used by patients during a fixation task is also preferentially used during the reading task or is used at least in some critical periods of the reading process. MRS was dramatically higher (by 40%, see model 2) for phakic eyes than for pseudophakic eyes. This difference seemed to be caused by the peripheral properties of intraocular lenses, as there is evidence that reading speed in non-AMD subjects after cataract surgery is not affected by intraocular lenses, except at very low contrasts or with tiny letters.[36] Our MRS measure is obtained with maximum contrast and letter size, and patients all have a dense macular scotoma forcing them to read with eccen-

Table 4. Model 2: Results for the Fixed Effects (267 Data Points)

	Estimate	SE	*df*	*t*	*P*
Intercept	3.567	0.107	201	33.3	<0.0001
Dry	−0.359	0.098	201	−3.6	0.0003
Scotoma area	−0.002	0.001	201	−2.7	0.0067
PRL fovea distance	−0.035	0.012	201	−2.9	0.0040
Interline spacing	0.194	0.038	201	5.1	<0.0001
Phakic	0.338	0.115	201	2.9	0.0036

See caption to Table 3 for further explanation.

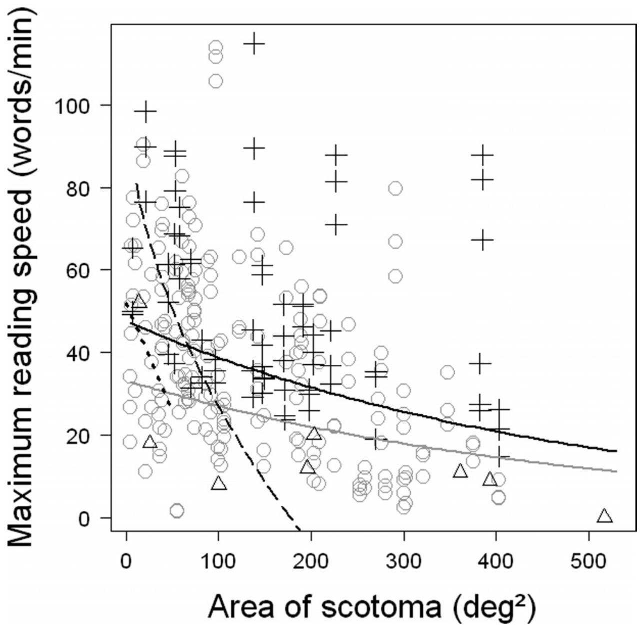

FIGURE 3. Scatterplots of MRS as a function of scotoma area. Symbols represent wet (+) and dry (○) eyes. *Solid lines*: the fixed effects of scotoma area as derived from mixed-effects model 2 for the wet (*black*) and dry (*gray*) AMD eyes. The *dotted* and *dashed lines* illustrate the relationships reported in Ergun et al.[6] and Sunness et al.,[7] respectively. Note the larger ranges of values collected. (△): the eight AMD eyes reported in Cummings et al.[8]

tric vision. Therefore, the phakic/pseudophakic difference reported here is most likely related to the decrease of visual sensitivity, with eccentricity reported in a recent study of the effect of intraocular lenses.[37]

The relationship between scotoma size and MRS has already been established with small samples and for small ranges of scotoma size.[6–8] It is currently difficult, however, to predict MRS as a function of scotoma size, because the predictions arising from these studies are very different. An additional difficulty is that two of these studies predict a null MRS for relatively small scotoma areas (much smaller than those encountered in clinical practice). In contrast, the relationship between MRS and scotoma area presented herein (Fig. 2) is robust, as its estimates are very stable; significant, irrespective of the additional factors added in mixed-effects analyses; and useful for predictive purposes, as it covers the typical range of scotoma areas. On average, MRS is reduced by a 0.82 factor when scotoma area is increased by 100 deg^2.

Our mixed-effects analysis confirms that the location of the fixation PRL relative to the scotoma is not a significant predictor of MRS in clinical studies of AMD patients.[5,12,13] However, the PRL used *during reading* was not measured in these clinical studies or in the present study. It is therefore not possible to know whether predominantly using a given PRL during reading is more advantageous for reading performance than using another one. The PRL used during fixation does not allow researchers to infer the reading PRL for two main reasons. First, different PRLs can be used by a given patient for fixation tasks and for reading tasks.[38,39] Second, more than one PRL can be used during word or sentence reading by a given patient.[40–42]

Evidence of a relationship between PRL location *during reading* and reading speed comes from experiments that "forced" or trained observers to use particular PRLs during reading. The general result is that using a lower PRL (in the visual field) during reading is beneficial.[43–48] In this context, one interpretation of our wet/dry effect is that patients with wet AMD either use a lower PRL during reading more often than those with dry AMD, or they use a more optimal combination of reading PRLs than those with dry AMD.

In summary, MRS is clearly higher in wet than in dry AMD, even when adjustment is made for the factors available in our study. It is likely that the cause of this difference is related to the different time courses of both types of disease before they eventually lead to total central field loss. Geographic atrophy begins with scattered small foci of atrophy (in the parafoveal region) that gradually increase in size and coalesce. A horseshoe of atrophy that spares the foveal region and is open to the left or to the right is often observed. Over time, the atrophy closes into a ring and eventually forms a disc as the fovea itself becomes atrophic.[49–51] These different temporal scales of disease progression probably induce different adaptation processes that could be related to the development of the PRL used during reading. Presumably, PRL strategies used by patients in dry AMD once the central field is completely lost are strongly constrained by their past enduring history when macular vision was partially functional. It has been suggested, for instance, that the initial opening of the horseshoe shape to the right or to the left causes the observed predominance of horizontal fixation PRLs in dry AMD with central field loss.[7] In contrast, the development of PRL strategies in wet AMD is probably more optimal in the sense that it is not biased by any previous strategy and can thus potentially evolve with flexibility. More generally, differential adaptation may concern the efficiency of the whole network of visuoattentional processes underlying dynamic eccentric viewing. It is obviously difficult to change a strategy that has been used for months or years. Psychological factors, as well as perceptual learning factors, may explain this difficulty, but a more subtle difficulty may be the absence during the long degradation process of any "signal" indicating when the patient would benefit from a change in strategy. In contrast, the sudden onset of the wet functional loss imposes a sudden constraint. In a very short time, these patients are forced to try different PRLs or sets of PRLs without being biased toward any particular strategy. This potentially allows them to find the most optimal choices with a higher probability than do patients with dry AMD.

If the general hypothesis based on differential adaptation processes is correct,[2] one important consequence concerns the patient's rehabilitation.[52] For instance, we would expect patients with dry AMD patients to benefit much more than those with wet AMD from the training of some reading PRLs considered to be either more optimal than the spontaneously chosen one[44,45] or simply complementary.[40] More generally, the present study suggests that patients with dry AMD who have central scotomas may benefit more from visual rehabilitation than those with wet AMD who have roughly similar scotomas.

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