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Full-field electroretinography in age-related macular degeneration: an overall retinal response

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ABSTRACT.

Purpose: **Age-related macular degeneration (AMD) is generally considered a disease of the macula. However, recent studies show peripheral retinal lesions are prevalent in patients with AMD, indicative of a disease process that is more widespread. Full-field electroretinography (ffERG) measures an electrical response, not only from the macula, but from the entire retina. We wanted to study the ffERG response in eyes with AMD.**

Methods: **We performed full-field electroretinography (RETI-port/scan 21, Roland, Berlin) in 13 patients with early AMD, 25 patients with late AMD and 24 individuals without vitreoretinal disease as a control group. Dawson–Trick–Litzkow fibre electrodes were used. Statistical analysis was performed and a p-value <0.05 was considered significant.**

Results: **After adjusting for multiple comparisons, both the light-adapted 3.0 a-wave implicit time ($p < 0.001$) and 30-Hertz flicker peak time ($p = 0.012$) showed significant difference between patients with late AMD and individuals without vitreoretinal disease. There was a significant difference in the light-adapted 3.0 a-wave implicit time ($p = 0.011$) between patients with early AMD and the control group, but the difference in 30 Hz flicker peak time was not significant ($p = 0.256$).**

Conclusion: **The difference in cone function measured by light-adapted 3.0 a-wave implicit time and 30-Hertz flicker peak time in early and late AMD when compared to healthy controls suggests a more diminished overall response when AMD has reached later stages.**

Key words: age-related macular degeneration – full-field electroretinography – functional testing – peripheral retina

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Introduction

Age-related macular degeneration (AMD) is the most prevalent cause of blindness in developed countries (Prokofyeva & Zrenner 2012). Age-related macular degeneration (AMD) is generally considered a disease that affects the central macula (Wong et al. 2014). While this area of the retina is affected earliest and most severely by the disease, studies using ultrawidefield imaging techniques show the increased prevalence of AMD-like lesions in the peripheral retina of eyes with AMD-affected maculas compared with eyes with normal maculas (Forshaw et al. 2019). The clinical relevance of these peripheral lesions and their effect on visual function is not yet known (Domalpally et al. 2017); however, they appear to be more common in eyes with late AMD (Tan et al. 2013).

Electroretinography (ERG) is an objective measure of retinal function. Changes in electrical polarization are graded according to the varying intensity and duration of the light stimulus. The International Society for Clinical Electrophysiology of Vision (ISCEV) has produced guidelines on how to obtain a full-field ERG (ffERG) using a standard protocol (McCulloch et al. 2015), thus enabling the comparison of ERG data from laboratories across the world. With regard to the two main classes of photoreceptors in the human retina, the components of the ffERG are said to be either rod- or cone-specific. In practice, it is difficult to test the rod and cone systems in isolation of one another. Dark and light adaptation are therefore used to activate either the rod- or the cone-driven retinal responses.

We studied retinal function in patients with AMD using ffERG, a method that generates a mass electrical

response (Tsang & Sharma 2018) reflecting the retina in its entirety. Although ERG changes are part of the normal ageing process (Birch & Anderson 1992), prolonged implicit times on ERG are indicative of a pathological process (Berson et al. 1969, Gerber et al. 2003). Focal lesions such as geographic atrophy (GA) and retinal pigment epithelial detachment can affect ERG (Walter et al. 1999), but the use of ffERG in detecting functional changes in patients with AMD remains controversial. This is because the macula accounts for only a small part of the overall response (Pedersen et al. 2010). However, it has been suggested that ffERG may indicate a global reduction of retinal function in AMD that is both present in the macula and elsewhere (Walter et al. 1999).

In our study, we wanted to investigate the overall retinal response in patients with AMD using ffERG.

Materials and Methods

All procedures performed in this study were in accordance with the ethical standards of the Region Zealand ethics committee (SJ-618) and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Sixty-one consecutive individuals from the outpatients' department of Zealand University Hospital were included. Thirty-seven patients were diagnosed with AMD by fundus examination and OCT, and 24 individuals without vitreoretinal disease were included as a control group.

The overall translucency of the ocular media was a match in both groups, and in the AMD sub-groups. All individuals had normal corneal transparency and had not undergone phacoemulsification or any other form of ocular surgery. A consultant ophthalmologist performed a detailed examination at the start of the study, during which all individuals included in the study were deemed to have bilateral operable age-related cataract. We did not perform formal cataract grading but patients with very dense cataract making ERG impossible were not included. Data from the right eye were used (Fig. 1), unless a patient had clinical evidence of AMD only in the fellow eye on ophthalmic examination. In three such cases, the left eye was used. Individuals were excluded from the study if they had a retinal pathology other than AMD, amblyopia, glaucoma or any other ocular disease that would damage retinal function. Visual acuity was measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart after best monocular refraction.

Patients with AMD were divided into two sub-groups: those with early- or late-stage disease. Patients with non-neovascular AMD without GA entered the early AMD sub-group and patients with neovascular AMD and/or GA entered the late AMD sub-group. Since peripheral retinal lesions are more prevalent in eyes with late AMD, this was the AMD sub-group of primary interest.

Full-field ERG (ffERG) was performed binocularly according to ISCEV standard protocol (McCulloch et al. 2015). Local anaesthesia (tetracaine 1%) was instilled for patient comfort and to minimize blink artefacts. The pupils were then fully dilated using topical tropicamide (1%) and phenylephrine (10%). A Ganzfeld stimulator (RETI-port/scan 21, Roland, Berlin) and Dawson–Trick–Litzkow fibre electrodes were used. Reference electrodes were placed on the orbital margin, adjacent to the lateral canthi, and a ground electrode was placed on the midline of the forehead, approximately 2 cm below the hairline. Impedance values of <7 kOhms were accepted, and an inter-electrode difference of >1 kOhm was rejected. Twenty minutes of dark adaptation and 10 min of light adaptation were observed. All ERG investigations were performed by one of the authors (T.R.J.F).

The ERG recordings consisted of an a-wave reflecting electrical activity in the outer retina and a b-wave reflecting activity in the inner retina. Since AMD is known to affect photoreceptors, we focused on a-waves primarily, but we also included data from b-waves as the inner retinal response may be rod- or cone-driven. Dark-adapted oscillatory potentials are thought to reflect the response of the amacrine cells and can be used to assess retinal vascular function. Oscillatory potentials are more relevant in retinal diseases other than AMD, such as diabetic retinopathy, and therefore, we chose not to include them in this study. Electroretinography (ERG) waveform marker placement was performed manually by one author (T.R.J.F), with two authors (S.A. and T.R.J.F) providing the analysis.

Statistical analysis was performed using SPSS 25 (IBM Corporation, Armonk, NY, USA). Data distribution

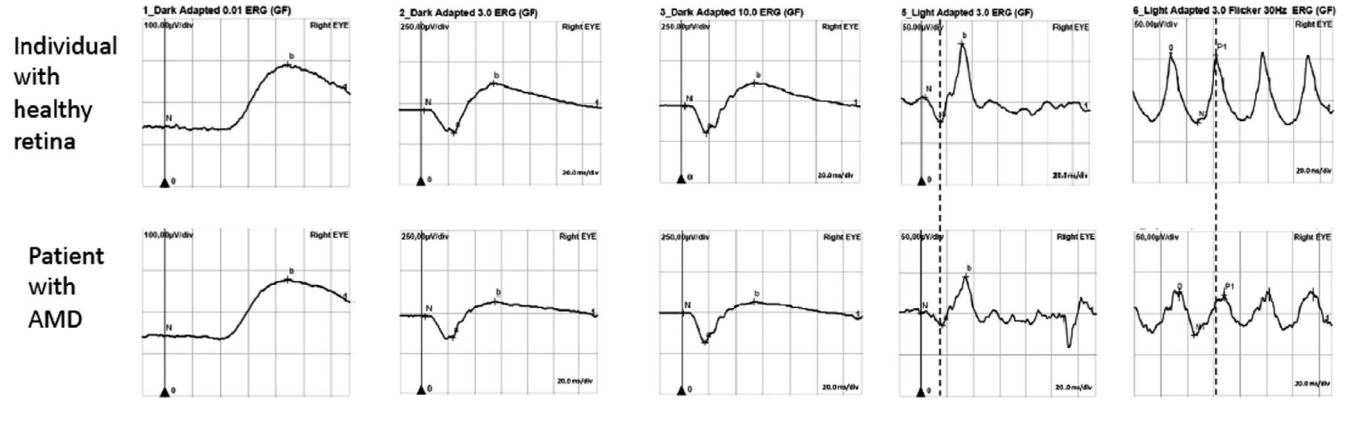

Fig. 1. Full-field electroretinography recordings from a patient with age-related macular degeneration and an individual with healthy retina. Vertical *dashed* lines indicate the 3.0 a-wave implicit time and the 30-Hertz flicker peak time.

Table 1. Patient characteristics.

	Late AMD	Healthy retina	p-value
Participants/number of eyes	25	24	–
Median age (years)	79.00 Range: 69–86 IQR: 75.5–82	72.00 Range: 59–86 IQR: 71–75	0.001*
Sex (males/females)	5/20	6/18	0.801†
Median visual acuity (ETDRS letters)	53.00 Range: 0–80 IQR: 24–67	76.00 Range: 46–85 IQR: 69–83	<0.001*
AMD phenotype (neovascular/geographic atrophy)	20/ 5	–	<0.001†

AMD = age-related macular degeneration, ETDRS = Early Treatment of Diabetic Retinopathy Study, IQR = interquartile range.
* Mann–Whitney *U* test.
† Chi-squared test.

was assessed by performing the Shapiro–Wilk test of normality. In the case of normal distribution, parametric tests (Pearson's coefficient; Independent samples *t*-test) were used. In the absence of normal distribution, non-parametric tests were used (Spearman's rho coefficient; Mann–Whitney *U* test). We used linear regression to adjust for the difference in age between the groups (Table 1). We did not use residuals for group comparisons but instead used age-adjusted values. The Holm–Bonferroni method of correction was used to allow multiple comparisons, and a p-value of <0.05 was considered statistically significant.

Results

From October 2017 to March 2019, a total of sixty-one consecutive individuals were included in this study. These were patients with early AMD ($n = 12$), patients with late AMD ($n = 25$) and individuals with healthy retina ($n = 24$), included as a control group.

We compared ffERG responses from patients with late AMD with those from the control group and descriptive data is provided (Table 1). The median best-corrected visual acuity (BCVA) was 53 (range: 0–80) ETDRS letters in the AMD group and 76 (range: 46–85) ETDRS letters in the healthy retina group ($p < 0.001$). The median age in the late AMD sub-group was 79 (range: 69–86) years and 72 (range:

Table 2. Dark-adapted full-field electroretinography responses.

ERG test	Light intensity (range) cd.s/m^2	Background light intensity (range) cd/m^2	Type of response	Late AMD	Healthy retina	p-value
0.01 b-wave implicit time (ms)	0.01 (0.0063–0.016)	0.025 (0.02–0.03)	Rod-initiated on pathways	92.8 IQR: 88–97.15	90.7 IQR: 85.5–96.6	0.978
0.01 b-wave amplitude (μV)	0.01 (0.0063–0.016)	0.025 (0.02–0.03)	Rod-initiated on pathways	115.7 IQR: 81.6–170.75	148.45 IQR: 122.55–169.15	0.182
3.0 a-wave implicit time (ms)	3.0 (2.7–3.4)	7.5 (6.7–8.4)	Photoreceptors and postreceptoral on pathways	24.7 IQR: 20.15–25.35	24.05 IQR: 18.8–24.95	0.486
3.0 a-wave amplitude (μV)	3.0 (2.7–3.4)	7.5 (6.7–8.4)	Photoreceptors and postreceptoral on pathways	133.2 IQR: 102.85–158.95	161.0 IQR: 134.9–200.8	0.149
3.0 b-wave implicit time (ms)	3.0 (2.7–3.4)	7.5 (6.7–8.4)	On and off bipolar cells	49.9 IQR: 49.75–49.9	49.9 IQR: 48.3–49.9	0.501
3.0 b-wave amplitude (μV)	3.0 (2.7–3.4)	7.5 (6.7–8.4)	On and off bipolar cells	241.4 IQR: 170.6–303.75	271.35 IQR: 234.85–310.95	0.643
10.0 a-wave implicit time (ms)	10 (8.9–11.2)	25 (18–34)	Photoreceptors and postreceptoral on pathways	18.8 IQR: 17.75–19.7	17.9 IQR: 17.45–18.8	0.818
10.0 a-wave amplitude (μV)	10.0 (8.9–11.2)	25 (18–34)	Photoreceptors and postreceptoral on pathways	168.7 IQR: 130.5–199.3	185.85 IQR: 158.65–231.45	0.171
10.0 b-wave implicit time (ms)	10 (8.9–11.2)	25 (18–34)	Predominantly rod bipolar cells (on pathways)	49.9 IQR: 48–49.9	49.9 IQR: 49.7–49.9	0.082
10.0 b-wave amplitude (μV)	10 (8.9–11.2)	25 (18–34)	Predominantly rod bipolar cells (on pathways)	243.7 IQR: 170.2–301.35	277.15 IQR: 235.6–324.75	0.280

After: McCulloch et al. (2015).
Median values for both groups provided.
μV = microvolts, AMD = age-related macular degeneration, cd.s/m^2 = candela-seconds per metre squared, cd/m^2 = candela per metre squared, ERG = electroretinography, Hz = Hertz, IQR = interquartile range, ms = milliseconds.

Table 3. Light-adapted full-field electroretinography responses.

ERG test	Light intensity (range) cd.s/m^2	Background light intensity (range) cd/m^2	Type of response	Late AMD	Healthy retina	p-value
3.0 a-wave implicit time (ms)	3.0 (2.7–3.4)	7.5 (6.7–8.4)	Cones with post-receptoral on and off pathways	17.6 IQR: 16.85 –18.95	16.1 IQR: 15.35 –16.7	<0.001*
3.0 a-wave amplitude (μV)	3.0 (2.7–3.4)	7.5 (6.7–8.4)	Cones with post-receptoral on and off pathways	22.6 IQR: 14.25 –29.5	27.0 IQR: 17.7–32.55	0.862
3.0 b-wave implicit time (ms)	3.0 (2.7–3.4)	7.5 (6.7–8.4)	On and off bipolar cells	35.5 IQR: 34.45 –36.4	34.35 IQR: 32.7–35.3	0.116
3.0 b-wave amplitude (μV)	3.0 (2.7–3.4)	7.5 (6.7–8.4)	On and off bipolar cells	88.7 IQR: 57.4–103.55	98.05 IQR: 70.75 –119.45	0.104
30-Hz flicker implicit time (ms)	3.0 (2.7–3.4)	7.5 (6.7–8.4)	Cone systems with post-receptoral on and off pathways	32.2 IQR: 31.1–34.3	30.05 IQR: 29.3–30.5	0.012*
30-Hz flicker amplitude (μV)	3.0 (2.7–3.4)	7.5 (6.7–8.4)	Cone systems with post-receptoral on and off pathways	60.5 IQR: 41.85 –68.55	63.5 IQR: 49.25 –79.6	0.581

After: McCulloch et al. (2015).
Median values for both groups provided.
μV = microvolts, AMD = age-related macular degeneration, cd.s/m^2 = candela-seconds per metre squared, cd/m^2 = candela per metre squared, ERG = electroretinography, Hz = Hertz, IQR = interquartile range, ms = milliseconds.
* Indicates difference is significant at the 0.05 level after Holm-Bonferroni correction.

59–86) years in the control group ($p < 0.001$; Mann–Whitney *U* test).

In the dark-adapted ffERG, the difference in the mixed rod-cone response between the two groups was not found to be statistically significant after linear regression and Holm–Bonferroni correction (Table 2). In particular, the difference in the 10.0 a-wave implicit time was statistically affected by age (i.e. no longer significant after linear regression). The light-adapted 3.0 b-wave implicit time and the light-adapted 3.0 b-wave amplitude were similarly statistically affected by age.

After linear regression and Holm–Bonferroni correction, we found two responses from the late AMD sub-group that were significantly worse than those of the control group. Compared with healthy controls, patients with late AMD had prolonged light-adapted 3.0 a-wave implicit times ($p < 0.001$) and 30-Hertz (Hz) flicker peak times ($p = 0.012$; Table 3). When we examined these cone-driven responses in patients with early AMD, we discovered that the 3.0 a-wave implicit time was similarly prolonged in patients with early AMD compared with healthy controls ($p = 0.011$). However, unlike the late AMD sub-group, the difference in the 30 Hertz flicker peak time between the early AMD sub-group and the healthy retina group was not significant ($p = 0.256$). Descriptive data for the age-matched AMD subgroups are provided (Table 4).

Table 4. Patient characteristics – early and late AMD subgroups.

	Early AMD	Late AMD	p-value
Participants/number of eyes	12	25	–
Median age (years)	77 Range: 63–87 IQR: 73–84	79.00 Range: 69–86 IQR: 74.5–82	0.395*
Sex (males/females)	7/5	5/20	0.02†
Median visual acuity (ETDRS letters)	74.5 Range: 35–82 IQR: 70–77	53.00 Range: 0–80 IQR: 24–67	0.021*

AMD = age-related macular degeneration, ETDRS = Early Treatment of Diabetic Retinopathy Study, IQR = interquartile range.
* Mann–Whitney *U* test
† Chi-squared test

We compared the ffERG responses from the AMD subgroups (Table 5). The median light-adapted 3.0 a-wave implicit time results were as follows: 17.9 milliseconds (ms) interquartile range (IQR): 16.1–18.5 in the early AMD sub-group and 17.6 ms IQR: 16.85–18.95 in the late AMD sub-group ($p = 0.689$). The median 30-Hz flicker peak time results were as follows: 31.0 ms IQR: 27.2–31.1 in the early AMD sub-group and 32.2 ms IQR: 31.1–34.3 in the late AMD sub-group. There was no statistically significant difference between the 30-Hz flicker response from the early and late AMD subgroups ($p = 0.181$). The 30-Hz flicker peak time results from the two subgroups are shown together with the results from the healthy retina group in Fig. 2.

Finally, we correlated the 30-Hertz flicker response in patients with late AMD with BCVA, a marker of central retinal function (rho −0.274; Spearman's Correlation; Fig. 3). However, this correlation was not significant ($p = 0.185$).

Discussion

The late AMD sub-group in our study had a prolonged light-adapted 3.0 a-wave implicit time and 30-Hz flicker peak time compared with the group

Table 5. Full-field electroretinography responses in early and late AMD.

ERG test	Early AMD	Late AMD	p-value
0.01 b-wave implicit time (ms)	98.8 IQR: 89.2–99.8	92.8 IQR: 88–97.15	0.027
0.01 b-wave amplitude (μV)	165.8 IQR: 104.9–193.2	115,7 IQR: 81.6–170.75	0.151
DA 3.0 a-wave implicit time (ms)	24.7 IQR: 18.8–24.95	24.7 IQR: 20.15–25.35	0.511
DA 3.0 a-wave amplitude (μV)	165.2 IQR: 133.2–172.4	133.2 IQR: 102.85–158.95	0.032
DA 3.0 b-wave implicit time (ms)	49.9 IQR: 49.3–49.9	49.9 IQR: 49.75–49.9	0.312
DA 3.0 b-wave amplitude (μV)	278.8 IQR: 196.9–357.5	241.4 IQR: 170.6–303.75	0.192
10.0 a-wave implicit time (ms)	19.0 IQR: 18.2–19.7	18.8 IQR: 17.75–19.7	0.511
10.0 a-wave amplitude (μV)	174.0 IQR: 141.4–190.9	168.7 IQR: 130.5–199.3	0.413
10.0 b-wave implicit time (ms)	49.9 IQR: 46.7–49.9	49.9 IQR: 48–49.9	0.312
10.0 b-wave amplitude (μV)	288.9 IQR: 183.8–358.5	243.7 IQR: 170.2–301.35	0.413
LA 3.0 a-wave implicit time (ms)	17.9 IQR: 16.1–18.5	17.6 IQR: 16.85–18.95	0.689
LA 3.0 a-wave amplitude (μV)	27.2 IQR: 23–32.4	22.6 IQR: 14.25–29.5	0.192
LA 3.0 b-wave implicit time (ms)	35.1 IQR: 33.8–36.1	35.5 IQR: 34.45–36.4	0.713
LA 3.0 b-wave amplitude (μV)	86.4 IQR: 60.2–96.1	88.7 IQR: 57.4–103.55	0.689
30-Hz flicker implicit time (ms)	31.0 IQR: 27.2–31.1	32.2 IQR: 31.1–34.3	0.203
30-Hz flicker amplitude (μV)	63.2 IQR: 45.6–99.3	60.5 IQR: 41.85–68.55	0.181

Median values for both groups provided.
μV = microvolts, AMD = age-related macular degeneration, DA = dark-adapted, ERG = electroretinography, Hz = Hertz, IQR = interquartile range, LA = light-adapted, ms = milliseconds.

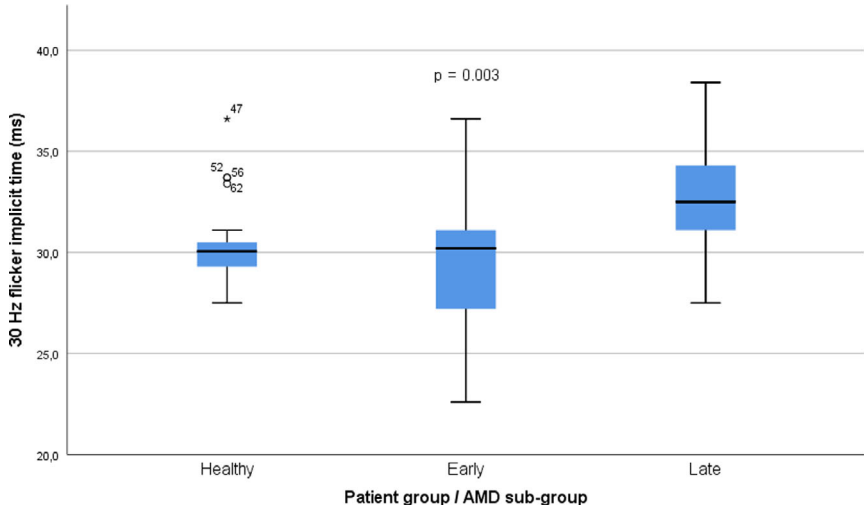

Fig. 2. Box plots showing the difference in 30-Hertz flicker peak time, a marker of cone function on full-field electroretinography, in individuals with healthy retina and patients with early and late age-related macular degeneration.

with healthy retina. This electrophysiological finding is indicative of AMD-related damage to the cone system that has progressed beyond the macula.

Prolonged ERG implicit times are a recognized indicator of progressive disease (Schroeder & Kjellström 2018). Generalized Stargardt disorder is associated with prolonged 30-Hz flicker implicit times, whereas ffERG is within normal parameters in patients with localized disease (Schroeder & Kjellström 2018). Moreover, in Best's vitelliform macular dystrophy, a localized disease that may be difficult to distinguish from AMD in older patients, ffERG shows normal photoreceptor response (Eksandh et al. 2001). Furthermore, rod-driven b-wave implicit times are prolonged in cases of GA compared with other AMD sub-groups (Walter et al. 1999).

Age-related macular degeneration (AMD) affects rods earlier and more severely than cones (Curcio et al. 1996; Schaal et al. 2015; Owsley et al. 2017; Pfau et al. 2020) and the disease is associated with reactive oxygen species and oxidative damage (Jarrett & Boulton 2012). Reactive oxygen species can inhibit sodium ion channel activity (Evans & Bielefeldt 2000), thus reducing the ability of neurons to generate action potentials and causing impaired rod-mediated phototransduction activation and prolonged dark adaptation (Owsley et al. 2007; Dimopoulos et al. 2013; Laíns et al. 2017; Chen et al. 2019). Prolonged rod-mediated dark adaptation consistent with the early degeneration of rod photoreceptors is therefore a functional biomarker for early AMD (Owsley et al. 2016).

Although rods dominate the macula, particularly the perifovea (Curcio et al. 1993), the photoreceptor subtype is relatively abundant across the whole retina: there are approximately 100 million rod photoreceptors and only 4.6–6.0 million cones (Quinn et al. 2019). Ninety percent of cones lie in the retinal periphery (McCannel et al. 2019), which is why the difference in the 30-Hz flicker peak time in the AMD group is suggestive of progressive and therefore more generalized disease. The peripheral retina is used in night vision (Ying et al. 2008) and for the detection of movement, but it is also useful in locomotion (Marigold 2008), mobility (Nakayama 1985; Vargas-Martin & Peli 2006) and postural stability (Black et al. 2008). Peripheral retinal function is also a better predictor for driving ability amongst elderly persons than visual acuity (Huestegge

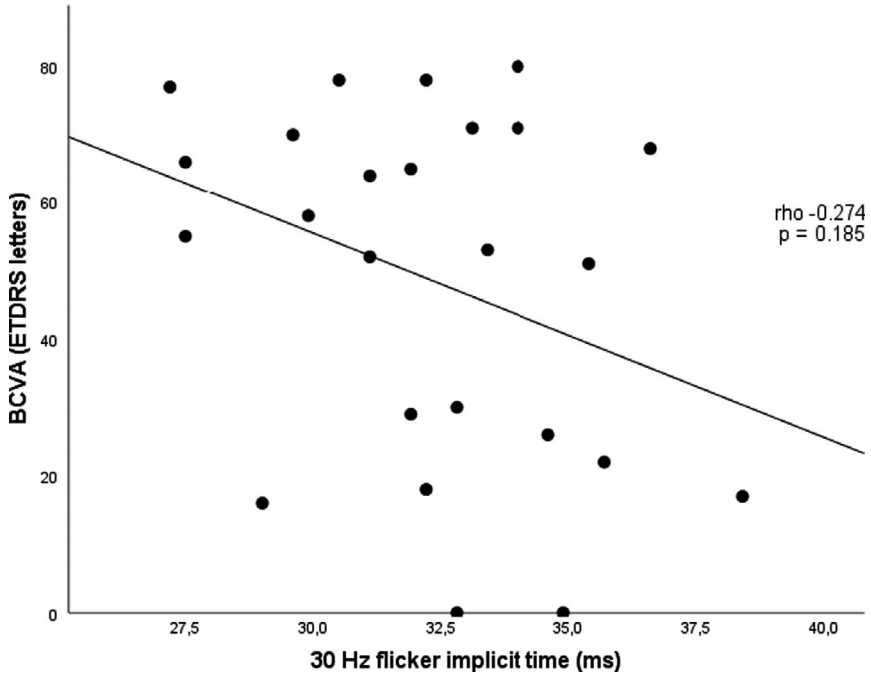

Fig. 3. Scatter plot of best-corrected visual acuity in Early Treatment Diabetic Retinopathy Study letters by 30-Hertz flicker peak time in milliseconds in patients with late age-related macular degeneration.

& Bockler 2016; Peli et al. 2016) and is therefore relevant in terms of vision-related quality of life in elderly people as a group. Moreover, it is especially important in those with central vision loss due to AMD, as these individuals come to depend on their peripheral retina for activities of daily living (Sørensen et al. 2011).

Age-related macular degeneration (AMD) is an exaggerated form of retinal ageing that manifests with morphological changes. A 2013 study that included 86 eyes with neovascular AMD, 114 with non-neovascular AMD and 86 normal eyes found that peripheral fundus autofluorescence abnormalities occur more frequently in eyes with neovascular AMD (86%) compared with non-neovascular AMD (72.8%) and normal eyes (18.4%) ($p < 0.001$) (Tan et al. 2013). Differences in AMD morphology may account for the non-significant data in our study, since AMD sub-groups have different photoreceptor membrane characteristics. For example, eyes with soft drusen and those with pigment epithelium detachment yield a faster ion exchange resulting in a more rapid synaptic transmission to the cone bipolar cells (Walter et al. 1999). In such cases of AMD, we can assume that the dark-adapted cone response from patients with AMD would not differ significantly from those of age-matched controls, a tendency reflected in our results after adjustment was made using linear regression.

Limitations of our study should be considered. The sample size in each group was relatively small. Statistically, this may explain why the difference in 30-Hz flicker peak time between the two AMD subgroups and the correlation between 30-Hz flicker peak time and BCVA in the late AMD subgroup yielded results that were not significant. There was also a gender disparity between the groups: most of the patients with early AMD were male, whereas the late AMD sub-group and healthy retina group were female-dominated. This may have an influence on the ERG results and might explain why certain ffERG parameters (e.g. the light-adapted 3.0 a-wave implicit time) appear worse in early AMD when compared with the late form of the disease. A further limitation of our study is that we did not include a pseudophakic group. Lenticular status has an effect on the ffERG response; arguably more so under dark-adapted than under light-adapted conditions. However, as long as a reasonable amount of diffuse light can reach the retina the ERG is able to reveal how well it can function (Granit 1963) and, in a study of thirty patients with dense cataracts, postoperative ERG amplitudes were not significantly larger compared to baseline (Ratanapakorn et al. 2010).

In conclusion, the difference in cone function measured by light-adapted 3.0 a-wave implicit time and 30-Hertz flicker peak time in early and late AMD compared to healthy controls suggests a more diminished overall response when AMD has reached later stages. Future studies could seek to perform ffERG in a larger cohort of patients with AMD using staging methods to include an intermediate AMD sub-group, which may help to establish further the link between phenotype and progressive deterioration in retinal function. In addition, the use of extended ISCEV protocols and other functional tests such as the multifocal ERG may allow further assessment of changes in latency that can be attributed to cone system dysfunction in eyes with AMD.

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