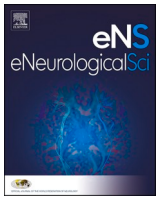
eNeurologicalSci 29 (2022) 100430

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci



Objective perimetry and progression of multiple sclerosis

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ARTICLE INFO

Keywords:
Objective perimetry
Multiple sclerosis
Disability progression
Pupillary response

ABSTRACT

Introduction: We re-examined the per-region response amplitudes and delays obtained from multifocal pupillographic objective perimetry (mfPOP) after 10 years in 44 persons living with multiple sclerosis (PwMS), both to examine which parts of the visual field had progressed in terms of response properties and to examine if the baseline data could predict the overall progression of disease.

Methods: Expanded Disability Status Scale (EDSS) scores were assessed in 2009 and 2019. Both eyes of each participant were concurrently tested at 44 locations/eye on both occasions. Several measures of clinical progression were examined, using logistic regression to determine the odds of progression.

Results: At the second examination the 44 PwMS (31 females) were aged 61.0 ± 12.2 y. Mean EDSS had not changed significantly (3.69 ± 1.23 in 2009, 3.81 ± 2.00 in 2019). mfPOP delay increased progressively from inferior to superior regions of the visual fields while amplitudes demonstrated a temporal to nasal gradient. The mean of the 3 most delayed visual field regions was correlated with progression of MS by 2019 ($p = 0.023$). Logistic regression indicated a significant association between delay and odds of progression ($p = 0.045$): an individual with 3 regions at least 1 SD (40 ms) slower than the mean in 2009 had 2.05× (±SE: 1.43× to 2.95×) the odds of progression by 2019. A 1 SD shorter delay was associated with 2.05× lower odds of progression. Amplitude changes were not predictive of progression.

Significance: mfPOP may provide a rapid, convenient method of monitoring and predicting MS progression.

1. Introduction

While grey matter loss is indicative of brain atrophy [1], neither this nor other measures of regional or global brain atrophy correlate well with disability progression in multiple sclerosis (MS) [2]. Functional visual testing in the form of visual evoked potentials (VEPs) continues to have value in the diagnosis of multiple sclerosis [3]. In particular, testing many parts of the visual fields concurrently using multifocal VEPs (mfVEPs) appears to improve diagnostic power, especially if sparsely-presented, transient onset-stimuli are used [4]. A related technology is multifocal pupillographic objective perimetry (mfPOP) which, like mfVEPs, is able to measure both response amplitude and response delay from many visual field regions of both eyes concurrently [5,6]. The mfPOP method operates much like a mfVEP in which both eyes are stimulated with independent stimuli but the neural response is measured in terms of relative changes in the diameter of the pupils. Responses to sparse mfPOP stimuli have been shown to be mediated through the extra-striate cortex [7]. Although initially developed for use in ophthalmic disorders [8–10], mfPOP has been used to study visual attention [11]. It has also been shown to have good diagnostic power in migraine [12], concussion [13], and epilepsy [14], with areas under Receiver Operating Characteristic plots (AUROCs) in the range 77.3% to 82.6%. A cross-sectional study of 85 people with MS showed that findings using an older version of mfPOP were correlated with disease severity [15] with AUROCs of up to 85.5%. Interestingly, as reported for sparse mfVEPs [4], sensitivity and specificity for diagnosing MS did not depend on a history of optic neuritis, suggesting that mfPOP might have been measuring something correlated with disease severity and progression rather than being a marker of previous inflammation. Others have reported a similar finding [16].We have recently reported similar

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https://doi.org/10.1016/j.ensci.2022.100430
Received 19 July 2022; Received in revised form 7 September 2022; Accepted 7 October 2022
Available online 8 October 2022

results, and AUROCs up to 96.5% using a new 5th generation mfPOP method [17].

The present study was set up to examine that question further. 44 of the participants in the earlier study [15] were re-examined just over 10 years later. We reassessed their clinical status and Expanded Disability Status Scale (EDSS) scores and repeated the mfPOP tests. We were thus able to examine which parts of the visual fields had changed over time in terms of per-region sensitivities and delays. More importantly, it was possible to investigate whether the original mfPOP findings were predictive of which subjects were going to progress over the intervening 10 years.

2. Methods

2.1. Study design and participants

Forty-four persons living with MS (PwMS) whom we had tested in 2009–10 [15] were re-evaluated in 2019. The original cohort of 85 PwMS was relatively old, 49.8 ± 11.3 y (mean ± SD). We were able to identify 46 of the original 85 participants as eligible and available for retesting but two of these were not included, one because there was doubt about the original diagnosis of MS, and because cystoid macular oedema had developed in one eye of the other. The study conformed to the Declaration of Helsinki guidelines and was approved by the ACT Health Human Research Ethics Committee (ETH.4.12.080) and the Human Research Ethics Committee of the Australian National University (2012/303). The individuals' clinical notes were reviewed to confirm that the diagnosis of MS was still correct and to assess their current clinical status. Up-to-date EDSS scores were evaluated by a neurologist. To rule out potential confounding by ocular abnormalities, all participants underwent ocular examination that included best corrected visual acuity (log-MAR), slit-lamp investigation, posterior pole and retinal nerve fibre layer optical Coherence Tomography scans (OCT, Spectralis, Heidelberg Engineering GmbH, Germany) to rule out ocular comorbidities. We also performed Matrix 24–2 automated perimetry (Carl Zeiss Meditec Inc., Dublin, CA). The mfPOP testing was performed on a prototype of the FDA-cleared ObjectiveFIELD Analyser (OFA) (Konan Medical USA, Irvine, CA). The OFA used was identical to the device used in 2009.

2.2. Objective perimetry

The mfPOP setup and stimuli have been described in detail previously [15,18]. Briefly, the device presented two stimulus arrays dichoptically at optical infinity. Fig. 1 shows the array of 44 lozenge-shaped yellow stimuli presented to each eye while the subject fixated a central cross. The array covered the central ±30° deg. of the visual field and images were updated at 60 frames/s. Background illumination was 10 cd·m^{-2} and individual stimuli varied in brightness from 125 to 280 cd·m^{-2} (Fig. 1**B**). The luminance at each region was modified to generate similar-sized pupillary responses from all regions across the visual field in normal subjects (luminance balancing) [18]. Stimuli persisted for 33 ms and were presented pseudo-randomly with a mean inter-stimulus interval of 4 s. In total, a stimulus was presented at each location 90 times. To make the test easier to perform, it was divided into 9 segments of just over 40 s each, resulting in a total test duration of just over 6 min. Pupil diameter was tracked by video cameras in real time. Diameters were standardised and the average per-region responses from the 90 presentations/region were obtained. Peak response amplitudes and times-to-peak were then extracted for each region. For both amplitude and delay the right eye data were flipped left-right to match corresponding regions from the left eyes.

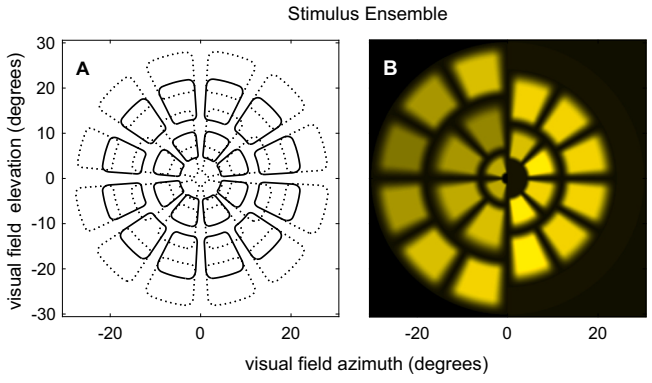

Fig. 1. mfPOP stimuli comprising 44 test regions per eye. During testing, stimuli were pseudo-randomly presented as transient-onset stimuli of duration 33 ms. Potentially overlapping stimuli were never presented simultaneously. (**A**) The stimulus array tested the central ±30° of the visual field with five interleaved rings of yellow stimuli. (**B**) illustrates luminance-balancing [18]. To aid visualization, only half of the regions in each of the rings are shown.

2.3. Statistics and analysis

Fig. 2 presents the baseline time-to-peak data from 2009. Fig. 2A shows the average per-region deviations of time-to-peak (delay) from normative data for the 85 participants in that study [15]. Darker tones indicate the parts of the visual field exhibiting longer delay: most participants had delays of >30 ms relative to control values in several parts of their visual field. Fig. 2B shows the distribution of the per-region delays across all participants. These figures illustrate two key features, namely that localised increases in delay were the norm, and that the half-width of the distribution was about 40 ms (the differences between the median and the 25th and 75th percentiles were − 34.0 and 40.5 ms, respectively).

The aim of this study was to determine whether the 2009 mfPOP data could predict progression. Comparing initial and review study data from 2009 and 2019, we derived five different measures of disease progression. The first was defined as 'Any Progression'. This included those individuals who changed from relapsing remitting MS (RRMS) to secondary progressive MS (SPMS), or who had primary progressive MS (PPMS) or SPMS and whose EDSS scores increased over the study period (two subjects). Second, we assessed only those individuals who had progressed clinically from a diagnosis of RRMS to SPMS. The remaining three categories involved subgroups in which the EDSS had: (a) increased by 0.5 units or more, (b) increased by 1.0 units or more, or (c) increased by 1.5 units or more. For each of the five measures of progression, we examined the discriminating power of the worst 3 per-region delays, comparing those participants who progressed with those who did not, by calculated Hedge's *g*, which is the Cohen's *d* standardised effect-size corrected for small sample sizes. All analyses were performed in Matlab (The MathWorks 2020b, Natick, MA).

The previous study showed that per-region delays had the greatest ability to discriminate control subjects from PwMS, although per-region response amplitudes (sensitivities) were not far behind [15]. In particular, the best diagnostic performance for discriminating PwMS from controls was generated when considering the means of the 3 most abnormal regions of each subject, looking at either response delay or amplitude. We have recently reported very similar results using newer 5th-generation mfPOP stimuli in MS [17]. We repeated this assessment in the current study, but it was not clear which measure would perform best in relation to predicting progression, specifically whether the best measure was still the mean of the 3 most abnormal regions of the visual field, or whether it might be some other number. To resolve this, we computed the means of the worst (relative to normal) 1, 2, 3, 6, 11, 22 and 44 regions/field in each participant for both delay and sensitivity. We then submitted those data to a stepwise regression to determine which of these was most predictive of progression. This number was then used in a logistic regression to determine the odds of progression. We used a generalised linear model (Matlab fitglm) with a binomial

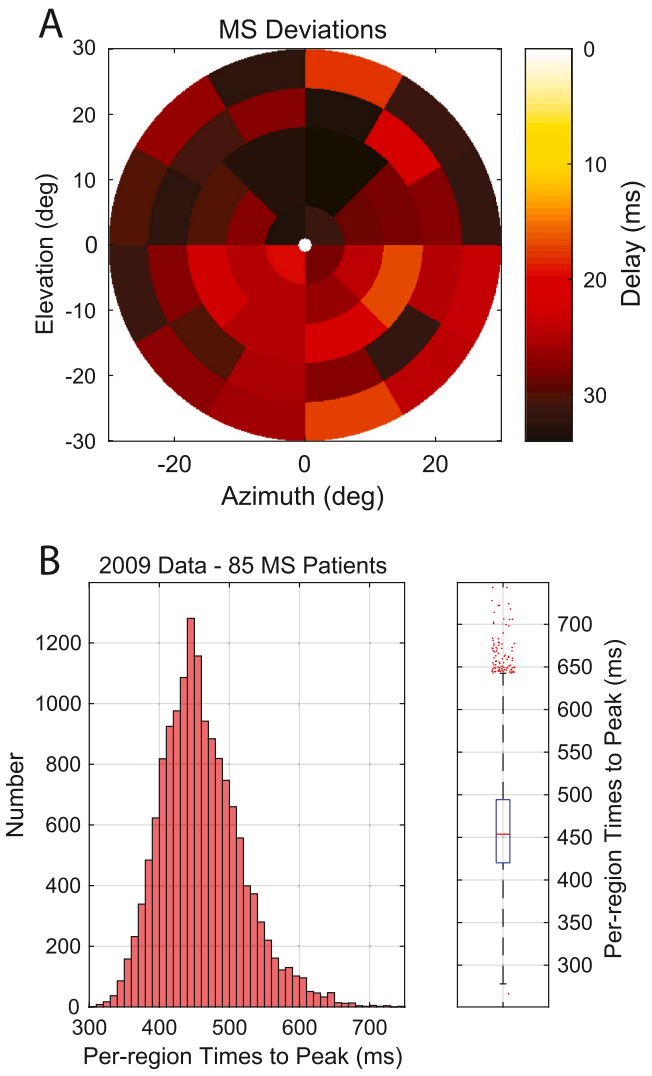

Fig. 2. A) Average deviations from normative time-to-peak data in the 85 participants in the 2009 study [15]. Average per-region delays of over 30 ms were not uncommon, especially in the superior field. **B**) The distribution of the per-region delays across all 170 participant fields in 2009. The insert at right is a box-plot showing median (red horizontal line), 25th and 75th percentiles (lower and upper edges of the blue box, respectively) and the 5th and 95th percentiles (dashed whiskers). The small red dots are outliers. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

distribution and a logit link function to determine the log(Odds) of progression. We undertook a similar assessment of the per-region response amplitudes.

3. Results

3.1. Demographics

Of the 44 participants, 31 were female. At the second assessment, the mean age was 61.0 ± 12.2 y. None of the participants had any significant abnormality on ocular examination. In 2009, 40 PwMS had been diagnosed as RRMS, 2 as PPMS, and 2 as SPMS. By 2019 the diagnoses were 31 RRMS, 2 PPMS, 11 SPMS. The mean EDSS scores in 2009 and 2019 were not significantly different (3.69 ± 1.23 and 3.81 ± 2.00 (mean ± SD), respectively), but individuals' EDSS scores could vary in both directions. Fig. 3 shows the change in the EDSS scores over the ten years of the study. The dot colours indicate their diagnosis in 2019.

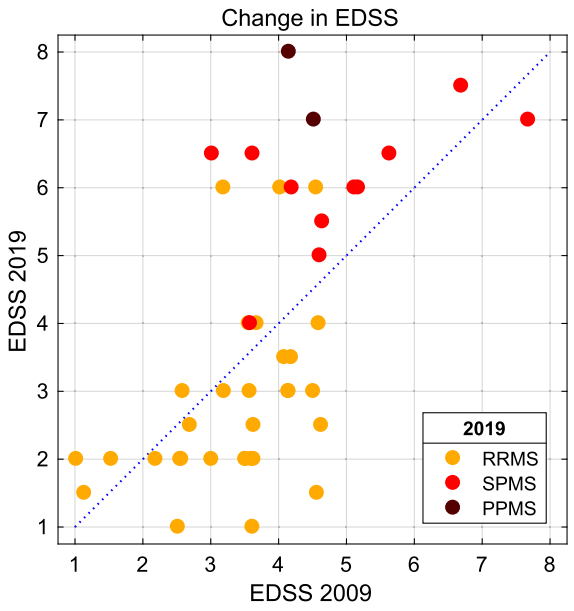

Fig. 3. Change in EDSS scores between 2009 and 2019 for the 44 PwMS. Their MS classification in 2019 is indicated by the colours of the dots (see text for clarification of abbreviations).

3.2. Analysis of progression

Stepwise regression analysis of disease progression between 2009 and 2019 found that the mean of the worst 2 per-region delays was most predictive ($p = 0.042$), closely followed by the mean of the worst 3 ($p = 0.046$) regions. Means of the worst 6, 11, 22, and 44 regions were also predictive, but less so, and were not used for subsequent analysis. To be conservative we chose the mean of the worst 3 per-region delays for all further analyses. Regression analysis looking at per-region response amplitudes showed that these did not perform as well as delay. Similarly, age and sex were not selected by the stepwise regression and were thus considered not to be predictive of progression.

Table 1 shows the results of comparing the mean of the 3 worst per-region delays in each participant who progressed according to each of the five definitions compared to the participants not included in those groups. Effect-size was computed as Hedge's g, which is Cohen's d corrected for small sample size. Looking at all five measures of progression, the measure with the largest standardised effect-size (0.72) involved taking any subject whose disease had progressed clinically over the 10 years, the 'Any Progression' discrimination. Those subjects increased their EDSS scores by 1.59 ± 0.41 ($p < 0.002$) and the 2009 per-region delay was significantly correlated with the likelihood of progression in clinical status by 2019 ($p = 0.023$).

A logistic regression of the odds of progression yielded a log(Odds) of 1.80 ± 0.90 per 100 ms of extra delay (p = 0.045). For comparison we

Table 1
Average per-region time-to-peak delay across the worst three regions of each participant for the 5 definitions of progression, comparing those who progressed in each group with all other subjects. The leftmost column gives the standardised effect-size as Hedge's *g*. For the 3 EDSS based groups the criterion level, e.g. ≥ 0.5, is the difference in EDDS (ΔEDDS) of the second and first visits.

		Mean of Worst 3 delays in 2009 (ms)		
Definition	**N**	**Progressed**	**Not progressed**	***g***
Any Progression	11	563.2 ± 46.9	529.7 ± 45.9	0.72
RRMS ➔ SPMS	9	559.4 ± 49.8	532.9 ± 46.6	0.55
ΔEDSS ≥0.5	19	546.8 ± 51.0	531.8 ± 45.3	0.30
ΔEDSS ≥1.0	13	546.6 ± 57.7	535.1 ± 43.5	0.23
ΔEDSS ≥1.5	7	551.7 ± 49.4	536.0 ± 48.0	0.32

performed similar analyses using the means of the worst two, and then the worst six, per-region delays in each participant from 2009: these generated similar log(Odds) with *p*-values of 0.047 and 0.049, respectively. There was just one number per subject so there was no potential issue with multiple comparisons. As above, Fig. 2B shows that the half-width in 2009 was about 40 ms. Using that value, the odds of progression for an individual with delay of >40 ms above the average in any three regions of the visual field were 2.05× (±SE: 1.43× to 2.95×). Conversely, individuals with delays that were 40 ms shorter than the average had 2.05× lower odds of progressing by 2019, meaning that between ±1 SD there was a four-fold spread in the odds of progression.

3.3. Visual field effects

Fig. 4A Illustrates the average per-region increase in response delays over the 10 years of the study for all 88 eyes. Based on a linear model, the average extra delay relative to baseline was 19.5 ± 5.12 ms (mean ± SE, $p < 0.0002$). Similar to the baseline delays shown in Fig. 2A, there was a vertical gradient, with more prominent increases in delay being seen in the superior visual field. The same analysis for response amplitudes showed a small, but significant, change, −0.86 ± 0.33 μm ($p < 0.01$). Unlike the inferior to superior gradient for latency, amplitude changes appeared to follow a temporal to nasal gradient. Interestingly, regions with shorter delay changes were associated with greater loss of sensitivity over time (Pearson correlations of $r = 0.460$, $p < 0.002$).

4. Discussion

This study looked at the change in EDSS and clinical characterisation of PwMS over a 10-year period and correlated this with metrics from mfPOP. There was minimal change in average EDSS scores over this period, and individual EDSS scores could change in both directions. As shown in Fig. 3, improvement in EDSS scores in 2019 was likely to occur in those PwMS who had had lower EDSS scores in 2009, while those with higher EDSS scores in 2009 were more likely to progress. The apparent improvement in those with lower scores may relate to inter-observer variability between 2009 and 2019, bearing in mind that inter-rater error is highest for low EDSS scores [19]. PwMS who had progressed on the 'Any Progression' criterion by 2019 were more likely to have demonstrated greater delay in their per-region pupillary responses in 2009 (Table 1). A delay of 40 ms in time-to-peak above the normative mean in 2009 was associated with double the risk of clinical progression by 2019, whereas shorter delays were associated with a similar reduction in risk of clinical progression. The other measures of progression assessed in this study were not significantly associated with changes in pupillary response latency.

Interestingly, the baseline per-region delays increased with a gradient from inferior to superior regions of the visual field (Fig. 3A). The explanation for this is not clear but, over the 10 years of the study, increase in delay was also more common superiorly (Fig. 4A), suggesting this is a real phenomenon worthy of further study. Note that aging itself is not a likely cause since mfPOP fields have been shown elsewhere to exhibit uniform decline of peripheral sensitivity with age [20]. By contrast, amplitude changes were more obvious in the nasal field (Fig. 4B) and greater reduction in amplitude was correlated with a smaller increase in delay. The explanation for this is not clear, but it is possible that reduction in amplitude precedes increase in delay. It is worth noting that the changes in amplitude were, in fact, relatively small over the study period, almost certainly explaining why amplitude measures were not predictive of progression. Annual testing might shed further light on the observed association between changes in per-region amplitude and delay.

We have previously reported that mfVEPs are 15 times larger than conventional methods if stimulus presentation is made more sparse temporally, and that doing this generates much higher sensitivity and specificity for MS [4]. Importantly in that study, diagnostic power was equally high for eyes with and without a history of optic neuritis. Sparse mfPOP stimuli perform similarly [15]. We have previously proposed that that the increased gain seen with sparse stimuli is due to involvement of cortico-thalamic feedback [21]. At least 3 times more axons travel down to the lateral geniculate nucleus (LGN) as travel from the LGN to the cortex [22]. Thus, if cortico-thalamic feedback were involved, testing with sparse stimuli might effectively be testing 4 times more axons as conventional VEPs, thereby increasing the chance of detecting changes due to small lesions. Of note, Graham and Klistorner [23] have pointed out that, while the optic radiations make up about 1% of total brain white matter, T2 lesions in the radiations account for 7–10% of the total lesion load.

Although involvement of the optic radiations may be important, it is worth noting that both the retinal nerve fibre layer and the ganglion cell inner plexiform layer also decline in the eyes of PwMS, both those with, and without, a history of optic neuritis [24]. These changes are distributed unevenly across the retina meaning that multifocal functional measures such as mfPOP are ideally suited to quantifying them. Studying the pupils may offer an additional advantage given that the whole accommodative triad has recently been shown to be affected by MS [25]. Despite a relatively small cohort, this study was able to obtain significant results but a larger, prospective study using the novel techniques with a similar duration of follow-up is clearly warranted.

The OFA is a portable desk-top device with FDA clearance. There are

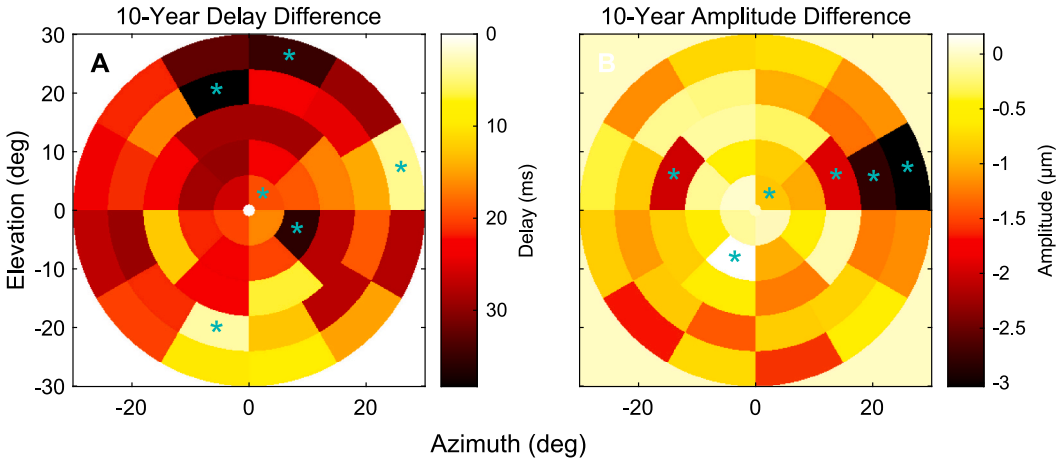

Fig. 4. A) Average per-region difference in time-to-peak between 2009 and 2019. B) Average difference in response amplitudes. *Significant per-region differences from the mean change ($p < 0.05$).

no electrodes involved so it has a much shorter set-up time than VEPs, and highly skilled staff are not required. Since the original testing in 2009 there have been significant improvements to the mfPOP stimulus parameters and the analytical methods used in OFA. These include the introduction of luminance-balanced stimuli [26] and delivery of stimuli in clustered volleys [27]. Data from 6 studies on 96 subjects assessing the more modern methods have shown 35%–57% higher signal-to-noise ratios and 2.3× − 3.4× better model R^2 than the earlier versions [28]. Most recently, a new 5th generation mfPOP method has allowed the overall testing duration to be reduced to <90 s while producing AUROCs of up to 96.5% +/− 2.30% [17]. These features mean that it is appropriate to combine functional data from OFA along with other candidate biomarkers as a possible tool for assessing and predicting disease progression in MS [29]. Testing subjects more often might also reveal fluctuating sub-clinical events.

One potential issue with our study was that different physicians were involved in EDSS assessments at the two time points at which the participants were studied. This may have produced some of the apparent improvement in EDSS scores seen in Fig. 3. Another consideration is that survival bias caused by our relatively old initial cohort may have meant that some persons who showed progression could not be tested. Nevertheless, the present results, combined with greatly improved mfPOP methods for diagnostic testing of MS [17], mean that a larger-scale, multi-centre study is now justified.

In summary, this study has demonstrated that changes in the latency of pupillary response assessed by mfPOP are correlated with the likelihood of disease progression in PwMS 10 years later. It is likely that the recent refinements to stimulus delivery and data analysis which have been incorporated into the current version of the OFA will provide additional information on disease progression. Given the portability of OFA and its ease of use, this technique may prove complementary to MRI scanning in the diagnosis and assessment of PwMS [2], and may prove useful in assisting clinicians to make decisions regarding treatment.

Credit author statement

Ted Maddess planned the study, analysed the data, and drafted the paper. Corinne F Carle planed the study, tested the subjects, and drafted the paper. Emilie MF Rohan and Jonathan Baird-Gunning[2], tested the subjects, and drafted the paper. Josh P van Kleef analysed the data, and drafted the paper. Christian J Lueck planed the study, provided clinical oversight, drafted the paper.

Funding

This research was supported by the Australian Research Council through the ARC Centre of Excellence in Vision Science (CE0561903) and the Our Health in Our Hands (OHIOH) ANU intramural grant.

Data availability statement

The data is available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ted Maddess reports financial support was provided by Australian Research Council. Ted Maddess reports a relationship with Australian Medical Research Future Fund that includes: funding grants. Ted Maddess reports a relationship with Konan Medcial USA Inc. that includes: funding grants. Ted Maddess, Corinne F Carle has patent #US9848771 licensed to Konan Medcial USA Inc. Ted Maddess, Corinne F Carle and Joshua van Kleef have a patent application # P0040304AU licensed to Konan Medical USA. Ted Maddess has patent #US8807753 licensed to Konan Medcial USA Inc. Ted Maddess has patent #US10064548 licensed to Konan Medcial USA Inc. Ted Maddess sits on an advisory panel of a small ophthalmic pharmaceutical EyeCo Pty Ltd., which develops products for retinal diseases.

Acknowledgements

We would like to acknowledge the participants in the study.

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