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Clinical applicability of the Macular Degeneration Detection Device (MDD-2): a novel photostress recovery measurement device

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Background: Diseases affecting the macula, such as age-related macular degeneration (AMD), diabetic retinopathy and central serous retinopathy can result in impaired photostress recovery time (PSRT) despite normal visual acuity and fundoscopic appearance. The MDD-2 Macular Degeneration Detection Device is a novel flash photostress recovery device. In this study, we examine the repeatability of the MDD-2 in a normal population and its suitability for incorporation into routine clinical practice.
Methods: One hundred (60 female) subjects (mean age 35 ± 8 years; range 18 to 66 years) were recruited to partake in this study. The photostress recovery time was measured using the MDD-2 on three occasions in the dominant eye and one final occasion in the non-dominant eye to assess measurement repeatability. All subjects were in good ocular health. Visual acuity and iris colour were recorded for each participant.
Results: Repeated measures analysis of variance revealed a statistically significant learning effect on intra-measurement repeatability ($p < 0.01$). Although paired t-test analysis revealed statistically significant differences between repeated measures both within and between eyes ($p < 0.05$ for all) the correlation between repeat measurements is statistically significant ($p < 0.05$ for all), and the coefficient of repeatability reaches clinically acceptable levels once the initial photostress recovery time, which demonstrated increased variability and latency compared to all subsequent measures, is excluded.
Conclusion: The MDD-2 provides highly repeatable measurements of photostress recovery time among young naïve subjects, following verbal explanation of the task and only one 'practise' measurement. The measurement is also highly repeatable between eyes, providing a potential immediate clinical biomarker of ocular health.

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Key words: age-related macular degeneration, macula, MDD-2, photostress recovery time

Early detection of visual loss, such as is associated with macular disease, including age-related macular degeneration (AMD), diabetic retinopathy and central serous retinopathy, is of prime concern to eye-care practitioners and health-care providers for a number of reasons, which include:

1. the increasing prevalence of ocular disease[1–3]
2. the likely increase in consequential visual impairment and blindness[4,5]
3. the possibilities for retarding disease progression through supplementation[6] and
4. recent advances in pharmacologic management of conditions, such as AMD, which are best applied at the

earliest stages of the development of abnormal pathology.[7]

In addition, it is also important that functional biomarkers provide prognostic information and guide clinical decisions around the need for treatment and its success.[8,9]

Although visual acuity (VA) alone is an inadequate marker of visual function in macular disease,[9] other biomarkers including photopic and scotopic light sensitivity,[10] flicker sensitivity,[11] colour vision,[12] contrast sensitivity,[13] dark adaptation[14,15] and photostress recovery[16] can provide additional capacity to detect the early signs of retinal degeneration. It has been suggested that these early signs are partially attributable to an increased effect of intraocular scattered light in the diseased eye,[17–19] along with excessive photoreceptor bleaching due to the relative lack of photo-protection in the affected retina. In particular, photostress recovery time (PSRT) has been shown to be adversely affected by retinal and macular disease.[16,20,21]

Photostress recovery time describes the time required to regain normal visual function after viewing a light source so intense as to bleach the visual pigments and saturate the response of the macular photoreceptors, and therefore cause transitory loss of vision.[22,23] This dynamic assessment of macular function, originally described for the assessment of central serous retinopathy[24] is an excellent indicator of retinal integrity, as normal recovery depends on an efficient and intact underlying retinal photoreceptor and pigment epithelial function.[25,26] Therefore, it can be used to indentify insidious, pre-clinical macular disease and potentially in advance of a reduction in VA, a defect on Amsler grid[27] or other clinical manifestations. A recent evaluation of potential biomarkers of early AMD found that PSRT achieved high diagnostic capacity and provided the optimal qualitative assessment of visual function in early AMD.[16] Abnormal PSRTs may also be used to differentiate retinal/macular from neural/optic nerve disease.[27,28]

Macular photostress can be induced either using a brief flash of intense light delivered to the macula or using a more sustained and lower-intensity light source such as the ophthalmoscope. Flash recovery testing is effective in the detection of early macular disease.[29] The MDD-2 Macular Degeneration Detection Device is a novel flash photostress recovery device. This device is capable of detecting functional visual loss in AMD and diabetic maculopathy.[20] No previous study has explored the clinical applicability of this test in terms of learning and repeatability. In this study, we examine the repeatability of the MDD-2 in a normal population and its suitability for incorporation into routine clinical practice.

METHODS

One hundred subjects (60 female) participated in this study (one additional subject was excluded on the basis of the presence of ocular pathology), which was approved by the Research Ethics Committee at Dublin Institute of Technology (DIT). Informed consent was obtained from each volunteer and the experimental procedures adhered to the tenets of the Declaration of Helsinki.

The study was conducted in the Vision Science Laboratory and National Optometry Centre at DIT. Recruitment of subjects was by word of mouth. All subjects were aged between 18 and 66 years, in good general (by self-report) and ocular (determined by ophthalmoscopy) health and with logMAR visual acuity of at least 0.2 (6/9) in the study eye. Exclusion criteria included any sign of retinal or ocular abnormality, any known systemic health condition and logMAR visual acuity less than 0.2. A computer-generated logMAR test chart (Thomson 2000 Pro; Thomson Software Solutions, Hatfield, United Kingdom) was used to determine logMAR acuity. Iris colour was recorded using an iris colour classification scheme, with iris colour matched to standard colour photographs and classified into one of five categories (grey, blue, green, light brown, brown) as described by Seddon.[30] All subjects recruited into the study were naïve to the MDD-2 test.

Photostress recovery time was measured using the MDD-2 Macular Degeneration Detection Device. The MDD-2 is a relatively simple device, comprising a spectrally broadband xenon flash light source with good short- (around one per cent) and long-term (around three per cent) output stability, a UV and IR filter and focussing (+8.00 D) lens. The test involves accurate identification (post-flash photostress) of a large (0.41 radian or 23.5°) angular subtense and stroke width of about 2.7°, requiring about 6/120 Snellen acuity (logMAR 1.3), internally presented and randomly generated numbers between zero and nine. The target is viewed through a 12 mm central aperture in the flash tube. The 200 µsec duration flash is generated by a xenon flash source (mouser type FT04050), mounted inside the flash tube within the subject's field of view (flash source to cornea distance of approximately 50 cm) and generates uniform maximum irradiance of 4.5 W/cm^2 at the viewing aperture across an angular subtense of 0.67 radians (38.4°).

The nature of the test and stimuli were described in detail to each subject and the subjects were requested to confirm their understanding of the task. The test was conducted using natural, undilated pupils in ambient room lighting conditions averaging 870 lux. The flash tube was positioned against the test eye and the subject was required to correctly identify a baseline, pre-photostress, numeric stimulus without their refractive correction. Subjects were instructed to stare into the device at the instant they were ready to begin the test, to fixate centrally at the position of the pre-bleach stimulus and to avoid blinking at the onset of the photostress flash. When ready to commence the test proper, the subject pressed a button on the device, which initiated three concurrent processes; the arc flash photostress, the photostress recovery timer and a new random number display. Once vision recovered sufficiently to allow number recognition, the subject was required to verbally identify the new number and simultaneously, to press the same button on the device to cease the test. The actual number presented by the device and the

subject's PSRT were vocally confirmed by the device, allowing the examiner to determine the accuracy of the subject response and to record the PSRT. Three successive measurements (PSRT 1, PSRT 2 and PSRT 3), separated by two-minute intervals (determined as a sufficient time interval to allow retinal recovery during a pilot study) were recorded for the subject's dominant eye (determined using the Miles Test).[31] One further reading was taken using the non-dominant eye (PSRT 4). Incorrect identification of the test stimulus at baseline resulted in exclusion from the study. A single incorrect response during the test phase was permitted (result discarded and test repeated following a two-minute interval) but a second incorrect response resulted in exclusion from the study.

The statistical software package SPSS (version 18) was used for analysis (SPSS Inc., Chicago, IL, US). A linear regression analysis was used to assess for an effect of age, sex and iris colour on photostress times. Pearson correlation coefficients were calculated to investigate the relationship between sequential measurements and between eyes. Bland–Altman analysis and plots, as well as the limits of agreement, were used to quantify the agreement between repeat measures of the PSRT. Intra-measurement repeatability is expressed as a coefficient of repeatability, which was calculated as the standard deviation of the mean difference between measurements and multiplied by 1.96. Repeated measures analysis of variance (ANOVA) was conducted to test for a learning or fatigue effect that might confound the test-retest analysis. A five per cent significance level was used throughout the analysis.

RESULTS

The mean age (± SD) of the sample was 35 ± 8 years and ranged from 18 to 66 years. The mean VA was logMAR -0.04 ± 0.06. The mean PSRT for each of the three measurements in the dominant eye and the final measurement in the fellow eye are presented in Table 1. They demonstrate a trend toward improved PSRT with each sequential measurement in the dominant eye, with the most substantial improvement in PSRT occurring between PSRT 1 and PSRT 2.

Repeated measures ANOVA, using a general linear model approach, with age, sex and iris colour as co-variates, confirmed the presence of an intra-measurement learning effect ($p < 0.001$), as demonstrated by a gradual shortening of successive PSRT measures in the dominant eye. Pearson's correlation revealed a moderate and significant relationship between PSRT 2 and PSRT 3 in the dominant eye ($r = 0.66$; $p < 0.01$; Figure 1a) and

Photostress measurement (eye)	Mean ± SD PSRT (seconds)	Range (seconds)
PSRT 1 (Dominant)	7.37 ± 3.2	3–24
PSRT 2 (Dominant)	5.50 ± 1.70	3–10
PSRT 3 (Dominant)	5.11 ± 1.51	3–11
PSRT 4 (Non-dominant)	5.83 ± 1.72	1–12

SD = standard deviation

Table 1. Mean photostress recovery times (PSRT) for the first (PSRT 1), second (PSRT 2) and third (PSRT 3) measurements of the dominant eye of participants and mean PSRT of the non-dominant eye (PSRT 4).

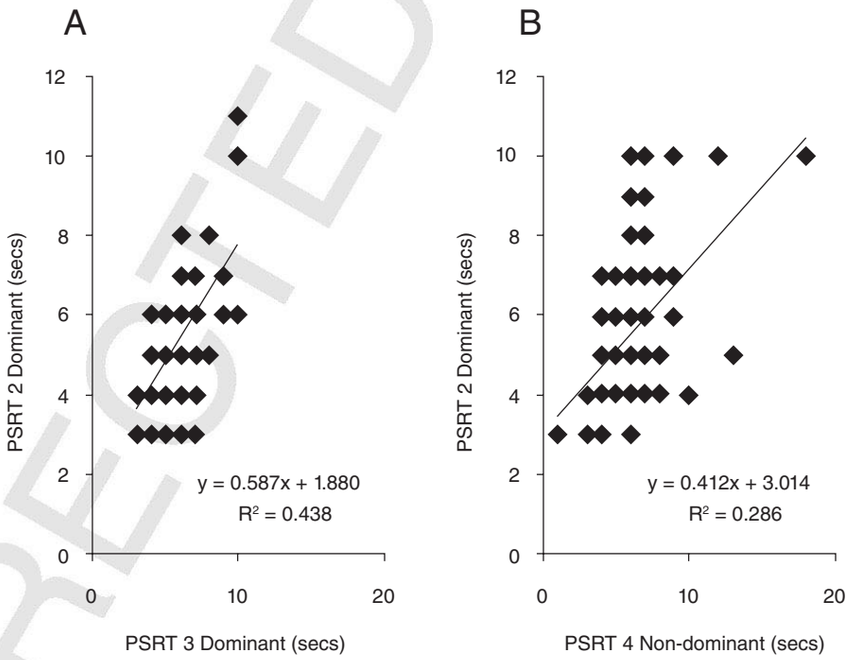

Figure 1. Correlation between (A) photostress recovery time for the second (PSRT 2) and third (PSRT 3) measurements of the dominant eye and (B) photostress recovery time for the second (PSRT 2) measurement of the dominant eye and the first measurement of the non-dominant eye (PSRT 4)

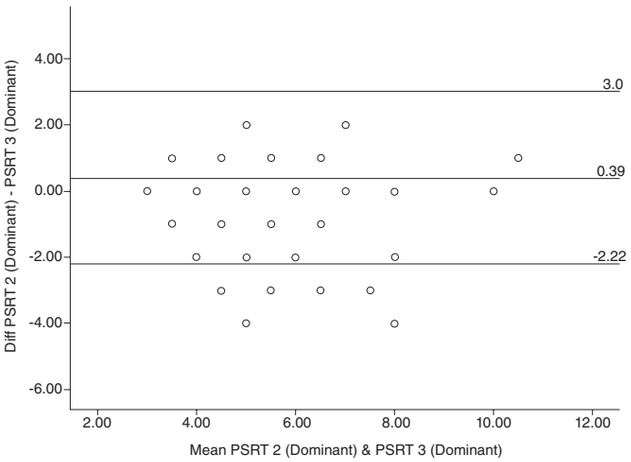

Figure 2. Bland–Altman plot showing 95 per cent limits of agreement for repeat measurements in the dominant eye (PSRT 2 and PSRT 3)

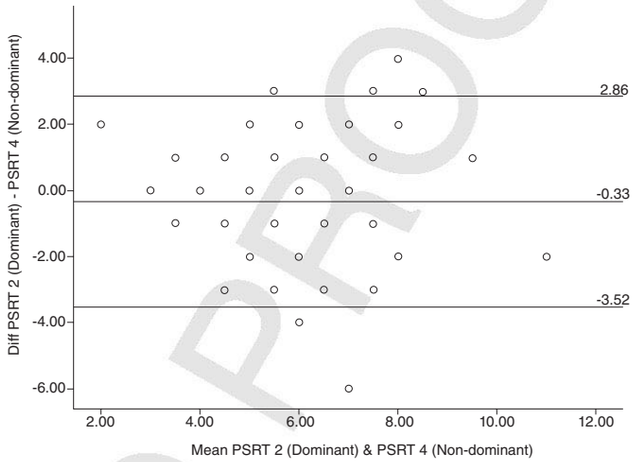

Figure 3. Bland–Altman plot showing 95 per cent limits of agreement for repeat measurements between eyes (PSRT 2 and PSRT 4)

a similarly significant inter-eye correlation ($r = 0.58$; $p < 0.01$; Figure 1b), indicating good within- and between-eye associations for repeated measures.

Bland–Altman analysis and plots were used to assess intra- and inter-eye agreement. The difference in mean recovery time between PSRT 2 and PSRT 3 in the dominant eye (0.39 seconds) and limits of agreement are presented in Figure 2. A paired t-test revealed a significant difference in PSRT between repeat measures of the same eye ($t = 2.93$, $p = 0.004$), indicating a bias toward shorter recovery times in PSRT 3. The coefficient of repeatability in the dominant eye was 2.61 seconds and for 76 per cent of subjects, the difference in recovery time between PSRT 2 and PSRT 3 was one second or less, indicating good within-eye repeatability. When comparing both PSRT 2 and PSRT 3 with PSRT 1, the coefficients of repeatability were significantly poorer at 4.69 seconds (PSRT 2) and 5.67 seconds (PSRT 3), respectively. In addition, differences between recorded recovery times were one second or less for only 49 per cent (PSRT 1 versus PSRT 2) and 37 per cent (PSRT 1 versus PSRT 3) of subjects, indicating poorer repeatability, when using the initial PSRT 1 as the baseline value.

The inter-eye difference between mean PSRT 2 and PSRT 4 (0.33 seconds) and limits of agreement are presented in Figure 3. A paired t-test revealed a significant difference in PSRT between eyes ($t = 2.24$, $p = 0.028$), indicating a bias toward longer recovery times in the fellow, non-dominant eye. The coefficient of repeatability for between eye measurements was 3.19 seconds and 67 per cent of subjects exhibited an inter-eye difference of one second or less, indicating good repeatability between eyes.

DISCUSSION

Although available evidence suggests that PSRT is sensitive to diseases like early AMD, it is little used in clinical practice. Despite its clinical simplicity and ability to detect worsening pathology even before ophthalmoscopic manifestations,[27] the macular photostress recovery test has not been widely used by clinicians for several reasons, typically due to the inherent variability of previous tests (for example, providing a single standard for an ophthalmoscopy-based technique would be almost impossible as the expected degree of photostress would vary with battery charge level, light bulb type and letter chart variability),[32] as well as difficulty implementing such tests into routine clinical practice (for example, the use of a perimeter to measure the recovery of sensitivity following photostress still requires an additional photostress source or alternatively, a non-standard perimetric routine).[28]

A legitimate criticism of the PSRT concept is the lack of any standardised test for the PSRT or clinical guidelines for implementation and interpretation, which can be used to reliably and efficiently provide an indicator of functional visual status and its relation to retinal and macular disease and perhaps to cataracts.[33] Numerous devices including the Scotometer,[34] the Brightness Acuity Test (BAT)[35] and the Eger Macular Stressometer[36] have been developed but not adopted for routine clinical practice. Device adaptations have also been used to provide a PSRT, using instruments such as the ophthalmoscope,[32] the electroretinogram[25] and the automated perimeter.[28] No device or technique has proved capable of providing a clinically acceptable gold standard measure of PSRT that is widely applicable and acceptable to routine clinical practice. The current results advance the possibility that the MDD-2 could

provide such a measure, although it remains premature to definitively conclude this.

The current study was designed to evaluate the repeatability of the MDD-2 within a single clinical session to determine:

1. whether a substantial practise session would be required before a reliable and repeatable baseline measure of PSRT could be determined among naïve subjects and
2. the degree of inter-eye symmetry that might be expected among normal subjects, which could provide an indication of the capacity of the device to detect unilateral or asymmetric bilateral pathology, such as central serous retinopathy or AMD (as an asymmetric PSRT) at a single visit.

Although the device is marketed as an AMD detection tool, it is likely that optometrists and eye-care practitioners would use the device routinely for 'normal' patients, both as an added ocular health check and as part of any preventive health or screening strategy for AMD. Therefore, it is essential that the device is first tested for repeatability and ease of use among a normal population, which represents the aim of the current study.

Statistical analysis reveals a significant learning effect and difference between repeat measures of PSRT both within and between eyes. The significance of these differences is of clinical relevance only for the PSRT 1 measurement, which is considerably more variable (the standard deviation and range of PSRT measures are two to three times larger than in any of the three subsequent measurements), and considerably slower (up to 44.2 per cent slower on average) than subsequent measures. The small variations observed among PSRT 2, PSRT 3 and PSRT 4 are certainly not clinically significant relative to the dramatically increased PSRT observed previously in patients with AMD or diabetic maculopathy compared to normal controls using the same device.[20]

Typically it might be expected that repeat testing at short two-minute intervals would cause further bleaching of photopigment and consequential delays in PSRT in normal, but particularly, in diseased retinae. The observation here that PSRT remains stable in normal eyes, despite such short repeat test intervals is of interest and may offer further diagnostic potential. The typical PSRT observed is so short and the repeat test values so stable that it is not unreasonable to speculate that the device might predominantly test neural recovery mechanisms rather than the mechanics of photopigment bleaching and recovery. Perhaps this could be considered a 'flash' variation of traditional nyctometric techniques, which evaluate the initial two minutes of macular recovery dynamics in response to sustained exposure to a bright light source.[38]

It has been shown previously that the dynamics of short-term macular recovery are impaired in diabetic retinopathy.[38,39] Therefore, it is plausible to suggest that short interval repeat testing could itself reveal early retinal and macular functional loss. This would manifest as deterioration in PSRT, compared to the initial PSRT measurement, on repeated short interval testing not seen in normal observers here. Of course, this is purely speculative at this stage but might represent a useful further investigation into the clinical applicability of the MDD-2 device. This device also appears to be robust to the possible effects of age or iris colour on PSRT within this sample population. Iris colour, for example, might be expected to influence PSRT, as relatively more light would pass through a light compared to a dark iris.[37] It appears that the small amount of light that could traverse the lightest of irides does not play a role in determining PSRT.

These combined results suggest that a single practise measurement is sufficient to overcome any learning effect. Furthermore, the degree of inter-eye symmetry observed suggests the MDD-2 may have the capacity to detect unilateral or asymmetric pathology, as a delayed PSRT in one eye. The capacity of a device to provide repeatable measurements does not provide absolute evidence that such a device can differentiate normal from diseased eyes. For example, the Eger Macular Stressometer is incapable of providing information regarding AMD severity or progression.[36] The MDD-2 is capable[20] of:

1. differentiating normal from AMD-affected eyes (PSRT doubled on average in early AMD)
2. differentiating early and late forms of AMD (PSRT doubled on average in late compared to early stages) and
3. detecting disease progression (in AMD and diabetic maculopathy) in the absence of other clinical signs of deterioration of visual acuity and Amsler grid findings.

These findings suggest that the MDD-2 is sensitive to subtle changes in macular health, despite the test design, which would not seem appropriate for the isolation of specific macular function (the target and photostress areas extend significantly beyond the macula). Such design features could prove advantageous by extending the usefulness of the device for non-macular disease, which may impact PSRT, such as cataract or glaucoma, although this concept remains to be tested).

Therefore, it appears that an instrument based on the principles of the MDD-2 provides a reliable and user-friendly means to assess ocular health in routine practice. The test is easily understood and consequently requires only a verbal description of the task, followed by a single practise demonstration in one eye, for naïve users to reach a learning plateau and provide repeatable measures of PSRT. Given the statistical significance of the differences in repeat measures between eyes, it would seem prudent to include a practise measurement routinely in each eye before valid clinical measures are recorded. Such valid measures will serve as the baseline for serial measurements of PSRT. The results of the current study suggest that deterioration of greater than three seconds in measurements of photostress recovery over time should be regarded as somewhat suspicious, although this concept warrants further detailed and longitudinal studies.

The results cannot be generalised to a specifically older population, which might exhibit relatively slower normal PSRT[20] and more variability in PSRT due conditions such as age-related cataracts.[33] As such, the repeatability of the test among

an older population more likely affected by AMD would require additional investigation. Furthermore, the device has yet to be proven capable of detecting the earliest signs of disease or to detect changes in PSRT within individuals over time as a consequence of disease.

Although the MDD-2 device has been designed and marketed as an AMD tool, the current study suggests that it would be of clinical value to incorporate this test into routine clinical practice for all patients. The simplicity, short duration and diagnostic capacity of the test further enhance the concept that it could become an important and routinely-used clinical test of functional macular and central retinal integrity that can readily provide a clinical biomarker of ocular health, disease progression and disease severity.

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