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First results of automated RAPD-SWIFT method in dynamic pupillometry

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Version: Accepted Manuscript

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Abstract: Erste Ergebnisse einer automatischen RAPD-SWIFT Methode
in dynamischer Pupillometrie

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Hintergrund und Zielsetzung.
Wir präsentieren erste Ergebnisse einer Pilotstudie über die Verwendung
eines kommerziellen Pupillometers (PupilX, Albomed) für den Nachweis und
die Quantifizierung des relativen afferenten Pupillendefektes (RAPD).

In dieser Untersuchung wurde die videogestützte Pupillometrie in
Verbindung mit einer geregelten LED-Beleuchtung eingesetzt, um den
traditionellen Wechselbelichtungstest (Swinging-Flashlight-Test) mit
Graufiltern für den RAPD zu simulieren.

Methoden.
Die Ergebnisse in dieser Studie folgen einer von Wilhelm et al.
beschriebenen Methode (Tübingen SWIFT Test), in der die Augen abwechselnd
beleuchtet wurden und die entsprechende Reaktion des Pupillendurchmessers
mittels videounterstützter Pupillometrie gemessen wurde.

Mit dem PupilX kann die LED-Intensität in logarithmischen Stufen bis zu
einem Wert von 1000 Lux programmiert werden: eine 50% Abschwächung in der
Lichtintensität entspricht jeweils mit einem Graufilter mit 0,3 Log-
Einheiten.

Ergebnisse.
Die Augen wurden jeweils mit Lichtintensitäten im Bereich 0 - 0,9 Log-
Einheiten einseitig stimuliert. Bei allen normalen Patienten wurde eine
symmetrische Pupillenreaktion gesehen: die Antwort war identisch
unabhängig davon welches Auge stimuliert wurde. Im Gegensatz dazu zeigten
RAPD-Patienten eine klare Asymmetrie zwischen den Antworten auf die
Stimulation des linken und rechten Auges.

Diskussion.
Unsere Ergebnisse zeigen eine gute qualitative Übereinstimmung mit der Tübingen SWIFT-Studie. Zusätzlich ist das Verfahren in der Lage, zwischen gesunden Probanden und Patienten mit einem bekannten RAPD zu unterscheiden, was darauf hinweist, dass das PupilX mit bestimmten Stimulus-Sequenzen und in Verbindung mit einer geeigneten Analysesoftware das Potenzial für eine Erkennung eines RAPD-Befundes hat. Weitere Studien mit einer umfangreichen Studienpopulation müssen zeigen, ob sich mit dem Verfahren RAPD sicher quantifizieren lässt und RAPD-Befunde zuverlässig von Normalbefunden getrennt werden können.

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Background.
This paper presents preliminary observations on the use of a commercial pupillometric instrument (Albomed PupilX) for the detection and quantification of Relative Afferent Pupillary Defect (RAPD). In this pilot study, video-based pupillometry was used in conjunction with calibrated LED illumination to simulate the effects of the traditional swinging-flashlight test using neutral density filters.

Methods.
The results presented in this study follow a method described by Wilhelm et al. (Tübingen SWIFT-test) in which the eyes are illuminated alternately and the response in pupil diameter measured by video pupillometry. Using the PupilX instrument, the LED intensity can be programmed in logarithmic steps starting from a maximum intensity of 1000 Lux, with each reduction of 50% in illumination intensity corresponding to a 0.3 log-units increase in filter density.

Results.
The eyes were stimulated unilaterally with illumination intensities corresponding to a neutral density range of 0.0 to 0.9 log-units. In all normal subjects a symmetrical pupil reaction was seen, independent of which eye was stimulated. In contrast, in a subject with known RAPD, a clear asymmetry in the reaction to stimulation of the left and the right eyes was seen.

Conclusions.
These measurements were compared with typical results from the original Tübingen SWIFT study and good qualitative agreement was seen. Furthermore, the method can clearly differentiate between healthy subjects and those with a known RAPD, indicating that the PupilX, programmed with specific stimulus sequences and in conjunction with a suitable analysis software, has the potential for recognition and quantification of RAPD, and prompting the suggestion for further study involving a range of patients including both normal subjects and those with a known and quantified RAPD.

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Prof. Dr. Lothar Schad
Editor-in-Chief
Zeitschrift für Medizinische Physik

Prof. Dr. Achim Langenbucher
Editor, Sonderband Optik

06 Oct 2015

Manuscript: First results of automated RAPD-SWIFT method in dynamic pupillometry
Revised version

Dear Prof. Schad, Prof. Dr. Langenbucher ;

We are pleased to submit the revised article entitled "First results of automated RAPD-SWIFT method in dynamic pupillometry" for publication in the Sonderband Optik section of *Zeitschrift für Medizinische Physik*.

This pilot study builds on the earlier work of the group of Prof. and Dr. Wilhelm in Tübingen and describes a process and mathematical calculation for the detection and quantification of Relative Afferent Pupillary Defect (RAPD) in adults. We believe that we have successfully demonstrated the adaptation of the original Wilhelm method to the latest pupillometric instrument (Albomed PupilX), and this paves the way for future studies using a reliable and reproducible technique for the quantification of RAPD.

We thank the reviewers for their detailed feedback and comments and have revised the paper accordingly and as detailed in the accompanying response to reviewers.

We are pleased to submit this revised version (V6) for inclusion in the Sonderband Optik section.

This manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose.

Many thanks for considering this contribution for publication.

Yours sincerely,

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*Detailed Response to Reviewers

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**Manuscript: First results of automated RAPD-SWIFT method in dynamic pupillometry
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Dear Prof. Schad, Prof. Dr. Langenbucher ;

We thank the reviewers for their detailed feedback and comments and have updated the paper in accordance with these comments as follows:

Reviewer #1:

1) Gender terms for 'RAPD' in the Abstract have been corrected.

2) Page 4, line 5 has been corrected to: 'An RAPD can be caused by, and is indicative of . . .'

3) Page 4, line 28: the term 'LED' is introduced as suggested: '. . . light emitting diodes (LEDs) . . .'

4) 'Lux' has been changed to 'lx' throughout where used in conjunction with a numerical value.

5) An explanation of the terms 'OD' and 'OS' used to refer to the right and left eyes has been introduced before their first appearance in Figure 2.

6) The referencing of figures and tables in the text has been changed as suggested.

7) The paragraph has been rewritten with the suggested rewording of the first sentence and also to clarify the origin of the quoted statement (the statement is from the 2007 Wilhelm paper, reference [4]).

Reviewer #2:

The scales for the y-axis of the graphs in both Fig 4 and Fig 5 are detailed in the graph subtitle. A further legend has been added against the axes themselves for clarity, as suggested.

We agree with the comments of both reviewers that the number of patients is limited. The primary intention of this paper is to describe the method and to demonstrate that we are able to reproduce the results of the earlier study. We agree that a further extended clinical study with a larger patient group is now indicated and this is planned for a later publication.

We are pleased to submit this revised version (V6) for inclusion in the Sonderband Optik section.

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Many thanks for considering this contribution for publication.

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First results of automated RAPD-SWIFT method in dynamic pupillometry

Erste Ergebnisse einer automatischen RAPD-SWIFT Methode in dynamischer Pupillometrie

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Abstract

Background. This paper presents preliminary observations on the use of a commercial pupillometric instrument (Albomed PupilX) for the detection and quantification of Relative Afferent Pupillary Defect (RAPD). In this pilot study, video-based pupillometry was used in conjunction with calibrated LED illumination to simulate the effects of the traditional swinging-flashlight test using neutral density filters.

Methods.   The results presented in this study follow a method described by Wilhelm et al. (Tübingen SWIFT-test) in which the eyes are illuminated alternately and the response in pupil diameter measured by video pupillometry. Using the PupilX instrument, the LED intensity can be programmed in logarithmic steps starting from a maximum intensity of 1000 lux (lx), with each reduction of 50% in illumination intensity corresponding to a 0.3 log-units increase in filter density.

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Zusammenfassung

Hintergrund und Zielsetzung. Wir präsentieren erste Ergebnisse einer Pilotstudie über die Verwendung eines kommerziellen Pupillometers (PupilX, Albomed) für den Nachweis und die Quantifizierung des relativen afferenten Pupillendefektes (RAPD).

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Ergebnisse. Die Augen wurden jeweils mit Lichtintensitäten im Bereich 0 – 0,9 Log-Einheiten einseitig stimuliert. Bei allen normalen Patienten wurde eine symmetrische Pupillenreaktion gesehen: die Antwort war identisch unabhängig davon welches Auge stimuliert wurde. Im Gegensatz dazu zeigten RAPD-Patienten eine klare Asymmetrie zwischen den Antworten auf die Stimulation des linken und rechten Auges.

Diskussion. Unsere Ergebnisse zeigen eine gute qualitative Übereinstimmung mit der Tübingen SWIFT-Studie. Zusätzlich ist das Verfahren in der Lage, zwischen gesunden Probanden und Patienten mit einem bekannten RAPD zu unterscheiden, was darauf hinweist, dass das PupilX mit bestimmten Stimulus-Sequenzen und in Verbindung mit einer geeigneten Analysesoftware das Potenzial für eine Erkennung eines RAPD-Befundes hat. Weitere Studien mit einer umfangreichen Studienpopulation müssen zeigen, ob sich mit dem Verfahren RAPD sicher quantifizieren lässt und RAPD-Befunde zuverlässig von Normalbefunden getrennt werden können.

Schlüsselwörter

Pupillometrie, RAPD, Relativer afferenter Pupillendefekt, Wechselbelichtungstest

Background and purpose

A Relative Afferent Pupillary Defect (RAPD) is a condition affecting the pathway from the eye to the visual cortex in the brain. Often occurring unilaterally, an RAPD manifests itself as a reduced sensitivity to visual stimuli with a corresponding reduction in the pupillary reflex. Normally, a stimulus such as a brief flash of light in one eye causes both pupils to contract (the *consensual reflex*). With an RAPD the reduced sensitivity on the affected side results in a weaker response, seen as a smaller depth of pupillary contraction when the eye on that side is stimulated. An RAPD can be caused by, and is indicative of, conditions such as optic neuritis (Marcus Gunn pupil), unilateral glaucoma and retinal disease [1], [2].

The established method for the detection and quantification of the RAPD involves the use of neutral density filters in conjunction with alternate illumination of the left and right eyes, usually achieved manually (the *swinging flashlight test*) [1], [2]. In this test, the operator directs the light from a handheld flashlight alternately into the right and left eyes and the pupil reaction is assessed visually. A weaker pupil reflex to stimulation of one eye in comparison with the other indicates the presence of an RAPD. The extent of the RAPD can be estimated by placing a neutral density filter in front of the eye that produces the larger response, thus reducing the intensity of the stimulus. The severity of the RAPD can then be assessed as strength of filter required to equalise the response to stimuli on either side. This traditional test is well established but is subjective and relies on the skill of the operator to interpret the pupil constriction visually.

Earlier and more reliable detection of RAPD would enable the earlier application of the appropriate treatments such as steroid therapy for optic neuritis, antibiotics in the case of infection or miotic eye drops to relieve pressure in glaucoma. An objective and quantitative measure of RAPD would also enable more accurate monitoring of the progress and effectiveness of treatment in these cases.

Binocular video pupillometry offers the opportunity for a reproducible and objective RAPD measurement. In 2001, Wilhelm et al. [3] described an automated process named SWIFT (for SWInging-Flashlight-Test) based on video pupillometry and computer analysis. This system uses light emitting diodes (LEDs) in front of the eyes with the intensities and timings of the illumination controlled to produce a reproducible swinging flashlight cycle with a brief pause between illumination phases. The 2001 paper [3] describes a measurement cycle of 2.5 seconds consisting of 2.0 s illumination followed by 0.5 s darkness, with the illumination phase alternating between left and right. The amplitude of pupil constriction following the onset of each light pulse is measured and the LED intensity varied to reproduce the effect of the neutral density filter. The RAPD value is then calculated in terms of the intensity difference required to equalise the amplitude of the pupil response.

This SWIFT system was used in 2007 by the Tübingen group to establish the range of RAPD values present in a sample of 102 normal subjects [4] in order to compile a representative sample of normative data.

The purpose of the current study was to reproduce this SWIFT process using a novel digital binocular pupillometer with an automated measurement procedure, in order to establish a standardised and reproducible RAPD measurement technique.

Methods and patients

The pupil measurements in the current study were made using the commercially-available PupilX pupillometer (Albomed GmbH, Schwarzenbruck, Germany) [5], [6], which was modified for the current study by programming specific stimulus sequences in order to reproduce the SWIFT process.

[Fig. 1]

The PupilX is a binocular video pupillometer using two video cameras to image both left and right eye simultaneously. Proprietary algorithms detect the pupils and measure the diameters in real time. The

cameras operate at 30 frames per second, giving a temporal resolution of 33 ms. The spatial resolution of the system is 45 microns per pixel in both horizontal and vertical directions.

Visual stimulation in the form of a uniformly illuminated field (white light) can be applied to each eye independently. For each eye, the illumination intensity is selectable from one of sixteen precalibrated light levels, ranging from zero to 1000 lx in a logarithmic sequence as listed in table 1:

[Table 1]

A close-fitting eyemask excludes all ambient light, ensuring a true zero lux illumination at the lowest light level and isolating the two sides so that each eye can be stimulated and measured independently. Each step represents a factor of two change in brightness, and therefore corresponds to 0.3 log-units of intensity change. Suitable choice of these precalibrated illumination levels can therefore be used to simulate the effect of neutral-density filters which are typically used in the manual swinging-flashlight test for RAPD [1], [2] and which are normally available in 0.3 log-unit gradations [7], [8].

The PupilX system provides facilities for specific stimulus sequences to be programmed, delivering timed pulses of light individually to each eye. The electronics allows for the illumination level to be changed up to 60 times a second, giving a time resolution for the visual stimulus of 16 ms.

A typical trace from the PupilX instrument is reproduced in figure 2 (the abbreviations 'OD' (Oculus Dexter) and 'OS' (Oculus Sinister) refer to the patient's right and left eye respectively):

[Fig. 2]

For the current study, a stimulus sequence of 2.0 s illumination followed by 0.5 s darkness, alternating between eyes was used, as described in Wilhelm [3].

For this preliminary study, three adult test subjects (25-55 years) were chosen: two normal subjects (P1, male, and P2, male) as controls and one (P3, female) with a previously diagnosed RAPD clinically manifest for more than 10 years, and with no other known disorder. All subjects were volunteers and participated in the study with full informed consent.

Results

Measurements of pupil constriction amplitude following each stimulus event were made using the measurement tool in the PupilX graph view. In each case, the amplitude was measured as the difference between maximum and minimum pupil diameter within the first 0.5 seconds from the onset of each stimulus.

[Fig. 3]

In this example, the OD stimulus intensity was 64 lx and OS 256 lx, simulating a +0.6 log-unit neutral density filter. A positive filter value indicates a lower intensity on the right hand (OD) side, and a negative value a lower intensity on the left (OS) side.

In this trace, for a normal subject, the constriction amplitude for the weaker OD stimulus is correspondingly smaller than that for the full intensity OS stimulus.

Following Wilhelm et al. [3], seven scans of 30 seconds duration were made with stimulus applied according to the scheme shown in Table 2, with the LED illumination intensity adjusted to achieve the same effect as the corresponding neutral density filter in 0.3 log unit equivalent steps as shown in table 2:

[Table 2]

For each of the seven scans, the average of OD and OS constriction amplitudes was calculated for each of the nine events 2 – 10 (the first event includes an initial constriction so was discarded) and then the average

and standard deviation of the four even-numbered events (OD stimulated) and five odd-numbered events (OS stimulated) were calculated.

The difference between these two mean reaction amplitudes (average OS – average OD) was plotted against the simulated filter density, with a positive filter value corresponding to a reduced intensity for the OD stimulus. In Figs 4 and 5 a linear regression line is fitted to the measured points and the intercept of this regression line with the horizontal axis indicates the measured RAPD value (in equivalent filter log units).

[Fig. 4]

In both these cases, the intercept of the least-squares fitted line is within ± 0.1 log units of the origin, indicating an absence of RAPD in either of these normal subjects.

[Fig. 5].

The intercept for P3 was $- 0.21 \pm 0.04$ log units.

Table 3 summarises the fit parameters for all three test subjects, compared with a typical result from the original 2001 SWIFT paper [3].

[Table 3]

Discussion

The potential advantages of the automated SWIFT test include standardisation of the measurement process, with a reproducible and standardised stimulus sequence. The design of the PupilX eyemask and optics provides a controlled environment in which all ambient light is excluded and left and right channels isolated, ensuring independent stimulation of each eye. These factors combine to give an objective measurement of RAPD. Limitations of the system include the 30 Hz frame rate which restricts the time resolution (e.g. for latency measurements) to 33 ms, and the fact that the spectrum of the LED illumination contains an excess of blue light, and thus does not perfectly reproduce normal daytime illumination. The maximum intensity of the LED illumination is currently limited to 1000 lx.

In comparing results from the current study with those reported by Wilhelm et al. [3], Table 3 shows high linearity of the regression plots from both the original SWIFT paper and those from the current PupilX implementation. The gradients are also comparable: these are expected to vary from patient to patient, depending on factors such as initial pupil size, with the larger values for subjects P1 – P3 instrument possibly indicating a higher sensitivity of the PupilX instrument.

The size of the error bars on the PupilX measured data points is consistent with the statement that measurement steps finer than 0.3 log-units are not necessary: as noted by Wilhelm et al. [4]: 'Kawasaki et al. [. . .] showed that steps smaller than 0.3 log units did not increase the accuracy of the measurement.' [9], [10].

The results from subject P3 with a known RAPD show an intercept of $- 0.21 \pm 0.04$ log units on the horizontal axis. While this significant shift of the regression line compared to those of the normal subjects is encouraging, we note that this is smaller than the 0.3 threshold reported by Wilhelm et al. and Volpe et al.. Further studies to establish the effectiveness and sensitivity of the PupilX procedure are therefore indicated.

In conclusion, these promising results show good qualitative agreement with typical measurements from the original SWIFT process. Additionally, the method was able to distinguish between normal subjects and a subject with a known RAPD. This indicates that the PupilX instrument, programmed with suitable stimulus sequences and in conjunction with appropriate analysis software, has the potential to be used as the basis of a reliable RAPD measurement.

Further planned investigations include:

1. A follow up study with repeated measurements to establish repeatability, reliability and reproducibility of the PupilX instrument and SWIFT process.

2. Measurements on a larger group of subjects (as in the Wilhelm 2007 study) including controls in addition to patients having known RAPD.

3. Investigation of the clinical relevance of the additional parameters such as latency of the pupil response and gradient of the regression line.

With the overall intention being to establish the combination of stimulus sequence and measurement parameters which best quantifies the RAPD and to implement an efficient automated measurement process, extracting the clinically relevant result in the briefest measurement time, convenient and practical for both patient and clinician.

# # #

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# # #

Figure legends

Fig 1. The PupilX instrument in use. The patient is seated opposite the operator. The flexible eyemask fits tightly, effectively excluding ambient light. Software eye tracking eliminates the need for clamps or chin rests, making the measurement process comfortable and non-threatening for the patient.

Fig 2. Typical PupilX trace. The grey portions of the bars above graph indicate the intensity of the stimuli applied (OD – right eye; OS – left eye) with a cycle time of 2.0 s illumination followed by a 0.5 s pause, with black indicating darkness (zero lux). The responses of the left and right pupils are plotted as two traces on the same axis.

Fig 3. Amplitude measurement of stimulus events 3 (OD) and 4 (OS). The constriction amplitude is indicated by the horizontal bars. In this example, the OD stimulus intensity was 64 lx and OS 256 lx, simulating a +0.6 neutral density filter. The constriction amplitude for the OD stimulus is correspondingly smaller than that for the OS stimulus.

Fig 4. Example linear regression plots. In each case, the difference in constriction amplitude (left eye stimulated – right eye stimulated) is plotted against the (simulated) filter density in log units according to Table 2, with a positive value indicating a reduced stimulus intensity (lux value) on the right side, and a negative value a reduced stimulus intensity on the left side. In these normal subjects the regression line passes close to the origin, indicating equal constriction amplitudes without filters and hence an absence of RAPD.
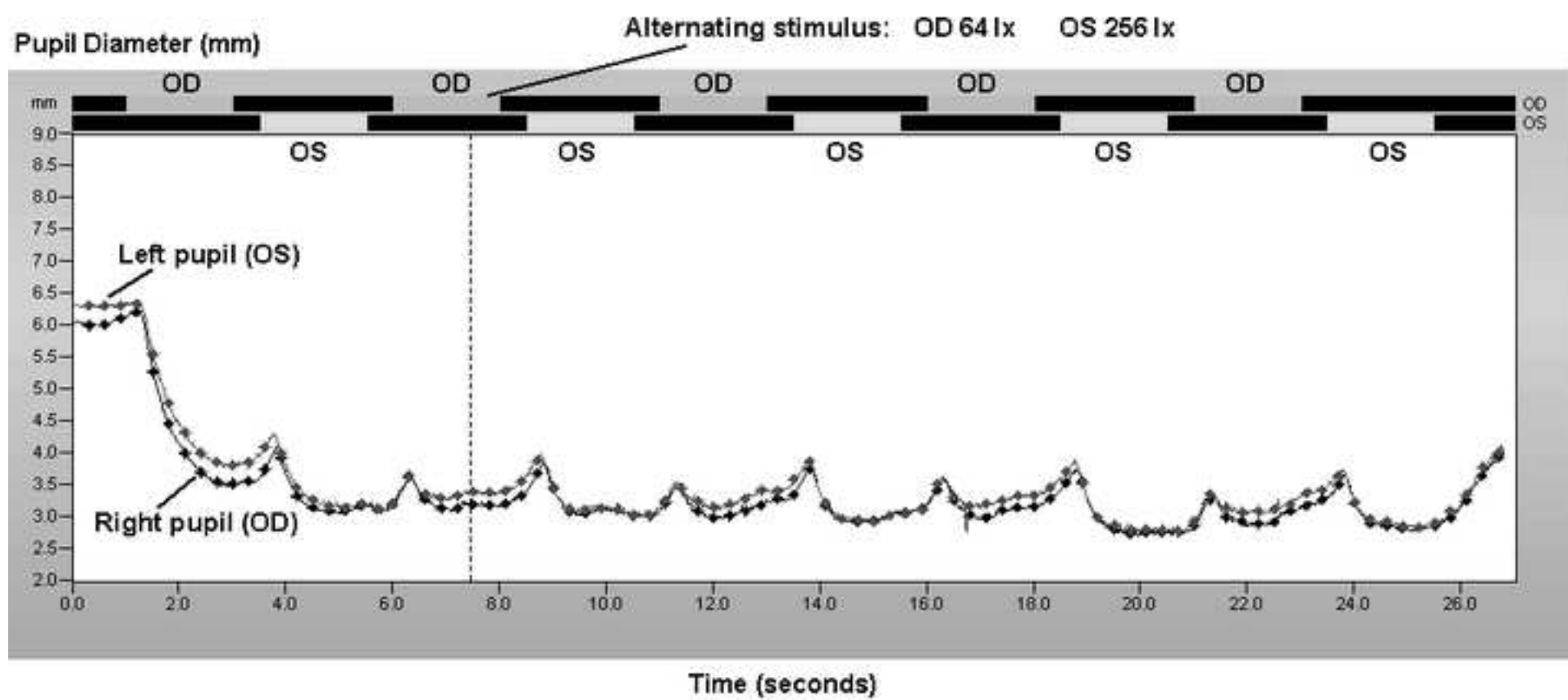
Fig 5. Example linear regression plot for subject with known RAPD. In this plot the difference in constriction amplitude (left eye stimulated – right eye stimulated) is plotted against the (simulated) filter density in log units according to Table 2, with a positive value indicating a reduced stimulus intensity (lux value) on the right side, and a negative value a reduced stimulus intensity on the left side. The displacement of the intercept on the horizontal (filter value) axis indicates the filter value required to equalise the constriction amplitudes, in this case giving an RAPD value of –0.21 log units. This illustrates how the SWIFT process is capable of interpolating between the 0.3 log unit stimulus intensity steps.
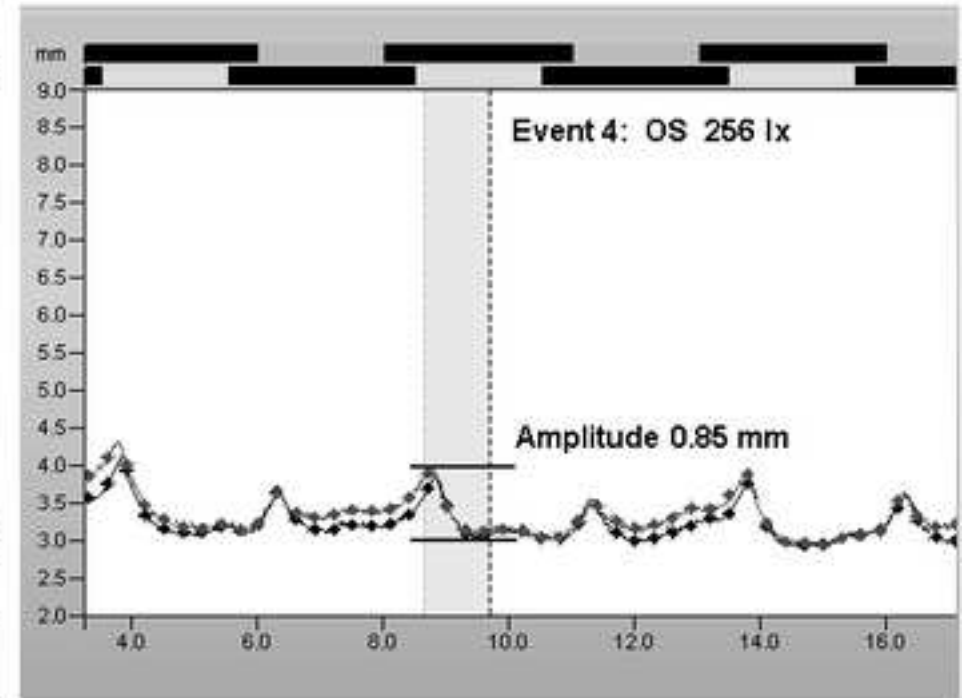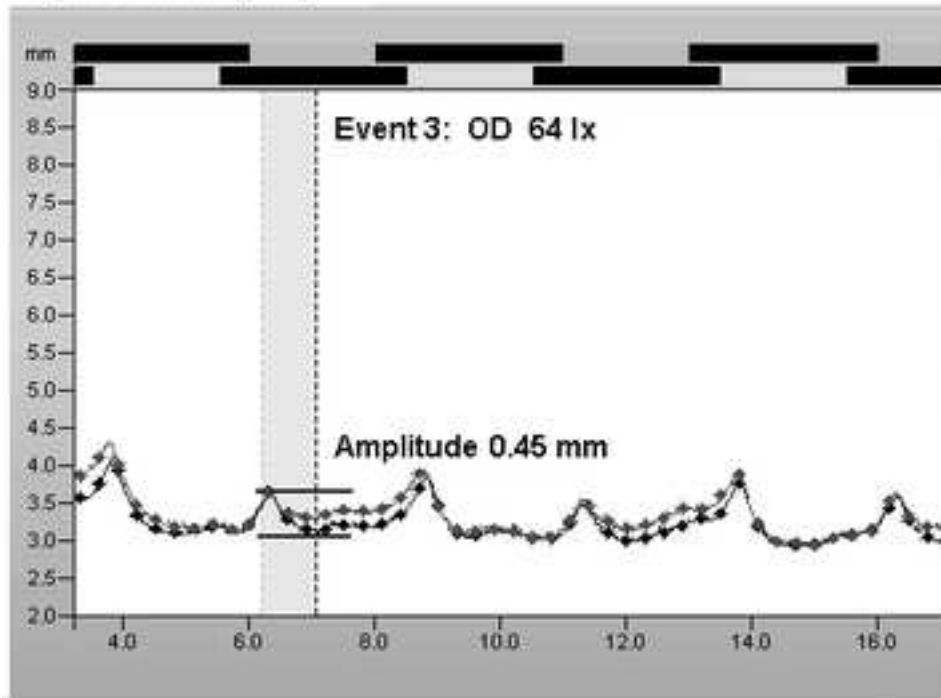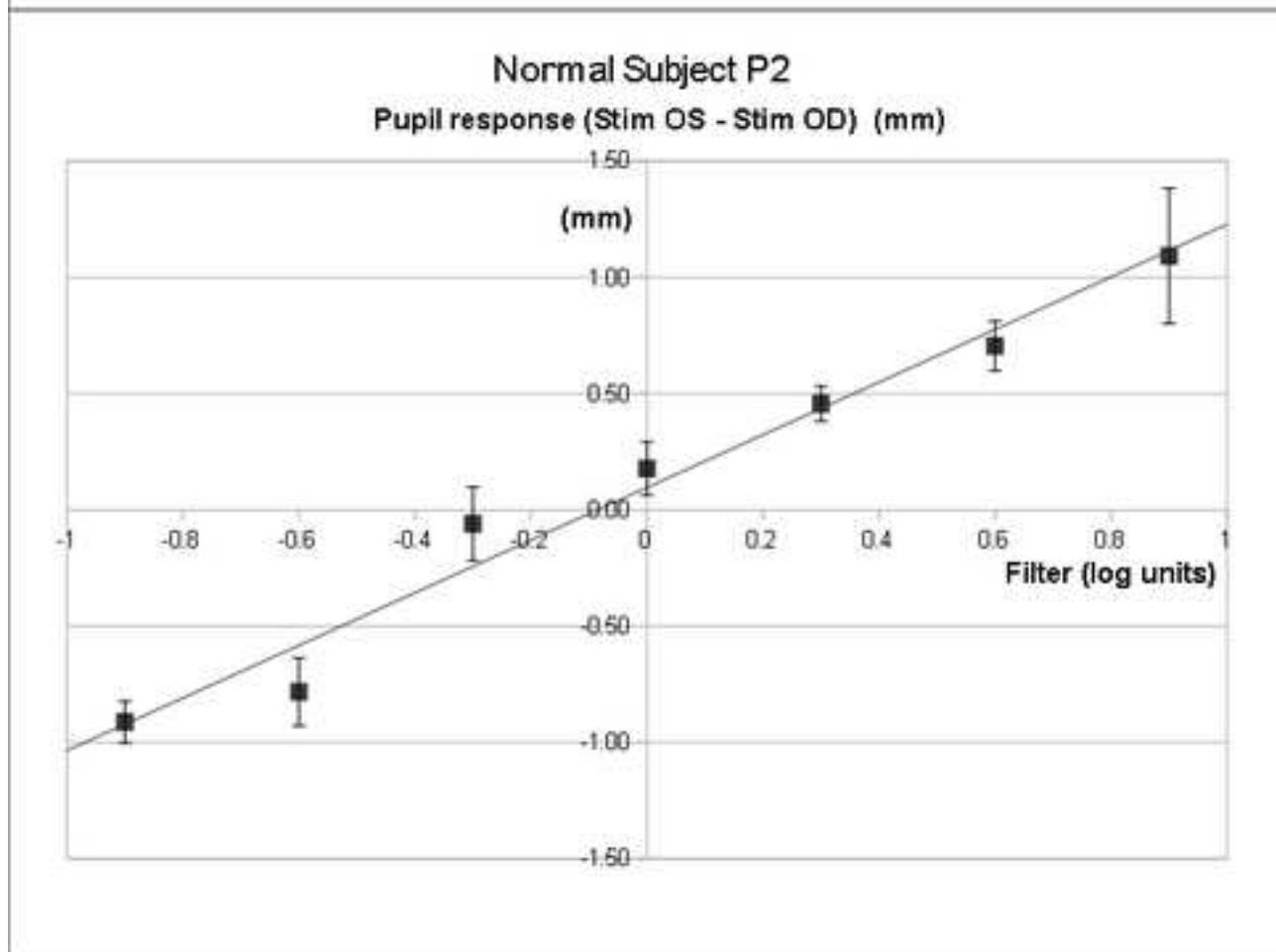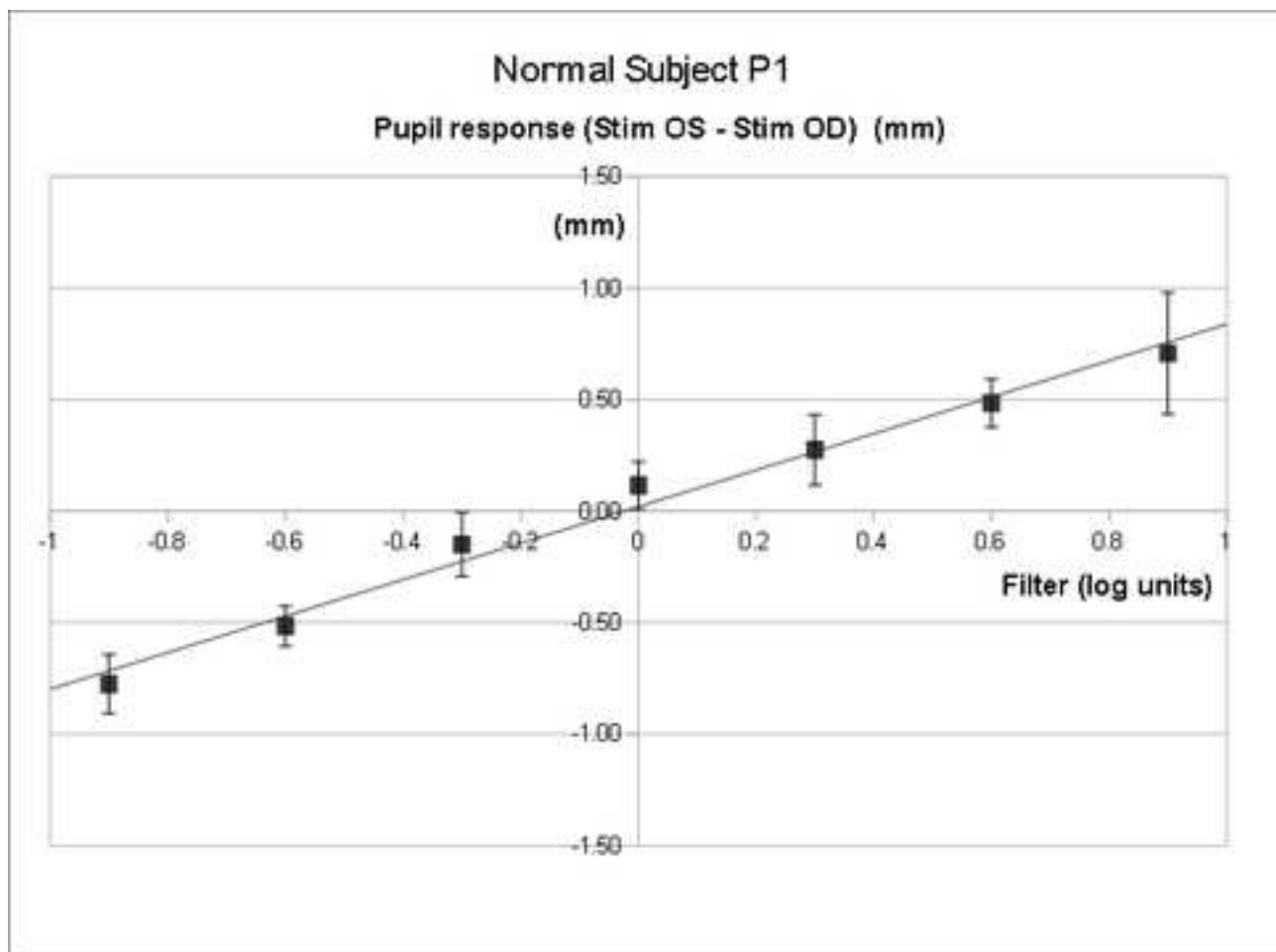
# # #

Pupil Diameter (mm)

Event 3: OD 64 lx

Amplitude 0.45 mm

Event 4: OS 256 lx

Amplitude 0.85 mm

Time (seconds)

Normal Subject P1
Pupil response (Stim OS - Stim OD) (mm)
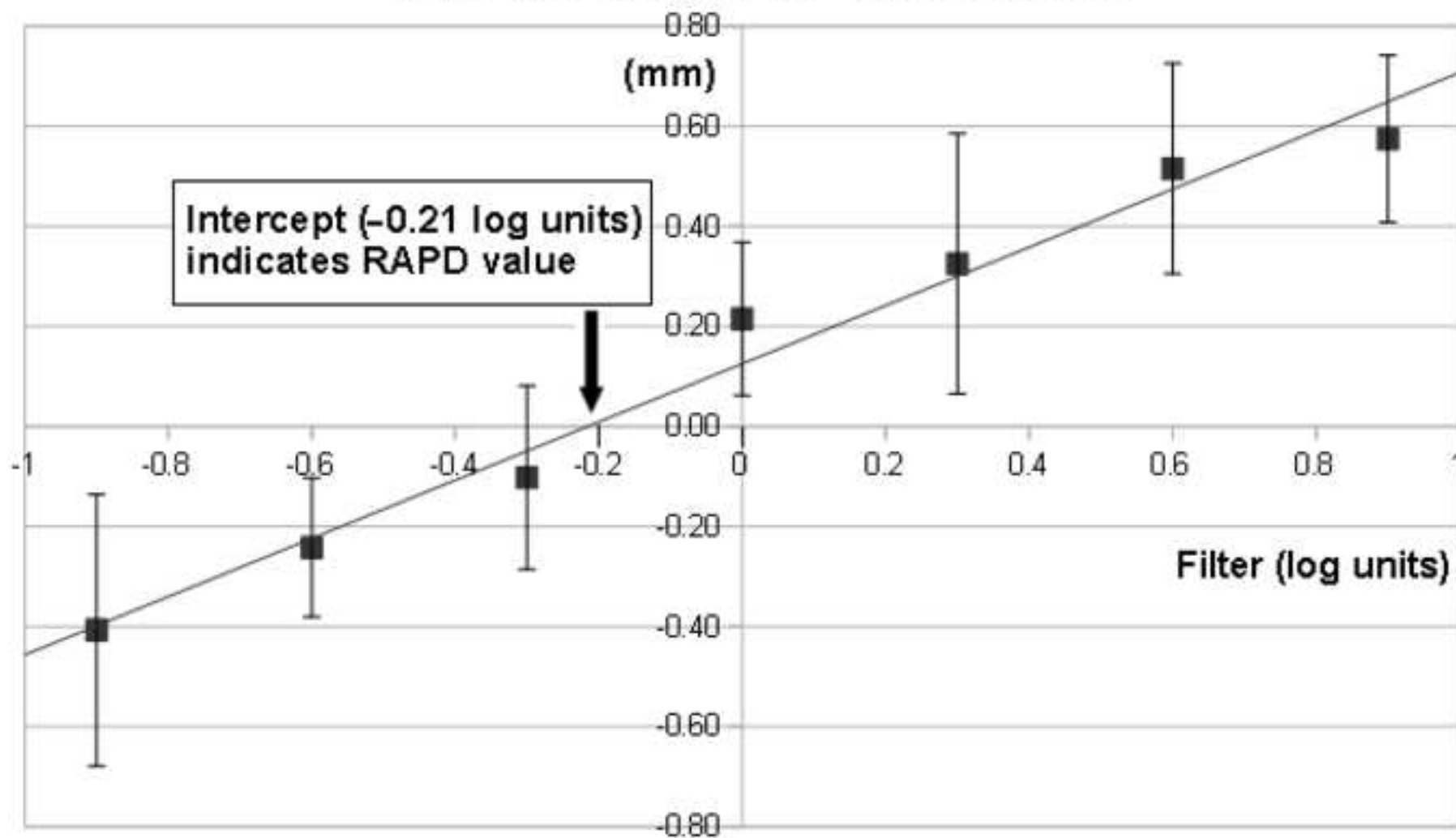
Normal Subject P2
Pupil response (Stim OS - Stim OD) (mm)

RAPD - Subject P3
Pupil response (Stim OS - Stim OD) (mm)

First results of automated RAPD-SWIFT method in dynamic pupillometry

List of Tables

Level	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Lux (lx)	0	0.06	0.12	0.25	0.50	1.0	2.0	4.0	8.0	16	32	64	128	256	512	1024

Table 1. PupilX calibrated illumination levels. Each step from level 1 to 15 represents a factor of two increase in intensity (lux value), equivalent to an increase of 0.3 log units.

OD (lx)	OS (lx)	Filter equivalent (log units)
256	256	0
256	128	- 0.3
128	256	+ 0.3
256	64	- 0.6
64	256	+ 0.6
256	32	- 0.9
32	256	+ 0.9

Table 2. PupilX SWIFT illumination levels in lux (lx) with corresponding filter values. Each factor of two difference in intensity is equivalent to 0.3 log units of neutral density filter. OD refers to the patient's right eye, and OS to the left eye.

Subject	Slope (mm / log unit)	RAPD (X-intercept) (log units)	Correlation Pearson r^2
P1	0.82 ± 0.04	- 0.03 ± 0.03	0.986
P2	1.13 ± 0.08	- 0.08 ± 0.04	0.974
P3	0.58 ± 0.04	- 0.21 ± 0.04	0.978
W1	0.34	+ 0.13	0.993

Table 3. Comparison of fitted regression data. P1 and P2 are normal subjects from the current study; P3 is subject with known RAPD and W1 is an example subject from the 2001 paper (Wilhelm et al., Fig 3).

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