Archived at the Flinders Academic Commons

http://dspace.flinders.edu.au/dspace/

This is the author's **final corrected draft** of this article. It has undergone peer review.

Citation for the publisher's version:

Publisher's website:

http://www.elsevier.com/wps/find/journaldescription.cws_home/620025/description#description Citation: Shankar, H. Pesudovs, K. A critical flicker fusion (CFF) test of potential vision. J Cataract & Refract Surg. 33 (2):232-239. 2007 Feb.

Shankar and Pesudovs, Critical Flicker Fusion Test. 2

Title: A Critical Flicker Fusion (CFF) test of potential vision

Short title: Critical Flicker Fusion test

Authors: Hema Shankar, BMBS, MA

Konrad Pesudovs. PhD

Location: NH&MRC Centre for Clinical Eye Research, Department of Ophthalmology, Flinders Medical Centre and Flinders University of South Australia, Bedford Park, South Australia, 5042, Australia

Sources of support: This work was supported in part by National Health and Medical Research Council (Canberra, Australia) Centre of Clinical Research Excellence Grant 264620, and in part by Flinders Medical Centre Foundation grant 0405. Konrad Pesudovs is supported by National Health and Medical Research Council (Canberra, Australia) Sir Neil Hamilton Fairley Fellowship 0061.

Corresponding author: Konrad Pesudovs, NH&MRC Centre for Clinical Eye Research, Department of Ophthalmology, Flinders Medical Centre, Bedford Park, South Australia, 5042, Australia.

Telephone: +618 8204 4899, Fax: +618 8277 0899

Email: Konrad.Pesudovs@flinders.edu.au

Proprietary Interest Statement: The authors have no personal financial interest in the development, production, or sale of a CFF test of potential vision. This test is not participant to patent application. However, it is intended to develop this test with Flinders Biomedical Engineering to the point of commercialization with the proceeds from sale going to Flinders Biomedical Engineering.

Word count for manuscript: 3606

ABSTRACT

Purpose: To continue developing a potential vision test based on the critical flicker fusion (CFF) phenomenon by using a brighter stimulus and optimizing its size.

Setting: The Flinders Eye Centre of the Flinders Medical Centre, Flinders University, South Australia.

Methods: A prospective, non-randomized study with 225 participants (134 females, 59.8%; mean age 71.4±13.2 yrs) assigned to four groups: normal (n=41), media opacity only (n=61), retinal/neural disease only (n=61), and cataract plus retinal/neural disease (n=61). Participants were recruited into these groups if aged over 20 years, but were excluded if they had any neurological disorder or medication known to affect CFF. CFF thresholds were measured for three stimulus sizes (0.5°, 1.0°, 1.5°). Discrimination between groups was tested with ANOVA and Receiver Operating Characteristic (ROC) analysis. The relationship between visual acuity (VA) and CFF in eyes without media opacity was determined with linear regression and used to predict visual outcome of 23 eyes undergoing cataract surgery.

Results: CFF thresholds were reduced in retinal/neural disease but resistant to image degradation from media opacity. The 1.5° stimulus had 88% sensitivity and 90% specificity for discriminating groups. Post-cataract surgery VA was accurately predicted within ± 1 line in 43%, ± 2 lines in 83% and ± 3 lines in 100% of eyes All eyes with poor VA (>0.50 logMAR) or dense cataract (>4.0 LOCSIII) were predicted within ± 2 lines.

Conclusion: CFF effectively discriminates between subjects with and without retinal/neural disease and accurately predicts visual outcome after cataract surgery. The use of a brighter stimulus enhanced performance in dense media opacity.

Key words: flicker fusion, cataract, age-related macular degeneration, potential vision test

Synopsis: A potential vision test based on the critical flicker fusion (CFF) phenomenon accurately predicts visual outcome after cataract surgery in eyes with dense cataract and poor visual acuity.

INTRODUCTION

Cataract surgery is established in the literature as being a relatively safe and effective procedure. 1,2 Over 95% achieve a visual acuity of 20/40 or better if there is no comorbid disease.³ However in patients with co-morbid disease, particularly age-related macular degeneration (ARMD), cataract surgery may result in poor visual outcome and subsequent patient disappointment.⁴ Indeed, the benefits of cataract surgery for patients with ARMD is open to debate.⁴⁻⁹ Whether to recommend surgery, or not, can pose an important clinical dilemma in these patients, as it is difficult to determine the relative contribution of each pathological process to the patient's existing visual disability. Potential vision tests (PVTs) can be a valuable aid in this decision making process if they can accurately predict visual function behind cataracts and other media opacity. The usefulness of existing potential vision tests in predicting visual acuity when preoperative vision is 20/200 or worse has been discredited by a major review by the Agency for Health Care Policy and Research (AHCPR). Therefore, there is a need to develop a test of potential vision that can predict visual outcome in eyes with very dense cataract or other media opacity, where the extent of the media opacity interferes with the clinician's ability gauge the benefit of cataract surgery in improving the patient's post operative visual outcome.

It has been known for over 100 years that posterior segment eye disease can impair CFF. 11-16 Recently, the phenomenon of critical flicker fusion frequency (CFF) has been suggested as a test of potential vision able to penetrate dense cataract. 17-19 This is

because CFF has been shown to be unaffected by the presence of cataract and other media opacities, ²⁰⁻²² as long as a bright stimulus is used, ^{14,23} yet sensitive to retinal and optic nerve disease. ^{12,14-16} Moreover, as CFF reduction due to retinal/neural disease correlates reasonably with visual acuity (VA), it can be used to predict post-operative VA.

CFF is known to be affected by a number of factors - target luminance, target color and target size.²⁴ We incorporated these factors into the design of a testing device. Working on the hypothesis that an even brighter stimulus may better penetrate dense cataract, we incorporated a brighter LED now available to double the stimulus luminance. Taking the lead from previous work, a red stimulus was selected to minimize the effect of short wavelength absorption from the ageing crystalline lens and nuclear cataract. 18,25 One problem with CFF as a PVT identified by Vianya-Estopa et al was that testing with a 1.5° target was limited in sensitivity to macular holes and early ARMD. 19 This is probably because foveal defects could be masked by surrounding healthy retina. Theoretically, a smaller target measures foveal vision specifically and may detect these small macular lesions. On the other hand, smaller targets give rise to lower CFF thresholds, 26-28 which truncates the range of CFF scores and hampers the differentiation of normal from abnormal eyes. 18 This may be partially offset by using a brighter stimulus to increase CFF. Therefore we chose to repeat the experiment conducted by Vianya-Estopa et al and test 3 small target sizes giving visual angles of 0.5°, 1.0° and 1.5°. The aims of this study were to determine the smallest size (1000 cd/m²) stimulus that gave good discrimination between eyes with normal and abnormal posterior segments and to test our hypothesis that a brighter target would penetrate dense cataracts more effectively in addition to optimizing the efficacy of a smaller target size. To use the CFF test as a PVT, the relationship between CFF threshold and visual acuity in eyes without media opacity was quantified for each of the three stimulus sizes, and used to predict VA. The ability of CFF to predict VA behind cataract was tested in a series of eyes undergoing cataract surgery and an attempt was made to quantify the repeatability of CFF thresholds.

METHODS

Participants

Participants were recruited from the Eye Clinic at Flinders Medical Centre, Bedford Park, South Australia, Australia. The study gained approval from the Flinders Clinical Research Ethics Committee and followed the Declaration of Helsinki for research involving human participants. Inclusion criteria varied by clinical population (see below) and patients 20 years or older were selected. Exclusion criteria included any neurological disease or medication known to affect CFF and any physical or language impediments to participating in the testing. Neurological disorders known to impair CFF include epilepsy, ²⁹ multiple sclerosis, ³⁰ Parkinson's disease, ³¹ Alzheimer's disease, ³² dementia, alcoholism, ³³ and cognitive impairment. ³⁴ Medications known to affect CFF include antihistamines, ^{35,36} tricyclic antidepressants, ³⁷ benzodiazepines, ³⁸ anti-epileptics, ²⁹ barbiturates, ³⁹ or other sedatives. ⁴⁰ The inability to understand English sufficiently to follow testing instructions, insufficient mental ability to perform the tests, being unable to see any of the three target sizes and any physical disability that made it arduous to

perform the tests (e.g. wheelchair user) precluded patients from being recruited for testing. Patients for whom both eyes satisfied the inclusion and exclusion criteria had both eyes included in the analyses.

Four groups were studied. The normal control group had no eye disease and VA better than 0.2 logMAR (~20/30 Snellen). A second group had retinal/neural disease only (no cataract or other media opacity). A third group had media opacity only (no retinal/neural disease) and a fourth group had cataract and retinal/neural disease. Included in the "retinal/neural disease" groups are patients with macular, optic nerve and visual pathways lesions. The rationale for this is that a potential vision test should be able to detect reduced visual potential regardless of the level at which the lesion occurs.

The Critical Flicker Fusion (CFF) Test Procedure

The CFF test apparatus was build by Flinders Biomedical Engineering at Flinders Medical Centre. The stimulus consisted of a red, Luxeon Star (Phillips Lumileds Lighting Company, San Jose, CA, USA) 1 Watt light-emitting diode (LED) with collimating optics of nominal luminous flux of 44 lumens, with a dominant wavelength of 625 nm (range 620.5 and 645.0 nm, bandwidth 20 (spectral width at 1/2 peak intensity)) and capable of emitting a frequency up to 110 Hz. The circular stimulus was 8 mm in diameter and subtended visual angles of 0.5°, 1.0° and 1.5° at viewing distances of 91.7 cm, 45.8 cm and 30.5 cm respectively. The measured LED mean luminance was 1000 cd/m² and the mean luminance of the surrounding screen was 160 cd/m². This intensity of stimulus is demonstrably safe to the retina, and there is no risk of inducing an

epileptic seizure from a small (0.5° to 1.5°) target with a 2 second duration.⁴¹ The stimulus was driven with a 350 mA current source, pulse width modulated to produce a sine wave with a modulation depth of 95%. The LED source was mounted at the centre of a matt white 20 cm² rectangular screen (Figure 1). The stimulus could be presented either continuously or as a two-second pulse. The CFF test apparatus was calibrated and metered in steps of 0.1 Hz. The LED flashing rate was measured by the integral crystal controlled frequency counter based on a common microcontroller. The basic accuracy of this counter was quoted as "20 parts per million" but the display resolution of 0.1Hz was the limiting factor. During the design phase we repeatedly confirmed the accuracy by using the frequency counting function of a Tektronix TDS 1002 digital storage oscilloscope.

Measurements were taken monocularly, employing natural pupils and with any refractive error, including presbyopia, corrected. Although it has been shown that CFF threshold is minimally affected by pupil dilation,⁴² for consistency we performed all testing with natural pupils. The participant was instructed to look directly at the centre of the red light. Care was taken with instruction and observation to ensure the participant did not employ eccentric fixation. Several stimuli were presented initially to orient the participant to the sensation of flicker (10-20 Hz) and fusion (55-65 Hz) before test measurements were recorded. Two-second pulse stimuli were used to prevent adaptation and therefore alteration of the CFF threshold.^{24,43,44} Threshold was determined using a staircase paradigm with five ascending and five descending presentations in 1 Hz steps. A fusion threshold was recorded for each ascending run (lowest frequency stimulus to

appear steady) and a flicker threshold recorded for the descending run (highest frequency stimulus to appear to flicker). The mean of the 10 recordings was calculated as the critical flicker fusion threshold. The procedure was performed for the three stimuli sizes in random order. CFF testing took approximately 15 minutes, which previous research has shown to cause little problem with fatigability.²⁸ Prior to CFF testing, all participants were refracted and visual acuity (VA) was measured using ETDRS logMAR charts at 4 meters, with a mean luminance of 160 cd/m² using by-letter scoring.⁴⁵ After testing, pupils were dilated and participants underwent a full ophthalmological examination to establish the diagnoses, including LOCS III grading of cataract.⁴⁶

Analyses

The groups were compared by ANOVA with post-hoc (Sheffé) testing for age, VA and CFF. The relationship between VA and CFF was explored using linear regression. This relationship was used to predict VA from CFF in preoperative cataract patients. The success of this prediction was tested using descriptive statistics. These statistical analyses were performed on SPSS v12.0.1 (Chicago, IL, USA). Optimal target size for differentiation between the media opacity and the retinal/neural disease groups was determined by means of a receiver operating characteristic (ROC) analysis using Analyse-It software v1.71 (Leeds, UK).

The within participant repeatability of the CFF threshold was evaluated for each target size by comparing the five ascending and five descending measures during each measurement. Repeatability was assessed in terms of the coefficient of repeatability,

which is obtained by calculating the SD of the difference between the repeated measures and multiplying this by 1.96.⁴⁷ This represents the 95% confidence interval for any discrepancy between test and retest data. This analysis was conducted in Microsoft Excel 2003 (Redmond, WA, USA).

RESULTS

A total of 225 participants (134 females, 59.8%) were included in the study (mean age 71.4 ± 13.2 yrs). One macular degeneration patient was excluded as they were unable to see any of the three CFF targets (VA was worse than 1.60 logMAR, Snellen 20/800). Two other macular degeneration participants (VA 20/250 and 20/400) could not see the 0.5° target, but could see the 2 larger targets; their data were included in the analyses. There were 41 normal participants, 61 participants with media opacity only, 61 participants with retinal/neural disease only and 61 participants with both media opacity and retinal/neural disease. The media opacity only participants comprised 59 with cataract, and 2 with posterior capsular opacification. The retinal/neural disease only group comprised 31 ARMD, 9 diabetic maculopathy, 7 diabetic retinopathy, 4 glaucoma, 3 cystoid macular edema, 2 vascular occlusions, 2 visual pathways lesions, and one case each of retinal detachment, amblyopia and macular hole. The participants with both media opacity and retinal/neural disease included 2 cases with corneal disease and 59 with cataract. Additionally this group included 26 ARMD, 15 glaucoma, 4 visual pathways lesions, 3 epiretinal membrane, 2 diabetic maculopathy, one case each of diabetic retinopathy, retinal detachment, amblyopia, vascular occlusion and cystoid macular edema and 6 participants had multiple conditions. The normal group (55.4 \pm 16.9 years) was significantly younger than the three disease groups ($F_{3, 220} = 38.83$, p <0.001) but the three disease groups were similar (Sheffé post hoc p>0.05) for age: media opacity only (74.3 \pm 6.7), retinal/neural disease only (73.1 \pm 11.3) and both media opacity and retinal/neural disease (77.6 \pm 7.8). Similarly, there was also no significant difference (Sheffé post hoc, p > 0.05) in visual acuity between the media opacity only (0.27 \pm 0.30 logMAR, Snellen 20/37) retinal/neural disease only (0.36 \pm 0.45 logMAR, Snellen 20/46) and both media opacity and retinal/neural disease groups (0.39 \pm 0.32 logMAR, Snellen 20/49). However, the normal group saw significantly better (-0.07 \pm 0.08 logMAR, Snellen 20/17, $F_{3, 220} = 19.63$, p <0.001).

The CFF thresholds by group are illustrated in Figure 2. For each target size, there are significant differences between groups: 0.5° ($F_{3, 163} = 23.21$, p < 0.001), 1.0° ($F_{3, 217} = 31.06$, p < 0.001) and 1.5° ($F_{3, 165} = 31.86$, p < 0.001) targets. Post-hoc analysis indicated that there were no significant differences in the CFF thresholds between the normal and the media opacity only group for any of the three target sizes (p > 0.50). However, significant differences existed between both the normal and the media opacity only groups and both the retinal/neural disease with or without media opacity groups for all target sizes (all p < 0.001). Therefore, retinal/neural disease affects CFF, but media opacity does not.

The relationship between CFF and VA for patients without media opacity was investigated using linear regression. A significant relationship (p<0.001) was found for all three target sizes (equation, coefficients of determination, r^2): (VA = 1.503 –

 $0.040CFF_{0.5^{\circ}}$, 0.50), (VA = $1.901 - 0.047CFF_{1.0^{\circ}}$, 0.54) and (VA = $2.217 - 0.053CFF_{1.5^{\circ}}$, 0.61); these are illustrated in Figure 3.

The ability of each target size to discriminate between media opacity and retinal/neural disease on an individual basis was assessed with receiver-operating characteristic (ROC) analysis. ROC curves were plotted for the three target sizes and for visual acuity (Figure 4). This analysis identifies the cut-off point for best discrimination between the two groups. Sensitivity (proportion of true positives) is the proportion of CFF values below the cut-off value among the retinal/neural disease participants and specificity (proportion of true negatives) is the proportion of CFF values above the cut-off value among the media opacity group. The point closest to the upper left-hand corner of the graph represents the highest sensitivity and specificity and therefore is the best criterion to differentiate between retinal/neural disease and media opacity participants. Figure 4 suggests that the 1.5° best discriminates between retinal/neural disease and media opacity cases as this target size gave the point of highest sensitivity (88.1%) and specificity (90.0%) which was at 40.5 Hz. The relative discriminative ability of the three target sizes can be quantified using the area under the curve (AUC) for each of the target size. The AUC was 0.93 for the 1.5° target (95% confidence interval, 0.88 to 0.98), compared with 0.94 (0.89 to 0.98) for the 1.0° target, and 0.89 (0.83 to 0.96) for the 0.5° target. All target sizes were statistically significantly different than random level performance (AUC equals 0.50), and from visual acuity (AUC 0.55 (0.44 to 0.65) Figure 4b). Pairwise comparisons showed that the 0.5° target size curve had significantly less AUC than the 1.5° target size curve (p<0.05) but the 1.0° target was indistinguishable from the other target sizes.

The coefficient of repeatability across all participants was \pm 1.9 Hz for the 0.5° target, \pm 1.9 Hz for the 1.0° target and \pm 2.1 Hz for the 1.5° target. The coefficient of repeatability was better for normal participants (0.5°, 1.0°, 1.5°: \pm 1.5, \pm 1.6, \pm 1.6) and media opacity only participants (\pm 1.9, \pm 1.7, \pm 1.8) and poorer for participants with retinal/neural disease (\pm 2.2, \pm 2.1, \pm 2.4).

The relationships between VA and CFF developed above using linear regression were used to predict visual acuity from CFF in 23 cases with cataract undergoing surgery. This group comprised 23 eyes of 21 patients (14 female) aged 74.8 ± 9.7 (51 to 90 years), with visual acuity of 0.35 ± 0.22 (0.10 to 0.80) logMAR and cataract graded on the LOCS III scale as NO 3.5 ± 0.8 (2.2 to 5.0) NC 3.5 ± 1.0 (2.2 to 6.0) C 2.7 ± 0.8 (1.0 to 4.5) P 1.5 ± 1.1 (0.1 to 3.6). Twelve had cataract alone and the remainder had cataract and comorbidity: 7 had ARMD, 3 had glaucoma and 1 had ARMD and a stroke. Postoperative visual acuity was 0.10 ± 0.14 (-0.16 to 0.42) logMAR, and was predicted from CFF to be 0.07 ± 0.18 (-0.22 to 0.59). In 10 cases (43%) post-operative visual acuity was correctly predicted within ± 1 line, this rose to 19 cases (83%) within ± 2 lines and all cases were predicted to within ± 3 lines. None of the 4 who were not predicted within ± 2 lines of VA had particularly dense cataract, and only 1 had comorbidity. All 6 eyes with poor VA (0.50 logMAR or worse) and all 8 eyes with dense cataract (any

individual LOCS III grade of 4.0 or greater) were correctly predicted within ±2 lines of VA.

DISCUSSION

The results of this study confirm the findings of several previous studies into the use of CFF as a potential vision test. 17-19 CFF thresholds were highly repeatable, 18 with 95% of cases varying less than ± 2Hz, with slightly better performance in normal eyes and slightly worse performance in eyes with retinal/neural disease. CFF thresholds are resistant to image degradation caused by cataract and other media opacities; 14,17-19 there was no significant reduction in CFF thresholds, for any of the three target sizes, in the media opacity group compared to the normal group, despite visual acuity being much worse in the media opacity group (Figure 2). The results also confirm that CFF thresholds are lower in the presence of retinal/neural disease (Figure 2). 11,14-19 Therefore it is safe to assume that in the presence of cataract and retinal/neural disease, any reduction in CFF is due to the latter and this has implications for poor visual outcomes post-operatively.

All three target sizes discriminate well between the media opacity and retinal/neural disease as shown by the ROC analysis (Figure 4). The 1.0° and 1.5° targets performed similarly based on the AUC analysis (0.94 & 0.93 respectively), but the point of optimal discrimination was closer to ideal for the 1.5° target. However, the 0.5° performed significantly worse than both larger targets (AUC 0.89). This may, in part, be related to lower CFF results being found with decreased target size for all groups which compresses

the range of scores and thus reduces discrimination. Based on these results, 1.0° or 1.5° targets would be the target sizes of choice for potential vision testing. Vianya-Estopa *et al* found a 1.5° target (AUC 0.79) discriminated better than a 1.0° target (AUC 0.75) or a 0.5° target (AUC 0.70). The main differences between the two studies is that the current study utilized a brighter stimulus (1000 vs. 500 cd/m²). Vianya-Estopa *et al* found lower CFF thresholds due to this lower luminance: normal eye and media opacity groups: 0.5°, 1.0°, 1.5°: 24 Hz, 28 Hz, 30 Hz. This suggests, as hypothesized, that a brighter stimulus enhanced performance both through better penetration of media opacities and higher CFF thresholds better separating the data from each group.

The linear regression of CFF against VA in eyes without media opacity shows a strong relationship, especially at 1.5° (r²=0.61) which is markedly better than that found by Vianya-Estopa (1.5°, r²=0.36) or Bueno del Romo (1.5°, r²=0.43).^{17,18} This relationship was used to predict VA from CFF in eyes with media opacity. However, inspection of the graphs in figure 3 shows significant variance around the mean. This suggests that the ability of CFF to predict VA should be considered to be fairly coarse. Therefore, CFF as a potential vision test may not be very useful in mild cataracts with good pre-operative visual acuity; nor is it really necessary as traditional ophthalmic judgement can perform well in such cases.¹⁷ The usefulness of this test lies in the strength of the VA/CFF correlation extending to eyes with very dense media opacity and poor pre-operative vision, which allows for accurate and effective prediction of visual outcome in these eyes which are difficult to predict with clinical judgement alone.¹⁷ Indeed, this study establishes the usefulness of CFF as a potential vision test; all eyes were correctly

predicted within ± 3 lines of VA, and 83% within ± 2 lines of VA. All eyes with poor VA (>0.50 logMAR) or dense cataract (>4.0 LOCS III) were accurately predicted within ± 2 lines of VA.

The prediction of visual outcome of cataract surgery in our study compares favorably with previous studies comparing PVTs.^{17,19} The classic PVTs - potential acuity meter (PAM) and laser interferometry - struggle to penetrate cataracts even at levels which only degrade VA to 6/12.¹⁹ Super-illuminated pinhole (SPH), PAM and laser interferometry were all shown to be ineffective in the presence of dense cataract.^{17,19} These 3 tests also tend to over-estimate visual acuity in macular disease.¹⁹ Bueno del Romo *et al* compared ophthalmic judgment in predicting post-operative visual acuity with PVTs (including CFF).¹⁷ He found that CFF was the best performed PVT in dense cataract (67% within 2 lines and 80% within 3 lines), in contrast to 53% within 2 lines and 60% within 3 lines for ophthalmic judgment and 27% within 2 lines and 40% within 3 lines for PAM and RPH; with our CFF arrangement the results are even better. The main limitation of CFF as a PVT identified by Vianya-Estopa *et al* and Bueno del Romo *et al* was an occasional failure to be sensitive to visual acuity loss from macular disease, particularly compared to the super illuminated pin-hole test (in mild to moderate cataract).¹⁹ Both these studies used the CFF testing model utilized in the earlier pilot study by Vianya-Estopa *et al*.¹⁸

The current study addressed some of the perceived shortcomings of the earlier model by increasing target luminance. We established both 1.5° and 1.0° to be ideal targets with improved performance compared to the earlier studies. It is possible that the use of a

smaller, brighter target will improve the sensitivity of CFF to macular disease, and this will be tested more extensively with our next prototype. Another potential source of error in macular disease is subtle eccentric fixation during testing as this would elevate CFF. Therefore, we intend to include more sophisticated fixation monitoring in our next prototype.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the assistance of Dr Russell Phillips, Dr Richard Mills, Dr John Pater, A/Prof Jamie Craig, and Prof Douglas Coster for facilitating access to clinical patients.

REFERENCES

- Spalton D, Koch D. The constant evolution of cataract surgery. BMJ 2000;321:1304
- 2. Desai P, Reidy A, Minassian DC, et al. Gains from cataract surgery: visual function and quality of life. Br J Ophthalmol 1996;80:868-873
- 3. Powe NR, Schein OD, Gieser SC, et al. Synthesis of the literature on visual acuity and complications following cataract extraction with intraocular lens implantation. Cataract Patient Outcome Research Team. Arch Ophthalmol 1994;112:239-252
- 4. Shuttleworth GN, Luhishi EA, Harrad RA. Do patients with age related maculopathy and cataract benefit from cataract surgery? Br J Ophthalmol 1998;82:611-616
- 5. Armbrecht AM, Findlay C, Kaushal S, et al. Is cataract surgery justified in patients with age related macular degeneration? A visual function and quality of life assessment. Br J Ophthalmol 2000;84:1343-1348
- 6. Klein R, Klein BE, Wang Q, Moss SE. Is age-related maculopathy associated with cataracts? Arch Ophthalmol 1994;112:191-196
- 7. Klein R, Klein BE, Wong TY, et al. The association of cataract and cataract surgery with the long-term incidence of age-related maculopathy: the Beaver Dam eye study. Arch Ophthalmol 2002;120:1551-1558
- 8. Pollack A, Marcovich A, Bukelman A, et al. Development of exudative agerelated macular degeneration after cataract surgery. Eye 1997;11:523-530

- 9. van der Schaft TL, Mooy CM, de Bruijn WC, et al. Increased prevalence of disciform macular degeneration after cataract extraction with implantation of an intraocular lens. Br J Ophthalmol 1994;78:441-445
- 10. AHCPR Report: Cataract Management Guideline Panel. Cataract in Adults: Management of Real World Impairment. Rockville, MD: Department of Health and Human Services, Public Health Service, Agency for Health care Policy and research. AHCPR Pub. No. 93-0542., 1993
- 11. Braunstein EF. Beitrag zur lehre des intermittierendem lichtreizes der gesunden und kranken. Z Psychol 1903;33:241-288
- 12. Han DP, Thompson HS, Folk JC. Differentiation between recently resolved optic neuritis and central serous retinopathy. Use of tests of visual function. Arch Ophthalmol 1985;103:394-396
- 13. Nakamura M, Yamamoto M. Variable pattern of visual recovery of Leber's hereditary optic neuropathy. Br J Ophthalmol 2000;84:534-535
- 14. Simonson E, Wohlrabe RG. The flicker fusion frequency in different testing arrangements, of healthy older persons, of patients with cataracts and patients with retinal disorders. Am J Ophthalmol 1963;55:1023-1032
- 15. Babel J, Rey P, Stangos N, et al. The functional examination of the macular and perimacular region with the aid of flicker-fusion thresholds. Doc Ophthalmol 1969;26:248-256
- Massof RW, Fleischman JA, Fine SL, Yoder F. Flicker fusion thresholds in Best macular dystrophy. Arch Ophthalmol 1977;95:991-994

- 17. del Romo GB, Douthwaite WA, Elliott DB. Critical flicker frequency as a potential vision technique in the presence of cataracts. Invest Ophthalmol Vis Sci 2005;46:1107-1112
- 18. Vianya-Estopa M, Douthwaite WA, Pesudovs K, et al. Development of a critical flicker/fusion frequency test for potential vision testing in media opacities. Optom Vis Sci 2004;81:905-910
- Vianya-Estopa M, Douthwaite WA, Noble BA, Elliott DB. Capabilities of potential vision test measurements: clinical evaluation in the presence of cataract or macular disease. J Cataract Refract Surg 2006;32:1151-1160
- Lachenmayr BJ, Gleissner M. Flicker perimetry resists retinal image degradation.
 Invest Ophthalmol Vis Sci 1992;33:3539-3542
- Ong J, Wong T. Effect of ametropias on critical fusion frequency. Am J Optom
 Arch Am Acad Optom 1971;48:736-739
- 22. Tyler CW. Analysis of normal flicker sensitivity and its variability in the visuogram test. Invest Ophthalmol Vis Sci 1991;32:2552-2560
- 23. Havener WH, Henderson JW. Comparison of flicker perimetry with standard perimetric methods. AMA Arch Ophthalmol 1954;52:91-105
- 24. Landis C. Something about flicker fusion. Sc Month 1951;73:308-314
- 25. Norren DV, Vos JJ. Spectral transmission of the human ocular media. Vision Res 1974;14:1237-1244
- Brown JL. Flicker and intermittent stimulation. In: Graham CH, ed. Vision and
 Visual Perception. New York: John Wiley & Sons, 1965: 251-320

- 27. Tyler CW, Hamer RD. Analysis of visual modulation sensitivity. IV. Validity of the Ferry-Porter law. J Opt Soc Am A 1990;7:743-758
- 28. Douthwaite WA, Halliwell JA, Lomas AM, et al. Critical fusion frequency in the central visual field. Ophthalmic Physiol Opt 1985;5:15-21
- 29. Steinhoff BJ, Freudenthaler N, Paulus W. The influence of established and new antiepileptic drugs on visual perception. II. A controlled study in patients with epilepsy under long-term antiepileptic medication. Epilepsy Res 1997;29:49-58
- Daley ML, Swank RL, Ellison CM. Flicker fusion thresholds in multiple sclerosis. A functional measure of neurological damage. Arch Neurol 1979;36:292-295
- 31. Riklan M, Levita E, Misiak H. Critical flicker frequency and integrative functions in parkinsonism. J Psychol 1970;75:45-51
- 32. Curran S, Wilson S, Musa S, Wattis J. Critical Flicker Fusion Threshold in patients with Alzheimer's disease and vascular dementia. Int J Geriatr Psychiatry 2004;19:575-581
- 33. Pillunat LE, Christ T, Luderer HJ, Stodtmeister R. Flicker fusion frequency and organic syndrome in alcoholics. Percept Mot Skills 1985;60:487-494
- 34. Bulbena A, Berrios GE. Cognitive function in the affective disorders: a prospective study. Psychopathology 1993;26:6-12
- 35. Hindmarch I, Johnson S, Meadows R, et al. The acute and sub-chronic effects of levocetirizine, cetirizine, loratadine, promethazine and placebo on cognitive function, psychomotor performance, and weal and flare. Curr Med Res Opin 2001;17:241-255

- 36. Kerr JS, Dunmore C, Hindmarch I. The psychomotor and cognitive effects of a new antihistamine, mizolastine, compared to terfenadine, triprolidine and placebo in healthy volunteers. Eur J Clin Pharmacol 1994;47:331-335
- 37. Timoshanko A, Stough C, Vitetta L, Nathan PJ. A preliminary investigation on the acute pharmacodynamic effects of hypericum on cognitive and psychomotor performance. Behav Pharmacol 2001;12:635-640
- 38. Mattila MJ, Vainio P, Nurminen ML, et al. Midazolam 12 mg is moderately counteracted by 250 mg caffeine in man. Int J Clin Pharmacol Ther 2000;38:581-587
- 39. Barzaghi N, Gatti G, Manni R, et al. Comparative pharmacokinetics and pharmacodynamics of eterobarbital and phenobarbital in normal volunteers. Eur J Drug Metab Pharmacokinet 1991;16:81-87
- 40. Debbas NM, Ankier SI, Warrington SJ. Trazodone conventional and controlledrelease formulations: pharmacodynamic effects after single and repeated administration. Curr Med Res Opin 1989;11:501-509
- 41. Zifkin BG, Inoue Y. Visual reflex seizures induced by complex stimuli. Epilepsia 2004;45 Suppl 1:27-29
- 42. Douthwaite WA, Williams P. Critical flicker frequency technique and interpretation using a new flickering source. Br J Physiol Opt 1974;29:30-42
- 43. Landis C. Determinants of the critical flicker-fusion threshold. Physiol Rev 1954;34:259-286
- 44. Ridell LA. The use of the flicker phenomenon in the investigation of the field of vision. Br J Ophthalmol 1936;20:385-410

- 45. Bailey IL, Lovie JE. New design principles for visual acuity letter charts. Am J
 Optom Physiol Opt 1976;53:740-745
- 46. Chylack LT, Jr, Wolfe JK, Singer DM, et al. The lens opacities classification system III. Arch Ophthalmol 1993;111:831-836
- 47. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res 1999;8:135-160.

FIGURES

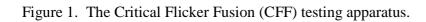
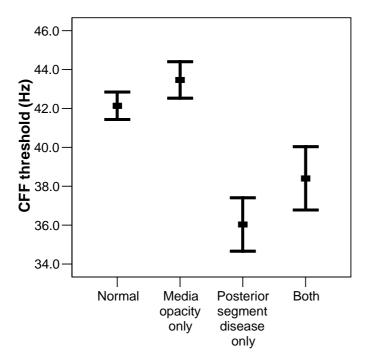


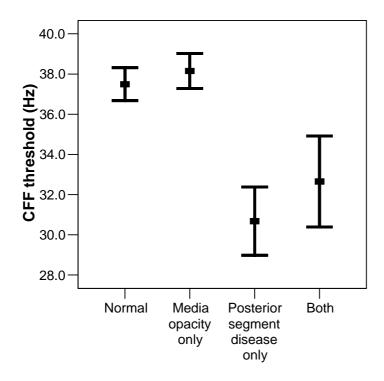


Figure 2. Mean and 95% confidence interval of CFF threshold for a) 0.5° target, b) 1.0° target and c) 1.5° target. At all three target sizes the normal and media opacity groups are indistinguishable, and the retinal/neural disease groups are significantly worse.

a)



b)



c)

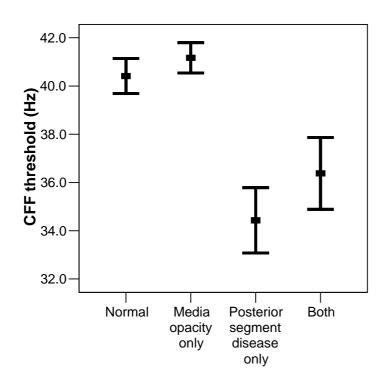
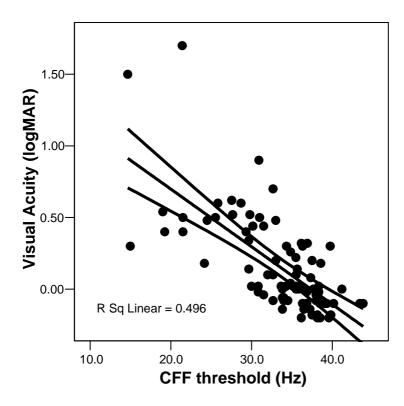
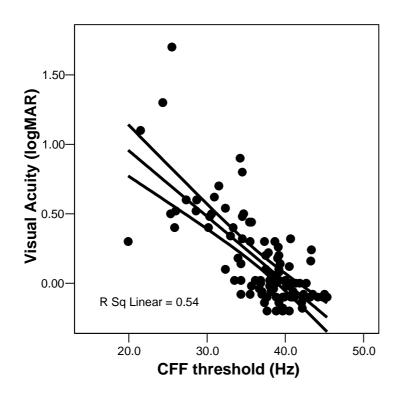


Figure 3. Scatterplot with linear regression (mean and 99% confidence interval) of CFF threshold against visual acuity in patients without media opacity for target sizes a) 0.5° , b) 1.0° and c) 1.5° .

a)



b)



c)

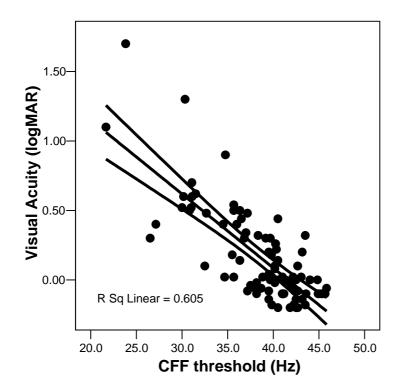
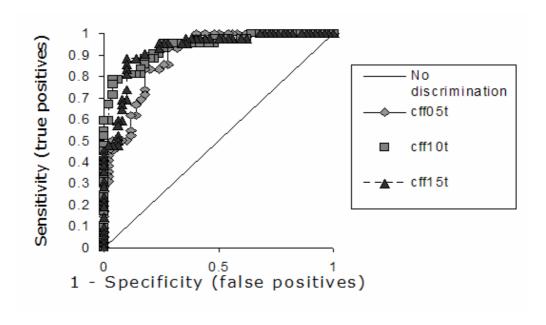


Figure 4. Receiver-operating characteristic (ROC) curves plotting sensitivity vs. (1-specificity) for 61 participants with media opacity and 61 participants with retinal/neural disease for a) CFF thresholds at three target sizes and b) visual acuity.

a)



b)

