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Assessment of novel binocular colour, motion and contrast tests in glaucoma

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Abstract:

The effects of glaucoma on binocular visual sensitivity for detection of different stimulus attributes were investigated at the fovea and in four paracentral retinal regions. The study employed a number of visual stimuli designed to isolate the processing of different stimulus attributes. We measured absolute contrast detection thresholds and functional contrast sensitivity using Landolt ring stimuli. This psychophysical Landolt C based contrast test of detection and gap discrimination allowed us to test parafoveally at 6° from fixation as well as foveally employing interleaved testing locations. First-order motion perception was examined using moving stimuli embedded in static luminance contrast noise. Red/green (RG) and yellow/blue (YB) colour thresholds were measured with the Colour Assessment and Diagnosis (CAD) test, which utilises random dynamic luminance contrast noise ($\pm 45\%$) to ensure that only colour and not luminance signals are available for target detection. Subjects were normal controls ($n = 65$) and glaucoma patients with binocular visual field defects ($n = 15$), classified based on their Humphrey Field Analyzer mean deviation (MD) scores. The impairment of visual function varied depending on the stimulus attribute and location tested. There was also a progression of loss for all tests as the degree of glaucoma increased. For subjects with mild glaucoma (MD -0.01dB to -6.00dB) significantly more data points fell outside the normal age-representative range for RG colour thresholds than for any other visual test, followed by Motion thresholds. This was particularly the case for the parafoveal data compared to the foveal data. The findings suggest that a multifaceted measure of binocular visual performance, incorporating RG colour and motion testing at multiple locations, may provide a better index for comparison with QOL measures in glaucoma.

Introduction

A wide range of ophthalmological and neurological conditions can give rise to binocular scotomata (relative and / or absolute) within the central 20°, but the extent to which different aspects of conscious vision are lost remains controversial (Petzold and Plant 2005). Glaucoma is a collective term for a complex group of conditions that cause progressive optic neuropathy, resulting in irreversible loss of visual function. Primary open angle glaucoma has a prevalence of around 2 in 100 of the population over 40, which increases with age (Rudnicka et al. 2006). It is generally bilateral, although rarely symmetrical in progression. Population growth coupled with the marked increase in life expectancy in western countries is likely to lead to a significant rise in the number of patients with glaucoma (Quigley and Broman, 2006). In assessing clinical interventions for disease, including glaucoma, cost effectiveness and clinical effectiveness are considered by those developing guidelines (e.g. National Institute for Clinical Excellence (NICE) 2009). A fundamental part of assessing

clinical effectiveness involves measuring quality of life (QOL). Although there is now increasing interest in the QOL of glaucoma sufferers, less than 2% of all glaucoma studies have focused on QOL (Glen et al 2011). A number of QOL papers have shown that even in early glaucoma some patients do experience limitations in their vision (Viswanathan et al. 1999, Janz et al. 2001, Nelson et al. 2003, Goldberg et al. 2009) and these studies have also reported that patients have difficulties with dark adaptation and disability glare. In busy hospital glaucoma clinics patients are unlikely to report difficulties with activities of daily living unless they complete a dedicated questionnaire addressing these issues (McCann 2012). The only readily available test for assessing the binocular visual field is the Esterman test, the results of which correlate poorly with measurements of patients' perceptions of their visual function (Sinclair 2012). Generation of the Integrated Visual Field, based on the best performance at each location within the field, shows some improvement in terms of a relationship with patient perceptions, but it is still limited (Crabb et al. 2005).

The detection of glaucomatous structural damage may precede, coincide with or follow the detection of a glaucomatous visual field defects (Kass et al 2002). Clinical assessment of visual function in parafoveal regions relies largely on examination of visual fields using standard automated perimetry. Perimetry plots often fail to fully represent the true extent of visual loss because conventional field assessments only examine a single attribute at the location tested, usually the differential light threshold. Absolute thresholds for detection of flashed stimuli, however useful, are often the final component of visual function to be affected in disease. Sensitivity for detection of fine spatial detail, motion and colour signals can be selectively damaged in many diseases of the eye and often precedes visual field loss (Barbur and Konstantakopoulou 2012, Bergin et al. 2011, Hawkins et al. 2003, Lee 1991, Westcott et al. 1998, Bullimore et al. 1993, Zihl et al. 1983, Marré and Marré 1986, Verriest 1963, Krastel and Moreland 1991). Cerebrovascular accidents have also been shown to cause impaired contrast sensitivity (Fisk et al. 2002) and colour vision loss (Rauscher et al. 2011). Furthermore, colour vision loss is often present in diseases of the optic nerve even when high contrast acuity is largely spared (Moro et al. 2007).

This study examined the extent to which the stage of glaucoma (defined as mild, moderate or severe) affected the patient's visual sensitivity for a number of different stimulus attributes known to be more sensitive to glaucomatous damage than conventional visual field assessment: contrast detection thresholds (CT), functional contrast sensitivity (FCS), first-order motion perception (MS) and red/green (RG) and yellow/blue (YB) colour sensitivity. These attributes were assessed binocularly in order to provide a better understanding of how a patient might be affected under natural viewing conditions and therefore it is hoped that outcomes would correlate more closely with QOL measures. Quantifying vision under 'natural' (binocular) viewing conditions may ultimately allow the production of a single index of visual loss that better correlates with quality of life than the currently used clinical reference standard of automated visual fields.

Materials and Methods

The study was approved by the ethics committees of each of the participating institutions and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from each participant.

Volunteers were recruited from two London hospitals, the Central Middlesex Hospital (North West London Hospitals NHS Trust) and St. Thomas Hospital, and the Fight for Sight Optometry Clinic at City University London.

The glaucoma subjects (n=15) were all under the care of consultant ophthalmologists, and the mean duration since glaucoma diagnosis was 9.2 years (SD = 6.1 years) with a median

of 8.0 years (IQR 4.3 to 12.0 years). Eleven of the 15 subjects were managed using a range of intraocular pressure lowering medications, primarily prostaglandin analogues and beta-blockers. The remaining 4 subjects had undergone drainage surgery and two of these had this treatment augmented with IOP-lowering medication. This patient group ranged from 52 to 79 years of age with a mean age of 69.5 years (SD = 8.4 years). The age distribution was skewed towards the older age groups, with a median age of 72 (IQR 64.5 to 75.5 years). The mean visual acuity of the better eye in the patient group was 0.01 LogMAR (SD = 0.07) (approximately equivalent to Snellen 6/6⁻¹). All glaucoma subjects had LogMAR visual acuity of 0.1 or better with no other significant eye disease reported other than glaucoma in the patient group. Glaucoma subjects were classified into mild, moderate and severe disease categories derived from their performance on the Humphrey Field Analyzer (HFA) SITA Standard 24-2, according to a method of glaucoma staging based on the global index mean deviation (MD) (Burr et al. 2007). This classification divided the glaucoma subjects into mild (MD -0.01dB to -6.00dB), moderate (MD -6.01dB to 12.00dB) and severe (MD -12.01dB and above) groups. The mean HFA global indices for the better eye of the whole glaucoma group were MD = -5.79 (SD = 6.75) and the pattern standard deviation (PSD) = 5.26 (SD = 4.25). Unreported significant additional eye disease was ruled out by a standard optometric eye examination. Patients were excluded if they produced unreliable monocular fields at this first visit, i.e. unsatisfactory False Negative rate (>33%), False Positive rate (>33%), or Fixation losses (>20%), as assessed by the standard HFA criteria.

A group of visually unimpaired subjects (n=65) served as a control group to the patient group. A full eye examination, including visual fields, was carried out in order to rule out any ocular abnormality before a volunteer was accepted for the study. Normal controls were grouped into six decades (20-79) to provide an 'age-representative range' based on the results of normal subjects for each visual function test. This allowed the results of each glaucoma subject to be compared against the results obtained from normals of a similar age. At least ten control subjects per decade were present for each visual attribute investigated. The control group had a mean age of 49.7 years (SD = 16.2). Specifically, the mean age was 64.1 years (SD = 6.78) across the three older decades combined (n=32). Additionally, we were able to employ reference data from 330 normal trichromats generated on the Colour Assessment and Diagnosis (CAD) test which, for example, enabled us to differentiate between congenital and acquired colour loss (Barbur and Connolly 2011). Mean distance visual acuity of the normal subjects included in the study was -0.05 (SD = 0.08) and -0.06 (SD = 0.10) on the LogMAR scale for the right eye and left eyes (approximately equivalent to Snellen 6/6⁺² and Snellen 6/6⁺³, respectively). The older three decades presented with a mean VA of R/L -0.03 LogMAR (SD = 0.08).

No subjects had any experience of psychophysical tests (controls or patients). The experience of the glaucoma patients at HFA perimetry depended on the duration of their condition. Each participant attended on two occasions separated by less than two weeks in order to complete all testing and minimise fatigue.

Experimental set-up

The P SCAN 100 system (Barbur 1991) was used to administer the psychophysical tests. It allowed binocular measurements of eye fixation and the generation of appropriate visual stimuli using a Sony Trinitron visual display (model 500PS). The study was carried out under binocular conditions to assess visual performance under natural viewing conditions likely to be more representative of an individual's own experience of their visual function. A luminance calibration program was used on a monthly basis, in conjunction with a LMT 1003 luminance meter, to calibrate automatically the luminance output of the monitor. This involved measurement of the luminance versus applied voltage relationship for each gun for each possible drive voltage value. The spectral output of each gun was measured using a Gamma Scientific Telespectroradiometer (Model 2030-31) and these data provided the chromaticity coordinates of each phosphor. Testing was completed in a darkened room

where the only light, in addition to that from the display, originated from a current-regulated halogen spotlight directed towards a white diffuser on the ceiling away from the visual display. This arrangement contributed negligible additional light to the actual display, but prevented dark adaptation. An infrared eye tracker was employed to monitor fixation for all tests and to remind subjects, if necessary, of the need for steady fixation. A number of specialised tests were employed to assess key aspects of visual performance both in patients and in the control group. The data from each test (colour and motion discrimination and two tests of visual performance in the contrast domain) were collected from various regions of the visual field, either at a number of locations per quadrant (visual field test), or at one of five fixed locations (at the fovea and with the stimulus centred at 6° eccentricity in each of the four quadrants: upper right (UR), upper left (UL), lower left (LL) and lower right (LR), respectively). Use of the same locations for each test facilitated data comparison between tests and between the patient and normal groups. The selection of these five locations allowed a focus on the most functionally important region of the field, i.e. that region of the visual field that has the greatest influence on visual performance. Due to the use of different stimuli, the testing distance required adjustment to ensure the stimuli fell on the same retinal areas for all tests (binocular visual field testing distance: 0.4 m, motion and colour tests: 0.7 m and both contrast tests: 1.5 m).

Tests employed

Visual fields

In addition to the initial field tests undertaken as part of the recruitment screening process (monocular SITA Standard 24-2 Humphrey® Field Analyzer (HFA)), binocular central visual fields were assessed using the Advanced Perimetry Program (APP) to map the sensitivity of the visual field over an area $\pm 20^\circ$ from fixation, and allow quantification of field loss for each quadrant for comparison with the other assessments of visual performance (Edgar et al. 2002). The test employed a high sampling density and interleaved stimuli at one of four contrast levels and 256 possible locations, to provide a simple plot of the field (final score at each location was the lowest suprathreshold contrast level detected at that location). Following trials (Rauscher et al. 2007), a grid pattern of 16x16 was selected as a compromise between testing time and resolution. The chosen stimulus size was 1° (scaled to compensate for the tangent screen) with a centre-to-centre stimulus separation of 2.5° , assessing 256 locations within the central 20° (64 locations per quadrant). The background luminance of the APP test was set to 12 cd/m^2 and stimuli patterns could be presented at four increasing contrast levels: 12%, 24%, 48%, 96% (Weber contrast, $\delta L/L$), corresponding to stimulus luminance values of 13.4, 14.9, 17.8, and 23.5 cd/m^2 , respectively.

The program employed a multiple stimulus paradigm (0-4 stimuli presented simultaneously) to minimise test duration. The stimuli in each pattern were arranged in a square grid pattern with one stimulus location between each of the corners of the square. Previous work indicated that the older normals were still capable of distinguishing between the individual elements of a more peripheral pattern with this arrangement (Edgar et al. 2002; Rauscher et al., 2007). Different stimuli configurations at different locations across the field were randomly interleaved using decreasing suprathreshold contrast levels, until the suprathreshold contrast level closest to threshold was determined for each individual stimulus location. Typical printouts of abnormal binocular visual fields following the test are shown in Figures 1a and 1b.

The average test duration for a normal, young individual was three minutes. This increased for those with a field defect, e.g. five to six minutes for individuals with significant central scotomata, whilst the use of four contrast levels permitted an improved spatial map of areas of reduced sensitivity than that obtained with a conventional suprathreshold strategy.

The lowest stimulus contrast detected at a particular location was given a score: 12%, 24%, 48% and 96% become levels 4, 3, 2, and 1 respectively, and 'not seen' was classed as 0. This conversion allowed for the calculation of a mean APP score per quadrant for comparison with the other visual attributes investigated, information that cannot easily be extracted from conventional visual field plots.

Insert Fig 1 and its caption here.

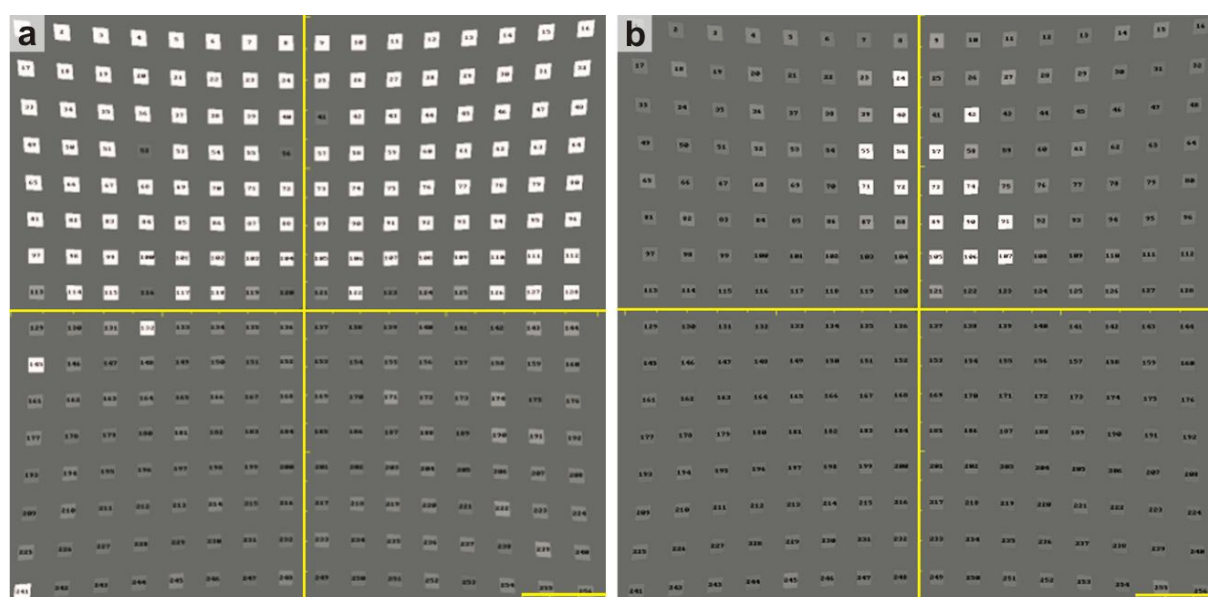


Fig 1 The Advanced Perimetry Program (APP) assesses the binocular visual field sensitivity with high sampling density and graded luminance contrast within $\pm 20^\circ$ from fixation (yellow meter in bottom right corner is equivalent to 6°). The two examples above illustrate how the new APP perimetry programme reveals general and more localised loss of visual field sensitivity.

Section 1a: Subject 55, 57 years old, longstanding diagnosis of glaucoma. The APP results showed large losses compared to the highest possible score of 4.0, and the APP quadrant results were calculated to be 0.16 for the upper right quadrant, 0.28 for the upper left quadrant, 2.48 for the lower left quadrant and 2.36 for the lower right quadrant.

Section 1b: Subject 91, 59 years old, longstanding diagnosis of glaucoma. The APP field test identified the superior field as being most affected, with upper right more than upper left, and there was also some binocular loss of field inferiorly. The APP results showed losses compared to the highest possible score of 4.0, and the APP quadrant results were calculated to be 2.22 for the upper right quadrant, 2.34 for the upper left quadrant, 3.64 for the lower left quadrant and 3.72 for the lower right quadrant.

Contrast

The contrast detection threshold (CT) and functional contrast sensitivity (FCS) tests were developed to permit rigorous psychophysical assessment of these functions at parafoveal locations in addition to the fovea. In both the aforementioned tests the display screen was viewed from a distance of 1.5 m and the subject was adapted to a uniform field of luminance 12 cd/m^2 (Chisholm et al. 2003). The fixation target was presented briefly in the centre of four, oblique guides used to facilitate steady fixation prior to each stimulus presentation. The CT and FCS tests employed identical stimuli, consisting of obliquely orientated Landolt rings with a gap size of $1/5^{\text{th}}$ of the overall ring diameter. The foveal target subtended 14 min of arc and the parafoveal targets, centred on a point located obliquely 6° from fixation in each of the four quadrants, subtended 38 min of arc , allowing for the reduction in resolution with eccentricity, such that the average normal observer would be expected to obtain a functional contrast threshold of 24% as optimised by Chisholm and colleagues (Chisholm et al. 2003). During each test, the five stimulus locations were randomly interleaved and the stimulus duration was restricted to 200 ms to limit the influence of saccadic eye movements. The contrast of the stimulus at each location was modified using an adaptive staircase procedure, with an initial step size of 6% contrast reducing to 0.2%, over 14 reversals (first six discounted in the calculation of threshold), identical to that optimised by Barbur and colleagues (Barbur et al. 1994).

Contrast detection threshold (CT)

The contrast threshold test determined the lowest contrast the subject required for detection of stimuli at each of the five locations described above. The subject's task was to press a response button to indicate whether they detected anything different from a uniform visual field (yes / no, two-alternative forced-choice procedure). Two consecutive positive responses were required to elicit a reduction in stimulus contrast at a particular location, and one negative response led to an increase in the contrast. The psychophysical paradigm was therefore comparable to that used in many commercially available visual field tests.

Functional Contrast Sensitivity (FCS)

This test determined the contrast required to detect the location of the gap in the Landolt ring stimulus. To the observer the test appeared identical to the detection task with the Landolt ring presented randomly in one of the five locations, but the task was to use the response box to indicate the orientation of the gap in the Landolt ring (up-right, up-left, down-right, down-left), making it a four alternative forced choice procedure. Two consecutive correct responses were required to elicit a reduction in stimulus contrast at a particular location, and one incorrect response resulted in an increase in stimulus contrast.

The Functional Contrast Sensitivity (FCS) test relies on gap detection and correct spatial localisation. In this respect, the test is similar to the FrACT test (*Manual of the Freiburg Vision Test "FrACT", Version 3.7*), but employs only one gap size foveally and one larger gap size parafoveally (approximately 3 min arc foveally and 7.5 min arc parafoveally), with contrast as the variable. One advantage of the FCS test is that it allows simultaneous psychophysical testing both foveally and parafoveally, with the random interleaving of stimulus locations during a single test run.

Motion

The motion sensitivity (MS) and colour assessment and diagnosis (CAD) tests employed in this study shared common features. The achromatic background chromaticity was the MacAdam white: $x=0.305$, $y=0.323$ (MacAdam 1942). The background luminance was set to 24 cd/m^2 and a fixation target was displayed continuously to help maintain the correct point

of regard. The screen was viewed from a distance of 0.7m giving a foreground size of 2.8° at the fovea and 5.3° at the parafoveal locations, and a stimulus square size of 0.9° at the fovea and 1.8° in the parafovea. These were the optimised values for stimulus size based on preliminary experiments which established that the displacement in the parafovea was not large enough with the same target size as implemented at the fovea and therefore the stimulus size was doubled for paracentral locations. The larger stimulus employed in the parafoveal regions had the additional benefit of decreasing these thresholds to values similar to those measured at the fovea.

Each presentation involved the stimulus moving diagonally from one corner of the test square to the opposite corner. The subject is required to press one of four response buttons to indicate the direction of motion (four-alternative forced choice procedure). Motion detection thresholds are measured using an achromatic target at the fovea and at the four parafoveal locations in each of the four quadrants. In order to minimise the involvement of parvo-cellular mechanisms, the moving, luminance contrast defined stimulus was buried in static random luminance contrast noise 'LCN' (0%, 6% and 12%). The subject pressed one of four response buttons to indicate the direction of motion (up-right, up-left, down-right, down-left, four-alternative forced choice procedure). The contrast of the moving stimulus was altered in accordance with the subject's responses using a staircase procedure with an initial step size of 6% reducing to 0.2% over 14 reversals (first four discounted in the calculation of threshold). Two consecutive correct responses were required to elicit a reduction in stimulus contrast at a particular location, and one incorrect response resulted in an increase in stimulus contrast. Thresholds for detecting a moving target were defined by luminance contrast and plotted against the LCN amplitude for each subject.

Colour

The extended Colour Assessment and Diagnosis (CAD) test was adapted for the current study (Barbur and Connolly, 2011; Rodriguez-Carmona et al. 2005; Barbur et al. 1992). The CAD test employs the same equipment as described above for the MS test. The CAD test measures motion thresholds defined by colour signals at the fovea and at the four parafoveal locations in each of the four quadrants. Each presentation involves the stimulus moving diagonally from one corner of the test square to the opposite corner. The subject is required to press one of four response buttons to indicate the direction of motion (four-alternative forced choice procedure). Random, dynamic luminance contrast noise ($\pm 45\%$) was employed to guarantee the use of colour by effective masking of subject-specific, residual luminance contrast signals that often remain in colored stimuli that are only isoluminant for the standard, CIE 'normal' observer. Using this technique we measured red/green (RG) and yellow/blue (YB) colour thresholds along colour directions that reflect L and M and S cone signals, respectively. (Barbur and Connolly, 2011, Barbur et al. 1994). The masking technique employed is important because although the stimulus itself is 'isoluminant' for the standard CIE observer, many 'normal' trichromats have variant L and M cone spectral responsivities and hence small residual luminance contrast signals. Moreover, such effects would be much larger in subjects with congenital or acquired loss of chromatic sensitivity. When the colour-defined stimulus is buried in dynamic noise, subjects with complete absence of red / green colour signals (i.e., protanopes and deuteranopes) become unaware of the moving stimulus, even for chromatic displacement amplitudes that are limited only by the phosphors of the display.

One major advantage of the CAD method is that it allows separate assessment of R, G, Y and B thresholds that relate specifically to isolation of L, M and S-cone signals, respectively (Barbur and Connolly, 2011), rather than measuring the usual RG and YB thresholds employed to describe normal chromatic sensitivity. Also, the thresholds measured on the CAD are directly proportional to the cone contrast signals generated (see Rodriguez-Carmona and Barbur, 2012). Thresholds are measured along colour directions that isolate both the R/G and the Y/B colour mechanisms (Barbur and Connolly, 2011). Symmetric colour

loss is defined as loss within one mechanism (RG or YB) with similar loss for R and G or for Y and B directions, whereas asymmetric loss requires greater loss in one colour direction (e.g., red) than the corresponding complementary direction (e.g., green) within each channel. The latter can occur when different classes of colour-coded, on-centre ganglion cells are selectively damaged in the retina or when the damage is very central and affects selectively neural substrates that are involved in the processing of different colours (Rauscher et al., 2011). The measured thresholds were plotted on the CIE - (x, y) chromaticity chart for comparison with the normal colour thresholds.

Each subject's results can be plotted as an ellipse on the CIE (x,y)- chromaticity diagram for comparison with the normal colour discrimination ellipse. In general, the orientation of the major axis of the ellipse shows significant variation in normal trichromats (Rodriguez-Carmona ML, 2006) with mean and standard deviation of $62 \text{ deg} \pm 7 \text{ deg}$. Therefore, since each subject's individual orientation is not known accurately, the CAD test employs a cluster of similar colours in each direction (four for the present study). These estimates are then averaged to obtain the best estimate for each colour direction. The standard templates plotted on each graph describe the median and the 2.5% and 97.5% limits for normal, trichromats. Normal, age-corrected threshold limits that describe the normal effects of ageing make it possible to detect threshold changes that fall outside normal limits, independent of age.

Statistical methods

Statistical analysis was conducted using Minitab Version 14. Normal observers aged from 20 years to 79.9 years of age were tested. They were divided into age groups based on decades to form six age groups (20-29.9; 30-39.9; 40-49.9; 50-59.9; 60-69.9; 70-79.9). Prior to any further analysis, outliers were identified using the '4 times the standard deviation rule' (Sachs 1998), and this conservative analysis was adopted before establishing normal age ranges based on the data from the normal group of subjects for all tests of visual performance.

In the second part of the analysis, data were plotted against the median age for each decade and the median value for each test per decade was established. The performance of the typical normal observer with reference intervals was established using non-parametric statistics, as the 'Kolmogorov-Smirnov' test for normality revealed that the data were frequently not normally distributed for subjects in the older age-groups. Visual function was clearly influenced by age, causing the distribution of the data to be skewed. To establish a reference interval against which the patient data could be compared, the 95th percentile was selected to identify the upper limit of normal visual function for each age group.

Standard normal units (SNU) were derived, based on the control data, to relate patient performance to the 95th percentile performance limits established based on the age-representative data from the control group. For this, the glaucoma subjects' thresholds were divided by the median threshold measured for 65 normal trichromats. Rank correlation tests (Spearman) were performed on the results of the visual field (both HFA and APP) and other visual function tests for both the foveal and parafoveal locations. Fisher's exact test was used to identify any significant differences between frequencies of glaucoma subjects falling outside the age-representative performance limits for each test of visual function.

Results

Based on the visual attributes examined in the control group, a reference interval for each visual function was established. These limits for the normal binocular observer provided age-representative control data for comparison with the results from the patient cohorts.

The fifteen patients were classified in terms of the severity of their glaucoma, based on the global index mean deviation of the monocular HFA fields data, classified according to the MD of the better eye. This classification applied to our glaucoma cohort divided them into mild (n=9), moderate (n=2) or severe loss (n=4) (Table 1).

In order to present the effects of glaucoma on those visual functions investigated, the percentages of glaucoma subjects with results that were outside the normal range (95th percentile) for each of the attributes tested are presented in figure 2a (foveal location) and in figure 2c (pooled for the four parafoveal locations). It is worth noting that some patients exhibited severe loss of sensitivity for a specific visual attribute at a particular test location, and were unable to see the stimulus even at the phosphor limits of the screen.

The display screen employed for testing the visual attributes had a maximum stimulus strength determined by the phosphor limits for each test (CT and FCS: 666% luminance contrast, motion 283% luminance contrast (for 0% LCN), 261% luminance contrast (for 6% LCN), and 242% luminance contrast (for 12% LCN)). The colour threshold signals were limited by the phosphors of the display in the following way: red R (337 °): 0.11 chromatic displacement, green G (157 °): 0.09 chromatic displacement, yellow Y (62 °): 0.22 chromatic displacement, blue B (242 °): 0.17 chromatic displacement. These were the upper limits the screen phosphors could reproduce for each specific test.

Impairment of visual function varied depending on the stimulus attribute and location tested. The test 'failed' (thresholds outside the age-matched normal range) by the largest proportion of the glaucoma subjects was the CAD colour test, followed by motion, then CT, and finally FCS (Table 1 and Figure 2). The impairment was location specific with a different pattern of loss for foveal (figure 2a) and parafoveal (figure 2c) locations.

All subjects classified as having severe glaucoma fell outside the age-representative range for every test at each of the five test locations. There were only two patients classified as having moderate glaucoma, making it difficult to identify trends: one exhibited foveal CT and FCS within the normal range but failed all other tests, whereas the other failed all tests at the fovea apart from FCS. The parafoveal results for these two individuals were more variable. The group of greatest interest contains those classified as having mild glaucoma. Here the pattern of loss varied between individuals but appeared to fall into two distinct sub-groups: those with no loss in the YB channel but one or more affected testing locations for RG (mild 1, n=4), and those with symmetrical loss of both RG and YB for the majority of their tested locations (mild 2, n=5), who were closer to the two moderate subjects in terms of their colour performance.

Insert Table 1 and its caption here.

Table 1

glaucoma stage based on HFA MD	visual function	CAD (RG)		CAD (YB)		MS		CT		FCS
	patient ID	fovea	parafovea	fovea	parafovea	fovea	parafovea	fovea	parafovea	fovea
mild	35	+	4	/	/	/	/	/	/	/
	98	/	4	/	/	/	1	/	/	/
	58	+	4	/	/	+	4	/	/	/
	56	+	4	/	/	+	4	+	4	/
	60	+	2	+	2	/	2	/	1	/
	95	+	4	+	2+2B	/	3	/	/	/
	62	+	4	+	4	+	4	/	/	/
	90	+	4	+	4	+	4	+	4	/
	91	+	4	+	2	+	4	+	2	/
moderate	79	+	4	+	3	+	4	+	2	/
	94	+	4	+	4	+	4	/	1	/
severe	55	+	4	+	4	+	4	+	4	/
	63	+	4	+	4	+	4	+	4	/
	110	+	4	+	4	+	4	+	4	/
	119	+	4	+	4	+	4	+	4	/

Table 1: Fifteen subjects grouped into mild, moderate and severe stages of glaucoma based on the Humphrey visual field mean deviation (MD). For each glaucoma subject and each visual attribute, the symbol '/' indicates performance within the normal group. The symbol + indicates foveal performance for that subject and that specific visual attribute fell outside the normal group. For the parafoveal locations the number from 1 to 4 indicates the number of parafoveal locations for that subject that fell outside the 95th percentile for that age group and that specific visual attribute. Visual attributes assessed were: (RG) red-green chromatic sensitivity using the Colour Assessment and Diagnosis (CAD) test, motion sensitivity (MS), (CT) contrast sensitivity (CTS) tests, and binocular central visual fields assessed using the Humphrey visual field test.

Insert **Fig.2** and its caption here.

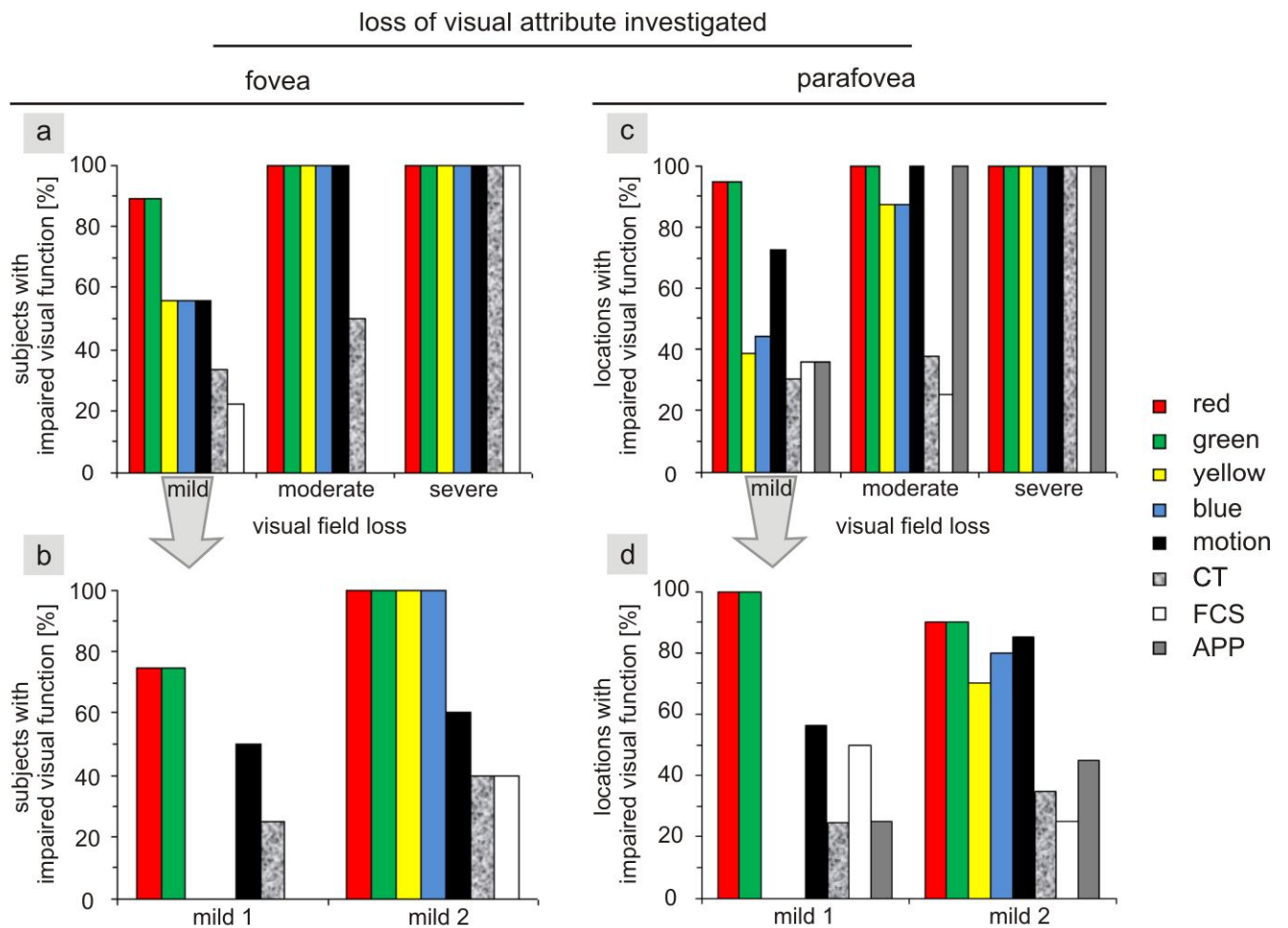


Fig. 2a Selected loss of visual function at the foveal location in subjects with glaucoma (n=15). The subgroups are labelled as mild, moderate and severe based on each subject's glaucoma stage (categories derived from their performance on the Humphrey Field Analyzer (HFA) SITA Standard 24-2, according to a method of glaucoma staging based on the global index mean deviation (MD) (Burr et al. 2007)). The percentages of subjects that showed loss of visual sensitivity at the fovea for each of the stimulus attributes indicated in the legend are presented for each of the glaucoma stage subgroups. For the fovea, mild loss presented with increased thresholds for RG chromatic sensitivity for 89% of the subjects, YB chromatic sensitivity for 56% of the subjects and loss of first order motion sensitivity for 56% of the subjects. A further 33% presented with affected contrast detection threshold above the 95th percentile of the normal control group, FCS was affected in 22% of the mild HFA group. Advancing glaucomatous damage modified the pattern of loss: chromatic sensitivity was impaired in both channels for 100% of the subjects in the moderate group, motion sensitivity

was affected in 100% of subjects and contrast detection threshold (50%), for functional contrast sensitivity the two moderate subjects had thresholds within the normal range. In the severe group, loss of visual functions examined at the fovea was present outside the normal range in all subjects, with some at the phosphor limits of the display.

Fig. 2b Detailed analysis of loss in chromatic sensitivity at the fovea in the mild group, based on HFA MD, highlights that there are two patterns of colour loss present: one subject has no foveal defect in chromatic sensitivity, three subjects present with loss solely in the RG channel, while five subjects, however, present with chromatic sensitivity thresholds outside the normal range for both RG and YB channels, i.e, only five out of nine mild glaucoma subjects have a defect in the YB channel. To highlight this graphically the inset presents the data for the HFA mild group in two streams. Mild 2 has more profound loss in motion, CT and FCS compared to mild 1, and most striking is the additional loss in chromatic sensitivity present in mild 2.

Fig. 2c Data similar to those shown in Fig. 2a, but showing losses at parafoveal testing locations in the four quadrants. The loss is presented as a percentage of locations with impaired visual function at the parafovea (a maximum of four parafoveal locations per subject). Parafoveal examination enables comparison with APP scores per quadrant. Loss of sensitivity on the APP test for this graphical display was chosen to be within normal limits for mean APP grades per quadrant of 3.5 and over. Chromatic sensitivity in the RG channel was affected in 94% of locations, 39%/44% exhibited Y/B loss and additionally motion sensitivity (72%) and functional contrast sensitivity and APP were affected in 36% of locations. A further 31% presented with loss for the CT test. Increased glaucomatous damage resulted in additional loss of chromatic sensitivity of the RG (100%) and the YB channels (87%) and increased loss of motion sensitivity, which now affected 100% of the locations. In the patient group with severe damage, all visual functions were affected in all subjects (100%) for all the parafoveal locations.

Fig. 2d Detailed analysis of loss in chromatic sensitivity in the mild group at the parafoveal locations highlights that there are two patterns of colour loss present: four subjects presented with colour loss solely in the RG channel for each of their four parafoveal locations, these were termed mild 1. Included here is the one subject with no foveal defect in chromatic sensitivity, this subject had only parafoveal RG loss. The remaining subjects, however, had RG and YB loss at the parafovea. The grouping based on foveal data is mirrored: The five subjects who presented with chromatic sensitivity thresholds outside the normal range for both RG and YB channels at the fovea (mild 2), also had at least two quadrants with RG and YB loss at the parafovea (mild 2). Less loss of chromatic sensitivity was present at the inferior locations of the field.

For foveal data, correlations (Spearman's rho) between visual function tests were generally modest. Apart from the strong correlation between CT and FCS ($\rho = 0.80$ $P < 0.001$), the correlations between these two tests and the other visual function tests (MD, APP, the CAD tests, and Motion) were low, ranging from 0.04 to 0.53. For the CAD tests there was a statistically significant correlation between RG and MD (0.72 $P = 0.002$) but the correlation between YB and MD was 0.45 and not statistically significant. Motion had a strong association with RG (0.80 $P < 0.001$) and a slightly weaker association with MD (0.65 $P = 0.009$). The correlations between APP (using the mean APP score for the four quadrants) and the other tests of visual function were always higher than those for MD. This was most notable for YB which had a rho of 0.71 ($P = 0.003$) for the association with APP compared with 0.45 ($P = 0.10$) for MD. As expected, correlations between MD and APP (0.85 $P = 0.0001$) and between the two CAD tests (0.86 $P < 0.0001$) were strong.

For the correlation analysis for parafoveal data, the visual function results for the four quadrants were averaged. Statistically significant correlations were found between all combinations of visual functions tested. As could be expected, the strongest association was between the two CAD tests ($\rho = 0.94$ $P < 0.0001$), closely followed by APP (mean quadrant scores) and Motion (0.91 $P < 0.0001$), and Motion and CT (0.93 $P < 0.0001$). The two CAD tests had more moderate associations with the APP results (RG, $\rho = 0.73$ $P = 0.002$ and YB, $\rho = 0.69$ $P = 0.005$).

An additional correlation analysis was performed following identification of the quadrant for each subject which exhibited the greatest loss of visual field on the APP test. For each subject the results of the other visual function tests in that quadrant were tabulated and the association between the results of each test for the glaucoma group was calculated. The results paralleled those for the average of the four quadrants with, in general, small increases in rho for each test compared with average data for the four quadrants e.g. rho increased from 0.62 for Motion and YB using the mean of the four quadrants data to 0.65 using the 'worst' quadrant, and from 0.73 to 0.78 for APP and RG.

The Fisher's exact test was applied to the data from the mild glaucoma group to identify any significant differences between frequencies of glaucoma subjects falling outside the age-representative performance limits for each test of visual function (Figure 2a). For the foveal data a significantly greater proportion of glaucoma subjects were CAD positive (8/9 for both R and G) than for CT (3/9 $P = 0.049$) or FCS (2/9 $P = 0.015$). There were no statistically significant differences between any other visual function tests.

For the parafoveal data, a significantly greater proportion of quadrants from mild glaucoma subjects were CAD positive for R and G (34/36 for both R and G) than for Y (14/36 $P < 0.0001$), B (16/36 $P < 0.0001$), Motion (26/36 $P = 0.02$), CT (11/36 $P < 0.0001$) or FCS (13/36 $P < 0.0001$). A significantly greater proportion of quadrants from glaucoma subjects were positive for Motion (26/36) than for Y (14/36 $P = 0.009$), B (16/36 $P = 0.03$), CT (11/36 $P = 0.0008$) or FCS (13/36 $P = 0.004$). There were no statistically significant differences between any other visual function tests.

The RG colour test identified more subjects with mild glaucoma as having results outside the age-representative range than any other test of visual function. This finding led to a more detailed investigation of colour discrimination. In each colour direction (R, G, Y and B), the individual colour discrimination thresholds were converted to standard normal units for each subject, and then the means $\pm$ one standard deviation were calculated for the mild, moderate, and severe groups at the fovea and each of the four parafoveal locations (Figure 3 a-c). The mean colour discrimination thresholds, for both RG and YB thresholds increase systematically with the severity of the disease (Figure 2 and Figure 3).

Insert **Fig.3** and its caption here.

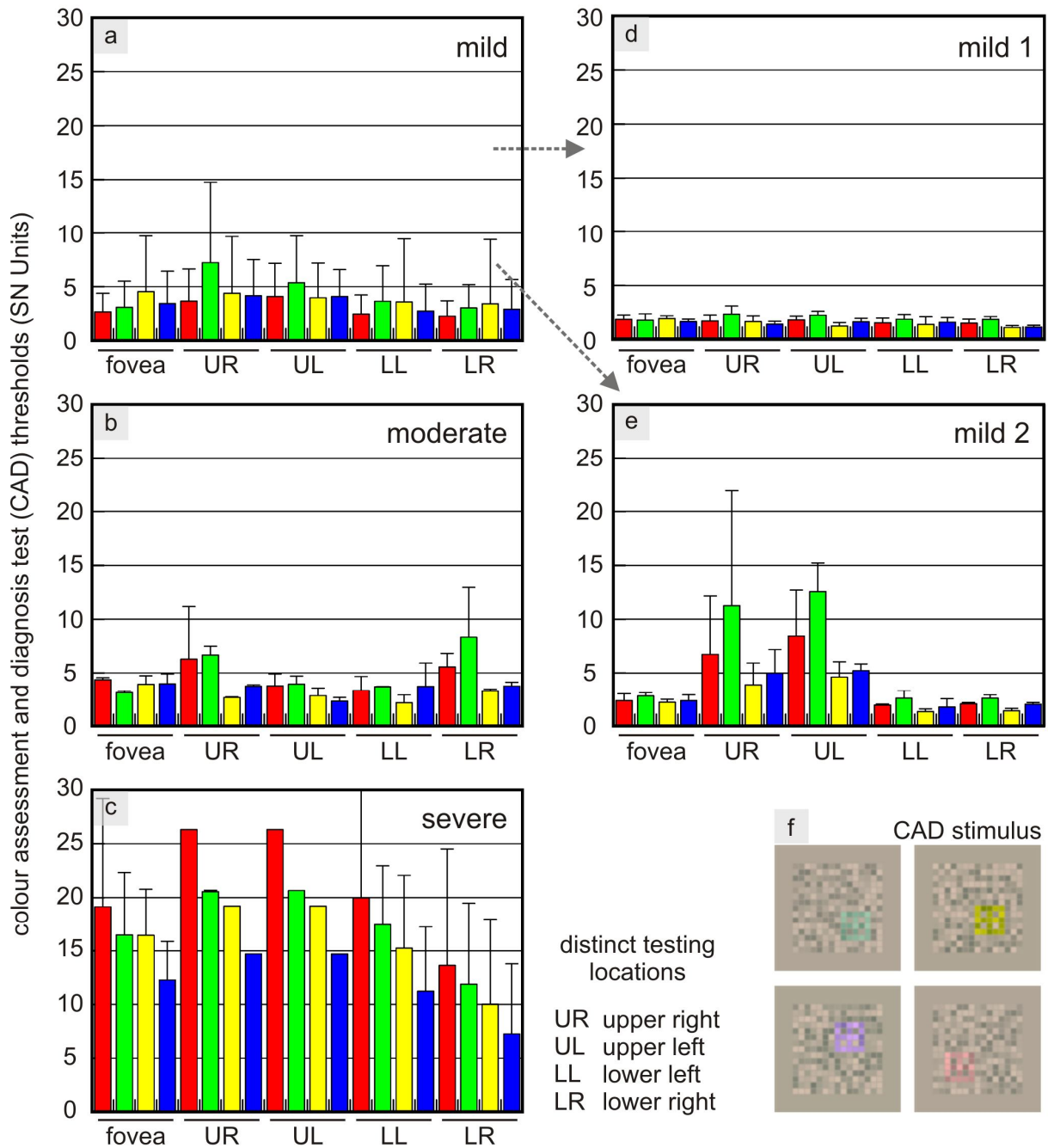


Fig. 3 The results for chromatic sensitivity have been transformed into Standard Normal Units (SNU), which represent the median threshold for the average normal observer based on 330 normal trichromats (Rodriguez-Carmona et al. 2005). CAD thresholds were measured at the fovea and in each of the four quadrants towards the red, green, yellow and blue directions of the spectrum locus. Separate results are presented for the three subgroups

of glaucoma subjects labelled as mild, moderate and severe (Fig 3 a – c). Mean thresholds and the corresponding standard deviations for each of the five clusters (one for each location) were calculated based on standard normal units previously computed from the colour thresholds (R, G, Y and B) for each subject and at each location. The results show, that both RG and YB thresholds increase systematically with the severity of the disease. For patients in the severe sub-group, the upper right (UR) and upper left (UL) thresholds measured showed no variation as they represent the largest achievable signals on the display device.

The group of greatest interest contains those classified as having mild glaucoma. Here the pattern of loss varied between individuals but appeared to fall into two distinct sub-groups referred to as mild 1 and mild 2. For an explanation of the rationale behind this subdivision see the caption to Figure 2 and the main text. The mean thresholds for subjects in the mild 1 sub-group ($n = 4$) revealed diffuse loss across the five locations tested (Figure 3d). Mean thresholds in subjects in the mild 2 sub-group (Figure 3e) ($n = 5$) exhibited colour losses which were closer to the two moderate subjects in terms of their colour performance. Mild 2 subjects had greater colour loss in the superior quadrants, which may reflect the tendency for the superior field to be affected first in glaucoma (Edgar and Rudnicka, 2007). Fig 3f illustrates the stimuli presented to subjects on the CAD test.

A clear variation in colour thresholds between test locations can be seen for the group data, but was also evident for many of the subjects, e.g. subject 91 (mild glaucoma) (Figure 4). For this subject, the LL quadrant (APP score 3.64) showed solely RG loss, while the LR quadrant (APP score 3.72) showed a degree of RG and YB loss. There is a trend for the colour thresholds to increase as the APP scores deteriorate in the remaining quadrants, with the UL (APP score 2.34) showing equal RG and YB loss and the UR quadrant exhibiting RG and YB losses that reached the phosphor limits of the display, coinciding with the region of densest visual field defect (APP score 2.22). A similar pattern of loss was seen in other subjects in both the mild and moderate groups, which would have led to a mixed classification of the disease had localised colour loss been used as the criterion.

Insert Fig.4 and its caption here.

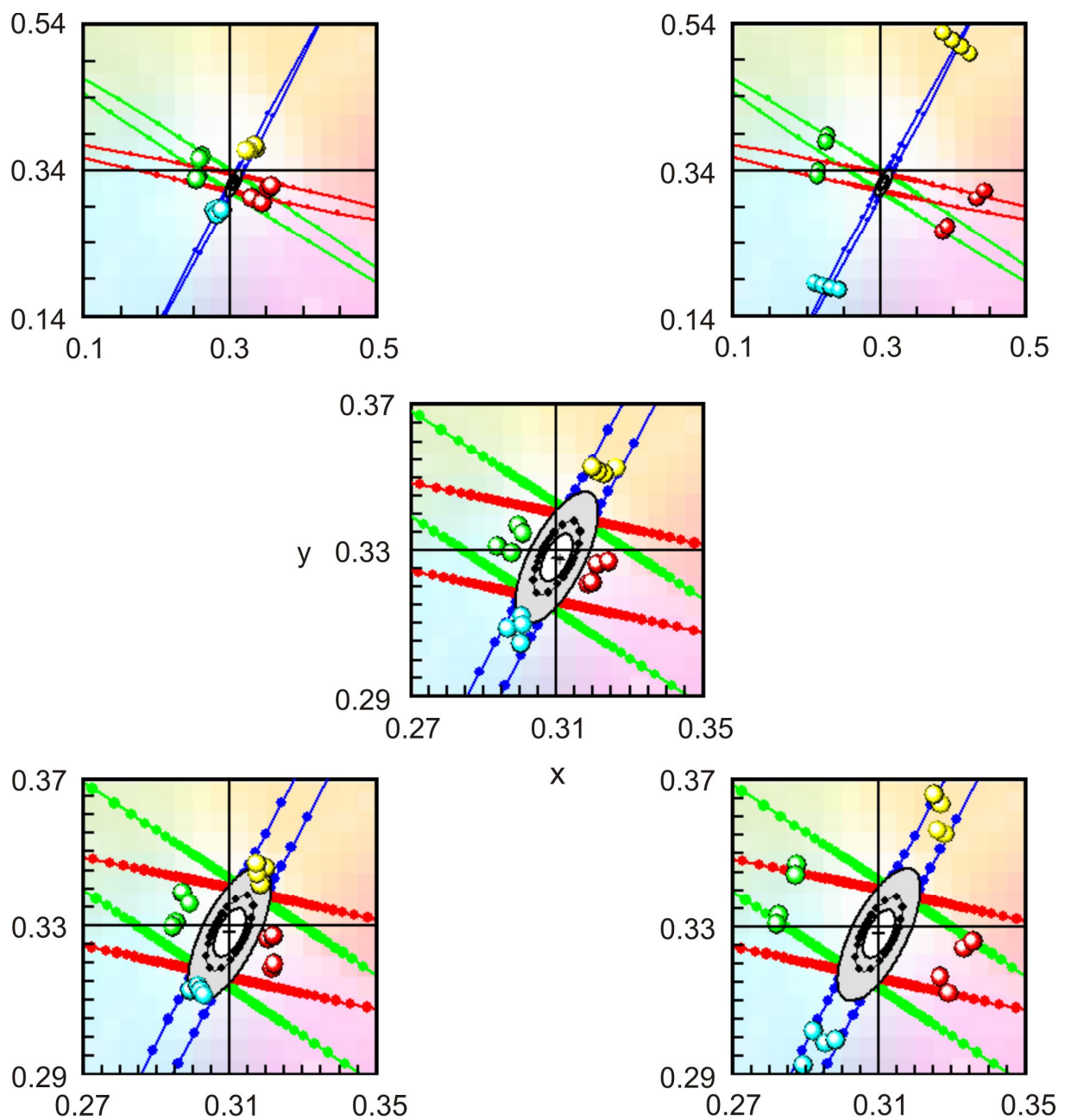


Fig. 4 Colour vision ellipses for one subject, generated at each of the five locations tested. The central ellipse is that obtained from the fovea, the upper left was from the upper left parafoveal location tested, etc. The ellipses shown provide a template against which the extent of colour vision loss in this particular patient with glaucoma can be judged visually. The coloured symbols represent distances away from the background chromaticity in the CIE (x,y)- chromaticity diagram. The results are plotted as an ellipse for comparison with the normal colour observer. These limits are expressed in Standard Normal Units (SNU), which represent the median threshold for the average normal observer based on 330 normal

trichromats (Rodriguez-Carmona et al. 2005). Data for subject 91 illustrates large chromaticity losses and variation in these losses with location tested. The lower left location and also the foveal location present with mild loss. The upper left location is classified as moderate colour loss, while the upper right location is severely affected up to the phosphor limits of the display. Interestingly, the lower right location is at a transition stage between mild and moderate loss: YB is already affected but not yet to the extent of the RG loss. The extremely large thresholds measured in the upper right quadrant reflect the largest chromatic displacements that can be generated at isoluminance on the visual display. Although the absolute threshold cannot be measured, the data indicate severe reduction in chromatic sensitivity normally associated with complete loss of colour vision. Note the different axes used in the upper quadrants. These are required to illustrate colour losses of this magnitude.

Discussion

The establishment of age-matched normal ranges for each test allowed a more relevant analysis of visual function that took into account the known deterioration of certain aspects of visual function with increasing age (Haegerstrom-Porknoy 2005).

The majority of glaucoma patients revealed a degree of loss for all aspects of visual performance assessed, which was related to the severity of the disease. The loss was consistent among the severe group but the mild group showed greater inter-subject variability and greater variability between quadrants, with loss frequently demonstrated in areas deemed normal by conventional perimetry. This finding is consistent with that of Bach and colleagues (Bach et al. 1998), who found for PERG that glaucoma began with pan-retinal damage of ganglion cells, but without necessarily the presence of a field defect by conventional perimetry. Loss of CT only occurred at locations coinciding with a known binocular visual field defect as identified by conventional perimetry. This is not surprising since they share the same stimulus attribute. Loss of both CT and FCS was a marker for profound loss of both colour and motion sensitivity. The loss of RG chromatic sensitivity alone, with sparing of YB sensitivity was only encountered in patients with mild glaucoma.

The division of our subjects with mild glaucoma into mild 1 and mild 2 sub-groups based on their individual colour losses identified two patterns of colour loss. In spatial terms losses in the mild 1 group tended to be diffuse (Figure 3d). In the mild 2 group, who had colour losses similar to those with moderate glaucoma, the loss was more localised with the superior quadrants more affected, which may reflect the tendency for the superior field to be affected first in glaucoma (Edgar and Rudnicka, 2007)

The generally modest correlations between the different visual function results for the fovea may reflect the late involvement of the fovea in the disease process. Most of the subjects (9/15) were classified as having mild stage glaucoma, so the disease is unlikely to have affected the fovea of these subjects. This is also a possible explanation for the poor correlations found between the visual field test results and the 'acuity' based tests CT and FCS. The correlation between MD and APP was 0.85, and the rho values for APP when calculating the correlation between it and all other visual functions was always higher than that obtained for MD and all other visual functions. This suggests that the APP test is an appropriate perimeter for assessing the binocular central visual field for glaucomatous field loss. The two tests with the strongest correlations with APP and MD were RG and Motion. However, correlation with white-on-white perimetry may not necessarily be the best indicator of a test that could be more sensitive to glaucomatous change than conventional methods, especially the earliest changes in visual function found in glaucoma. For parafoveal data the Motion test had the strongest correlation with APP field results, closely followed by CT. CT and APP do, of course, measure the same stimulus attributes and therefore a strong correlation would be expected.

When comparing the visual function test results with the age-representative reference limits generated from our normal database there were notable statistically significant differences between the frequencies with which subjects with mild glaucoma fell outside the normal range for our tests. For the fovea, a significantly greater proportion of these subjects had foveal CAD results (for R and G) outside normal age-representative range than the proportions for CT and FCS. However, this was based on a small sample of 9 subjects.

In the parafoveal region, a significantly greater proportion had R and G CAD results outside normal age-representative range than the proportions for Y, B, Motion, CT and FCS. Interestingly, for this mild glaucoma sub-group, a significantly greater proportion had parafoveal Motion results outside the normal age-representative range than the proportions for Y, B, CT and FCS. This occurred in quadrants free from significant binocular visual field

loss i.e. these quadrants could be said to mimic early glaucoma. These results suggest that the CAD and Motion tests are candidate tests for identification of mild glaucoma. One limitation of the analysis for the parafoveal data is that each of the 9 subjects contributed four items of data (one for each quadrant) to the analysis, so the 36 items of data were not independent.

Motion thresholds have previously been proposed as being useful in the detection of early glaucoma, and appear to be capable of differentiating between normal, suspect and early glaucoma cases (Westcott et al. 1999). There is evidence that neural damage in glaucoma is selective for the magno-cellular pathway (Silverman et al. 1990, Trick et al. 1995, Sample et al. 1997, Bosworth et al. 1997, Willis and Anderson 2000), but other work has indicated that this may not be the case (McKendrick et al. 2004; Yucel et al. 2003). However, many tests have been designed to isolate this pathway and studies using random dot kinematograms showed that minimum displacement thresholds were elevated in patients with suspected glaucoma (Bullimore et al. 1993, Westcott et al. 1999). In patients with glaucomatous field defects, motion coherence thresholds were higher in those regions of the visual field showing glaucomatous loss compared to unaffected areas of the visual field (Bosworth et al. 1997, Westcott et al. 1998, 1999, Membrey et al. 1999). Different motion tests do not necessarily yield similar results, as studies employ a variety of stimuli (for example: single small dots, random dot kinematograms, real objects, and two dot apparent motion), resulting in subtle differences in the motion processing mechanisms that may be affected differentially in disease. The test stimulus employed is important, as neurons can be selectively sensitive to bars or random dot kinematograms, gratings or plaids (Azzopardi and Cowey 2001). A relatively recent development is the Moorfields Motion Displacement Test (MDT) which is a computer software programme providing a test that can be presented on a laptop. This first order motion test has shown greater resilience to the effects of cataract and other media opacities compared with conventional perimetry and the frequency doubling technology (FDT) test (Bergin et al 2011).

Colour vision processing is thought to be mediated by the parvo-cellular pathway (Lennie, Krauskopf and Sclar 1990, Dacey et al. 1996). Signals from the three classes of cone photoreceptors in the retina are compared and combined into mechanisms that extract spatial changes in the spectral content of the stimulus. It is generally believed that there are two channels along which signals from cells with opposing cone inputs are transmitted: the red-green channel (R/G) in which signals from L- and M-cones are compared (type I cells), and the yellow-blue channel (YB) in which signals from S-cones are compared with a combined signal from L- and M-cones (type II cells).

Colour vision loss can be either congenital or acquired. Acquired red-green deficiency occurs in most diseases of the optic nerve, whereas yellow-blue losses are more frequently encountered in diseases of the retina. This is known as Köllner's rule (Köllner 1912, Verriest 1963). However, there can be exceptions to Köllner's rule, for example defects of the yellow-blue channel have been shown in individuals with glaucoma, as well as in ocular hypertensive patients (Verriest 1963, Pacheco-Cutillas et al. 1999, Karwatsky et al. 2004). Although blue on yellow perimetry (Short Wave Automated Perimetry or SWAP) can detect early stage glaucoma in some patients before visual field loss can be detected using conventional perimetry (Johnson et al. 1993b, Johnson et al. 1993a), this increased sensitivity is associated with decreased specificity, and an increase in false positives (Jampel et al 2011). On the other hand, findings from earlier studies of glaucomatous patients, found preferential loss of the red-green chromatic sensitivity, but mostly in advanced stages of glaucoma (Adams et al. 1982, Pacheco-Cutillas et al. 1999, Castelo-Branco et al. 2004). Our data are supportive of this reported tendency for preferential impairment of red-green over yellow-blue chromatic loss, although we demonstrated loss in all subjects and most notably, in mild cases in locations free from visual field loss. Our findings identified that YB testing had some advantage over conventional visual field testing but strongly suggest that

parafoveal RG testing might be better still at identifying glaucoma cases at an early stage of the disease.

All testing was undertaken binocularly to assess visual performance under natural viewing conditions that would be more relevant to day-to-day visual activities. Since glaucoma is essentially a bilateral disease, binocular testing would allow for the examination of relationships with QOL measures. This will be considered in future work once a suitable index of vision has been established for comparison with QOL, based on the key attributes of RG colour and Motion identified in this study. Binocular measurements of visual field sensitivity are best predicted by the monocular sensitivity of the better location (Crabb and Viswanathan 2005). There is evidence to suggest that this relationship also applies to binocular performance for other aspects of visual performance such as colour and motion thresholds, even though the better performing eye may differ depending on the visual attribute under test (Rauscher 2009). Binocular testing therefore has the additional advantage of reflecting the performance of the better eye for a particular visual attribute, without having to determine which eye this is.

Conclusions

The findings of this study suggest that the loss of binocular visual sensitivity in glaucoma gradually progresses from normal sensitivity to mild and finally extreme loss. The relatively small number of glaucoma cases and inherent variability between patients limits the findings but useful conclusions can be drawn nevertheless.

Parafoveal loss was found to precede foveal loss and colour thresholds showed the greatest sensitivity to early glaucomatous changes, with R/G losses that tended to precede FCS and perimetric loss of binocular visual field sensitivity, even under binocular testing conditions. To our knowledge, this is the first study to illustrate the value of assessing specific visual attributes under binocular viewing conditions.

Perimetric tests provide relatively crude information on the loss of visual sensitivity over a wide area of the visual field. Simple measures of perimetric sensitivity cannot detect selective loss of specific visual attributes and have failed to show a strong correlation with quality of life measures. A multifaceted approach to binocular visual function testing that incorporates RG colour assessment may be required to provide a measure that is more strongly applicable to quality of life.

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