VARIABILITY OF THE PERIMETRIC RESPONSE IN NORMALS AND IN GLAUCOMA

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This study investigated the variability of response associated with various perimetric techniques, with the aim of improving the clinical interpretation of automated static threshold perimetry.

Evaluation of a third generation of perimetric threshold algorithms (SITA) demonstrated a reduction in test duration by approximately 50% both in normal subjects and in glaucoma patients. SITA produced a slightly higher, but clinically insignificant, Mean Sensitivity than with the previous generations of algorithms. This was associated with a decreased between-subject variability in sensitivity and hence, lower confidence intervals for normality.

In glaucoma, the SITA algorithms gave rise to more statistically significant visual field defects and a similar between-visit repeatability to the Full Threshold and FASTPAC algorithms.

The higher estimated sensitivity observed with SITA compared to Full Threshold and FASTPAC were not attributed to a reduction in the fatigue effect.

The investigation of a novel method of maintaining patient fixation, a roving fixation target which paused immediately prior to the stimulus presentation, revealed a greater degree of fixational instability with the roving fixation target compared to the conventional static fixation target.

Previous experience with traditional white-white perimetry did not eradicate the learning effect in short-wavelength automated perimetry (SWAP) in a group of ocular hypertensive patients. The learning effect was smaller in an experienced group of patients compared to a naïve group of patients, but was still at a significant level to require that patients should undertake a series of at least three familiarisation tests with SWAP.

SITA, fatigue effect, learning effect, SWAP, roving fixation

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CHAPTER 1. AUTOMATED STATIC PERIMETRY.

1.1 Introduction.

With the eyes directed straight ahead, it is possible to detect the presence of objects away from the direct line of sight. The visual field can be defined as this region of space in which objects can be detected by a steadily fixating eye. At the boundaries of this region, only large or bright stimuli can be detected, with smaller or dimmer objects becoming visible nearer the point of fixation. The visual field has been described as "an island of vision in a sea of blindness" (Traquair 1927).

The summit of the photopic hill of vision, which corresponds to the fovea, has the maximum sensitivity to light and sensitivity decreases as the hill slopes down towards the sea. The slope of the hill is steeper nasally than temporally. The normal monocular visual field extends, from fixation, 60 degrees nasally and superiorly, 75 degrees inferiorly and 100 degrees temporally (Anderson 1992). This is the relative visual field, as the field is limited by the nose and by the orbital bones. Deep set eyes and the size of the palpebral aperture therefore affect the measured visual field (Fisher 1967, Meyer, et al. 1993). By moving the head, whilst maintaining fixation at the same location, the absolute visual field can be plotted. Located 15 degrees temporal to, and 1.5 degrees below, fixation there is a physiological blind spot. This represents the projection, through the optics of the eye, of the optic nerve head, an area of the retina devoid of photoreceptors. This blind spot extends approximately 5.5 degrees horizontally and 7.5 degrees vertically.

The aim of the perimetrist is to assess the dimensions of the hill of vision, and hence the integrity of the visual system as a whole; this involves pre-retinal factors, the retina and the pathways to the visual cortex. The visual field is usually investigated by measuring the differential light threshold in different locations of the field. The differential light threshold is the minimum stimulus luminance (ΔL) required to elicit a visual response against a constant background luminance (L) and is usually expressed in terms of sensitivity ($L/\Delta L$).

A localised area of reduced sensitivity is known as a relative scotoma, or as focal loss. An absolute scotoma is an area with no light perception. A general reduction of sensitivity over the whole visual field can be termed a depression of the field or as a diffuse loss, whereas constriction of the field is the loss of peripheral sensitivity with a normal central field. Damage at different sites in the visual pathway produces characteristic types of visual field defects. Quadrantopias are reductions in sensitivity affecting a quadrant of the visual field. When one half of the visual field is affected, the defect is called a hemianopia. Hemianopias can be homonymous, affecting the same side of the field, or heteronymous, when opposite sides of the field are involved. Congruence describes the degree of symmetry of defect between eyes. The central visual field is assumed to be that part within thirty degrees from fixation, further than thirty degrees is termed the peripheral visual field.

There are two techniques usually employed to record the differential light threshold: kinetic and static perimetry. The principles of the two techniques are summarised in Figure 1.1.

Kinetic perimetry involves moving a stimulus of a given constant luminance and size, usually from non-seeing to seeing, until it is seen by the subject. The locus of points at which the subject sees the stimulus is plotted and is called an isopter. Using several different stimuli, a number of isopters are plotted to describe the hill of vision in a similar way that contour lines on a map describe geographical topography. The area within each isopter depends on the size, luminance and colour of the stimulus used to plot it. A moving stimulus will be detected more peripherally than a stationary stimulus because of successive lateral spatial summation (Greve 1973). The rate of stimulus movement and the reaction times of the subject and the perimetrist influence the variability of the technique (Lynn 1969, Greve 1973). Greve (1973) suggested that the optimum stimulus velocity is 2 degrees per second for the central field and 5 degrees per second for the periphery. At stimulus velocities of four degrees per second or greater, the size of the isopter may be reduced (Johnson and Keltner 1987). The reaction time is slower in the periphery (Keele 1986).

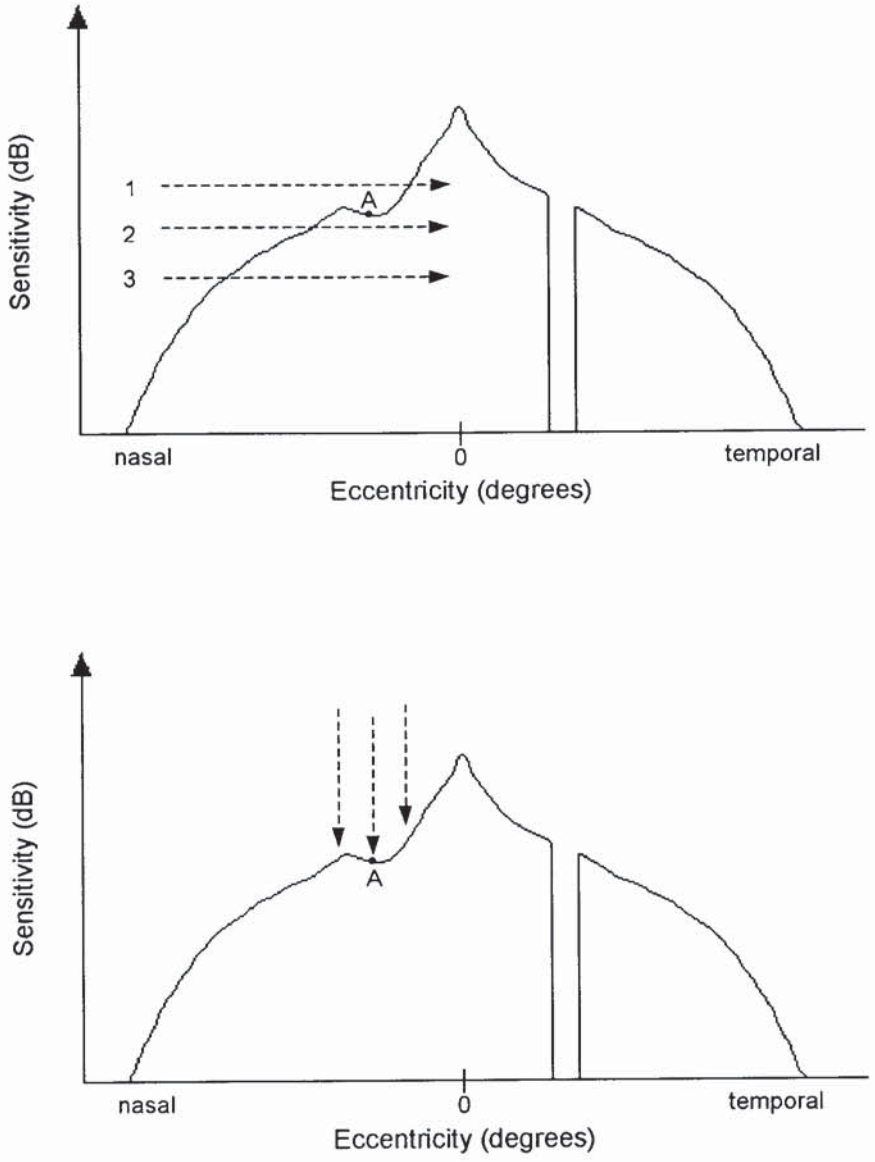


Figure 1.1. (Top) Schematic representation of kinetic perimetry. The dotted lines represent a stimulus of fixed luminance moving towards fixation, increasing in luminance or diameter from 1 to 3. The reduction in sensitivity at A, due to a relative scotoma, would not be discovered using the three stimuli depicted here. (Bottom) In static perimetry, the stimuli are presented at fixed locations with increasing levels of luminance (dotted lines). By comparison with the adjacent stimuli, the reduction in sensitivity at A would be detected with the static technique.

Static perimetry involves the presentation of the stimulus at fixed locations and the luminance is varied. Stimulus luminance is altered in steps until threshold is crossed. Although static perimetry may be more time consuming than kinetic perimetry, thresholds are not affected by the reaction time of the subject (Greve 1975, Trope and Britton 1987). Static perimetry is able to detect small isolated scotoma, which often occur in glaucoma, more efficiently than kinetic perimetry (Greve and Verduin 1977) and has been shown to be more precise (Drance, et al. 1967, Armaly 1971).

Stato-kinetic dissociation describes the difference in measured sensitivity between identical static and kinetic stimuli. In the periphery of normal subjects, the difference between the two techniques is approximately 4 dB, when determined by automated perimetry (Hudson and Wild 1992). The difference is independent of stimulus size, meridian and eccentricity.

With automated perimetry, the decision process of the examination strategy is exclusively controlled by computer (Greve 1982). This allows for standardised examination procedures and parameters, data storage and statistical analysis (Fankhauser, et al. 1972). Commercially available automated perimeters use different background illuminations, methods of stimulus presentation and examination strategies (Heijl 1977a, Greve 1982).

1.2 Principles of Perimetry.

1.2.1 Units of Measurement.

The differential light threshold is an expression of the Weber-Fechner Law:

$$\Delta L/L=K$$

Where, ΔL is the difference between stimulus and background luminances that can be detected; L is the background luminance and K is a constant. The absolute stimulus luminance is the sum of ΔL plus L. The units of measurement in perimetry are the candela per square metre (cdm^{-2}) and the decibel (dB). The candela per square metre is used to quantify absolute luminances whereas the decibel is a relative unit used to describe

sensitivity. The decibel scale is measured relative to the maximum luminance of the instrument, which is designated as zero decibels. Sensitivity is measured on a logarithmic scale, where:

$$\text{Sensitivity (dB)} = k + 10.\text{Log}\,(L/\Delta L)$$

In the Humphrey Field Analyzer, L is 10 cdm^{-2} and the maximum stimulus luminance (ΔL) is 3183 cdm^{-2}, which gives a value for k of 25. Ten decibels equal one log-unit, and a 1.0 log-unit filter attenuates the light to one tenth of its original intensity, a 2.0 log-unit filter reduces the intensity to 1/100 of its original value. Hence, increasing decibel values represent increasing sensitivity. Since each instrument's decibel scale is calculated from the background illumination and the maximum possible stimulus intensity, a particular decibel value on one instrument does not indicate a similar sensitivity as the same decibel value on another instrument (Anderson 1992).

1.2.2 Stimulus Parameters.

1.2.2.1 Background Illumination and Dynamic Range.

The level of background illumination determines the state of retinal adaptation. The change in retinal sensitivity does not occur at a uniform rate over the whole retina. At higher levels of illumination, the profile of retinal sensitivity has a steeper gradient, becoming flatter as the background illumination decreases towards the mesopic range. At the lower levels of scotopic background illumination the foveal sensitivity peak disappears and becomes a central physiological scotoma.

The dynamic range of a perimeter has been defined as "the measurement range over which the neuro-visual system can be tested, using specific equipment with a given set of experimental variables" (Fankhauser 1979). With a large dynamic range, deeper defects can be investigated. The dynamic range of the perimeter is derived from the maximum stimulus luminance of the perimeter and the threshold stimulus luminance of the normal eye (Fankhauser 1979). The threshold stimulus luminance is dependent on the background

luminance of the instrument. The relationship between ΔL and L has been assumed to follow the linear Weber-Fechner Law, although this has been shown to apply only at background luminances of greater than 31.8 cdm^{-2} (Aulhorn and Harms 1972). The Weber-Fechner Law has been shown to hold at background luminances of 10 cdm^{-2} and above (Aulhorn and Harms 1972, Greve 1973, Klewin and Radius 1986, Wood, et al. 1988). At the levels of low photopic background illumination commonly found in current perimeters (1.3 cdm^{-2} to 10 cdm^{-2}) and in the mesopic range, the Rose-de Vries Law shows a good approximation (Fankhauser 1979, Flanagan, et al. 1991):

$$\Delta L/L^{0.5} = \text{constant}$$

A reduction in the background illumination to the scotopic range, i.e. below 0.3 cdm^{-2}, results in a linear relationship:

$$\Delta L = \text{constant}$$

The variability in the approximations of the Laws is due to a considerable overlap in the luminance ranges at which each law holds.

As the retina has greater sensitivity to light at lower levels of background illumination, the dynamic range of an instrument can be increased by minimising the background illumination and maximising the stimulus luminance. However, at high stimulus luminances, light scatter around the stimulus becomes significant and the localised retinal adaptation may be affected (Wilson 1967, Fankhauser and Haeberlin 1980, Dengler-Harles, et al. 1990).

The difference between background and general room illumination determines the time needed for the retina to adapt to the perimeter before testing can commence. Testing before adaptation is complete results in perimetric artefacts, such as spiralling of the isopters with kinetic perimetry, and increased variability with static perimetry. Changing the level of

stimulus and background luminances also affect the diameter of the pupil. However, changes in retinal adaptation due to pupil size only occur in the mesopic range.

1.2.2.2 Stimulus Size.

The size of the stimulus and the duration of stimulus presentation also affect stimulus visibility. Due to the convergent nature of neural processing within the retina, a ganglion cell may respond equally to a small bright stimulus or a larger dim stimulus. This phenomenon is known as spatial summation and can be described mathematically by:

$$\text{Luminance} \times (\text{Stimulus Area})^{K} = \text{Constant}$$

As the stimulus area approaches the critical area of the ganglion cell, complete summation and Ricco's Law apply (k=1). As the stimulus area exceeds the critical area, partial summation applies. Pieron's Law (k=0.3), Piper's Law (k=0.5) and Goldmann's approximation (k=0.8) have been proposed to describe partial summation. Under the assumption that spatial summation may be affected by disorders of the visual system, Goldmann suggested the use of stimulus sizes that changed in steps equivalent to luminance changes of 5 dB. Thus, Goldmann sizes I (0.108° diameter) to V (1.724° diameter) have become the standard for use in modern projection perimeters.

Larger stimulus sizes have been shown to result in a larger dynamic range (Fankhauser 1979, Heijl 1985, Choplin, et al. 1990, Zalta 1991). For a background illumination of 1.27 cdm^{-2}, changing the stimulus size from Goldmann I to III has been shown to correspond to an increase in the dynamic range of 12 dB at an eccentricity of 50 degrees, and an increase of 4 dB at fixation. With the same change in stimulus size, combined with a reduction of background illumination from 12.7 cdm^{-2} to 1.27 cdm^{-2}, the dynamic range can be increased by a factor of 50 (17 dB) at an eccentricity of 50 degrees (Fankhauser 1979).

The Goldmann size III has become the standard for use in automated static perimetry as it is affected less than size I, by optical defocus (Fankhauser, et al. 1972, Heijl 1985, Atchison 1987) and media opacity (Radius 1978, Wood, et al. 1987a). The use of stimuli size III may

fail to detect small shallow relative scotoma that could be detected with smaller stimulus sizes (Zalta and Burchfield 1990). Larger stimulus sizes have been shown to extend the dynamic range and therefore be of benefit in the clinical management of end-stage glaucoma (Zalta 1991). Locations in the visual field with absolute loss to a size III stimulus have been shown to exhibit visual sensitivity to a size V stimulus (Wilensky, et al. 1986) although relative scotoma are greatly underestimated centrally (Zulauf and Caprioli 1993). Variability in the estimation of threshold is influenced by stimulus size. Variability is greater with sizes smaller than Goldmann size III in normals (Gilpin, et al. 1990, Gundersen, et al. 1993) and in glaucoma (Wall, et al. 1993). Variability for stimulus size V relative to size III is either similar (Gilpin, et al. 1990) or reduced (Wall, et al. 1997) within 30 degrees eccentricity.

1.2.2.3 Stimulus Duration.

The visual system sums signals over time. Stimuli appear brighter as the length of stimulus duration is increased. This process is known as temporal summation and can be described by Bloch's Law:

$$\text{Luminance} \times (\text{Stimulus Duration})^{K} = \text{Constant}$$

At stimulus durations less than the critical time, complete temporal summation occurs and k=1. With stimulus durations greater than the critical time, partial summation occurs and k falls from one to zero. The critical time in normals is of the order 60 ms to 100 ms but is dependent upon retinal eccentricity and adaptation (Barlow 1958, Greve 1973, Saunders 1975). At low background illuminances (at or less than 3.2 cdm^{-2}) the critical time can exceed 100 ms (Dannheim and Drance 1971). Temporal summation is greater for lower background illuminances and for smaller stimuli (Barlow 1958, Saunders 1975). Stimulus durations of between 0.5 and 1 second have been suggested to eliminate the effects of temporal summation (Aulhorn and Harms 1972, Greve 1973). However, at these longer durations, subjects may alter fixation towards the stimulus, and hence affect the measured sensitivity, as the latency of saccadic eye movements is around 250 ms (Robinson 1964). Short stimulus durations have been suggested for use when testing patients with poor fixation

(Greve 1973). Shorter stimulus durations may also improve the detection of some ocular disorders in which temporal summation is increased (Wilson 1967, Wood, et al. 1986). In normal subjects, stimulus durations between 65 ms and 500 ms have little effect on the fluctuation of the threshold estimate (Pennebaker, et al. 1992). The default stimulus duration in most perimeters is between 100 ms and 200 ms and represents a compromise between reducing temporal summation and the number of fixation losses.

1.2.2.4 Background Configuration and Stimulus Generation.

Traditionally, perimeters have presented stimuli on to a flat screen or on to a hemispherical bowl. Flat screens have been used to examine the central visual field only. Examination of the peripheral field requires the use of large hemispherical bowls and hence large perimeters, which occupy large spaces in examination rooms. The Humphrey Field Analyzer (HFA) mark 2 incorporates an aspheric bowl which permits examination out to 60 degrees eccentricity whilst being considerably smaller than the original bowl in the mark I HFA. The Henson 4000 and Henson Pro perimeters have LEDs set into bowls which allow examination of the central 60 degrees. The Dicon and other Henson perimeters have flat screens. The Octopus 1-2-3 perimeter uses a direct projection system in which the stimulus, background illumination and fixation target are projected onto the retina from optical infinity.

Various methods of stimulus generation have been used. These include light-emitting diodes (LED), fibre-optics and projection systems.

Light-emitting diode systems offer a silent, rapid and relatively inexpensive method of stimulus generation. They are physically robust and require little maintenance. Their light intensity is varied by means of high pulse electrical current and they can tolerate high luminances. As LEDs can be independently controlled, multiple and single stimulus strategies can be employed to rapidly evaluate the visual field; as used in the Dicon range of perimeters. However, as each LED acts as separate light source and has a degree of directional dependence they must be individually calibrated and precisely mounted. LED stimuli are limited to predetermined position, size and colour, together with a fixed number of locations. Large numbers of LEDs are required to produce high spatial sampling of the visual

field. The technique of roving fixation has been used to improve the spatial resolution with a constant number of stimuli (see Chapter 5). Unless covered by a diffusing filter when mounted slightly behind the perimeter surface, the LED can produce a "black hole" effect, which can cause localised changes in retinal adaptation (Britt and Mills 1988).

The now obsolete Fieldmaster and Tubinger 2000 perimeters made use of fibre-optics. The advantages of fibre-optics included the use of a single light source, which was channelled to discreet stimulus locations. This enabled luminance and colour to be varied by a single set of neutral density and colour filters in front of the light source. The single light source also simplified calibration. However, fibre-optic systems suffered from similar disadvantages as LED systems, namely fixed locations and stimulus sizes. In addition, fibre-optic systems were more expensive to manufacture.

The Humphrey Field Analyzer and Octopus automated perimeters use the projection method of stimulus generation. A single light source is passed through a series of condensing lenses, apertures and filters and is projected onto the perimeter background via a series of mirrors. This method allows a true increment threshold to be measured. In the Humphrey Field Analyzer, the stimulus luminance is altered by a rotating neutral density filter placed in the light path. Aperture and filter wheels are used to control stimulus size and chromaticity. Stimulus location within the visual field is determined by moving mirrors controlled by stepper motors with a resolution between adjacent stimulus locations of 0.2° (Fankhauser 1979, Heijl 1985). The chief advantage of projection perimeters is the spatial resolution. The accuracy of the stepper motors, and the fact that incandescent light sources change with age, necessitate regular careful calibration of the instruments. This can be accomplished, when the instrument is powered up, by self-calibration routines involving photoelectric cells. The flexibility and accuracy of the projection system is offset by the relative expensive of manufacture and service costs due to their inherent mechanical frailty. A further disadvantage of projection systems is the fact that the stepper motor can provide audible clues or distractions to the subject. The Octopus 1-2-3 perimeter projects a single 592nm

LED onto the retina using a series of mirrors to combine the benefits of LED technology and the projection system.

1.3 Examination Strategies.

1.3.1 The Psychometric Function.

The ability to detect a given stimulus is determined by a number of factors; for example stimulus intensity, size, duration of presentation, colour and background luminance. Any of these parameters can be adjusted to promote or prevent detection of the stimulus. With automated static perimetry, usually the stimulus intensity is altered. As the stimulus intensity is increased, the likelihood of a positive response from the subject increases until it approaches 100%. If stimulus intensity is plotted against probability of a positive response, the psychometric function or a frequency-of-seeing (FOS) curve is generated. This usually has a characteristic, cumulative frequency or sigmoid appearance (Figure 1.2). Threshold is usually defined as the stimulus intensity at which the subject gives a positive response 50% of the time. The curve can usually be described by the integral of a normal Gaussian function, centred on the threshold stimulus intensity. The standard deviation (σ) of the Gaussian function is a measure of the slope of the psychometric function. The slope of the central part of the curve is often used as a measure of response variability. The frequency-of-seeing curve never actually reaches 100% or 0% as the psychometric function is influenced by false-positive and false-negative responses.

The slope of the frequency-of-seeing curve has been shown to demonstrate large between-subject and between-location variation and to be highly correlated with the threshold level (Weber and Rau 1992, Chauhan, et al. 1993, Olsson, et al. 1993). These relationships hold for normals, glaucoma patients and glaucoma suspects. Glaucoma patients can show elevated thresholds with steep, precise curves and 'noisy', flatter curves with near normal thresholds (Chauhan, et al. 1993). Knowledge of the statistical nature of the psychometric function in visual field assessment is essential when designing examination strategies.

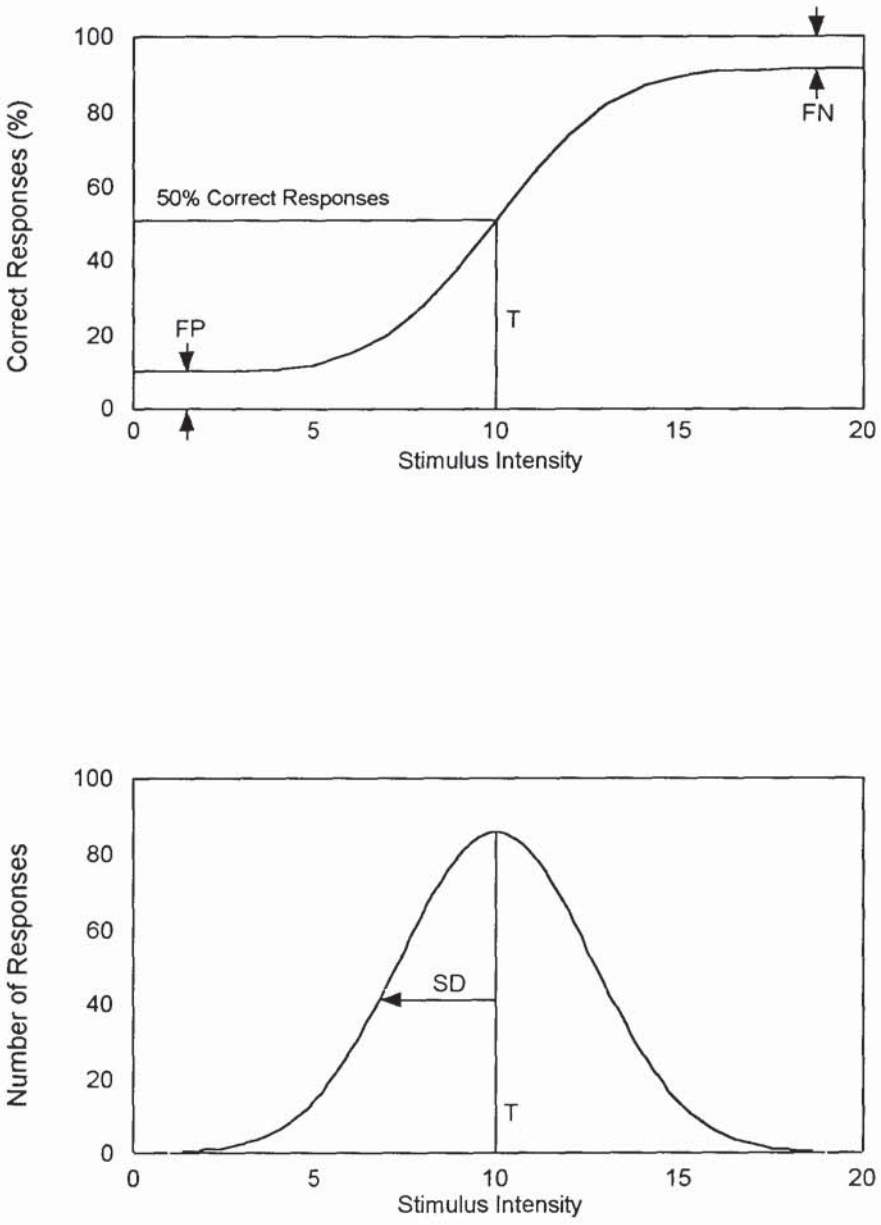


Figure 1.2. (Top) Graphical representation of the classic psychometric function. The curve is the integral of a Gaussian function centred on the threshold value. The threshold value (T) is the stimulus intensity that gives a correct response to 50% of the presentations. FN is the percentage of false negative responses. FP is the percentage of false positive responses. (Bottom) Distribution of the number of responses around the threshold value. SD is the standard deviation of the Gaussian function and is a measure of the slope of the psychometric function and hence an estimate of measurement variability.

1.3.2 Screening Strategies.

Generally, screening of the visual field is done to confirm normality in a population expected to be predominantly normal. By using supra-threshold stimuli which the subject is expected to see, the visual field can be quickly assessed at a large number of locations. Locations at which the stimuli are not seen can then be further investigated if required. Supra-threshold strategies fall into three main categories.

A single intensity strategy presents a single intensity stimulus at all locations in the test pattern. However, as the sensitivity of the visual field decreases with eccentricity, stimuli that will be close to threshold in the periphery will be more easily seen centrally.

A Gradient Adapted strategy attempts to account for the decline in sensitivity with visual field eccentricity. This is done by either making the stimulus brighter or of greater size and is a better suprathreshold strategy for detecting focal loss (Keltner, et al. 1979).

However, there exists a large inter-individual variation in the normal hill of vision. Therefore, a further refinement of visual field screening is to use a Threshold Related Gradient Adapted strategy. The threshold is determined at one or more central locations and this is used to determine a generalised model for the expected hill of vision. Screening of further locations is then performed at a predetermined level (usually 4 to 6 dB) brighter the expected values. Consistently missed stimuli can then be re-assessed with brighter stimuli, to ascertain an idea of defect depth, or indeed, the points can have the threshold estimated with a more detailed strategy. The latter procedure is employed by the Automatic Diagnostic Test of the Humphrey Field Analyzer (Haley 1987) and the Quantify Missed Points program on the Dicon LD400 Autoperimeter.

1.3.3 Threshold Estimation Strategies.

The alternative to screening for deviations from normal is to estimate the actual thresholds in more detail and then to compare the measured thresholds with a database of normal values. Most modern automatic perimeters use a sequential 'up-down' staircase procedure

(Cornsweet 1962) to estimate the threshold at each individual location. The full staircase requires several, time-consuming 'reversals' of the change in direction of the stimulus presentation (i.e. from seeing to non-seeing or from non-seeing to seeing) and is abbreviated in clinical perimetry. The sizes of step change in stimulus intensity, the starting point and endpoint of the staircase vary between different threshold algorithms. A new generation of threshold estimation algorithms have been developed, which make use of prior knowledge of normal and glaucomatous fields and sophisticated computation during the examination. Threshold estimation strategies will be discussed further in Chapters 3 and 4.

1.3.4 Stimulus Locations.

The ability of any program to detect visual field loss is also dependent upon the number, and spatial location, of the stimulus locations tested. Therefore, a large number of points with a small separation between them will represent the ideal, theoretical arrangement for the detection of visual field defects. However, this will increase the examination duration.

The prevalence of isolated peripheral field defects has been shown to be low at 0.5% (Ogawa and Suzuki 1979) and 0.8% (Blum, et al. 1959). Visual field loss in glaucoma occurs primarily in the central visual field and most routine static perimetry is confined to this area. Three possible alternatives to stimulus arrangement exist: systematic sampling by evenly spaced stimuli, higher density of sampling in high risk areas of the field, or a combination of both (Gutteridge 1984).

Greve (1975) has shown that a theoretical, circular defect with a diameter of 9° has a 95% probability of detection when 50 locations are evenly distributed out to 30 degrees eccentricity. With 100 locations, a defect of 7.5 degrees diameter has a 100% chance of detection. The probability of detection decreases as defect size decreases, when the number of stimuli remains constant. Greve reports that 452 stimuli are required to detect a 3 degrees diameter defect with 95% confidence. However, since most defects are not likely to be circular, and hence easier to detect with an even grid, 150 locations would be the optimal arrangement (Greve 1975). Any increase in the number of locations produces no significant

improvement in the detection of clinically significant field loss (Johnson and Keltner 1981). The spatial arrangement of Octopus Programs 31 and 32 and Humphrey Field Analyzer Programs 30-1 and 30-2, an even grid with a separation of 6 degrees, has the ability to detect an 8.4 degrees diameter and a 6 degrees diameter defect with probabilities of 100% and 79% respectively (Fankhauser and Bebie 1979).

As the number of stimulus locations increases, the sensitivity of the visual field screening increases in a logarithmic relationship, and the specificity of the test increases in a linear relationship (Henson, et al. 1988). Non-uniform arrangement of stimuli, concentrated in susceptible regions of the field, with a greater number of stimuli paracentrally and in the nasal field, have been used in the design of stimulus programs (e.g. Armaly screening pattern, 40 or 80 stimulus locations set on concentric circles). The G1X and G2 programs on the Octopus 1-2-3 perimeter uses such a non-uniform test pattern in which the central stimuli are separated by 2 degrees increasing to 8 degrees at an eccentricity of 55 degrees (Flammer, et al. 1987). Another method of increasing the spatial resolution of the sample is to combine two complimentary grids such as the Programs 30-2 and 30-1 grids of the Humphrey Field Analyzer. However, it is more desirable to repeat the examination with a single grid than to combine the two grids (Weber and Diestelhorst 1992, Heijl 1993).

Increasing the number of stimulus locations corresponds to an increase in the spatial resolution and to a longer test duration. A further way to increase the sensitivity of visual field testing is to use a spatially adaptive technique, in which spatial resolution is increased locally in areas that have shown a defect at a generally lower resolution. The increased resolution can be done manually, as in the Henson series of visual field screeners, or by automation, as with the SAPRO and Automatic Diagnostic Test strategies for the Octopus and Humphrey perimeters, respectively. SAPRO increased resolution in three steps in the presence of abnormality determined by the coarser grids (Haeberlin and Fankhauser 1980). The Automatic Diagnostic Test procedure increases the grid resolution locally, from 6 degrees to 3 degrees, when the first and second presentations are missed at 6 dB above threshold.

Both procedures increase the test duration, and there is no significant increase in test sensitivity or specificity with the fine grids over the coarse grids (Asman, et al. 1988).

1.4 Reliability Parameters.

Due to the demanding nature of automated perimetry, the reliability of the subjective responses of the patient must be assessed during each examination. Patient reliability has been traditionally assessed by performing specific catch trials for false-positive and false-negative responses and for assessing the accuracy of fixation. The evolution of perimetric threshold strategies has produced algorithms that use more sophisticated methods of estimating the reliability of each individual's responses.

1.4.1 False Positive and False Negative Responses.

By making the audible sounds associated with a stimulus presentation, but not actually presenting a stimulus, the perimeter checks for false-positive responses. If the patient responds to one of these catch trials, the response is recorded as a false-positive, and is indicative of inattentive, over-eager or anxious behaviour. Conversely, the perimeter will occasionally present a supra-threshold stimulus at a location where the threshold is known. Failure to respond to the brighter stimulus results in a false-negative response being recorded. When the number of false-positive or false-negative responses exceed 33% of their respective total number of catch trials, an unreliable response is indicated. The sensitivity and specificity of the test is reduced with this level of false responses (Sanabria, et al. 1991).

A high percentage of false-positive responses frequently give rise to a higher mean sensitivity and a better mean deviation and mean defect both in normals (Katz and Sommer 1990, Cascairo, et al. 1991, Demirel and Vingrys 1995) and in glaucoma (Katz and Sommer 1990). A lower mean sensitivity and a worse mean deviation and mean defect is frequently associated with a higher percentage of false-negative responses (Katz and Sommer 1990, Cascairo, et al. 1991, McMillan, et al. 1992). A higher level of false-negative responses have been shown to occur in glaucoma (Katz and Sommer 1988, Reynolds, et al. 1990, Katz, et

al. 1991b, Johnson and Nelson-Quigg 1993). Whereas, a higher level of false-positive responses are seen in perimetrically inexperienced subjects (Bickler-Bluth, et al. 1989, Sanabria, et al. 1991). A high level of false-responses is also correlated with a higher pattern standard deviation in normal subjects (Katz and Sommer 1990, Cascairo, et al. 1991). Short-term fluctuation is greater when false-positive rates are over 33%, and lower when false-negative responses are over 20% (Cascairo, et al. 1991).

The use of specific catch trials to investigate the reliability of response means that additional stimulus presentations are required which are not used in the estimation of threshold. The extra presentations result in increased test duration. In order to limit the test duration, the number of catch trials is reduced to a level that may not accurately estimate the true level of false-responses (Katz, et al. 1991b). Other methods of false-response estimation which require few, if any, specific catch trials have been developed. A heuristic test procedure, MOBS, estimated subjective reliability as a function of the number of locations at which patient inconsistency necessitated the re-evaluation of threshold (Johnson and Shapiro 1991). A maximum likelihood technique, which utilises the complete data set of responses from the staircase procedure, to estimate false-positive and false-negative response rates has been described by Olsson et al (1988). The technique does not require specific catch trials in normal subjects and enables a 50% reduction of catch trials in subjects with visual field loss (Olsson, et al. 1988). The use of all positive and negative responses, to all stimuli, together with real time 'listening' for false-positive responses during the test are used as measures of reliability in a new generation of threshold algorithms discussed further in Chapters 3 and 4.

1.4.2 Fixation Losses.

In order to ensure that the desired location in the visual field is examined, the patient must maintain steady fixation. Variations in the patient's point of fixation will result in the averaging of a larger area of receptors than expected. Fixation can be monitored, most basically, by the operator physically viewing the patient's eye with a telescope or video camera integral to the fixation target. An additional method is the Heijl-Krakau method (Heijl and Krakau 1975b,

Heijl and Krakau 1977), in which a bright stimulus is presented within the boundaries of the physiological blind spot. A positive response to such a presentation results in a fixation error being recorded. The accuracy of this technique is dependent upon a number of factors, such as the correct initial estimation of the position of the blind spot (Sanabria, et al. 1991). Reductions in precision are likely to occur in the case of a large blind spot, either natural or one enlarged through disease (Fankhauser 1993). Conversely, a small optic disc or light scatter from the optical media or from the disc itself may result in the perception of the stimulus and hence an inaccurate fixation error recorded by the perimeter (Fankhauser 1993). A patient with a tendency for false-negative responses may miss a fixation error trial and thus disguise poor fixation (Fankhauser 1993, Henson and Darling 1995). In addition, a patient with a high rate of false-positive responses may respond to a fixation error trial whilst maintaining very good fixation. False-positive responses have been shown to account for 7% of subjects with poor fixation estimates (Sanabria, et al. 1991). With Program 30-2 of the Humphrey Field Analyzer, approximately 10% of the total number of stimulus presentations are fixation error trials (Katz and Sommer 1988). The small number of fixation error trials indicates the limitation of the technique due to the limited sampling of fixation.

A fixation error rate of over 20% is generally assumed to indicate an unreliable test (Haley 1987). At this rate, fixation losses account for the cases of poor reliability (Katz and Sommer 1988, Bickler-Bluth, et al. 1989, Katz, et al. 1991b, Johnson and Nelson-Quigg 1993, Birt, et al. 1997). It has been suggested that the acceptable rate of fixation losses should be increased to 33% (Katz and Sommer 1988, Johnson and Nelson-Quigg 1993, Birt, et al. 1997).

The Octopus perimeters continually monitor fixation using four infrared corneal reflexes, two on either side of the pupil equator (Octopus 1-2-3 operating instructions, 1990). Prolonged closure of the eyelids or significant deviation of fixation results in a temporary pause in the program until the problem is rectified.

The Humphrey Field Analyzer II "gaze tracking" system uses infra-red light to monitor the distance from the position of the first Purkinje image relative to the centre of the pupil (Humphrey Field Analyzer II user's guide, 1994). This distance is unaffected by lateral head movement. A Gaze Graph is produced, which consists of a series of vertical spikes deviating from a line of origin. Upward spikes indicate a loss of fixation and downward spikes indicate a blink or that the system was unable to detect the position of gaze. The gaze tracking system may be adversely affected by excessive lacrimation or by reflections from high-powered trial lenses.

1.5 Threshold Fluctuation.

Due to a large number of factors, threshold estimation suffers from both within- and between-test variation.

1.5.1 Short-Term Fluctuation.

The precision, or measurement error, of the threshold estimation within a visual field examination is estimated by calculating the Short-term Fluctuation (SF) (Bebie, et al. 1976a, Flammer, et al. 1984b). The SF is the root mean square (RMS) of the differences between threshold estimations at each location with multiple estimations. The Octopus perimeter assumes a constant variance at all locations and expresses the SF as:

$$SF = \sqrt{\frac{1}{m}\sum_{i=1}^{m}(SD_i)^2}$$

where, m is the number of locations, i is the test location, and SD_i is the standard deviation of the threshold estimates at location i (Flammer 1986). However, the SF varies with eccentricity (Brenton and Phelps 1986), being up to 27% greater at four peripheral points than at the six most central locations (Heijl, et al. 1987a). The Humphrey Field Analyzer takes in to account the variation of SF with eccentricity and calculates a weighted SF using the expression:

$$SF = \sqrt{\left\{\frac{1}{10}\sum_{j=1}^{10} s_{2j}{}^{2}\right\} \cdot \left\{\frac{1}{10}\sum_{j=1}^{10} \frac{(X_{i1} - X_{i2})^2}{2\left(s_{2j}{}^{2}\right)}\right\}}$$

where, X_{i1} is the first and X_{i2} is the second threshold estimate. The normal within-test variance at location i is denoted by $s_{2j}{}^{2}$. Weighting with $1/s_{2j}{}^{2}$ minimises the SF in normal individuals (Heijl, et al. 1987b) and slightly reduces SF in glaucoma patients (Flanagan, et al. 1993c). The unweighted SF demonstrates a positively skewed distribution in a normal population (Flammer, et al. 1984a), and is approximately 0.3 dB greater with the Octopus compared with the HFA (Brenton and Argus 1987).

SF has been shown to be independent of background intensities in the low photopic range used in most perimeters (1.3 cdm^{-2} and 10 cdm^{-2}), but to increase with mesopic illumination, at or less than 0.1 cdm^{-2} (Crosswell, et al. 1991). Smaller stimulus sizes result in a larger SF, compared with Goldmann size III (Gilpin, et al. 1990). Conversely, size V stimuli produce steeper FOS curves and hence reduced variability in threshold estimation (Wall, et al. 1997). SF is unaffected by changes in stimulus duration (Pennebaker, et al. 1992). The SF is dependent upon the strategy used to estimate threshold (Bebie, et al. 1976a, Flanagan, et al. 1993a, Flanagan, et al. 1993b, Weber and Klimaschka 1995).

Natural pupil size has little effect on the magnitude of the SF (Flammer, et al. 1984a, Rebolleda, et al. 1992). Reduced pupil diameter, due to pilocarpine treatment in glaucoma patients, results in a slight increase in the SF (Flammer, et al. 1984a). Increasing age may (Haas, et al. 1986, Chauhan, et al. 1990b) or may not (Flammer, et al. 1984a) be associated with a greater SF. Patient fatigue increases the SF (Marra and Flammer 1991, Wild, et al. 1991, Hudson, et al. 1994) and perimetric experience decreases the SF (Werner, et al. 1988, Heijl, et al. 1989c, Wild, et al. 1989b, Werner, et al. 1990, Searle, et al. 1991). Patients with high false-response rates also demonstrate a higher SF (Flammer, et al. 1984a, McMillan, et al. 1992).

Flammer et al (1984) proposed that SF was independent of stimulus eccentricity. Most studies, however, have found that SF increases with eccentricity (Greve and Wijnans 1972, Werner and Drance 1977, Brenton and Phelps 1986, Heijl, et al. 1987a). Greater values of SF are seen in regions of the visual field with reduced sensitivity (Holmin and Krakau 1979, Flammer, et al. 1984b, Liao, et al. 1988). In glaucoma patients, the SF is greater in areas with apparently normal visual function, especially at the borders of a scotoma (Flammer, et al. 1984b). In the presence of slight fixation losses, threshold determination at the border of a scotoma may include some responses from within and some responses from outside the scotoma (Henson and Bryson 1991, Vingrys and Demirel 1993).

The number of stimulus locations used in the calculation of the SF has a direct consequence on the magnitude of the estimated variance. The Octopus G1X and G2 programs use data from the double determination of threshold at all 59 locations. The Humphrey Field Analyzer central field programs estimate the SF from the double determination of threshold at ten predetermined locations. However, the use of ten locations provide an estimation of SF with an accuracy of only plus or minus 25% (Bebie, et al. 1976a). Indeed, using ten locations in the calculation significantly underestimates the SF in glaucoma patients, and therefore, using all available double determinations of threshold would be more representative of the 'true' estimation (Flanagan, et al. 1993c). The estimation of the SF for more repeats of threshold estimation at fewer locations is more consistent by computer simulation than fewer repeats at a large number of locations. Nevertheless, a good spatial sampling of the visual field is required; ideally five threshold estimations at four stimulus locations is optimal (Casson, et al. 1990). However, no significant difference in global SF has been found when estimated from two repetitions at 19 locations through various combinations to 15 repetitions at two locations (Chauhan, et al. 1991).

Image processing of the raw data from a single visual field examination can provide an estimation of measurement variability (Schulzer, et al. 1990, Crabb, et al. 1995). Schulzer et al (1990) investigated a series of three Humphrey Field Analyzer Program 24-2 visual fields by fitting polynomial surfaces to the visual field data, from each examination, and calculating

the variance of the residual deviations of each measured threshold from the estimated surface. The estimation of fluctuation by this method is affected less by aberrant estimations of threshold at one or two locations and is claimed to be more precise than the conventional method of double determination at ten pre-selected locations.

Crabb et al (1995) calculated the mean difference, for the central 36 stimulus locations of Program 30-2, between the measured thresholds and those computed following an image filtering technique. This value of local spatial variability (LSV) was found to be significantly correlated with the SF obtained from the 10 standard stimulus locations. The value of LSV was derived from more locations than the conventional SF estimation and required no repetition of threshold estimation. However, the calculations by Crabb et al (1995) used visual fields in which double determinations of thresholds occurred and hence may affect the image processing results.

1.5.2 Long-Term Fluctuation.

The Long-term Fluctuation (LF) is the variability in threshold over a series of examinations when SF, learning effects and age have been taken into account (Bebie, et al. 1976a, Flammer, et al. 1984b). The LF consists of two components. The homogenous LF (LF_{Ho}) describes the constant variation in threshold over the whole visual field, whereas, the heterogeneous LF (LF_{He}) describes variation which occurs in localised areas of the field. LF_{Ho} may be considered as the fluctuation of Mean Sensitivity or Mean Defect/Deviation over time, whilst LF_{He} represents localised fluctuation (Zulauf, et al. 1991). LF has also been considered to consist of a single component (Heijl, et al. 1987a, Katz and Sommer 1987, Boeglin, et al. 1992).

The magnitude of the components of LF are generally smaller than the SF. Values for LF_{Ho} of 0.5 dB^2 and for LF_{He} of 0.2 dB^2 have been demonstrated in normal subjects (Flammer, et al. 1984b). The same study showed a significantly higher value of LF_{Ho} in patients with suspect glaucoma and patients with glaucoma. LF_{He} was only found to be significantly greater in patients with established glaucoma. An increase in LF with increasing stimulus

eccentricity has been shown in normals (Heijl, et al. 1987a, Rutishauser and Flammer 1988) and in glaucoma patients (Zulauf, et al. 1991, Boeglin, et al. 1992). The relationship between LF and age is equivocal (Heijl, et al. 1987a, Katz and Sommer 1987). Flammer et al (1984) showed a correlation between LF_{Ho} and LF_{He}. LF has been shown to be correlated with SF (Flammer, et al. 1984b). However, the magnitude of the LF_{Ho} and LF_{He} have been shown to be in the order of 2.8 dB^2 and 3.4 dB^2, respectively (Hutchings, et al. 1993). Hutchings et al (1993) also demonstrated little correlation between the magnitude of the LF and SF.

1.6 Presentation of Results.

A number of different methods of data display have been developed to illustrate the location and severity of visual field loss.

1.6.1 Numerical Presentation.

The simplest method of display is to present the estimated threshold values in a tabular form corresponding to the spatial arrangement of the stimulus locations. The disadvantage of this simple presentation is that it is difficult to interpret such data in a meaningful way.

1.6.2 Graphical Presentation

1.6.2.1 Greyscale.

The Greyscale is a qualitative representation of the raw data with the intention of making interpretation easier. The sensitivity values are usually grouped into bands of 5 dB and each band displays a grey tone, with each tone becoming darker as the sensitivity band successively decreases in magnitude. Different perimeters have a different greyscales due to the differences in their maximum stimulus luminances and their dynamic ranges. The regions of the visual field that do not correspond with a stimulus location are represented on the greyscale by interpolation. Interpolation may be performed by taking the mean of the neighbouring four locations (Fankhauser and Bebie 1979), by linear calculations parallel to the x and y axes of the grid (Weber and Geiger 1989) or a combination of both. Weber and

Geiger (1989) suggested that the linear interpolation gives a smoother outline to the borders of scotoma but that mixed interpolation is better for research purposes.

A greyscale printout is easy to read, but easy to miss-interpret, as the interpolation between points gives the impression there is more date than there actually is (Heijl 1984). In common with most graphical displays, the greyscale is a poor representation of diffuse field loss (Flammer 1986). In addition, greyscales are not corrected for age which, for example, may complicate prolonged follow-up of large numbers of serial fields. It is also theoretically possible for a significant defect to be present in the numeric data but not revealed in the greyscale because it occurs within a single grey tone.

1.6.2.2 Three-Dimensional and Profile Plots.

The visual field can be represented qualitatively by a three-dimensional hill of vision plot. Interpretation can be difficult, as sharp depressions and sections on the opposite side from which the 'hill' is viewed, can be obscured by sharp elevations elsewhere. Computer simulations can rotate the hill and overcome some of these problems (Hart and Hartz 1982). In addition, differences in grid resolution and sensitivity scales prevent direct comparison between three-dimensional plots (Wild, et al. 1987). The results can also be expressed as profile plots along a selected meridian, simulating a cross-sectional view of the hill of vision. Again, regions between direct measurements are interpolated (Whalen 1985).

1.6.3 Analytical Presentation.

1.6.3.1 Probability Plots

At each stimulus location, the difference (or total deviation) between the measured sensitivity and the age-matched normal value of sensitivity is determined. Each deviation is compared to the distribution of deviations in the normal eye at that location and the probability that the deviation is normal is then calculated. For early probability plots, Gaussian distributions of deviations were assumed to apply at each location (Schwartz and Nagin 1985). However, Gaussian functions become less suitable to describe the distributions as the eccentricity of the location increases (Brenton and Phelps 1986, Heijl, et al. 1987a). Empirically derived

probability distributions improved the sensitivity and specificity of probability plots, in normals, by up to 10% in the mid-periphery (Heijl and Asman 1989). However, the distributions of deviations in short-wavelength automated perimetry (SWAP) can be described by a Gaussian function out to an eccentricity of 24 degrees (Wild, et al. 1995). The Total Deviation plot from the Humphrey Field Analyzer shows the numeric deviations from normality at each location, and, also graphically represents four levels of probability of normality (<5%, <2%, <1% and <0.5%) with a non-interpolated greyscale. Darker symbols represent a decreasing likelihood of normality. The same type of analysis, numerical and statistical significance of the deviation from age-matched normal values, is present on the Seven-in-One Report of the Octopus as the Comparison Probability plot.

The existence of diffuse visual field loss due to glaucoma is equivocal (Langerhorst, et al. 1989, Asman and Heijl 1994a, Chauhan, et al. 1997). However, the visual field may show an overall depression due to other factors. The Total Deviation plots may hide focal field loss (Haley 1987, Heijl, et al. 1987b, Heijl and Asman 1989) especially if cataract is also present (Bengtsson, et al. 1997a). The Pattern Deviation plot, for the Humphrey Field Analyzer, was designed to remove individual variations in overall height of the hill of vision. General elevation or depression of the visual field is estimated by ranking the deviations in ascending order of deviation from age-matched normal values. Visual field locations at an eccentricity greater than 24 degrees and above and below the blind spot are excluded from this analysis. The highest ranked deviations are assumed to be unaffected by focal loss. Thus, the measured visual field is adjusted for overall height variation by adding the value of the seventh (85th percentile) rank to all locations (Heijl and Asman 1989). The removal of a generalised elevation or depression in the statistical analysis of Octopus visual field data is presented as the Corrected Probability graph on the Seven-in-One report.

1.6.3.2 Glaucoma Hemifield Test

Early glaucomatous visual field defects usually initially occur in isolation in one hemifield (Drance, et al. 1979, Hart and Becker 1982, Mikelberg and Drance 1984). Hemifield analyses of visual field data have been proposed as identifiers of glaucomatous damage (Duggan, et al. 1985, Sommer, et al. 1987, Asman and Heijl 1992b). The advantage of this

system is that the individual field provides its own reference level. The Glaucoma Hemifield Test (GHT) for the Humphrey Field Analyzer (Asman and Heijl 1992a, Asman and Heijl 1992b) compares the pattern deviation probability values in five clusters of locations in the superior hemifield with their mirror images in the inferior field. The clusters of between 3 and 6 locations were chosen to correspond with the arrangement of the retinal nerve fibre layer. Scores for each cluster are calculated using the Statpac pattern deviation probability values at each stimulus location. The sum of probability scores in each cluster, and the differences between mirror image clusters are determined. 'General reduction in sensitivity' and 'abnormally high sensitivity' are determined using the same method as used for correcting overall height changes when determining the pattern deviation plots. Different levels of significance between- and within-mirrored clusters denote the field 'outside normal limits', 'borderline' or 'within normal limits'. Colour coding of the GHT results has been introduced to indicate diffuse or localised field loss (Asman 1995).

As a measure of repeatability, Katz et al (1995) showed that 17.1% of normal subjects had different GHT results between two field tests separated either four months or one year apart. Twenty percent of a sample of ocular hypertensive and 9.5% of a sample of glaucoma patients, in whom the presence or absence of field loss was defined by manual perimetry, gave two different GHT results over the same time period. The use of a single GHT correctly excluded 84% of glaucomatous visual fields from an ocular hypertensive study. This specificity was improved to nearly 90% if two abnormal GHT results were required. However, 10% of patients with established manual field loss demonstrated two consecutive normal GHT results. If two abnormal GHT results were required to define glaucomatous field loss the specificity was almost 90% compared with 81% if a single abnormal GHT was used as the definition. Thus, 10% of ocular hypertensive patients would have been included as having glaucomatous visual field loss where none existed on manual perimetry. This may be because visual field loss can be present with automated static perimetry at least one year prior to detection by manual kinetic perimetry (Katz, et al. 1995b). There was good consistency in the locations deemed defective by the GHT over repeat testing. However, the

improved specificity of testing twice would suggest the use of repeat testing to accurately define visual field normality or abnormality (Katz, et al. 1995a)

Investigation of the predictive value of the GHT has shown that for eyes defined as abnormal with a single abnormal GHT, 59% will be confirmed to be abnormal by the same technique 3 years later. If two consecutive abnormal GHTs are used, confirmed abnormal fields occur in 84% of patients and 89% show confirmed abnormality 3 years later if three consecutive GHTs are used (Katz, et al. 1996). It is therefore inappropriate to rely on a single abnormal GHT to identify incident field loss and three abnormal GHT results give only a slightly better confirmation than two GHT results. The use of hemifield analysis should not be used in exclusion of the other analytical information available on a visual field printout or relied upon to provide information on the progression of visual field defects (Katz, et al. 1991a).

1.6.3.3 Bebié Curve

In order to differentiate diffuse from localised visual field loss, a cumulative defect curve, or Bebié curve, has been suggested for use in visual field interpretation (Bebie, et al. 1989). The defect values at all individual stimulus locations are plotted in ascending order as a function of rank order. Larger defects appear on the right hand side of the curve. A series of curves showing the 5th, 95th and 99th percentiles of the age-matched normal data are also shown. Significant defects are therefore represented by points below the 95th or 99th limits. Visual field results that produce a defect curve below the 95th or 99th percentiles with a similar slope to the 'normal' curves indicate diffuse loss. Localised loss is indicated by a steep fall of the curve out of the normal range. Combined diffuse and localised loss is represented by a curve that falls below the normal range but with a steeper slope. The differentiation between diffuse and localised loss is often ambiguous (Funkhouser, et al. 1992). As the spatial characteristics of any visual field loss are lost when forming the Bebié curves (Asman and Olsson 1995), visual field interpretation should also include the use of spatial displays (Kaufmann and Flammer 1989).

In order to examine the effect of the loss of spatial information, Asman and Olsson (1995) investigated the eccentricity of the locations that gave the largest defect on the Bebié curve in both a normal and a glaucomatous population. They found that in normal subjects, the most depressed ranks were to be found in the more peripheral part of the Humphrey Field Analyzer Program 30-2 visual field. In glaucomatous visual fields, the most depressed ranked points were often generated from locations within central or paracentral scotoma. The deviations in the glaucoma group were often inside the level of statistical significance as they were compared to locations in the normal visual field associated with a high degree of normal variability. In conclusion, Bebié curves were limited in their use since typical central scotomas in glaucoma, that is a small diameter scotoma close to fixation deviating only slightly from the normal age-matched value, may be camouflaged by larger normal variations from peripheral locations.

1.7 Global Statistical Analysis

Visual field indices were developed as an aid to the differentiation between normal and abnormal visual fields by reducing the large amounts of numerical data into single summary statistics (Bebie 1985, Flammer 1986, Heijl, et al. 1987b). The graphical methods of data display do not allow the easy definition of either diffuse loss or of change over a series of visual fields. Various visual field indices have been developed for the Octopus (Flammer 1986) and the Humphrey Field Analyzer (Heijl, et al. 1987b) perimeters. Indices for the Humphrey Field Analyzer incorporate a weighting function in order to allow for the variation in sensitivity across the visual field within- and between-subjects. The use of the weighting function in the calculation of the indices gives more influence to the central locations of the test grid as opposed to the more peripheral locations.

1.7.1 Mean Sensitivity.

Mean Sensitivity (MS) represents the arithmetic mean of the measured sensitivities at all stimulus locations within the visual field. MS has the advantage of not requiring any normal

values for its calculation. MS is influenced by diffuse changes and is not influenced greatly by small areas of localised loss (Flammer 1986). MS can be defined as

$$MS = \frac{1}{n}\sum_{i=1}^{n} X_i$$

Where, n is the number of stimulus locations and, X_i is the result of a threshold estimation at location i.

1.7.2 Mean Defect and Mean Deviation.

Mean Defect (MD_O) is the arithmetic mean of the differences between the measured sensitivity and the normal value at each stimulus location. Mean Defect is similar to MS but the comparison with a normal reference field allows easier interpretation as a value of zero indicates normality and a positive value indicates a depressed visual field (Flammer 1986). A more positive value indicates a poorer visual field. Mean Defect can be defined as

$$MD_O = \frac{1}{n}\sum_{i=1}^{10} (N_i - X_i)$$

where, N_i is the age-corrected normal sensitivity value at location i.

Mean Defect is analogous to the Mean Deviation (MD) index for the Humphrey Field Analyzer. MD is defined as

$$MD = \frac{\left\{\frac{1}{n}\sum_{i=1}^{10} \frac{(X_i - N_i)}{s_{1i}^{\,2}}\right\}}{\left\{\frac{1}{n}\sum_{i=1}^{10} \frac{1}{s_{1i}^{\,2}}\right\}}$$

Where, $s_{1i}^{\,2}$ is the variance of normal thresholds at location i. Mean Deviation becomes more negative as the visual field worsens.

The model of the normal visual field used by the Octopus perimeter assumes a uniform change in sensitivity of 0.1 log unit per decade. This model assumes that the shape of the normal hill of vision remains constant throughout life and that each location within the field exhibits the same degree of within-individual variation. The model of normal sensitivity used by the Humphrey Field Analyzer takes in to consideration the greater degree of variation in sensitivity in the mid-peripheral locations of the visual field (Heijl, et al. 1987b). This latter model is based on empirical data and allows the normal hill of vision to vary in both height and shape with age.

The effect of the weighting factor on the magnitude of visual fields indices has been debated (Funkhouser and Fankhauser 1991, Asman and Heijl 1992c, Heijl, et al. 1992, Flanagan, et al. 1993c). When the fact that the two indices have a different sign is taken into account, no significant difference has been found between the unweighted mean defect and the weighted mean deviation for the Octopus (Funkhouser and Fankhauser 1991) or for the Humphrey Field Analyzer (Flanagan, et al. 1993c) in glaucomatous visual fields. Funkhouser and Fankhauser (1991) also suggested that weighting for the normal fluctuation in responses might ignore fluctuation in the mid-periphery arising from abnormality.

Heijl et al (1992) argued that weighting the MD does not produce a major change in magnitude but does improve the accuracy of the index. The reason for the absence of a difference, found by Funkhouser and Fankhauser (1991), was due to the use of a flatter distribution of variability in the weightings compared with the distribution used by Heijl et al (1987). Heijl et al (1992) also noted that the dependence of stimulus location on threshold variability meant that weighting was more important for interpretation of sensitivity at individual stimulus locations and for perimetric hemifield analyses.

Flanagan et al (1993) found that the Humphrey Field Analyzer programs 30-2 and 24-2 produced similar indices and that the weighting function produced slightly elevated pattern and corrected pattern standard deviations compared to the non-weighted values of these

indices. Asman and Heijl (1992) showed that weighted versions of hemifield and cluster analyses gave a higher level of sensitivity and specificity than the unweighted analyses.

1.7.3 Loss Variance and Pattern Standard Deviation.

The Loss Variance (LV) index for the Octopus perimeter calculates the variance of the localised departures from the age-matched normal values. LV is expressed in dB^2 and is defined by:

$$LV = \frac{1}{(n-1)} \sum_{i=1}^{n} (N_i - MD_O - X_i)^2$$

The analogous index for the Humphrey Field Analyzer is the Pattern Standard Deviation (PSD). Again the PSD, expressed in dB, is a weighted index and is described by:

$$PSD = \sqrt{\left\{ \frac{1}{n} \sum_{i=1}^{n} {s_{1i}}^2 \right\} \cdot \left\{ \frac{1}{n-1} \sum_{i=1}^{n} \frac{(X_i - N_i - MD)^2}{{s_{1i}}^2} \right\}}$$

Weighting with ${s_{1i}}^2$ optimises PSD in normal subjects but increases the value in patients with glaucoma (Flanagan, et al. 1993c).

These indices are an indication of the non-uniform change in shape of the visual field. Normal visual fields and fields with shallow localised defects produce a low positive value of LV and PSD, whereas, fields with deep defects produce a high positive value. The magnitudes of the LV and PSD are increased in the presence of a high SF. Therefore, visual fields with increased values of LV and PSD should be examined to investigate whether the field has an early defect or a high degree of variability (Flammer 1986).

An image processing technique that does not require the use of normal data has been used to investigate localised changes in the shape of the hill of vision (Crabb, et al. 1995). The root mean square of the difference between the measured sensitivity value and the filtered

value at each location over the whole visual field is assumed to describe the Local Spatial Variability (LSV). LSV and PSD are significantly correlated.

1.7.4 Corrected Loss Variance and Corrected Pattern Standard Deviation.

The Corrected Loss Variance separates the variance due to visual field loss from that due to the SF. CLV is expressed in dB^2 and is defined by:

$$CLV = LV - \frac{1}{n}(SF)^2$$

CLV has been shown to significantly co-vary with MD_O in subjects with early to moderate glaucomatous visual field defects, defined as MD_O less than 18 dB (Pearson, et al. 1990). The use of a different index, described by $(CLV)^{-0.5} - MD_O$, has been advocated to differentiate between the severity of glaucomatous visual field loss (Gollamundi, et al. 1988).

The Humphrey Field Analyzer Corrected Pattern Standard Deviation (CPSD) index is analogous to CLV. It is described by:

$$CPSD = \sqrt{PSD^2 - k * SF^2}$$

Where k is a constant greater than one, and is used to compensate for the non-uniform spatial arrangement of the SF estimate. CPSD is never assigned a value less than zero because although the estimates may be less than zero, variances are never negative.

1.7.5 Third Central Moment and Skewness

The Third Central Moment (M3) of the distribution of deviations from age-corrected normal values is sensitive to deviations at a small number of locations. This is due to a cubic function within the calculation of M3. The M3 index, in dB^3, is described by the equation:

$$M3 = \frac{1}{n}\sum_{i=1}^{n}(N_i - MD - X_i)^3$$

Skewness (Q) is a standardisation of M3 with respect to LV and has been proposed as better index to identify locations in which the threshold deviates from the expected value (Brechner and Whalen 1984). Q is expressed by:

$$Q = \frac{M3}{\sqrt{(LV)^3}}$$

The Q statistic is more effective with very early defects and in visual fields with low variability. The Q statistic is less effective in the presence of larger defects and with diffuse loss. Therefore, in glaucoma suspects and in patients with glaucoma, high variability in threshold estimation and advancing visual field loss may render the Q statistic of little or no use (Pearson, et al. 1989).

1.7.6 Spatial Correlation and Cluster Analysis

Two or more adjacent abnormal stimulus locations constitute a cluster (Chauhan, et al. 1989b). For use in the detection of glaucoma, clusters can be defined as adjacent stimulus locations that correspond with the spatial arrangement of the retinal nerve fibre layer (Asman, et al. 1992). The Spatial Correlation (SC) index can be described as the average value obtained by multiplying the mean defect at each location by the defect value at each of the adjacent locations (Bebie 1985). Mathematically, SC is expressed as:

$$SC = \frac{1}{p}\sum_{(ij)}(N_i - MD - X_i)\cdot(N_j - MD - X_j)$$

where p is the number of pairs of stimulus locations (ij) used in the calculation. SC is low when abnormal locations are widely distributed throughout the visual field and high if defects are clustered.

The basis of cluster analysis is the low probability of two or more adjacent abnormal stimulus locations being present in a normal visual field (Chauhan, et al. 1989a, Chauhan, et al. 1989b, Heijl, et al. 1989a). The stimulus locations designated for inclusion as clusters in glaucoma have been defined using the retinal nerve fibre layer arrangement (Asman and Heijl 1992b, Asman, et al. 1992, Asman and Heijl 1993), from an empirical perimetric map (Weber and Ulrich 1991) or from actual patterns of glaucomatous visual field loss (Mandava, et al. 1992, Mandava, et al. 1993). An expert system for cluster analysis has been described (Fankhauser, et al. 1993). Chauhan et al (1990) defined a series of cluster indices; cluster size (SIZ), cluster depth (CLUS), centroid (mean x,y co-ordinate), the number and percentage (PCLUS) of locations that are clustered, and the total size and depth of clustered points. The cluster indices have been shown to be more effective than MD and CLV at detecting early visual field loss (Chauhan, et al. 1990a, Asman and Heijl 1993). Cluster analysis may reduce the effects of long-term fluctuation by the grouping of locations and allow better indication of the degree of visual field progression, especially if the confidence limits for abnormality of superior field defects relative to inferior defects are considered (Chauhan, et al. 1990a, Asman, et al. 1992, Asman and Heijl 1993, Mandava, et al. 1993). The effectiveness of cluster analysis is reduced in advanced visual field loss (Fankhauser, et al. 1993).

1.7.7 Defect Volume

The Defect Volume (DV) index is an expression of the three-dimensional hill of vision (Langerhorst, et al. 1985, van den Berg, et al. 1985). The normal visual field is assumed to be a conic section with a sensitivity gradient of 0.25 dB per degree of eccentricity. The measured visual field volume (VOL_{meas}) is subtracted from the normal age-corrected visual field volume (VOL_{norm} VOL_{meas}).

$$DV = VOL_{norm} - VOL_{meas}$$

1.7.8 Diffuse Loss Index

The Mean Defect index is often assumed to indicate the level of diffuse visual field loss. However, localised defects contribute to the calculation of MD and as such MD is not a true representation of diffuse loss. The GHT (Asman and Heijl 1992b) has a provision for indicating a general reduction in sensitivity if the visual field is depressed in the absence of typical focal glaucomatous defects. Another method of separating diffuse from focal loss is the Bebié curve (Bebie, et al. 1989). However, the separation of diffuse loss and early localised loss is not well defined with this method (Funkhouser, et al. 1992). The general reduction in sensitivity (GRS) index has been devised as an alternative method for estimating the diffuse component of any visual field loss (Langerhorst 1988, Langerhorst, et al. 1989). The GRS has the advantage of separating the two types of field loss, but it is difficult to treat statistically and the presence of hypersensitive locations result in an underestimation of the diffuse component (Funkhouser, et al. 1992). Funkhouser et al (1992) proposed a refinement of the Bebié curve, the Diffuse Loss (DL) index. A plateau region of the curve was defined and the mean loss of the plateau expressed the magnitude of DL.

1.7.9 Learner's Index

Perimetric experience is associated with an improvement in reliability and a reduction in the artefacts associated with the measured sensitivity (Heijl, et al. 1989c). This 'learning effect' has been demonstrated in normal subjects, ocular hypertensive and glaucoma patients (Wood, et al. 1987b, Werner, et al. 1988, Wild, et al. 1989b, Werner, et al. 1990). Typically, visual fields from inexperienced subjects show depression of the mid-peripheral visual field (between eccentricities of 15 to 30 degrees) and a normal central field. The Learners Index (LI) was designed to detect the patterns of sensitivity associated with naïve observers (Asman, et al. 1993, Asman and Heijl 1994b). The Learners Index is a discriminant linear function based on five concentric zones of the visual field in individuals who demonstrate a learning effect. An average 'learner' produces a LI value of one and a 'non-learning' individual a value of zero.

1.8 Analytical Programs

A number of computer packages exist to aid interpretation of single and serial visual fields.

1.8.1 STATPAC

STATPAC is a software program for the Humphrey Field Analyzer which provides statistical analysis of visual fields (Heijl, et al. 1987b). The program contains a database of normal values of sensitivity and the distribution of these values at each location. The database allows the generation of global field indices and of total and pattern deviation plots. Evaluation of serial visual fields is facilitated by various forms of data reduction. Overview printouts allow subjective inspection of a number of compressed fields. Box and whisker plots are a method of compressing the distribution of pointwise deviations from age-matched normal values at each stimulus location. The median value of the distribution is marked as a horizontal line on the box. The upper limit of the box represents the eighty-fifth percentile and the lower limit of the box is the fifteenth percentile of the distribution. The upper and lower whiskers indicate the maximum and minimum deviations, respectively. A number of box plots are generated on the Change Analysis printout, together with a series of plots indicating changes in the global indices with time. The analysis of MD also accounts for the learning effect.

The STATPAC 2 statistical analysis package additionally contains the Glaucoma Hemifield Test and Glaucoma Change Probability analysis (Heijl, et al. 1991). The Glaucoma Change Probability analysis compares follow-up fields with a baseline set of values. At each location, the probability of change is calculated from an empirical database of examinations from stable glaucomatous patients. Originally, the analysis was based upon the change in total deviation. The evaluation of visual field progression with the total deviation plots is complicated in the presence of advancing cataracts. A change probability analysis based on the pattern deviation plots has been developed to improve the analysis (Bengtsson, et al. 1997a).

1.8.2 Octosmart and Program Delta

Presentation of the test results from the Octopus perimeter is provided by the Octosmart program. The program provides the numerical deviations, global indices, rudimentary cluster analysis, a Bebié curve and a summary diagnostic statement (Funkhouser, et al. 1991). The diagnostic capability of Octosmart showed a similar performance to experienced observers in cases of obvious field loss (Hirsbrunner, et al. 1990, Funkhouser, et al. 1991). The Seven-in-One report for the Octopus combines many of the analyses previously described; raw numerical data, a greyscale plot, a Bebié curve, global indices and the Comparison and Corrected Comparison Probability plots.

Program Delta also allows serial field analysis (Bebie and Fankhauser 1981). Deterioration in MS is determined by the use of a paired comparison t-test of two examinations.

1.8.3 Peridata.

Peridata is a stand-alone PC based computer program that can analyse both Humphrey Field Analyzer and Octopus visual fields (Brusini, et al. 1991). The program displays the usual indices from each perimeter and, in addition, the fields can be analysed in hemifields, quadrants, sectors, and rings or in a pattern related to the retinal nerve fibre layer. Visual field progression is investigated by Graphical Analysis of Topographical Trends (GATT). Two visual field greyscales are compared and deterioration in the field is represented by horizontal stripes. Improvement in sensitivity is represented by vertical stripes and a checked pattern indicates high variability.

1.8.4 Fieldview

Fieldview is the analytical program for the Dicon Autoperimeter. It is a stand-alone program run on a separate PC from the perimeter, although direct downloading of results from the instrument is possible. Fieldview displays numeric, greyscale and total deviation plots together with a hill of vision deviation plot, designed to extract localised defect information. Global mean sensitivity and quadrant analysis of mean defect are also displayed.

1.8.5 Other Methods of Change Analysis

Pointwise analysis of sensitivity described by a combined topographical and longitudinal model has been used to evaluate visual field progression (Wild, et al. 1993). The topographical element of the model comprised a second order polynomial function to described the pointwise sensitivity at any stimulus location. A linear function was used to describe the change in sensitivity with time, for the longitudinal element of the model. The combined model allowed prediction of the pointwise sensitivity at the nth field to an accuracy of 3 dB.

Linear regression analysis against time to follow-up of pointwise sensitivity, MD, CPSD and clusters of locations in the GHT has also been used to investigate visual field progression (O'Brien and Schwartz 1990, Birch, et al. 1995, Smith, et al. 1996, Katz, et al. 1997, Wild, et al. 1997b). Significant progression of visual field loss has been shown to occur in less than 33% of subjects, followed over six years (Katz, et al. 1997). Average threshold changes of less than 1 dB/year could not be detected with seven tests over six years. Increased frequency of testing would be required to detect statistically significant small changes. However, the use of linear regression analysis has been shown to delineate visual field progression in a number of studies (O'Brien and Schwartz 1990, Birch, et al. 1995, Smith, et al. 1996, Wild, et al. 1997b), and the technique is improved by taking into account the eccentricity of the stimulus locations and the change in age of the patient during the regression period (Wild, et al. 1997b). Linear regression analysis can be improved by spatially filtering the field results before applying the regression calculations (Crabb, et al. 1997).

The Progressor program derives pointwise linear regression slopes of change in sensitivity at each location in the visual field (Noureddin, et al. 1991, Fitzke and McNaught 1994, McNaught, et al. 1995, Fitzke, et al. 1996). The results are displayed as colour coded bar charts at each stimulus location. The length of the bar represents the depth of defect and the colour is an indication of the nature and significance of the regression slope. Progressor has been shown to give a similar incidence of progression to Statpac 2 (Fitzke and McNaught

1994, Birch, et al. 1995, McNaught, et al. 1995, Fitzke, et al. 1996, McNaught, et al. 1996, Viswanathan, et al. 1997). Progressor was found to detect progression at an earlier stage than Statpac 2 (Viswanathan, et al. 1997). However, both Statpac 2 and Progressor overestimated progression when compared to the clinical findings (Birch, et al. 1995).

1.9 Factors Affecting Perimetric Data Collection

A number of inter-subject factors can affect visual field measurement, some of which can give rise to artefacts, which may resemble the defects found in some ocular disorders. The principle physical factors such as orbital bones and lid ptosis have been mentioned in section 1.1. Other factors are described below.

1.9.1 Age

The sensitivity of the eye to a variety of psychophysical and electrophysical tests is known to decline with increase in age (Johnson and Choy 1987). The decline in sensitivity has been attributed to changes in pupil size (see section 1.9.2), changes in the ocular media (see section 1.9.4) and changes in retinal function.

For automated static perimetry, a linear decrease in sensitivity with increase in age of between 0.4 and 1.1 dB per decade has been demonstrated out to thirty degrees eccentricity (Brenton and Phelps 1986, Haas, et al. 1986, Jaffe, et al. 1986, Heijl, et al. 1987a). However, two separate stages in the decline of sensitivity with age have been shown for various visual functions. Individuals under the age of fifty years show a shallower decline with age than individuals over the age of fifty (Johnson and Choy 1987). The change in the slope of visual field sensitivity has been shown to occur closer to forty than fifty years of age (Henson 1993). The between-individual variation in sensitivity may (Henson 1993) or may not (Heijl, et al. 1987a) increase with increasing age. Any between-individual variation in measured sensitivity may be due to the increased variation in media transmission in the older population. The majority of studies also show a change in the shape of the 'hill of vision'

along with an overall depression (Haas, et al. 1986, Jaffe, et al. 1986, Heijl, et al. 1987a). The superior field becomes steeper at a greater rate than the inferior field. Brenton and Phelps (1986) suggested an even decline in sensitivity out to 30 degrees eccentricity, arguing that any regional differences were due to fatigue effects being more significant in the mid-periphery in older individuals. The higher incidence of cataract in the older individuals would also steepen the perimetric profile (see section1.9.4). The model of the normal hill-of-vision in STATPAC takes into account the changes in shape and height with increasing age.

The majority of the decline in sensitivity is thought to be due to changes in the neural component of the visual pathway (Johnson, et al. 1989). Photoreceptors, ganglion cells and retinal pigment epithelium cells all decline at a rate of 0.2% to 0.4% per year (Mikelberg, et al. 1989, Repka and Quigley 1989, Jonas, et al. 1992, Panda-Jonas, et al. 1995). This is in concordance with the 0.2% (0.064 dB per year) decline in differential light sensitivity reported by Zulauf et al (1994). For the photoreceptors, the decline is more pronounced at an eccentricity of 5 to 8 mm than at eccentricities greater than 14 mm. The rods decline at a greater rate than the cones (Panda-Jonas, et al. 1995).

1.9.2 Pupil Size

The diameter of the pupil affects the amount of light reaching the retina and thus can affect perimetric thresholds. The amount of retinal illumination (D), measured in trolands, is given by:

$$D = 0.36 \cdot \tau_{\lambda} \cdot s \cdot B$$

where, τ_{λ} is the transmission factor of the optical media, s is the area of the pupil in cm^2 and B is the luminance of the light source. The value of τ_{λ} varies from 0.1 with violet light to 0.7 in the red part of the spectrum. With white light, τ_{λ} is approximately 0.5 (Davson 1990).

Although constriction of the pupil will reduce the intensity of the background, it will also affect the stimulus intensity. Therefore, in photopic conditions where Weber's Law applies, the

contrast of the stimulus should be unaffected by changes in pupil size. At low photopic and mesopic conditions, Weber's Law no longer applies and a brighter stimulus luminance is required to elicit a visual response. With the level of background illumination employed by the Humphrey Field Analyzer, a four-fold drop in pupil area (from 16.29 to 4.32 mm^2) resulted in a mean reduction of sensitivity of 0.67 dB (Lindenmuth, et al. 1989). Considering a change in retinal illumination due to pupil size alone, a four-fold reduction in pupil area would be expected to correspond to a 6 dB reduction in sensitivity (Henson 1993). The difference between these two values indicates that the visual system closely, but not exactly, follows Weber's Law at this background luminance.

As the pupil diameter decreases below two millimetres, the retinal illumination enters the mesopic range. The area of the pupil reduces with increase in age (Winn, et al. 1995). The age effect is independent of gender and refractive error. However, the reduction in pupil size with age is not the principle contribution to the normal decline in measured sensitivity with age (Johnson, et al. 1989).

Pharmacologically induced pupil miosis leads to a reduction in the Mean Deviation index, with no significant changes in foveal threshold, SF or PSD (Lindenmuth, et al. 1989, Webster, et al. 1993). Conversely, pupillary dilation leads to an increase in sensitivity (Wood, et al. 1988, Lindenmuth, et al. 1990, Rebolleda, et al. 1992), with equivocal effects on foveal threshold, SF and PSD.

The effective area of the pupil is geometrically smaller to stimuli presented at greater eccentricities. This effect would be expected to contribute to the decline in sensitivity with increase in eccentricity. Sensitivity decreases at all pupil diameters but at a slower rate with larger pupils (Wood, et al. 1988, Herse 1992).

1.9.3 Refractive Defocus

Uncorrected refractive error gives rise to optical defocus which, in turn, results in reduced visual acuity and impaired contrast sensitivity at high spatial frequencies (Campbell and

Green 1965). Similarly, optical defocus will increase the area of the stimulus on the retina whilst reducing the luminance of the centre of the image. The change in luminance gradient at the edge of the target will alter the effectiveness of the stimulus.

Stimuli smaller than, or equal to, Goldmann size III are affected by refractive defocus to a greater degree than larger stimuli (Atchison 1987). The central visual field is affected to a greater degree than the peripheral field (Benedetto and Cyrlin 1985, Atchison 1987, Herse 1992). Thus, increasing optical defocus flattens the perimetric profile. Up to ±2.00 DS of blur creates a depression of the central field whilst the peripheral field is unaffected by this level of defocus. With a blur of greater than ±3.00 DS the peripheral field is affected although not to as great an extent as the central field (Benedetto and Cyrlin 1985). However, a uniform depression out to 25 degrees eccentricity has been demonstrated (Heuer, et al. 1987).

A smaller pupil will increase the depth of focus and thus the change in sensitivity per Dioptre of blur will be greater with larger pupils. The change in sensitivity per Dioptre of defocus is lower at greater eccentricities than along the optical axis of the eye (Herse 1992).

Correcting for refractive error and for the cupola distance can also induce artefacts due to prismatic effects (Atchison 1987) and to the lens rim (Zalta 1989). Theoretically, the prismatic effect of a correcting spectacle or trial frame lens will alter the position of the image on the retina thus altering the measured threshold. In practice, however, the effect is negligible for spectacle powers of less than ±10.00 DS when compared with optical blur (Atchison 1987). Correcting high myopes and aphakic patients with contact lenses will reduce the prismatic effect. Lens rim artefacts are due to an excessive vertex distance and should easily be avoided (Zalta 1989).

1.9.4 Media Opacity

Opacities within the cornea, crystalline lens or vitreous may affect the light entering the eye in a combination of two ways; by absorption which filters the amount and wavelength of light reaching the retina or by scattering the light and hence reducing the stimulus contrast. The

degree of image degradation is dependent on the size and position of the opacity within the ocular media. Opacities close to the nodal point of the eye, such as a posterior capsular cataract will elicit a greater effect (Baraldi, et al. 1987). Increasing media opacity with age also complicates the detection of progression of glaucomatous visual field damage (Bengtsson, et al. 1997a).

Ageing of the crystalline lens typically produces a discolouration of the layers within the lens and hence light absorption. The absorption is wavelength dependent and preferentially attenuates the shorter wavelengths (Sample, et al. 1988b, Moss, et al. 1995). For conventional white-on-white perimetry, the stimulus and background are both affected and where Weber's Law applies, the threshold estimates are unaffected.

Light scatter is the principle cause of visual loss in cataract (Philipson 1969). Light scatter can be subdivided into, forward light scatter, which is straylight reaching the retina and backward light scatter, which is light reflected away from the crystalline lens. Forward light scatter is assumed to be the main cause of image degradation with lens opacities (Bettleheim and Chylack 1985). With a glare source present, forward light scatter (FLS) can be described by:

$$FLS = \frac{L}{E}\left(\frac{M_2}{M_1} - 1\right)$$

where, L is the stimulus luminance, E is the illuminance of the glare source and M2 and M1 are the thresholds measured with and without the glare source respectively (Paulsson and Sjostrand 1980). The degree of light scatter shows little dependency on the wavelength of incident light (Whitaker, et al. 1993).

In normal individuals, increased forward light scatter from simulated cataracts has been shown to produce a steepening of the Octopus visual field profile with a Goldmann size III target at a low background illumination (1.3 cdm^{-2}). Conversely, the smaller LED stimuli of

the Dicon AP3000 perimeter and higher background illumination (10 cdm^{-2}) produced flattening of the sensitivity gradient (Wood, et al. 1987a). The difference in results was attributed to the larger stimuli saturating the central retina and therefore becoming insensitive to small changes in light intensity. Non-nuclear age-related cataracts were shown to influence the same stimulus parameters in the same manner (Wood, et al. 1989). Nuclear cataracts, however, attenuated the central visual field greater than the peripheral field for both the size III and the smaller LED stimuli (Wood, et al. 1989). This former finding was in agreement with earlier work using kinetic perimetry which showed that the greatest isopter contraction occurred with smaller sized targets than Goldmann size III. Isopters from size III to V changed only with advanced cataracts corresponding to a visual acuity of worse than 6/90 (Radius 1978). The removal of cataract significantly improves the MD of normal visual fields, whilst the SF and PSD are unaffected (Lam, et al. 1991). This study also showed a steepening of the slopes of the hill of vision postoperatively, along with the overall increase in height, but the percentage change was similar over the whole visual field out to an eccentricity of 30 degrees.

With glaucomatous visual fields, simulated light scatter produces a diffuse reduction in MS, with normal and abnormal areas of the visual field depressed equally (Budenz, et al. 1993), especially when age-matched normal values are corrected for light scatter (Dengler-Harles, et al. 1990). However, in glaucoma, extraction of nuclear cataracts has minimal effect on the MD, PSD or the total decibel loss within GHT sectors (Stewart, et al. 1995). A possible explanation for the absence of an improvement in the MD was the presence of advanced field loss in some subjects, which would not be able to show an improvement. Alternatively, Stewart et al (1995) postulated that light scatter might invoke a response from a larger area of retina which, would be of benefit in glaucomatous eyes. Therefore, in the pseudophakic glaucomatous eye, the absence of light scatter would mean that the stimuli are incident upon a smaller area of retina and would require a brighter stimulus to elicit a response. Further investigation into spatial summation in glaucoma was suggested.

1.9.5 General Health and Medication

A number of systemic factors have been investigated with regard to their influence on the visual field. In individuals who suffer from migraine headaches with visual symptoms, the peripheral visual field may be affected for several days (Drummond and Anderson 1992). Physical exercise may result in an improvement of the MD (Koskela, et al. 1990). A low level of systemic blood alcohol has been shown to correlate with reduced patient reliability (Zulauf, et al. 1986) or deterioration of the visual field indices: MD, PSD and CPSD (Wild, et al. 1990) and an increase in the required number of stimulus presentations (Wild, et al. 1990).

Systemic drugs acting on the central nervous system may influence the measurement of the visual field. The benzodiazepine, diazepam, may have a slight derogatory effect on the mean sensitivity (Haas and Flammer 1985). Constriction of the visual field has also been reported with diazepam (Elder 1992) and with the anti-convulsant drug, Vigabatrin (Eke, et al. 1997). SF has been shown to be influenced by some antihistamines; the other visual field indices and the reliability parameters remain unaffected by these types of drugs (Wild, et al. 1989a). Chloroquine and hydroxychloroquine, which are known to cause retinal toxicity, do not significantly affect any of the visual field indices (Mann, et al. 1989).

1.9.6 The Learning Effect

As subjects initially become more familiar with the process of perimetry, performance improves. This learning effect exists in normal individuals (Wood, et al. 1987b, Heijl, et al. 1989c), glaucoma suspects (Wild, et al. 1989b) and glaucoma patients (Kulze, et al. 1990, Heijl and Bengtsson 1996) and manifests itself as an increase in MS and a reduction in SF (Werner, et al. 1988, Werner, et al. 1990). The learning effect may be present within- and between-examinations. Wood et al (1987) reported three groups of normal individuals with respect to learning effects: one group in whom a large increase in measured sensitivity occurred between the first and second visits; a second group in whom no significant increase occurred and a third group who showed a gradual improvement over the first five sessions analysed.

The learning effect is not uniform over the central field, being greater for the superior hemifield than the inferior hemifield (Wood, et al. 1987b) and greater for the more peripheral locations (Heijl, et al. 1989c, Wild, et al. 1989b, Kulze, et al. 1990, Heijl and Bengtsson 1996). In glaucomatous visual fields with moderate defects, the improvement is greater than with mild or severe losses (Heijl and Bengtsson 1996). In addition, locations that had higher sensitivities after learning had levelled off had improved by a greater degree than locations in defective areas of the visual field. Following completion of initial training the learning effect is no longer present at follow-up examinations nine months later (Wild, et al. 1991).

1.9.7 The Fatigue Effect

As the examination duration progresses the performance of the subject declines. This fatigue effect may manifest itself as a reduction in sensitivity or as increased fluctuation, and has been demonstrated in normals (Searle, et al. 1991, Hudson, et al. 1994) ocular hypertensives (Wild, et al. 1991, Hudson, et al. 1994) and glaucoma patients (Heijl and Drance 1983, Johnson, et al. 1988b).

The reduction in sensitivity is greater as the duration of the examination increases (Heijl and Drance 1983, Hudson, et al. 1994), is greater for the second eye tested (Hudson, et al. 1994) and is greater in areas of the visual field adjacent to or within a scotoma (Heijl and Drance 1983). The loss variance also increases with examination duration and this increase is greater for normals than for ocular hypertensive patients (Hudson, et al. 1994). The fatigue effect is also eccentricity dependent (Johnson, et al. 1988b, Hudson, et al. 1994), particularly in glaucoma patients (Johnson, et al. 1988b), with the peripheral stimulus locations affected to a greater extent. Fatigue remains present at long-term follow-up although the learning effect does not (Wild, et al. 1991). The fatigue effect will be discussed in more detail in Chapter 5.

CHAPTER 2. RATIONALE AND DESCRIPTION OF THE RESEARCH

This thesis was a continuation of work previously undertaken in the Department concerned with sources of variability associated with conventional white-on-white (W-W) automated perimetry. These sources included light scatter due to cataract (Wood, et al. 1987a, Wood, et al. 1989, Dengler-Harles, et al. 1990), the learning effect (Wood, et al. 1987b, Wild, et al. 1989b, Searle, et al. 1991, Wild, et al. 1991), the fatigue effect (Searle, et al. 1991, Wild, et al. 1991, Hudson, et al. 1994), stato-kinetic dissociation (Hudson and Wild 1992), threshold estimation (Flanagan, et al. 1993a, Flanagan, et al. 1993b) and the identification of visual field progression (Wild, et al. 1993, Wild, et al. 1997b). In addition, research was undertaken to investigate short-wavelength automated perimetry (SWAP), with specific regard to the optimisation of the stimulus parameters (Hudson, et al. 1993), the influence of light scatter and media and macular pigment absorption (Moss and Wild 1994, Moss, et al. 1995, Wild and Hudson 1995), the learning effect in normal subjects (Wild and Moss 1996) and the efficiency of threshold estimation (Wild, et al. 1998).

2.1 Rationale.

The conventional staircase strategy for visual field testing crosses threshold initially using a step size of 4 dB followed by a second crossing of threshold with a 2 dB step size. Testing out to an eccentricity of 30 degrees with Program 30-2 of the Humphrey Field Analyzer takes an average of 15 minutes per eye. Further threshold strategies have been developed in order to reduce the test duration. The FASTPAC strategy for the Humphrey Field Analyzer uses a single crossing of threshold with a 3 dB step size. FASTPAC gives a 40% reduction in test duration over the 4-2 dB staircase but at the expense of increased measurement variability. A Dynamic strategy, which uses variable step sizes depending on the stimulus intensity, has been shown to reduce the measurement variability at normal thresholds but with little difference at reduced sensitivities. At the outset of the research a newer, third generation of threshold strategies became available for the Humphrey Field Analyzer. These

algorithms, under the acronym SITA, use a more interactive thresholding strategy reliant upon sophisticated computations during the test procedure, adapting detailed prior models of normal and glaucomatous visual field responses. The SITA strategies have subsequently been reported to reduce the test durations of the 4-2 dB staircase by half (Bengtsson, et al. 1997b, Bengtsson, et al. 1998).

The aim of the first part of the thesis was to determine the validity of the SITA Standard and SITA Fast algorithms in the estimation of normal sensitivity. The specific aims were, firstly, to determine the extent of any differences in the estimation of sensitivity between the SITA Standard, SITA Fast, Full Threshold and FASTPAC algorithms and, secondly, to determine any between-algorithm differences in the magnitude of the between-subject normal variation in sensitivity and hence differences in the magnitude of the respective confidence limits for normality.

This initial study indicated that the measured sensitivities were higher, and the confidence limits for normality were likely to be narrower, for the SITA strategies compared to the Full Threshold and FASTPAC algorithms. The aim of the second part of the thesis was to investigate the validity and reproducibility of SITA Standard and SITA Fast in the estimation of visual field sensitivity in a glaucomatous population. The specific aims were; firstly, to determine the extent of any differences in the estimation of both global and pointwise sensitivity between the SITA Standard, SITA Fast, FASTPAC and Full Threshold algorithms; secondly, to determine the influence of the narrower confidence limits for normality on glaucomatous visual fields; and thirdly, to investigate the reproducibility of the algorithms.

The first and second parts of the thesis indicated that the SITA Algorithms produced higher threshold estimates and narrower confidence limits for normality resulting a statistically greater defect compared to the Full Threshold and FASTPAC algorithms. A possible explanation for the performance of SITA may have been a reduction in the fatigue effect. The fatigue effect is the decrease in sensitivity that occurs with increase in the test duration. The fatigue effect is greater for the second eye tested and increases with increasing age. As

study was undertaken to determine the between-algorithm influence of the fatigue effect over a prolonged examination period in a sample of normal subjects and glaucoma patients. The experimental protocol permitted the investigation of the fatigue effect for a variable number of stimulus locations over a controlled time period and for a fixed number of stimulus locations over a variable time period.

Visual field testing is often a tedious, tiring task for the patient. One particular method to improve patient compliance is to make use of a roving fixation target. The theory behind the use of such a fixation target is that firstly, roving fixation promotes a higher level of concentration from the patient and secondly, that the change in fixation after each stimulus presentation is thought to provide positive feedback to the patient (DICON LD400 operation manual). The converse opinion is that subjects may find it difficult to follow the fixation light with accuracy for the duration of a visual field examination. The predominant reason for visual fields recorded with static fixation to be deemed unreliable is the number of fixation losses (Katz and Sommer 1988, Bickler-Bluth, et al. 1989, Katz, et al. 1991b, Johnson and Nelson-Quigg 1993, Birt, et al. 1997). Fixation errors may cause the underestimation of normal sensitivity and the over or under estimation of defect depth. The accuracy of fixation with the roving fixation technique is unknown. The fourth part of the thesis was concerned with the evaluation of roving fixation perimetry in a sample of patients with early glaucomatous field loss.

The learning effect has been described as the improvement in sensitivity at a given stimulus location which increases with perimetric experience. The learning effect can complicate the initial diagnosis of visual field loss. The learning effect can occur within- and between-eyes at a single examination and between serial examinations of a given eye (Heijl, et al. 1989c, Searle, et al. 1991). The effect is greater for the initial series of examinations and at the more peripheral locations in the visual field (Wood, et al. 1987b, Heijl, et al. 1989c, Wild, et al. 1989b, Kulze, et al. 1990, Heijl and Bengtsson 1996). The learning effect in W-W perimetry has been shown to vary in normal subjects (Wood, et al. 1987b) and is greater at stimulus locations exhibiting mild to moderate loss (Heijl and Bengtsson 1996). Short-wavelength

automated perimetry (SWAP) has been suggested for use in the early detection of glaucomatous visual field loss (Heron, et al. 1988, Sample, et al. 1988a, Hart 1989, de Jong, et al. 1990). SWAP uses a high intensity yellow background to adapt the rods, and the medium- and long-wavelength sensitive cones and a blue stimulus to preferentially stimulate the short-wavelength sensitive cones. Visual field loss with SWAP has been shown to precede defects for conventional achromatic automated perimetry by up to five years (Sample and Weinreb 1990, Sample and Weinreb 1992, Casson, et al. 1993, Johnson, et al. 1993c, Johnson, et al. 1993b, Sample, et al. 1993, Johnson, et al. 1995, Wild, et al. 1995) and be present in a high proportion of ocular hypertensive patients (Johnson, et al. 1993b, Sample, et al. 1993, Johnson, et al. 1995, Wild, et al. 1995). Work within the Department has investigated the variability in SWAP due to variations in macular pigment and lenticular changes (Moss and Wild 1994, Moss, et al. 1995, Wild and Hudson 1995, Cubbidge, et al. 1996) and to the learning effect for SWAP in normal subjects. The final part of the study was concerned with the investigation of the learning effect in SWAP in a sample of ocular hypertensive patients. The aim of the study was to investigate the effect of prior experience with W-W perimetry on the SWAP learning effect especially with regard to the detection of early visual field loss.

2.2 Logistics.

The research was conducted within the Department of Vision Sciences, Aston University, Birmingham, and at the Department of Ophthalmology, Birmingham Heartlands Hospital, Birmingham. The studies had approval from the Aston University Human Science Ethical Committee and where applicable from the City Hospitals Health Trust Research and Ethics Committee and from the Birmingham Heartlands Research and Ethics Committee. The research followed the tenets of the Declaration of Helsinki; informed consent was obtained from the subjects after explanation of the nature and possible consequences of the studies.

Normal control subjects were recruited from students and staff of the University and from local old-age pensioner associations. Confirmation that normal subjects were free from significant eye or medical history was obtained by a full ophthalmic examination and in any cases where a second opinion was necessary, it was provided by one of the consultant ophthalmologists from the hospital Eye Departments.

Ocular hypertensive and glaucoma patients were recruited from the Birmingham and Midland Eye Centre, University Hospital Birmingham and Birmingham Heartlands Hospital with the help of consultant ophthalmologists who confirmed the diagnoses of ocular hypertension or glaucoma, and the eligibility of the volunteers with regards to the respective inclusion criteria.

The recruitment of normal subjects did not provide any significant problems. The recruitment of suitable ocular hypertensive and glaucoma patients was more difficult due to rigid inclusion criteria. This was especially the case for subjects who were required to be naïve to automated static threshold perimetry for the study concerning the learning effect in SWAP (Chapter 7). Recruitment of such subjects required their enrolment before perimetry was undertaken at the given hospital clinic. The majority of potential ocular hypertensive or glaucomatous volunteers were suffering from other ocular or general health conditions, which frequently prevented their inclusion into the various studies. Additionally, participation in one of the studies required several visits for perimetry and therefore a great deal of commitment on the part of the potential volunteer. It was often found that patients who complied with the inclusion criteria were unable, or unwilling, to participate in any of the studies due to work commitments or due to difficulties in travelling. There were also incidences of volunteers who did not complete the required number of visits. In total, 190 volunteers provided 1789 visual fields for analysis in this thesis.

CHAPTER 3. THE BETWEEN-ALGORITHM, BETWEEN-INDIVIDUAL, DIFFERENCES IN NORMAL PERIMETRIC SENSITIVITY

3.1 Introduction

3.1.1 Psychophysical threshold algorithms

The differential light threshold can be estimated using various methods. The method of limits involves either the subject or the investigator adjusting the intensity of the stimulus in small steps until it can just be perceived by the subject. The method of limits has been used in manual static perimetry. Although quick to perform in relation to the other methods, the technique suffers from a number of disadvantages. The subject's criterion for detection (the conscious decision of what can be perceived) and bias (the preference for a particular stimulus) can significantly influence the final level of the stimulus. There may also be a substantial degree of redundant data as many stimulus presentations are often far from the threshold. Data collected at stimulus levels close to threshold reveal greater information on the threshold value (Taylor 1971).

With the method of constant stimuli, the subject is presented with a large number of stimuli, at each of several predetermined intensities. The numbers of positive and negative responses are recorded for each stimulus intensity and are used to plot the psychometric function. The threshold is then calculated from the curve produced. Again, this technique requires a large number of potentially less informative stimulus presentations, is particularly time consuming and suffers from response bias and criterion effects. This method also requires the stimulus intensity levels to be determined before the measurement commences.

Adaptive methods of stimulus presentation do not rely on predetermined intensity levels but determine the next stimulus intensity following the subject's response to the previous stimulus. The adaptive methods of threshold estimation require fewer stimulus presentations (Cornsweet 1962) and concentrate the stimuli at levels close to threshold. Adaptive procedures that involve stepped increases or decreases in stimulus intensity are termed staircases (Wetherill and Levitt 1965). There are several variants of the standard staircase:

the number of correct or incorrect responses to produce an intensity change and the magnitude of the intensity change can both be varied (Levitt 1971). Staircase procedures are non-parametric, as they do not rely on prior knowledge of the subject's response characteristics. Parametric procedures that uses prior knowledge of response distributions have been developed, such as Best PEST, QUEST and ZEST (Taylor and Creelman 1967, Watson and Pelli 1983, King-Smith, et al. 1994). These maximum likelihood methods determine the next stimulus intensity following detailed computations of the most probable threshold value. The maximum likelihood method compares each subjective response to a number of previously determined hypotheses of response patterns (e.g. a number of frequency-of-seeing curves spanning a number of possible thresholds). During a test, the probability of each specific response is calculated for each of the hypotheses and the next stimulus is chosen as the value of threshold from the most likely hypothesis found in the previous stage (Green 1993). This procedure continues until a predetermined set number of stimulus trials have occurred. The threshold value found using the maximum likelihood method is relatively unaffected by an incorrect estimation of the slope of the psychometric function and the starting value of the stimulus. The variability in threshold estimation decreases with the square root of the number of trials at each stimulus location (Green 1993). The threshold obtained with the maximum likelihood method correlates well with the threshold found using a traditional three-down one-up staircase procedure (Gu and Green 1994). The maximum likelihood method can also be improved by specific attention to the estimation of false responses from the subject (Gu and Green 1994).

3.1.2 First Generation Perimetric Threshold Algorithms.

The estimation of differential light sensitivity in the clinical setting represents a compromise between the length of the examination and the optimisation of the precision and reproducibility of the measurement (Johnson, et al. 1992). The current most popular staircase algorithm used in perimetry is the truncated method of limits (Anderson 1992, Treutwein 1995).

The standard perimetric method for estimating threshold utilises a staircase strategy with an initial crossing of threshold in 4 dB increments and a final crossing in 2 dB increments (Spahr 1975, Bebie, et al. 1976b, Heijl 1977a). The algorithm is incorporated into the Humphrey Field Analyzer (HFA) as the Full Threshold strategy. In the case of central field examination, the Full Threshold algorithm initially determines the threshold twice at each of four seed locations situated along each oblique meridian at approximately 13 degrees eccentricity in each quadrant. The starting luminance at these initial seed locations is 25 dB, the final 2 dB crossing of threshold occurs in either an ascending or descending direction and the threshold is designated as the last seen stimulus luminance. Threshold is then determined at the immediate adjacent locations. The initial starting luminance at these secondary locations is 2 dB brighter than the expected value derived from knowledge of the sensitivity at the primary location and of the slope of the hill of vision. A repeat determination of threshold is obtained at any location that initially deviates from the predicted threshold by greater than 4 dB. Additionally, a repeat determination of threshold is obtained at ten preselected locations. These ten double determinations are used to calculate the Short-term Fluctuation. In the normal eye, the time required to complete Humphrey Field Analyzer Program 30-2 (i.e. to threshold 76 locations within approximately 27° eccentricity) is generally in the region of 15 minutes. Perimetric sensitivity recorded with the 4-2 dB staircase double reversal strategy decreases with increase in examination duration in normal subjects, ocular hypertensive patients and glaucoma patients (Johnson, et al. 1988b, Heijl, et al. 1989c, Wild, et al. 1989b, Searle, et al. 1991, Hudson, et al. 1994, Heijl and Bengtsson 1996). The effect becomes greater with increasing stimulus eccentricity and with increasing age and is more pronounced in areas of, and adjacent to, field loss (Heijl and Drance 1983, Johnson, et al. 1988b). This reduction in sensitivity has been attributed to fatigue and occurs both within- and between-eyes at a given visit (Searle, et al. 1991, Hudson, et al. 1994).

3.1.3 Second Generation Perimetric Threshold Algorithms.

A number of faster staircase algorithms have been developed with the aim of reducing test duration. The use of computerised simulation of the visual field examination enabled the development of RIOTS (Real-time Interactive Optimised Test Sequence) (Johnson and

Shapiro 1991). This algorithm first uses a modified binary search (MOBS) procedure to obtain thresholds at twelve seed points and two blind spot locations. The MOBS procedure (Tyrell and Owens 1988) gives a threshold value by bracketing presentations around threshold and continually halving the interval between stimulus intensity boundaries. The thresholds obtained are used to estimate the thresholds at all remaining locations. The response to each subsequent stimulus presentation is evaluated heuristically according to the interdependency of the spatial arrangement of sensitivity among locations. The RIOTS algorithm resulted in an approximate halving of test duration compared with the Humphrey Field Analyzer 30-2 Full Threshold program, with a slight increase in precision.

A more recent and alternative threshold algorithm for the Humphrey Field Analyzer, the FASTPAC strategy, employs a single crossing of threshold with a constant 3 dB step size and threshold is designated as the last seen stimulus luminance. The procedure for obtaining the threshold at the four primary locations and for calculation of the expected value at the secondary locations is identical to that of the Full Threshold algorithm. However, the initial starting luminance for the secondary locations is 2 dB dimmer than the expected threshold when the expected value is an odd number and 1 dB brighter when the expected value is an even number. The examination duration of the FASTPAC algorithm is 30% to 43% shorter than that of the Full Threshold algorithm but is at the expense of an approximate 25% increase in the within-test variability (short-term fluctuation) (Flanagan, et al. 1993a, Flanagan, et al. 1993b, Mills, et al. 1994, O'Brien, et al. 1994, Glass, et al. 1995, Schaumberger, et al. 1995). Mean sensitivity has been shown to be greater (Mills, et al. 1994), and the global indices MD and PSD to be smaller (Flanagan, et al. 1993b, O'Brien, et al. 1994, Schaumberger, et al. 1995), with FASTPAC compared to the Full Threshold algorithm. The FASTPAC starting value influences the threshold at each location, thresholds being underestimated with sub-threshold initial values and overestimated with supra-threshold initial values (Glass, et al. 1995). The difference in the examination duration and mean deviation index between the FASTPAC and the Full Threshold algorithm decreases with increasing age (Flanagan, et al. 1993b). As the severity of visual field defect increases

the time saving for FASTPAC decreases and the SF increases compared to the Full Threshold algorithm (Flanagan, et al. 1993b).

The Dynamic Strategy uses variable step sizes dependent on the stimulus intensity and location with the aim of reducing test duration (Weber and Klimaschka 1995). When compared with the Full Threshold algorithm, the Dynamic strategy has been shown to reduce the measurement variability at normal thresholds but exerts little influence on variability at reduced sensitivities, such as those seen in glaucomatous visual field loss.

A novel method of estimating the sensitivity at a number of locations in the visual field with a greatly reduced examination duration has been described (Gonzalez de la Rosa, et al. 1990). The technique initially obtains thresholds at four critical points. The thresholds from these four points are then compared against a large database of visual fields, from normal subjects and glaucoma patients, and the most likely threshold value at each of other visual field locations is then calculated. The procedure has been termed Delphi perimetry and the mean examination duration of the test is approximately one minute per eye (Gonzalez de la Rosa, et al. 1990, Wishart, et al. 1998). However, the results from the Delphi perimetry program did not show a good correlation with the visual fields obtained with the Humphrey Field Analyzer Program 24-2 in terms of the number of correctly identified glaucoma patients or in terms of the spatial localisation of field defects (Wishart, et al. 1998).

The interdependency between adjacent stimulus locations has been considered in the development of a faster thresholding strategy for the Octopus perimeters. This procedure has been termed Tendency Orientated Perimetry (TOP) (OCTOPUS Tendency Orientated Perimetry (1997), Interzeag AG, Switzerland). TOP divides the 76 stimulus locations of the standard 32 test program into four sub-matrixes of 19 locations. The locations in each sub-matrix are separated by 12 degrees. A modified binary search procedure is used to begin the estimation of thresholds for the first sub-matrix. The initial estimates of threshold for the first sub-matrix are used to update the estimates of thresholds for the remaining sub-matrices by linear interpolation. Stimuli are then presented in turn at the locations of the remaining sub-

matrices. Each threshold estimation is used to modify the values at the neighbouring locations until all locations have been examined. However, TOP has not been subjected to detailed independent research.

3.1.4 Third Generation Perimetric Threshold Algorithms.

The lengthy examination time of the Full Threshold algorithm and the level of accuracy obtainable with FASTPAC and other faster algorithms are both incompatible with the financial and resource constraints operative within current health care provisions. A third generation threshold algorithm, Swedish Interactive Threshold Algorithm (SITA), has become commercially available for the Humphrey Field Analyzer Mark II which are claimed to reduce examination time without loss of accuracy (Bengtsson, et al. 1997b, Bengtsson, et al. 1998). Two SITA algorithms are currently available, SITA Standard and SITA Fast, which are analogous to the Full Threshold and FASTPAC algorithms, respectively.

The characteristics of SITA are considerably more sophisticated than previous generations of algorithm. The SITA Standard algorithm uses a 4-2 dB step size and the SITA FAST algorithm a 4 dB step size. Both SITA algorithms compare each response of the patient with previously determined models of the normal and glaucomatous visual fields (Olsson and Rootzen 1994). The two models are based upon a knowledge of the age-corrected normal threshold values, the between-subject variability in the estimation of threshold (Heijl, et al. 1987a, Heijl, et al. 1989a), the variation in the shape of the frequency-of-seeing curve between stimulus locations (Weber and Rau 1992, Olsson, et al. 1993) and the interdependence of threshold values at adjacent visual field locations (Heijl, et al. 1989a, Asman and Heijl 1993, Olsson and Rootzen 1994). At each stimulus location, two likelihood functions are calculated prior to the examination, one for normal responses and one for glaucomatous responses. Both likelihood functions are adjusted following the positive or negative response to a stimulus and the shape of the function changes with increase in the number of responses. The peak of the function at any given time represents the most likely threshold value and the width of the function is an indication of the accuracy of the threshold estimate. The thresholding procedure at any given location can be terminated at a

predetermined level of accuracy, which is specified by the Error Related Factor (Bengtsson, et al. 1997b). At end of the examination, the current best estimations of threshold are recalculated. This latter procedure enables the thresholds calculated at the beginning of the examination to be re-evaluated using all succeeding patient response information. The resultant threshold determined by SITA is assumed to represent the stimulus intensity that has a 50 percent chance of seeing from the psychometric function (Bengtsson, et al. 1998).

The examination duration is further shortened by a reduction in the number of catch trials required for false-response estimation (Olsson, et al. 1997) and by the use of an inter-stimulus interval based upon on the patient's reaction time. The rate of false-positive answers is investigated by recording positive subject responses during periods when no response is expected. Such periods include the duration between stimulus onset and the minimum reaction time of the patient. The pattern of responses is also analysed at the conclusion of the test to extract rates of false-positive and false-negative responses (Olsson, et al. 1988). The SITA algorithms also use a minimal number of traditional false-negative catch trials. All types of false-response analysis are combined to estimate the false-response rates (Olsson, et al. 1997).

The validity of the SITA algorithms compared to the existing algorithms is unknown. Knowledge of such information is essential before the algorithms can be considered for routine use in the clinical situation.

3.2 Aim of study.

The aim of the study was to determine the validity of the SITA Standard and SITA Fast algorithms in the estimation of normal sensitivity. The specific aims were, firstly, to determine the extent of any differences in the estimation of global and pointwise sensitivity between the SITA Standard, SITA Fast, FASTPAC and Full Threshold algorithms and, secondly, to

determine any between-algorithm differences in the magnitude of the between-subject normal variation in sensitivity.

3.3 Methods.

3.3.1 Sample.

The sample comprised 50 clinically normal subjects (24 males) experienced in Full Threshold automated perimetry with the Humphrey Field Analyzer. The sample was selected such that the age distribution was stratified within and between decades from the third decade onwards. The mean age was 52.9 years (SD 18.5 years) with a range from 23 to 82 years. The inclusion criteria comprised a visual acuity of 6/9 or better in either eye, a distance refractive error less than or equal to 5 dioptres mean sphere and less than 2.5 dioptres cylinder, lenticular changes not greater than NCIII, NOIII, CI or PI by LOCS III (Chylack, et al. 1993), intraocular pressure less than 22 mmHg in either eye, normal optic nerve head appearance, open angles, no history of a congenital colour vision defect, no systemic medication known to affect the visual field, no previous ocular surgery or trauma, no history of diabetes mellitus and no family history of glaucoma or diabetes mellitus.

3.3.2 Examination Protocol.

Perimetry was undertaken at each of three visits on one randomly assigned eye of each subject. Each visual field examination used the default white-on-white stimulus parameters of the Humphrey Field Analyzer. Specifically, a Goldmann size III stimulus is presented against a 10 cdm^{-2} white background with a stimulus duration of 200 ms. Refractive correction appropriate for the viewing distance of the perimeter bowl was used for each subject.

The study adopted a two period cross-over design with order randomisation within visits. At the first visit, threshold was determined for Program 30-2 using three different algorithms: SITA Standard and SITA Fast with the Humphrey Field Analyzer 750 and Full Threshold with

the Humphrey Field Analyzer 640. Each algorithm was separated by a rest period of five minutes. The order of algorithm was randomised between subjects. The first visit was considered as a familiarisation period and the results were discarded from the analysis. At the second visit, one half of the sample was examined with the same three algorithms as at the first visit. For a given subject, the order of algorithms within the session was identical to that administered at the first visit and the procedure followed an identical protocol. The remaining half of the sample was examined with the FASTPAC and Full Threshold strategies using the Humphrey Field Analyzer 750. The order of the two strategies within the session was randomised between subjects. Each algorithm was separated by a rest period of five minutes. At the third visit, each half of the sample was examined with the remaining protocol. The three sessions for each subject were completed within a maximum period of four weeks.

3.3.3 Analysis.

The results for left eyes were converted into right eye format. The two stimulus locations immediately above and below the blind spot were omitted from the analysis. The results were analysed in three separate ways. Firstly, Mean Sensitivity and examination duration were analysed separately for each separate pair of algorithms using ANOVA for a two period cross over design with order randomisation within visits. The type of algorithm and the order of presentation of the algorithm within a session were considered as separate within-subject factors. The order of the type of session and the subject age were considered as separate between-subject factors.

Secondly, the difference between the measured sensitivity recorded with the 'gold standard' algorithm and that with the comparison algorithm was determined for each stimulus location for each patient. Additionally, the resulting data at each stimulus location was expressed as the square root of the group mean of the squared differences i.e. the root mean square error. The data were then illustrated in terms of the cumulative ranking of the 74 stimulus locations as a function of the extent of the RMS deviation. Identical, but separate, analyses were undertaken for each of the inferior, superior, nasal and temporal hemifields and for central

and peripheral annuli. The root mean square analysis gives an indication of the variance of differences between algorithms.

Thirdly, the ratio of the standard deviations (SDs) of the group mean sensitivity at each stimulus location was separately calculated for each of the comparison algorithms relative to the 'gold standard' algorithm.

3.4 Results.

All visual fields met the inclusion criteria for reliability, specifically less than 20% fixation losses and less than 33% false-negative and false-positive catch trials.

3.4.1 Analysis of Variance for Mean Sensitivity and for Examination Duration

The group mean Mean Sensitivity and group mean examination duration for each algorithm together with the group mean short-term fluctuation for the FASTPAC and Full Threshold algorithms are shown in Table 3.1. The short-term fluctuation is not calculated by the SITA algorithms. Figure 3.1 shows the decline in Mean Sensitivity and increase in examination duration as a function of subject age.

Mean Sensitivity decreased ($p<0.001$) and examination duration increased ($p<0.001$) with increase in age for each of the algorithms. The decline in sensitivity for the HFA 640 Full Threshold algorithm was 0.79 dB per decade. The corresponding values for the decline in sensitivity with age for the HFA 750 Full Threshold, FASTPAC, SITA Standard and SITA Fast algorithms were 0.73, 0.75, 0.72 and 0.62 dB per decade respectively. The examination duration increased by 19 seconds per decade for the HFA 640 Full Threshold algorithm. The corresponding values for the increase in examination duration with age for the HFA 750 Full Threshold, FASTPAC, SITA Standard and SITA Fast algorithms were 10.5, 7.3, 11.8 and 3.4 seconds per decade respectively.

	FT_{640}	FT_{750}	FASTPAC	SITA Standard	SITA Fast
MS (dB)	28.30 (1.98)	28.47 (1.80)	28.30 (1.86)	29.27 (1.82)	29.77 (1.59)
Duration (min)	13.31 (1.36)	12.94 (0.94)	7.69 (0.75)	6.56 (0.69)	3.84 (0.44)
SF (dB)	1.22 (0.53)	1.18 (0.32)	1.58 (0.50)		

Table 3.1. The group mean Mean Sensitivity and examination duration for the Full Threshold (FT), FASTPAC, SITA Standard and SITA Fast algorithms and the Short-term Fluctuation (SF) for the Full Threshold and FASTPAC algorithms. The values in parenthesis indicate one standard deviation of the mean.

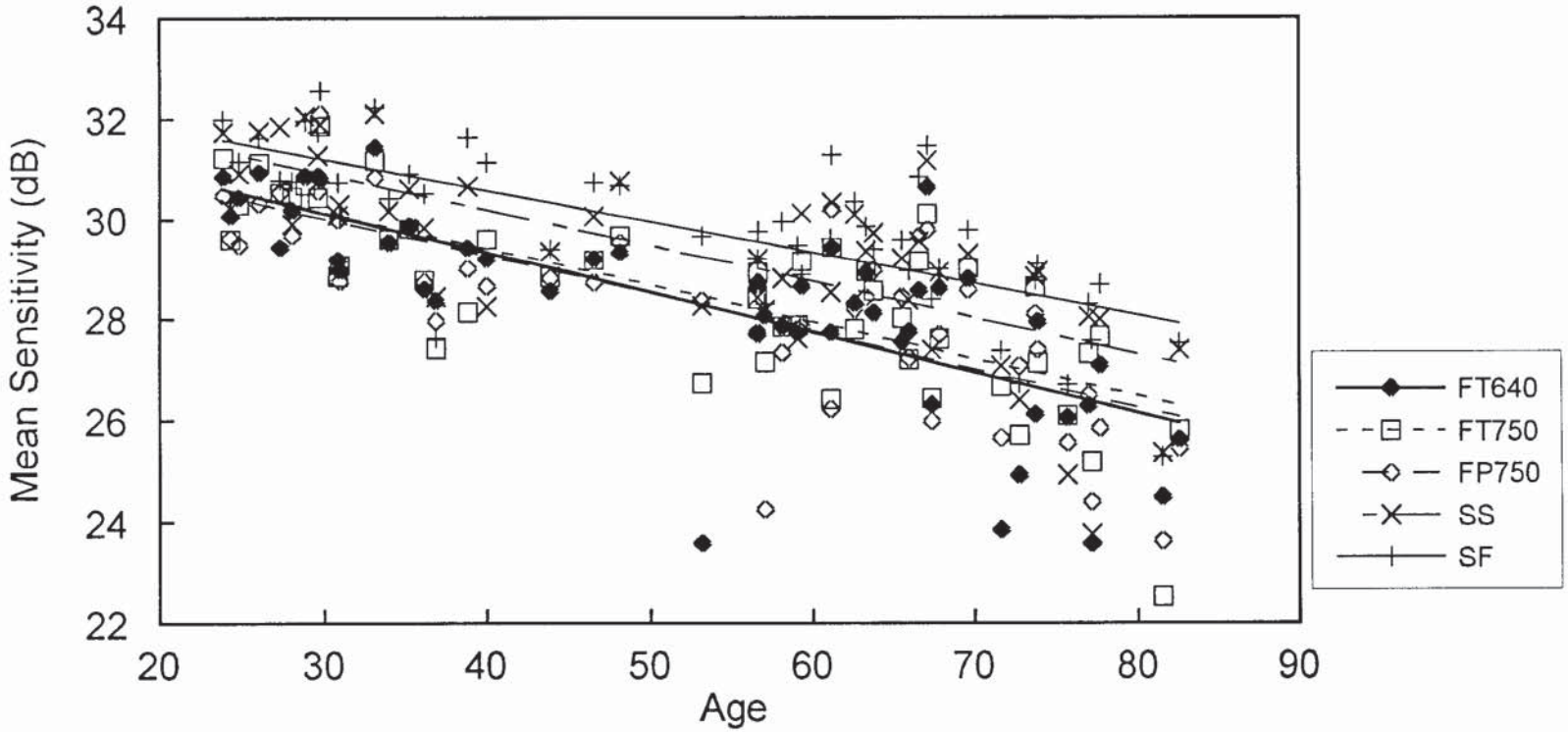


Figure 3.1a. Mean Sensitivity as a function of age for the Full Threshold (FT), FASTPAC (FP), SITA Standard (SS) and SITA Fast (SF) algorithms.

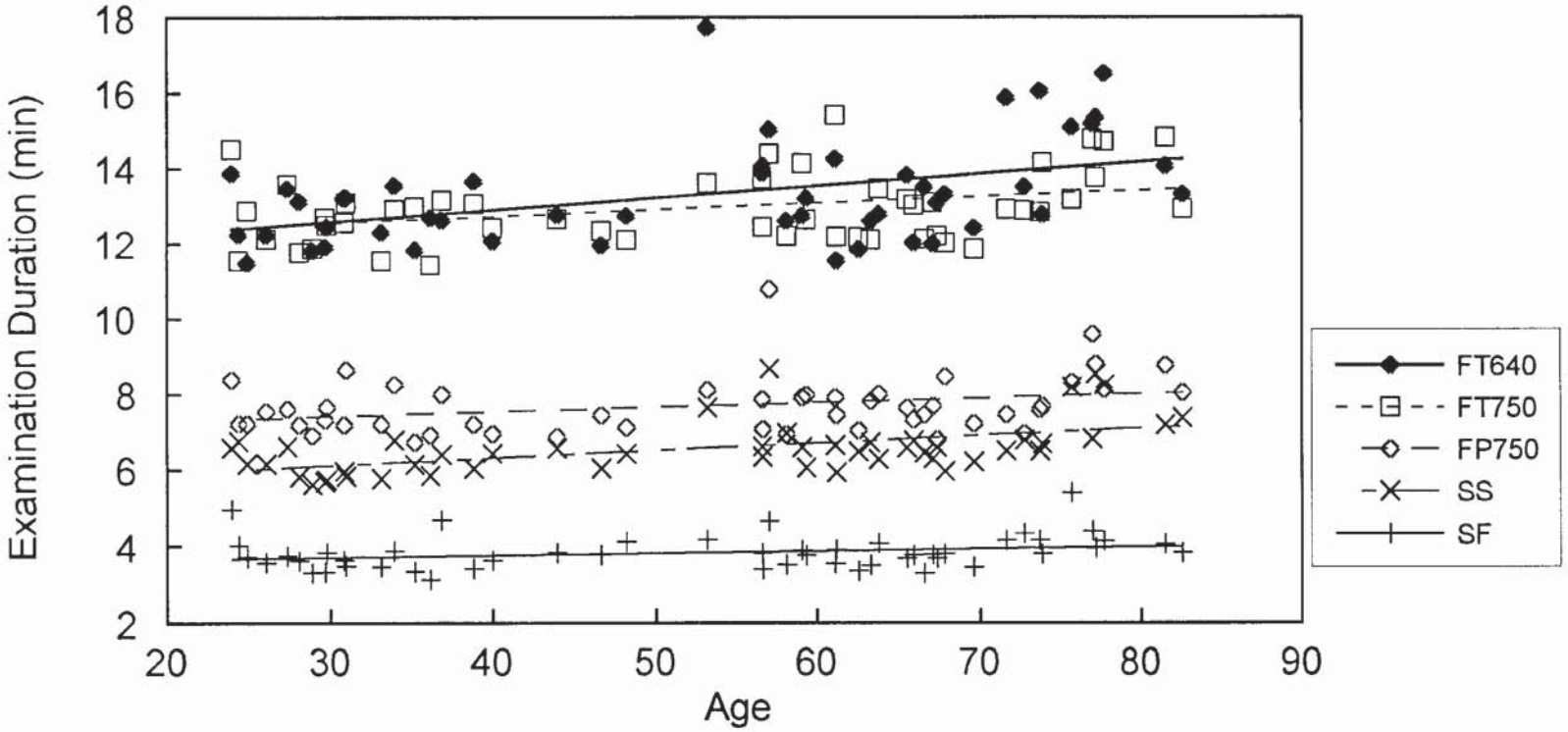


Figure 3.1b. Examination duration as a function of age for the Full Threshold (FT), FASTPAC (FP), SITA Standard (SS) and SITA Fast (SF) algorithms.

3.4.1.1 HFA 750 and HFA 640 Full Threshold algorithms

The group mean Mean Sensitivity was similar between the two algorithms (p=0.214) regardless of age (p=0.398). The group mean examination duration for the HFA 750 Full Threshold algorithm was 22.2 seconds (2.9%) shorter than for the HFA 640 Full Threshold algorithm (p=0.031) and this difference was independent of age (p=0.381). The group mean short-term fluctuation was similar between the two algorithms (p=0.680) irrespective of age (p=0.826).

3.4.1.2 HFA 750 Full Threshold and FASTPAC algorithms

The group mean Mean Sensitivity for the HFA 750 Full Threshold algorithm was similar to that for the FASTPAC algorithm (p=0.100) and this similarity was independent of age (p=0.783). Mean sensitivity varied as a function of the order of algorithm (p=0.003); it was approximately 0.75 dB higher for the FASTPAC algorithm when undertaken prior to the HFA 750 Full Threshold algorithm compared to that obtained when the FASTPAC algorithm was undertaken subsequent to the Full Threshold algorithm. The group mean examination duration for the FASTPAC algorithm was 5.25 minutes (40.6%) shorter than the HFA 750 Full Threshold algorithm (p<0.001) and this difference was independent of age (p=0.381). The group mean short-term fluctuation for the FASTPAC algorithm was 0.4 dB (33.9%) greater than the HFA 750 Full Threshold algorithm (p<0.001) and this difference was also independent of age (p=0.381).

3.4.1.3 HFA 750 Full Threshold and SITA Standard algorithms

The group mean Mean Sensitivity for the SITA Standard algorithm was 0.8 dB greater than that for the HFA 750 Full Threshold algorithm (p<0.001) and this difference was independent of age (p=0.879). The group mean examination duration for the SITA Standard algorithm was 6.38 minutes (49.3%) shorter than that for the HFA 750 Full Threshold algorithm (p<0.001) and this difference was also independent of age (p=0.719).

3.4.1.4 HFA 750 Full Threshold and SITA Fast algorithms

The group mean Mean Sensitivity for the SITA Fast algorithm was 1.30 dB greater than that for the HFA 750 Full Threshold algorithm ($p<0.001$) and this difference was irrespective of age ($p=0.072$). The group mean examination duration for the SITA Fast algorithm was 9.10 minutes (70.3%) shorter than that for the HFA 750 Full Threshold algorithm ($p<0.001$) and this difference was independent of age ($p=0.072$).

3.4.1.5 FASTPAC and SITA Standard algorithms

The group mean Mean Sensitivity for the SITA Standard algorithm was 0.97 dB greater than that for the FASTPAC algorithm ($p<0.001$) irrespective of age ($p=0.703$). The group mean Mean Sensitivities were higher for both algorithms at the second session (i.e. the third visit) compared to those at the first session. The group mean examination duration for the SITA Standard algorithm was 1.13 minutes (14.7%) shorter than that for the FASTPAC algorithm ($p<0.001$) and this difference was also independent of age ($p=0.130$).

3.4.1.6 FASTPAC and SITA Fast algorithms

The group mean Mean Sensitivity for the SITA Fast algorithm was 1.47 dB greater than that for the FASTPAC algorithm ($p<0.001$). Some evidence was present ($p=0.057$) to suggest that the difference in mean sensitivity between the algorithms increased with increase in age. The group mean examination duration for the SITA Fast algorithm was 3.85 minutes (50.1%) shorter than for the FASTPAC algorithm ($p<0.001$); however, this difference was independent of age ($p=0.206$).

3.4.1.7 SITA Standard and SITA Fast algorithms

The group mean Mean Sensitivity for SITA Standard was 0.5 dB greater than for SITA Fast ($p<0.001$) The magnitude of the Mean Sensitivity for both SITA algorithms varied within a session as a function of the order of algorithm by, on average, approximately 0.3 dB ($p=0.025$); the reduction in sensitivity over the session was similar for both algorithms ($p=0.213$) and is indicative of a fatigue effect. The difference in sensitivity between algorithms was independent of session ($p=0.091$) and of age ($p=0.239$). The group mean

examination duration for SITA Fast was 2.72 minutes (41.4%) shorter than for SITA Standard (p=0.001) and was independent both of the order of algorithm within a session (p=0.767) and of the two sessions (p=0.843). The difference between the two SITA algorithms increased with increase in age (p=0.001) i.e. the saving of time with SITA Fast became greater the older the patient.

3.4.2 Pointwise Between-Algorithm Difference in Sensitivity.

3.4.2.1 Absolute Sensitivity as a Function of Stimulus Location

The group mean sensitivity (upper value), and one standard deviation of the mean (lower value), at each stimulus location for each algorithm is shown in Figure 3.2.

3.4.2.2 Absolute Difference in Sensitivity as a Function of Stimulus Location

The between-algorithm difference in sensitivity at each location is shown in Figure 3.3. The upper value at each location is the group mean difference in sensitivity and the lower value at each location is one standard deviation of the mean.

The majority of locations showed a between-algorithm difference in sensitivity of between +/- 0.5 dB for the HFA640 Full Threshold and HFA750 Full Threshold algorithms and for the HFA750 Full Threshold and FASTPAC algorithms. At 72 of the 75 stimulus locations, the sensitivity for the SITA Standard algorithm was greater than that of the HFA750 Full Threshold algorithm. The difference in sensitivity exceeded 1 dB at 22 of the locations.

All stimulus locations exhibited a greater sensitivity for the SITA Fast compared to the Full Threshold algorithm. The difference exceeded 1 dB at 64 stimulus locations and 1.5 dB at 19 locations.

When compared to FASTPAC, SITA Standard and SITA Fast both exhibited higher sensitivity at all stimulus locations. The number of locations differing by at least 1 dB for SITA Standard and SITA Fast were 35 and 69 respectively. The corresponding numbers of locations that differed by at least 1.5 dB were 7 and 38.

HFA640 Full Threshold

			23.30 4.54	23.56 4.72	22.34 4.02	22.11 5.49			
		25.32 3.69	25.88 3.76	26.58 3.39	25.70 4.24	25.78 3.52	25.96 3.47		
	25.70 4.02	27.30 2.79	28.00 2.19	28.16 2.47	27.88 2.54	27.84 2.74	27.34 2.71	26.94 3.63	
25.72 3.61	27.18 2.94	29.32 2.48	30.74 2.51	30.14 2.65	29.60 2.35	29.24 2.32	28.52 2.72	28.12 2.64	27.76 2.99
26.26 3.69	28.28 2.16	30.48 2.17	31.38 2.15	31.84 2.29	31.60 2.14	29.80 2.41		29.00 2.62	28.82 3.32
26.50 3.40	28.30 2.36	30.60 2.33	31.24 1.88	31.68 1.61	31.96 1.82	30.68 2.15		29.64 2.38	29.36 2.72
25.64 3.38	27.82 3.09	29.92 1.76	31.38 1.93	30.62 1.65	30.96 2.26	30.84 2.29	29.88 2.19	29.64 2.24	28.86 2.54
	26.88 2.41	28.48 2.21	29.20 2.07	29.42 2.44	30.10 2.06	29.80 2.39	29.86 1.82	28.84 2.25	
		26.70 2.51	27.54 2.42	28.04 2.36	29.08 2.07	29.24 1.93	28.40 2.42		Fovea
			25.90 3.03	26.62 2.47	27.48 2.38	27.68 2.04			36.74 2.00

Figure 3.2a. The group mean sensitivity for each stimulus location (upper value) and one standard deviation of the mean (lower value) for the HFA640 Full Threshold algorithm.

HFA750 Full Threshold

			24.00 4.54	24.54 3.77	23.28 4.08	22.82 4.47		
		26.02 2.92	26.48 2.72	26.70 2.80	26.42 3.12	25.80 3.26	25.90 2.66	
	26.44 2.62	27.76 2.33	28.06 2.12	28.26 2.22	28.06 2.02	27.64 2.56	27.42 2.27	27.08 2.79
26.02 2.94	27.56 2.38	29.10 1.95	30.72 2.41	29.96 2.22	29.68 2.15	29.16 2.21	28.16 2.85	27.92 2.75	27.36 3.24
26.52 2.86	28.56 2.58	30.24 2.25	31.20 1.87	31.32 2.09	31.48 2.19	30.32 1.95		29.26 2.03	28.44 2.77
26.48 2.64	28.84 2.02	30.60 2.07	31.16 2.24	31.80 1.65	32.10 1.57	31.08 1.98		29.48 2.19	29.12 2.88
25.80 2.47	27.76 2.62	29.50 2.37	31.72 1.84	30.96 1.92	31.12 1.77	31.16 2.30	29.60 2.57	29.28 2.20	28.34 2.96
	26.94 2.82	28.80 2.10	29.48 1.76	29.46 2.61	29.76 2.43	30.16 2.16	29.98 1.98	28.58 2.30	
		27.58 2.10	28.20 2.17	28.66 2.42	29.18 2.08	29.56 1.99	29.00 2.20		Fovea
			26.96 2.38	26.70 3.20	28.26 2.06	28.04 2.20			35.76 1.94

FASTPAC

			24.03 3.68	24.71 3.83	23.45 3.76	22.80 3.78		
		25.74 3.13	26.46 3.10	26.26 2.96	26.61 3.08	26.43 3.00	25.82 2.94	
	26.14 2.85	27.29 3.11	27.84 2.27	28.44 2.62	27.93 2.54	27.95 2.56	27.71 2.32	26.94 3.14
25.58 3.16	27.07 2.76	29.11 2.66	30.88 2.40	30.23 2.01	29.33 2.03	29.23 2.49	28.14 2.62	27.89 2.98	27.21 2.99
26.19 3.45	28.52 2.40	29.96 2.46	30.99 1.98	31.36 1.86	31.36 2.26	30.23 2.19		28.62 2.38	28.23 3.07
26.49 3.02	28.10 2.75	30.35 2.32	31.32 2.42	31.36 1.74	31.86 1.87	30.97 2.40		28.77 2.43	28.64 2.47
26.21 2.67	27.83 2.90	29.48 2.30	30.95 2.89	30.42 2.37	30.56 2.40	31.09 2.30	29.13 2.43	28.86 2.11	28.42 2.30
	26.96 2.48	28.65 2.18	29.65 2.08	29.15 2.63	29.89 3.01	30.25 2.77	29.70 1.78	28.54 2.50	
		27.30 2.46	27.97 2.55	28.21 2.41	29.21 2.33	29.45 2.38	28.73 2.67		Fovea
			26.32 2.60	26.28 2.89	27.21 3.42	27.90 2.58			34.90 2.18

Figure 3.2b. The group mean sensitivity for each stimulus location (upper value) and one standard deviation of the mean (lower value) for the HFA750 Full Threshold and FASTPAC algorithms.

SITA Standard

			25.48 3.97	25.20 3.48	24.14 3.99	23.32 4.23		
		26.62 3.21	27.32 3.04	27.20 2.81	26.42 2.60	26.64 2.33	26.28 4.20	
	27.10 2.89	28.90 2.36	29.54 1.67	29.22 1.94	28.86 1.93	29.36 2.10	28.40 2.24	26.96 4.21	
26.16 3.37	28.24 3.27	30.54 1.95	31.14 2.68	31.44 1.72	30.80 1.91	29.94 1.88	29.56 2.24	28.20 3.14	27.30 5.02
27.16 3.06	29.22 1.87	31.38 1.76	32.16 1.60	32.76 1.78	32.20 1.80	31.18 1.98		29.48 2.49	29.24 2.66
26.94 3.68	29.44 2.34	31.70 1.83	32.64 1.75	32.90 1.79	33.00 1.69	31.72 1.91		29.98 2.58	29.82 2.44
26.42 3.43	28.76 1.97	30.88 1.71	32.44 1.64	32.16 1.66	31.88 1.78	31.92 1.91	30.78 2.18	29.82 1.85	29.32 3.08
	27.78 2.79	29.82 1.35	30.56 1.73	30.64 2.13	30.62 2.13	31.28 1.64	30.56 1.75	29.56 2.60	
		28.34 2.65	28.70 2.20	29.40 1.95	30.08 2.09	30.18 1.55	29.68 2.41		
			26.92 2.84	27.50 2.57	28.66 2.40	28.70 2.95		Fovea 37.50 2.62

SITA Fast

			25.60 3.21	25.60 2.75	24.26 3.04	24.36 3.29		
		27.44 2.98	27.72 2.28	28.12 1.97	27.34 2.77	27.02 2.41	27.48 2.77	
	27.82 2.36	28.98 1.93	29.52 2.14	29.54 1.76	29.44 1.96	29.12 1.86	28.56 2.33	28.38 3.03	
27.42 2.62	28.96 1.78	30.56 2.02	31.58 1.81	31.60 1.75	31.22 1.57	30.42 2.06	29.76 2.56	29.50 2.03	28.88 2.87
27.90 2.21	29.76 1.74	31.76 1.61	32.26 1.78	32.96 1.86	32.72 1.51	31.30 1.75		30.50 2.06	29.78 2.23
27.56 2.36	30.16 1.87	32.16 1.57	32.66 1.75	33.24 1.71	33.30 1.50	32.46 1.53		30.72 1.62	30.42 1.89
27.08 3.19	29.38 1.83	31.36 1.54	32.36 1.83	32.46 1.36	32.26 1.63	32.16 1.71	31.04 2.33	30.40 1.67	29.96 2.59
	28.72 2.70	30.08 1.72	31.00 1.75	30.78 2.87	31.14 2.11	31.26 1.85	31.00 1.58	30.18 2.68	
		28.78 2.67	29.46 1.76	29.64 2.22	30.48 1.94	30.50 1.66	29.94 2.05		
			27.82 2.59	28.32 2.06	28.68 3.23	28.96 2.81		Fovea 37.14 2.29

Figure 3.2c. The group mean sensitivity for each stimulus location (upper value) and one standard deviation of the mean (lower value) for the SITA Standard and SITA Fast algorithms.

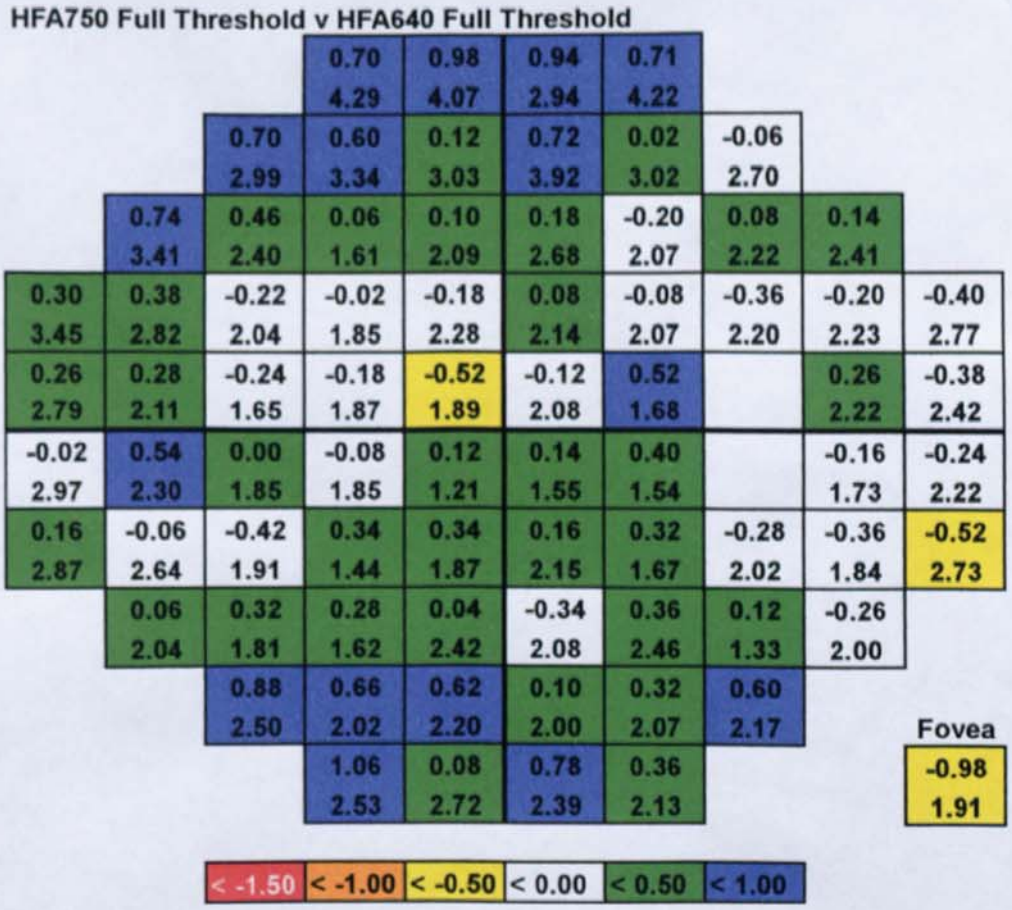


Figure 3.3a. The group mean between-algorithm difference in sensitivity for each stimulus location (upper value) and one standard deviation of the mean (lower value) between the HFA750 Full Threshold and the HFA640 Full Threshold algorithms.

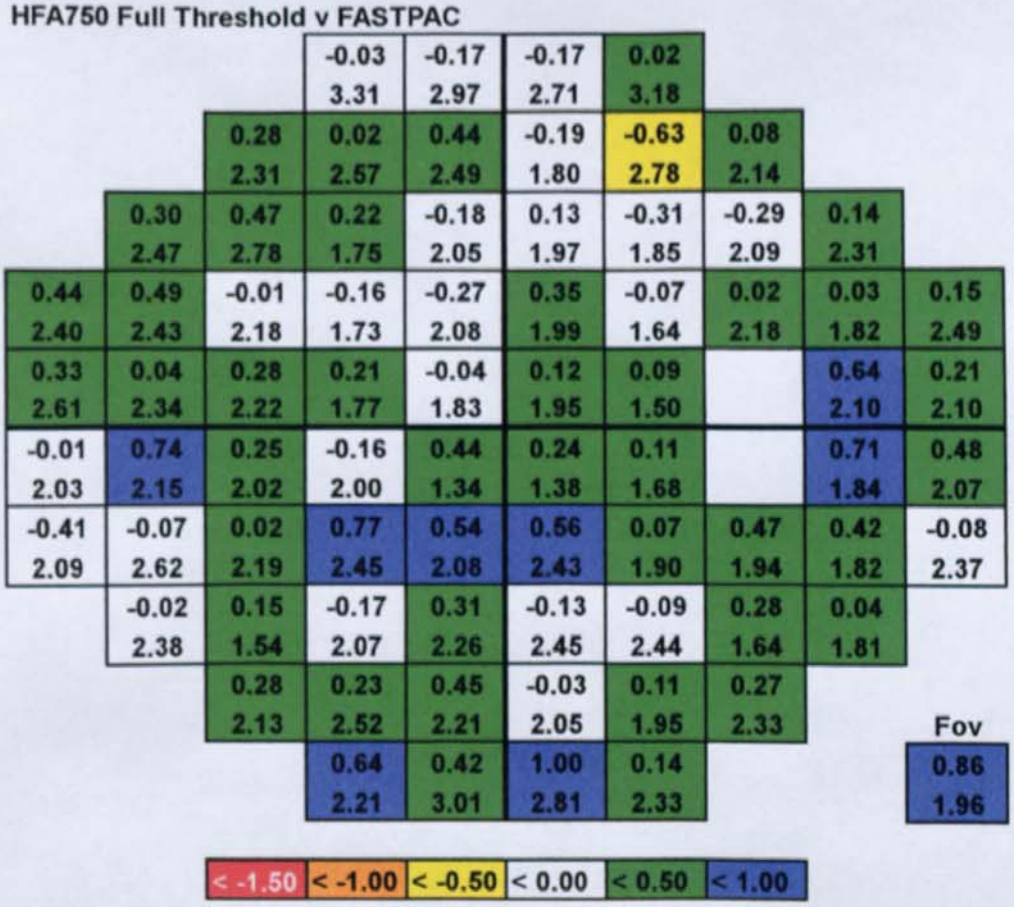


Figure 3.3b. The group mean between-algorithm difference in sensitivity for each stimulus location (upper value) and one standard deviation of the mean (lower value) between the HFA750 Full Threshold and the FASTPAC algorithms.

HFA750 Full Threshold v SITA Standard

			-1.48 3.74	-0.66 2.85	-0.86 3.49	-0.50 4.31			
		-0.60 2.17	-0.84 2.14	-0.50 2.23	0.00 2.47	-0.84 2.79	-0.38 3.78		
	-0.66 2.39	-1.14 2.07	-1.48 1.85	-0.96 1.86	-0.80 1.85	-1.72 1.75	-0.98 1.97	0.12 3.38	
-0.14 2.86	-0.68 2.86	-1.44 1.53	-0.42 2.13	-1.48 1.91	-1.12 1.60	-0.78 1.66	-1.40 2.25	-0.28 2.12	0.06 4.65
-0.64 2.08	-0.66 1.89	-1.14 1.84	-0.96 1.48	-1.44 1.59	-0.72 1.88	-0.86 1.48		-0.22 2.38	-0.80 2.20
-0.46 2.88	-0.60 1.88	-1.10 1.66	-1.48 1.85	-1.10 1.39	-0.90 1.39	-0.64 1.75		-0.50 1.94	-0.70 1.96
-0.62 2.53	-1.00 2.13	-1.38 1.60	-0.72 1.46	-1.20 1.58	-0.76 1.73	-0.76 1.57	-1.18 1.78	-0.54 1.85	-0.98 3.24
	-0.84 2.15	-1.02 1.78	-1.08 1.54	-1.18 2.45	-0.86 1.82	-1.12 1.56	-0.58 1.42	-0.98 2.21	
		-0.76 2.03	-0.50 1.83	-0.74 1.97	-0.90 1.91	-0.62 1.50	-0.68 2.26		
			0.04 2.41	-0.80 2.43	-0.40 2.31	-0.66 2.35			

Fov
-1.74 2.27

HFA750 Full Threshold v SITA Fast

			-1.60 3.89	-1.06 2.94	-0.98 3.62	-1.54 4.00			
		-1.42 2.07	-1.24 1.99	-1.42 1.90	-0.92 2.18	-1.22 3.04	-1.58 2.25		
	-1.38 2.76	-1.22 1.85	-1.46 1.94	-1.28 1.70	-1.38 2.01	-1.48 2.08	-1.14 2.29	-1.30 2.53	
-1.40 2.26	-1.40 2.08	-1.46 1.79	-0.86 1.86	-1.64 1.64	-1.54 1.83	-1.26 1.55	-1.60 1.90	-1.58 2.15	-1.52 2.83
-1.38 2.04	-1.20 1.87	-1.52 1.87	-1.06 1.46	-1.64 1.71	-1.24 1.99	-0.98 1.44		-1.24 1.82	-1.34 2.21
-1.08 2.01	-1.32 1.61	-1.56 1.59	-1.50 1.46	-1.44 1.05	-1.20 1.41	-1.38 1.28		-1.24 1.62	-1.30 2.36
-1.28 2.98	-1.62 2.00	-1.86 1.91	-0.64 1.41	-1.50 1.53	-1.14 1.83	-1.00 1.54	-1.44 2.21	-1.12 1.80	-1.62 2.85
	-1.78 2.17	-1.28 1.41	-1.52 1.49	-1.32 2.07	-1.38 1.69	-1.10 1.66	-1.02 1.29	-1.60 2.60	
		-1.20 2.36	-1.26 1.78	-0.98 1.95	-1.30 1.47	-0.94 1.87	-0.94 2.08		
			-0.86 2.43	-1.62 2.51	-0.42 2.31	-0.92 2.33			

Fov
-1.38 1.69

< -1.50	< -1.00	< -0.50	< 0.00	< 0.50	< 1.00

Figure 3.3c. The group mean between-algorithm difference in sensitivity for each stimulus location (upper value) and one standard deviation of the mean (lower value) between the HFA750 Full Threshold and the SITA Standard (top) and SITA Fast (bottom) algorithms.

FASTPAC v SITA Standard

			-1.45 3.18	-0.49 3.26	-0.69 2.97	-0.52 4.48		
		-0.88 3.08	-0.86 2.26	-0.94 2.68	0.19 2.43	-0.21 2.25	-0.46 4.05	
	-0.96 2.79	-1.61 1.87	-1.70 1.94	-0.78 2.23	-0.93 2.15	-1.41 1.75	-0.69 1.69	-0.02 3.33	
-0.58 2.87	-1.17 2.31	-1.43 1.80	-0.26 2.40	-1.21 1.70	-1.47 1.89	-0.71 1.83	-1.42 1.86	-0.31 2.38	-0.09 4.06
-0.97 2.36	-0.70 2.12	-1.42 2.07	-1.17 1.54	-1.40 1.69	-0.84 1.93	-0.95 1.47		-0.86 2.28	-1.01 2.53
-0.45 2.71	-1.34 2.20	-1.35 1.55	-1.32 2.02	-1.54 1.62	-1.14 1.67	-0.75 2.08		-1.21 1.95	-1.18 2.23
-0.21 2.94	-0.93 2.77	-1.40 1.65	-1.49 2.21	-1.74 2.10	-1.32 1.95	-0.83 1.54	-1.65 2.00	-0.96 1.96	-0.90 2.90
	-0.82 2.69	-1.17 1.68	-0.91 2.09	-1.49 2.60	-0.73 2.26	-1.03 2.02	-0.86 1.56	-1.02 2.23	
		-1.04 2.35	-0.73 2.32	-1.19 1.99	-0.87 2.55	-0.73 2.14	-0.95 2.39		
			-0.60 2.69	-1.22 2.90	-1.45 2.85	-0.80 2.53			Fov -2.60 1.91

FASTPAC v SITA Fast

			-1.57 2.95	-0.89 2.68	-0.81 2.94	-1.56 3.27		
		-1.70 2.49	-1.26 2.08	-1.86 2.26	-0.73 2.00	-0.59 2.75	-1.66 2.54	
	-1.68 2.52	-1.69 2.63	-1.68 2.09	-1.10 2.10	-1.51 2.23	-1.17 2.00	-0.85 2.16	-1.44 2.69	
-1.84 2.77	-1.89 2.25	-1.45 2.12	-0.70 1.95	-1.37 1.59	-1.89 1.90	-1.19 1.66	-1.62 2.59	-1.61 2.53	-1.67 1.97
-1.71 2.83	-1.24 1.93	-1.80 1.75	-1.27 1.67	-1.60 1.84	-1.36 2.00	-1.07 1.72		-1.88 2.17	-1.55 2.70
-1.07 2.05	-2.06 2.11	-1.81 1.75	-1.34 2.00	-1.88 1.46	-1.44 1.65	-1.49 1.79		-1.95 2.02	-1.78 2.24
-0.87 2.86	-1.55 2.42	-1.88 2.29	-1.41 2.37	-2.04 1.99	-1.70 1.94	-1.07 1.57	-1.91 2.36	-1.54 1.69	-1.54 2.27
	-1.76 2.22	-1.43 1.78	-1.35 2.02	-1.63 2.58	-1.25 2.42	-1.01 2.35	-1.30 1.43	-1.64 2.84	
		-1.48 2.41	-1.49 2.36	-1.43 2.11	-1.27 2.05	-1.05 2.25	-1.21 2.37		
			-1.50 2.65	-2.04 2.56	-1.47 2.85	-1.06 3.00			Fov -2.24 2.02

< -1.50	< -1.00	< -0.50	< 0.00	< 0.50	< 1.00

Figure 3.3d. The group mean between-algorithm difference in sensitivity for each stimulus location (upper value) and one standard deviation of the mean (lower value) between the FASTPAC and the SITA Standard (top) and SITA Fast (bottom) algorithms.

SITA Standard v SITA Fast

			-0.12 3.17	-0.40 2.44	-0.12 3.37	-1.04 3.75		
		-0.82 2.38	-0.40 2.14	-0.92 1.95	-0.92 2.02	-0.38 2.23	-1.20 3.07	
	-0.72 3.16	-0.08 2.02	0.02 1.80	-0.32 1.83	-0.58 1.75	0.24 1.53	-0.16 2.13	-1.42 3.17	
-1.26 2.89	-0.72 2.71	-0.02 1.77	-0.44 2.41	-0.16 1.57	-0.42 1.57	-0.48 1.27	-0.20 2.27	-1.30 2.87	-1.58 3.93
-0.74 2.28	-0.54 1.72	-0.38 1.51	-0.10 1.46	-0.20 1.58	-0.52 1.36	-0.12 1.53		-1.02 2.11	-0.54 1.95
-0.62 2.51	-0.72 1.57	-0.46 1.37	-0.02 1.45	-0.34 1.45	-0.30 1.53	-0.74 1.47		-0.74 1.89	-0.60 1.95
-0.66 3.04	-0.62 1.56	-0.48 1.46	0.08 1.64	-0.30 1.46	-0.38 1.63	-0.24 1.33	-0.26 2.02	-0.58 1.73	-0.64 3.10
	-0.94 1.99	-0.26 1.60	-0.44 1.68	-0.14 2.39	-0.52 1.58	0.02 1.61	-0.44 1.15	-0.62 2.34	
		-0.44 2.37	-0.76 1.64	-0.24 1.45	-0.40 1.93	-0.32 1.57	-0.26 2.07		Fov
			-0.90 2.82	-0.82 2.21	-0.02 2.95	-0.26 2.40			0.36 2.03

< -1.50	< -1.00	< -0.50	< 0.00	< 0.50	< 1.00

Figure 3.3e. The group mean between-algorithm difference in sensitivity for each stimulus location (upper value) and one standard deviation of the mean (lower value) between the SITA Standard and SITA Fast algorithms.

Whilst all but five locations had a higher sensitivity for SITA Fast when compared to SITA Standard the difference was greater than 1 dB at only seven stimulus locations. No consistent spatial dependency was present in the difference in sensitivity between any pair of algorithms; i.e. the shape of the hill-of-vision was the same for each algorithm.

3.4.2.3 Root Mean Square Deviation

The cumulative ranking of the stimulus locations as a function of the root mean square difference between the Full threshold algorithm and the FASTPAC, SITA Standard and SITA Fast algorithms, respectively, are shown in Figure 3.4a and between the FASTPAC and SITA Standard and SITA Fast algorithms, respectively, in Figure 3.4b. The magnitude of the deviation between the Full threshold algorithm and the SITA Standard algorithm up to the 37th stimulus location (i.e. the 50th percentile) was 2.2 dB. The 10th percentile deviation (i.e. up to the 8th stimulus location) was 1.8 dB and the 90th percentile (i.e. up to the 67th stimulus location) was 2.9 dB. The magnitudes of the root mean square differences between the Full Threshold and the SITA Standard Algorithm were similar to that between the Full Threshold and FASTPAC algorithm. The corresponding figures for the root mean square difference between the Full Threshold and the SITA Fast algorithm for the three percentiles were 1.9 dB, 2.4 dB and 3.1 dB.

The deviations corresponding to the 50th percentile between the FASTPAC and the SITA Standard and SITA Fast algorithms were 2.4 dB and 2.7 dB respectively. The 10th percentiles were 2.0 dB and 2.1 dB respectively and the 90th percentiles 3.2 dB and 3.1 dB. The corresponding data between the SITA Standard and SITA Fast algorithms are shown in Figure 3.4c. The 10th, 50th and 90th percentiles for the difference in RMS deviation between SITA Standard and SITA Fast were 1.5 dB, 2.0 dB and 3.1 dB respectively.

The 50th percentile of the cumulative ranking of the stimulus locations as a function of the RMS deviation between the various algorithms for the central and peripheral annuli and for the inferior, superior, nasal and temporal hemifields are given in Table 3.2. The stimulus locations used for the central and peripheral annuli are shown in Figure 3.5, 14 peripheral

locations, selected at random, were excluded from the analysis in order to ensure an identical number of central and peripheral locations. The 50th percentile RMS deviation was smallest for the central annulus and smallest between the SITA Standard and SITA Fast algorithms. The percentile was greatest for the peripheral annulus and greatest between the FASTPAC and SITA algorithms.

3.4.2.4 Between-Subject Between-Algorithm Variability

The SDs of the group mean sensitivity at each of the 74 stimulus locations (i.e. the between-subject normal variability) for the FASTPAC, SITA Standard and SITA Fast algorithms expressed as a ratio of that of the Full Threshold algorithm at the corresponding location is shown in Figure 3.6. At the edge locations in the nasal, inferior and temporal locations, the SDs were larger for the SITA Standard algorithm compared to the Full Threshold algorithm by approximately 18%. However, within approximately 21° eccentricity the SDs for the SITA Standard algorithm were smaller by, on average, 8%. The SITA Fast algorithm exhibited 43 locations with SDs which were smaller by at least 10% compared to the Full Threshold algorithm. Of these 43 locations, 25 exhibited SDs which were smaller by 20% or more. The between-subject variability of the edge locations for the SITA Fast algorithm was similar to that of the Full Threshold algorithm. Within approximately 21° eccentricity, the SDs for the SITA Fast algorithm were on average 15% lower than those of the corresponding locations for the Full Threshold algorithm.

The ratios of the SDs at each stimulus location for the SITA Standard and SITA Fast algorithms relative to those for the FASTPAC algorithm are shown in Figure 3.7. The SITA Standard algorithm exhibited a higher between-subject variability at the edge locations and lower variability for the more central locations compared to FASTPAC. The SDs for the SITA Fast algorithm were smaller than those for FASTPAC at the majority of stimulus locations by approximately 18%.

a)

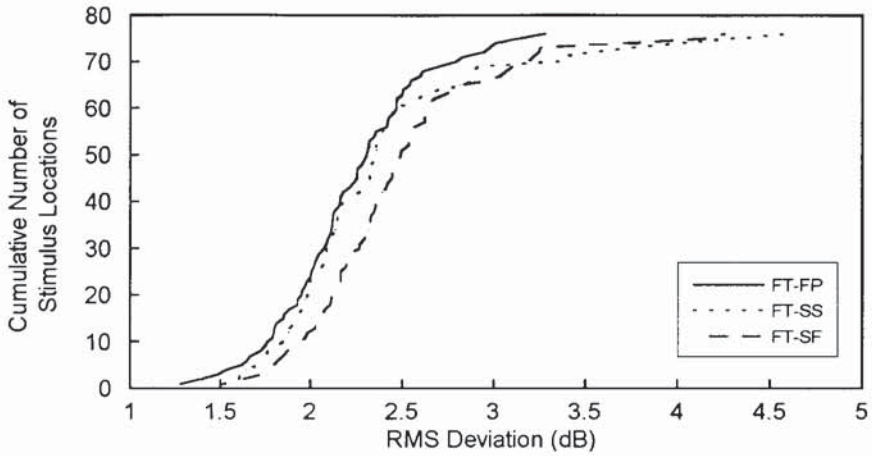
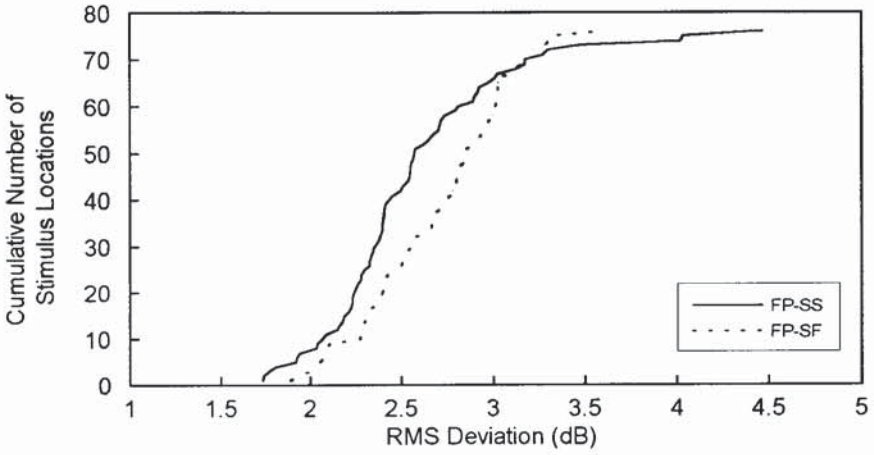


Figure 3.4. The cumulative number of stimulus locations as a function of the Root Mean Square (RMS) deviation between the HFA750 Full Threshold and the FASTPAC, SITA Standard and SITA Fast algorithms.

b)



c)

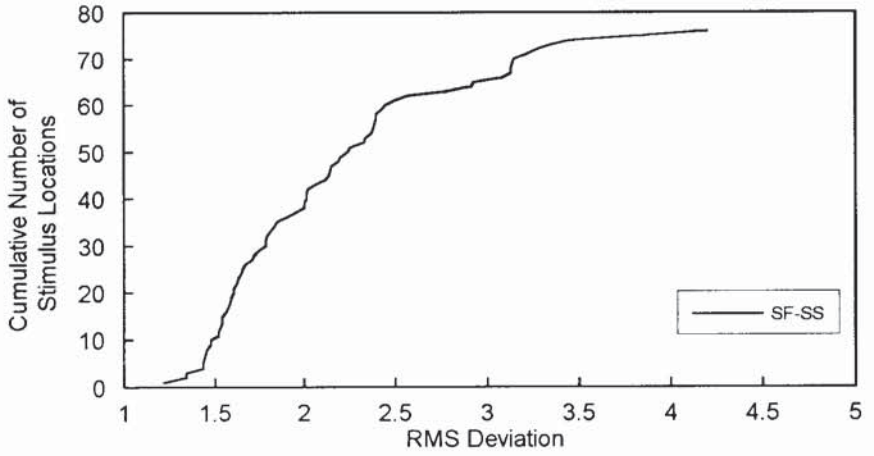


Figure 3.4 continued. The cumulative number of stimulus locations as a function of the Root Mean Square (RMS) deviation between b) the FASTPAC and the SITA Standard and SITA Fast algorithms and c) between the SITA Standard and SITA Fast algorithms.

	Central	Peripheral	Superior	Inferior	Temporal	Nasal
FT_{750}-FT_{640}	1.94	2.56	2.39	2.08	2.17	2.27
FT_{750}-FP	1.99	2.30	2.16	2.12	2.06	2.24
FT_{750}-SS	2.00	2.32	2.32	2.06	2.12	2.19
FT_{750}-SF	2.15	2.51	2.42	2.17	2.36	2.34
FP-SS	2.27	2.56	2.41	2.43	2.36	2.54
FP-SF	2.46	2.93	2.68	2.72	2.67	2.78
SF-SS	1.58	2.33	2.15	1.72	2.01	1.82

Table 3.2. The 50th percentile of the cumulative RMS deviation for all algorithm comparisons for the central, peripheral, superior, inferior, temporal and nasal regions of the visual field. FT_{640} indicates HFA640 Full Threshold, FT_{750} indicates HFA750 Full Threshold, FP indicates FASTPAC, SS indicates SITA Standard and SF indicates SITA Fast.

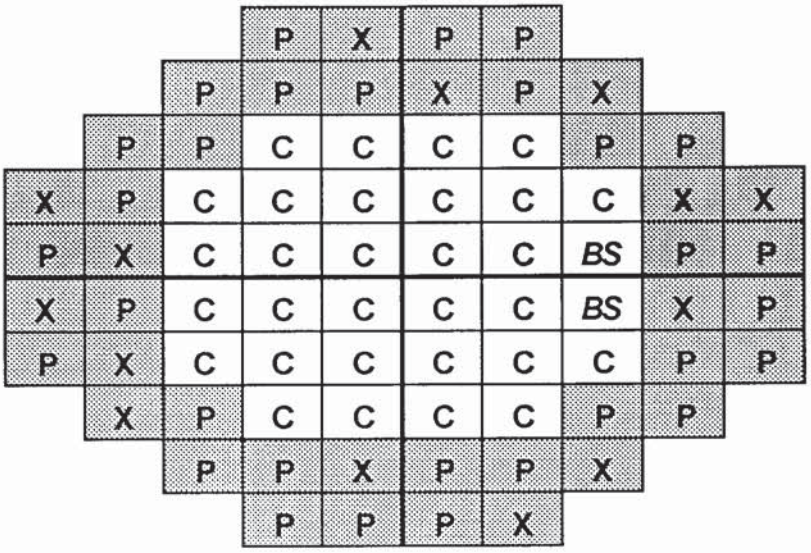


Figure 3.5. The stimulus locations used for the central and peripheral annuli analysis. BS denotes a blind spot location excluded from all analyses; C denotes a central location; P denotes a peripheral location included in the analysis; X denotes a peripheral location excluded from the analysis.

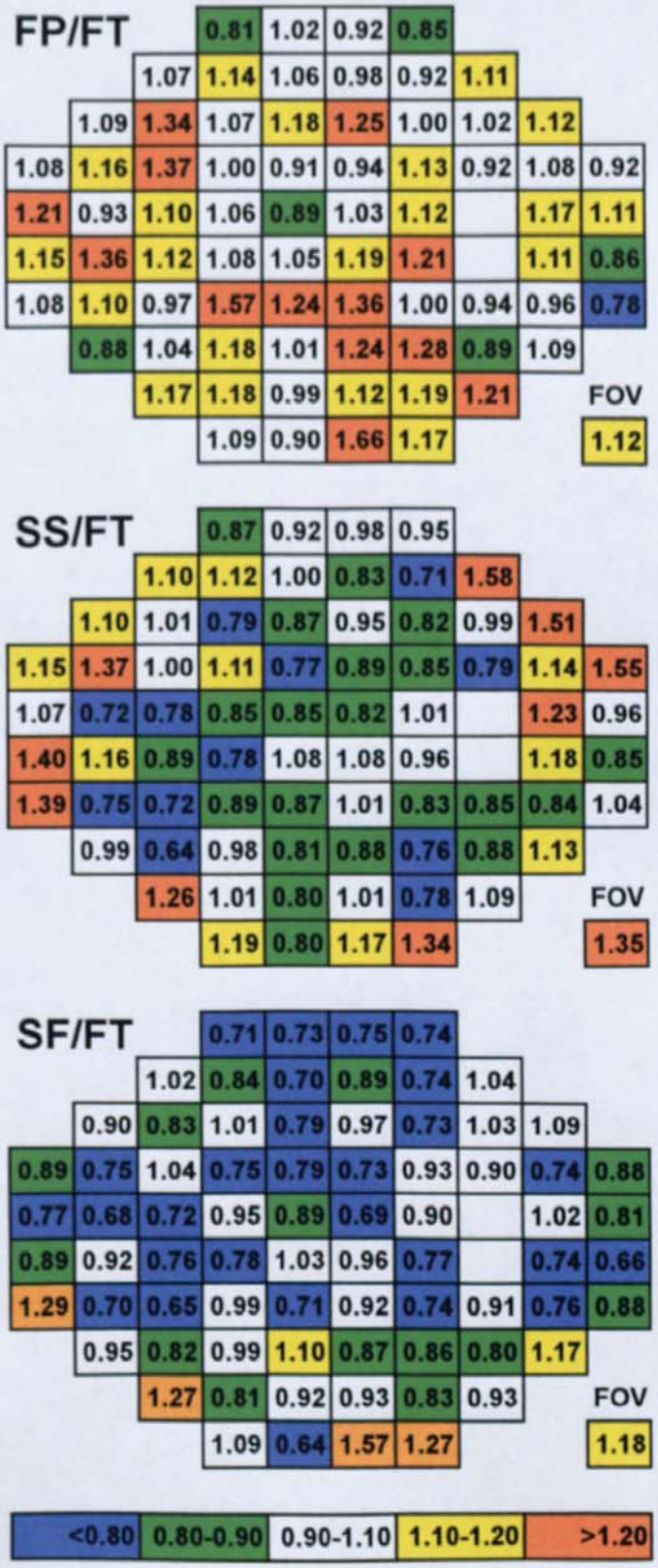


Figure 3.6. The standard deviation of the group mean sensitivity at each of the 74 stimulus locations (ie the between-subject normal variability) for the FASTPAC (FP), SITA Standard (SS) and SITA Fast (SF) algorithims expressed as a ratio of that of the HFA750 Full Threshold (FT) algorithm at the corresponding location.

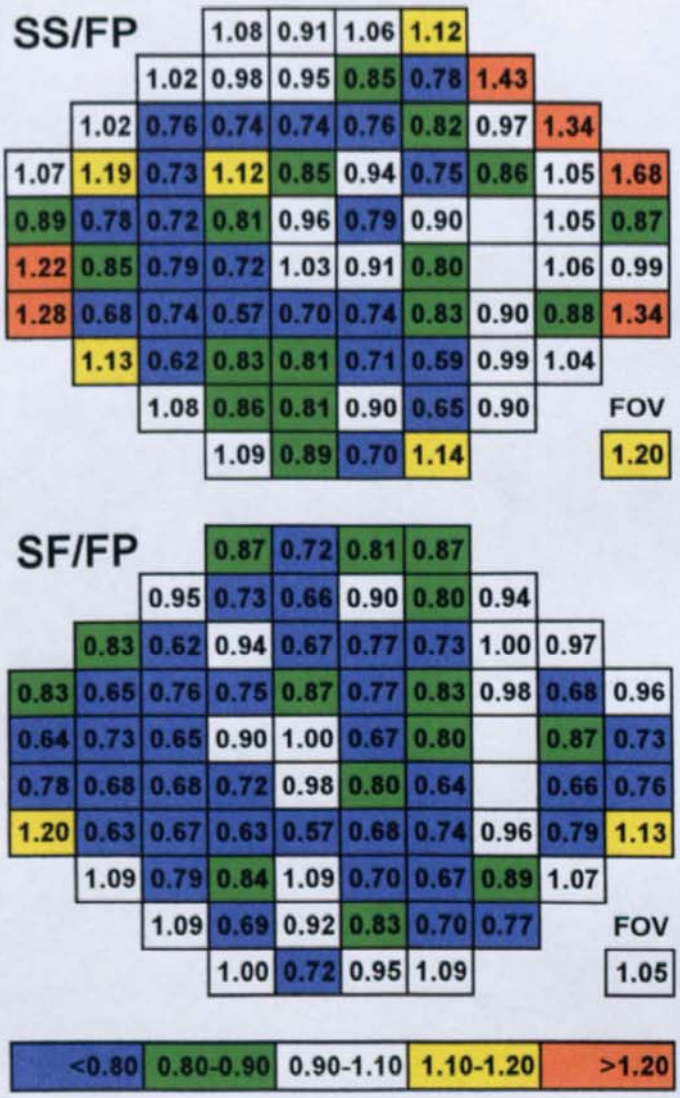


Figure 3.7. The standard deviation of the group mean sensitivity at each of the 74 stimulus locations (ie the between-subject normal variability) for the SITA Standard (SS) and SITA Fast (SF) algorithims expressed as a ratio of that of the FASTPAC (FP) algorithm at the corresponding location.

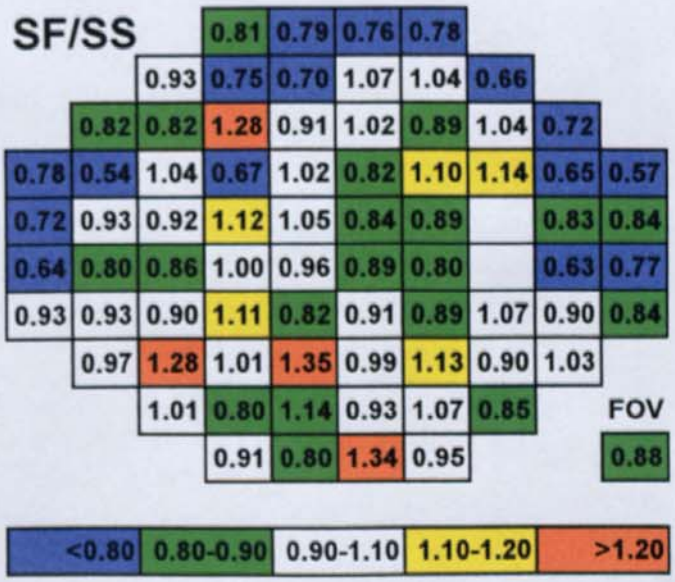


Figure 3.8. The standard deviation of the group mean sensitivity at each of the 74 stimulus locations (ie the between-subject normal variability) for the SITA Fast (SF) algorithim expressed as a ratio of that of the SITA Standard (SS) algorithm at the corresponding location.

The ratios of the SDs at each stimulus location for the SITA Fast relative to SITA Standard are shown in Figure 3.8. Within an eccentricity of approximately 21° there was little difference in the SDs between the two algorithms. However, the SDs at the edge locations were 15% greater with SITA Standard.

3.4.3 The Effect of Age on the Between-Algorithm Difference in Sensitivity and Between-Subject Variability

The group mean sensitivity and one standard deviation of the mean are shown in Figure 3.9 for each algorithm for the 21 subjects below 50 years of age and for 21 randomly selected subjects from the 29 aged over 50 years.

For each algorithm, at each location the standard deviation of the measured sensitivities for the subjects less than 50 years of age were expressed as a ratio of the standard deviation of the measured sensitivities for subjects greater than 50 years of age. The mean ratio for the 74 stimulus locations and for the central and peripheral annuli (defined in Figure 3.5) are shown in Table 3.3a. These results indicate that the between-subject variability is narrower for the younger subjects than for the older subjects for each of the algorithms. This is likely to lead to narrower confidence limits for normality in the younger age groups compared to the older age groups.

Table 3.3b shows the between-algorithm between-subject variability for each pair of algorithms for the subjects aged less than 50 years for all the 74 stimulus locations and for the central and peripheral annuli. The corresponding data for the subjects aged greater than 50 years is shown in Table 3.3c. The between-algorithm between-subject variability for the Full Threshold and FASTPAC algorithms is similar for both age groups. Both the SITA strategies show a lower between-algorithm between-subject variability than either the Full Threshold or the FASTPAC algorithms in the older age group. This would indicate that the confidence limits for normality with SITA would increase with age at a lower rate than the confidence limits for normality with Full Threshold or FASTPAC. The effect of age on the

between-algorithm between-subject variability is proportionately the same at all eccentricities.

HFA640 Full Threshold

Less than 50 years

			25.86 3.38	26.24 3.66	24.14 3.20	23.88 4.51			
		27.43 2.06	27.90 2.36	27.95 2.73	27.76 2.41	27.43 2.11	28.10 2.64		
	27.76 1.73	28.67 1.15	29.52 1.66	29.29 2.03	29.05 2.33	29.33 1.88	29.00 2.19	28.81 2.18	
27.90 1.95	28.19 2.52	30.86 1.74	32.33 1.46	31.67 1.32	31.05 1.72	31.00 1.34	30.33 1.39	29.52 2.09	29.81 1.78
27.76 2.32	29.57 1.69	31.76 1.34	32.67 1.32	33.19 1.54	32.86 1.49	31.52 1.66		30.52 1.89	30.71 2.03
28.29 2.12	29.29 2.31	32.10 1.73	32.43 1.29	32.52 1.40	33.00 1.18	32.05 1.20		31.24 1.34	30.95 1.86
27.48 3.12	29.90 1.61	30.95 1.36	32.67 1.35	31.71 1.06	32.38 1.36	32.38 1.20	31.14 1.85	30.76 1.73	30.48 1.66
	28.52 1.66	29.90 1.26	30.52 1.54	30.90 1.95	31.29 1.31	30.81 1.99	31.05 1.47	30.19 1.25	
		28.05 1.36	28.86 1.74	29.48 2.27	30.10 1.48	30.29 1.45	29.38 1.91		
			27.86 2.20	27.90 1.73	29.00 1.26	29.00 1.55			Fovea 38.05 1.28

Greater than 50 years

			21.62 4.27	22.14 4.07	21.05 4.13	21.38 5.85			
		24.24 3.78	24.86 4.08	25.76 3.19	24.05 4.70	24.52 3.82	24.00 3.11		
	25.14 2.73	26.62 2.84	27.00 1.82	27.90 2.28	27.14 2.41	26.76 2.79	25.81 2.48	26.00 2.72	
24.29 3.84	26.81 2.04	28.48 1.40	30.14 1.77	29.33 2.48	28.76 2.14	28.33 1.74	27.14 2.59	27.14 2.52	26.29 2.55
25.33 4.23	27.57 2.01	29.76 2.14	30.86 1.62	31.38 1.63	31.14 1.62	28.62 2.20		27.76 2.57	28.05 2.16
24.90 3.81	27.90 2.05	29.52 2.09	30.71 1.59	31.29 1.31	31.43 1.80	29.95 1.96		28.48 2.36	28.29 2.85
24.33 2.89	26.62 2.73	29.33 1.32	30.71 1.45	29.86 1.35	29.71 2.39	30.10 2.19	29.14 1.85	28.95 2.25	27.29 2.47
	25.81 1.66	27.67 2.03	28.43 1.57	28.48 2.18	29.10 2.23	29.00 2.53	29.14 1.35	27.71 2.31	
		26.19 2.44	26.62 2.33	27.00 1.67	28.48 2.36	28.19 1.89	27.76 2.64		Fovea
			24.48 2.82	25.76 2.49	26.33 1.93	26.62 1.63			36.05 1.86

Figure 3.9a. The group mean sensitivity for each stimulus location (upper value) and one standard deviation of the mean (lower value) for the HFA640 Full Threshold algorithm for the subjects aged less than 50 years (top) and aged greater than 50 years (bottom).

HFA750 Full Threshold

Less than 50 years

			26.67 3.07	27.00 2.26	24.95 3.23	24.95 3.77		
		27.62 1.72	27.90 2.47	28.10 2.34	28.62 2.36	27.81 2.36	27.43 2.25	
	28.19 1.57	29.38 1.77	29.38 1.77	29.24 1.92	29.29 1.52	28.81 1.94	28.57 2.16	28.19 1.94	
27.81 1.21	29.19 1.75	30.52 1.36	32.19 1.50	31.05 1.72	31.14 1.28	30.52 1.66	29.48 2.27	29.90 1.41	29.24 2.28
28.19 1.75	30.00 1.70	31.33 1.68	32.33 1.43	32.57 1.66	32.57 1.57	31.71 0.96		30.29 1.76	30.05 2.11
28.14 1.80	30.24 1.26	31.95 1.50	32.67 1.53	32.76 1.18	33.10 0.94	32.33 1.32		30.19 2.09	30.67 2.22
27.00 2.35	29.38 1.28	31.10 1.41	32.95 1.36	32.38 1.20	31.81 0.98	32.52 1.47	30.67 2.08	30.19 1.89	29.71 3.48
	28.29 2.22	29.95 1.47	30.57 1.21	30.90 1.73	30.90 1.95	30.62 2.01	30.76 1.92	29.38 1.99	
		28.24 2.07	29.48 1.66	29.62 1.28	30.29 1.71	30.48 1.47	29.81 1.99		
			28.33 2.08	28.67 1.71	29.38 1.43	29.10 2.05			

Fovea

36.67 1.68

Greater than 50 years

			21.71 4.57	23.05 3.64	22.33 4.62	22.00 3.78		
		24.52 3.27	25.33 2.56	25.48 2.87	24.52 2.94	24.24 3.46	24.29 2.49	
	25.05 2.58	26.43 2.16	27.19 1.86	27.48 1.91	26.81 1.91	27.00 2.10	26.19 1.97	26.67 2.61	
24.71 3.24	26.33 1.98	28.19 1.60	29.81 2.52	28.76 2.23	28.33 2.11	27.71 2.05	26.76 3.08	26.52 2.16	25.86 3.48
25.52 2.93	27.62 2.87	29.43 2.58	30.43 1.80	30.57 1.86	30.52 2.16	28.90 1.92		28.29 1.95	27.14 2.43
25.10 2.53	27.76 2.05	29.67 1.88	29.90 1.84	30.95 1.53	31.33 1.49	30.10 2.07		29.14 2.15	28.14 2.26
25.00 2.21	26.81 2.52	28.10 1.89	30.67 1.71	29.71 1.76	30.43 2.23	30.19 2.54	28.71 2.87	28.52 2.29	27.43 2.09
	26.10 2.36	27.90 2.23	28.76 1.84	28.48 2.80	28.76 2.41	29.71 2.10	29.19 1.83	27.67 2.37	
		27.05 2.11	27.19 1.89	27.76 3.18	28.38 1.86	28.71 2.19	28.43 2.44		
			25.76 2.23	24.62 3.53	27.71 1.62	27.52 2.06			

Fovea

35.24 1.87

Figure 3.9b. The group mean sensitivity for each stimulus location (upper value) and one standard deviation of the mean (lower value) for the HFA750 Full Threshold algorithm for the subjects aged less than 50 years (top) and aged greater than 50 years (bottom).

FASTPAC

Less than 50 Years

			26.69 2.56	26.57 2.87	25.69 2.65	25.05 2.50		
		27.33 2.24	28.24 2.02	27.81 2.04	28.33 2.15	27.88 2.94	27.90 2.05	
	27.90 1.87	28.81 2.04	29.38 1.56	29.45 2.34	29.10 2.14	29.17 2.17	28.95 2.20	28.67 1.98
27.81 1.69	28.74 1.64	30.67 2.13	32.07 1.43	31.31 1.66	30.31 1.94	30.50 2.29	29.17 2.16	30.02 1.68	28.67 2.13
28.33 1.96	30.10 1.14	30.95 2.20	32.24 1.45	32.38 1.43	32.74 1.85	31.52 1.21		29.55 1.84	30.02 1.81
28.64 1.64	29.71 1.50	31.93 1.63	33.00 1.73	32.29 1.09	32.98 1.25	32.19 1.44		29.93 1.58	30.00 2.36
27.79 1.89	29.43 2.11	30.57 1.96	32.64 1.49	31.71 1.79	31.90 1.76	32.43 1.11	29.62 1.96	29.48 1.69	29.76 1.89
	28.26 1.69	29.79 1.71	30.86 1.39	30.71 1.95	31.33 2.35	31.62 2.60	30.40 1.59	29.71 1.52	
		28.24 2.05	29.14 2.08	29.81 1.78	30.19 2.32	30.48 1.47	29.98 2.40		
			27.52 2.06	27.79 2.10	29.05 1.24	29.40 2.19			Fovea 36.05 1.91

Greater than 50 years

			21.95 3.21	23.26 4.18	21.38 3.92	21.12 3.75		
		24.76 3.48	24.86 3.32	25.05 3.09	25.36 3.25	25.48 2.62	24.10 2.61	
	25.10 3.04	26.79 2.21	26.57 2.16	27.57 2.80	27.33 2.82	27.33 2.28	26.55 1.95	26.05 3.02	
24.36 2.76	26.14 2.01	28.50 2.01	30.43 2.70	29.86 2.01	28.62 1.98	28.21 2.48	27.69 2.36	26.90 2.32	26.62 2.69
25.00 2.95	27.86 2.15	29.57 2.66	30.21 1.37	30.43 1.72	30.83 1.74	29.12 2.37		28.02 2.23	27.14 2.83
25.45 2.62	26.86 3.23	29.43 2.13	30.21 2.21	30.64 1.85	31.07 2.00	30.21 2.86		28.14 2.55	27.95 2.07
25.14 2.65	26.93 2.97	28.50 2.31	29.74 3.19	29.43 2.56	29.57 2.52	30.21 2.75	28.64 2.87	28.33 2.33	27.52 2.30
	26.07 2.68	27.79 2.37	28.86 2.20	28.00 2.32	28.79 3.49	29.21 2.52	29.43 1.76	27.52 2.89	
		26.81 2.54	27.43 2.84	26.93 2.18	28.36 1.93	28.36 2.76	27.64 2.34		Fovea
			25.07 2.89	24.74 2.92	26.57 3.50	26.93 1.93			34.19 1.99

Figure 3.9c. The group mean sensitivity for each stimulus location (upper value) and one standard deviation of the mean (lower value) for the FASTPAC algorithm for the subjects aged less than 50 years (top) and aged greater than 50 years (bottom).

SITA Standard

Less than 50 years

			27.57 3.08	27.62 1.99	26.14 2.94	24.62 4.46		
		28.52 2.09	29.05 2.13	28.86 2.03	28.05 2.38	28.00 1.82	28.24 3.03	
	28.71 2.41	30.19 1.50	30.38 1.28	29.90 2.00	29.71 1.93	30.62 1.66	29.81 1.54	28.90 2.34
28.05 2.01	29.81 1.54	31.71 1.49	32.43 1.33	32.19 1.99	31.81 1.72	31.29 1.71	30.81 1.81	29.62 1.50	29.19 1.91
28.71 2.26	30.19 1.69	32.14 1.62	33.14 1.46	33.86 1.88	33.14 1.53	32.38 1.24		30.67 1.83	30.76 2.17
28.95 1.83	30.67 1.46	32.81 1.47	33.71 1.71	34.05 1.47	34.05 1.28	32.90 1.55		31.05 1.96	31.14 1.93
28.43 1.78	29.95 1.20	32.05 1.20	33.57 1.12	33.10 1.09	32.90 1.30	33.00 1.34	31.67 1.96	30.67 1.49	30.86 1.82
	29.29 2.00	30.62 1.32	31.62 1.12	31.71 2.05	31.90 1.95	32.14 1.28	31.52 1.44	31.00 2.24	
		29.95 2.04	30.00 1.18	30.43 1.47	31.33 1.39	31.05 0.86	30.81 2.44		
			28.14 1.65	29.05 1.75	30.10 1.48	30.24 2.12		Fovea 38.71 2.31

Greater than 50 years

			24.10 3.91	23.71 3.05	23.00 3.30	22.57 3.60		
		25.29 3.05	26.38 2.75	26.29 2.24	25.29 2.31	25.67 1.80	25.57 3.08	
	26.43 1.91	28.48 1.60	29.14 1.46	29.05 1.50	28.29 1.42	28.62 1.60	27.38 1.96	26.33 3.01
25.33 2.29	27.95 1.63	30.05 1.32	30.62 1.16	31.14 1.15	30.05 1.53	28.86 1.49	28.90 1.70	27.81 1.54	26.81 2.68
26.62 2.71	28.81 1.57	31.19 1.40	31.62 1.28	32.05 1.12	31.62 1.75	30.29 2.15		28.86 1.74	28.14 2.43
26.14 3.38	28.90 2.32	31.10 1.45	32.00 1.18	32.33 1.43	32.19 1.44	30.90 1.76		29.00 1.97	29.19 1.83
25.57 3.11	28.05 1.56	30.00 1.48	31.67 1.53	31.52 1.78	31.00 1.95	31.14 2.03	30.05 2.13	29.24 1.70	28.76 2.41
	26.81 2.32	29.29 1.10	29.90 1.64	30.00 1.79	29.48 1.83	30.62 1.72	29.90 1.51	28.62 2.11	
		27.48 2.34	28.10 1.87	28.76 1.51	29.00 1.97	29.57 1.75	29.00 1.82		Fovea
			25.90 3.25	26.57 2.11	27.76 1.61	28.10 1.95			36.48 2.68

Figure 3.9d. The group mean sensitivity for each stimulus location (upper value) and one standard deviation of the mean (lower value) for the SITA Standard algorithm for the subjects aged less than 50 years (top) and aged greater than 50 years (bottom).

SITA Fast

Less than 50 years

			27.19 2.18	26.81 2.09	26.19 1.60	25.95 2.25		
		29.10 2.32	29.14 1.46	29.10 1.41	28.71 1.65	28.10 2.00	29.05 2.20	
	29.10 1.92	30.48 0.93	30.81 1.25	30.33 1.49	30.48 1.91	30.00 1.79	29.57 2.44	29.90 3.05
29.05 2.01	30.00 1.18	31.71 1.19	32.90 1.22	32.67 1.43	32.00 1.76	31.90 1.67	31.10 2.23	30.33 2.06
29.29 1.62	30.71 1.27	32.81 0.98	33.24 1.37	34.00 1.45	33.57 1.43	32.43 1.21		31.33 1.98
29.00 1.58	31.19 1.08	33.14 1.11	33.81 1.40	34.24 1.37	34.14 1.20	33.29 1.15		31.62 1.32
28.76 2.49	30.52 1.08	32.10 1.18	33.14 1.62	33.14 1.15	33.19 1.21	33.14 1.11	32.19 2.09	31.29 1.55
	30.00 1.76	30.86 1.15	32.05 1.63	32.29 1.59	32.33 1.43	32.19 1.54	31.52 1.50	31.05 3.47
		30.24 2.30	30.38 1.60	30.76 1.81	31.62 1.63	31.48 1.08	30.86 2.08	
			29.00 2.05	29.29 1.62	30.05 1.47	30.05 2.89		

								Fovea
								38.19 2.18

Greater than 50 years

			24.81 2.94	24.86 2.85	22.67 2.87	23.57 3.52		
		26.29 3.12	26.90 2.21	27.48 2.27	26.10 3.40	26.33 2.52	26.19 2.42	
	27.00 2.07	28.00 1.76	28.62 2.27	29.05 1.80	28.67 1.65	28.48 1.72	27.76 2.07	27.38 2.27
26.33 2.56	28.29 1.85	30.24 1.87	30.71 1.59	30.86 1.74	30.71 1.23	29.38 1.77	28.62 2.69	28.86 2.03
27.05 2.20	29.33 1.62	31.29 1.52	31.76 1.61	32.38 1.80	32.24 1.34	30.24 1.79		29.90 2.10
26.81 2.14	29.52 1.91	31.67 1.24	31.95 1.40	32.57 1.47	32.76 1.37	31.90 1.61		30.00 1.38
26.14 2.54	28.86 1.56	30.81 1.44	31.90 1.70	31.95 1.20	31.76 1.61	31.43 1.63	30.14 2.13	29.81 1.40
	28.10 2.02	29.33 2.01	30.19 1.47	29.48 3.41	30.43 2.13	30.67 1.74	30.52 1.60	29.62 1.83
		27.43 2.42	28.76 1.41	28.95 1.94	29.81 1.40	30.00 1.14	29.24 1.84	
								Fovea
			26.76 2.51	27.19 2.16	28.38 1.66	28.57 1.94		36.62 2.04

Figure 3.9e. The group mean sensitivity for each stimulus location (upper value) and one standard deviation of the mean (lower value) for the SITA Fast algorithm for the subjects aged less than 50 years (top) and aged greater than 50 years (bottom).

a)

	Whole Field	Centre	Periphery
640[Y/O]	0.779	0.810	0.748
FT[Y/O]	0.777	0.742	0.844
FP[Y/O]	0.756	0.768	0.751
SS[Y/O]	0.938	1.022	0.861
SF[Y/O]	0.872	0.858	0.882

b)

	Whole Field	Centre	Periphery
640/FT[Y]	1.045	1.032	1.012
FP/FT[Y]	1.085	1.180	0.995
SS/FT[Y]	1.002	1.032	0.939
SF/FT[Y]	0.954	0.961	0.913
SS/FP[Y]	0.957	0.899	0.973
SF/FP[Y]	0.904	0.835	0.942
SF/SS[Y]	0.969	0.945	0.997

c)

	Whole Field	Centre	Periphery
640/FT[O]	1.034	0.943	1.124
FP/FT[O]	1.113	1.159	1.125
SS/FT[O]	0.840	0.767	0.919
SF/FT[O]	0.841	0.836	0.863
SS/FP[O]	0.771	0.677	0.834
SF/FP[O]	0.780	0.750	0.790
SF/SS[O]	1.040	1.124	0.971

Table 3.3. a).The standard deviation of the measured sensitivities (between-subject variability) for the subjects aged less than 50 years (Y) expressed as a ratio of the standard deviation of the measured sensitivities for subjects aged greater than 50 years of age (O) for all 74 stimulus locations and for the central and peripheral annuli for each algorithm. b).The between-algorithm between-subject variability, relative to the HFA750 Full Threshold, FASTPAC and SITA Standard algorithms for the subjects aged less than 50 years for each region of the visual field. c).The between-algorithm between-subject variability for each pair of algorithms for the subjects aged greater than 50 years for each region of the visual field. 640 is HFA640 Full Threshold, FT is HFA750 Full Threshold, FP is FASTPAC, SS is SITA Standard and SF is SITA Fast.

3.5 Discussion.

The HFA 640 was used to determine the validity of the Full Threshold algorithm with the HFA 750. The two instruments, which are platform independent in terms of software, yielded similar group mean Mean Sensitivities. The finding of similar Mean Sensitivities and of similar Short-term Fluctuations are compatible with the results of Johnson et al (1997) who found a similarity in the Mean Deviation, the Short-term Fluctuation and the Corrected Pattern Standard Deviation between the two instruments in ocular hypertension, and in early and moderate glaucoma. Johnson et al (1997) also found similar local Mean Sensitivities as a function of eccentricity and of quadrant but did not analyse the data in terms of each individual stimulus location. In the current study, the 10th, 50th, and 90th percentiles for the root mean square deviation between the Full threshold algorithm of the two instruments were 1.7 dB, 2.2 dB and 3.1 dB respectively. Such differences are minimal when placed in the context of the 2 dB final step size of the algorithm. The 22 second reduction in examination time of the HFA 750 compared to the HFA 640 Full Threshold algorithm is likely to have arisen from the aspheric shape and smaller size of the perimeter bowl of the HFA 750, the faster stepper motor used for the stimulus presentation and from the faster speed of the microprocessor. The saving of examination time should be proportionately similar in ocular hypertension and in glaucoma.

The validity of the sample as representative of the normal population was confirmed by the difference in the examination duration and in the Short-term Fluctuation between the HFA 750 Full Threshold and the FASTPAC algorithms. The approximate 40% reduction in the examination duration and the approximate 34% increase in the short-term fluctuation are comparable with that reported previously for the normal visual field (Flanagan, et al. 1993a).

The group mean Mean Sensitivity of SITA Standard was 0.8 dB higher than that of the Full Threshold algorithm; however, the two means can essentially be considered to be clinically equivalent. The pointwise root mean square deviations between the Full threshold algorithm and the SITA Standard were also clinically equivalent although the upper tail of the

distribution was longer than that between the Full Threshold and FASTPAC algorithms. The Group mean Mean Sensitivity for the SITA Fast algorithm was 1.3 dB higher than that of the Full Threshold algorithm. The pointwise root mean square deviations reflected this tendency across the entire distribution of stimulus locations (the corresponding curve in Figure 3.4a (top) shifts to the right relative to the other two curves). The deviations also exhibited a longer tail than that between the Full Threshold and FASTPAC algorithms. The difference in measured sensitivity between algorithms does however reflect upon the different assumptions of what constitutes threshold. The SITA algorithms calculate the stimulus intensity that has a 50 percent chance of detection on the FOS curve, whereas the Full Threshold and FASTPAC algorithms assume that the final seen stimulus in the staircase corresponds to the threshold. Thus, an expected difference between the algorithms exists as the 'true' threshold for the Full Threshold algorithm lies within the range of the final 2 dB staircase step. The 3 dB step size of the FASTPAC algorithm therefore increases the range in which the threshold may occur. Our differences in sensitivity of 0.8 dB and 1.3 dB would seem to agree with the theoretical differences for normal subjects (Bengtsson, et al. 1998).

The accuracy and precision of the measured sensitivities for the SITA algorithms compared to those of the Full Threshold and FASTPAC algorithms could theoretically be increased by reducing the magnitude of the designated Error Related Factor. However, such an alteration would be at the expense of an increase in the examination duration. It would be theoretically possible to create a whole family of SITA algorithms by alterations in the Error Related Factor (Bengtsson, et al. 1997b).

Both SITA algorithms utilise prior knowledge of the shape of the frequency-of-seeing (FOS) curve. The accuracy and precision of a staircase threshold algorithm is dependent upon the starting level of the staircase, the size of the staircase steps, the number of staircase reversals and the stimulus size (Johnson, et al. 1992, Glass, et al. 1995, Schaumberger, et al. 1995, Wall, et al. 1995, Weber and Klimaschka 1995, Wall, et al. 1997). The original 4-2 dB staircase was developed on the assumption that the shape of the frequency-of-seeing (FOS) curve was independent of stimulus location. However, the shape of the FOS curve

varies with threshold level and, consequently, covaries with stimulus eccentricity and with defect depth (Weber and Rau 1992, Chauhan, et al. 1993, Olsson, et al. 1993). It is different between normal subjects and glaucoma patients for a given threshold level and is also different between glaucoma patients (Weber and Rau 1992, Chauhan, et al. 1993, Olsson, et al. 1993). Stimulus locations exhibiting normal sensitivity in glaucoma can also exhibit considerable variation in the shape of the curve (Weber and Rau 1992, Chauhan, et al. 1993). The characteristics of the FOS curves used by the SITA algorithms have not been described. Until such information becomes available, the manner in which the prior knowledge of the curves contributes to the SITA algorithms remains unknown.

Initial step sizes, which vary in magnitude as a function of eccentricity and of defect depth, are used in the Dynamic strategy (Weber and Klimaschka 1995) as a means of reducing examination duration without loss of efficiency. The Dynamic strategy reduces the variance associated with the measurement of normal sensitivity compared to the 4-2 dB strategy; however, the variance is greater at locations exhibiting relative loss (Weber and Klimaschka 1995). The precision of the models incorporated in the SITA algorithms evidently renders the use of dynamic step sizes unnecessary for the measurement of normal sensitivity.

Fundamental to the delineation of visual field loss is the establishment of confidence intervals for normality at each stimulus location. Such intervals, based either upon Gaussian or upon empirical distributions, are used to identify abnormalities in the height and in the shape of the visual field. Fifty-eight of the 74 stimulus locations exhibited a Gaussian distribution of sensitivity for the HFA 750 Full Threshold algorithm, 57 locations for the SITA Standard and 58 locations for the SITA Fast algorithm. Of the 58 locations for the Full Threshold algorithm, 57 were common to the SITA Standard and 45 to the SITA Fast algorithm. The shape of the distribution of sensitivity for the Full Threshold algorithm is equivocal; it has been previously described as either non-Gaussian (Heijl, et al. 1987a, Wild, et al. 1995) or predominantly Gaussian (Wild, et al. 1998). It is clear from the data in Figures 3.6 and 3.7 that the between-subject variability, and hence the confidence limits for normality, for both the SITA algorithms are smaller than those of the Full Threshold and

FASTPAC algorithms, particularly within the central regions of the field, and that the limits for the SITA Fast and SITA Standard algorithms are similar within the central region (Figure 3.8). The narrower confidence limits for SITA indicate that visual field abnormality will be statistically detected at an earlier stage than with the Full Threshold algorithm. The reason for the reduced confidence limits of SITA is not clear. The finding may be explained, in part, by the reduction in the between-individual variation in the fatigue effect arising from the shorter examination duration of SITA. Alternatively, the magnitude of the designated ERF together with the model for the normal hill of vision and the post processing may inadvertently and artificially reduce or 'smooth' the appearance of the field thereby reducing the between-subject variation in normal sensitivity. The reason for the greater between-subject variation of the SITA Standard algorithm at the edge locations compared to the Full Threshold algorithm is unclear but may reflect the reduced efficacy of the SITA algorithm at these locations. The fatigue effect may contribute to the increased variability for SITA Standard at the edge locations since thresholds for locations in the outer ring of Program 30-2 are routinely estimated at the end of the test. However, the use of Program 24-2, which omits all the edge locations of Program 30-2 except those in the nasal field either side of the horizontal midline, would minimise this limitation. The false-positive rate associated with the narrower confidence limits of the SITA algorithms remains unknown.

The grey scale representation of sensitivity is not age-related and does not take into account the increase in variability with increase in eccentricity. Consequently, a given level of grey can be associated with differing probability symbols within and between locations for a given patient and between patients. The narrower confidence limits for the SITA algorithms would be expected correspond to lighter levels of grey than those for the Full Threshold.

3.6 Conclusions

The approximate halving of the examination duration for SITA Standard and SITA Fast without loss of accuracy compared to the Full Threshold and FASTPAC algorithms,

respectively, has profound implications for the role of perimetry in the clinical management of glaucoma. The reduced examination duration will effectively permit either the same patients to undergo perimetry approximately twice as frequently or the throughput of patients for visual field examination to approximately double per unit time. The likely reduction, or even elimination, of the fatigue effect with SITA will initially have potential ramifications for the examination of the visual field in glaucoma. The fatigue effect is most apparent at those locations which exhibit relative loss, varies between individuals in magnitude, and leads to an overestimation of the defect depth (Heijl and Drance 1983, Johnson, et al. 1988b, Hudson, et al. 1994). It is possible, therefore, that some glaucomatous fields will appear less severe when examined with either of the SITA algorithms compared to the immediate previous examination undertaken with the Full Threshold algorithm. However, the narrower confidence limits associated with the SITA algorithms may mitigate against such an eventuality.

CHAPTER 4. THE VALIDITY AND REPRODUCIBILITY OF PERIMETRIC THRESHOLD ALGORITHMS IN GLAUCOMA

4.1 Introduction

The development and utility of perimetric threshold algorithms has been discussed in Chapter 3. The compromise between the examination duration required for the accurate estimation of threshold and the level of patient compliance, together with the current restraints on health care resources, is particularly relevant in the measurement of the visual field in glaucoma. As the length of the examination increases a more accurate estimation of threshold can be obtained but at the expense of an increase in the fatigue effect. In addition, with a longer examination duration, the number of patients that can be investigated per unit time, or alternatively the frequency at which patients can be monitored, is reduced. Therefore, the optimisation of threshold estimation, in terms of accuracy, precision and examination duration, is a continuous goal for perimeter design.

In patients with glaucomatous visual field loss, the test duration of the Full Threshold 4-2 dB staircase algorithm can approach 20 minutes for Program 30-2 of the HFA. At this test duration patient compliance is reduced and the fatigue effect is exaggerated (Heijl 1977b, Heijl and Drance 1983, Johnson, et al. 1988b, Marra and Flammer 1991, Searle, et al. 1991, Wild, et al. 1991, Hudson, et al. 1994). The fatigue effect can give rise to an apparent increase in both the depth and area of the field defect. The FASTPAC algorithm reduces the test duration by up to 40% but compared to the Full Threshold algorithm exhibits decreased accuracy and precision (Flanagan, et al. 1993a, Flanagan, et al. 1993b, Iwase, et al. 1993, Mills, et al. 1994, O'Brien, et al. 1994, Glass, et al. 1995, Schaumberger, et al. 1995). Specifically, the FASTPAC algorithm often underestimates the depth and area of the visual field defect associated with glaucoma, producing shallower Mean Deviation and Pattern Standard Deviation indices. The different strategies for the confirmation of suspicious initial estimates of sensitivity between the Full Threshold and FASTPAC algorithms may also diminish the saving in test duration for FASTPAC over Full Threshold in glaucoma. The larger initial step sizes in the Full Threshold algorithm compared to FASTPAC reduce the

number of stimulus presentations required to cross threshold at locations with reduced sensitivity (Flanagan, et al. 1993b). Additionally, at locations immediately adjacent to locations with absolute loss, the FASTPAC algorithm initially presents a dimmer stimulus than the Full Threshold algorithm. Therefore, in regions with advanced loss the FASTPAC strategy may employ more stimulus presentations than the Full Threshold Algorithm, hence decreasing the difference in examination duration between the two algorithms (Flanagan, et al. 1993b). The dynamic strategy of Weber improves the variability of normal threshold estimation but at lower sensitivities, such as those seen in glaucoma, the benefit is reduced (Weber and Klimaschka 1995).

In the previous Chapter, a 47% reduction in test duration for SITA standard over the 4-2 dB Full Threshold staircase and a 50% reduction in test duration for SITA Fast over FASTPAC was demonstrated in normal subjects. This was accompanied by an approximately 1 dB higher estimation of sensitivity and a lower between-individual variability of the threshold estimation. The reduced variability of threshold estimation led to the conclusion that the SITA algorithms would have narrower confidence limits for normality and hence, that glaucomatous field loss should be identified statistically sooner with the SITA algorithms than with either the Full Threshold or FASTPAC algorithms.

4.2 Aim of Study

The aim of the study was to investigate the validity and reproducibility of SITA Standard and SITA Fast in the estimation of visual field sensitivity in a glaucomatous population. The specific aims were, firstly, to determine the extent of any differences in the estimation of both global and pointwise sensitivity between the SITA Standard, SITA Fast, FASTPAC and Full Threshold algorithms. Secondly, to determine the influence of the possible narrower confidence limits for normality on glaucomatous visual fields, specifically in relation to the pattern deviation probability values for each of the algorithm. Thirdly, to investigate the between-algorithm difference in reproducibility of the algorithms.

4.3 Methods

4.3.1 Sample

The sample comprised 29 patients (19 male) with primary open angle glaucoma (POAG). All patients manifested an optic nerve head appearance characteristic of POAG together with a repeatable visual field defect consistent with POAG. The mean age of the sample was 67.3 years (SD 10.2, range 42-79). The inclusion criteria comprised a visual acuity of 6/9 or better in either eye, a distance refractive error less than or equal to 5 dioptres mean sphere and less than 2.5 dioptres cylinder, lenticular changes not greater than NCIII, NOIII, CI or PI by LOCS III (Chylack, et al. 1993), no systemic medication known to affect the visual field and no history or family history of diabetes mellitus. All patients manifested well controlled intraocular pressures (mean 17.4 mmHg SD 3.1) and stable visual fields. Eighteen patients were controlled on a single topical agent (either a selective or non-selective β blocker, a topical carbonic anhydrase inhibitor, an alpha-adrenergic agonist or a prostaglandin); six patients required more than one topical agent for intraocular pressure control. No patients were on systemic carbonic anhydrase inhibitors or topical cholinergics. Six patients had undergone previous trabeculectomy (at least 12 months prior to inclusion in the study) and two of these patients required no further medical treatment for intraocular pressure control. All patients were experienced in automated threshold static perimetry having undergone a minimum of three previous examinations.

4.3.2 Examination Protocol

Perimetry was performed on one eye of each patient using the HFA 750. The designated eye from each patient was selected so as to bias the severity of the field defect within the sample towards mild loss but at the same time, provide a continuum of severity across the sample. The degree of field loss was described using the system of Hodapp et al (1994). This classification describes the severity of loss in terms of the Mean Deviation visual field index and in terms of the number, severity and proximity to fixation of the Pattern Deviation probability symbols. Each visual field examination used the default white-on-white stimulus parameters of the Humphrey Field Analyzer: a Goldmann size III stimulus presented against

a 10 cdm^{-2} white background with a stimulus duration of 200 ms. Appropriate refractive correction for the viewing distance of the perimeter was used for each subject.

At the first visit, threshold was determined for Program 30-2 using four different algorithms: Full Threshold, FASTPAC, SITA Standard and SITA Fast. At one session, patients underwent perimetry with the Full Threshold and SITA Fast algorithms and at a second session with FASTPAC and SITA Standard. The two sessions were carried out at the same visit separated by an interval of 45 min. The order of algorithms within a session and the order of sessions within a visit were randomised, but held constant, within each patient for each visit. The protocol was repeated at a further two visits and the three visits were completed within four weeks. The mean interval between the first and second visit was 9 days (SD 4.5 days) and between the second and third 8 days (SD 3.4). The first visit was considered as a familiarisation period and the results were discarded prior to the analysis.

4.3.3 Analysis

The results for left eyes were converted into right eye format. The stimulus locations immediately above and below the physiological blind spot were excluded from the analyses. The data were analysed in three separate ways.

For the first analysis, the differences in the visual field index Mean Sensitivity (MS) between the 4 algorithms within each of the two visits, and the differences within-algorithm between-visits, were analysed using separate repeated measures Analysis of Variances (ANOVA) for a four period cross-over trial within visit, with the treatment sequence being replicated at the second visit. The age of the patient and the severity of the visual field were considered as separate between-subject factors. The type of algorithm, the order of the two sessions and the order of presentation of the algorithm within a session were considered as separate within-subject factors. Similar, but separate, analyses were undertaken for examination duration, Mean Deviation (MD) and Pattern Standard Deviation (PSD). The Short-term Fluctuation (SF) and therefore the Corrected Pattern Standard Deviation (CPSD) are not calculated by the SITA algorithms.

For the second analysis, the difference in sensitivity for each patient at each stimulus location between each pair of algorithms at the second visit was calculated (i.e. the within-visit between-algorithm variability). The data for all patients was combined and expressed as a function of the sensitivity at the given stimulus location recorded at the second visit with the comparison algorithm of the given pair. The derived data was then additionally expressed as the square root of the group mean of the sum of the squared deviations at each sensitivity level (i.e. the Root Mean Square value) for each pair of algorithms. Similarly, the difference in sensitivity at each stimulus location across all patients for a given algorithm between the second and third visits (i.e. the within-algorithm between-visit variability) was calculated and expressed as a function of the sensitivity recorded at the second visit at the given stimulus location with the given algorithm. The derived data was then additionally expressed as the Root Mean Square value at each sensitivity level for each algorithm.

For the third analysis, the between-algorithm differences in the Pattern Deviation probability values at each stimulus location across all 29 patients, at visit two, was expressed as a 5x5 contingency table for each pair of algorithms. An identical analysis was undertaken for the within-algorithm between-visit differences in the Pattern Deviation probability values. The differences in the distribution of values for each within-visit between-algorithm comparison and for each within-algorithm between-visit comparison were then analysed using separate Wilcoxon Signed Rank Tests.

4.4 Results

All visual fields met the inclusion criteria for reliability, specifically less than 20% fixation losses and less than 33% false-negative and false-positive catch trials. The sample comprised 14 eyes with early loss, seven with moderate loss and 8 with severe loss.

4.4.1 Global Indices

The group mean MS, MD, PSD and examination duration for each algorithm for the second and third visits are given in Table 4.1.

The group mean MS was independent of age ($p=0.734$). The group mean MS varied as function of algorithm ($p<0.001$) regardless of visit ($p=0.541$); the SITA Standard group mean MS was 1.0 dB high than the Full Threshold MS and 0.8 dB higher than the FASTPAC MS and the SITA Fast group mean MS was 0.9 dB higher than that of the SITA Standard. Group mean MS declined as a function of the severity of field loss ($p<0.001$) irrespective of algorithm ($p=0.052$). The differences between the four algorithms were similar between visits ($p=0.956$) and were also independent of age ($p=0.800$). Group mean MS varied as a function of the order of test ($p<0.001$) and this order effect was different between tests ($p=0.01$). The sub-group mean MS for the Full Threshold algorithm and for the SITA Standard algorithm was lower when the algorithms were undertaken as the second test at any given session whilst that for the FASTPAC algorithm was higher as the second test of any session.

The group mean MD was independent of age ($p=0.075$). It was similar for all four algorithms ($p=0.291$) regardless of visit ($p=0.961$). The Group mean MD became more negative as a function of the severity of field loss ($p<0.001$) irrespective of algorithm ($p=0.577$). It varied as a function of order of test ($p<0.001$) and this order effect was different between tests ($p=0.004$). The sub-group mean MD for the Full Threshold algorithm and for the SITA Standard algorithm was more negative when the algorithms were undertaken as the second test at any given session whilst that for the FASTPAC algorithm was less negative as the second test of any session.

		Full Threshold	FASTPAC	SITA Standard	SITA Fast
Mean Sensitivity (dB)	Visit 2	22.2 (4.3)	22.4 (3.9)	23.2 (4.8)	24.1 (4.1)
	Visit 3	22.3 (4.4)	22.5 (4.1)	23.2 (4.7)	24.0 (4.2)
Mean Deviation (dB)	Visit 2	-5.0 (4.1)	-5.0 (3.8)	-5.1 (4.4)	-4.9 (4.0)
	Visit 3	-4.9 (4.1)	-5.1 (4.1)	-5.2 (4.6)	-4.8 (4.1)
Pattern Standard Deviation (dB)	Visit 2	6.9 (3.8)	6.7 (3.8)	7.2 (4.4)	6.8 (4.1)
	Visit 3	7.3 (3.9)	6.7 (3.8)	7.5 (4.3)	6.4 (4.3)
Short-term Fluctuation (dB)	Visit 2	1.85 (0.92)	2.12 (0.77)	-	-
	Visit 3	1.88 (1.24)	2.26 (1.03)	-	-
Corrected Pattern Standard Deviation (dB)	Visit 2	6.16 (3.72)	5.99 (4.19)	-	-
	Visit 3	6.76 (4.02)	5.78 (4.07)	-	-
Examination Duration (min)	Visit 2	15.03 (1.54)	9.56 (1.40)	8.03 (1.14)	4.81 (0.93)
	Visit 3	14.89 (1.76)	9.46 (1.37)	7.78 (0.91)	4.68 (0.85)

Table 4.1. The group mean Mean Sensitivity, Mean Deviation, Pattern Standard Deviation and examination duration for the Full Threshold, FASTPAC, SITA Standard and SITA Fast algorithms, together with the Short-term Fluctuation and Corrected Pattern Standard Deviation for the Full Threshold and FASTPAC algorithms. One standard deviation of the mean is given in parenthesis.

Severity	Full Threshold	FASTPAC	SITA Standard	SITA Fast
Early	14.11 (1.17)	8.60 (0.90)	7.28 (0.58)	4.15 (0.47)
Moderate	16.09 (1.45)	9.87 (0.83)	7.97 (0.81)	4.67 (0.45)
Severe	15.46 (1.78)	10.78 (1.29)	8.93 (0.99)	5.86 (0.67)

Table 4.2. Mean examination duration (min) for the Full Threshold, FASTPAC, SITA Standard and SITA Fast algorithms as a function of severity of field loss. One standard deviation of the mean is shown in parenthesis.

The group mean PSD decreased with increase in age (p=0.004). It varied as function of algorithm (p<0.001) regardless of visit (p=0.368); the SITA Standard group mean PSD was 0.2 dB higher than the Full Threshold PSD and 0.6 dB higher than the FASTPAC PSD. The difference in the PSDs between algorithms increased as a function of the severity of field loss (p<0.001); the SITA Standard sub group mean PSD was 0.8 dB higher than the Full Threshold for the severe field loss category (p=0.002). The differences between the four algorithms were similar between visits (p=0.067) and were also independent of age (p=0.763). Group mean PSD varied as a function of order of test (p<0.001) but this order effect was not noticeably different between tests (p=0.092).

The examination duration was independent of age (p=0.284). The group mean examination duration for the SITA Standard algorithm was approximately 53% of that for the Full Threshold algorithm and was approximately 50% shorter for the SITA Fast algorithm compared to the FASTPAC algorithm (p<0.001) regardless of visit (p=0.145) and of age (p=0.932). The between algorithm differences in group mean examination duration were similar between visits (p=0.967). The examination duration increased as a function of the severity of field loss (p<0.001) and this increase in time was proportionately greater for the SITA algorithms than for the Full Threshold and FASTPAC algorithms (p<0.001) particularly that of SITA Fast (Table 4.2). The group mean examination duration also varied as a function of order of test (p<0.001) and this order effect was different between tests (p<0.001). The sub-group mean examination time for the Full Threshold algorithm and for the SITA Standard algorithm was longer when the algorithms were undertaken as the second test at any given session whilst that for the FASTPAC algorithm was shorter as the second test of any session.

4.4.2 Pointwise differences in sensitivity

The 10th, 50th and 90th percentiles of the distribution of the within-visit between-algorithm difference in sensitivity at each sensitivity level between each of the four algorithms at the second visit are illustrated in Figure 4.1. The 50th percentile of the differences between the Full Threshold and FASTPAC algorithms approximated to zero for sensitivities between 34

dB and 20 dB after which the value became more variable. The magnitude of the 10th and the 90th percentiles increased as sensitivity decreased; in the case of the 90th percentile the magnitude peaked at a sensitivity of approximately 16 dB after which it declined. The 50th percentiles of the differences between the Full Threshold and the SITA Standard and SITA Fast algorithms exhibited a negative value (indicating a higher sensitivity for SITA) which became more negative as sensitivity decreased from 34 dB to approximately 12 dB after which the magnitudes became more variable but then tended to converge towards zero. The magnitude of the 10th and 90th percentiles also increased as sensitivity decreased. The 90th percentile for both distributions was largest at a sensitivity of approximately 15 dB after which it declined. The magnitude of the 10th percentile continuously increased for both distributions up to a sensitivity of approximately 4 dB. A similar trend was present between the FASTPAC and the SITA Standard and the SITA Fast algorithms. The 50th percentiles were both negative (indicating that the SITA Fast algorithm yielded a higher sensitivity) and were more negative for the SITA Fast algorithm.

The RMS deviations between the Full Threshold and the FASTPAC and SITA algorithms (Figure 4.2 top), between the FASTPAC and the SITA algorithms (Figure 4.2 centre) and between the SITA Standard and SITA Fast algorithms (Figure 4.2 bottom) increased with decrease in sensitivity up to approximately 10 dB for Full Threshold and 5 dB for FASTPAC after which it declined. The deviations between any given two algorithms were generally similar in magnitude to each other, with the exception of those involving the SITA Fast algorithms.

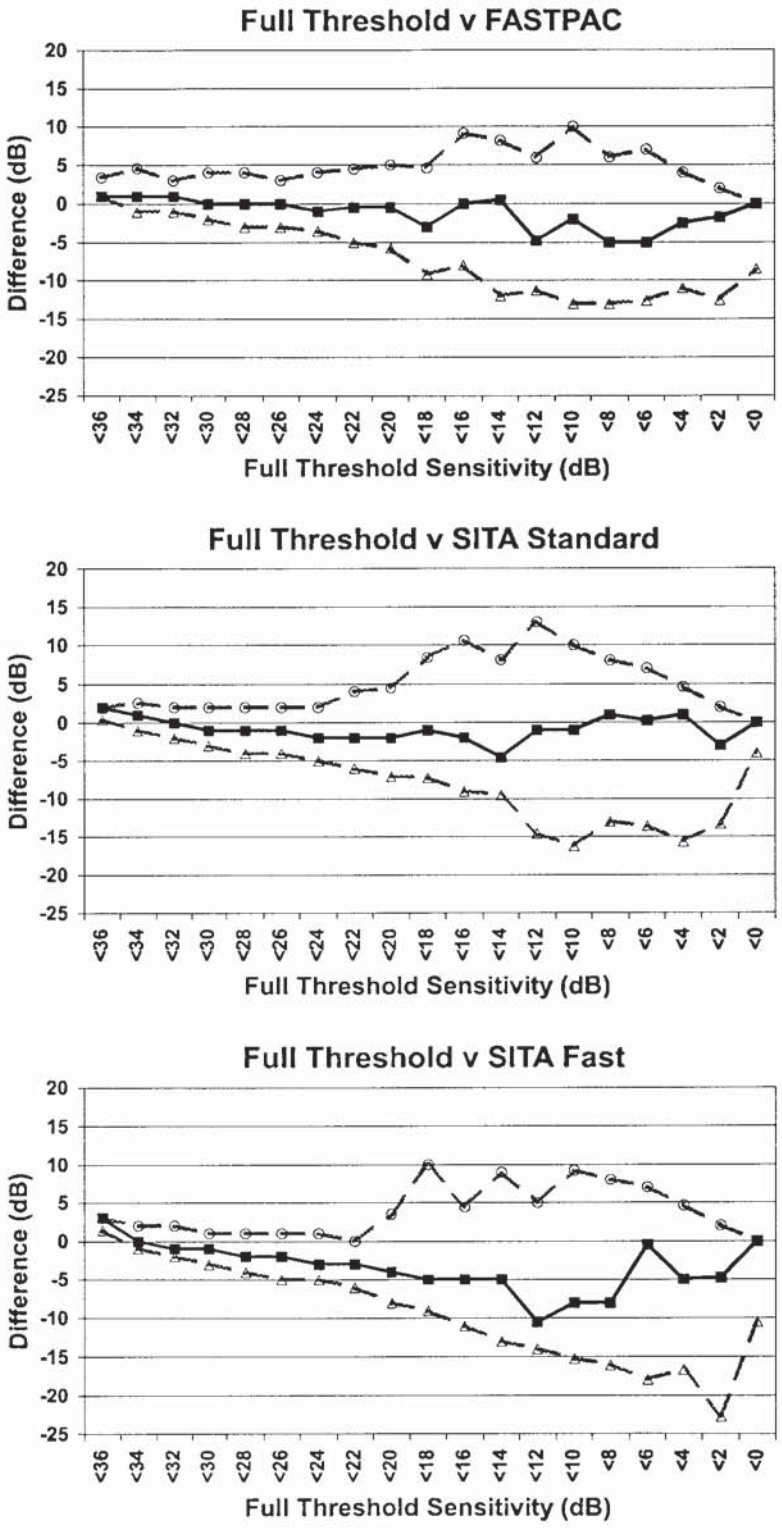


Figure 4.1a. The 90th, 50th and 10th percentiles of the distribution of the differences in sensitivity across all locations, at visit 2, between the Full Threshold and the FASTPAC (top), the SITA Standard (centre) and the SITA Fast algorithms (bottom).

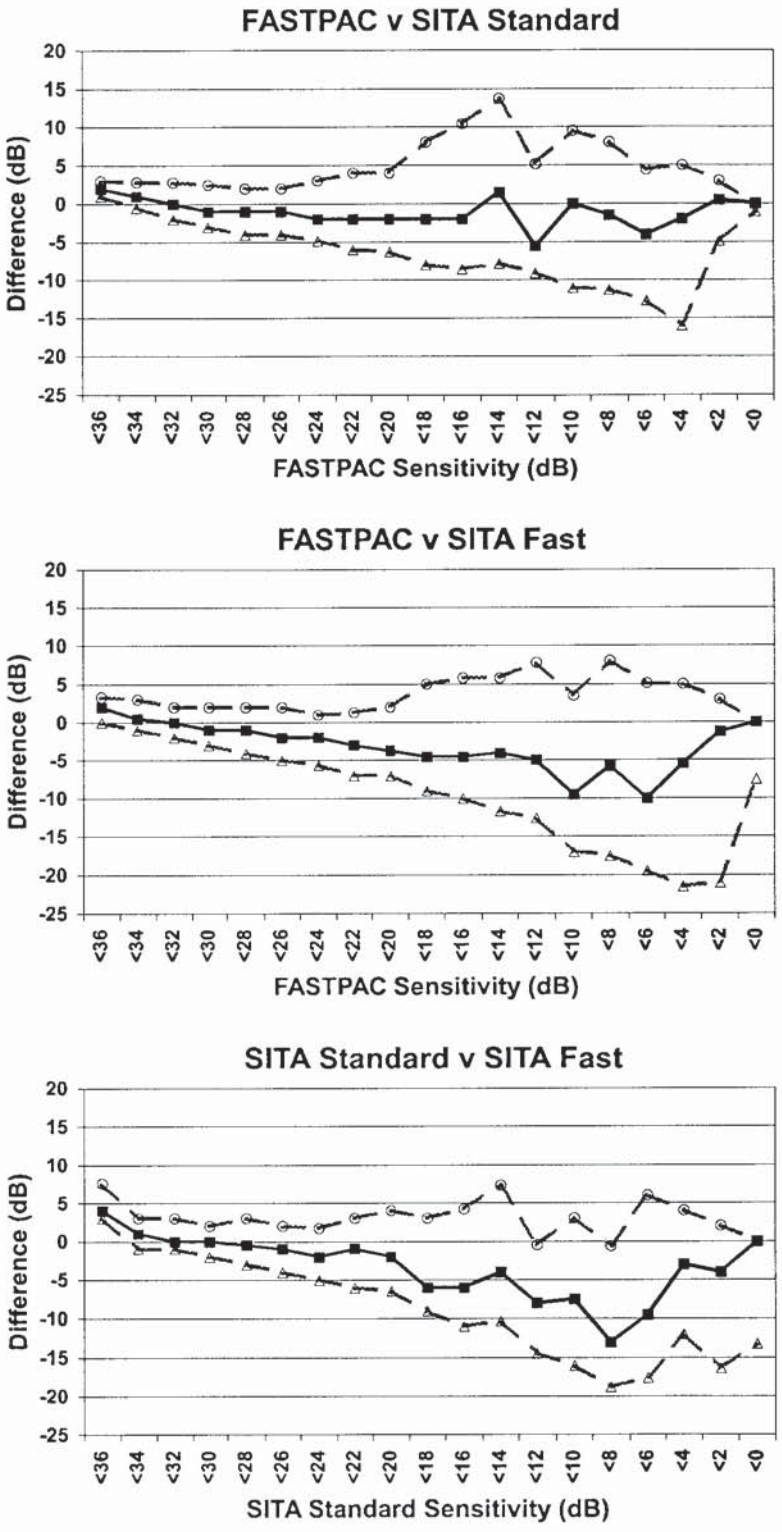


Figure 4.1b. The 90th, 50th and 10th percentiles of the distribution of the differences in sensitivity across all locations, at visit 2, between the FASTPAC and SITA Standard algorithms (top), the FASTPAC and SITA Fast algorithms (centre) and SITA Standard and SITA Fast algorithms (bottom).

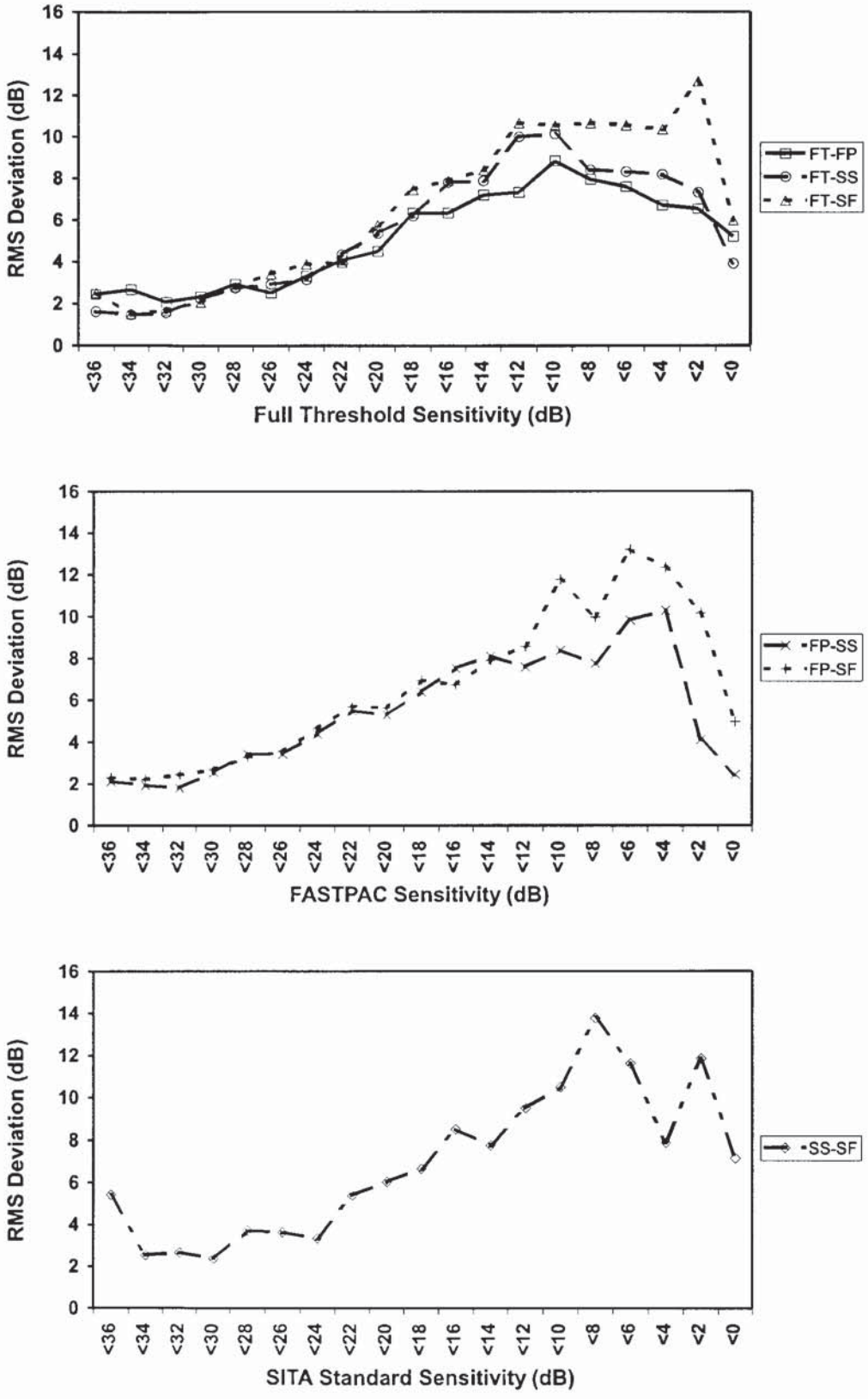


Figure 4.2. The Root Mean Square (RMS) deviation for the difference in sensitivity at a given stimulus location between each pair of algorithms at the second visit as a function of the reference algorithm at the given location at the second visit (i.e. the within-visit between-algorithm evaluation). FT is Full Threshold, FP is FASTPAC, SS is SITA Standard, SF is SITA Fast.

The 10th, 50th and 90th percentiles of the distribution of the within-algorithm between-visit difference in sensitivity at each sensitivity level for the four algorithms between visits two and three are illustrated in Figure 4.3. The corresponding within-algorithm RMS deviation at each sensitivity level is given in Figure 4.4. The distributions of between-visit between-algorithm variability throughout the range of sensitivities were similar for each of the four algorithms. In addition, the between-visit within-algorithm variability over the range of sensitivities was equal to or less than the between-algorithm within-visit variability. Therefore, it is likely that the long-term fluctuation for the follow-up of visual fields would be unaffected by any change in the threshold algorithm used for the examination.

4.4.3 Pointwise differences in Pattern Deviation probability values

The pointwise within-visit between-algorithm differences in the Pattern Deviation probability between each of the four algorithms at the second visit for all 29 individuals are given in Figure 4.5. The differences in the Pattern Deviation probability values between the Full Threshold and FASTPAC algorithms and between the SITA Standard and SITA Fast algorithms did not reach statistical significance ($p=0.857$ and $p=0.083$ respectively). A more significant probability level (i.e. a more statistically significant defect depth) was found for the SITA Standard algorithm compared to the Full Threshold and FASTPAC algorithms (both $p<0.001$) and for the SITA FAST compared to the Full Threshold and FASTPAC algorithms (both $p<0.001$).

The pointwise between-visit within-algorithm differences in the Pattern Deviation probability four each of the four algorithms between the second and third visits are given in Figure 4.6. Figure 4.6a shows the four contingency tables for each algorithm. The differences in the distribution of the p values between the two visits were not statistically significant for three of the four algorithms (Full Threshold, $p=0.427$; SITA Standard, $p=0.972$; SITA Fast, $p=0.286$). However, FASTPAC exhibited more significant Pattern Deviation probability values at the second test ($p=0.006$).

The proportion of locations that exhibited an identical probability value over the two tests declined in rank order from Full Threshold, through FASTPAC and SITA Standard to SITA Fast. This suggests a slightly higher between-visit variability for the SITA strategies. However, when the analysis was performed only for those locations that appeared outside the 95% confidence limits for normality at both visits, the Full Threshold and SITA Standard algorithms had very similar levels of repeatability. The FASTPAC and SITA Fast algorithms also give a similar level of between-visit variability with this type of analysis, but exhibited a greater degree of between-visit variability than either the Full Threshold or SITA Standard algorithms.

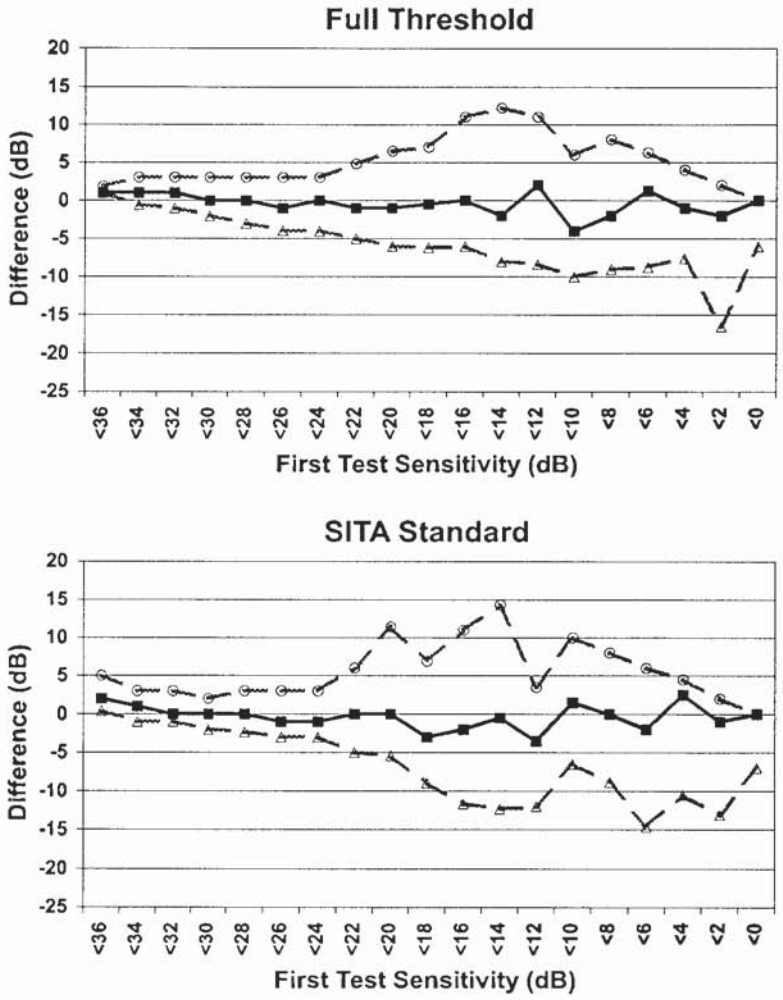


Figure 4.3. The 90th, 50th and 10th percentiles of the distribution of the differences in sensitivity across all locations for each of the algorithms between visit 2 and visit 3, as a function of the sensitivity of the reference algorithm at the second visit (i.e. the within-algorithm between-visit evaluation).

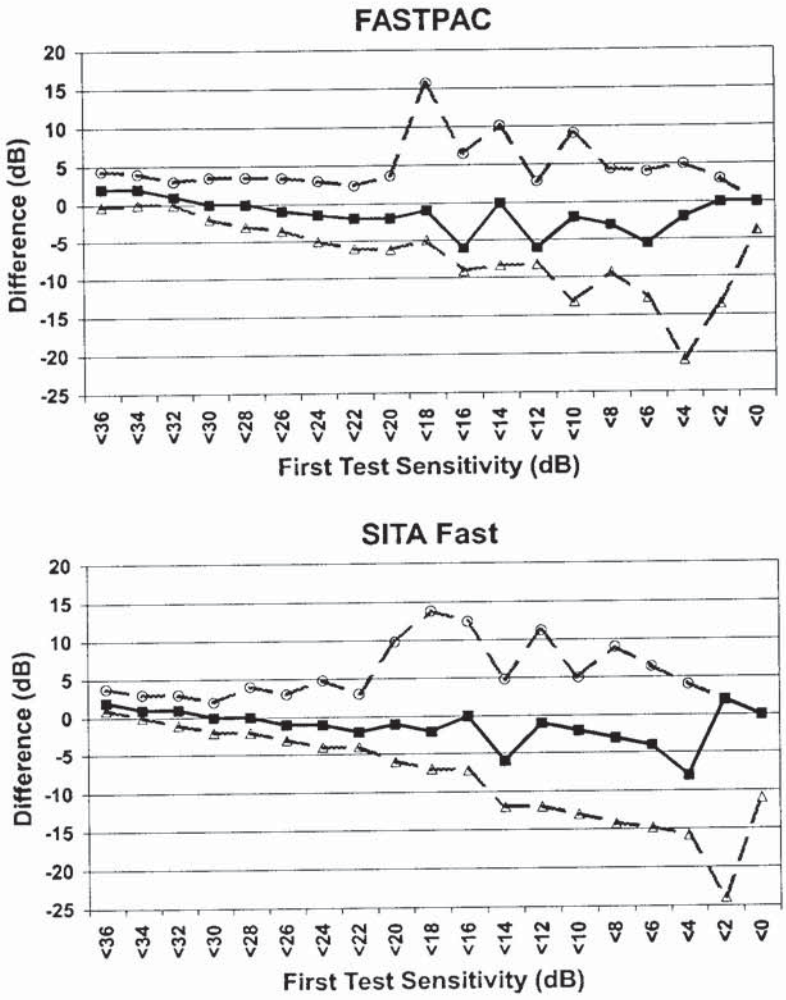


Figure 4.3 continued. The 90th, 50th and 10th percentiles of the distribution of the differences in sensitivity across all locations for each of the algorithms between visit 2 and visit 3, as a function of the sensitivity of the reference algorithm at the second visit (i.e. the within-algorithm between-visit evaluation).

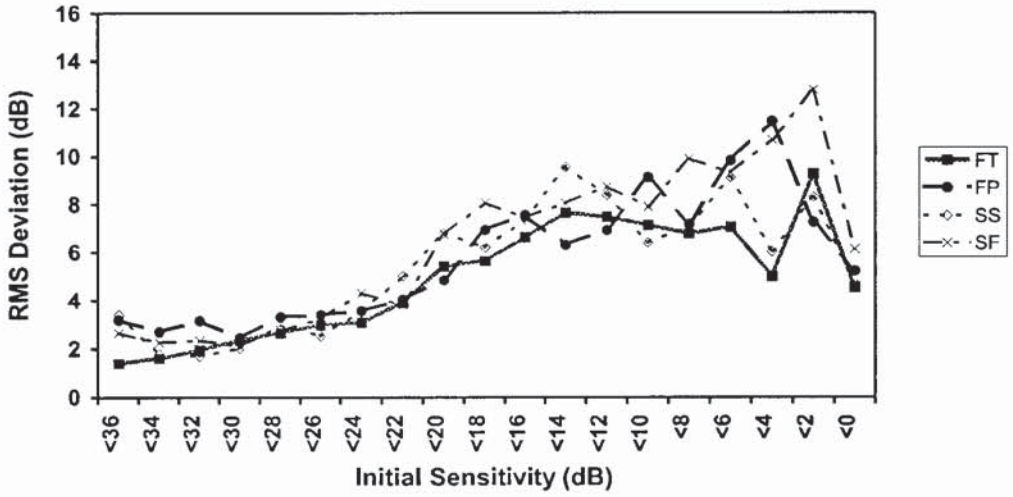


Figure 4.4. The Root Mean Square (RMS) deviation for the difference in sensitivity at a given stimulus location for each individual algorithm between visit 2 and visit 3, as a function of the sensitivity of the reference algorithm at the given location at the second visit (i.e. the within-algorithm between-visit evaluation). FT is Full Threshold, FP is FASTPAC, SS is SITA Standard, SF is SITA Fast.

a)

Full Threshold vs FASTPAC

	NS	<5%	<2%	<1%	<0.5%
NS	1486	69	33	10	19
<5%	49	16	12	7	14
<2%	34	8	22	13	13
<1%	16	7	13	18	19
<0.5%	20	19	11	13	205

FASTPAC vs SITA Standard

	NS	<5%	<2%	<1%	<0.5%
NS	1401	97	37	26	44
<5%	52	22	16	8	21
<2%	22	15	10	14	30
<1%	11	6	3	5	36
<0.5%	16	9	2	21	222

Full Threshold vs SITA Standard

	NS	<5%	<2%	<1%	<0.5%
NS	1412	109	34	23	39
<5%	39	19	12	9	19
<2%	27	11	11	13	28
<1%	8	3	6	15	41
<0.5%	16	7	5	14	226

FASTPAC vs SITA Fast

	NS	<5%	<2%	<1%	<0.5%
NS	1388	100	49	35	33
<5%	52	21	12	12	22
<2%	31	13	5	16	26
<1%	12	8	6	5	28
<0.5%	23	13	13	25	196

Full Threshold vs SITA Fast

	NS	<5%	<2%	<1%	<0.5%
NS	1398	110	48	30	31
<5%	45	17	9	10	17
<2%	27	13	7	17	26
<1%	13	5	10	12	33
<0.5%	23	10	13	24	198

SITA Standard vs SITA Fast

	NS	<5%	<2%	<1%	<0.5%
NS	1327	87	36	23	29
<5%	83	26	14	16	10
<2%	32	11	5	11	9
<1%	24	7	9	11	23
<0.5%	40	24	23	32	234

b)

	FT-FP	FT-SS	FT-SF	FP-SS	FP-SF	SS-SF
More statistically significant defect with 1st algorithm (%)	8.9	6.3	8.5	7.3	9.2	13.3
Identical with 1st and 2nd algorithms (%)	81.4	78.4	76.0	77.4	75.3	74.7
More statistically significant defect with 2nd algorithm (%)	9.7	15.2	15.4	15.3	15.5	12.0

Figure 4.5. a)The within-individual within-visit between algorithm-difference in the number of probability values at each stimulus location across all 29 patients for each of the between-algorithm comparisons (top left Full threshold compared to FASTPAC; middle left Full Threshold compared to SITA Standard; bottom left Full Threshold compared to SITA Fast; top right FASTPAC compared to SITA Standard; middle right FASTPAC compared to SITA Fast; bottom right SITA Standard compared to SITA Fast). b)The data is expressed as a percentage in the summary table.

a)

Full Threshold Visit 2 / Full Threshold Visit 3

	NS	<5%	<2%	<1%	<0.5%
NS	1519	49	17	13	19
<5%	56	16	7	6	13
<2%	32	10	26	6	16
<1%	12	12	5	14	30
<0.5%	9	10	5	14	230

FASTPAC Visit 2 / FASTPAC Visit 3

	NS	<5%	<2%	<1%	<0.5%
NS	1477	70	27	15	16
<5%	67	14	17	11	10
<2%	42	12	21	5	11
<1%	18	8	7	18	10
<0.5%	28	24	10	17	191

SITA Standard Visit 2 / SITA Standard Visit 3

	NS	<5%	<2%	<1%	<0.5%
NS	1366	68	28	23	17
<5%	79	29	23	7	11
<2%	25	16	13	6	8
<1%	17	2	11	16	28
<0.5%	24	16	7	18	288

SITA Fast Visit 2 / SITA Fast Visit 3

	NS	<5%	<2%	<1%	<0.5%
NS	1334	81	39	30	22
<5%	87	25	17	17	9
<2%	30	15	11	11	20
<1%	20	11	12	26	24
<0.5%	25	13	15	24	228

b)

Including repeated NS locations	FT	FP	SS	SF
More statistically significant defect at Visit 2 (%)	7.7	10.9	10.0	11.7
Identical at 1st and 2nd Visits (%)	84.1	80.2	79.8	75.7
More statistically significant defect at Visit 3 (%)	8.2	8.9	10.2	12.6

c)

NOT including repeated NS locations	FT	FP	SS	SF
More statistically significant defect at Visit 2 (%)	26.32	34.83	27.56	31.03
Identical at 1st and 2nd Visits (%)	45.61	36.47	44.36	35.71
More statistically significant defect at Visit 3 (%)	28.07	28.70	28.08	33.25

Figure 4.6. a)The within-individual within-algorithm between-visit difference in the number of probability values at each stimulus location across all 29 patients for each of the four algorithms (top left Full threshold; bottom left SITA Standard; top right FASTPAC; bottom right to SITA Fast). The data is expressed as a percentage in the summary tables, b) including locations that were non-significant at the 95% level at both visits and c) excluding locations that were non-significant at the 95% level at both visits.

4.5 Discussion.

The validity of the sample as representative of the glaucomatous population was confirmed by the difference in the group mean examination duration and in the group mean Short-term Fluctuation and group mean MD, PSD and CPSD between the Full Threshold and the FASTPAC algorithms. The approximate 36% reduction in the examination duration and the approximate 18% increase in the short-term fluctuation is comparable with that reported previously for the glaucomatous visual field (Flanagan, et al. 1993b, O'Brien, et al. 1994).

The SITA algorithms yield slightly higher values of MS than the Full Threshold and FASTPAC algorithms. The group mean MS for SITA Standard was 1.0 dB higher than for Full Threshold and 1.7 dB higher for SITA Fast than FASTPAC. These results compare favourably with the corresponding differences found in the normal eye of 0.8 dB and 1.5 dB respectively (see Chapter 3). Although the differences in MS are statistically significant, they become clinically insignificant in the context of the identical MDs which describe alterations in the height of the hill of vision relative to the respective age corrected normal values of each algorithm. The differences in the PSDs between the algorithms, although reaching statistical significance, were also clinically insignificant. Furthermore, the indices themselves are of limited clinical value as they are merely summary measures of the sensitivities at all stimulus locations (Chauhan, et al. 1990a, Asman, et al. 1992, Heijl and Molder 1992, Bengtsson, et al. 1997a).

The purpose of the within-visit between-algorithm and the within-algorithm between-visit pointwise analyses was to determine the within-individual differences in the absolute value of sensitivity at each stimulus location, not the difference in pointwise deviations from each respective normal database. The results of the within-visit between-algorithm pointwise analysis indicate that the SITA algorithms exhibit a slightly higher absolute value of pointwise sensitivity, that this difference increases as sensitivity declines and that the difference is greatest for SITA Fast. The finding of a slightly higher sensitivity for the SITA algorithms is of limited clinical value since the statistical definition of abnormality is dependent upon the establishment of age-corrected confidence limits for normality at each location which, in turn,

are based upon the normal data base specific to each algorithm. The difference in the measured sensitivity between algorithms can be attributed to the intrinsic difference between-algorithms in the method of obtaining threshold (Bengtsson, et al. 1998). The SITA algorithms calculate the stimulus intensity that has a 50 percent chance of detection (using all of the patient's responses from all of the stimuli), whereas the Full Threshold and FASTPAC algorithms assume that the final seen stimulus in the given staircase corresponds to threshold. Thus, an expected difference exists between the algorithms since the 'true' threshold for the Full Threshold algorithm lies within the range of the final 2 dB staircase step. The 3 dB step size of the FASTPAC algorithm therefore increases the range in which the 'true' threshold may lie. The differences in sensitivity of 1.0 dB and 1.7 dB between the Full Threshold and SITA Standard algorithms are in agreement with the theoretical differences for normal subjects between the corresponding algorithms (Bengtsson, et al. 1998). However, the differences in the magnitude of the confidence limits between algorithms are the crucial issue.

The increased spread of the 10th and 90th percentiles of the distributions of the within-visit between-algorithm and of the within-algorithm between-visit differences in sensitivity between approximately 20 dB and 10 dB are caused in part by the inherent increased variability displayed at this level of sensitivity (Heijl, et al. 1989b) which is present at both examinations. The irregularity of the increased spread of these percentiles can also be attributed, in part, to the lower number of data points within the mid-range sensitivity levels. Table 4.3 shows the number of stimulus locations throughout the whole sample within each sensitivity level for each of the algorithms. The distributions of the number of locations per sensitivity level are more skewed towards the higher sensitivity levels for the SITA algorithms compared to the Full Threshold and FASTPAC algorithms. This is consistent with the findings of a greater MS for the SITA algorithms. In addition, for each individual algorithm the distribution is more skewed towards the higher sensitivity levels for the central field compared to the peripheral annulus.

The greater divergence of the 10th percentile for sensitivities of less than 10 dB compared to the 90th percentile is the mathematical consequence of a high value at the second test being subtracted from, and referenced to, a low value with large variability at the first test, hence biasing the differences towards negative values.

The pointwise analyses of differences in absolute sensitivity do not take into account the between-individual differences in sensitivity due to age and the within- and between-individual differences at any given stimulus location due to the partial covariance of sensitivity with increase in eccentricity and with defect depth. The age of the sample ranged from 42 to 72 years with a mean of 67 years. The age decline in sensitivity of the normal eye, based upon cross-sectional data, varies between stimulus locations but is approximately 0.7 dB per decade irrespective of algorithm (see Chapter 3). Thus the maximum between-individual discrepancy at any given stimulus location due to age would be in the region of 2.1 dB i.e. generally within one interval of the scale on the abscissa of Figure 4.2.

	<36	<34	<32	<30	<28	<26	<24	<22	<20	<18	<16	<14	<12	<10	<8	<6	<4	<2	<0
Full Threshold (Centre)	3	41	147	205	160	104	49	24	21	23	16	7	10	2	2	5	4	5	42
Full Threshold (Periphery)	0	4	52	138	209	208	192	99	75	46	43	33	18	23	19	13	11	9	84
Full Threshold (ALL)	3	45	199	343	369	312	241	123	96	69	59	40	28	25	21	18	15	14	126
FASTPAC (Centre)	7	41	139	200	152	113	68	39	9	12	7	10	4	6	2	7	12	4	38
FASTPAC (Periphery)	1	3	46	159	206	217	167	106	87	48	40	27	21	15	18	12	19	16	68
FASTPAC (ALL)	8	44	185	359	358	330	235	145	96	60	47	37	25	21	20	19	31	20	106
SITA Standard (Centre)	5	104	194	195	128	73	38	15	11	20	11	4	3	5	3	3	2	7	49
SITA Standard (Periphery)	0	21	109	187	220	203	136	94	46	42	24	14	13	21	14	15	14	13	90
SITA Standard (ALL)	5	125	303	382	348	276	174	109	57	62	35	18	16	26	17	18	16	20	139
SITA Fast (Centre)	13	100	224	198	136	65	41	12	6	4	3	2	4	4	3	5	4	5	41
SITA Fast (Periphery)	0	20	141	217	223	207	132	76	39	29	32	21	11	7	16	12	11	6	76
SITA Fast (ALL)	13	120	365	415	359	272	173	88	45	33	35	23	15	11	19	17	15	11	117

Table 4.3 The number of stimulus locations at each sensitivity level, for all regions of the visual field, with each of the algorithm

The magnitude of the normal gradient of sensitivity across the Program 30-2 field varies with region, has an upper limit of approximately 9 dB and governs the maximum within- and between-individual discrepancy between a normal peripheral value and an abnormal central value. The impact of age on the pointwise between-individual differences in sensitivity could have been reduced by considering the between-algorithm difference in sensitivity at the given stimulus location as a function of the deviation of measured sensitivity of the reference algorithm from the age-corrected normal value. Such an approach was adopted by Heijl and colleagues (1989) but does not distinguish normal reductions in sensitivity due to eccentricity from identical but abnormal values due to a defect. Moreover, such a technique would reduce the impact of any between-algorithm comparison of absolute values of sensitivity since the generated deviation values would be derived from each individual normal database. A comparison of the distributions of the within-visit between-algorithm (Figure 4.7) and of the within-algorithm between-visit (Figure 4.8) differences in sensitivity as a function of central and peripheral stimulus location yielded similar distributions between the two zones indicating that any potential differences in stimulus eccentricity were masked by the underlying field loss. However, the analysis of the pointwise Pattern Deviation probability values overcomes any limitations in the comparison of the absolute values of sensitivity since the confidence limits are corrected for both age and eccentricity.

The results of the Pattern Deviation probability analysis are consistent with the report of narrower pointwise confidence limits for normality for both the SITA Standard and the SITA Fast algorithms (see Chapter 3). The results also confirm the suggestion that the narrower confidence limits for the SITA algorithms correspond to lighter levels of grey in the greyscale print-out than those for the Full Threshold algorithm, particularly for the proportionately larger deviations from normality, and that the widths of the confidence limits for SITA are such that multiple changes in probability level can occur within a given level of grey (Figure 4.9).

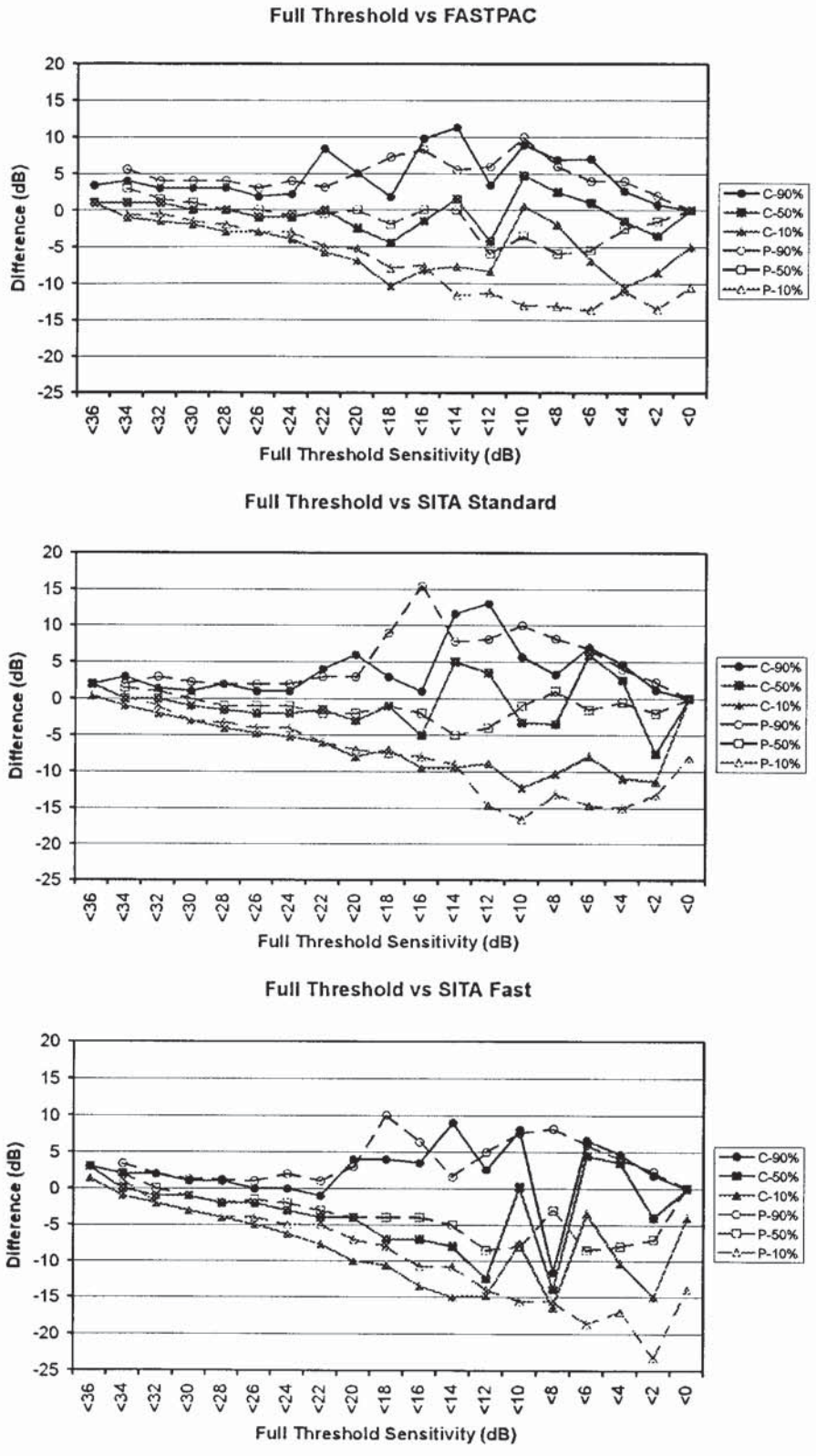


Figure 4.7a. The 90th, 50th and 10th percentiles of the distribution of the differences in sensitivity across all locations, at visit 2, between the Full Threshold and the FASTPAC (top), the SITA Standard (centre) and the SITA Fast algorithms (bottom) analysed separately for the central and peripheral annuli.

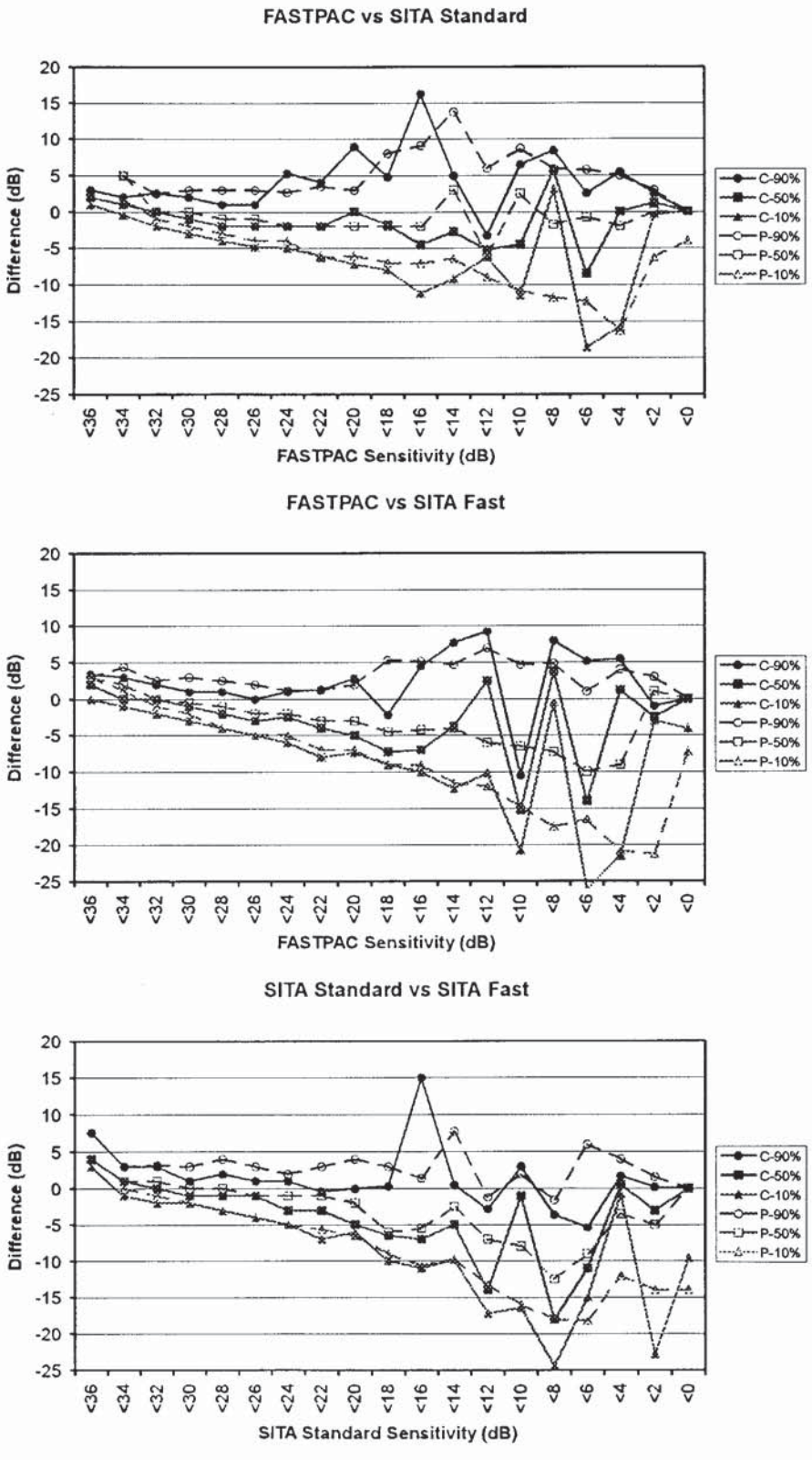


Figure 4.7b. The 90th, 50th and 10th percentiles of the distribution of the differences in sensitivity across all locations, at visit 2, between the FASTPAC and SITA Standard algorithms (top), the FASTPAC and SITA Fast algorithms (centre) and SITA Standard and SITA Fast algorithms (bottom) analysed separately for the central and peripheral annuli.

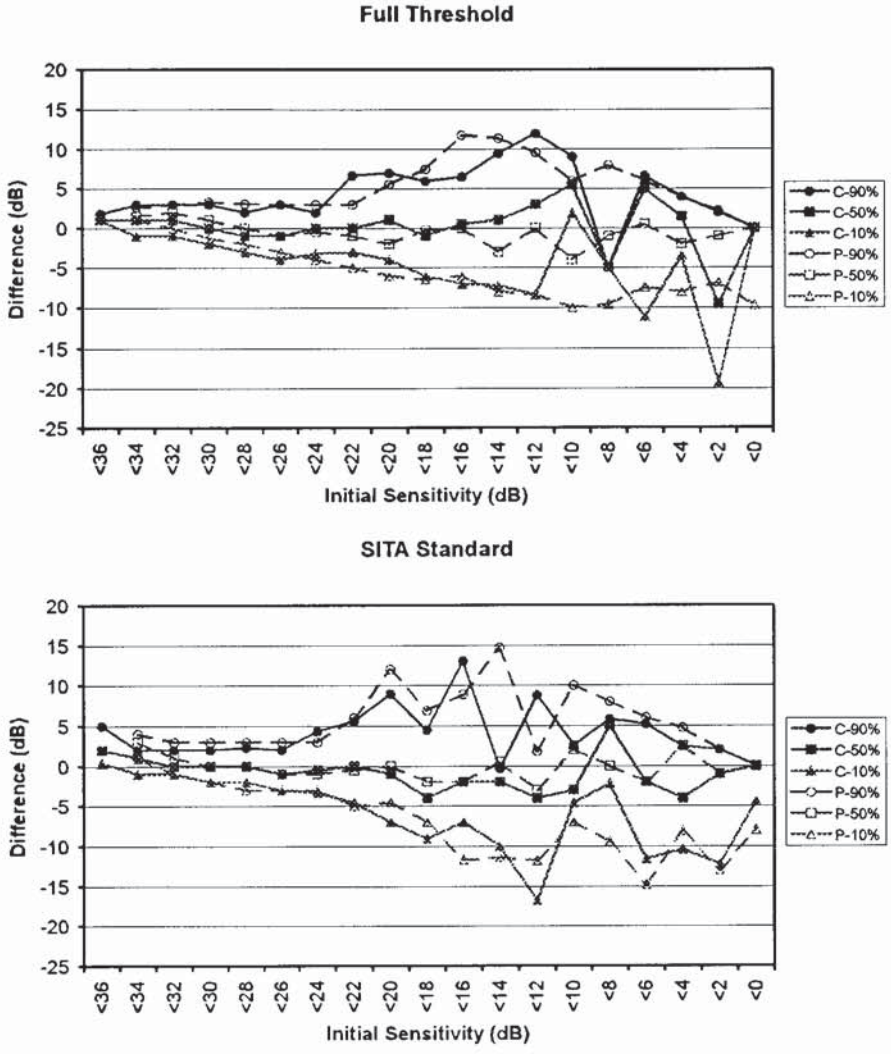


Figure 4.8. The 90th, 50th and 10th percentiles of the distribution of the differences in sensitivity across all locations for each of the algorithms between visit 2 and visit 3, as a function of the sensitivity of the reference algorithm at the second visit (i.e. the within-algorithm between-visit evaluation) analysed separately for the central and peripheral annuli.

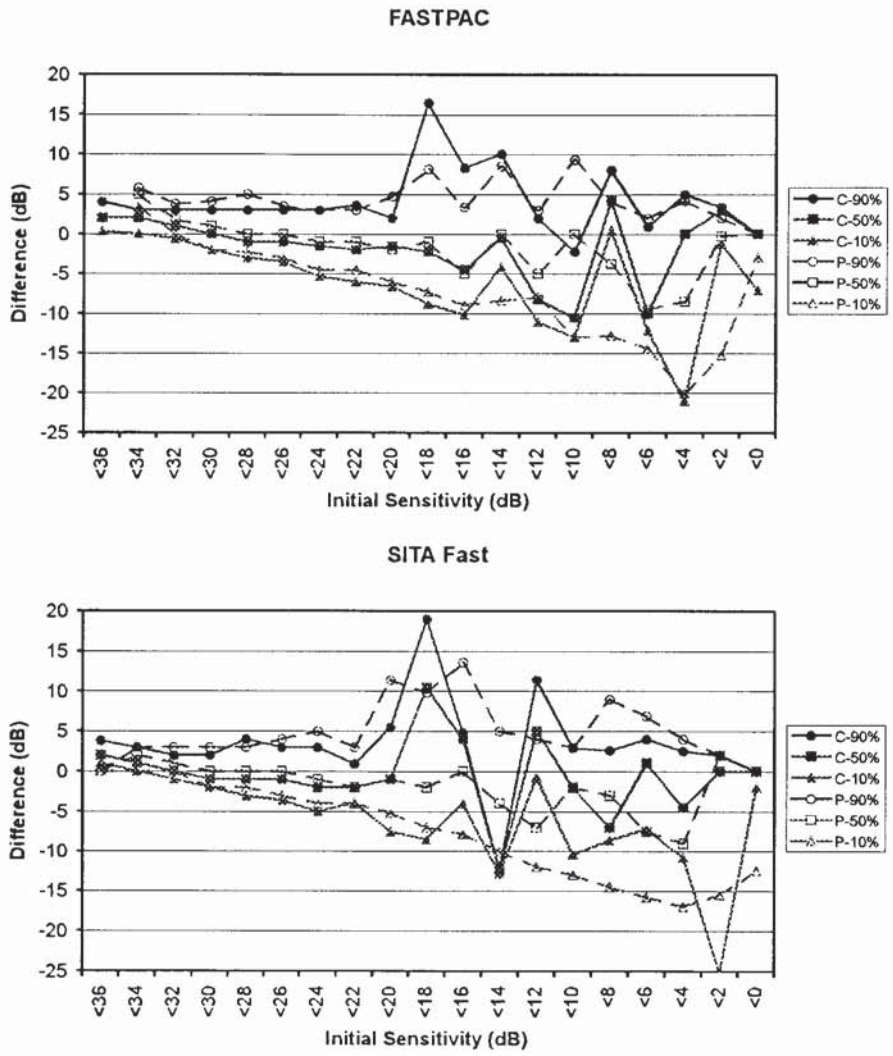


Figure 4.8. The 90th, 50th and 10th percentiles of the distribution of the differences in sensitivity across all locations for each of the algorithms between visit 2 and visit 3, as a function of the sensitivity of the reference algorithm at the second visit (i.e. the within-algorithm between-visit evaluation) analysed separately for the central and peripheral annuli.

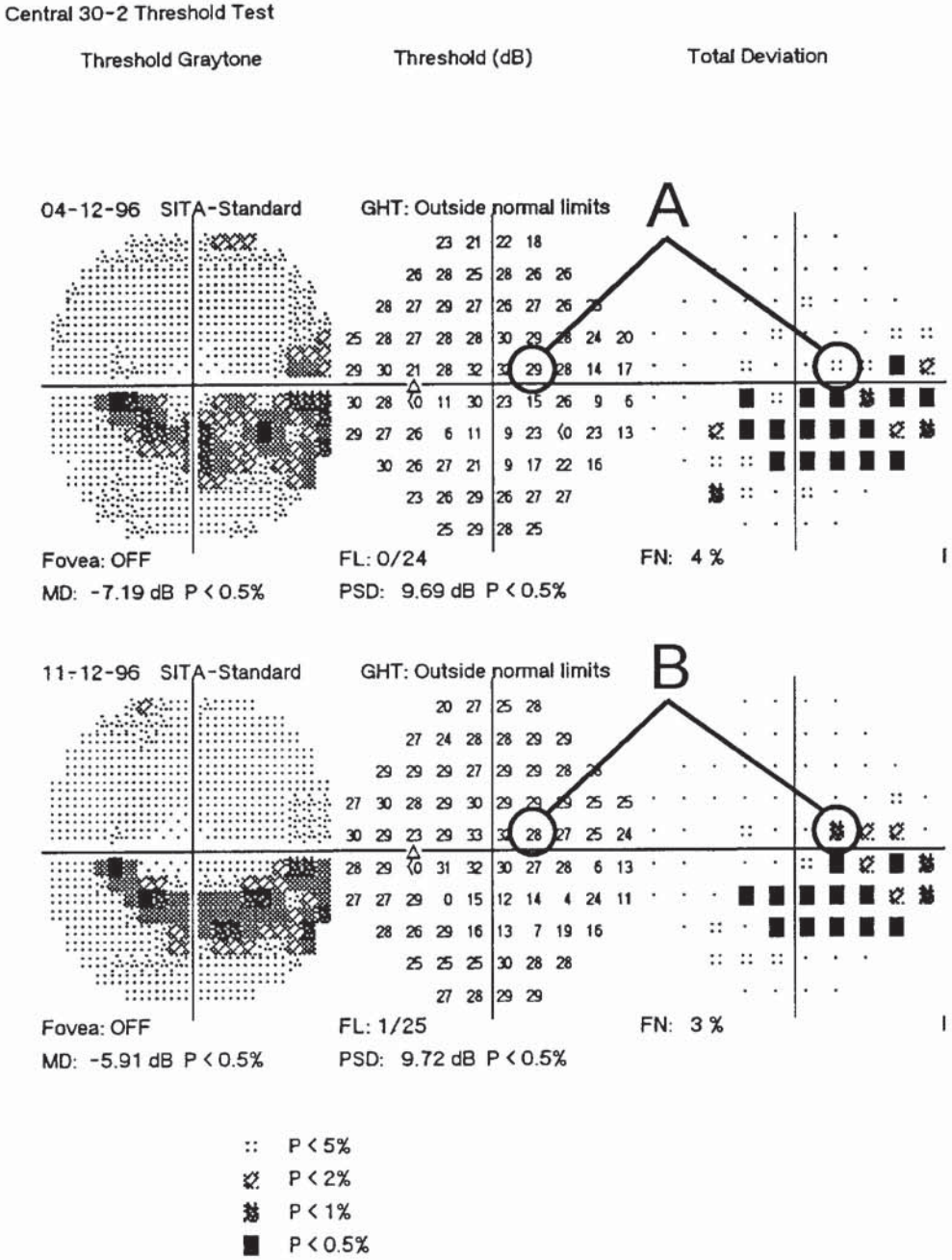


Figure 4.9. Part of a Statpac overview printout showing the greyscale, threshold values and the Total Deviation plots from two SITA Standard examinations, separated by one week, on a 55 year old male glaucoma patient. The locations circled A and B differ in absolute sensitivity by 1 dB and fall within the same level of grey on the greyscale. However, the Total Deviation probability levels assigned to each sensitivity skip the P<2% level.

The results of the Pattern Deviation probability analysis also confirm that the long term follow-up of patients with the Full Threshold algorithm can, in general, be safely continued using the SITA Standard algorithm. However, some patients are likely to exhibit glaucomatous fields which appear less severe when initially examined with either of the SITA algorithms compared to the immediate previous examination undertaken with the Full Threshold algorithm. This can be attributed to a reduction in the fatigue effect associated with the 15-16 minute duration of the Full Threshold algorithm and Program 30-2. The fatigue effect is most apparent at stimulus locations which exhibit relative loss, varies in magnitude between individuals, and leads to an overestimation of the defect depth (Heijl 1977b, Heijl and Drance 1983, Johnson, et al. 1988b, Marra and Flammer 1991, Searle, et al. 1991, Wild, et al. 1991, Hudson, et al. 1994). However, it is likely that the statistically deeper defect depth of the SITA algorithms will largely mitigate against such an eventuality in these patients. Alternatively, some patients who do not manifest a fatigue effect may exhibit fields that are worse with SITA Standard as a result of the statistically deeper SITA defect depth. These potential problems could be resolved at the designated follow-up by undertaking a Full Threshold examination followed, within a short time frame, by two SITA examinations. In this way, the SITA baseline for successive examinations would have been established.

4.6 Conclusions

The profound reduction in the examination time of the SITA algorithms together with the capability to detect a statistically deeper defect depth offers an opportunity for a revision of visual field examination in glaucoma practice. The reduced examination time compared to both the Full Threshold and FASTPAC algorithms dictates either that a given patient can undergo a visual field examination more frequently or that more patients can be seen per unit time. The opportunity for a more frequent re-examination of the same patient provides greater scope for the recognition of progressive visual field loss in that the natural history of the disease process can be followed more regularly and that the adverse statistical impact of the long-term fluctuation can be reduced by more frequent examinations. The utility of the

SITA algorithms is also such that should either an apparent visual field abnormality be detected for the first time or an apparent progression of an existing abnormality be identified, then the findings can be immediately verified by the use of SITA Fast without causing a significant loss of clinical time.

The SITA algorithms produce marginally higher Group mean MSs and pointwise sensitivities compared to the existing Full Threshold and FASTPAC algorithms. However, both SITA algorithms detect a more statistically significant deeper and/or wider defect together with a halving of the examination duration for SITA Standard compared to the Full Threshold algorithm and for SITA Fast compared to FASTPAC. The narrower confidence limits, a similar between-visit variability combined with a markedly reduced examination duration compared to the existing 'gold standard' perimetric threshold algorithms, ensure that the SITA algorithms will generate a quantum leap for the visual field examination in the detection and management of primary open angle glaucoma.

CHAPTER 5. THE EFFECT OF PATIENT FATIGUE ON THE VISUAL FIELD DERIVED WITH SITA

5.1 Introduction

5.1.1 The fatigue effect in perimetry

The fatigue effect in perimetry describes the reduction in sensitivity and the increase in variability of patient responses with increasing examination duration. The fatigue effect is present in both manual and automated perimetry. The presence of a fatigue effect in manual perimetry was noted by Greve (1973) who suggested the use of rest periods during the examination to minimise the effect. The fatigue effect generally exerts a greater influence on the results from automated perimetry and may partly explain the greater incidence of visual field defects seen in automated perimetry (Heijl and Krakau 1975a, Heijl 1977b, Heijl and Drance 1983).

The fatigue effect opposes the learning effect. The learning effect describes the process whereby sensitivity increases with familiarity of the test procedures (see Chapter 7). Up to the first five examinations, the learning effect can be dominant. At subsequent examinations the learning effect decreases and the influence of the fatigue effect becomes more apparent (Searle, et al. 1991, Wild, et al. 1991, Hudson, et al. 1994).

The investigation of the fatigue effect in automated perimetry has been determined by the repeated thresholding of selected stimulus locations (Heijl 1977b, Heijl and Drance 1983, Langerhorst, et al. 1987, Johnson, et al. 1988b, Marra and Flammer 1991, Searle, et al. 1991, Fujimoto and Adachi-Usami 1993) or by the evaluation of staged examination of the central visual field (Hudson, et al. 1994). The fatigue effect has been demonstrated in normal subjects (Heijl 1977b, Langerhorst, et al. 1987, Johnson, et al. 1988b, Searle, et al. 1991, Fujimoto and Adachi-Usami 1993, Hudson, et al. 1994) and in patients with ocular hypertension (Heijl and Drance 1983, Langerhorst, et al. 1987, Hudson, et al. 1994), with glaucoma (Heijl 1977b, Heijl and Drance 1983, Langerhorst, et al. 1987, Johnson, et al. 1988b, Wild, et al. 1991, Fujimoto and Adachi-Usami 1993, Hudson, et al. 1994) and with

optic neuropathy (Johnson, et al. 1988b, Fujimoto and Adachi-Usami 1993). The fatigue effect has been shown to occur during the examination of a given eye (Heijl 1977b, Heijl and Drance 1983, Johnson, et al. 1988b, Searle, et al. 1991, Hudson, et al. 1994) and to be present between eyes at a single examination (Searle, et al. 1991, Wild, et al. 1991, Hudson, et al. 1994).

The reduction in sensitivity is greater as the duration of the examination increases (Heijl 1977b, Heijl and Drance 1983, Johnson, et al. 1988b, Searle, et al. 1991, Hudson, et al. 1994), is greater for the second eye tested (Searle, et al. 1991, Wild, et al. 1991, Hudson, et al. 1994) and is greater in areas of the visual field adjacent to or within a scotoma (Heijl and Drance 1983, Johnson, et al. 1988b). The fatigue effect is also eccentricity dependent, particularly in glaucoma patients, with the peripheral stimulus locations affected to a greater extent (Langerhorst, et al. 1987, Johnson, et al. 1988b, Searle, et al. 1991, Hudson, et al. 1994). Marra and Flammer (1991) were unable to detect a significant overall fatigue effect but did note that some subjects showed a trend towards a decline in sensitivity at the more peripheral eccentricities. Additionally, the superior visual field has been shown to be affected by the fatigue effect to a greater extent than the inferior hemifield in terms of the magnitude of the decline in sensitivity (Searle, et al. 1991) and in terms of the increase in the Loss Variance index relative to the inferior field (Hudson, et al. 1994).

The discovery that the fatigue effect is greater at stimulus locations adjacent to areas of reduced sensitivity has led to the hypothesis that perimetric fatigue could be used as a provocative test for glaucoma (Heijl 1977b, Heijl and Drance 1983). However, Langerhorst et al (1987) demonstrated considerable overlap in the magnitude of the fatigue effect between groups of normal subjects and ocular hypertensive and glaucoma patients, mitigating against the use of fatigue as a provocative test. The fatigue effect has also been shown to be greater in older patients (Langerhorst, et al. 1987, Hudson, et al. 1994).

The magnitude of the fatigue effect is unaffected by changes in background luminance between 0.1 cdm^{-2} and 10 cdm^{-2} (Heijl and Drance 1983), whereas, a reduction in the fatigue

effect has been reported for stimulus durations of 100 ms compared to stimulus durations of 200 ms (Searle, et al. 1991). The provision of a 1.5 minute rest period during the examination of a given eye has been shown to reduce, but not eliminate, the fatigue effect (Johnson, et al. 1988b); however, a three minute rest period between eyes was insufficient to alter the fatigue effect in the second eye (Hudson, et al. 1994).

5.1.2 The mechanism of the fatigue effect

The precise mechanism of the perimetric fatigue effect is unknown. The decline in sensitivity for the superior hemifield relative to the inferior hemifield may be due to an increase in the degree of upper lid ptosis during the examination.

The cessation of eye movements during a perimetric examination leads to a stabilised retinal image. The Troxler phenomenon describes the fading of stabilised a retinal image, which reappears immediately eye movements occur (Riggs, et al. 1953, Davson 1990, Steinman and Levinson 1990). One or two seconds after the onset of a stabilised retinal image, observers report a blurring of the stimulus contours, followed by a reduction in subjective brightness and chromatic saturation and ultimately fading of the image which appears to continue to get subjectively darker for several minutes (Gerrits, et al. 1966). A combination of the Troxler effect and the even illumination of the perimeter bowl, leading to Ganzfeld blankout (Bolanowski and Doty 1987, Gur 1989, Fuhr, et al. 1990, Gur 1991), have been suggested as the principle factors in the perimetric fatigue effect (Searle, et al. 1991, Hudson, et al. 1994). There are two Ganzfeld related effects. Ganzfeld blankout, where the complete visual field briefly appears black, has been shown to occur only with monocular viewing (Bolanowski and Doty 1987, Gur 1991) in situations with at least a 0.75 log unit difference of retinal luminance between the eyes (Bolanowski and Doty 1987). Fade-out is a gradual change in the brightness, hue and saturation of the evenly illuminated background (Gur 1989, Gur 1991). Fade-out can occur in the binocularly viewed field (Gur 1991) and is more pronounced for backgrounds of longer wavelengths (Gur 1989). The use of a translucent occluder delays the onset of blankout and has been suggested for use in

perimetry, in order to reduce the fatigue effect (Fuhr, et al. 1990). The fading of images in the fatigue effect may be explained by the increase the size of the receptive field of cortical cells in the presence of a continuous image (Campbell and Andrews 1992). The physiological process may be accomplished by the activation of usually dormant dendrites.

Psychological factors may influence perimetric fatigue. Perimetry is a form of vigilance task, requiring sustained attention. Vigilance tasks have been shown to be affected by a number of factors (Stroh 1971, Warm 1984), although the exact causes of the changes in performance are not well understood (Mackworth 1969). The decline in performance at tasks requiring a high level of attention is termed the 'vigilance decrement' (Stroh 1971, Warm 1984). The vigilance decrement is correlated with long test durations (Stroh 1971, Warm 1984), with at least 50% of the decline in performance occurring within the first 15 minutes (Teichner 1974). The vigilance decrement is more pronounced with stimuli presented close to threshold (Warm 1984) and is improved by increasing the temporal frequency of test stimulus presentations, by the introduction of short periods of rest or by the addition of response feedback to the subject (Stroh 1971). Additionally, vigilance is affected by spatial uncertainty; that is, the phenomenon whereby observers bias their responses towards the spatial location with a higher proportion of signals (Niceley and Miller 1957, Milosevic 1974, Cohn and Wardlaw 1985, Lindblom and Westheimer 1992). Spatial uncertainty can be reduced by the addition of cues to indicate the position of the next stimulus (Hubner 1996). The addition of non-signal stimuli (stimuli not requiring a response) has a detrimental effect on the vigilance decrement, which is proportionate to the rate of presentation of the non-signal stimuli (Jerrison and Pickett 1964). This latter finding is thought to be part of the habituation process (Warm 1984) which is defined as 'the waning of neural responses as a result of repetitive stimulation' (Mackworth 1969). Habituation can be reversed suddenly by changes in the method of stimulation (Mackworth 1969, Warm 1984) leading to arousal. Arousal is a continuum of states between coma and emotional excitement leading to a degree of physiological and behavioural excitation (Duffy 1962). Thus, the habituation process is unable to completely explain the fatigue effect due to the phenomenon of the sudden reversal of habituation to arousal.

5.1.3 The effect of patient fatigue on the visual field derived with SITA

The evaluation of SITA in normal subjects and in glaucoma patients has been reported in Chapters 3 and 4. It was found that SITA exhibited a reduction in the test duration of approximately 50%, together with a reduction in the between-subject variability of normal sensitivity compared to the Full Threshold and FASTPAC algorithms. A systematic difference in the estimation of threshold also exists, namely approximately 1.0 dB between the Full Threshold and SITA Standard algorithms and 1.5 dB between FASTPAC and SITA Fast. The difference between the measured sensitivities for the SITA and the Full Threshold algorithms found in Chapters 3 and 4 did not deviate appreciably from the expected values. It was hypothesised that the narrower confidence limits for normality with SITA might have occurred due to a likely reduction in the fatigue effect, resulting from the reduction in examination duration. However, a 0.9 dB greater than expected difference in sensitivity between SITA and Full Threshold has been reported (Bengtsson, et al. 1998). This difference between the expected and measured sensitivities was attributed to a reduction in the fatigue effect with SITA.

Patient response errors during a staircase procedure affect the accuracy of the estimation of threshold (Johnson, et al. 1992). The standard perimetric staircases estimate threshold based on the final seen stimulus. If the staircase has been adversely affected by poor patient responses, errors in the threshold estimation may occur. One of the potential benefits of SITA is the fact that all patient responses are used to estimate threshold thus, the influence of erroneous responses may be reduced. However, the precise effect of patient fatigue on the visual field derived by SITA is unknown.

5.2 Aim of study

The aim of the study was to investigate the fatigue effect associated with SITA Standard compared to that with the Full Threshold algorithm. The specific aims were firstly, to investigate any differences in the decline of sensitivity with the increase in examination

duration between the two algorithms. Secondly, to investigate any regional differences in the fatigue effect between algorithms.

5.3 Methods

5.3.1 Sample

The sample comprised 20 patients with primary open angle glaucoma (POAG) and 20 normal controls. The mean age of the glaucoma patients was 62.2 years (SD 15.5 years) with a range from 22 to 79 years. The normal group had a mean age of 62.8 years (SD 13.9 years) and a range from 27 to 82 years. The inclusion criteria for both groups was a visual acuity of 6/9 or better in either eye, a distance refractive error less than or equal to 5 dioptres mean sphere and less than 2.5 dioptres cylinder, lenticular changes not greater than NCIII, NOIII, CI or PI by LOCS III (Chylack, et al. 1993), open angles, no history or family history of diabetes mellitus and no systemic medication known to affect the visual field.

Further inclusion criteria for the normal group were an intraocular pressure of less than 22 mmHg in either eye, normal optic nerve head appearance, no previous ocular surgery or trauma and no known family history of glaucoma.

All patients in the glaucoma group manifested an optic nerve head appearance characteristic of POAG and a repeatable visual field defect consistent with POAG on the Humphrey Field Analyzer using the Full Threshold algorithm. All individuals were experienced in automated threshold static perimetry having undergone a minimum of three previous examinations. Fourteen of the glaucoma patients had participated in the study from Chapter 4 and 17 of the normal subjects had participated in the study described in Chapter 3. All of the glaucoma patients had well controlled intraocular pressures (mean 16.5 mmHg SD 3.5) and stable visual fields. Fourteen patients were controlled on a single topical agent (either a selective or non-selective β-blocker, a topical carbonic anhydrase inhibitor, an alpha adrenergic agonist or a prostaglandin) and five patients required more than one topical agent for IOP control. No

patients were on systemic carbonic anhydrase inhibitors or topical cholinergics. Five had undergone previous trabeculectomy at least six months before the study commenced, three of who required no further medical control of intraocular pressure.

5.3.2 Examination Protocol

Perimetry was performed on one eye of each individual using the HFA 750 over two visits. The designated eye from each normal subject was selected at random to provide an equal number of left and right eyes. The designated eye from each glaucoma patient was selected to provide a continuum of severity across the sample. The degree of field loss was described using the system of Hodapp et al (1994). This classification, which was outlined in Chapter 4, describes the severity of loss in terms of the Mean Deviation visual field index and in terms of the number, severity and proximity to fixation of the Pattern Deviation probability symbols. Each visual field examination used the default white-on-white stimulus parameters of the Humphrey Field Analyzer: a Goldmann size III stimulus presented against a 10 cdm^{-2} white background with a stimulus duration of 200 ms. Refractive correction appropriate for the viewing distance of the perimeter bowl was used for each individual.

At one visit, the designated eye of the individual was examined with the Full Threshold algorithm using a consecutive series of four custom programs (i.e. four phases). The first custom program (designated FT_{A1}) contained 38 of the 76 stimulus locations associated with Program 30-2 (defined in Figure 5.1). The second custom program (FT_{B1}) contained the remaining 38 stimulus locations associated with Program 30-2. Thus, the first and second custom programs resembled a complete examination of one eye with Program 30-2. The two custom programs were repeated on the same eye (FT_{A2} and FT_{B2}) to replicate the examination with a second Program 30-2. At the other visit, the same eye underwent four consecutive Program 30-2 examinations with the SITA Standard algorithm (designated SS_{A1}, SS_{B1}, SS_{A2} and SS_{B2}). The order of visits was randomised between patients. At each visit, each examination was completed without rest periods, unless specifically requested by the patient. Rest periods between examinations were limited to the time taken for the post-test

processing of patient responses by SITA and the time taken to save and print the results for each individual examination and to recall the next program.

The experimental design permitted examination of the fatigue effect according to two different protocols (Figure 5.2). The first protocol permitted the investigation of the within- and between-algorithm fatigue effects over a similar examination duration. The sensitivity derived from the locations of FT_{A1} could be compared with that from FT_{A2} and with that from the same locations in SS_{A1} and SS_{A2}. In a similar manner, the sensitivity with FT_{B1} could be compared with that from FT_{B2} and with that from SS_{B1} and SS_{B2}.

The second protocol permitted investigation of the within- and between-algorithm fatigue effect over all 76 stimulus locations of Program 30-2 irrespective of the examination duration. The combination of FT_{A1} and FT_{B1}, replicated one Program 30-2 field whilst that of FT_{A2} and FT_{B2} replicated the examination with a second Program 30-2. The results from FT_{A1} and FT_{B1} were compared with those from SS_{A1}. The results from FT_{A2} and FT_{B2} were compared with those from SS_{B1}.

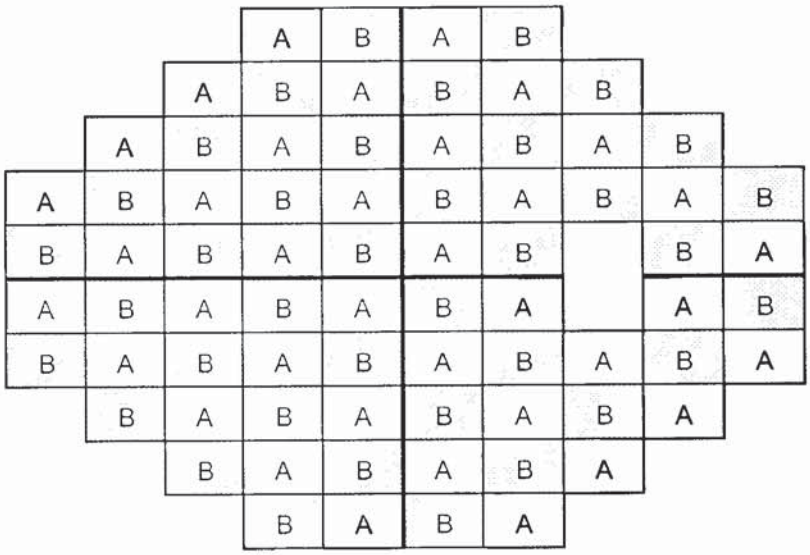


Figure 5.1. The stimulus locations used for the custom test with the Full Threshold algorithm. Locations designated A were thresholded at the first (FT_{a1}) and third (FT_{a2}) examinations and locations designated B were thresholded at the second (FT_{b1}) and fourth (FT_{b2}) examinations. The stimulus configuration for the examination of the right eye is shown, the configuration for the left eye is a mirror image of that shown above.

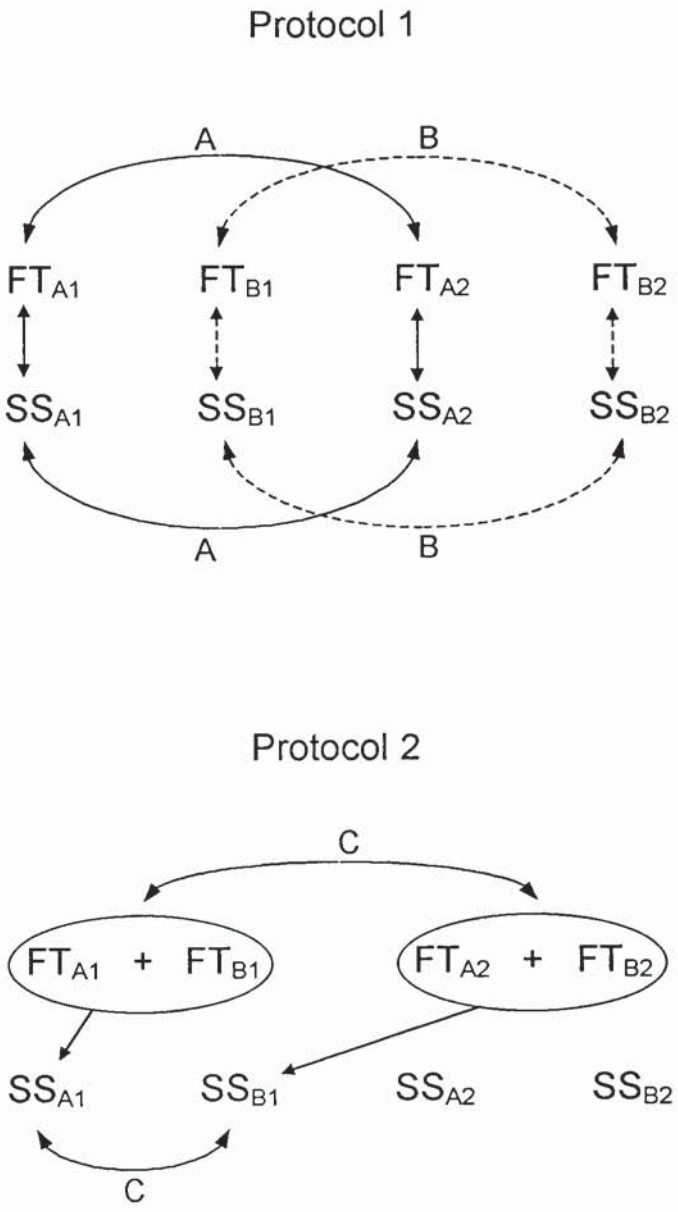


Figure 5.2. Diagrammatic representation of the two analytical protocols. (Top) For the first protocol, data from phase one was compared to the third phase (A), which used the same stimulus locations, both within-algorithm and between-algorithms. A similar comparison was performed for phases two and four (B). (Bottom) For the second protocol, the first and second 37 point phases with Full Threshold were combined to simulate a complete Program 30-2 examination. The third and fourth 37 point phases were combined to simulate a second Program 30-2 examination. These two 74 point examinations were compared to the first and second 74 point SITA Standard examinations (C). Data from the third and fourth SITA Standard examinations (SS_{A2} and SS_{B2}) were excluded from the analysis in protocol 2.

5.3.3 Analysis

The results for left eyes were converted into right eye format. The stimulus locations immediately above and below the physiological blind spot were exclude from the analysis.

5.3.3.1 Global analysis of Examination Duration and Mean Sensitivity

A Repeated Measures ANOVA was performed for examination duration for the individual phases of the first protocol with each algorithm. A separate Repeated Measures ANOVA was performed for each of, the Mean Sensitivity for all stimulus locations out to an eccentricity of 30 degrees, for the Mean Sensitivity for the central annuli and for the Mean Sensitivity for the peripheral annuli of Program 30-2 for the specific combination of phases of both of the protocols. For each ANOVA, the age of the individual, the diagnostic category and the severity of the glaucoma were all considered as between-subject factors. The type of algorithm, the sequence of the examination and the order of visits were considered as within-subject factors.

5.3.3.2 Pointwise analysis of sensitivity

For the first protocol, for each normal subject and glaucoma patient, the difference in sensitivity at each stimulus location between the first and third phases and between the second and fourth phases was calculated. The data for all patients, within a group, were combined and the distributions of differences were expressed as a function of the sensitivity at the first of the two phases. A similar calculation was performed for the different phases of the second protocol.

5.4 Results

All visual fields met the inclusion criteria for reliability, specifically less than 20% fixation losses and less than 33% false-negative and false-positive catch trials. The glaucoma group comprised nine eyes with early loss, six with moderate loss and five with severe loss.

5.4.1 The within- and between-algorithm effects for a controlled examination duration (protocol 1)

Table 5.1 shows, for each phase of each algorithm in the normal and glaucoma groups, the group mean examination duration and the group mean MS for each region of the visual field.

5.4.1.1 Examination duration

Figure 5.3 shows the group mean examination duration for each phase of each algorithm in both the normal and glaucoma groups. For the first and third phases at each visit, the examination duration was independent of age ($p=0.479$) regardless of the diagnostic category ($p=0.078$). The examination duration was longer for the glaucoma group than for the normal group ($p<0.001$) and was longer with increasing severity of the field loss ($p<0.001$) regardless of age ($p=0.104$).

The examination duration was longer for Full Threshold than for SITA Standard at the first and third phases ($p<0.001$) regardless of diagnostic group ($p=0.263$), grade of defect ($p=0.767$) or age ($p=0.124$). The examination duration increased from phase 1 to 3 ($p=0.002$) irrespective of algorithm ($p=0.927$) and age ($p=0.399$). The examination duration for the glaucoma group increased from phase 1 to 3 by an average of 18 seconds more than the normal group ($p=0.047$) and this was irrespective of the grade of defect ($p=0.555$).

For the second and fourth phases at each visit, the examination duration was independent of age ($p=0.483$) regardless of the diagnostic category ($p=0.028$). The examination duration was longer for the glaucoma group than for the normal group ($p<0.001$) and was longer with increasing severity of the field loss ($p<0.001$) regardless of age ($p=0.049$).

The examination duration was longer for Full Threshold than for SITA Standard at the second and fourth phases ($p<0.001$) regardless of diagnostic group ($p=0.364$), grade of defect ($p=0.064$) or age ($p=0.084$). The examination duration was similar between phase 2 and phase 4 ($p=0.222$) irrespective of algorithm ($p=0.317$), diagnostic group ($p=0.255$), grade of defect ($p=0.750$) and age ($p=0.428$).

		NORMAL				GLAUCOMA			
		P1	P2	P3	P4	P1	P2	P3	P4
Examination duration (min)									
FT	mean	6.67	6.85	6.73	6.89	8.09	8.40	8.59	8.40
	sd	0.64	0.67	0.88	0.78	0.92	1.04	1.23	0.84
SS	mean	6.27	6.44	6.42	6.42	7.56	7.64	8.00	8.00
	sd	0.58	0.58	0.67	0.73	1.02	1.03	1.06	0.95
WHOLE MS (dB)									
FT	mean	28.11	27.42	27.35	27.27	24.15	23.14	22.75	22.23
	sd	1.89	1.89	1.92	2.06	2.23	2.51	2.86	3.11
SS	mean	28.83	28.16	28.18	28.02	25.18	23.94	23.57	23.17
	sd	1.75	1.89	1.88	1.92	2.57	2.63	2.91	3.04
CENTRE MS (dB)									
FT	mean	29.84	29.10	29.07	28.98	26.31	24.91	24.85	24.19
	sd	1.91	1.71	1.72	1.71	2.36	3.33	2.95	3.27
SS	mean	30.83	30.17	30.16	30.01	27.60	25.96	25.90	25.16
	sd	1.28	1.47	1.42	1.36	2.97	3.63	3.53	3.98
PERIPHERY MS (dB)									
FT	mean	26.92	26.28	26.19	26.11	22.69	21.93	21.31	20.89
	sd	2.00	2.07	2.14	2.35	2.60	2.85	3.45	3.79
SS	mean	27.46	26.80	26.83	26.66	23.53	22.56	22.01	21.81
	sd	2.13	2.22	2.24	2.33	2.85	2.91	3.77	3.46

Table 5.1. The group mean examination duration and group mean MS for each phase (P1, P2, P3, P4) of the Full Threshold (FT) and SITA Standard (SS) algorithms for the normal and glaucoma groups. The results for MS are expressed as a function of the whole central field, and also for the central and peripheral annuli of the central field.

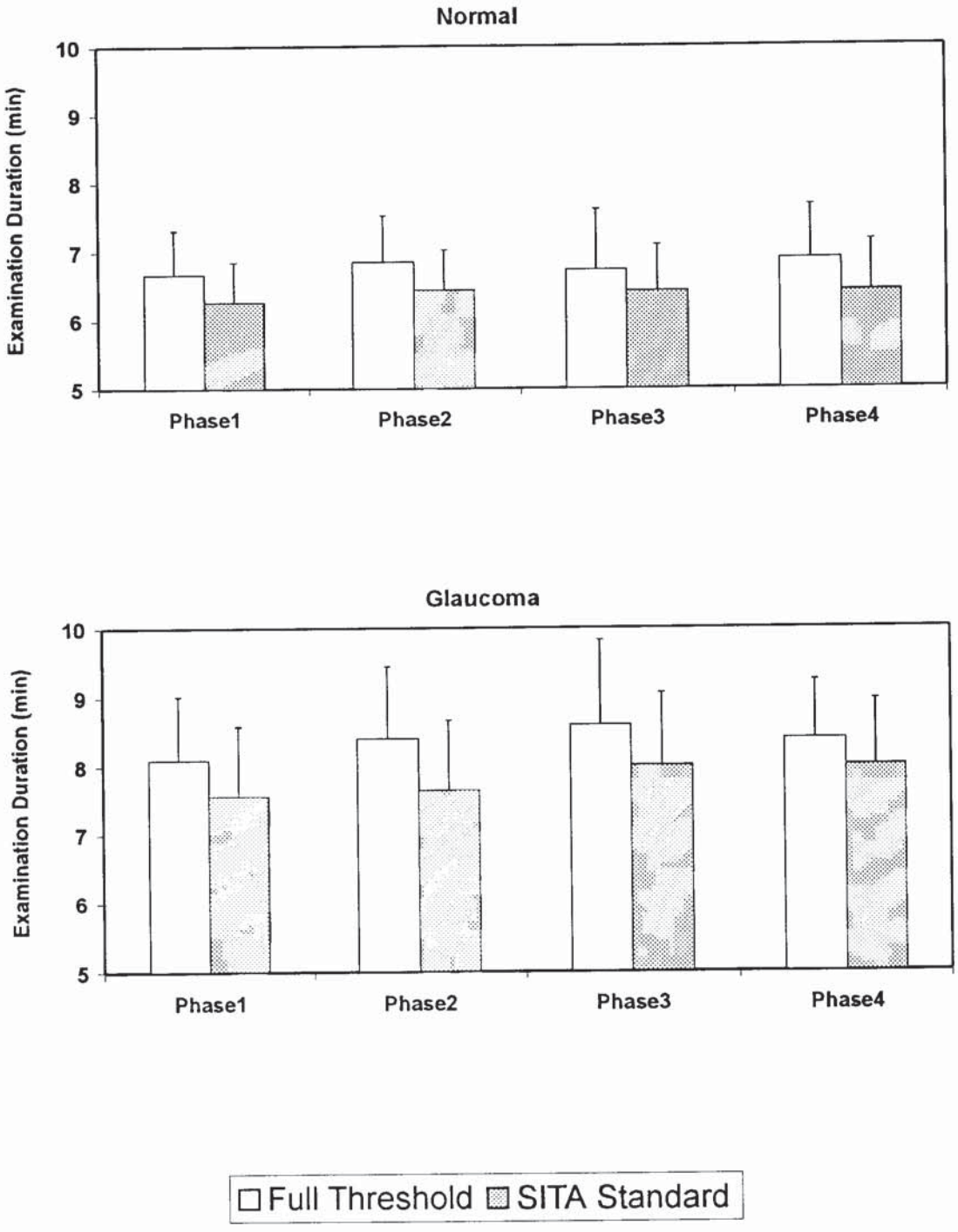


Figure 5.3. The group mean examination duration for each phase of each algorithm in both the normal (top) and glaucoma (bottom) groups. The error bars indicate one standard deviation of the mean.

5.4.1.2 Mean Sensitivity for the whole central field

Figure 5.4 shows the group mean MS for the whole central field for each phase of each algorithm for both normal and glaucoma groups. For phases 1 and 3, the magnitude of the MS was independent of age ($p=0.248$) regardless of the diagnostic group ($p=0.296$). As would be expected, the MS was lower in the glaucoma group than in the normal group ($p<0.001$) and was lower as the field loss increased ($p=0.026$) regardless of age ($p=0.304$).

For phases 1 and 3, the MS was higher for SITA Standard than for Full Threshold ($p<0.001$), regardless of diagnostic group ($p=0.628$), grade of defect ($p=0.195$) or age ($p=0.884$). The MS declined between first and third phases ($p<0.001$) and the magnitude of the decline was irrespective of age ($p=0.706$). The reduction in sensitivity for the glaucoma group was approximately twice that for the normal group ($p=0.011$) and this difference was independent of defect grade ($p=0.887$) and algorithm ($p=0.878$).

For phases 2 and 4, the magnitude of the MS was independent of age ($p=0.199$) regardless of the diagnostic group ($p=0.398$). Again, as would be expected, the MS was lower in the glaucoma group than in the normal group ($p<0.001$) and was lower as the field loss increased ($p=0.017$) regardless of age ($p=0.742$).

For phases 2 and 4, the MS was higher for SITA Standard than for Full Threshold ($p<0.001$), regardless of diagnostic group ($p=0.679$), grade of defect ($p=0.247$) or age ($p=0.569$). The MS declined between the second and fourth phases ($p=0.002$) and the magnitude of the decline was irrespective of age ($p=0.689$). The reduction in sensitivity for the glaucoma group was approximately six times that for the normal group between the second and fourth phases ($p=0.026$) and this difference was independent of defect grade ($p=0.684$) and algorithm ($p=0.811$).

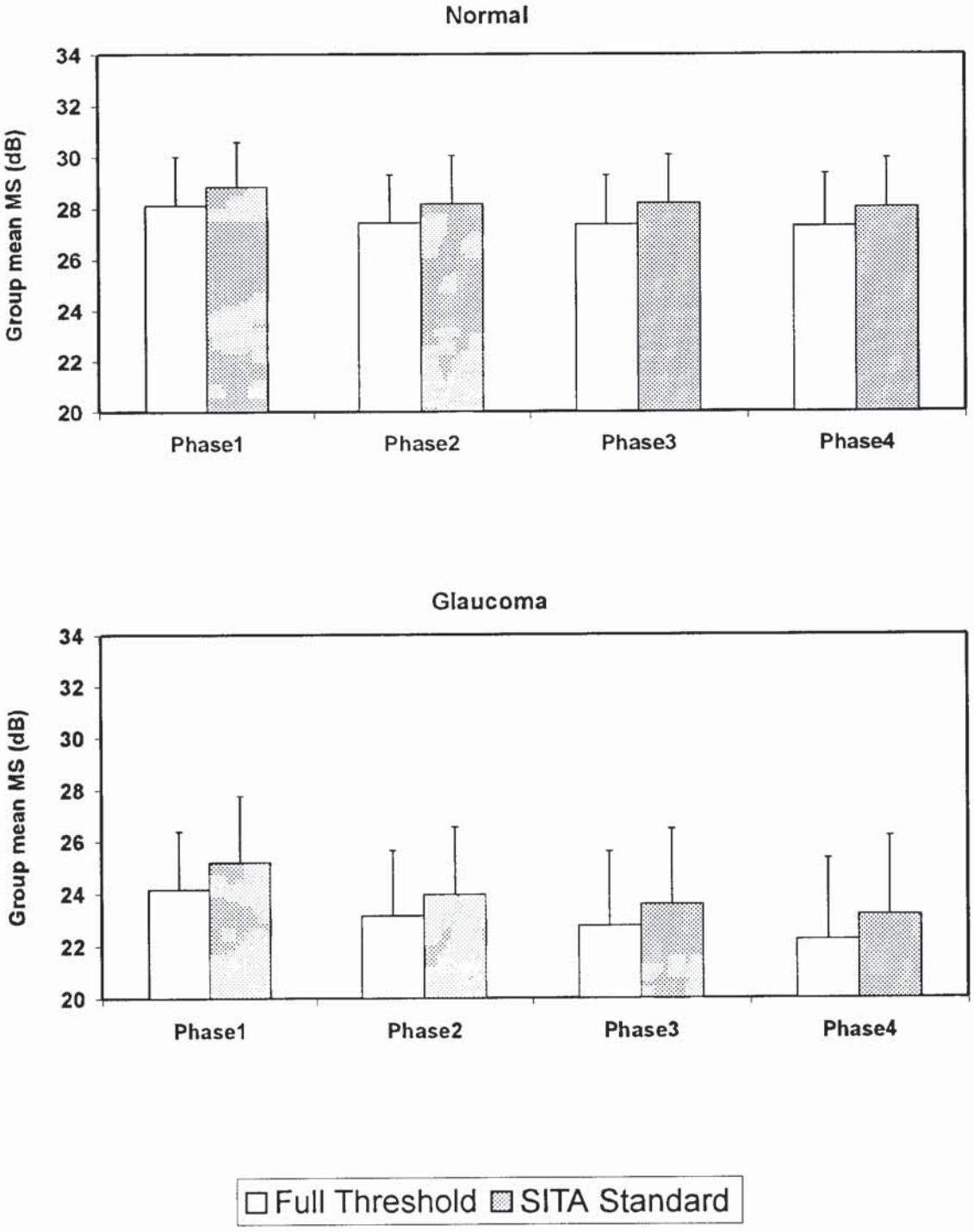


Figure 5.4. The group mean MS for the whole central field for each phase of each algorithm in both the normal (top) and glaucoma (bottom) groups. The error bars indicate one standard deviation of the mean.

5.4.1.3 Mean Sensitivity for the central annulus of the central field

Figure 5.5 shows the group mean MS for the central annulus of the central field for each phase of each algorithm for both normal and glaucoma groups. For phases 1 and 3, the magnitude of the MS was independent of age ($p=0.783$) regardless of the diagnostic group ($p=0.223$). Again, the MS was lower in the glaucoma group than in the normal group ($p<0.001$) and was lower as the field loss increased ($p<0.001$) regardless of age ($p=0.209$).

For phases 1 and 3, the MS was higher for SITA Standard than for Full Threshold ($p<0.001$), regardless of diagnostic group ($p=0.690$), or age ($p=0.884$). However, the difference between the algorithms decreased as the severity of the defect increased ($p=0.004$). The MS declined between first and third phases ($p<0.001$) and the magnitude of the decline was irrespective of age ($p=0.241$). The reduction in sensitivity for the glaucoma group was approximately twice that for the normal group ($p=0.011$) and this difference was independent of defect grade ($p=0.274$) and algorithm ($p=0.821$).

For phases 2 and 4, the magnitude of the MS was independent of age ($p=0.697$) regardless of the diagnostic group ($p=0.136$). Again, the MS was lower in the glaucoma group than in the normal group ($p<0.001$) and was lower as the field loss increased ($p<0.001$) regardless of age ($p=0.407$).

For phases 2 and 4, the MS was higher for SITA Standard than for Full Threshold ($p<0.001$), regardless of diagnostic group ($p=0.882$), or age ($p=0.569$). However, the difference between the algorithms decreased as the severity of the defect increased ($p=0.011$). The MS declined between the second and fourth phases ($p=0.001$) and the magnitude of the decline was independent of age ($p=0.757$). The reduction in sensitivity for the glaucoma group was approximately six times that for the normal group between the second and fourth phases ($p=0.017$) and this difference was independent of defect grade ($p=0.483$) and algorithm ($p=0.812$).

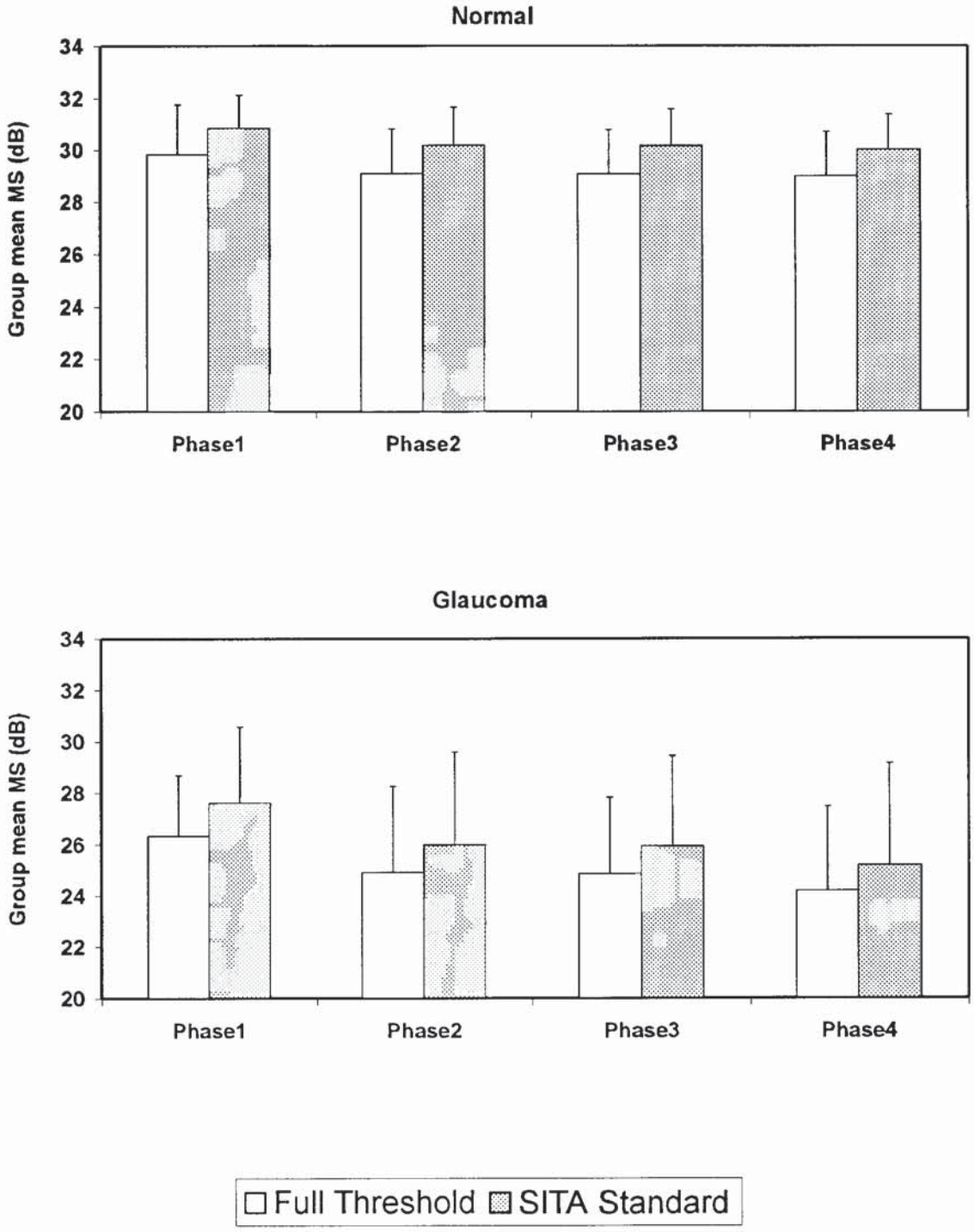


Figure 5.5. The group mean MS for the central annulus of the central field for each phase of each algorithm in both the normal (top) and glaucoma (bottom) groups. The error bars indicate one standard deviation of the mean.

5.4.1.4 Mean Sensitivity for the peripheral annulus of the central field

Figure 5.6 shows the group mean MS for the peripheral annulus of the central field for each phase of each algorithm for both normal and glaucoma groups. For phases 1 and 3, the magnitude of the MS was independent of age ($p=0.166$) regardless of the diagnostic group ($p=0.428$). Again, the MS was lower in the glaucoma group than in the normal group ($p<0.001$) but the difference between groups was irrespective of defect grade ($p=0.254$) and age ($p=0.461$).

For phases 1 and 3, the MS was higher for SITA Standard than for Full Threshold ($p<0.001$), regardless of diagnostic group ($p=0.644$), grade of defect ($p=0.225$) or age ($p=0.921$). The MS declined between first and third phases ($p<0.001$) and the magnitude of the decline was irrespective of age ($p=0.884$). The reduction in sensitivity for the glaucoma group was approximately twice that for the normal group ($p=0.048$) and this difference was independent of defect grade ($p=0.311$) and algorithm ($p=0.965$).

For phases 2 and 4, there was a slight tendency for the magnitude of the MS to decline with age ($p=0.048$) regardless of the diagnostic group ($p=0.770$). As would be expected, the MS was lower in the glaucoma group than in the normal group ($p<0.001$) but the difference between groups was irrespective of defect grade ($p=0.287$) and age ($p=0.906$).

For phases 2 and 4, the MS was higher for SITA Standard than for Full Threshold ($p=0.001$), regardless of diagnostic group ($p=0.543$), grade of defect ($p=0.711$) or age ($p=0.563$). The MS declined between the second and fourth phases ($p=0.010$) and the magnitude of the decline was irrespective of age ($p=0.509$). The reduction in sensitivity for the glaucoma group was similar to that for the normal group between the second and fourth phases ($p=0.065$) and this was independent of defect grade ($p=0.621$) and algorithm ($p=0.682$).

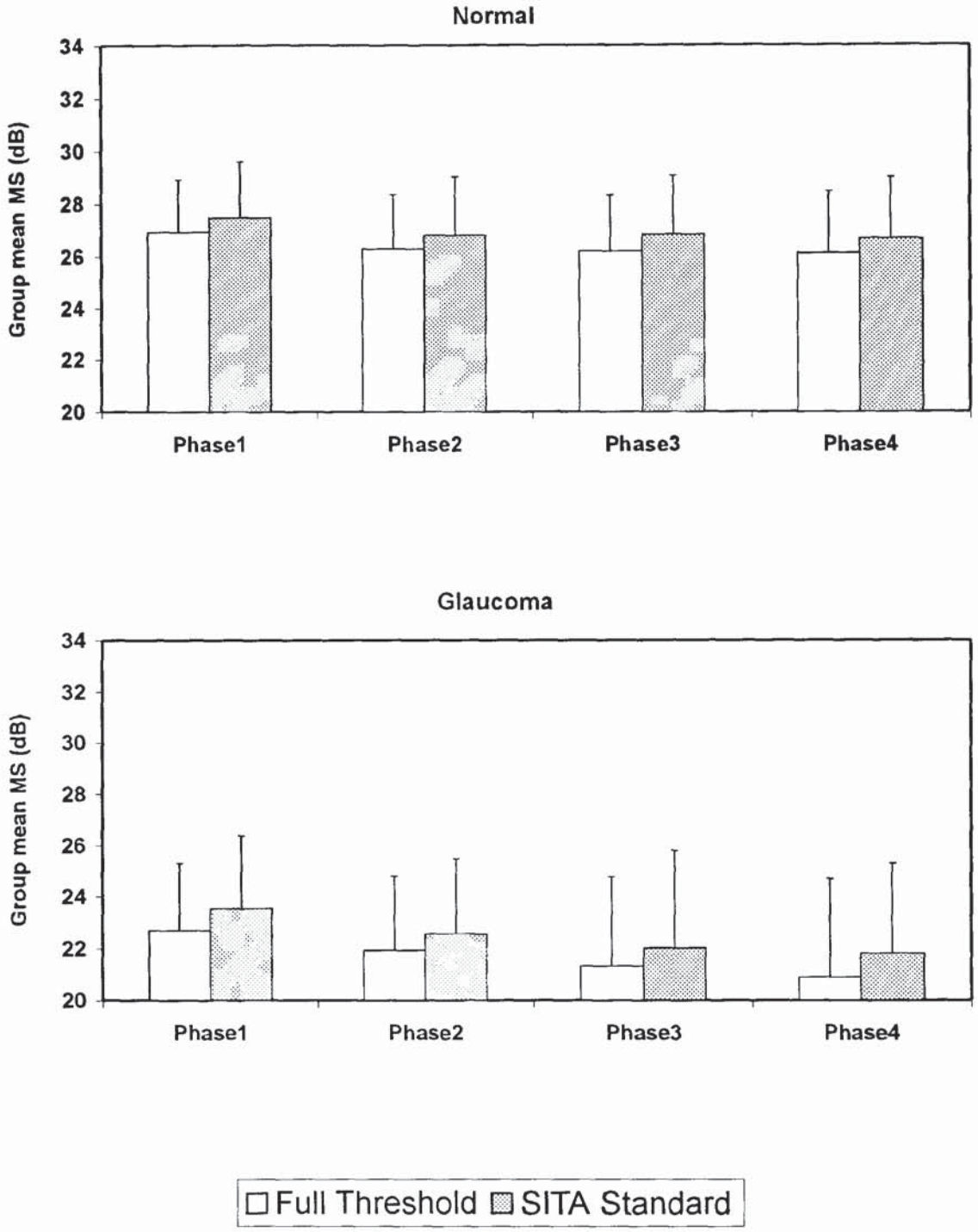


Figure 5.6. The group mean MS for the peripheral annulus of the central field for each phase of each algorithm in both the normal (top) and glaucoma (bottom) groups. The error bars indicate one standard deviation of the mean.

5.4.1.5 Pointwise analysis of sensitivity

The 10th, 50th and 90th percentiles of the distribution of the differences in sensitivity between phases 1 and 3, expressed as a function of the sensitivity at phase 1, for each algorithm in each patient group are illustrated on the left hand side of Figure 5.7. In the normal group, for both algorithms, the median difference between phases approximated to zero at stimulus locations with sensitivities of greater than 20 dB at phase 1. The 10th and 90th percentiles of the distribution were similar across this range of sensitivities. There were insufficient stimulus locations, from either SS_{A1} or FT_{A1}, with a sensitivity of 20 dB or less to calculate any meaningful distributions of differences in sensitivity between phase 1 and 3.

In the glaucoma group, for both algorithms, the median difference between phases 1 and 3, represented a decline in sensitivity of approximately 1 dB at locations with an initial sensitivity of 15 dB or greater. At locations with an initial sensitivity of between 1 and 15 dB, the median difference in sensitivity between phases for the Full Threshold algorithm was a decline of 3.0 dB. With the SITA Standard algorithm, the median difference in sensitivity between phases, at locations with an initial sensitivity of less than 5 dB, represented a slight increase in sensitivity of approximately 1.5 dB. The 90th percentile for both algorithms approximated to a maximal decline in sensitivity between phases (i.e. an absolute defect at the third phase) for locations with an initial sensitivity of 15 dB or less. The 10th percentile for each algorithm indicated that there were a number of locations in the mid to low range of initial sensitivity levels that improved from phase 1 to 3 and this effect was greatest in SITA Standard at initial sensitivities of less than 10 dB.

The 10th, 50th and 90th percentiles of the distribution of the differences in sensitivity between phases 2 and 4, expressed as a function of the sensitivity at phase 2, for each algorithm in each patient group are illustrated on the right hand side of Figure 5.7. This analysis demonstrated no appreciable difference in sensitivity between the two phases for each algorithms. In the normal group, the distributions of the difference in sensitivity between-phases increased at the lower initial sensitivities.

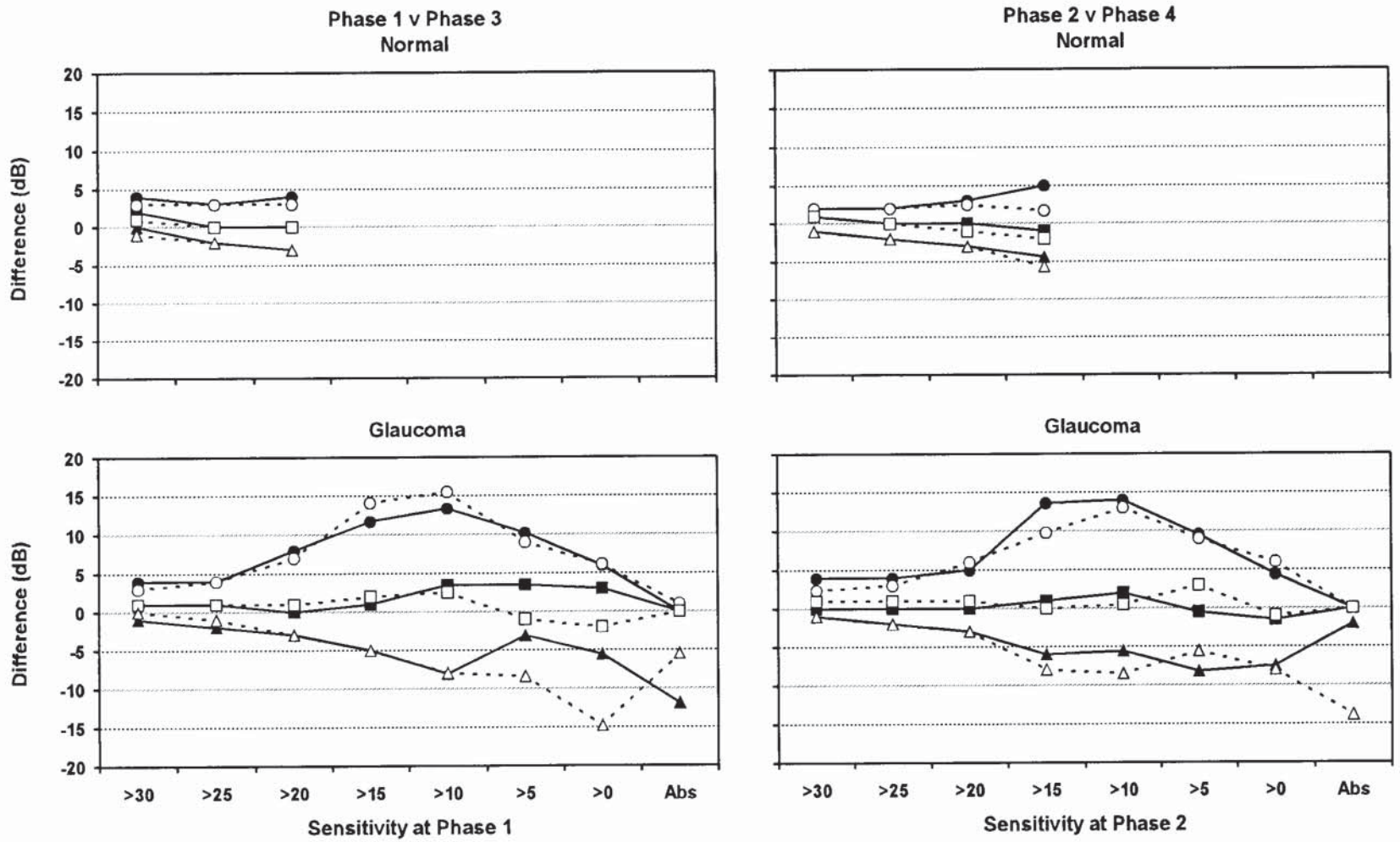


Figure 5.7. The 10th (triangles), 50th (squares) and 90th (circles) percentiles of the distribution of the differences in sensitivity between phases for Protocol 1, expressed as a function of the sensitivity at the first phase of the comparison, for the Full Threshold (closed symbols) and SITA Standard (open symbols) algorithms in each group. A positive difference indicates a decline in sensitivity over the two phases and a negative difference indicates an increase in sensitivity over the two phases.

In the glaucoma group, the median difference between phases was approximately zero for all sensitivity levels with the Full Threshold algorithm and approximately 1 dB with SITA Standard. At the mid range of initial sensitivities, the range of differences between phases 2 and 4 was wider than at the high or very low initial sensitivities.

5.4.2 The within- and between-algorithm effects for the same number of stimulus locations (protocol 2)

Table 5.2 shows, for each algorithm in the normal and glaucoma groups, the group mean MS for each region of the visual field for the comparison of two full examinations with 74 locations on each eye.

5.4.2.1 Mean Sensitivity for the whole central field

Figure 5.8 shows the group mean MS for the whole central field for the 74 stimulus locations of each algorithm for both normal and glaucoma groups. The magnitude of the MS was independent of age ($p=0.170$) regardless of the diagnostic group ($p=0.305$). As would be expected, the MS was lower in the glaucoma group than in the normal group ($p<0.001$) and was lower as the field loss increased ($p=0.009$) regardless of age ($p=0.562$).

The MS was higher for SITA Standard than for Full Threshold ($p<0.001$), regardless of diagnostic group ($p=0.094$), grade of defect ($p=0.147$) or age ($p=0.958$). The MS declined between the two phases ($p<0.001$) and the magnitude of the decline was irrespective of age ($p=0.867$). The reduction in sensitivity for the glaucoma group was greater than for the normal group ($p=0.045$) and this difference was independent of defect grade ($p=0.984$) and algorithm ($p=0.633$).

		NORMAL		GLAUCOMA	
		P1	P2	P1	P2
WHOLE MS (dB)					
FT	mean	27.76	27.31	23.64	22.49
	sd	1.85	1.96	2.27	2.91
SS	mean	28.83	28.19	25.18	23.95
	sd	1.74	1.87	2.40	2.63
CENTRE MS (dB)					
FT	mean	29.47	29.02	25.61	24.52
	sd	1.79	1.68	2.68	3.03
SS	mean	30.87	30.16	27.43	26.02
	sd	1.28	1.46	2.63	3.43
PERIPHERY MS (dB)					
FT	mean	26.60	26.15	22.31	21.10
	sd	1.95	2.20	2.59	3.49
SS	mean	27.45	26.85	23.65	22.55
	sd	2.10	2.21	2.77	3.06

Table 5.2. The group mean MS for each region of the visual field for the comparison of two full examinations with 74 locations on each given eye with the Full Threshold (FT) and SITA Standard (SS) algorithms for the normal and glaucoma groups.

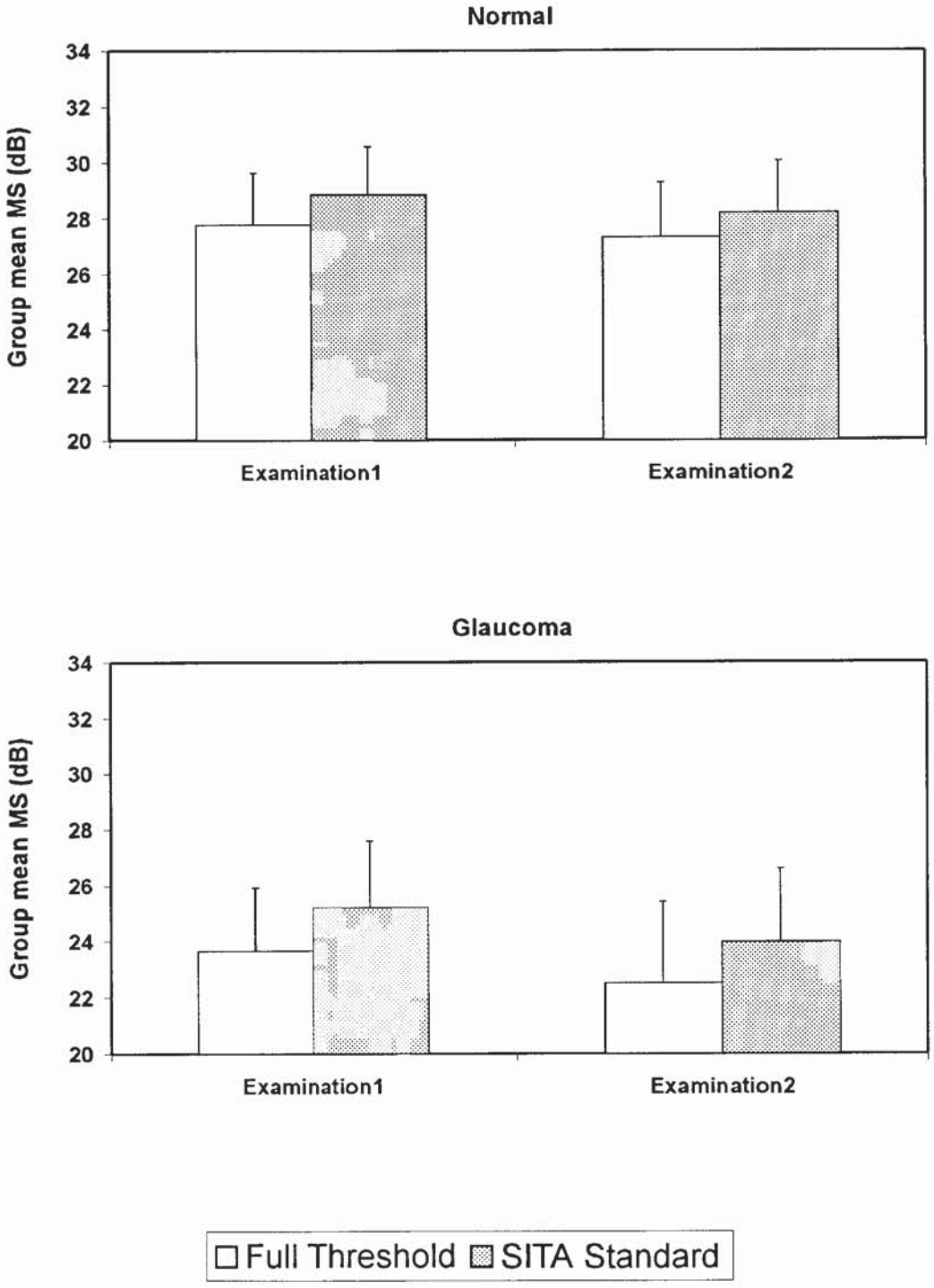


Figure 5.8. The group mean MS for the whole central field for the 74 locations of each algorithm in both the normal (top) and glaucoma (bottom) groups. The error bars indicate one standard deviation of the mean.

5.4.2.2 Mean Sensitivity for the central annulus of the central field

Figure 5.9 shows the group mean MS for the central annulus of the central field for the 74 stimulus locations of each algorithm for both normal and glaucoma groups. The magnitude of the MS was independent of age ($p=0.873$) regardless of the diagnostic group ($p=0.165$). As would be expected, the MS was lower in the glaucoma group than in the normal group ($p<0.001$) and was lower as the field loss increased ($p<0.001$) regardless of age ($p=0.255$).

The MS was higher for SITA Standard than for Full Threshold ($p<0.001$), regardless of diagnostic group ($p=0.199$), grade of defect ($p=0.186$) or age ($p=0.425$). The MS declined between the two phases ($p<0.001$) and the magnitude of the decline was irrespective of age ($p=0.425$). The reduction in sensitivity for the glaucoma group was greater than for the normal group ($p=0.026$) and this difference was independent of defect grade ($p=0.536$) and algorithm ($p=0.283$).

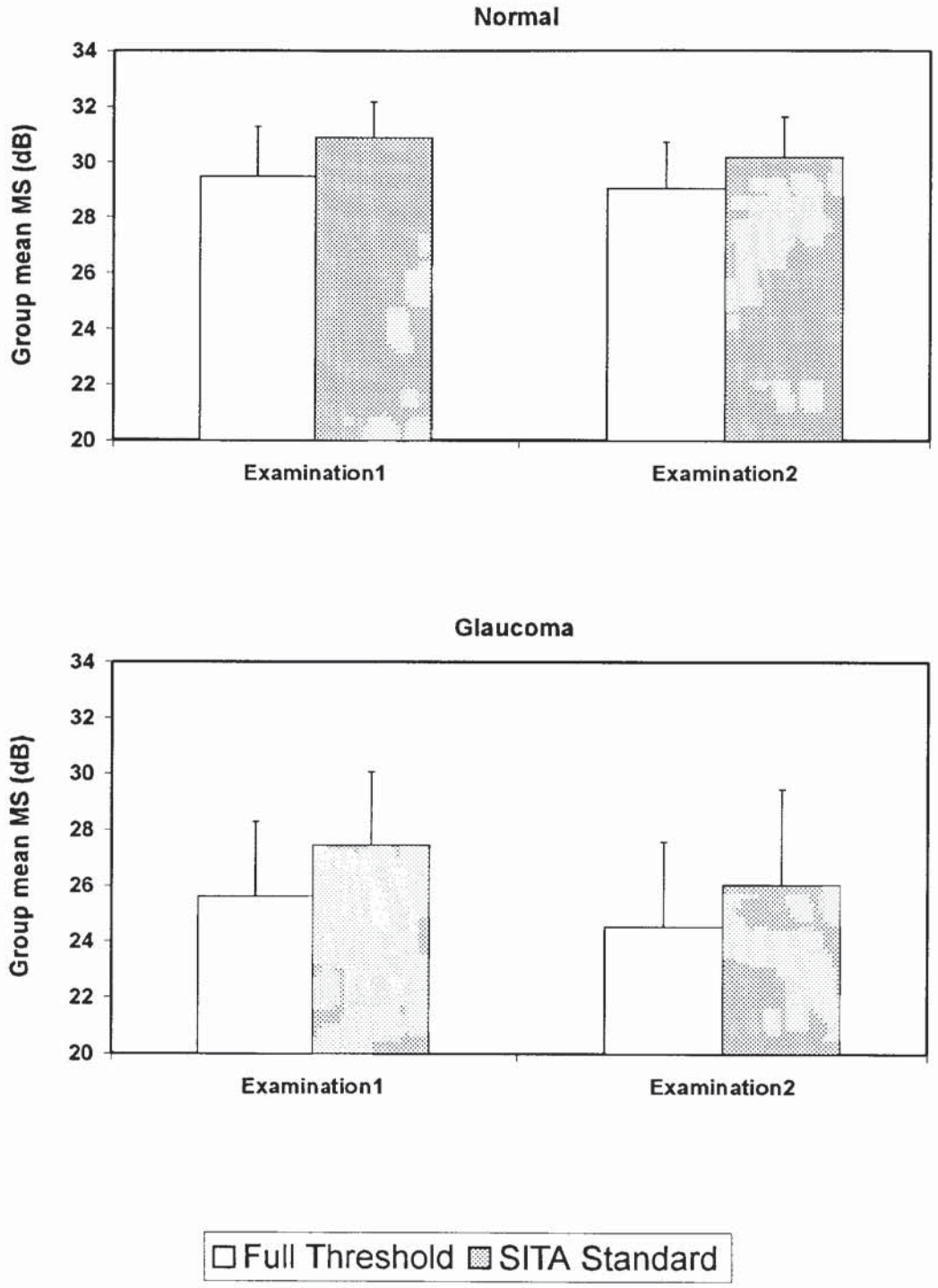


Figure 5.9. The group mean MS for the central annulus of the central field for the 74 locations of each algorithm in both the normal (top) and glaucoma (bottom) groups. The error bars indicate one standard deviation of the mean.

5.4.2.3 Mean Sensitivity for the peripheral annulus of the central field

Figure 5.10 shows the group mean MS for the peripheral annulus of the central field for the 74 stimulus locations of each algorithm for both normal and glaucoma groups. The magnitude of the MS was independent of age ($p=0.077$) regardless of the diagnostic group ($p=0.506$). As would be expected, the MS was lower in the glaucoma group than in the normal group ($p<0.001$) but the difference between groups was irrespective of defect grade ($p=0.165$) and age ($p=0.775$).

The MS was higher for SITA Standard than for Full Threshold ($p<0.001$), regardless of diagnostic group ($p=0.110$), grade of defect ($p=0.227$) or age ($p=0.6445$). The MS declined between the two phases ($p<0.001$) and the magnitude of the decline was irrespective of age ($p=0.433$). The reduction in sensitivity for the glaucoma group was similar to that for the normal group ($p=0.145$) and this was independent of defect grade ($p=0.623$) and algorithm ($p=0.981$).

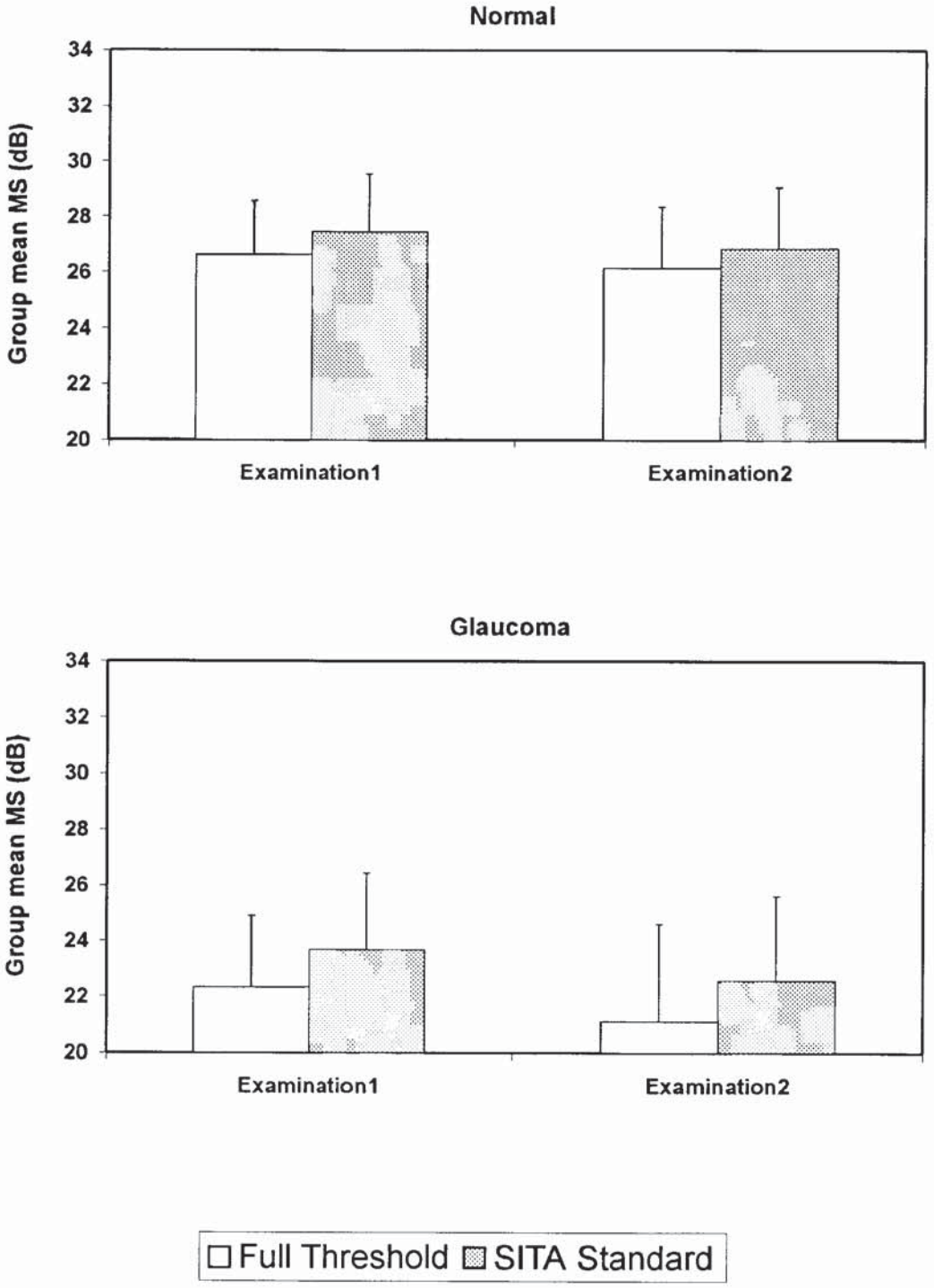


Figure 5.10. The group mean MS for the peripheral annulus of the central field for the 74 locations of each algorithm in both the normal (top) and glaucoma (bottom) groups. The error bars indicate one standard deviation of the mean.

5.4.2.4 Pointwise analysis of sensitivity

The 10th, 50th and 90th percentiles of the distribution of the differences in sensitivity between phases, expressed as a function of the sensitivity at phase 1, for each algorithm in each patient group are illustrated in Figure 5.11. In the normal group, the difference in sensitivity between phases was similar between algorithms. The median between-phase difference in sensitivity was approximately zero and the width of the distribution of differences increased as the initial sensitivity decreased for both algorithms.

In the glaucoma group, the median difference in sensitivity between phases was approximately 1 dB across all sensitivity levels for both algorithms. The range of differences between phases, at the mid range of initial sensitivities, was wider than at the high or low initial sensitivities. The magnitude of each percentile was similar for each algorithm across all sensitivity levels, except for the 10th percentile at initial sensitivities of 5 dB or less, which was wider with the SITA Standard algorithm than with Full Threshold.

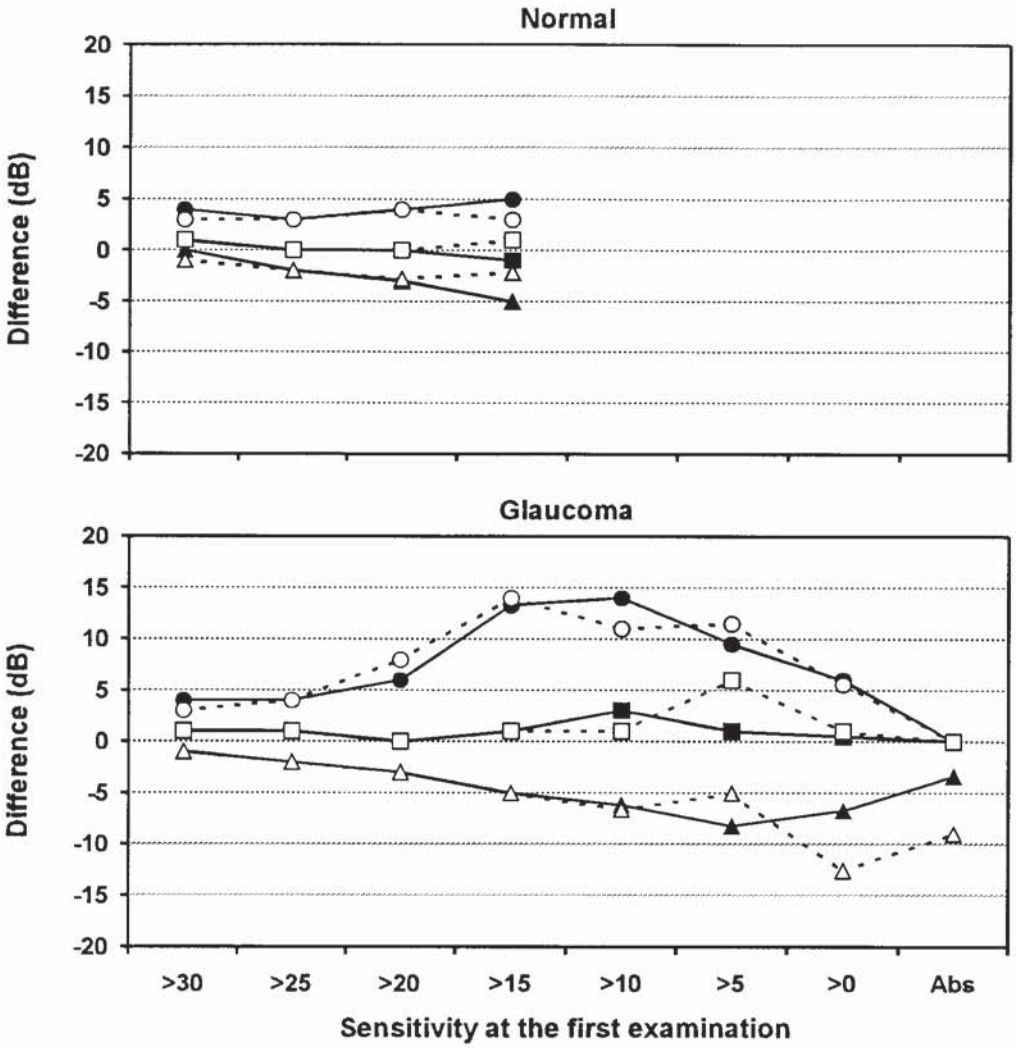


Figure 5.11. The 10th (triangles), 50th (squares) and 90th (circles) percentiles of the distribution of the differences in sensitivity between phases for Protocol 2, expressed as a function of the sensitivity at the first phase of the comparison, for the Full Threshold (closed symbols) and SITA Standard (open symbols) algorithms in each group. A positive difference indicates a decline in sensitivity over the two phases and a negative difference indicates an increase in sensitivity over the two phases.

5.5 Discussion

There is evidence from the first protocol of a fatigue effect occurring between phases 1 and 3. This protocol compared sensitivities measured by the end of the first 8 minutes of perimetry with those measured between, on average, the 14th and 22nd minutes of perimetry for a given eye. It is therefore impossible to define the precise examination time at which the fatigue effect commences. It is theoretically possible that a sensitivity estimated within the first minute of perimetry could have been compared with a sensitivity estimated within the 22nd minute of perimetry. The data from phases 2 and 4 indicate that there was little absolute change in sensitivity measured within 8 to 14 minutes of perimetry compared to that measured within 22 to 32 minutes of perimetry. A direct comparison between phases 1 and 2, and also between phases 3 and 4, is inappropriate as phases 1 and 3 estimate sensitivity from a separate sets of stimulus locations to those at phases 2 and 4. However, it can be inferred that the majority of the decline in sensitivity occurred within the first phase and no appreciable further decline occurred.

For the comparison of sensitivity using the same stimulus locations (the second protocol), the decline in sensitivity between the first and second 8 minute sessions of perimetry with SITA Standard was similar to that between the first and second 16 minute sessions of perimetry with Full Threshold. It is therefore likely that the majority of the fatigue effect occurs within eight minutes. This is comparable with the finding that the majority of the fatigue effect occurs within the first three minutes of a perimetric examination in normal subjects and patients with ocular hypertension (Hudson, et al. 1994).

The decline in pointwise sensitivity from phase 1 to 3, as described by the 50th percentile, exhibited the same trend as that for MS in both groups. The absence of a decline in pointwise sensitivity between phases 2 and 4 was compatible with the absence of a decline in MS. The trend of the pointwise differences in sensitivity between the phases of protocol 2 were also similar to the changes in MS. However, the fatigue effect exhibited the greatest variability at those locations manifesting a sensitivity of between 20 and 10 dB at baseline.

The fatigue effect for MS was similar with both the Full Threshold and SITA Standard algorithms. The variability of the pointwise estimates of threshold, under fatigue conditions, was greater than any difference between the two algorithms. These findings indicate that the mechanism associated with the fatigue effect is not algorithm specific. This suggests that the perimetric fatigue effect is likely to be associated with the vigilance decrement and or instigated by the Ganzfeld or Troxler effects. Indeed, the blank-out and fade-out effects have been shown to occur in a similar time frame to the suggested time frame of the fatigue effect.

This study investigated the fatigue effect for a prolonged examination of one eye of the given individual over 30 minutes. The influence of the fatigue effect on the second eye of a clinical perimetric examination is cannot be inferred from the results of the study. In the context of a clinical examination, the fatigue effect would occur within the first few minutes of the examination of the first eye. If the fatigue effect was characterised by an increase in the Troxler effect, a between-eye rest period should reduce or eliminate the Troxler effect from influencing the initial phases of the examination of the second eye. At the examination of the second eye, the fatigue effect would therefore be expected to appear in a similar way as occurred in the first eye. In this study, no rest periods were given, and as such the fatigue effect would have continued through all four phases.

The subjects employed in this study had been informed of the nature and length of the experimental protocol prior to volunteering for enrolment in the study. Therefore, it could be argued that a bias was introduced in to study by the use of seemingly motivated and co-operative individuals. It could be hypothesised that the fatigue effect might be greater in uncooperative and less informed patients.

It has been suggested that a reduction in the fatigue effect for SITA contributes to the reduction in between-subject variability in the estimation of sensitivity (Chapter 4) and to the higher than expected difference in Mean Sensitivity between Full Threshold and SITA Standard (Bengtsson, et al. 1998). This study would not support either argument as the fatigue effect has been shown to be similar between the two algorithms. The reduction in

between-subject variability for the estimation of sensitivity with SITA may be due to the level of the ERF and the associated relationship with the prior models of the visual field. For a large value of the ERF, the estimate of threshold is less likely to deviate from the prior model by a significant amount. Consequently, the estimated normal thresholds will be more similar between individuals than for earlier generations of algorithms. The higher than expected Mean Sensitivities may be due to the form and mathematical derivation of the underlying FOS curves used for the calculation of threshold.

5.6 Conclusions

Within the constraints of the experimental design, the fatigue effect primarily occurred within the first eight minutes of perimetry, irrespective of the threshold algorithm employed. The fatigue effect was greater in glaucoma patients than in normal subjects for the cumulative examination duration or for the examination of an identical number of stimulus locations.

CHAPTER 6. FIXATION VARIABILITY WITH STATIC AND ROVING FIXATION TARGETS

6.1 Introduction

The outcome of automated perimetry is dependent upon the performance of the patient. The reliability of the patient to consistently identify the threshold is determined by estimating the percentage of false-positive and false-negative responses made during the test (Katz and Sommer 1988, Olsson, et al. 1988, Bickler-Bluth, et al. 1989, Katz and Sommer 1990, Reynolds, et al. 1990, Cascairo, et al. 1991, Katz, et al. 1991b, Sanabria, et al. 1991, Johnson and Nelson-Quigg 1993, Birt, et al. 1997, Olsson, et al. 1997). However, the predominant reason for the lack of reliability in a visual field examination is inaccurate fixation by the patient (Katz and Sommer 1988, Bickler-Bluth, et al. 1989, Katz and Sommer 1990, Katz, et al. 1991b, Johnson and Nelson-Quigg 1993, Birt, et al. 1997). Inaccurate fixation causes stimuli intended for one retinal location to stimulate another retinal location. Thus, if the intended retinal location falls within a scotoma and the unintended retinal location is from an area of normal sensitivity, the scotoma may be underestimated (Vingrys and Demirel 1993). Alternatively, the sensitivity from a normal area of the visual field may be underestimated if the unintended retinal location falls within a scotoma. The difference in sensitivity between the intended and unintended retinal locations forms part of the overall variability of the threshold response, especially in the presence of steep sided scotoma (Henson and Bryson 1991).

The majority of commercially available perimeters utilise a stationary fixation target positioned in the centre of the cupola. The large number of stimulus presentations required to obtain statistically reliable static thresholds for the central visual field results in a lengthy examination duration. It is known that sensitivity declines with increase in examination duration. This effect has been termed the fatigue effect and has been attributed to a combination of the Troxler effect and a reduction in patient vigilance (see Chapter 5). In addition, fixation stability tends to decline with increasing examination duration (Demirel and

Vingrys 1993), thus, potentially reducing the reliability of responses from the later parts of the test.

The technique of roving fixation was developed for perimetry with the aim of improving patient compliance. The only commercially available perimeters that employ the roving fixation technique are the Dicon series of perimeters. The fixation target moves between stimulus presentations and the subject is required to maintain fixation on the target which stops immediately prior to the presentation of the stimulus. The rationale behind the use of this technique is that the roving fixation target promotes a higher level of concentration, provides positive feedback to the patient and is less tiring for the patient than the static fixation technique (Dicon LD400 operation manual). Subjectively, the majority of patients prefer the roving fixation technique (Lewis, et al. 1991, Wong, et al. 1995).

The relationship between the magnitude of sensitivity recorded with the two types of fixation is equivocal. In normal subjects, the Mean Sensitivity with the Humphrey Field Analyzer has been shown to be between 1 dB (Lewis, et al. 1991) and 2.5 dB (Wong, et al. 1995) higher than with the Dicon perimeter. Using the Dicon perimeter alone, the roving fixation technique has been reported to produced a 2 dB greater sensitivity in normal subjects and a 1.5 dB greater sensitivity in glaucoma patients when compared to the static fixation technique (Li and Mills 1992).

There is some evidence that the reliability of visual fields obtained with the static and roving fixation techniques is not the same. It has been reported that the numbers of fixation losses and false-positive responses are higher with the roving fixation technique (Lewis, et al. 1991, Wong, et al. 1995, Asman and Fingeret 1997). These studies either involved normal subjects (Lewis, et al. 1991, Wong, et al. 1995) or used perimetrically naïve patients with glaucoma (Asman and Fingeret 1997).

It is known that a learning effect is present in automated perimetry with static fixation (see Chapter 7) whereby sensitivity increases during and between the initial examinations for

patients with ocular hypertension or with glaucoma and also for normal subjects. The increase in sensitivity is greater with increasing eccentricity from fixation. However, the response to the catch trials shows little improvement with repeated examinations. The influence and time course of any learning effect on the outcome of automated perimetry using the roving fixation target is unknown, both in terms of the magnitude of sensitivity and of the response to the catch trials, particularly for fixation losses.

6.2 Aim of study

The aim of the study, therefore, was to investigate the accuracy of fixation for the roving and static fixation techniques normal subjects and patients with glaucoma who were experienced in the requirements of automated perimetry using static fixation.

6.3 Methods

6.3.1 Sample

The sample comprised 24 patients with primary open angle glaucoma and 19 normal individuals. The mean age of the glaucoma patients was 59.9 years (SD 12.8 years) with a range from 42 to 82 years. The normal group had a mean age of 61.8 years (SD 11.7 years) and a range from 37 to 77 years. The inclusion criteria for both groups was a visual acuity of 6/9 or better in either eye, a distance refractive error less than or equal to 5 dioptres mean sphere and less than 2.5 dioptres cylinder, lenticular changes not greater than NCIII, NOIII, CI or PI by LOCS III (Chylack, et al. 1993), open angles, no history or family history of diabetes mellitus and no systemic medication known to affect the visual field.

Further inclusion criteria for the normal group were an intraocular pressure of less than 22 mmHg in either eye, normal optic nerve head appearance, no previous ocular surgery or trauma and no known family history of glaucoma.

All patients in the glaucoma group manifested an optic nerve head appearance characteristic of POAG and a repeatable early visual field defect consistent with POAG recorded with the Humphrey Field Analyzer. An early visual field defect was defined as less than seven contiguous stimulus locations within either the superior or inferior hemifield depressed by 10 dB or more from the age-matched normal value (Heijl, et al. 1987b) of the Humphrey Field Analyzer Program 24-2 stimulus configuration. All normal subjects and glaucoma patients were experienced in automated threshold static perimetry with the Humphrey Field Analyzer, having undergone a minimum of three previous examinations, but were naïve to the use of roving fixation. All patients had well controlled intraocular pressures (mean 16.5 mmHg SD 3.5) and stable visual fields. Fourteen patients were controlled on a single topical agent (either a selective or non-selective β-blocker, a topical carbonic anhydrase inhibitor, an alpha adrenergic agonist or a prostaglandin) and five patients required more than one topical agent for IOP control. No patients were on systemic carbonic anhydrase inhibitors or topical cholinergics. Five patients had undergone previous trabeculectomy at least six months before the study commenced, three of who required no further medical control of intraocular pressure.

6.3.2 Examination Protocol

Perimetry was undertaken on one eye of each individual with both the Dicon LD400 and Humphrey Field Analyzer 750 perimeters at a single visit. Each subject attended for two sessions, each separated by a period of approximately 90 minutes. At the first session, each individual was examined with the Dicon LD400 perimeter. At the second session, the individuals were examined with the Dicon perimeter and with the Humphrey Field Analyzer 750. The two examinations with the Dicon LD400 were undertaken to determine the presence of any learning effect on the magnitude of sensitivity and on the false-response

rates to the catch trials. The order of examination at the second session was randomised between subjects in order to minimise the effects of fatigue.

For normal subjects, the eye tested was chosen so as to provide equal numbers of right and left eyes for analysis. For the glaucoma patients with bilateral field defects, the eye with least field loss was chosen. Subjects wore their distance refraction, in full aperture trial lens form, together with the appropriate near correction for the perimeter working distance.

Program #9 was used for the Dicon perimeter. This program estimates threshold at 76 locations of the visual field in an evenly spaced six-degree grid. This arrangement corresponds to the locations in Program 30-2 of the Humphrey Field Analyzer. Whilst the exact details of the Dicon threshold strategy have not been published, it is believed to use a modified 6-3 dB step algorithm (Wong, et al. 1995). Program 30-2 with the FASTPAC threshold algorithm was used for the Humphrey Field Analyzer. The FASTPAC strategy employs a single reversal staircase with 3 dB step sizes and a repetition of threshold if the initial estimate deviates from the expected value by 4 dB or more (Flanagan, et al. 1993b). The FASTPAC algorithm was used with the Short-term Fluctuation option de-activated. The selection of FASTPAC, without the Short-term Fluctuation option, was taken in order that the examination with the Humphrey Field Analyzer was as close as possible to that of the Dicon in terms of test duration and threshold estimation.

The Dicon stimuli take the form of fixed position LEDs. The stimuli are positioned behind a flat translucent screen and approximate to a Goldmann size IV (0.86 degree diameter). The stimuli are intensity-attenuated to make them comparable to a size III stimulus (Wong, et al. 1995) and emit light with a peak wavelength of 570 nm. The fixation target for the Dicon perimeter is attached to an X-Y plotter and moves at a rate of approximately 7 degrees per second (Li and Mills 1992). The Humphrey Field Analyzer employs a stationary fixation target in the centre of the evenly illuminated bowl. The stimuli are projected onto the anterior surface of the bowl and the default stimuli are a white Goldmann size III (0.43 degree diameter). Both perimeters use a background luminance of 10 cdm^{-2} and have a maximum

stimulus luminance of 3183 cdm^{-2} assigned to 0 dB. The stimulus duration is 250 ms for the Dicon and 200 ms for the Humphrey Field Analyzer. In addition, the Dicon employs a computerised synthetic voice system to periodically instruct and encourage the patient.

6.3.3 Analysis

The Means Sensitivity, the examination duration, the response to the fixation loss catch trials and the sensitivity at the presumed physiological blind spot location from the roving fixation technique at the first and second sessions were analysed using separate Wilcoxon Signed Rank Tests.

The Mean Sensitivity and the examination duration at the second session were evaluated for each instrument. The accuracy of each fixation technique at the second session was then assessed in two ways. Firstly, the percentage of fixation losses recorded by the Heijl-Krakau blind spot monitor was evaluated for each fixation technique. Secondly, the sensitivity recorded at the presumed normal location of the physiological blind spot (15 degrees temporal and 3 degrees inferior to fixation) was used as a measure of fixation stability.

6.4 Results

The inclusion criteria for the glaucoma group included a definition of early visual field loss. Specifically, early field loss was defined as less than seven contiguous stimulus locations within either the superior or inferior hemifield depressed by 10 dB or more from the age-matched normal value (Heijl, et al. 1987b) of the Humphrey Field Analyzer Program 24-2 stimulus configuration. This diagnosis of early field loss was based upon the last threshold visual field examination prior to enrolment of the patient in the study. At the completion of the study, the grade of visual field defect was redefined according to the criteria of Hodapp et al (1994) based upon the visual field derived with FASTPAC strategy. Using this classification,

16 patients were defined as having early field loss, seven patients had moderate field loss and a single patient had severe field loss. The patient who was deemed to have severe loss was defined as such due to a sensitivity of 0 dB within 5 degrees of fixation. All other grading criteria would have placed this patient in the lower range of moderate field loss.

Table 6.1 shows the group mean Mean Sensitivity, the examination duration, the group mean percentage of Heijl-Krakau fixation errors, the group mean measured sensitivity at the presumed location of the blind spot and the number of false-positive and false-negative errors for each group at each of the three tests.

6.4.1 Between-session comparison for roving fixation

6.4.1.1 Mean Sensitivity

The MS with the roving fixation technique at the first and second session is shown in Figure 6.1 for each individual in both groups. Each data point represents a single observer. Approximately 50% of individuals had a greater MS at the first session than at the second session. In the normal group, the group mean MS was 26.4 dB (SD 1.1 dB, range 24.3 to 28.0 dB) at the first session and 26.2 dB (SD 1.3 dB, range 22.5 to 28.5 dB) at the second session. The difference between the two sessions did not reach statistical significance ($p=0.888$, Wilcoxon Signed Rank Test).

In the glaucoma group, the group mean MS was 24.5 dB (SD 1.7 dB, range 19.5 to 26.9 dB) at the first session and 24.5 dB (SD 1.5 dB, range 21.0 to 27.0 dB) at the second session. The difference between the two sessions did not reach statistical significance ($p=0.891$).

		Roving Fixation		Static Fixation
		First Test	Second Test	
Normal	MS (dB)	26.37 (1.11)	26.24 (1.31)	27.20 (1.86)
N=19	Time (min)	7.45 (0.45)	7.41 (0.73)	7.68 (0.83)
	FL (%)	15.34 (16.28)	9.43 (11.61)	3.47 (5.09)
	FL (trials)	14.26 (0.81)	14.42 (1.22)	14.95 (1.08)
	BS (dB)	11.37 (9.65)	12.47 (10.87)	2.42 (5.26)
	FP errors	19	15	2
	FN errors	0	0	2
POAG	MS (dB)	24.48 (1.73)	24.47 (1.54)	24.53 (2.35)
N=24	Time (min)	8.26 (1.06)	8.04 (0.65)	8.57 (0.86)
	FL (%)	7.98 (10.54)	11.26 (12.35)	2.62 (4.57)
	FL (trials)	15.46 (1.91)	15.25 (1.11)	16.21 (1.44)
	BS (dB)	10.58 (10.59)	10.58 (9.84)	2.88 (5.07)
	FP errors	37	24	2
	FN errors	0	0	12

Table 6.1. The group mean Mean Sensitivity, the group mean examination duration, the group mean percentage of Heijl-Krakau fixation errors, the group mean measured sensitivity at the presumed location of the blind spot and the number of false-positive and false-negative errors for each group at each of the three tests.

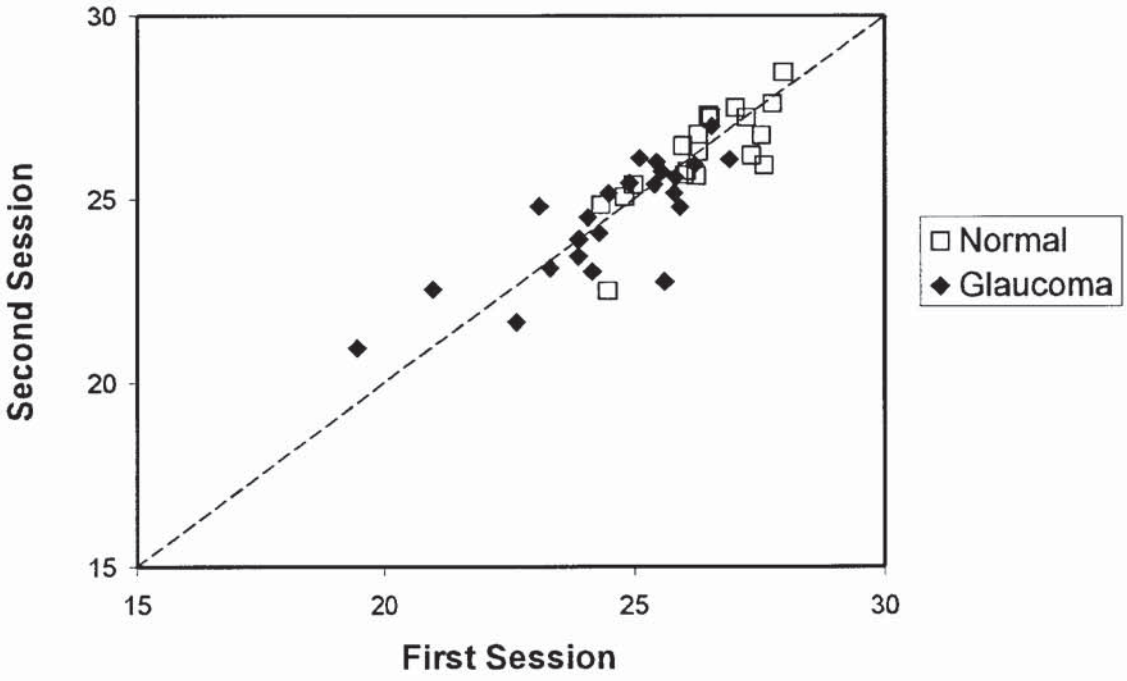


Figure 6.1. The Mean Sensitivity (dB) for the roving fixation technique at the first session against that at the second session, for both normal (open squares) and glaucoma (closed diamonds) groups. Each point represents a single individual.

6.4.1.2 Examination Duration

Figure 6.2 shows the examination duration with the roving fixation technique at the first and second session for each individual in both groups. There was a trend for the normal group to have a slightly shorter examination duration at the second session: 7.5 min (SD 0.4 min, range 7.0 to 8.4 min) at the first session and 7.4 min (SD 0.7 min, range 6.7 to 10.1 min) at the second session. However, this difference did not reach statistical significance (p=0.067).

In the glaucoma group, the group mean examination durations were 8.3 min (SD 1.1 min, range 7.2 to 12.4 min) at the first session and 8.0 min (SD 0.6 min, range 7.1 to 9.4 min) at the second session. The difference between the two sessions did not reach statistical significance (p=0.209).

6.4.1.3 Heijl-Krakau fixation loss rate

Figure 6.3 shows the Heijl-Krakau fixation loss rate at the first and second sessions with roving fixation, for the normal and glaucoma groups. Each data point represents a single observer and the line of unity is shown. In the normal group, four subjects recorded a zero percent fixation loss rate for both sessions and three subjects showed a higher fixation loss rate at the second session. The mean fixation loss rates were 15.3% (SD 16.3%, range 0% to 61.5%) at the first session and 9.4% (SD 11.6%, range 0% to 35.7%) at the second session. The difference in the fixation loss rates between the two sessions did not reach statistical significance (p=0.117).

In the glaucoma group, seven patients recorded a zero percent fixation loss rate at both sessions and 12 patients had a higher fixation loss rate at the second session. The mean fixation loss rates were 7.98% (SD 10.5%, range 0% to 35.7%) at the first session and 11.3% (SD 12.4%, range 0% to 38.9%) at the second session. The difference in the fixation loss rates between the two sessions did not reach statistical significance (p=0.200).

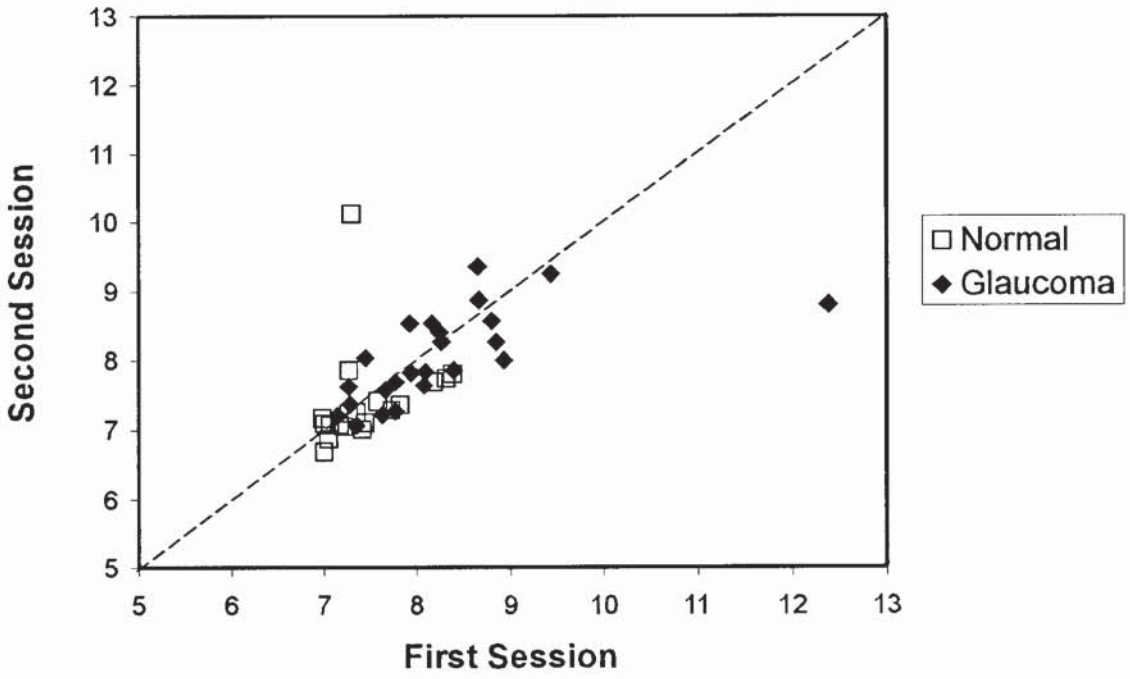


Figure 6.2. The examination duration (min) for the roving fixation technique at the first session against that at the second session, for both normal (open squares) and glaucoma (closed diamonds) groups. Each point represents a single individual.

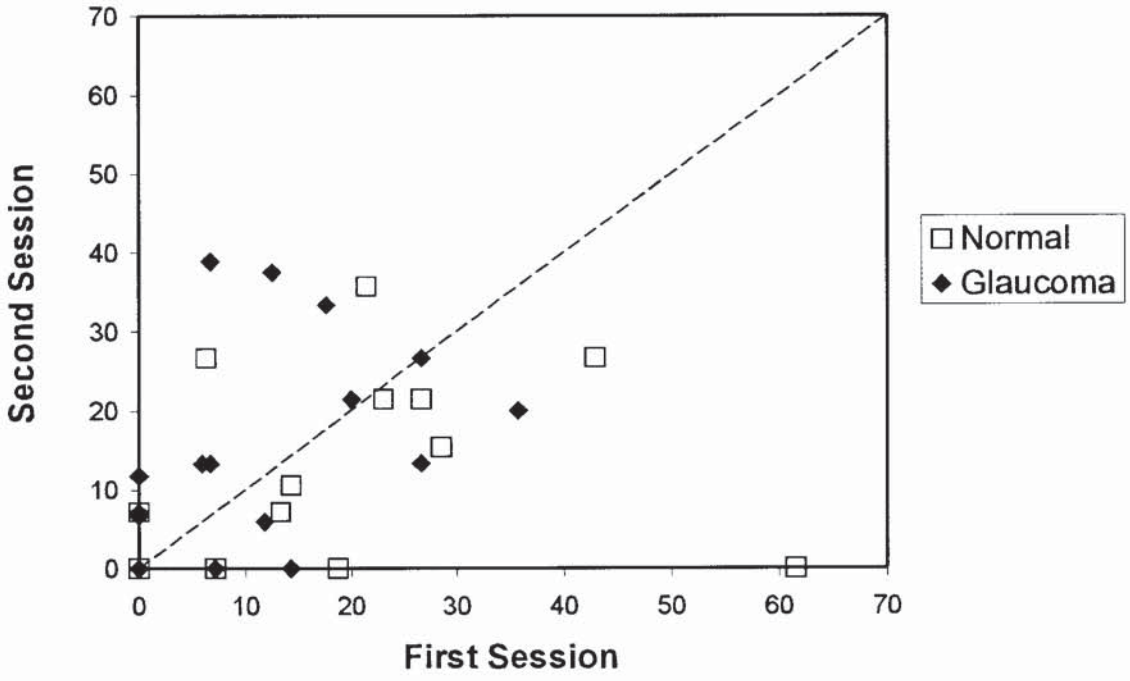


Figure 6.3. The percentage fixation loss rate, as determined by the Heijl-Krakau method, for the roving fixation technique at the first session against that at the second session, for both normal (open squares) and glaucoma (closed diamonds) groups. Each point represents a single individual.

6.4.1.4 Absolute sensitivity at the physiological blind spot

Figure 6.4 shows the measured sensitivity, at the blind spot location, for each individual for the roving fixation technique at each session.

In the normal group, the group mean sensitivity at the blind spot was 11.4 dB (SD 9.7 dB, range 0 to 29 dB) at the first session and 12.5 dB (SD 10.9 dB, range 0 to 33 dB) at the second session. The difference between the two sessions did not reach statistical significance (p=0.834).

In the glaucoma group, the group mean sensitivity at the blind spot was 10.6 dB (SD 10.6 dB, range 0 to 36 dB) at the first session and 10.6 dB (SD 9.8 dB, range 0 to 28 dB) at the second session. The difference between the two sessions did not reach statistical significance (p=0.972).

6.4.2 Roving fixation vs. Static fixation at the second session

6.4.2.1 Mean Sensitivity

The MS with the roving fixation and static fixation techniques at the second session for each individual of both groups is shown in Figure 6.5. Seventeen of the 19 normal subjects had a greater MS with the static fixation technique than with the roving fixation technique. The group mean MS for static fixation was 27.2 dB (SD 1.9 dB, range 21.8 to 29.9 dB) compared to 26.2 dB (SD 1.3 dB, range 22.5 to 28.5 dB) with roving fixation. The difference in MS between techniques was statistically significant (p=0.001).

In the glaucoma group, the group mean MS for static fixation was 24.5 dB (SD 2.4 dB, range 17.4 to 27.7 dB) compared to 24.5 dB (SD 1.5 dB, range 21.0 to 27.0 dB) with roving fixation. The difference in MS between techniques was not statistically significant (p=0.648).

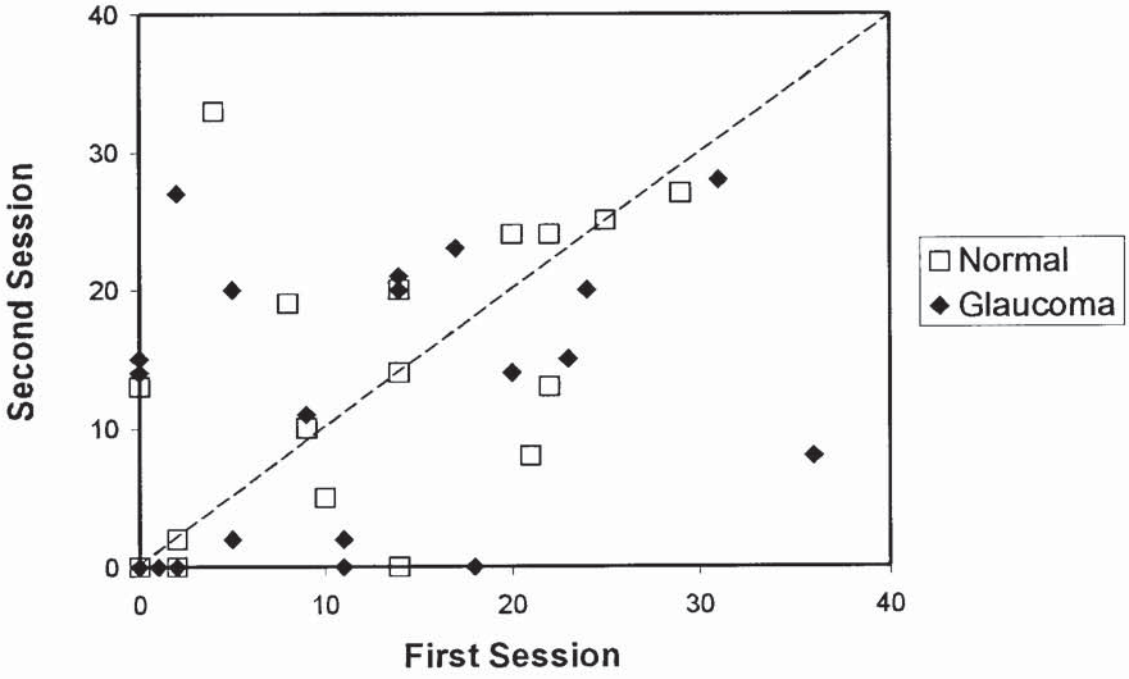


Figure 6.4. The sensitivity measured at the presumed location of the blind spot for the roving fixation technique at the first session against that at the second session, for both normal (open squares) and glaucoma (closed diamonds) groups. Each point represents a single individual.

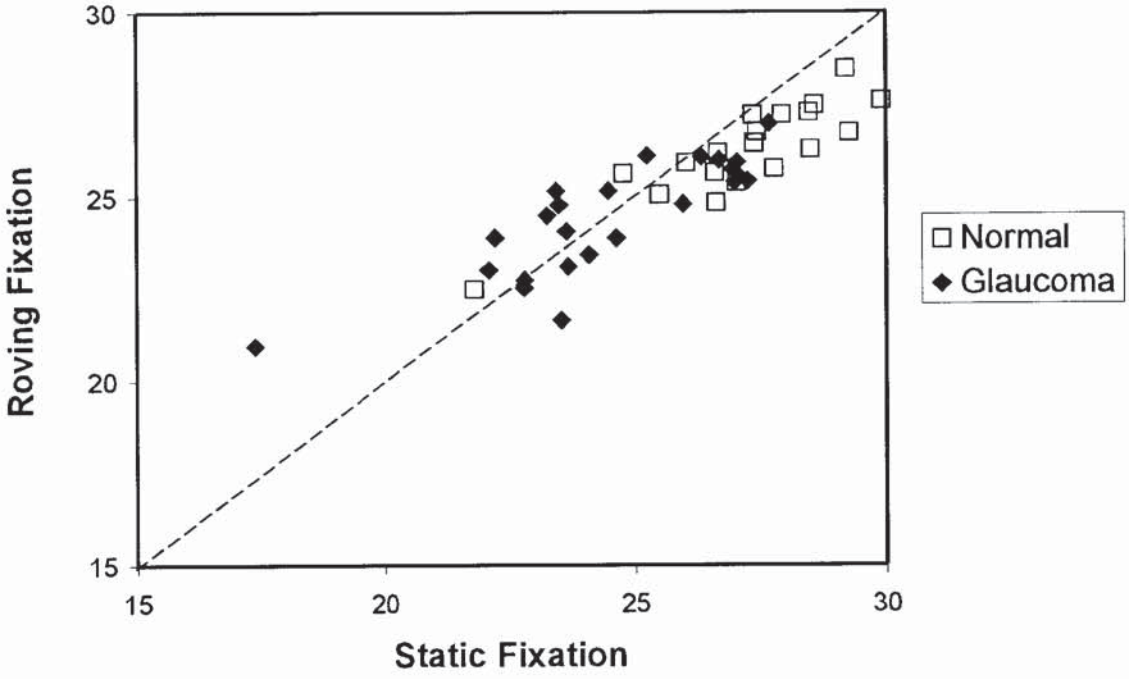


Figure 6.5. The Mean Sensitivity (MS) for the roving fixation technique against the static fixation technique at the second session, for both normal (open squares) and glaucoma (closed diamonds) groups. Each point represents a single individual.

6.4.2.2 Examination Duration

Figure 6.6 shows the examination duration with both the roving fixation and static fixation techniques at the second session for each individual of both groups. Both groups showed a trend towards a longer examination duration with the static fixation technique. In the normal group, 13 subjects exhibited a longer duration with static fixation. The group mean examination durations were 7.7 min (SD 0.8 min, range 6.2 to 9.6 min) with static fixation and 7.4 min (SD 0.7 min, range 6.7 to 10.1 min) with roving fixation. The difference between techniques did not reach statistical significance (p=0.159).

In the glaucoma group, 17 subjects exhibited a longer duration with static fixation. The group mean examination durations were 8.6 min (SD 0.9 min, range 7.5 to 10.5 min) with static fixation and 8.0 min (SD 0.6 min, range 7.1 to 9.4 min) with roving fixation. The difference between techniques was statistically significant (p=0.009).

6.4.2.3 Heijl-Krakau fixation loss rate

Figure 6.7 shows the Heijl-Krakau fixation loss rate for the second session with the static fixation technique and with the roving fixation technique, for both the normal and the glaucoma groups. Each data point represents a single observer and the line of unity is shown. A zero percent fixation loss rate for both techniques was seen in six of the 19 normal subjects and in 7 of the 24 glaucoma patients. Three normal subjects and two glaucoma patients had a higher fixation loss rate for the static fixation technique than with the roving fixation technique. Therefore, the majority of individuals, 10 normal subjects and 15 glaucoma patients, demonstrated a higher fixation loss rate with the roving fixation technique than with the static fixation technique.

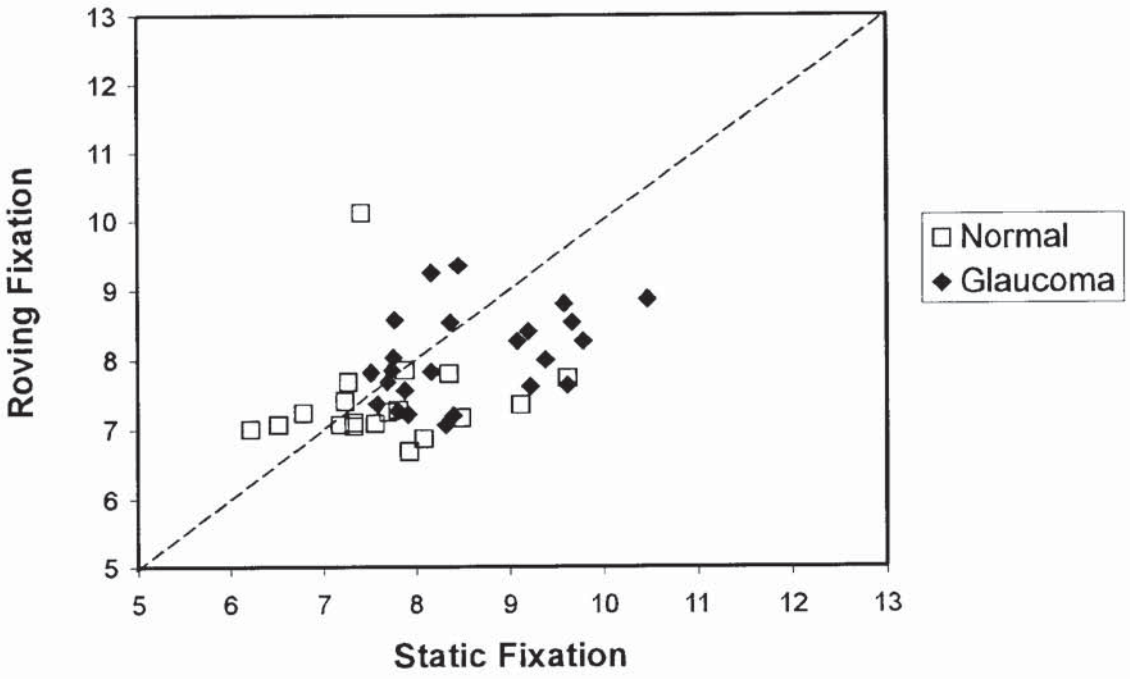


Figure 6.6. The examination duration (min) for the roving fixation technique against the static fixation technique at the second session, for both normal (open squares) and glaucoma (closed diamonds) groups. Each point represents a single individual.

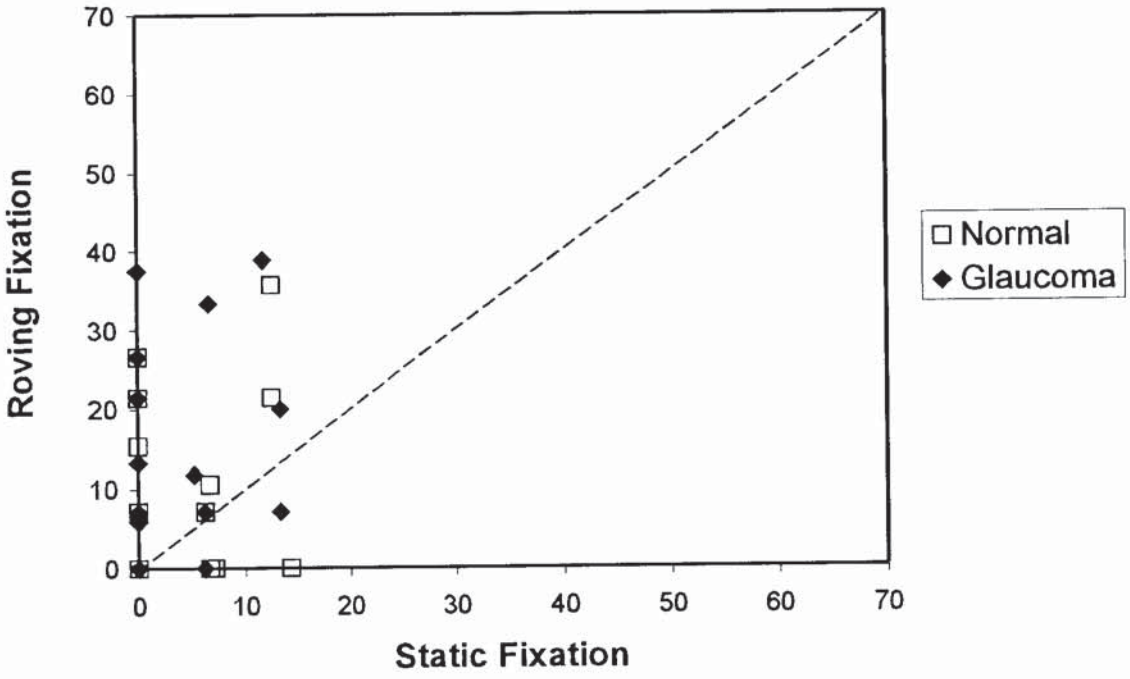


Figure 6.7. The percentage fixation loss rate, as determined by the Heijl-Krakau method, for the roving fixation technique against the static fixation technique at the second session, for both normal (open squares) and glaucoma (closed diamonds) groups. Each point represents a single individual.

In the normal group, the mean fixation loss rate with static fixation was 3.5% (SD 5.1%, range 0% to 14.3%) and with roving fixation was 9.4% (SD 11.6%, range 0% to 35.7%). The difference reached statistical significance (p=0.039). In the glaucoma group, the mean fixation loss rate with static fixation was 2.6% (SD 4.6%, range 0% to 13.3%) and with roving fixation was 11.3% (SD 12.4%, range 0% to 38.9%). The difference reached statistical significance (p=0.001

6.4.2.4 Absolute sensitivity at the physiological blind spot

Figure 6.8 shows the measured sensitivity, at the presumed blind spot location, for each individual at the second session, with the static fixation technique and with the roving fixation technique for both the normal group and the glaucoma group. The measured sensitivity at the blind spot was the same for both static fixation and roving fixation in six of the normal subjects and in six of the glaucoma patients. The measured sensitivity was greater for static fixation than with roving fixation in two normal subjects and three glaucoma subjects. Therefore, the majority of subjects, 11 normal subjects and 15 glaucoma patients, had a greater measured sensitivity with roving fixation than with static fixation.

Fifteen normal subjects and 15 glaucoma patients exhibited an absolute loss at the blind spot with the static fixation technique. Whereas, there were only five normal subjects and eight glaucoma patients with an absolute loss at the blind spot with the roving fixation technique.

In the normal group, the mean sensitivity at the blind spot with static fixation was 2.4 dB (SD 5.3 dB, range 0 to 18 dB) and with roving fixation was 12.5 dB (SD 10.9 dB, range 0 to 33 dB). The difference between the two techniques reached statistical significance (p=0.003). In the glaucoma group, the mean sensitivity at the blind spot with static fixation was 2.9 dB (SD 5.1 dB, range 0 to 22 dB) and with roving fixation was 10.6 dB (SD 9.8 dB, range 0 to 28 dB). The difference between the two techniques reached statistical significance (p=0.003).

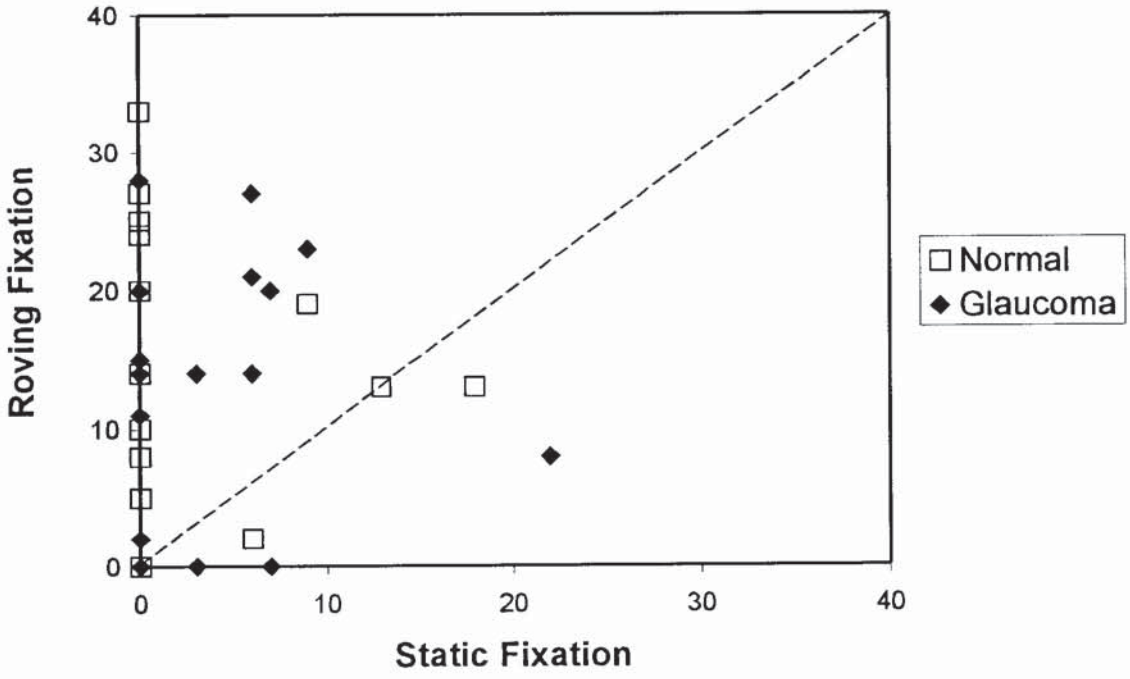


Figure 6.8. The sensitivity measured at the presumed location of the blind spot for the roving fixation technique against the static fixation technique at the second session, for both normal (open squares) and glaucoma (closed diamonds) groups. Each point represents a single individual.

6.5 Discussion

The 1 dB higher group mean MS for the static fixation technique compared to the roving fixation technique in normal subjects, is consistent with the previously reported relationship between the Humphrey Field Analyzer and the Dicon perimeter (Lewis, et al. 1991, Wong, et al. 1995).

The results indicate that there is a difference in the accuracy of fixation with static and roving fixation targets in perimetry. In both of the normal and glaucoma groups, the roving fixation technique was associated with an increased fixation instability as estimated by the Heijl-Krakau fixation monitor. The sensitivity measured at the presumed location of the physiological blind spot was also greater with the roving fixation technique than with the static fixation technique.

Inaccurate fixation and an overestimation of sensitivity at the location of the blind spot may be linked. Inaccurate fixation will mean that stimuli intended for one retinal location will stimulate another retinal location which is likely to have a different sensitivity thus leading to an underestimation of scotoma depth and/or width or to an underestimation of normal sensitivity. The margins of focal defects are likely to appear to have a wider slope in the presence of inaccurate fixation and the variability of responses will be higher (Henson and Bryson 1991).

The current recommendation for the delineation of reliable visual field results is a criteria of less than 20% fixation losses and less than 33% false-positive and false-negative responses, respectively (Haley 1987). Using a criteria of less than 20% fixation errors, six normal subjects exhibited unreliable visual fields with the roving fixation technique at the first session and five unreliable fields at the second session. Using the same criteria for the glaucoma group, three patients from the first session and five patients from the second session exhibited unreliable fields. None of the visual fields from the static fixation technique exhibited a fixation loss rate greater than or equal to 20%. It has been proposed that the

permitted fixation error rate should be increased to 33% (Katz and Sommer 1988, Johnson and Nelson-Quigg 1993, Birt, et al. 1997). Even at a rate of 33%, seven visual fields would have been deemed unreliable with the roving fixation technique. This indicates that even at the second examination the roving fixation technique still produced clinically unreliable test results due to fixation errors with the blind spot catch trials.

It is possible that the actual position of the blind spot in some individuals might not correspond to the location of the blind spot used by the instruments in this study (i.e. 15 degrees temporal, and 3 degrees inferior, to fixation). This can occur due to variations in anatomy or to head tilt when the head is positioned against the head rest. Variations in the anatomical position of the optic nerve head, and therefore the position of the physiological blind spot, should affect the results from both fixation techniques equally. A majority of the sample recorded a sensitivity of 0 dB at the blind spot location with the static fixation technique suggesting that the assumed location was correct in most cases. Variations in the degree of head tilt is a more random effect that could change the position of the blind spot within the examination of a given patient, between-patients with a given test or between-tests for a given patient. The Dicon perimeter does not have a chin rest but requires the patient to maintain the correct head position against the forehead rest. If a head tilt is consistent from the start of the examination then the deviation from the normal blind spot location would be discovered by the perimeter and the actual position of the blind spot could be plotted. Any changes in the degree of head tilt during the examination would alter the position of the retina and blind spot in relation to fixation and hence would increase the degree of examination variability.

The cessation of the movement of the fixation target may act as a cue to the patient, thus reducing the effect of temporal uncertainty (Westheimer and Ley 1996). When an observer is prompted as to the time interval during which a stimulus is likely to appear, the sensitivity has been shown to be higher than when the stimulus could occur at random time intervals (Milosevic 1974, Westheimer and Ley 1996). The movement of the fixation target towards the edge of the screen also provides a cue to the most probable spatial location of the next

stimulus thus reducing the effect of spatial uncertainty (Hubner 1996). The reduction of spatial uncertainty is also associated with a higher rate of detection of stimuli (Niceley and Miller 1957, Milosevic 1974, Cohn and Wardlaw 1985, Lindblom and Westheimer 1992).

It is also possible that the cessation of movement of the fixation target may elicit a false-positive response from the individual who may be anticipating a stimulus to appear. If the false-positive response occurred at the same time as a fixation catch trial then the false-positive response would be recorded as a fixation error. The Dicon perimeter printout does not record the ratio of false-positive and false-negative catch trials but only the number of errors. Nevertheless, it would appear that more false-positive responses were present with the roving fixation technique. Only four false-positive responses, one from each of 4 individuals across both groups, were found for static fixation. With the roving fixation technique, a total of 56 false-positive errors were present in 23 individuals at the first session (a maximum of 7 in one individual) and 39 false-positive errors were present in 24 individuals at the second session (a maximum of 4 in one individual). The roving fixation technique however did not seem to generate a disproportionately large number stimulus locations with abnormally high sensitivities as would be expected with a large false-positive response rate. The tendency towards false-positive responses may, however, lead to an underestimation of field loss. Indeed, the group mean MS for the normal subjects recorded with the roving fixation technique was lower than that recorded with the static fixation technique. This would suggest that the higher sensitivity recorded at the blind spot with the roving fixation technique was not due to false-positive responses but due to fixation errors.

The Heijl-Krakau fixation monitoring technique is influenced by the limited sampling of fixation position and by the size of the physiological blind spot. With the Humphrey Field Analyzer and with the Dicon LD400 perimeters, the number of fixation catch trials is approximately 6% of the total number of stimulus presentations. This fixation rate is adequate to detect regular fixation errors greater than 5 degrees (Demirel and Vingrys 1993), although the rate of fixation errors of less than 5 degrees could not be accurately estimated with sampling rates of up to 25%. The accuracy of the technique is dependent

upon the size of the physiological blind spot and upon the size of the stimulus used in the catch trials. For a given optic nerve head diameter, smaller eye movements will be detected at a higher rate with a larger stimulus than with a smaller stimulus. The use of a smaller stimulus for the catch trial allows for a greater movement of the optic nerve head before the stimulus is projected onto the peripapillary retina. The presence of scotoma involving the physiological blind spot may mask larger eye movements. The difference in fixation loss rates recorded by the two instruments in this study may be due to the different stimulus sizes employed. However, this is unlikely, as the area of the Goldmann size IV stimulus used by the Dicon perimeter is still 45 times smaller than the area of the physiological blind spot.

Both the Dicon perimeter and the Humphrey Field Analyzer automatically replot the position of the physiological blind spot if the patient responds positively to either of the first two fixation error catch trials. The Humphrey Field Analyzer allows for the perimetrist to replot the position of the physiological blind spot at any time during the examination. The position of the blind spot determined by the Humphrey Field Analyzer was not replotted by the perimetrist in order to maintain a constant effect between the two instruments. It was theoretically possible that one or both of the perimeters might have been unable to plot the position of the blind spot. This can occur if the blind spot is significantly above the horizontal midline or if the blind spot is very small. However, the blind spot was plotted by the perimeter in all cases.

The finding of increased fixation errors for the roving fixation technique could still have been influenced by the degree of perimetric experience required for optimal fixation of the roving fixation target despite the incorporation of a 'training' examination. In this study, the glaucoma patients and normal subjects were all fully experienced in the static fixation technique of the Humphrey Field Analyzer and in automated perimetry in general. The fact that there was no significant improvement in the accuracy of fixation over the two sessions with the roving fixation technique and that there was still a significant difference in fixation accuracy between the two fixation techniques at the second session would indicate that the learning effect is unlikely to explain the difference between the two techniques. Indeed

considering the current financial constraints of modern healthcare provisions it would be unfortunate if the roving fixation technique required more than two examinations to achieve sufficiently reliable responses from perimetrically experienced observers.

6.6 Conclusions

This study raises concerns about the suitability of the roving fixation technique for perimetry. One of the main protocols for the development of the roving fixation technique was to improve patient compliance and reliability. It would seem that the technique may have the opposite effect; it is associated with fixation instability as measured by the Heijl-Krakau fixation monitor and with an underestimation of the depth of the physiological blind spot. Therefore, roving fixation may also be associated with an underestimate of the depth and width of glaucomatous field loss.

CHAPTER 7. THE EFFECT OF PREVIOUS PERIMETRIC EXPERIENCE ON BASELINE SHORT-WAVELENGTH AUTOMATED PERIMETRY EXAMINATIONS

7.1 Introduction

7.1.1 The organisation of visual processing

The human visual system is organised such that many different aspects of the visual environment are processed simultaneously as information is passed through the visual system (DeValois, et al. 1966, Wiesel and Hubel 1966, de Monasterio and Gouras 1975, Derrington and Lennie 1984, Shapley and Perry 1986, Livingstone and Hubel 1987). The process is initiated in the retina where the photoreceptors create the primary input to the visual system by transforming light energy into neural responses (Wald 1964). The photoreceptors are subdivided into rods and into short-wavelength sensitive (SWS), medium-wavelength sensitive (MWS) and long-wavelength sensitive (LWS) cones. The information from the light incident on the retina is conveyed to the lateral geniculate nucleus (LGN) via at least two parallel visual pathways after partial processing of information has been performed within the neural layers of the retina. The identification of the two pathways arises from the anatomical arrangement of neural synapses in the LGN. The LGN is composed of six distinct lamellae, four dorsal parvocellular layers and two ventral magnocellular layers. The midget and small bistratified retinal ganglion cells, which synapse in the parvocellular layers (approximately 80% of the total number of ganglion cells), are termed P-cells and the parasol ganglion cells, which synapse in the magnocellular layers (approximately 10% of the total), are termed M-cells (Shapley and Perry 1986). These two types of cell tend to code for separate aspects of vision. The M-cells have relatively large receptive fields, are more sensitive to low spatial frequency and high temporal frequency stimuli and in general give a similar type of response to all wavelengths of light. Conversely, the P-cells have smaller receptive fields, provide the perception of colour, are more sensitive to higher spatial frequency stimuli and are less sensitive to high temporal frequency stimuli (Merigan and Maunsell 1990, Shapley 1990, Callaway 1998).

The magnocellular and parvocellular pathways may not exclusively code for specific visual behaviours. The M- and P-cells have been shown to demonstrate similar responses to stimuli of similar spatial frequency (Crook, et al. 1988) and there exists an overlap in the range of luminances over which each system operates (Pupura, et al. 1990). It is also unlikely that the processing of visual stimuli by the two pathways remains segregated as the two pathways reach the temporal and parietal regions of the primary visual cortex (Merigan and Maunsell 1993). However, it is still believed that colour vision is predominantly mediated by the parvocellular pathway (Schiller, et al. 1990, Merigan and Maunsell 1993).

The two classic theories of colour vision from Helmholtz and Hering have been combined into a two-stage colour vision model in which the three groups of cones (Wald 1964) combine into a colour-opponent organisation in the inner layers of the retina forming subsets of ganglion cells within the parvocellular pathway (Hurvich and Jameson 1957). Two separate channels for colour vision have been described; a red-green channel which receives antagonistic input from the LWS and MWS cones and a blue-yellow channel which receives input from the SWS cones antagonistic to input from a combination of the LWS and MWS cones (DeValois, et al. 1966). A third opponent channel exists to differentiate luminance changes. This channel is assumed to be mediated predominantly by the MWS and LWS cones together with some input from the rods. The input to the luminance channel from the SWS cones is equivocal (Gouras 1969, Eisner and MacLeod 1980, Ingling and Martinez 1980, Stockman, et al. 1991, DeValois and DeValois 1993).

The remaining 10% of ganglion cells project to various layers within the LGN, including the thin layers between the parvocellular and magnocellular layers, and have a relatively unknown function. This third pathway, known as the koniocellular pathway, ultimately projects to sections of the visual cortex that may be involved in colour vision, object recognition or visual resolution (Casagrande 1994). In addition, the koniocellular pathway may have a modulatory effect on activity in the M and P pathways and may also play a part in the suppression of vision during saccadic eye movements (Casagrande 1994, Callaway 1998). The ability to discriminate colour has been reported in individuals in whom the

parvocellular pathway does not function due to cortical lesions (Troscianko, et al. 1996). The presence of colour discrimination in these individuals was attributed to visual processing by a pathway with characteristics differing from either the parvocellular or the magnocellular pathways (Troscianko, et al. 1996). The blue-on colour opponent cells have been shown to contribute to the koniocellular pathway in New World monkeys (Martin, et al. 1997).

In summary, it is generally agreed that the midget ganglion cells transfer LWS and MWS information via the parvocellular pathway and the majority of the SWS information is transferred by the small bistratified ganglion cells via the parvocellular pathway. However, SWS information may also have a further, as yet totally substantiated, input to the visual cortex.

7.1.2 The effect of glaucomatous optic neuropathy on visual function

The results from histological studies have shown that between 40% and 50% of ganglion cell nerve fibres are damaged in glaucoma before visual field defects are detected by conventional white-white perimetry (Quigley, et al. 1982, Quigley, et al. 1989). These findings have been corroborated by optic nerve head and retinal nerve fibre analysis (Sommer, et al. 1991, Tuulonen, et al. 1993, Zeyen and Caprioli 1993). In addition, it has been postulated that glaucoma preferentially damages ganglion cells with larger diameter axons (Quigley, et al. 1987, Quigley, et al. 1988). The hypotheses for the selective damage to larger nerve fibres are, the relative susceptibility of the fibres to mechanical and physiological damage and their anatomical position in the weakest area of the optic nerve head (Quigley, et al. 1987, Radius 1987, Miller and Quigley 1988). Ganglion cells with larger diameter axons constitute the majority of the magnocellular pathway and a subset of the parvocellular pathway that particularly processes responses from the SWS mechanism (de Monasterio 1979). The ganglion cells in the koniocellular pathway have the smallest diameter axons (Callaway 1998).

The pathophysiological findings that glaucoma causes selective ganglion cell atrophy have led to the desire for more sensitive methods of detecting early visual loss. Psychophysical

tests that endeavour to isolate visual function performed by a subset of ganglion cells have been developed. Tests designed to identify defects in the magnocellular pathway include the investigation of the temporal contrast sensitivity function (Atkin, et al. 1979, Tyler 1981, Lundh and Gottvall 1985, Korth, et al. 1989, Breton, et al. 1991, Casson, et al. 1993, Anderson and O'Brien 1997), motion perception (Silverman, et al. 1990) and the frequency doubling illusion (Johnson and Samuels 1997). Sensitivity to temporally modulated contrast gratings is reduced in eyes with glaucoma, although the optimum temporal frequency to maximise the sensitivity and specificity of the test is equivocal, varying between 2 Hz (Lundh and Gottvall 1985) and 40 Hz (Tyler 1981). It is possible that these tests do not fully isolate the M pathway as both M and P cells will respond to a range of temporal frequencies (Merigan and Maunsell 1993). Frequency Doubling Perimetry (FDP) has been shown to give high sensitivity and specificity for the detection of glaucomatous field loss (Johnson and Samuels 1997) and is subject to longitudinal studies to determine the clinical benefit of the test.

Tests designed to isolate the parvocellular pathway include, the investigation of spatial contrast sensitivity (Arden and Jacobsen 1978, Atkin, et al. 1979, Korth, et al. 1989, Falcao-Reis, et al. 1990), Resolution perimetry (Frisen 1992, Sample, et al. 1992, Frisen 1993, Anderson and O'Brien 1997) and Pattern Discrimination perimetry (Drum, et al. 1986, Drum, et al. 1989, Nutaitis, et al. 1992, Stewart, et al. 1992). However, tests investigating spatial contrast sensitivity suffer from a lack of specificity and the newer perimetric tests are the subject of prospective longitudinal studies to establish their sensitivity to early progression of glaucomatous damage.

Colour vision and isoluminant colour contrast sensitivity have been shown to be affected by glaucomatous optic neuropathy, especially along the blue-yellow tritanopic confusion axis (Gunduz, et al. 1988, Falcao-Reis, et al. 1991, Yu, et al. 1991, Devos, et al. 1995, Felius, et al. 1995b, Greenstein, et al. 1996). Yu et al (1991) measured peripheral isoluminant colour contrast thresholds using an annular stimulus with a diameter of 25 degrees centred on fixation. Colour contrast defects were found along all three chromatic confusion axes.

However, the test failed to detect 20% of early glaucomatous scotoma due to the fact that the method combined the response from a large area of retina (Devos, et al. 1995). Modification of the technique to use blue-yellow stimuli consisting of an arc positioned randomly in each quadrant of the visual field resulted in a sensitivity of 95% (Devos, et al. 1995).

The observations that tritanopic colour detection or discrimination thresholds are elevated and that the ganglion cells with the largest diameter axons (including those from the SWS channel) are damaged in glaucoma has led to the development of blue-on-yellow perimetry, also known as short-wavelength automated perimetry (SWAP) (Heron, et al. 1988, Sample, et al. 1988a, Hart 1989, de Jong, et al. 1990). SWAP measures the differential light sensitivity to a blue stimulus (used to stimulate the SWS pathway) superimposed on a bright yellow background (used to adapt the MWS and the LWS channels and to simultaneously suppress rod activity). The differential light sensitivity measured in this manner is mediated by the chromatic channel rather than by the luminance channel (Felius, et al. 1995a).

An alternative theory for the variation in the ability of certain psychophysical tests to differentiate between normal and glaucomatous eyes is termed reduced redundancy. The rationale behind this theory is the fact that SWS ganglion cells are less numerous than the MWS and LWS ganglion cells (de Monasterio, et al. 1985, Curcio and Sloan 1992) and that the glaucomatous disease process may reduce the numbers of each cell type equally. Therefore, the proportionate loss would be greater for the M-cells and the small bistratified cells (and the cells of the koniocellular pathway) and any psychophysical test designed to isolate the SWS mechanism would seem to detect a selective loss for this pathway. Indeed, raised thresholds along all chromatic confusion axes and along the luminance axis have been reported (Felius, et al. 1995b, Greenstein, et al. 1996)

7.1.3 The Optimum Parameters for SWAP

The ideal parameters for use in SWAP are equivocal. The spectral properties of the stimulus and of the background and the luminance of the background should be chosen such as to provide maximal isolation of the SWS channel from the MWS and LWS channels.

A background luminance of 90 cdm^{-2} (with a Wratten #12 yellow filter) has been used (Sample and Weinreb 1990, Sample, et al. 1993) on the basis that a greater background luminance would raise SWS thresholds rather than increase SWS isolation. However, a background luminance of between 120 and 300 cdm^{-2} is required to ensure saturation of the rods (Aguilar and Stiles 1954). Additionally, in the normal eye at pupil diameters of 3mm or greater, the SWS pathway has been shown to have isolation from the MWS and LWS pathways only at background luminances of greater than 140 cdm^{-2} (Yeh, et al. 1989). SWS pathway isolation of 1.1 to 1.5 log units has been demonstrated with a background luminance of 200 cdm^{-2} and a Schott OG530 filter (Johnson, et al. 1988a). Some SWS isolation at background luminances as low as 10 cdm^{-2} was shown (Johnson, et al. 1988a) although this level of isolation is insufficient for clinical tests. A higher background luminance of 330 cdm^{-2} has been used with the aim of providing greater SWS isolation (Hudson, et al. 1993, Wild and Hudson 1995) due to increasing adaptation of the MWS and LWS channels. However, the commercially available parameters for SWAP with both the Humphrey Field Analyzer and the Octopus perimeters utilise a background luminance of 100 cdm^{-2} and a Schott OG530 filter (Sample, et al. 1996).

SWS isolation is also dependent on the characteristics of the stimulus used. SWS isolation increases as the bandwidth of the spectral distribution of the stimulus filter decreases. However, the reduction in spectral transmission associated with a monochromatic filter coincides with a reduction in the maximum stimulus luminance and hence a reduction of the dynamic range of the perimeter. Therefore, a stimulus filter with a broader spectral transmission (such as an OCLI blue dichroic, transmitting wavelengths below 500 nm) has been used (Johnson, et al. 1988a, Adams, et al. 1991, Hudson, et al. 1993, Johnson, et al. 1993c, Johnson, et al. 1993b, Moss and Wild 1994, Johnson, et al. 1995, Moss, et al. 1995,

Wild and Hudson 1995). This stimulus filter may allow some stimulation of the MWS pathway and hence incomplete isolation of the SWS pathway (Sample and Weinreb 1990, Sample, et al. 1993). In addition, a cataract would affect the peak retinal wavelength of a narrowband stimulus less than the peak retinal wavelength of a broadband stimulus. The commercially available SWAP stimulus for the Humphrey Field Analyzer uses a narrowband 440 nm (27 nm half-bandwidth) filter (Sample, et al. 1996). The stimulus for SWAP with the Octopus perimeter is generated using a 440 nm (15 nm bandwidth) filter.

The default stimulus for SWAP is a Goldmann size V (1.7 degree diameter) stimulus together with a stimulus duration of 200 ms. The effect of stimulus size and spatial summation is greater at shorter wavelengths and temporal summation is maximal at 200 ms for stimuli preferentially stimulating the SWS pathway (King-Smith and Carden 1976). The use of stimulus sizes less than Goldmann size IV produce minimal, if any, SWS isolation (Adams, et al. 1991). The optimal parameters for maximal SWS channel isolation result in a reduction of the dynamic range of the perimeter. The parameters chosen for clinical testing are a compromise between isolation of the SWS channel and maximisation of the dynamic range. In the presence of disease, the stimulus may be detected by the MWS and LWS channels due to a reduction in the SWS isolation. Thus, the benefit of SWAP in defective areas of the visual field may be reduced, especially when the reduced dynamic range of SWAP compared to W-W perimetry is taken into consideration. SWAP is therefore more suited to the examination of patients with ocular hypertension, patients with early W-W field loss and for the investigation of any extension in the width of existing field loss.

In the normal eye, the SWAP profile is steeper than the conventional white-on-white (W-W) perimetric profile (de Jong, et al. 1990) and this effect is greater in the superior visual field (Sample, et al. 1997). The normal age-related decline in SWS channel sensitivity is greater than for the MWS and LWS channels by approximately 0.3 dB per decade with a greater rate of decline occurring with increasing eccentricity and in the superior nasal field (Johnson, et al. 1988a). The SF is greater in SWAP than in W-W perimetry (Nelson-Quigg, et al. 1990, Moss, et al. 1995, Wild, et al. 1995, Wild, et al. 1998). The increase can be attributed to a

flatter FOS curve for SWAP (Olsson, et al. 1998). The shape of the FOS curve in SWAP may explain why the normal between-subject variability at each stimulus location is also greater for SWAP than for W-W perimetry (Wild, et al. 1995, Wild, et al. 1997a). This greater variability for SWAP is more pronounced at greater eccentricities and with increased age (Wild, et al. 1995, Wild, et al. 1997a). In addition to the flatter FOS curves, the increased variability for SWAP is due to within- and between-subject variations in media absorption (Moss, et al. 1995) and intraocular light scatter (Moss and Wild 1994) and in the between-subject variation in the density of macular pigment (Wild and Hudson 1995).

7.1.4 The use of SWAP in glaucoma

SWAP has been shown to detect glaucomatous visual field changes prior to conventional W-W perimetry (Heron, et al. 1988, Sample, et al. 1988a, de Jong, et al. 1990, Hart, et al. 1990, Adams, et al. 1991, Sample and Weinreb 1992, Casson, et al. 1993, Johnson, et al. 1993c, Johnson, et al. 1993b, Sample, et al. 1993, Johnson, et al. 1995, Wild, et al. 1995). However, many studies have utilised elite perimetric observers. Moreover, the analysis of abnormality has largely been based upon deviations in the height, rather than the shape, of the visual field.

Heron et al (1988) found that patients with glaucoma had a significant loss of SWS function throughout the central visual field. The observation that glaucomatous eyes have a wider and/or deeper early visual field defects with SWAP than with W-W perimetry has been corroborated by several investigators (de Jong, et al. 1990, Hart, et al. 1990, Sample and Weinreb 1990, Adams, et al. 1991, Sample and Weinreb 1992, Casson, et al. 1993, Wild, et al. 1995). However, in the presence of more advanced visual field defects the extent of visual deficit is similar between the two techniques (Hart, et al. 1990, Wild, et al. 1995).

Visual field defects for SWAP have also been demonstrated in ocular hypertensive (OHT) patients or glaucoma suspect eyes prior to confirmed W-W field loss (Heron, et al. 1988, de Jong, et al. 1990, Sample and Weinreb 1990, Johnson, et al. 1993b, Sample, et al. 1993,

Johnson, et al. 1995, Wild, et al. 1995). The predominant area for damage is the superior nasal field (Sample and Weinreb 1990, Sample, et al. 1993). The proportion of OHT and glaucoma suspect patients with abnormal SWAP fields varies from 19% or less (Heron, et al. 1988, Johnson, et al. 1993b, Wild, et al. 1995) to 42% or greater (Sample and Weinreb 1990, Casson, et al. 1993, Sample, et al. 1993). When the OHT patients are graded to reflect the risk of W-W field loss due to factors such a intraocular pressure, cup-to-disk ratio, family history of glaucoma and age, then the proportion of patients with SWAP defects is proportional to risk (Sample, et al. 1993, Johnson, et al. 1995). The incidence of SWAP defects is associated with age and with cup-to-disk ratio, but no relationship is present for IOP or family history (Johnson, et al. 1995).

Johnson et al (1993) reported that five of nine OHT eyes with SWAP defects developed W-W loss within five years of the onset of a SWAP defect. Two of the five OHT patients with SWAP defects in the study of Wild et al (1995) progressed to W-W loss. All of the OHT patients who progressed to W-W loss in the studies of Sample et al (1993) and Casson et al (1993) initially had a defect with SWAP. In glaucomatous eyes with progressive W-W field loss, the baseline SWAP defect was larger than the W-W defect (Sample and Weinreb 1992, Casson, et al. 1993, Johnson, et al. 1993c). SWAP may indicate significant visual function damage prior to conventional W-W perimetry.

The majority of investigators have taken in account the preferential absorption of the short-wavelength stimulus by the ocular media (Johnson, et al. 1988a, Sample and Weinreb 1990, Sample and Weinreb 1992, Casson, et al. 1993, Johnson, et al. 1993b, Johnson, et al. 1993c, Sample, et al. 1993, Johnson, et al. 1995, Wild and Hudson 1995, Wild, et al. 1998). Correction of the sensitivity due to media absorption has, however, been shown not to significantly reduce the between-subject variability in older subjects (Johnson, et al. 1988a, Sample, et al. 1994, Wild, et al. 1995, Wild, et al. 1998). Specifically, Sample et al (1994) found that correction for ocular media absorption had no effect on the ability of the Glaucoma Hemifield Test to detect field visual defects in SWAP.

7.1.5 The learning effect in perimetry

The learning effect in perimetry occurs as the patient becomes familiar with the requirements of the test. Perimetric experience is manifest as an increase in sensitivity and a decrease in the measurement variability. The learning effect has been described for manual static perimetry (Aulhorn and Harms 1967) whereby sensitivity improved over the first ten examinations by up to one log unit. A reduction in the variability of responses with increased perimetric experience was shown by Greve (1973). The influence of learning was considered clinically insignificant, as focal losses were not affected by the uniform increase in sensitivity. The learning effect has been attributed to a steepening of the FOS curve (Greve 1973) or to a change in the subjective criterion for stimulus detection (Tate and Lynn 1977). Feedback given to the patient improves the rate of learning (Tate and Lynn 1977).

The learning effect has also been demonstrated for automated static perimetry in normal subjects (Wood, et al. 1987b, Heijl, et al. 1989c, Autzen and Work 1990, Guttridge, et al. 1991, Marra and Flammer 1991, Searle, et al. 1991) and in ocular hypertensive and glaucoma patients (Gloor, et al. 1980, Werner, et al. 1988, Wild, et al. 1989b, Kulze, et al. 1990, Werner, et al. 1990, Marchini, et al. 1991, Marra and Flammer 1991, Heijl and Bengtsson 1996).

7.1.5.1 The learning effect in normal subjects

Wood et al (1987) used Program 21 of the Octopus 201 perimeter to investigate the learning effect in a group of ten normal subjects naïve to psychophysical testing. Eight of the ten subjects produced a learning effect with a mean increase in sensitivity of approximately 10 dB over five consecutive days. For nine of the subjects, the SF decreased by 3 dB. The learning effect was greater in the superior visual field, at eccentricities greater than 30 degrees and was retained at examinations performed 10, 11 and 39 days after the fifth examination. Three patterns to the learning effect were evident: a rapid improvement in performance over the first two examinations with little improvement subsequently; a steady improvement over the first five examinations; and no negligible improvement with repeated examination.

Heijl et al (1989) found an improvement in perimetric performance for 84 normal subjects drawn randomly from the general population using Program 30-2 of the Humphrey Field Analyzer. Seventy-four subjects were followed bi-monthly for three examinations and 10 subjects were followed weekly for ten examinations. The group MS increased by 1.3 dB and the SF decreased by 0.3 dB. The improvement was greater at peripheral eccentricities. A large between-subject variability in the learning effect was also present. Subjects with a lower initial MS exhibited a more pronounced learning effect. From this data, Heijl et al (1989) concluded that a single examination was insufficient as baseline information.

In a group of naïve subjects, Autzen and Work (1990) demonstrated an increase in MS of 0.95 dB and a reduction in SF of 0.3 dB. Guttridge et al (1991) reported an increase of 5 dB in the peripheral field of 12 normal subjects using Programs 30-2 and 60-2 of the Humphrey Field Analyzer. A large between-subject variation in the pattern of learning was also found. Searle et al (1991) found an increase of 1.5 dB in group mean MS at the second visit in opposition to a within-examination fatigue effect. The SF, the number of stimulus presentations and test duration all decreased at the second examination. It was suggested that confidence limits for normality should take into account the order in which the eyes were examined.

7.1.5.2 The learning effect in glaucoma patients

The presence of a learning effect in ocular hypertension and in glaucoma is equivocal. Werner et al (1988) retrospectively examined the visual fields of 20 glaucomatous eyes obtained with Program 32 of the Octopus 201 perimeter. The patients were all experienced in manual perimetry. There was no improvement in global MS or a reduction in the number of defective stimulus locations (defined as a difference in sensitivity from the age-matched normal value of 5 dB or greater). However, a significant reduction in SF between the first and second examinations was found. They concluded that a single baseline field was adequate in glaucoma patients experienced in manual perimetry. Katz and Sommer (1987) were also unable to find a learning effect and attributed this to the fact that their subjects were also experienced at manual perimetry.

Werner et al (1990) found no significant improvement in global mean MS over four visits in a group of glaucoma suspects experienced in either manual perimetry or in multiple stimulus supra-threshold perimetry. However, sensitivity at eccentricities greater than 20 degrees increased over the first two visits whilst the SF and the number of defective stimulus locations decreased.

Marra and Flammer (1991) were also unable to find a learning effect in a group of 70 normal subjects, 16 glaucoma patients and 14 cataract patients following the repeated testing of three stimulus locations. There was no difference in performance between perimetrically experienced and naïve subjects or between normal and abnormal eyes.

Other studies have confirmed the need for perimetric training for patients. Gloor et al (1980) reported a learning effect in a sample of 32 patients with glaucoma. The effect occurred between the first and second examinations and reduced the depth of focal defects, and a 2 dB increase in sensitivity occurred at normal locations. No effect was present between the second and third examinations.

Wild et al (1989) examined 19 naïve patients with suspected glaucoma using a custom program of the Humphrey Field Analyzer to investigate stimuli out to an eccentricity of 60 degrees. An improvement in the global, superior, inferior, central and peripheral mean sensitivities together with a decrease in SF and in the number of stimulus presentations was seen over the first three visits. The main changes occurred between the first and second examinations. The increase in sensitivity was greater for the peripheral locations than for the central locations.

In a group of 15 stable glaucomatous eyes, Marchini et al (1991) found a statistically significant reduction in the MD and SF indices between the first and second examinations with program G1 of the Octopus. Kulze et al (1990), in a retrospective study of the visual fields from 45 glaucoma patients, found a decrease in group MD of 1.7 dB between the first and second examinations. The learning effect was unaffected by the time interval between

tests, age, gender, race or the number of perimetric examinations prior to enrolment in the study. The learning effect was positively correlated to defect depth. They concluded that the identification of patients who required further baseline tests to minimise learning was difficult. The Learners Index (see Chapter 1) was developed in order to aid identification of patients in whom the learning effect was clinically significant and required further baseline examinations (Asman, et al. 1993).

Twenty-five patients with newly diagnosed glaucoma were examined by Heijl and Bengtsson (1996). A learning effect was seen in 21 of the 37 eyes: the group MD increased by 2.8 dB between the first and second tests with no further significant improvement between the second and fifth tests. The visual fields exhibiting moderate loss improved more than fields with early or severe defects. The increase in sensitivity increased with increase in eccentricity. In addition, deeper defects did not improve by the same magnitude as locations with normal sensitivity. Heijl and Bengtsson (1996) concluded was that baseline fields for the detection of change should include more than a single examination.

7.1.5.3 The learning effect in SWAP

A learning effect with SWAP has been demonstrated in normal subjects (Wild and Moss 1996). The subjects were divided into groups dependent on previous perimetric experience and on age and were examined at each of three consecutive days and then after one week. The global MS increased by 3% over the three days and the increase was independent of age or experience. The SF decreased by approximately 10% over the first three days and was independent of perimetric experience. The decrease in SF was greater for the younger groups. There was no significant effect of eccentricity on the improvement in MS but the superior hemifield improved to a greater degree than the inferior hemifield.

7.2 Aim of Study

Clinically, it is possible that SWAP may be requested for patients naïve to any form of perimetry, for patients experienced in manual kinetic perimetry and for patients who have

been previously examined with conventional W-W automated static perimetry. The aim of the study was to determine the influence of the learning effect in SWAP in OHT patients as a function of previous experience in W-W perimetry. This study specifically investigated the influence of the learning effect on the within-eye changes in sensitivity between visits, the between-eye differences in sensitivity at a single visit and the between-eye between-visit effects.

The aim of the study was to investigate how the degree of previous experience with W-W perimetry may affect the initial series of examinations with SWAP in a group of OHT patients. The examination of OHT patients is particularly relevant as SWAP is likely to be employed in the early stages of the disease process. This is due to the predictive nature of SWAP in detecting detrimental changes in visual function.

7.3 Methods

7.3.1 Sample

At the cut-off time for the completion of the thesis, the sample comprised 26 consecutively recruited patients with ocular hypertension. The sample was divided in to two groups based upon previous experience with conventional W-W automated threshold perimetry. The experienced group comprised 17 patients (mean age 58.7 years, SD 11.4, range 32-77) who had previously undertaken at least three Humphrey Field Analyzer threshold automated visual field examinations. The naive group comprised nine patients (mean age 64.7, SD 10.0, range 47-77) who had not been previously examined with any form of static automated perimetry.

The inclusion criteria for both groups comprised a visual acuity of 6/9 or better in either eye, a distance refractive error less than or equal to 5 dioptres mean sphere and less than 2.5 dioptres cylinder, lenticular changes not greater than NCII, NOII, CI or PI by LOCS III (Chylack, et al. 1993), no systemic medication known to affect the visual field and no history

or family history of diabetes mellitus. The patients were required to have demonstrated a consistently raised pre-therapy intraocular pressure of 22 mmHg or greater.

Each eye of each patient was classified, after Hart et al (1979), according to the risk of conversion to glaucomatous W-W field loss based upon age, family history of glaucoma, intraocular pressure and vertical cup-to-disc ratio. This classification system uses weighting factors for each of the predictive variables based on a retrospective study (Hart, et al. 1979), the largest weighting factor being applied to the vertical cup-to-disc ratio. The classification was divided into low-, medium- or high-risk categories at the probability levels used by Johnson et al (1995). Specifically, low risk was considered as a p-value derived from Hart's predictive risk model of less than 0.2, p-values of 0.2 to less than 0.6 were considered to be of medium risk and p-values of 0.6 or greater were considered to be of high risk.

Three patients from the naïve group and nine patients from the experienced group were not receiving medical therapy to control intraocular pressure. All patients on treatment for ocular hypertension were controlled with a single topical agent: the majority of patients were using a topical β-blocker, the exceptions were one patient from the naïve group who was using a topical carbonic anhydrase inhibitor and one patient from the experienced group using a sympathomimetic.

7.3.2 Examination Protocol

SWAP was undertaken using the commercially available modifications to the Humphrey Field Analyzer 640 (Sample, et al. 1996) and software version 9.31. Specifically, these are a 100 cdm^{-2} broad-band yellow background and a narrow-band 440 nm (27 nm half-bandwidth) Goldmann size V (1.74 degree diameter) stimulus, with a stimulus duration of 200 ms.

Each patient was required to attend for SWAP examination on five occasions each separated by one week. At each visit, both eyes were examined using Program 24-2 of the Humphrey Field Analyzer and the right eye was always examined before the left eye. In

order to minimise the fatigue effect, rest periods of approximately 1 minute were given at 4 minute intervals during the examination of each eye and at least a 5 minute break was given between eyes. Prior to the examination of each eye, each patient was required to look into the perimeter bowl for 3 minutes in order to ensure adequate adaptation of the MWS and LWS mechanisms. Each patient was given the same instructions at the beginning of and throughout, each test in order to reduce operator bias.

Refractive correction, in the form of a full aperture trial lens, appropriate for the viewing distance of the perimeter bowl was used for each eye of each patient and the non-tested eye was occluded with an opaque patch. In addition, to the standard Heijl-Krakau technique, fixation was monitored continuously with the video monitor of the Humphrey Field Analyzer as the efficiency of the Heijl-Krakau fixation monitoring technique may be reduced due to the lower absolute maximum stimulus luminance for SWAP compared to W-W perimetry. In addition, the estimation of false-negative responses may be impaired in SWAP. The method for false-negative catch trial estimation in SWAP and W-W perimetry uses a stimulus with an intensity 8 dB brighter than the previously determined threshold at that location. In SWAP the false-negative catch trial may be missed due to the increased within- and between-subject variability found in SWAP compared to W-W perimetry.

7.3.3 Analysis

The principle analysis was concerned with the change in the global indices, Mean Sensitivity (MS), Mean Defect (MD), Short-term Fluctuation (SF) and Corrected Pattern Standard Deviation (CPSD) within- and between-eyes and between groups over the five visits. Additionally, the relationship between the MS for the central and peripheral annuli, and for each of the superior nasal, superior temporal, inferior nasal and inferior temporal quadrants of the visual field was investigated.

7.4 Results

The clinical details of each patient are shown in Table 7.1. In the naïve group, 3 patients were classified as high risk ocular hypertensives in either eyes, 2 patients were high risk in one eye and a medium risk eye in the other eye, 3 patients were medium risk in one eye and a low risk in the other eye and the final patient was considered as low risk in both eyes. There were two low risk, three medium risk and four high risk right eyes and three low risk, two medium risk and four high risk left eyes.

In the experienced group 6 patients were classified as high risk in both eyes, 2 patients were high risk in one eye and a medium risk in the other eye, 3 patients were medium risk in both eyes, one patient was at medium risk in one eye and at low risk in the other eye and 5 patients were low risk in both eyes. There were five low risk, four medium risk and eight high risk right eyes and six low risk, five medium risk and six high risk left eyes.

All visual fields met the inclusion criteria for reliability, specifically less than 20% fixation losses and less than 33% false-negative and false-positive catch trials.

Exp./Naïve	ID	Eye	Age	Family History	CD Ratio		IOP		Risk		Treatment
					RE	LE	RE	LE	RE	LE	
Naive	CJ	R	60.4	yes	0.2	0.2	24	24	0.066	0.066	nil
Naive	SD	R	69.2	no	0.3	0.3	27	33	0.139	0.293	Trusopt 2%
Naive	DM	R	67.0	no	0.4	0.3	28	27	0.353	0.121	nil
Naive	KR	R	50.3	no	0.5	0.4	29	26	0.396	0.108	nil
Naive	PV	R	47.9	no	0.5	0.5	37	29	0.659	0.356	Teoptic 1%
Naive	PrJ	R	77.8	no	0.4	0.5	25	26	0.424	0.744	Teoptic 1%
Naive	TW	R	68.6	yes	0.5	0.6	25	30	0.850	0.977	Teoptic 1%
Naive	LD	R	73.1	yes	0.8	0.6	25	25	0.997	0.964	Teoptic 1%
Naive	PJ	R	67.5	yes	0.7	0.8	21	25	0.970	0.995	Timolol 0.25%
		Mean	64.6		0.48	0.47	26.8	27.2	0.54	0.51	
		SD	10.0		0.19	0.19	4.5	2.9	0.35	0.40	
Exp	BA	R	32.7	no	0.2	0.2	28	26	0.004	0.003	nil
Exp	MD	R	60.9	no	0.2	0.2	28	28	0.030	0.030	nil
Exp	CD	R	56.9	no	0.3	0.3	26	26	0.054	0.054	nil
Exp	MM	R	49.4	yes	0.2	0.3	27	27	0.049	0.148	nil
Exp	MT	R	73.0	no	0.3	0.2	28	24	0.199	0.038	nil
Exp	JC	R	47.4	no	0.4	0.4	32	28	0.201	0.119	Timolol 0.5%
Exp	BM	R	72.1	no	0.3	0.3	31	32	0.270	0.302	nil
Exp	SA	R	57.8	no	0.5	0.5	25	25	0.375	0.375	nil
Exp	BB	R	60.2	no	0.5	0.4	32	30	0.681	0.316	Timolol 0.5%
Exp	EW	R	77.1	yes	0.3	0.3	28	28	0.593	0.593	Propine
Exp	BR	R	60.0	yes	0.6	0.4	23	26	0.884	0.516	nil
Exp	PG	R	73.3	yes	0.4	0.5	23	22	0.633	0.833	nil
Exp	RJ	R	55.8	no	0.6	0.6	26	30	0.673	0.794	Timolol 0.5%
Exp	DeM	R	45.5	yes	0.7	0.5	31	30	0.970	0.706	Timolol 0.5%
Exp	HD	R	63.1	yes	0.7	0.5	32	30	0.992	0.894	Timolol 0.5%
Exp	OR	R	51.9	yes	0.7	0.7	26	25	0.959	0.952	Teoptic 1%
Exp	CB	R	60.3	yes	0.6	0.7	30	30	0.959	0.987	Timolol 0.5%
		Mean	58.7		0.44	0.41	28.0	27.5	0.50	0.45	
		SD	11.4		0.18	0.16	3.0	2.7	0.37	0.36	

Table 7.1. Clinical details for each individual patient including the risk of developing glaucomatous field loss.

7.4.1 Group mean global indices

7.4.1.1 Mean Sensitivity

Figure 7.1 shows the group mean MS for each eye of the naïve and experienced groups at each of the visits. The group mean MS for the experienced group was higher than that for the naive group in each eye for each visit. The group mean MS increased for each eye of each group over the five weeks. For the experienced group, the group mean MS increased from 23.2 dB to 25.0 dB in the first eye tested (the majority of change occurring from week 1 to 2) and from 22.8 dB to 24.2 dB in the second eye tested (increasing to a plateau at week 3). For the naïve group, the group mean MS increased from 19.1 dB to 22.6 dB in the first eye (a continual increase to week 5) and from 19.7 dB to 22.4 dB in the second eye (increasing to a plateau at week 3). The increase in the naïve group was twice the absolute increase over the five weeks of the experienced group.

For the experienced group, the first eye had a greater group mean MS than the second eye at each of the five weeks. The mean difference between eyes for all visits was approximately 0.6 dB (SE 0.2 dB). For the naïve group, the second eye initially showed a greater group mean MS than the first eye by approximately 0.5 dB (SE 0.8 dB). The mean difference between eyes in the naïve group converged to approximately zero (SE 0.9 dB) at week 4.

At the first visit, the group mean difference in MS between the experienced and the naïve groups was 4.1 dB for the first eye and 3.2 dB for the second eye. The between-group difference in MS decreased over the visits reaching a plateau by week 3 for the right eyes and by week 2 for the left eyes. At week 5, the between-group differences were 2.3 dB and 1.8 dB for the first and second eyes respectively.

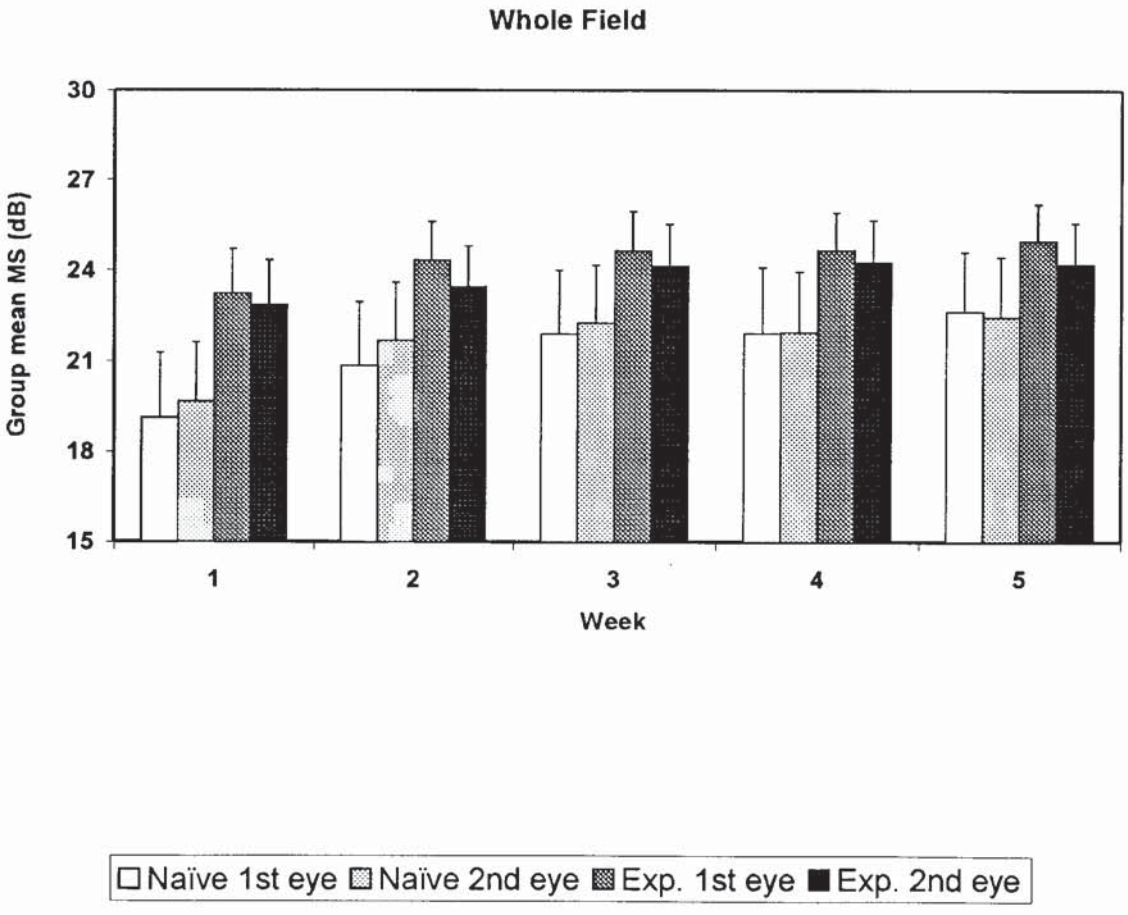


Figure 7.1. The group mean MS for each eye of each group at each of the visits. The error bars represent one standard error of the mean.

For each patient, the percentage change in MS from week 1 was calculated for each eye at each visit. Figure 7.2 shows the group mean percentage change in MS from week 1 for each subsequent visit. At the second visit, the greatest rate of increase in MS occurred in the second eye of the naïve group; the least improvement occurred in the second eye of the experienced group. The relationship between eyes for the experienced group remained constant throughout the 5 visits, improving by approximately 11% for the first eye and by approximately 10% for the second eye, reaching a plateau by visit 3. In the naïve group, the percentage increase in MS relative to week 1 for the right eye continued to increase at each visit reaching 23% at week 5; the left eye stabilised at approximately 13.5% by week 3.

7.4.1.2 Mean Defect

Figure 7.3 shows the group mean MD for each eye of the naïve and experienced groups at each of the visits. The group mean MD for the experienced group was higher than that for the naive group for each eye at each visit. The group mean MD in the first eye of the experienced group increased from 1.5 dB to 3.1 dB over the five weeks with an approximate 1.4 dB increase over the first two visits. For the second eye, the group mean MD increased from 0.9 dB to 2.3 dB and exhibited a steady increase to a plateau at week 3. In the naïve group, the group mean MD at the first visit was -1.5 dB in the first eye and -0.9 dB in the second eye. The group mean MD then became steadily more positive in the first eye until week 5 reaching a value of 1.9 dB; the second eye tended to plateau by week 2 or 3 at a value of approximately 1.4 dB.

For the experienced group, the between-eye difference in group mean MD was similar across all visits. For the naïve group, the first eye showed a more negative MD than the second eye at the first three visits and both eyes had a similar MD at the fourth and fifth visits.

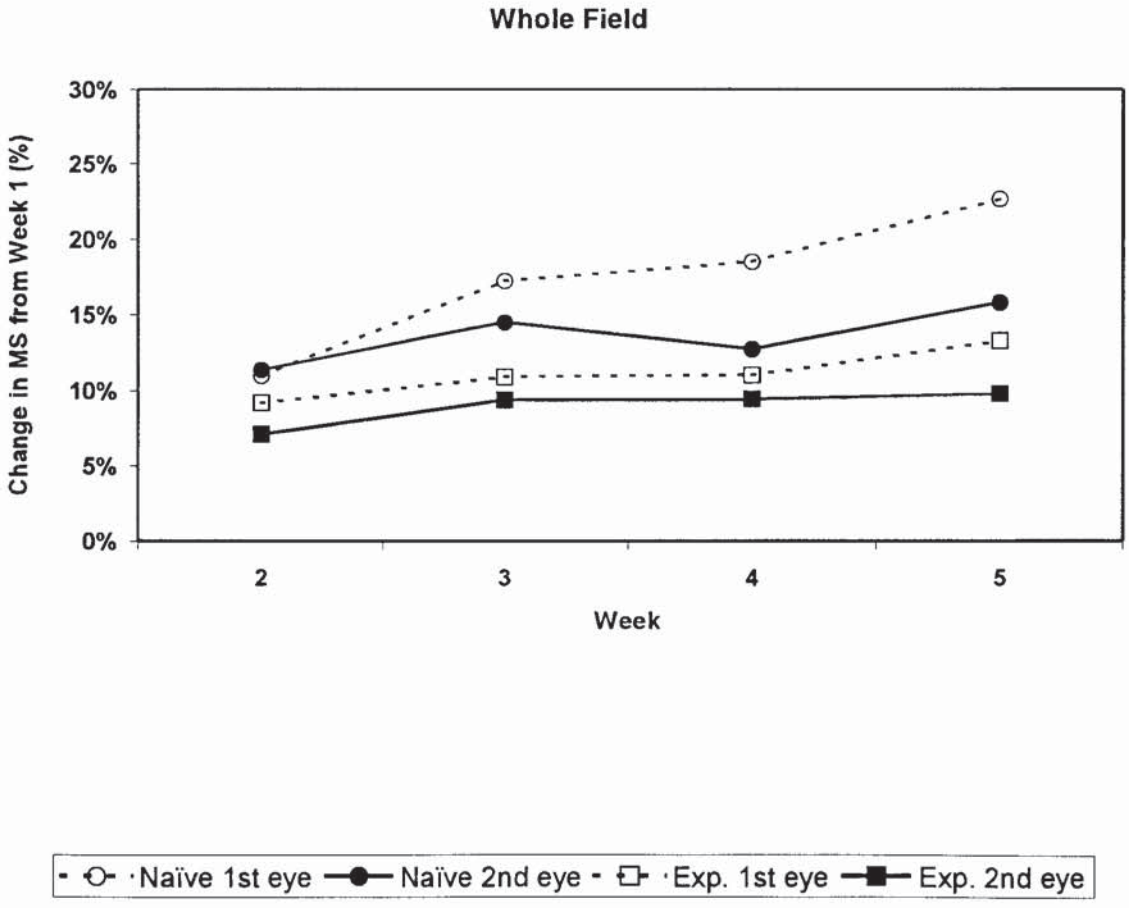


Figure 7.2. The change in group mean MS from week 1 for each eye of each group expressed as a percentage.

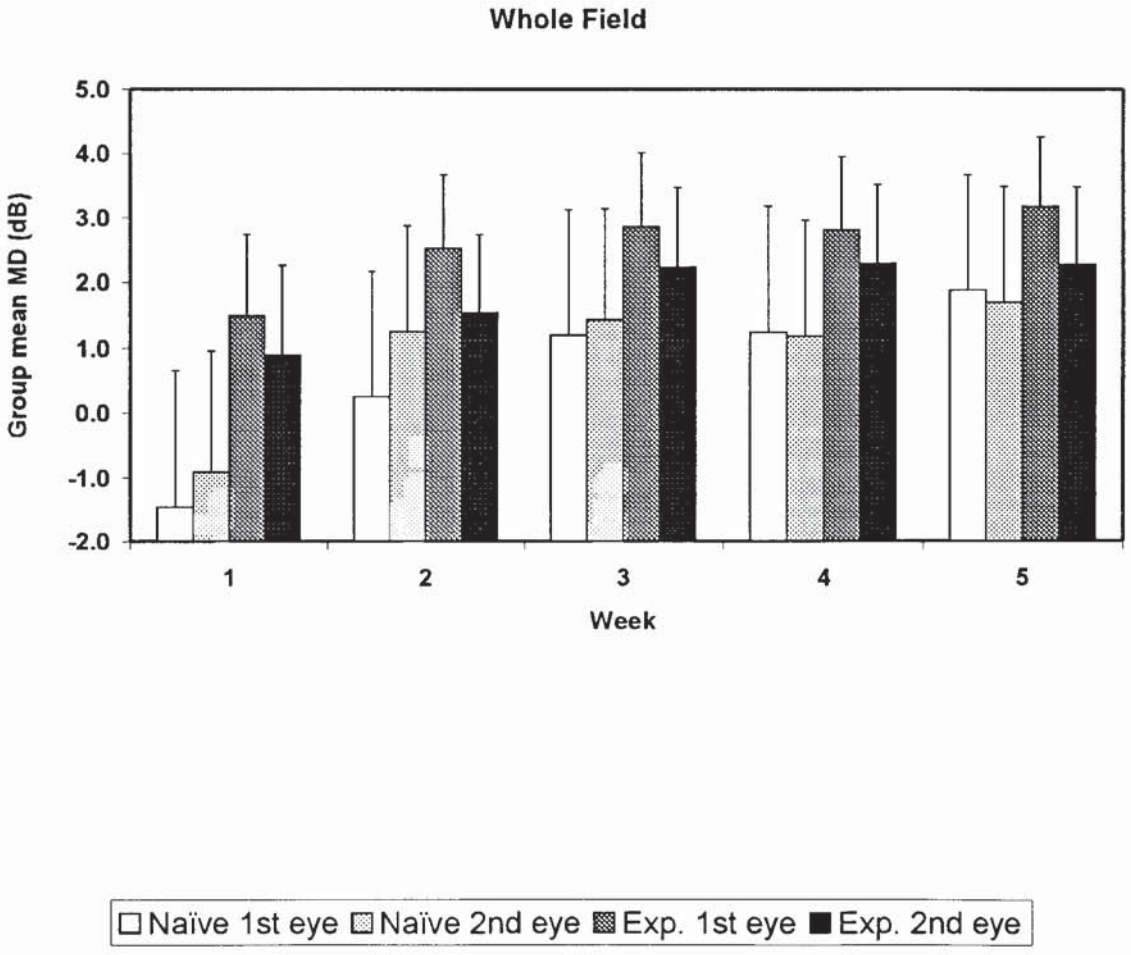


Figure 7.3. The group mean MD for each eye of each group at each of the visits. The error bars represent one standard error of the mean.

Over the five visits, the between-group difference in group mean MD decreased for each eye. The difference in MD between groups for the first eye was 3.0 dB at the first visit and 1.3 dB at week 5 and for the second eye was 1.8 dB at the first visit and 0.6 dB at the final visit. For the first eye, the between-group difference in MD decreased linearly over the five weeks. For the second eye, the reduction in the between-group difference in MD predominantly occurred between the first and second visits.

7.4.1.3 Short-term Fluctuation

Figure 7.4 shows the group mean SF for each eye of each group at each of the visits. At the first visit, the SF was lower in the second eye than in the first eye by 0.3 dB for each group. The SF for both eyes was 0.2 dB lower in the experienced group than in the naïve group. The group mean SF for the experienced group tended to gradually decrease with each visit whereas the SF for the naïve group remained fairly constant. In addition, the between-subject variability in SF was lower for the experienced group at the later visits (indicated by the narrower error bars).

7.4.1.4 Corrected Pattern Standard Deviation

Figure 7.5 gives the group mean CPSD for each eye of each group at each of the visits. In both eyes of each group, the CPSD remained fairly constant over the period of the study. For both eyes, over the five visits, the group mean CPSD for the naïve group was 0.7 dB higher than for the experienced group.

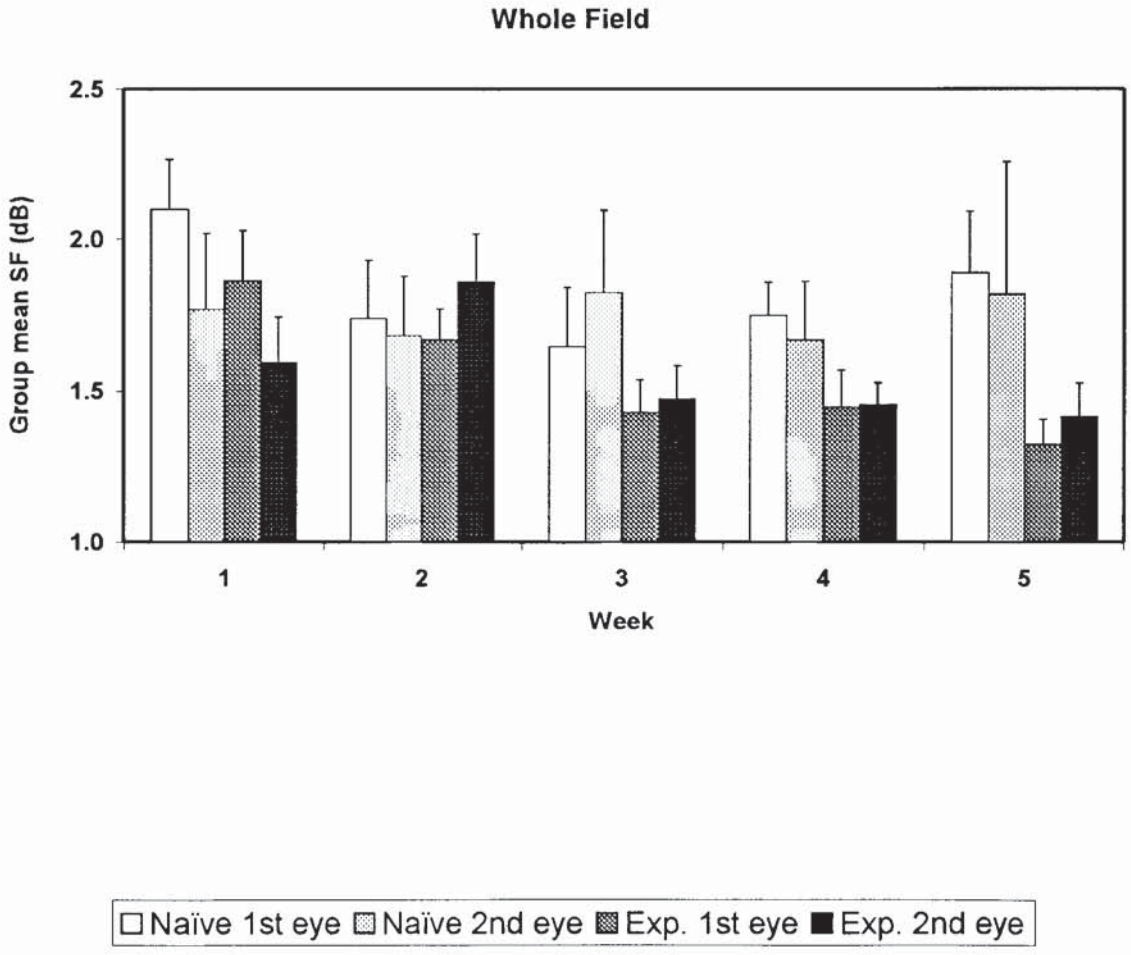


Figure 7.4. The group mean SF for each eye of each group at each of the visits. The error bars represent one standard error of the mean.

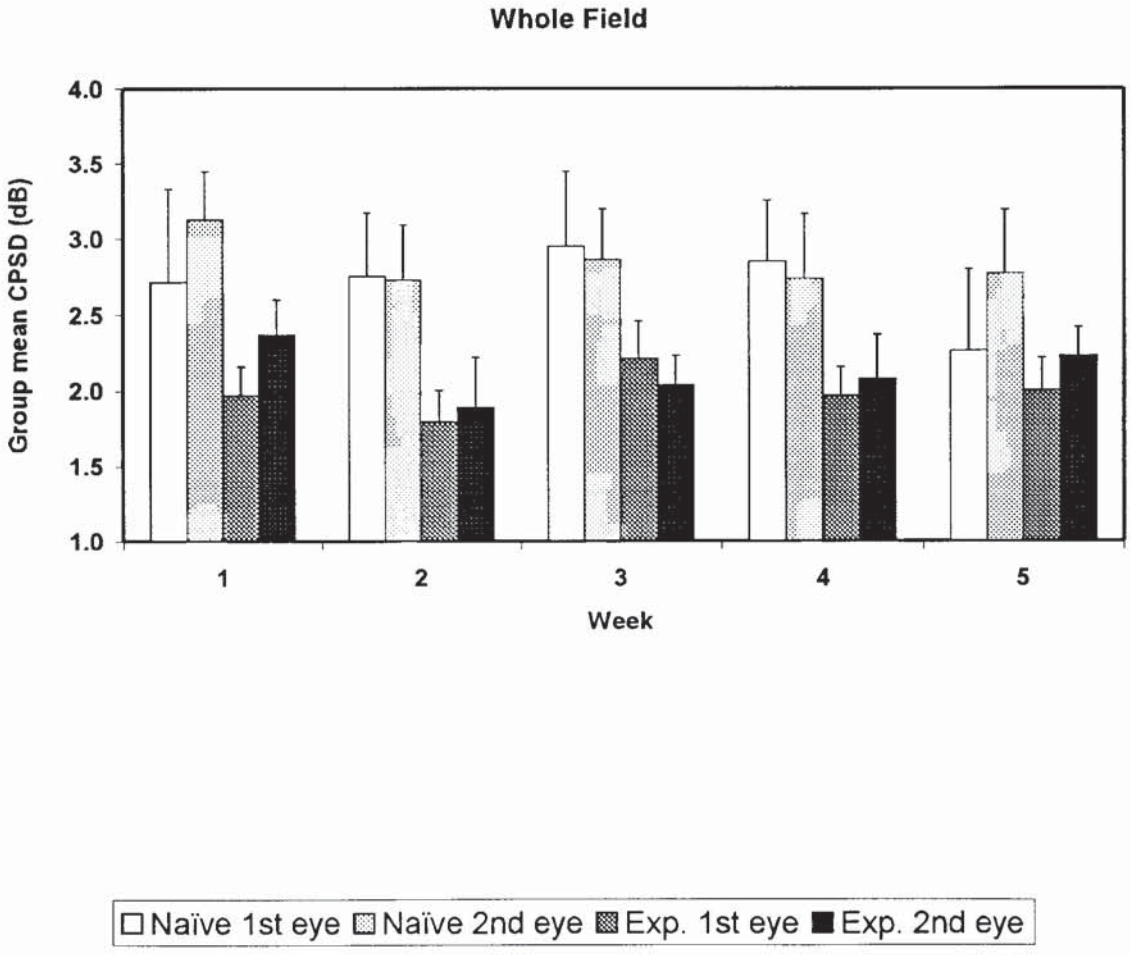


Figure 7.5. The group mean CPSD for each eye of each group at each of the visits. The error bars represent one standard error of the mean.

7.4.2 Regional analysis of MS

7.4.2.1 The effect of eccentricity on MS

The group mean MS for each eye of each group, divided into the central and the peripheral regions of the Program 24-2 stimulus grid are shown in Figure 7.6. The central or peripheral regions are shown in Figure 7.7. For each of the central and the peripheral regions, the same between-eye and between-group trends that were seen in the global MS analysis apply.

For each eye, the difference in group mean MS between centre and periphery is smaller for the experienced group than for the naïve group. For the experienced group, the between-region within-eye difference remained constant throughout the study. However, for both eyes of the naïve group, the between-region difference decreased by approximately 0.5 dB over the five visits; from an initial difference of 4.4 dB to 4.0 dB at the 5th visit in the first eye and from 4.9 dB to 4.3 dB in the second eye.

There is a corresponding change in between-group difference in MS in each region of the visual field. In the central region, the between-group difference was 3.5 dB in the first eye and 2.1 dB in the second eye at the first visit. At week 5, this between-group difference had reduced to 2.1 dB in the first eye and 0.9 dB in the second eye. In the peripheral region, the between-group difference in MS was 4.5 dB for the first eye and 4.0 dB for the second eye at week 1. At week 5, the between-group difference was 2.5 dB for the first eye and 2.4 dB for the second eye.

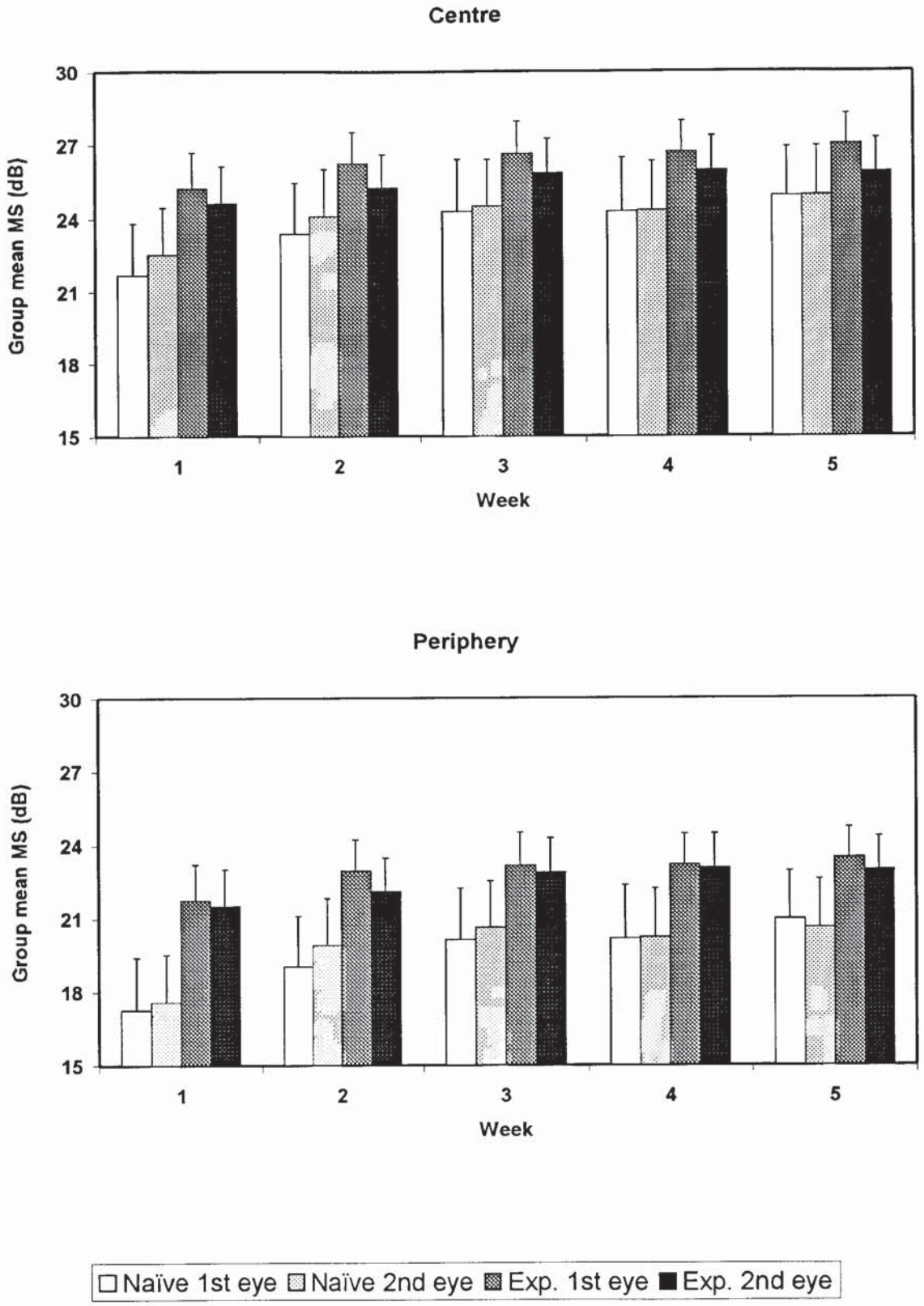


Figure 7.6. The group mean MS for each eye of each group at each of the visits as a function of central and peripheral regions. The error bars represent one standard error of the mean.

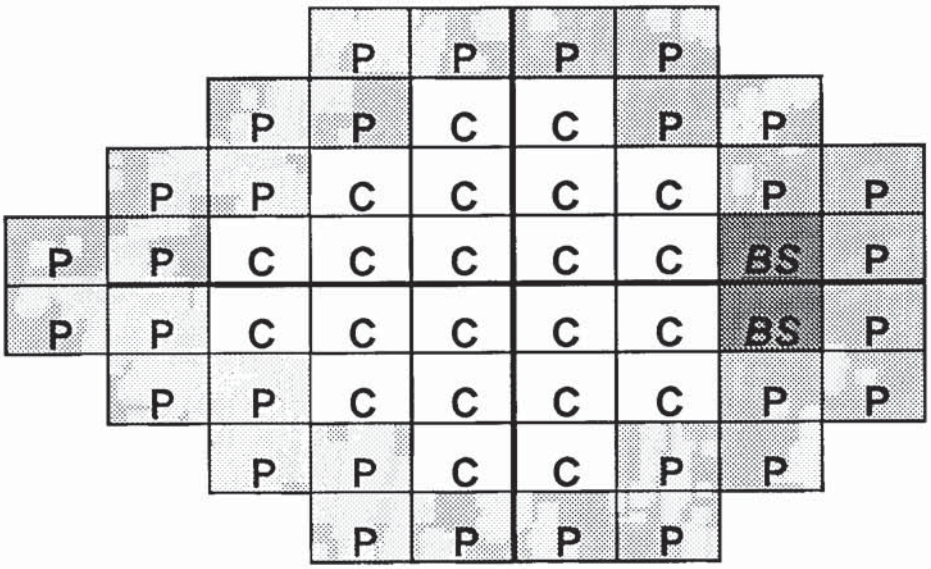


Figure 7.7. The Humphrey Field Analyzer Program 24-2 stimulus grid for the right eye indicating the locations defined as central (C) or peripheral (P). BS indicates blind spot locations excluded from the analysis. Grid for the left eye is a horizontal mirror image.

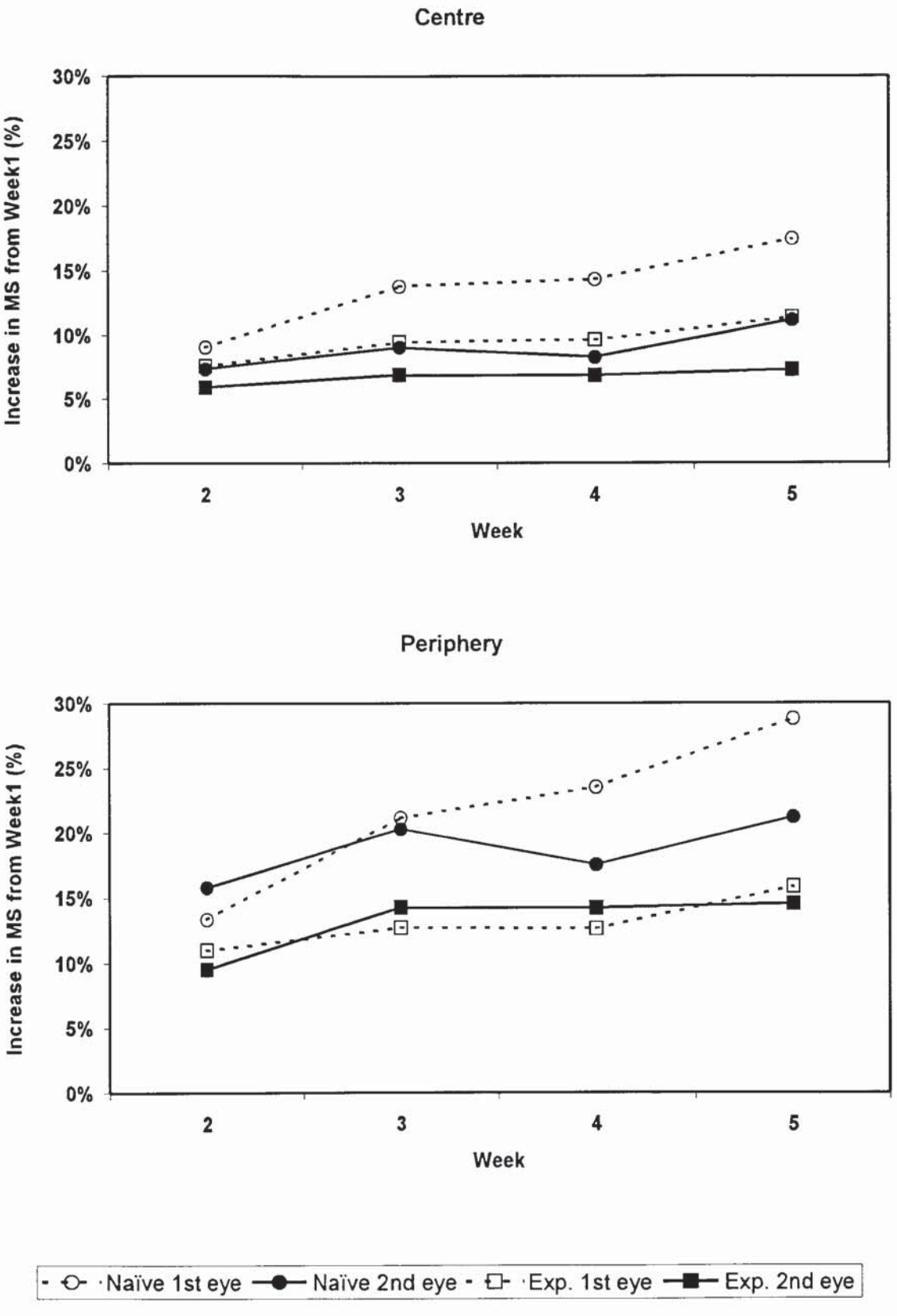


Figure 7.8. The change in group mean MS from week 1 for each eye of each group expressed as a percentage and expressed as a function of central and peripheral regions.

Figure 7.8 shows the group mean MS for the central and peripheral regions, expressed as a percentage increase from week one. All eyes, except the first eye from the naïve group, revealed a steady increase in group mean MS reaching a plateau at week 3 for both central and peripheral regions of the field. The group mean MS for the first eye of the naïve group increased throughout each visit. In all eyes, the increase in sensitivity was greater for the peripheral region than for the central region. For the naïve group, the peripheral increase in sensitivity (first eye 29%, second eye 20%) was twice that of the increase centrally (first eye 15%, second eye 10%). In the experienced group, the between-region difference in MS was smaller for the first eye (14% peripherally to 10% centrally) than for the second eye (14% peripherally to 7% centrally).

Therefore, the group mean MS for the peripheral region of the naïve group increased at a greater rate than the central region and the naïve group mean MS increased at a greater rate than the experienced group in both regions.

7.4.2.2 Quadrant analysis

Figure 7.9 shows the same graphical analysis of the group mean MS as in previous figures, but divided into the four quadrants of the visual field. It can be seen that the superior quadrants generally have a lower group mean MS than the inferior quadrants and that the nasal and temporal quadrants generally have a similar group mean MS. However, the group mean MS in the superior nasal and the inferior nasal quadrants of the first eye at the first visit in the naïve group is 1 dB lower than the superior temporal and inferior quadrants respectively.

The percentage increase in MS from week one for each quadrant is shown in Figure 7.10. In all quadrants, the first eye of the naïve group continued to increase over the five visits whilst all other eyes tended to reach a plateau by the third visit. For all eyes, the general trend is towards a greater percentage increase in MS for the superior quadrants than for the inferior quadrants by approximately 4.5%. The percentage increase in MS for the inferior nasal quadrant was 3.5% greater than for the inferior temporal quadrant. In the superior nasal

quadrant, both the naïve eyes showed a greater increase in sensitivity than the experienced eyes. In the superior temporal quadrant, the first eye of each group showed a greater increase in sensitivity than the second eye for both groups. In both superior quadrants, the smallest increase in sensitivity was seen for the second eye of the experienced group.

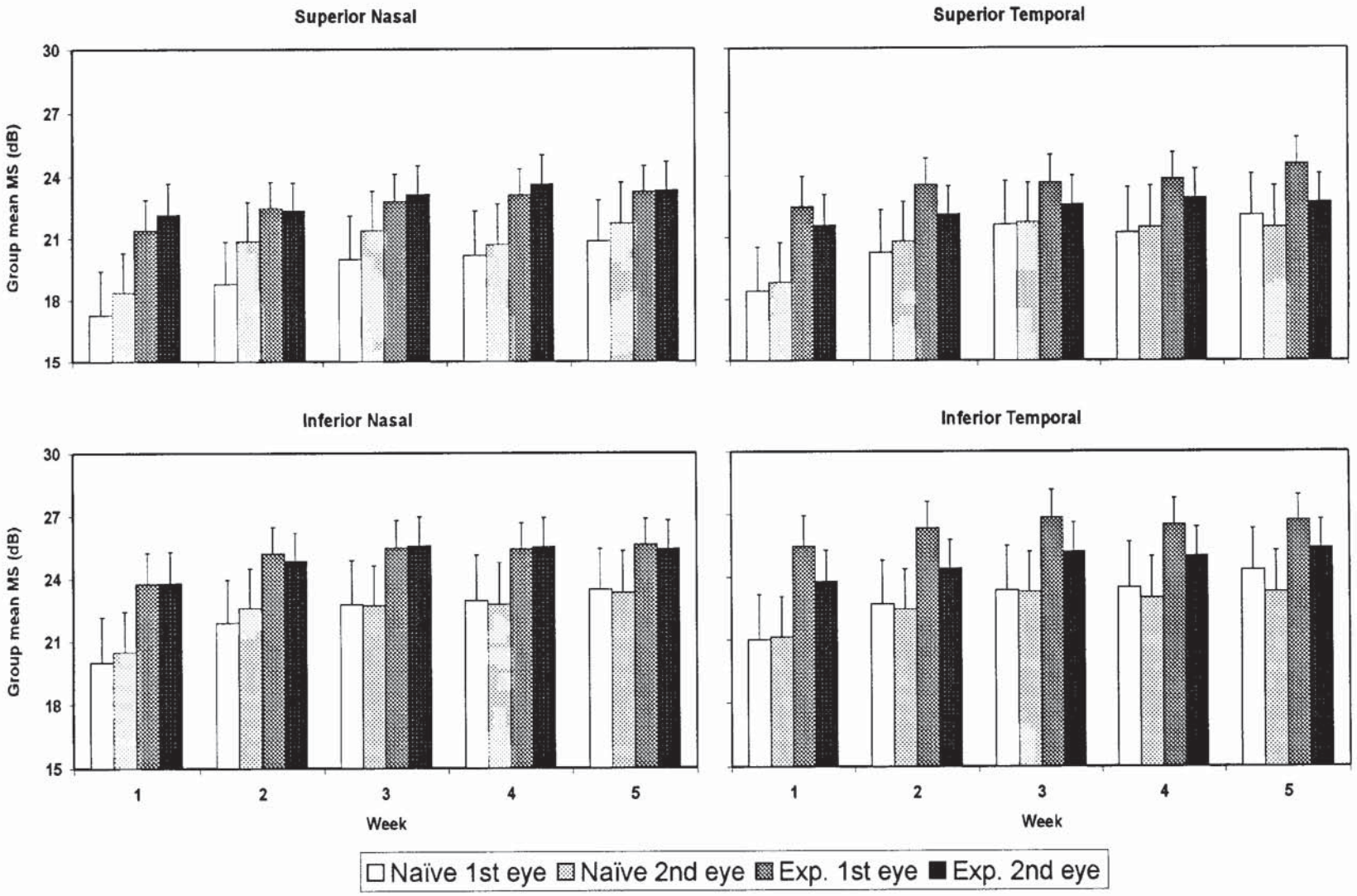


Figure 7.9. The group mean MS for each eye of each group at each of the visits expressed as a function of quadrant.

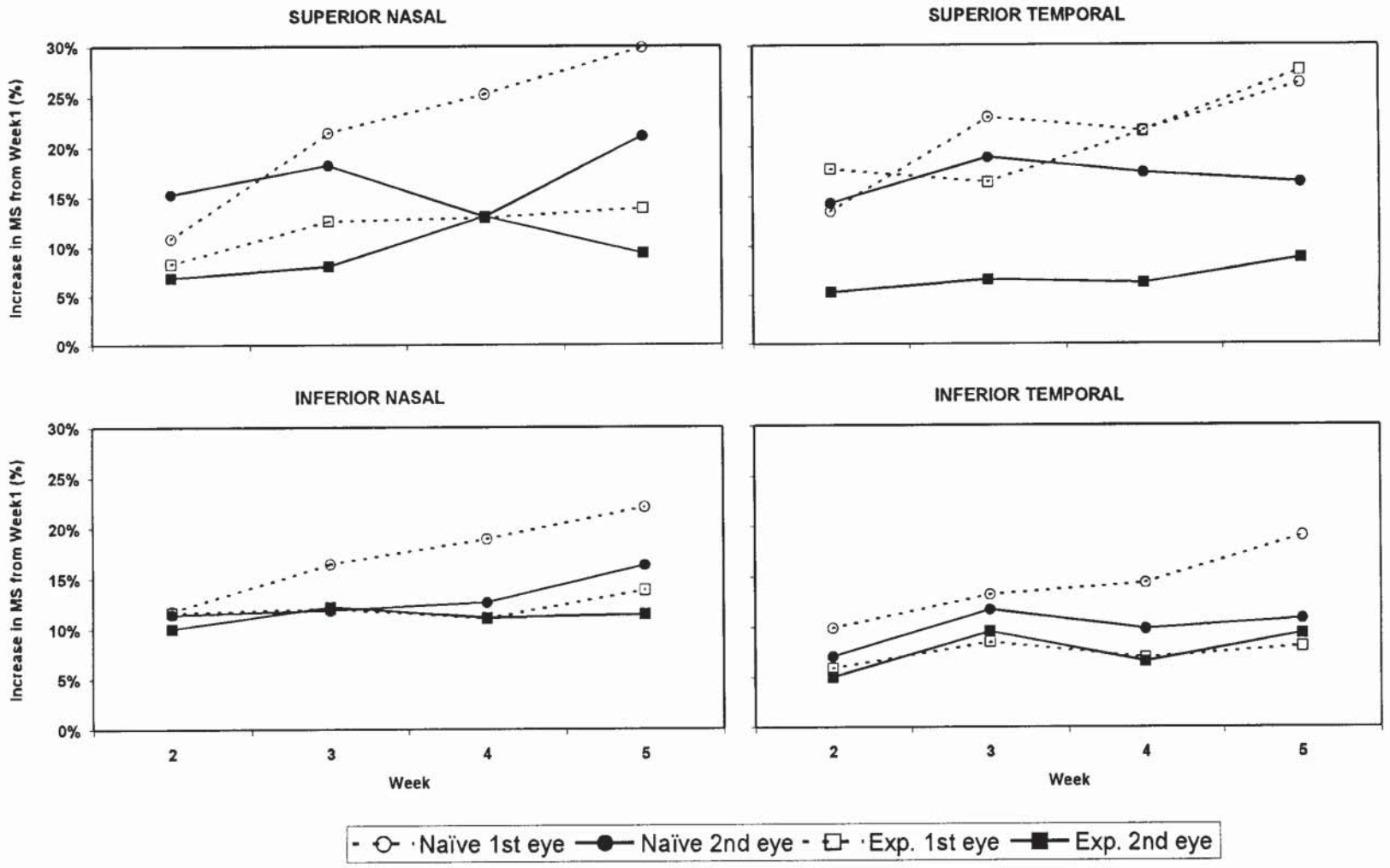


Figure 7.10. The change in group mean MS from week 1 for each eye of each group expressed as a percentage and expressed as a function of quadrant.

7.5 Discussion

The results have been described qualitatively. The use of ANOVA was considered inappropriate due to the incomplete nature of the study. It had been hoped that the sample sizes would exceed twenty patients in each of the naïve and experienced groups. In addition, it was also hoped to investigate the learning effect in a sample of glaucoma patients with early visual field loss, divided into naïve and experienced groups. However, considerable difficulties were encountered recruiting suitable patients, especially for the naïve groups. At the start of the study, one of the hospitals used for patient recruitment operated an early diagnostic clinic for new referrals to the Hospital Eye Service from optometrists and general practitioners. This particular clinic used semi-automated supra-threshold visual field screening with the Henson 4000 central field screener, in addition to measuring intraocular pressure and examination of the optic nerve head. Thus, it was possible to recruit patients who were naïve to automated threshold perimetry. After some initial success with patient recruitment, the early diagnostic clinic then began using automated threshold perimetry as the method of examining visual function, thus, eliminating the main source of naïve patients. Only three naïve glaucoma patients had completed the five visits and since the results from such a small sample would be inconclusive, their data have not been presented.

Retrospectively, the exclusion criteria used for the study may have been too stringent, specifically with regards to the level of visual acuity and the degree of age-related lenticular changes permitted. The original rationale for the selection of the exclusion criteria was to eliminate significant potential variation in the results due to media absorption. Therefore, the exclusion criteria for visual acuity and age-related lenticular changes were chosen to provide a sample in which media absorption and light scatter would be negligible. It had also been intended to include only high-risk OHT patients. As the study progressed, the inclusion of medium-risk and then low-risk OHT patients was permitted with the aim of increasing the sample sizes. The recruitment of experienced observers was easier as it was possible to search the hospital records for suitable patients.

There were also incidences, of course, when suitable patients were found who could not or would not participate in the study. The study requires a great deal of commitment from the patients in order to attend on the same day for five consecutive weeks. This required level of commitment also eliminated a number of prospective patients. In addition, there were four naïve and three experienced OHT patients who were unable to complete the study. Generally, only one or two visits were completed and the results have been excluded from the analysis.

Despite the limitations due to sample size, the results tend to indicate that there is a learning effect in SWAP and that the learning effect is present irrespective of any prior experience with conventional W-W perimetry. For both groups, the MS and MD increased over at least the first three weekly examinations with SWAP. The magnitude of the learning effect reported here (1.5 to 3.5 dB) is in the lower half of the 1 to 10 dB increase seen in W-W perimetry (Wood, et al. 1987b, Heijl, et al. 1989c, Searle, et al. 1991, Heijl and Bengtsson 1996) but greater than the 0.7 dB increase reported in normal subjects for SWAP (Wild and Moss 1996).

The learning effect and the fatigue effect coexist during an automated perimetric examination (Brenton and Phelps 1986, Searle, et al. 1991, Wild, et al. 1991, Hudson, et al. 1994). At the baseline examinations the learning effect is greater than the fatigue effect and therefore imparts the greater influence over the initial series of examinations. Following the elimination of the learning effect after repeated examinations, the fatigue effect influences the results both within and between eyes.

The naïve group exhibited a higher initial sensitivity and rate of increase in sensitivity in the second eye compared to the first eye. This is evidence for a between-eye learning effect in SWAP. By week 3, the sensitivity of the first eye had reached the same magnitude as the second eye and continued to increase whereas the second eye did not increase further throughout the remaining visits. This indicates that the between-eye fatigue effect may be significant for SWAP as the learning effect continues longer in the first eye and the sensitivity

of the second eye is unable to increase further. The higher sensitivity seen in the first eye than in the second eye in the experienced group indicates that the fatigue effect may have been evident in this group from the first visit.

It is possible that the naïve and experienced groups could be conceived as subsets of a longer process than can be seen in five visits. Initially, the naïve patient would be unaware of the requirements of the test and their performance would be below full capability. For the examination of the second eye at the first test, the learning effect is evident as the sensitivity is seen to increase. The learning effect produces an increase in sensitivity in both eyes until the fatigue effect for the second eye limits the improvement in sensitivity, represented by the plateau for the second eye of the naïve group. As fatigue affects the second eye within a visit to a greater extent than the first eye (Hudson, et al. 1994), the learning effect may continue in the first eye for a greater number of examinations than in the second eye, until reaching a plateau, as evidenced by week 3 in the experienced group.

The influence of the risk factor on the magnitude of the learning effect could not be evaluated due to the limited sample size within the study. However, none of the individuals showed a SWAP defect as determined by STATPAC for SWAP at the completion of the five week period.

The difference in MS between the naïve and experienced groups could be attributed in part to differences in the mean age of the sample. The mean age of the experienced group was approximately 6 years younger than that of the naïve group. However, the age difference is unlikely to account for the approximate 3.5 dB difference in initial sensitivity between the two groups. For each decade increase in age, the increase in ocular media absorption for short-wavelengths is 0.03 to 0.06 log units and the decrease in SWS sensitivity is 0.05 to 0.09 log units (Johnson, et al. 1988a). In normal subjects, the decline in sensitivity for SWAP is approximately 1.9 dB per decade without correction for variations in ocular media absorption (Wild, et al. 1998).

The presence of a learning effect for SWAP in the experienced group is likely to be due to the difference in stimulus parameters from W-W perimetry and may be due to differences in the subjective criterion for the detection of the SWAP stimulus compared to the W-W stimulus. The higher background luminance used with SWAP may exaggerate the Troxler effect compared to W-W perimetry. The Troxler effect occurs in the presence of a between-eye difference in intensity of 0.75 log units (Bolanowski and Doty 1987, Fuhr, et al. 1990). For W-W perimetry with the Humphrey Field Analyzer, using an opaque occluder in front of the non-tested eye, the between eye difference in intensity is 1 log unit. The 100 cdm^{-2} background luminance of the commercially available version of SWAP would result in a 2 log unit difference in intensity between-eyes. Therefore, patients experienced in W-W perimetry would have to adapt their blink rate or attention to counteract the higher incidence of the Troxler effect in SWAP. The use of a translucent occluder has been shown to improve performance in W-W perimetry (Fuhr, et al. 1990). The use of a translucent occluder with SWAP may reduce the fatigue effect and the inherent variability associated with the technique; although, this requires further investigation. The different stimulus with SWAP also requires a different criterion for detection. Detection of the size III white stimulus is based mostly on the detection of the edge contrast with the white background. Detection of the blue size V stimulus is based mainly on the chromatic contrast with the yellow background (Felius, et al. 1995a). This criterion is in accordance with the fact that the blue stimulus is more resistant to optical defocus (Johnson, et al. 1993a). Patients who are experienced in W-W perimetry would therefore have to adopt a different criterion for detection to that previously utilised. However, such patients would be familiar with the general principles of perimetry and would be conversant with the procedure for responding to a stimulus. This would serve to give the experienced patient an advantage over the naïve patient and could explain why the learning effect is less in the experienced group than in the naïve group.

There is also a mathematical element to the greater learning effect seen in the naïve patients relative to the experienced patients. The naïve group initially has a lower MS than the experienced group and therefore the same absolute increase in sensitivity would create a

larger percentage increase than that calculated for the experienced group with a larger initial MS. However, the magnitude of the absolute increase in sensitivity was also generally greater in the naïve group than that seen in the experienced group. The between-group difference in SF also indicates that the experienced group was more consistent with their responses during each examination. This factor has been previously observed in the learning effect (Wood, et al. 1987b, Werner, et al. 1988, Heijl, et al. 1989c, Wild, et al. 1989b, Autzen and Work 1990, Werner, et al. 1990, Marchini, et al. 1991, Wild and Moss 1996).

The analysis of MD was performed to reduce the effect of differences in patient age within- and between- the two groups. The trends observed in the analysis of MD did not differ appreciably from the analysis of MS thus indicating that the learning effect is likely to be independent of age. However, this supposition requires further investigation with a larger sample and a controlled range of ages. The similarity between the MS and MD results support the use of MS in investigating the secondary effects of eccentricity and regional differences in the learning effect.

The analysis of the regional differences in the learning effect for SWAP revealed that the peripheral stimulus locations exhibit a significantly greater increase in sensitivity than the more central locations for both groups. This finding is consistent with the greater learning effect in peripheral regions for W-W perimetry (Wood, et al. 1987b, Heijl, et al. 1989c, Kulze, et al. 1990, Heijl and Bengtsson 1996). The observation that the learning effect in the peripheral field is greater for the naïve group than in the experienced group reinforces the need to ensure adequate perimetric regimes before changes in patient management are sanctioned. The apparent correlation of learning with increasing eccentricity is particularly relevant since the trends seen in this study are manifest at eccentricities of less than 24 degrees, i.e. within the stimulus location grid of Program 24-2.

The greater learning effect for SWAP in the superior quadrants compared to the inferior quadrants is also in agreement with W-W perimetry (Wood, et al. 1987b). It has been

suggested that the initial field loss seen for SWAP occurs in the superior nasal quadrant (Sample and Weinreb 1990, Sample, et al. 1993) and that the normal SWAP profile is steepest in the superior hemifield (Sample, et al. 1997). The results of this study also indicate that the initial sensitivity is lower in the superior nasal field, especially in the naïve group. However, this region of the visual field also showed the greatest improvement in sensitivity over the five visits.

7.6 Conclusions

A learning effect for SWAP is present in patients naïve to automated W-W perimetry and in patients who have undertaken a number of W-W examinations. Those patients who have experience with automated W-W perimetry show a smaller improvement in performance than the patients with who lack experience with automated W-W perimetry. The learning effect is greater in the more peripheral stimulus locations and in the superior hemifield. The learning effect can continue over at least five visits but even patients who are experienced perimetric observers may still require at least three examinations to eliminate the possibility of the erroneous diagnosis of SWAP defects. The initial SWAP visual field from a patient may show a global reduction in sensitivity which may also include the presence of localised reductions in sensitivity, especially in the superior quadrants, giving the appearance of apparent diffuse and/or focal loss. However, any such apparent defects may disappear after the learning effect has diminished.

CHAPTER 8. SUMMARY, CONCLUSIONS AND FUTURE WORK

8.1 Summary of results and conclusions

8.1.1 The between-algorithm, between-individual differences in normal perimetric sensitivity

The ideal strategy for automated perimetry would determine the sensitivity at a large number of stimulus locations, with a short examination duration and a high degree of accuracy and precision. The most popular threshold algorithms used by modern perimeters are a compromise between the length of examination duration required for the accurate estimation of threshold, the maintenance of a high level of patient compliance and the current restraints on healthcare provisions. The 'gold standard' strategy is the 4-2 dB double reversal staircase, incorporated into the Humphrey Field Analyzer as the Full Threshold algorithm. In the normal eye, the Full Threshold algorithm takes in the region of 15 minutes to threshold 76 locations within an eccentricity of 27 degrees. With these long examination durations, the fatigue effect and a reduction in patient compliance are major factors inhibiting the interpretation of the visual field. A second generation of threshold algorithms, for example FASTPAC and the Dynamic Strategy, was developed with the aim of reducing the examination duration. However, these faster algorithms exhibit a reduction in the accuracy and precision of threshold determination, often resulting in an underestimation of the depth and area of field loss. A third generation of threshold algorithms, SITA, has become commercially available for the Humphrey Field Analyzer 750. SITA is claimed to reduce the examination duration without loss of accuracy. Two versions of SITA are available, SITA Standard and SITA Fast, which are analogous, in the estimation of threshold, to Full Threshold and FASTPAC respectively. A study was undertaken to determine the variability in the measurement of normal sensitivity associated with SITA compared to that of the first and second generation of threshold algorithms. The examination duration for SITA Standard and SITA Fast was 50% of that for Full Threshold and FASTPAC respectively. Both SITA algorithms produced a higher mean sensitivity than either the Full Threshold or the FASTPAC algorithms. The difference in sensitivity could be attributed to the systematic differences in threshold estimation between SITA and the Full Threshold and FASTPAC

algorithms. SITA calculates the threshold as the stimulus intensity that has a 50% probability of seeing from the FOS curve. The Full Threshold and FASTPAC strategies determine threshold as the last stimulus intensity seen after the final staircase step crosses threshold. The difference in measured sensitivity was uniform over the stimulus locations examined, indicating that the shape of the hill of vision is similar for each of the algorithms within, approximately, the central 21 degrees. The between-subject variability of threshold estimation was lower for the two versions of SITA than for either Full Threshold or FASTPAC. This indicates that the confidence limits for normality are likely to be narrower. It was concluded that the reduction in examination duration, leading to a probable reduction in the perimetric fatigue effect, and the likely narrower confidence limits for normality would identify visual field loss statistically sooner with SITA than with either the Full Threshold or the FASTPAC algorithms.

8.1.2 The validity and reproducibility of perimetric threshold algorithms in glaucoma

The influence of the reduced examination duration and the narrower confidence limits for normality associated with SITA in the determination of visual field loss in glaucoma patients were investigated using the commercially released age-matched normative database. The differences in mean sensitivity between the SITA algorithms and the Full Threshold and FASTPAC algorithms were similar to the theoretical differences due to the systematic disparities for threshold estimation. The clinical insignificance of the systematic difference in sensitivity between the algorithms was apparent by the identical global deviations from the age-matched hill of vision for each of the algorithms. Each of the algorithms suffered equally from the inherent variability in pointwise sensitivities between 20 dB and 10 dB. The between-algorithm within-visit variability in sensitivity for each of the algorithms was similar to the between-visit within-algorithm variability in sensitivity. Thus, the difference between algorithms in measured sensitivity was clinically insignificant when compared to the test-retest repeatability of a given algorithm. Analysis of the Pattern Deviation probability values showed that the SITA algorithms assigned a greater degree of significance to the depth

and/or width of visual field defects than the Full Threshold and FASTPAC algorithms. The greater degree of significance for the field defects with SITA was attributed to the narrower confidence limits and was attributed to a possible reduction in the fatigue effect.

8.1.3 The effect of patient fatigue on the visual field derived with SITA

It was suggested in Chapters 3 and 4 that the shorter examination duration of SITA, compared to Full Threshold and FASTPAC, would improve the quality of visual fields due to a reduction in the fatigue effect. A study was undertaken to investigate the influence of patient fatigue on the visual field obtained with the SITA Standard and Full Threshold algorithms in normal subjects and in glaucoma patients. A custom program was designed, for use with the Full Threshold algorithm, to obtain thresholds at half of the stimulus locations from the Humphrey Field Analyzer Program 30-2 stimulus configuration. This design permitted the evaluation of the fatigue effect for two different paradigms: for a controlled examination duration or for a fixed number of stimulus locations. The fatigue effect primarily occurred within the first eight minutes of perimetry irrespective of the threshold algorithm employed. The fatigue effect was greater in glaucoma patients than in normal subjects, regardless of the protocol. Therefore, the higher recorded sensitivity and the lower between-subject variability with SITA compared to the Full Threshold and FASTPAC algorithms cannot be attributed to a reduction in the fatigue effect with SITA.

8.1.4 Fixation variability with static and roving fixation targets

One of the factors associated with poor patient compliance in automated perimetry is the requirement for the patient to maintain steady fixation for several minutes. Inaccurate fixation could lead to an underestimation of visual field defects and of normal sensitivity. As a consequence, the technique of roving fixation has been developed for perimetry. The roving fixation technique is preferred by patients and, as such, is becoming popular as a method of maintaining fixation for perimetry in general practice. A study was undertaken to evaluate the accuracy of fixation, of normal subjects and glaucoma patients, during a perimetric

examination with a roving fixation target relative to a static fixation target. The roving fixation technique was shown to be associated with a greater rate of fixation losses, measured with the Heijl-Krakau fixation monitor, and with an underestimation of the depth of the physiological blind spot compared to that with static fixation. It was concluded that the roving fixation technique may also underestimate the magnitude of defect depth and as such should not be advocated for routine clinical use.

8.1.5 The effect of previous perimetric experience on baseline short-wavelength automated perimetry examination

The increasing amount of research indicating the benefit of SWAP for the diagnosis and follow-up of glaucoma means that SWAP may be requested for patients with a wide range of experience with conventional W-W automated static perimetry. The influence of previous perimetric experience with W-W perimetry on the outcome of SWAP is unknown. A study was therefore undertaken to determine the learning effect for SWAP in OHT patients experienced in W-W perimetry and in patients naïve to any form of automated threshold perimetry. A learning effect was present in both groups of patients. The magnitude of the learning effect in the naïve group was twice that of the experienced group. The learning effect was greater at the more peripheral stimulus locations and in the superior hemifield. The learning effect could be present over at least five visits but in patients who are experienced perimetric observers, it was generally minimised after three visits. It was concluded that the reduction in sensitivity recorded at initial SWAP examinations may give the appearance of visual field defects and that these apparent defects may be reduced or even disappear when the learning effect has been eliminated.

8.2 Future work

8.2.1 The development of perimetric threshold algorithms

SITA Standard uses a 4-2 dB step size to alter the intensity of stimuli presented during an examination and SITA Fast uses a 4 dB step size. The threshold is calculated from the responses of the patient to all of the stimulus presentations following a predetermined number of staircase reversals or interruption of the staircase if the responses are within a predetermined level of accuracy, as defined by the Error Related Factor (ERF). The similar levels of between-visit variability seen in SITA compared with the Full Threshold and FASTPAC algorithms may be due to the effect of the ERF at the lower sensitivity values seen in glaucoma. It is likely that the ERF exerts a greater influence on the measurement of sensitivities close to the age-matched normal value. The influence of different levels of the ERF at the various levels of sensitivity seen in glaucoma is unknown. In order to counter a possible longer test duration, which would be associated with an increase in the accuracy of threshold estimation by tuning the ERF, the use of variable staircase step sizes may improve the efficiency of SITA further.

The confidence limits for the analysis of progressive visual field loss associated with the SITA algorithms will need to be determined. The extent of any between-algorithm differences in the magnitude of these confidence limits is unknown.

The influence of fatigue the effect would appear to be independent of algorithm. The effect of fatigue on the second eye during a clinical examination with SITA requires investigation. The effect of fatigue on the FOS curves for perimetry is also unknown. Investigation of the changes in the FOS curves as patients become tired may reduce the variability of SITA even further. This would especially be true at the more peripheral locations in the central visual field as the thresholds at these locations are routinely estimated at the end of the examination.

8.2.2 The effect of previous perimetric experience on baseline short-wavelength automated perimetry examination

The recruitment of patients for this study should be continued and the inclusion criteria should be relaxed to allow a higher degree of lenticular changes that would be representative of the general population. If possible, naïve patients could be enrolled at their initial visit to the Hospital Eye Service and the five SWAP fields be obtained prior to a W-W perimetric examination. The recruitment of patients with either OHT or glaucoma and experienced in automated perimetry should be continued in order to determine the effect of OHT risk factor or the extent of field defect on the learning effect in SWAP.

8.2.3 SWAP

The greater within- and between-subject variability in the measurement of sensitivity for SWAP compared to W-W perimetry further limits the application of SWAP to routine clinical practice. The application of a more sophisticated threshold algorithm, SITA, to W-W perimetry has been associated with a reduction in the between-subject variability of threshold estimation. This improvement was based, in part, upon prior knowledge on the nature of the FOS curves together with extensive knowledge of normal and abnormal visual fields. The detailed investigation of the FOS curves in SWAP would lead to an adaptation of SITA for use in SWAP and should reduce the between-subject variability associated with this technique.

The reduction in the variability of threshold estimation in SWAP could be combined with data analysis that does not rely upon comparison to age-matched normal values. Image analysis techniques extract localised information from a single field and therefore may be applied with success to SWAP.

It is possible that the more variable response in SWAP may not be sufficiently overcome by improving the method of threshold estimation or by analysis of the results. This could be due to the effect of media absorption and light scatter on the stimulus used in perimetry. The

evaluation of characteristics of the ocular media have traditionally been time consuming requiring the dark adaptation the patient or requiring sophisticated equipment. The development of other psychophysical tests that can account for the effect of ocular media changes may be of greater benefit for the detection of early visual function changes. For example, measuring isoluminant colour contrast sensitivity has been shown to exhibit a high level of sensitivity and specificity for the identification of glaucoma. The stimulus is adapted for each patient to take into preferential absorption of short-wavelength light. The procedure generally used, a heterochromatic flicker brightness test, is relatively quick and uses the same apparatus as is used for the rest of the test. In addition, the stimuli used are modulated along the tritanopic colour confusion axis (or any colour confusion axis) and do not rely upon adaptation techniques and therefore do not require a high background luminances. This may have the effect of reducing the fatigue effect.

The development of the SITA algorithms for conventional W-W automated perimetry represents an exciting challenge in both research and clinical practice. In particular the development of the SITA thresholding procedures for SWAP is eagerly awaited. The concomitant development of novel perimetric techniques such as Frequency Doubling Perimetry may provide earlier opportunities for the earlier detection of damage and of the detection of progressive loss in glaucoma. Such techniques may be appropriate for the investigation of glaucomatous damage selective to the larger ganglion cell fibres or based upon the theory of reduced redundancy. In addition, the development of imaging techniques for the investigation of optic nerve head and nerve fibre layer structure provides further opportunity for research concerning the structural and functional relationships in glaucoma. Considerable scope therefore exists for research in automated perimetry.

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APPENDIX: A.1

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