SUPRA-THRESHOLD CONTRAST PERCEPTION

IN GLAUCOMATOUS AND NORMAL HUMAN SUBJECTS

by

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SUPRA-THRESHOLD CONTRAST PERCEPTION IN

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ABSTRACT

SUPRA-THRESHOLD CONTRAST PERCEPTION IN GLAUCOMATOUS AND NORMAL HUMAN SUBJECTS

The lateral inhibition mechanism of the sensorineural retina provides our visual system with a mean to sharpen the boundary between different luminances. Contrast is defined as the ratio of the difference in the luminance of two adjacent areas to the summation these luminance values. Contrast sensitivity is a measure of the ability of an individual to detect a difference in the luminance between two areas.

Especially in the early stages of the chronic open angle glaucoma, contrast sensitivity changes are seen earlier that visual field and optic nerve head changes. The usefulness and benefit of contrast-sensitivity testing include uncovering the hidden loss of vision not apparent through other visual evaluations, providing a visual method to monitor the impact of treatment intervention, and providing insights into the extent of patients' visual disability and functional performance problems.

The simultaneous lightness contrast (SLC) effect demonstrates that the lightness of an object depends on its immediate surround. A region seen against a dark background looks lighter than an identical region seen against a light background.

A modified SLC test was used to uncover the changes in the normal enhancement of contrast increments and decrements, due to deleterious effects of the glaucoma on neurosensorial retina. Both normal and glaucomatous subjects were found to overestimate contrast decrements in a similar manner. However, glaucomatous subjects failed to demonstrate enhancement of the contrast increments, except for the largest increment. The test seem to detect the supra-threshold contrast sensitivity changes that occur before the visual field defects appear and classical threshold contrast sensitivity tests appear abnormal. It can be the first-line test in early stage and suspected glaucoma cases. Additionally, other subjective visual assessment tests performed on glaucomatous patients should be revised based on this concept.

Keywords: Contrast sensitivity function, glaucoma, simultaneous lightness contrast, supra-threshold contrast perception

ÖZET

GLOKOMLU VE NORMAL OLGULARDA

EŞİK-ÜSTÜ KONTRAST ALGILANMASI

Sensörinöral retinanın lateral inhibisyon mekanizması, görme sistemimizin farklı aydınlatma bölgeleri arasındaki sınırı keskinleştirmesine izin verir. Kontrast, komşu iki bölgenin aydınlatmalarının farkının, bu aydınlatma değerlerinin toplamına oranı olarak tanımlanır. Kontrast duyarlılık, kişinin iki alan arasındaki aydınlatma farkını saptayabilme kabiliyetidir.

Özellikle kronik açık açılı glokomun erken evrelerinde, kontrast duyarlılık değişiklikleri, görme alanı ve optik sinir başı değişikliklerinden daha önce görülür. Kontrast duyarlılık testlerinin yararları arasında; diğer görsel değerlendirmeler ile gösterilemeyen gizli görme kayıplarının saptanabilmesi, tedavi sonuçlarının takip edilmesine olanak vermesi, hastanın görsel yetersizlik ve fonksiyonel performans problemlerinin ortaya çıkarılabilmesi sayılabilir.

Eş-zamanlı aydınlatma kontrastı (EAK) etkisi, bir cismin aydınlık derecesinin, kendi çevresine bağlı olduğunu gösterir. Aynı cisim, koyu zemin üzerinde olduğunda, açık renk zemin üzerinde olduğu duruma göre daha açık algılanır. Uyarlanmış bir EAK testi, glokomun sensörinöral retina üzerindeki yıkıcı etkileri sonucu, normal olarak gözlenen kontrast artımı ve azalımı güçlendirmesi değişimlerini ortaya çıkarmak amacıyla uygulandı. Hem normal hem glokomlu olgular kontrast azalımlarını benzer şekilde güçlendirirken; glokomlu olguların, en yüksek kontrast artımı dışında, kontrast artımlarını güçlendiremediği gözlendi.

Bu eşik-üstü kontrast duyarlılık testi ile, görme alanı değişiklikleri ortaya çıkmadan ve klasik eşik-değerde kontrast duyarlılık testleri ile anormallik saptanmadan önce, kontrast duyarlılık değişikliklerini saptanabilir. Erken evre glokom ve glokom-şüphesi bulunan olgularda, bu test ilk uygulanacak test olabilir. Ayrıca, glokomlu olgularda uygulanan diğer subjektif görsel değerlendirme testleri de, bu kavram doğrultusunda gözden geçirilmelidir.

Anahtar kelimeler: Kontrast duyarlılık fonksiyonu, glokom, eşzamanlı aydınlatma kontrastı, eşik-üstü kontrast algılaması

"Many people do not realize that perception is a problem; we perceive the world so effortlessly and so continuously that we take the mechanism for granted. Perception is one of the most neglected of all the major problems of science and this may be because it is the most difficult problem of them all".

Howard, 1982

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LIST OF ABBREVIATIONS

LGN	Lateral geniculate nucleus
M cell	Magnocellular
P cell	Parvocellular
K cell	Koniocellular
SLC	Simultaneous lightness contrast
I-D	Increment – decrement
CSF	Contrast sensitivity function
POAG	Primary open angle glaucoma
IOP	Intraocular pressure
c/d	Cup / Disc ratio
HRT	Heidelberg retina tomography
RTA	Retinal thickness analyzer
MD	Mean deviation
PSD	Pattern standard deviation
CPSD	Corrected pattern standard deviation
ERG	Electroretinogram
VEP	Visual evoked potential
SWAP	Short wavelength automated perimetry
HPRP	High-pass resolution perimetry
OCT	Optical coherence tomography
RNFL	Retinal nerve fiber layer

cpd	Cycles per degree
MTF	Modulation transfer function
VCTS	The VisTech chart
SWCT	Sine-wave contrast test
FACT	Functional acuity contrast test

1. ORGANIZATION OF THE NEUROSENSORIAL RETINA

The neurosensorial retina consists of three main neuron groups; the photoreceptors, bipolar cells and ganglion cells (Figure 1-1). These three main types of neurons have important roles in color and contrast perception. These neurons are orderly positioned from outer side to the inner side of the retina. Photoreceptors are the outermost cells, bipolar cells are placed in the middle and ganglion cells are placed at the innermost side of the retina (1-3).

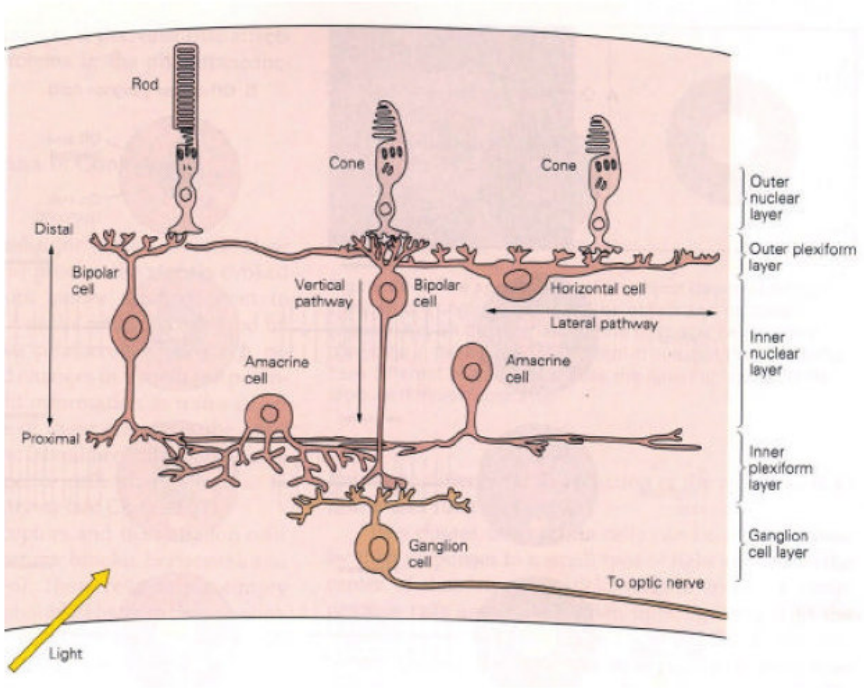


Figure 1.1 The neural junctions and layers in the retina

The photoreceptor cells are the neuroepithelial cells that are extremely sensitive to light stimulus. The two main types of photoreceptor cells are **the rods** and **the cones**. The cone cells have three types; red (570nm) and green (540nm) color sensitive cones are more densely located in the fovea, whereas blue color (440nm) sensitive cones are mostly located 1° outside the foveal center. The rods are most sensitive to dark green color (~500nm), and are located mainly in the extrafoveal areas.

Visual information is sent from the retina via the optic nerve to the lateral geniculate nucleus (LGN) and then on to higher neural areas via three general pathways: the magnocellular (M-cell), parvocellular (P-cell), and koniocellular (K-cell) pathways. These pathways include retinal ganglion cell axons and their synaptic connections to neurons in the LGN, the axons of geniculate cells that carry information to the primary visual cortex, and the fibers from the visual cortex that connect to higher brain centers. Each pathway conveys a basic component of visual information, as shown in Table 1-1.

Table 1.1 Characteristics of the M-, P-, and K-cell pathways

Type of cell pathway	M	P	K
Approximate percent of retinal ganglion cells	10%	80%	9%
Receive input from	Parasol retinal ganglion (M) cells	Midget retinal ganglion (P) cells	Mainly bistratified (blue-ON) retinal ganglion cells
Location in LGN	Most ventral layers 1 and 2	Most dorsal layers 3 to 6	Within and between principal layers (interlaminar)
Sensitive to	Higher temporal frequencies (movement)	Higher spatial frequencies (detail), color	Shorter wavelengths (blue-yellow color)

While incoming light hyperpolarizes photoreceptors, this signal in turn triggers both hyperpolarization and depolarization within the bipolar and ganglion cells. There are 2 types of bipolar cells; depolarizing (ON) and hyperpolarizing (OFF) cells, both of which are stimulated with the light exposure of the rod and cone cells. The ON and OFF bipolar cells respond differently to the photoreceptor signals because they express different receptors

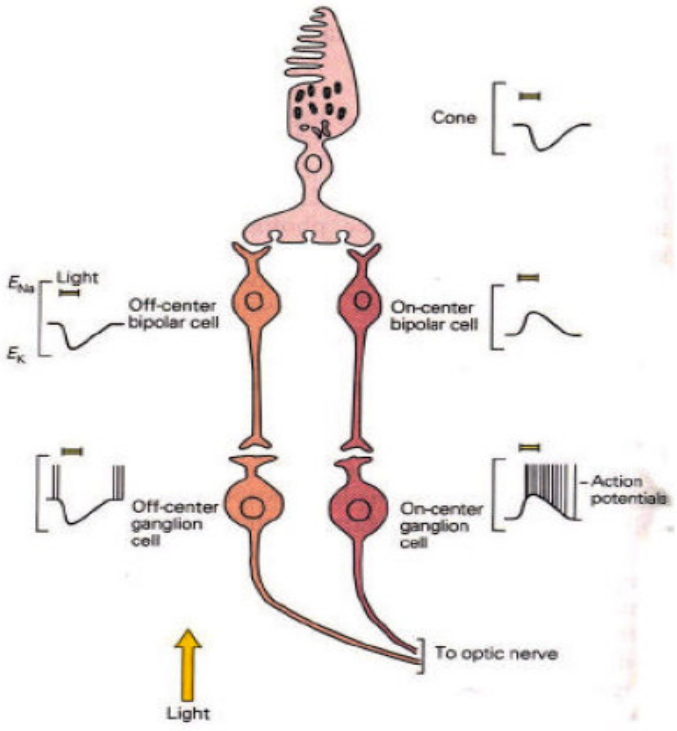
(metabotropic and ionotropic glutamate receptors, respectively). They also make synaptic contact with ganglion cells in different strata of the inner plexiform layer. The ON and OFF bipolar and ganglion cells respectively detect increases and decreases in luminance within their receptive fields. Therefore, both the negative and positive signals from rods and cones are propagated to the amacrine and ganglion cells, via separate bipolar cells. The receptive fields of ON and OFF retinal cells have a **center-surround organization**: stimulation of the region surrounding their receptive fields elicit opposite responses (Figure 1-2). The center-surround organization of the ganglion cells' receptive fields is due to the lateral inhibitory action of horizontal cells. This **lateral inhibition** provides our visual system with a mean to emphasize areas of difference (contrast), i.e., it sharpens the boundary between objects of different luminance. The output of the retina originates from two classes of ganglion cells, both showing the on-off center-surround patterns of activation. **The parasol cells** predominate in the peripheral retina and receive inputs mainly from rods. They have large receptive fields and sensitive to visual motion; they participate very little in color perception. **The midget cells** predominate in the central retina and receive input mainly from cones. They have small receptive fields and are sensitive to color.

The horizontal and **amacrine cells** are the modulator cells, which arrange and conduct the electrical signals from the photoreceptors to the ganglion cells. Horizontal cells responds to the transmitters released from the rods and cones, as the depolarizing bipolar cells; therefore, are stimulated by light. Then, they inhibit the adjacent bipolar cells and form the lateral inhibitory pathway of the retina. Amacrine cells form another pathway for the transmission of the lateral signals; but with excitatory signals. Amacrine cells give very fast responses to the stimuli from the bipolar cells, but the signals dies quickly. Therefore; amacrine cells are considered to create strong signals to the brain, to give information about the sudden changes in light intensity. The axons of approximately 1 million ganglion cells in the inner aspect of the sensorial retina form **the optic nerve**, after passing through the lamina cribrosa.

In short, depolarizing bipolar cells conduct the excitatory signals from rods and cones to the ganglion cells. Hyperpolarizing bipolar cells and horizontal cells are stimulated from the

nearby rods and cones and conduct inhibitory signals to the adjacent bipolar cells and the ganglion cells. Amacrine cells conduct transient, short-living signals directly to the ganglion cells, which change according to the retinal illumination level. Therefore, all cell types have different functions in stimulating the ganglion cells (1, 4, 5).

Most of the ganglion cells do not respond to the real illumination in the visual area; but only respond to the contrast borders in the area. If the retina is stimulated thoroughly (ie, all photoreceptors are equally stimulated with the incoming light), the contrast type ganglion cells are neither stimulated, nor inhibited. The directly conducted signals from the photoreceptors through the depolarizing cells are excitatory; whereas, the signals conducted through the adjacent hyperpolarizing cells and horizontal cells are inhibitory. Therefore; the direct excitatory signal coming from one pathway are neutralized by the inhibitory signals via the lateral pathway.



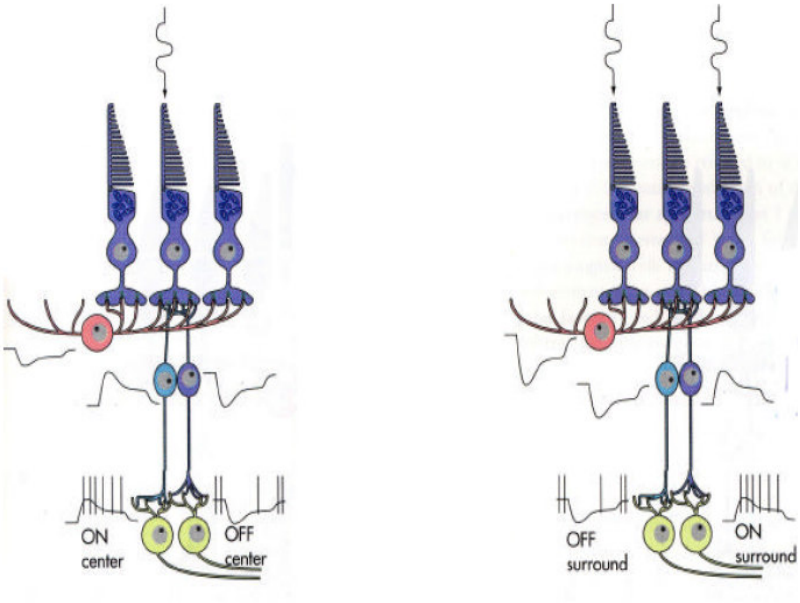


Figure 1.2 The center-surround organization of bipolar cells

If any photoreceptor is stimulated by incoming light and the neighbouring photoreceptor cells stay in dark; the darkness of the adjacent photoreceptors cause inhibition of the horizontal cells. Therefore, the inhibitory effects of these cells on the bipolar cells disappear and the bipolar cell in light is stimulated more. In presence of contrast, direct and lateral signal pathways thus, reinforce each other. The function of the lateral inhibitory pathway in visual process is to carry the information about contrast and reinforcement of the sensation.

In Figure 1-3, suppose we record signal from nerve fiber of receptor A. Illumination of receptor A alone causes a large response. If you add illumination to three nearby receptors at B, this causes the response at A to decrease. Increasing the illumination of B further decreases A's response. Thus, illumination of the neighboring receptors inhibited the firing of receptor A. This inhibition is called lateral inhibition because it is transmitted laterally, across the retina, in a structure called **the lateral plexus**.

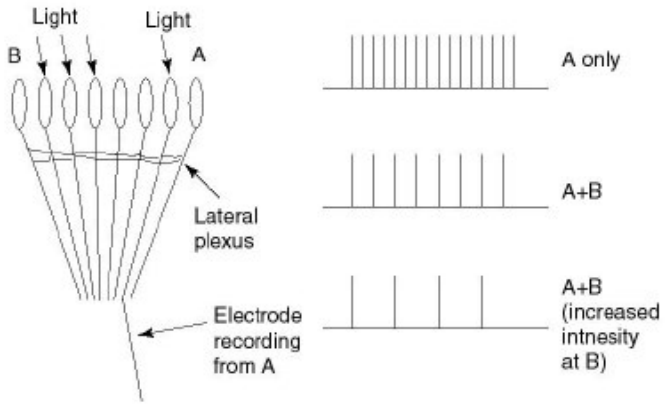


Figure 1.3 The lateral inhibition mechanism

A neural signal is assumed to be generated by a weighted contribution of many spatially adjacent rods and cones. Some receptors exert an inhibitory influence on the neural response. The weighting values are, in effect, the impulse response of the human visual system beyond the retina (Figure 1-4).

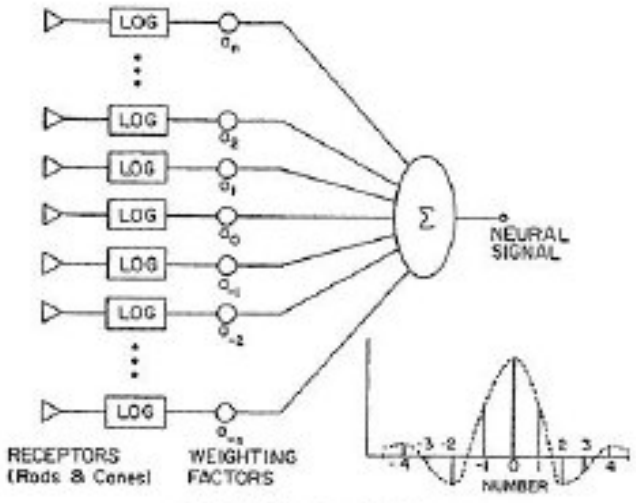


Figure 1.4 The neural signal as a weighted contribution of adjacent photoreceptors

2. SIMULTANEOUS LIGHTNESS CONTRAST

Luminance is an objective measurement of the overall intensity of a stimulus, expressed in candelas /m^2. The photometers measure the radiant energy with a filter that mimics the sensitivity of the average human observer, thus specifically measuring light. **Lightness** refers to the apparent intensity as a consequence of surface reflectance; that is, the extent to which an object appears as it does because it reflects more (or less) light to the eye than other surfaces in the scene. **Brightness** on the other hand, indicates the extent to which the apparent intensity of light coming from a given portion of a scene is attributable to the region in question being a primary source of light.

In order to achieve lightness constancy on a target, it is necessary to discount the luminance variations resulting from changes of the illumination falling on a surface, because the luminance is determined by at least three fundamental aspects of the physical world: the illumination of objects, the reflectance of object surfaces, and the transmittance of the space between objects and observer. Changing any of these real-world variables will necessarily change the relative intensity of the light reaching the eye. As a result of this conflation; an infinite number of different combinations of illumination, reflectance, and transmittance can give rise to the same luminance. Various cues could be used in the process of the visual system responding differently to luminance changes due to illumination and reflectance; such as straightness of the boundary, X-junctions and T-junctions that preserve a consistent contrast ratio (6).

It is commonly presumed that the objective measure of light intensity (ie, luminance) and the ensuing sensations of lightness or brightness should be directly proportional because increasing the luminance of a target stimulus increases the number of photons captured by photoreceptors and thus the output activity of the retina at any given level of background light (7). However, although two objects in a scene that return the same measured amount of light to the eye should appear equally light or bright; 2 patches of the same photometric intensity look different when they are presented on different backgrounds. **The simultaneous lightness contrast** (SLC) is a textbook illusion, which demonstrates that the lightness of an object may

depend on its immediate surround. A region seen against a dark background looks lighter than an identical region seen against a light background (Figure 2-1). It is generally believed that it is not absolute but relative luminance (or luminance contrast) that determines lightness (8,9).

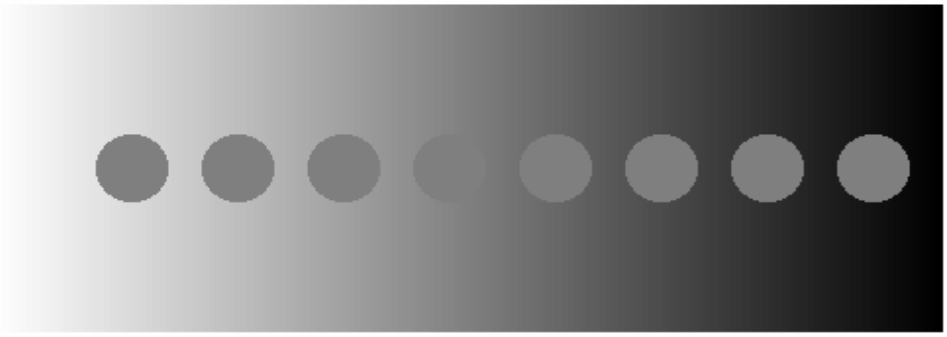


Figure 2.1 Simultaneous lightness contrast

The SLC is classically described as perception of a gray test figure lighter when placed on a black background, than when placed on a white background (Figure 2-2).

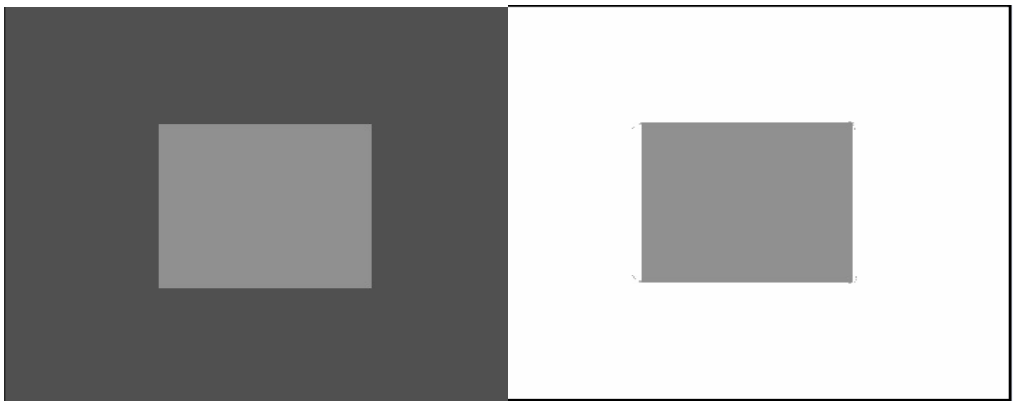


Figure 2.2 The classical simultaneous lightness contrast display

In the classical SLC display, the target region on the dark background is a local luminance increment, whereas the identical target region on the light background is a local luminance decrement (one increment and one decrement, I-D) (Figure 2-2). The local increments and decrements are thought to be produced as a result of lateral inhibition effect (Figure 2-3).A weaker effect also obtains when the luminance of the two target regions is lower than both backgrounds' (double decrements); or higher than both backgrounds (double increments) (10) (Figure 2-4).

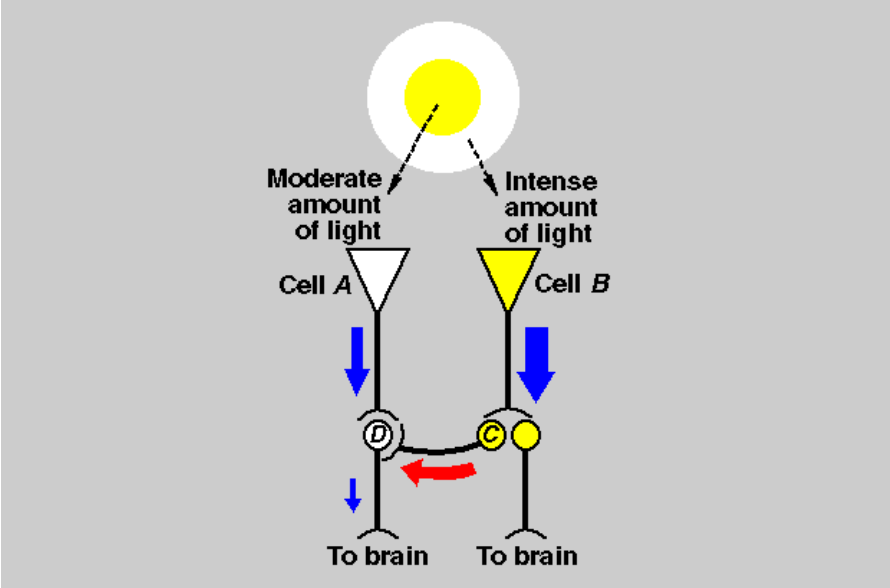


Figure 2.3 The mechanism of local decrement formation by SLC effect

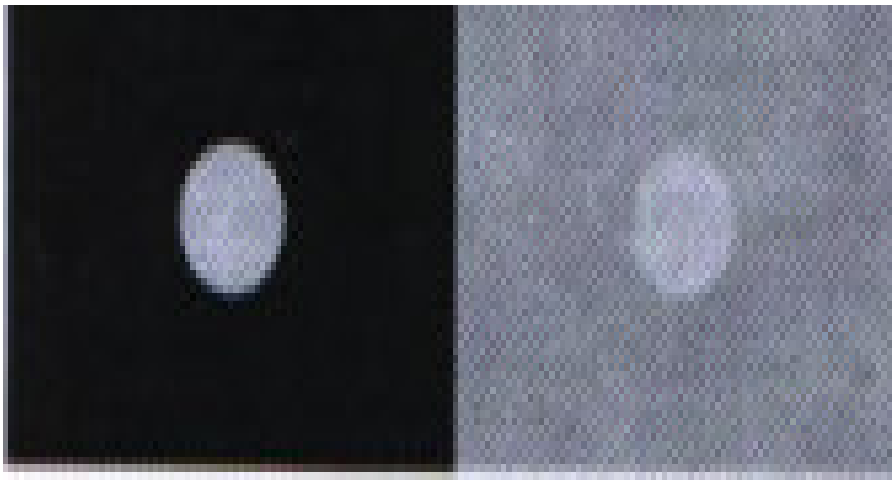


Figure 2.4 Simultaneous lightness contrast with double increments

SLC is shown to be enhanced when the dark and light backgrounds of the display are replaced by articulated fields of equivalent average luminance (11) (Figure 2-5).

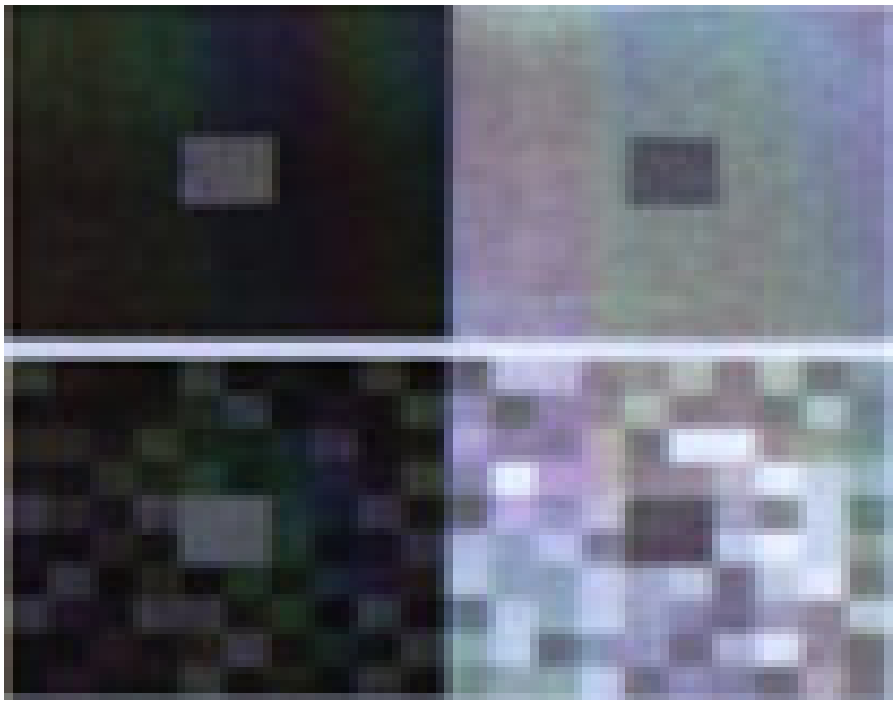


Figure 2.5 Simultaneous lightness contrast with articulated surrounds

This effect is commonly attributed to a low-level inhibitory process which induces contrast enhancement at the edges of the regions varying in lightness (12); although the effect can extend far from the edges and usually shifts the perceived lightness of the entire figure (13). Other explanations of the SLC include unconscious inference, which attributes the effect of an erroneous evaluation of the illumination, Gestalt theory, which uses the concept of perceptual belongingness (14,15), and spatial filtering with an incomplete set of basis functions (16, 17). SLC is a serious violation of lightness constancy, but its magnitude is predictable, at least in simple stimulus configurations, based on the ratio of the test-field luminance to the luminance of the background (18).

A modified SLC test offers a means for supra-threshold contrast sensitivity measurement. The perception of the contrast increments or decrements is expected to vary significantly in conditions that affect the contrast sensitivity. The applicability of this contrast sensitivity test in various clinical conditions has not been studied before. This thesis study is going to be the first in this area; whereby the modified SLC effect is tested in glaucomatous and normal subjects, in order to figure out the deleterious effects of the disease on the contrast sensitivity.

3. GLAUCOMA

Primary open angle glaucoma (POAG) is diagnosed by raised intraocular pressure (IOP) and cupping of the optic disc in association with characteristic visual field changes (19).

3.1 AQUEOUS HUMOR DYNAMICS

3.1.1 AQUEOUS HUMOR FORMATION

The humor aqueous is being continuously produced by the ciliary processes and secreted to the posterior chamber and at the same time, leaves the eye via the outflow pathways (trabecular system and uveoscleral outflow). Three different mechanisms play role in the production of the aqueous humor (20):

a. **Active transport** by using enzymes like carbonic anhydrase and N^+/K^+ ATPase, in the reverse direction of electrochemical gradient.

b. **Ultrafiltration** of water by the hydrostatic pressure gradient.

c. **Diffusion** of the lipophillic materials in the direction of the concentration gradient.

The average rate of formation of aqueous humor is 2-3 µl/min; however, it has diurnal variation and is less at nights. Additionally, the integrity of the blood-aqueous humor barrier, ciliary body blood flow, neurohumoral regulation of the vascular tissue and ciliary epithelium also affect the aqueous humor secretion.

Under normal conditions, the equilibrium between the aqueous humor formation and outflow is maintained by the Goldmann equation (20). According to this equation;

$$F = (IOP-Pv)\ C + U \qquad (3.1)$$

$$IOP = (F-U) / C + Pv$$

F : Rate of aqueous humor formation (µl / min)

U : Uveoscleral flow rate (µl / min)

IOP : Intraocular pressure (mmHg)

Pv : Episcleral venous pressure (mmHg)

C : Ease of trabecular outflow (µl / min / mmHg)

According to this equation, the IOP is directly proportional with the rate of aqueous humor formation and inversly proportional with the ease of outflow. The IOP increases directly proportional to the episcleral venous pressure; and inversly proportional with the uveoscleral outflow rate.

3.1.2 AQUEOUS HUMOR OUTFLOW

The aqueous humor reaches the anterior chamber via pupillary space and 80-90% of it leaves the eye via trabecular system (conventional drainage) and 10-20% leaves via uveoscleral and uveo-vortex system (20, 21).

The conventional trabecular drainage system includes passage of the aqueous humor through trabecular meshwork, Schlemm's and intrascleral collector channels, to the episcleral veins and systemic circulation. This system maintains IOP, by unidirectional valve structure of the interior wall structure of the Schlemm's channel and trabecular meshwork structure. The maximum resistance to the drainage of the aqueous humor is seen at the level of juxtacanalicular portion of the trabecular meshwork.

The uveoscleral drainage is formed by passage of the humor aqueous through ciliary body between the ciliary muscle fibers, to supraciliary and suprachoroidal space (uveal vessels).

3.2 MECHANISM OF THE DEVELOPMENT OF GLAUCOMA

Theoretically, there are 2 mechanisms for IOP rise in glaucoma. Firstly, the rate of aqueous humor formation may increase; which is not practically seen in the clinical setting.

The second mechanism forms the basis of almost all types of glaucoma, which is based on the inhibition of aqueous humor outflow. This may arise at different levels of outflow pathway, by different mechanisms.

3.2.1 OPEN ANGLE GLAUCOMA

Although the gonioscopic examination reveals open iridocorneal angle, the changes in the trabecular system at the histological level can lead to rise in IOP. Pseudoexfoliative glaucoma; which is characterized by glycosaminoglycane material accumulation on the surface of zonullary fibrilles and in the interfibrillary matrix and hyperpigmentation in the trabecular meshwork, is also considered to be a subgroup of open angle glaucoma (22, 23).

3.2.2 ANGLE CLOSURE GLAUCOMA

The iridocorneal angle is detected to be closed by the peripheral iris in the gonioscopic examination. This situation may accompany pupillary block between the iris margins and the crystalline lens, and lead to acute or chronic angle closure glaucoma. Plato iris syndrome is a rare subtype of angle closure glaucoma, without the pupillary block. In this case, the anterior position of the peripheral iris at the iridocorneal angle leads to accummulation of the iris tissue at the angle by pupillary dilatation and blockage of the trabecular outflow (20).

3.3 CLASSIFICATION OF GLAUCOMA

3.3.1 PRIMARY GLAUCOMAS

a. Open Angle Glaucomas

    i. Primary open angle glaucoma

    ii. Normal-tension glaucoma

    iii. Ocular hypertension

b. Angle Closure Glaucoma

i. Latent angle closure glaucoma

ii. Intermittent (subacute) angle closure glaucoma

iii. Acute angle closure glaucoma

iv. Chronic angle closure glaucoma

3.3.2 SECONDARY GLAUCOMAS

a. Glaucomas secondary to other ocular pathologies

i. Secondary to corneal endothelial pathologies

ii. Secondary to iris and ciliary body pathologies

iii. Secondary to lenticular pathologies

iv. Secondary to retina, choroid and vitreous pathologies

b. Glaucomas secondary to systemic diseases and medications

c. Glaucomas secondary to inflammation and trauma

d. Glaucomas secondary to intraocular surgery

3.3.3 CONGENITAL GLAUCOMAS

a. Primary congenital glaucomas

b. Glaucomas related to other ocular congenital abnormalities

c. Glaucomas related to extraocular congenital abnormalities

3.4 CLINICAL EVALUATION OF GLAUCOMA

3.4.1 THE INTRAOCULAR PRESSURE

The IOP is the pressure on the cornea and sclera, exerted by the aqueous humor filling the anterior and posterior chamber. In epidemiologic studies, the mean IOP was found to be 16±3 mmHg in the normal population. The normal IOP range has been considered to be between 10-21 mmHg; however, with the evolution of the concepts of ocular hypertension and normal-tension glaucoma, the normal value of IOP is accepted to change from person to person. Therefore, the current glaucoma treatment is based on achieving the target IOP that would prevent the damage at the optic nerve head. The target IOP differs for each patients; and thus, there is no "normal" IOP level which is correct for all people (20).

3.4.2 TONOMETRY

The principle of the method of tonometry is based on the relationship between the intraocular pressure and the force necessary to deform the natural shape of the cornea by a given amount. The deformation can be achieved by indentation, as with the Schiotz tonometer, or by applanation, as with the Maklakoff and the Goldmann tonometers (24). Although the pressure measured is external to the eye, the term used is "intraocular pressure". **Applanation tonometry** determines IOP by evaluating the force required to applanate or flatten a given surface area of cornea. However, **the indentation tonometer** measures the amount of corneal indentation that occurs when a given weight is placed on the cornea. The result is inversely proportional to the intraocular pressure and the actual pressure must be obtained from a table of values.

The most frequently used instrument is the Goldmann applanation tonometer, mounted at the slit lamp. The method involves illumination of the biprism tonometer head with a blue light obtained using a cobalt filter and applanation of the cornea after applying topical anesthesia and fluorescein in the tear film. The scaled knob on the side of the instrument is then turned until the hemicircle of fluorescent tear meniscus visualized through each prism just overlap (Figure 3-1).

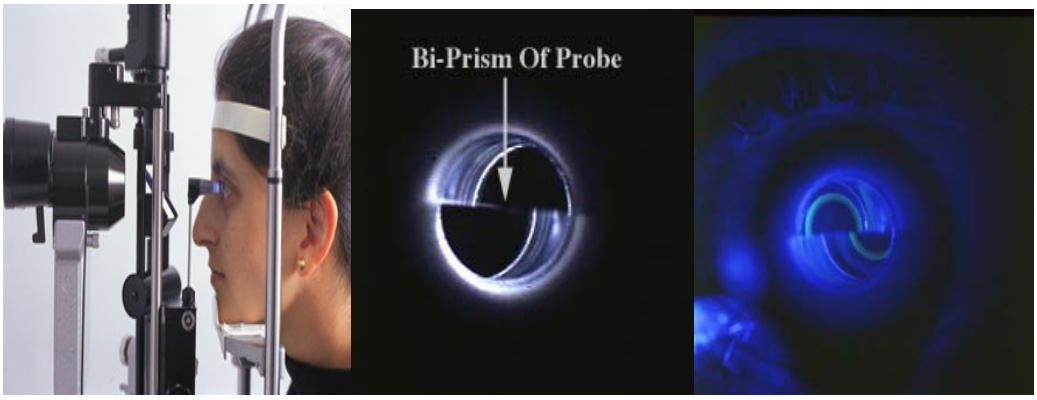


Figure 3.1 Intraocular pressure measurement with Goldmann applanation tonometer

Goldmann's original equation is based on **the Imbert-Fick principle** which states that for an ideal, dry, thin-walled sphere, the pressure inside the sphere (P) equals the force necessary to flatten its surface (F) divided by the area of flattening (A) (i.e. P=F/A). The IOP is proportional to the pressure applied to the radius of curvature of the globe (in practice the cornea) and the thickness of the globe (i.e. the thickness of the cornea and sclera). This principle assumes that the cornea has a constant radius of curvature, the rigidity is the same in all eyes, the globe is spherical, the aqueous does not move away from the anterior chamber during measurement. These assumptions cause the inter- and intraobserver variability (25).

Air-puff tonometry is a noncontact tonometer which uses the Goldmann applanation principle but instead of using a prism, the central part of the cornea is flattened by a pulsed jet of air. The time required to sufficiently flatten the cornea relates directly to the level of IOP. The exposure time of the air jet is between 1 and 3 msec. Since this is 0.002 of a cardiac cycle, the ocular pulsation can be a significant source of variability for IOP measurements.

Pneumatonometry is a contact tonometer, in which a sensor measures the air pressure, which flattens the cornea through a diaphragm at the end of the probe. Tono-Pen is a hand-held contact type instrument that has a software to automatically select the acceptable measurement and reject the inappropriate ones. An average of at least three good IOP measurements are determined and displayed. These latter instruments are useful in patients with cornea edema, scar and irregularities (26-29).

3.4.3 GONIOSCOPY

For the evaluation of aqueous humor outflow, the structures in the iridocorneal angle could be examined with direct or indirect gonioscopy, by using a contact goniolens (Figure 3-2).

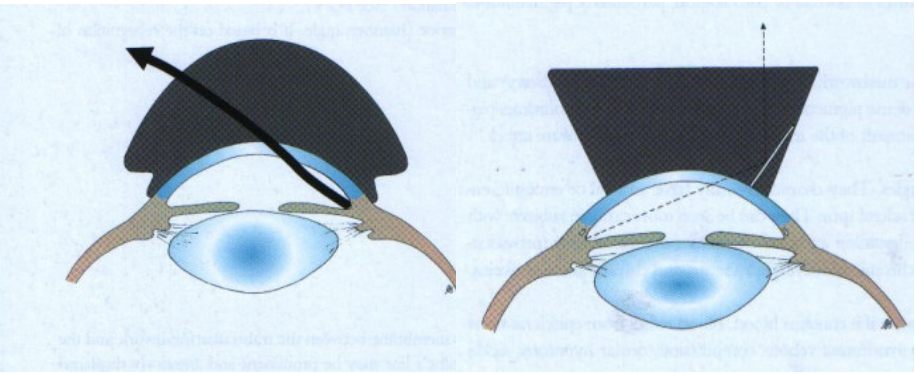


Figure 3.2 Direct and indirect gonioscopy

The structures in the iridocorneal angle are evaluated by using different classifications; the most commonly used of which is the Shaffer system. **The Shaffer system** evaluates the anterior chamber angle according to the visible anatomical structures between the two imaginary lines passing through the anterior surface of iris and internal surface of trabeculum (Figure 3-3).

Grade IV (35º - 45º): The band of cilliary body can be seen. There is no possiblity for angle closure.

Grade III (20º - 35º): The scleral spur can be seen. There is no possiblity for closure.

Grade II (20º): The trabecular meshwork is visible. There is tendency for closure.

Grade I (10º): The Schwalbe line and a very little portion of the trabeculum can be seen. There is high risk for angle closure.

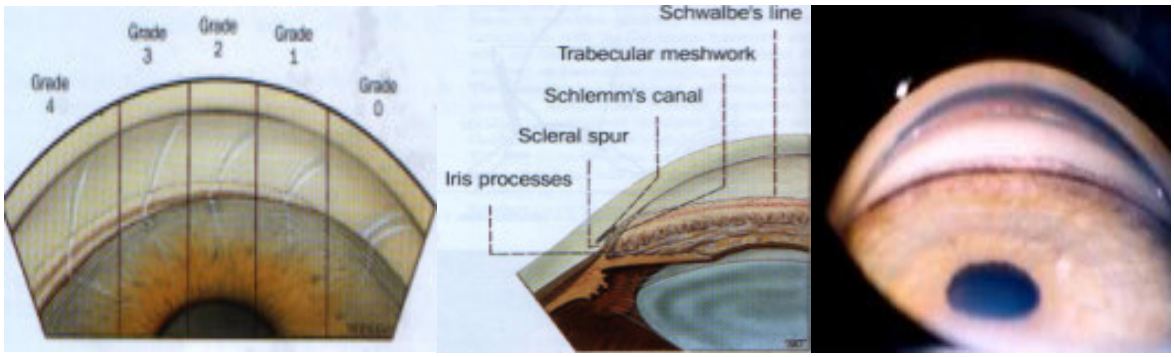


Figure 3.3 The iridocorneal angle

3.4.4 OPTIC NERVE HEAD

The intraocular portion of the optic nerve is called as **the papilla, the optic disc** or **the optic nerve head.** The axons of the retinal ganglion cells form the papilla of 1mm length and 1.5mm diameter. There are 800 000 to 1 200 000 nerve fibers. The optic nerve leaves the eye passing through the lamina cribrosa, located at 0.8mm superior and 3mm nasal to foveola (30, 31). The optic nerve head could be examined as 4 separate parts in antero-posterior direction.

The nerve fiber layer

The axons of the ganglion cells travel parallel to and very close to the retina and accumulate at the papilla. They approach to the prelaminar area with right angle. The unmyelinated nerve fibers at this area are nourished by the retinal arterioles (30-33).

The prelaminar area

The axons of the ganglions occupy the 90% area of the anterior portion. Towards the posterior parts, the number of the neuroglial cells and the astrocytes increase and the ratio of the axons to these cells diminish. The prelaminar area is adjacent to the choroid and is nourished by the branches of the peripapillary choroidal vessels.

The laminar area

The collagen and elastic fibers of the sclera form the lamina cribrosa, between the fibers of the nerve fiber bundles. The thickness of the lamina cribrosa varies between 250µm to 750µm. The axons are unmyelinated in this area; and the amount of neuroglial supporting

tissue is maximum. This area is nourished by the branches of short posterior cilliary artery that enter the sclera and form the circle of Zinn-Haller (30-33).

The retrolaminar area

The optic nerve begins at the retrolaminar area, where the diameter increases to 3-4mm due to the myelination of the nerve fibers. The astrocytes are replaced by the oligodendrocytes which secrete the myelin coat. This part is nourished by the posterior cilliary arteries, pial arteries and centrifugal branches of the central retinal artery (30-33).

The optic nerve head examination techniques include:

a. Ophthalmoscopic examination

The cup/disc ratio (c/d) on the optic nerve is one of the important clinical criteria for evaluating the glaucomatous nerve fiber loss at the optic nerve head. A c/d value of 0.5 or asymmetrical c/d ratios on fellow eyes should arise suspicion about glaucoma (Figure 3-4).

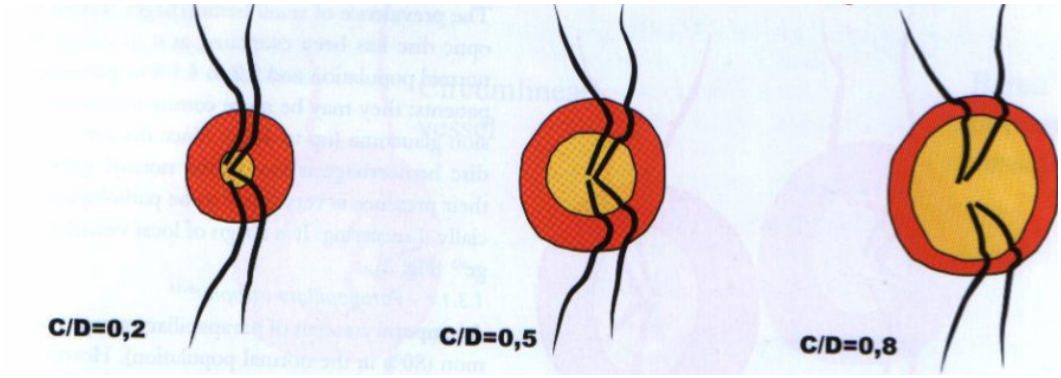


Figure 3.4 The optic nerve head c/d ratio

b. Optic disc photography

c. Computerized analysis of optic nerve head

i. Optic nerve head analyzers

ii. Confocal scanning laser ophthalmoscope

d. Topographic scanning system

e. The optical coherence tomography

f. Retinal thickness analyzer (RTA)

3.4.5 THE VISUAL FIELD

The visual field is a three-dimensional structure which could be defined as a visual island surrounded by darkness sea and has the dimensions of 50º superiorly, 60º nasally, 70º inferiorly, 90º temporally (Figure 3-5). The visual field consists of concentric areas called **"isopters"** that are formed by joining the points with same threshold values. The **"scotomas"** are the areas that have reduced retinal sensitivity compared with its surrounding. Scotomas follow the anatomical distribution of the retinal nerve fibers (Figure 3-6). The **"blind spot"** is the absolute scotoma area of 10º-20º, temporal to the fixation point (20, 34).

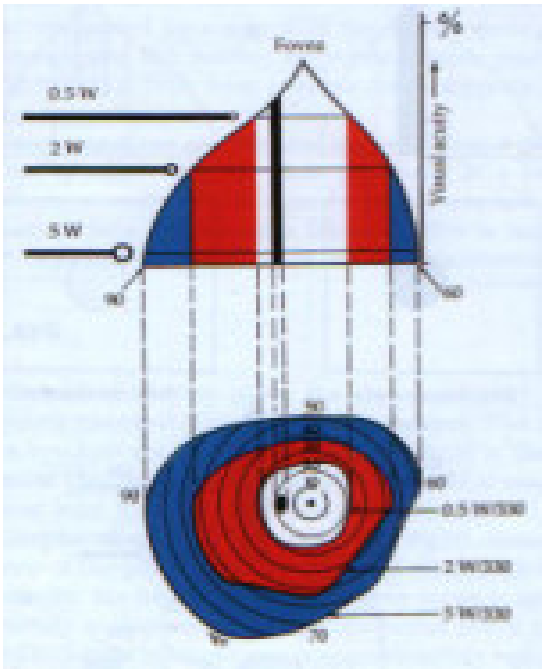


Figure 3.5 Three dimensional visual field hill

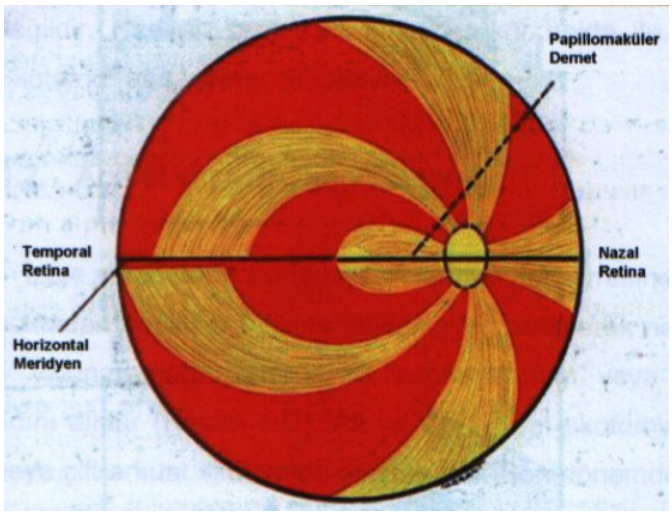


Figure 3.6 The distribution of the retinal nerve fibers

Terminology

Fixation: The central foveal region of the visual field.

Central area: The central 30˚ visual field including the fixation.

Arcuate area (Bjerrum area): The central visual field area that is nasal to the fovea, extending from the "blind spot" as the superior and inferior arcuates and finishing at the horizontal raphe.

Peripheral area: The area behind the central 30˚ visual field.

Isopter: The concentric line in the visual field that corresponds to equal lightness threshold in the visual field.

Threshold: The light intensity, which is perceived with probability of equal to or greater than 0.5, at a specific retinal point.

Depression: Decrease in sensitivity of light perception.

Scotoma: Localised defect or depression in the visual field.

Absolute scotoma / defect: The visual field defect that occurs with maximum defect.

Relative scotoma / defect: The visual field defect that is lost when the intensity of the stimulus is increased.

Fluctuation: The variations in the visual field measurements

Short-term fluctuation: The variations of the responses during testing.

Long-term fluctuation: The variations in different tests of the same eye at different times.

Mean deviation / defect (MD): The mean difference between the normal sensitivity (corrected for age) and the retinal sensitivity of the subject (calculated from all the points tested). The absolute value of MD increase with media opacities, diffuse loss or severe localized loss. A retinal sensitivity value worse than normal is indicated by a negative symbol in Humphrey perimeters (mean deviation) and a positive symbol in Octopus perimeters (mean defect). The MD is probably the best measure of diffuse ganglion cell damage that occurs in glaucoma patients (35).

Pattern standard deviation (PSD): This is the standard deviation or variance of the deviations and is thus a measure of the degree to which the shape of a patient's field differs from a normal, age-corrected, reference field. It indicates the extent of focal loss in the visual field.

Corrected pattern standard deviation (CPSD): This indicates the extent of focal loss in the visual field, taking short term fluctuation into account.

It has been suggested by anatomical evidence that large ganglion cells (M cells) located in the retinal mid-periphery are selectively damaged in human and experimental glaucoma, whereas the smaller and more central ganglion cells (P cells) are relatively spared. The physiological properties of M-cell and P-cell pathways differ considerably. The M-cells have greater contrast sensitivity and contrast gain, although their response tends to saturate at high contrast; the conduction velocity is much higher and the response time course of M-cells tends to be more transient. In contrast, the great majority of cells in the P-pathway display clear color opponency, whereas most M cells are not color coded. The finding of greater

vulnerability of larger ganglion cells in glaucoma implies that a specific test for detection of M cell activity would address early detection of glaucoma. Several tests addressing visual functions subserved primarily by the M pathways (high frequency flicker sensitivity, motion detection, stereopsis) were reported to be abnormal in many glaucoma suspects with normal automated perimetry; however, the visual functions subserved primarily by the P-pathway, including color perimetry, color discrimination sensitivity, colour pattern electroretinography (ERG) and colour visual evoked potentials (VEP), have also shown to be abnormal in early glaucoma (36). Thus, the anatomical picture in glaucoma does not necessarily correlate with the visual function; and the visual dysfunction is not limited to the M pathway. The deficits in both M-cell and P-cell pathways in glaucoma patients were shown by increased thresholds by all types of cone excitation and decreased sensitivity to achromatic contrast (37). This fact was also clinically proven in clinical perimetric studies, in which although blue/yellow color-contrast perimetry was more sensitive for the detection of incipient glaucomatous damage, in the manifest stages of visual field damage blue/yellow color-contrast perimetry was no more sensitive than the conventional (luminance-increment) perimetry for defining the extent of glaucomatous visual fiels defects (38).

The Visual Field Testing Methods

The visual field testing is performed by firstly adapting the eye to the background lightning, followed by presenting brighter stimuli than the background lightning to the eye. The test can be done by kinetic, static or combined methods (39).

a. Kinetic Perimetry: The visual field test in which the size and intensity of the stimulus remains stable, while its position is changing. The stimulus is usually presented from the periphery and approaches to the patient with the speed of 2˚ per second (until the patient perceives the light). The whole 360˚ area is scanned with 15˚ separations and an isopter is obtained. The brightness and size of the stimulus could be changed to obtain different isopters.

Goldmann manual perimetry is an example to this kind.

b. Static perimetry: Most of the automated perimetry types depend on the principle of static perimetry. The threshold value of many test points in the visual field is tested by changing the intensity of the stimuli without changing their sizes or positions.

There are 3 testing strategies in static perimetry.

Full threshold test: In order to scan the central 360˚ visual field by 6˚ separations, 75-80 points are tested. The threshold level is found at each point by increasing the intensity by 4 dB and after the patient perceives the stimulus, by decreasing the intensity in 2 dB steps, until the the stimulus is lost. Each point is scanned twice. This strategy is the most commonly used strategy.

Threshold dependent test: In this test, 4dB more intensity than the stimulus normally expected to be seen is presented to the patient. The responds are recorded as “seen” or “not seen”, and other points are tested. The disadvantage of this strategy is that, only supra-threshold stimuli are tested and defects over this level can be detected. The suspected variations could be missed.

Zone test: Three zones are tested. The first zone is the supra-threshold level 4-5dB higher than normal values, and regarded as “normal” if the patient perceives. Otherwise, the intensity of the light is increased until the patient detects the stimulus, and it is then classified as “relative defect”. If the patient does not see any light, it is classified as “absolute defect”. The responses are evaluated in 3 zones called “normal”, “relative defect” and “absolute defect”. This strategy has the advantage of being fast, although it can only detect major defects.

c. Combined static and kinetic perimetry: This method combines the sensitivity of the static perimetry with the speed of the kinetic perimetry. Generally, the peripheral area is tested by kinetic method and the central area is tested by static method. This method is used routinely in manual perimeters, rarely in automated perimeters.

Perimetry Techniques

a. Standard Perimetry: This achromatic test uses a small (0.47˚) white light spot for 200 milliseconds. The central 30-2 full threshold test in the Humphrey perimetry and the G1 program of the Octopus perimetry scan the 30˚ test the visual field starting from the 3˚ superior and 3˚ inferior of the horizontal line. The standard perimetry is nonspecific to ganglion cell type. Irreversible ganglion cell loss occurs before visual field defect can be detected.

b. Short-Wavelength Automated Perimetry (SWAP): This test is based on the theory that the yellow light of the background can reduce the sensitivity of some photoreceptors and leave active blue cones that carry the stimulus using P type ganglion cells. SWAP uses a large blue target (5nm) on a bright yellow background. However, in advanced stages of glaucoma, the number of cones sensitive to short-wavelength light decreases and this test becomes invaluable. This test is greatly affected by the crystalline lens density. SWAP test is used in Humphrey and Octopus perimetries.

c. Frequency-Doubling Perimetry: This test is based on the theory that by using low spatial and high temporal stimuli, it is possible to detect the loss of the M type ganglion cells that are the first to be involved in glaucoma cells. This method makes use of the frequency-doubling illusion, to which the magnocellular cells contribute. This perimetry holds the advantages of being a fast test in a hand-held device, with good reproducibility and possible specificity for the magnocellular ganglion cells.

d. Motion Automated Perimety: In order to test the magnocellular ganglion cell function, random-dot kinematogram on a uniform gray background is used. Fourteen different localisations that correspond to nerve fiber bundle defects in glaucoma are tested in an area of 30˚.

e. High-Pass Resolution Perimetry (HPRP): This test is based on the theory that P type ganglion cells can be detected particularly well by high spatial and low temporal stimuli.

f. Objective Perimetry: This perimetry is obtained by combining the multifocal VEP and multifocal ERG. Although little is known about its benefit in glaucomatous diseases, the results are in correlation with the standard perimetry.

Evaluation of the visual field

Glaucomatous visual field loss patterns: These defects arise from the glaucomatous defects in optic nerve head and follow the anatomical distribution of the retinal nerve fiber bundles as localised or generalised defects. The superior visual field defects represent the nerve fiber defects at the inferior pole of the optic nerve head; and vice versa.

1. Localized defects The most common characteristic of the glaucomatous visual field loss is its nasal localization, in correspondance with the horizontal meridian. Another characteristic is its localization in the Bjerrum area (temporally in 10˚-20˚ of fixation and nasally in 2˚-25˚ of fixation) (Figure 3-7).

Isolated paracentral scotoma: The early glaucomatous scotomas in the paracentral areas which do not join with the "blind spot". With the progression of glaucoma, these defects become wider, deeper and are converted to arcuate scotomas. The widening of the blind-spot can be seen in glaucoma, but it is a non-specific sign. If this defect joins with a paracentral scotoma, it is called **"Seidel scotoma"**.

Arcuate / Bjerrum scotoma: Demonstrating the complete path of a nerve fiber bundle, it originates from the "blind spot", moving around the fixation point as an arc, finishes at the horizontal raphe. Superior or inferior arcuate scotomas can turn into superior and inferior arcuate scotomas later on.

Nasal step / depression: Nasal side of the visual field is affected in the earlier stages of glaucoma. The nasal step at the horizontal raphe can be located peripherally, centrally or both.

Temporal step / depression: This defect can be seen mostly in the late stages of glaucoma, alone or together with other glaucomatous defects.

Central /temporal visual field island: In the advanced stages of glaucoma, most of the superior and inferior axons are lost and only maculopapillary bundle and some nasal fibers survive, forming central and temporal visual field islands. The 10-2 threshold test demonstrates the central island at the latest stages, better than 30-2 threshold test does.

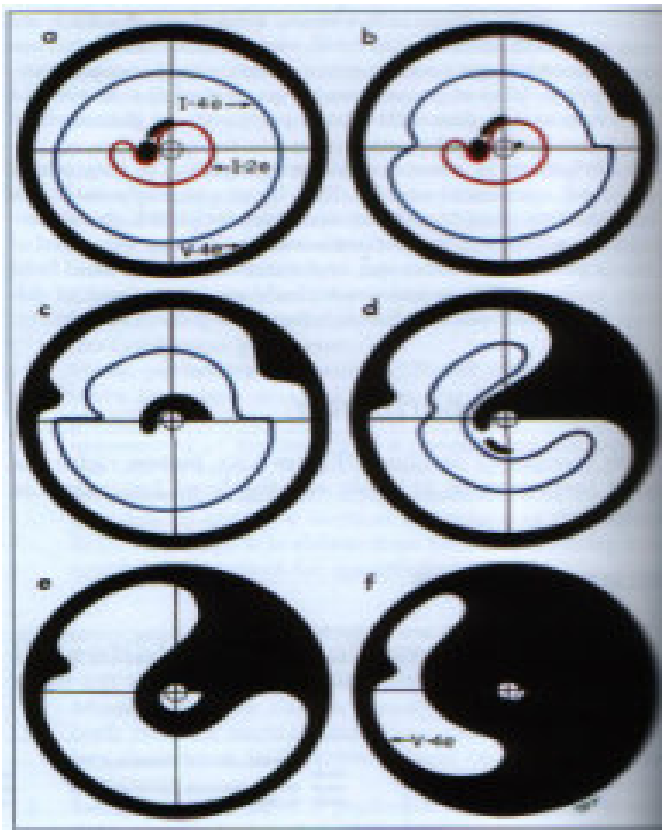


Figure 3.7 Localized visual field defects

a. Arcuate scotoma

b. Nasal (Roenne) step

c. Coalescence of the scotoma in the Bjerrum area

d. Peripheral breakthrough of the scotoma

e. Ring scotoma

f. temporal island

2. Generalized defects: The generalized decrease in sensitivity of the nerve fiber layer can be the earliest sign of glaucoma. It is harder to detect generalized defects, since age, media opacities, miosis etc. can also cause generalized depression in the visual field.

3.4.6 OPTICAL COHERENCE TOMOGRAPHY

The optical coherence tomography (OCT) is an interferometric, non-invasive optical tomographic imaging technique offering millimeter penetration (approximately 2-3 mm in tissue) with sub-micrometer axial and lateral resolution. By using low coherent light in the 810nm wavelength, OCT displays two dimensional sections of the retina in high resolution. Measurements of retinal nerve fiber layer (RNFL) thickness with OCT are potentially useful in the early diagnosis of glaucoma and the early detection of glaucomatous progression (40, 41), which provides objective assessment. The high longitudinal resolution of OCT enables direct measurement of RNFL with micron-scale resolution. The RNFL is highly backscattering and therefore is contrasted from the intermediate retinal layers because the nerve fibers are oriented perpendicularly to the OCT probe beam.

Radial OCT tomograms acquired directly through the optic disc provide cross-sectional information on cupping and neuroretinal rim area. Three-dimensional information on disc parameters may be obtained from multiple radial tomograms acquired at different angular orientations, or from a series of parallel tomograms offset at various distances from the center of the disc (Figure 3-8). A circular tomogram evaluates the cross-sectional structure of the RNFL in a cylindrical section surrounding the optic disc, and may be displayed “unwrapped” as a flat image on the page. The circular scan allows the variations in the RNFL thickness in different regions around the disc to be assessed and compared (Figure 3-9). The optic nerve head cup and disc diameters, c/d ratio, neuroretinal rim area and RNFL thicknesses at each clock meridian and each of the 4 quadrants are calculated by the OCT and displayed in tabular or graphical forms.

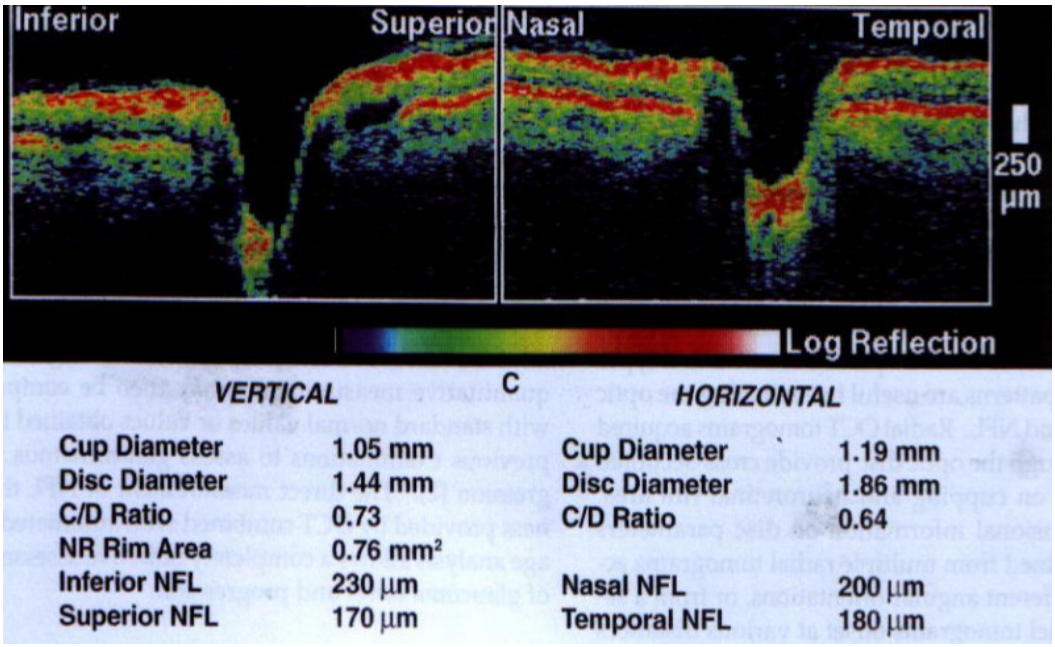


Figure 3.8 The optic nerve head cross-sectional images by the OCT

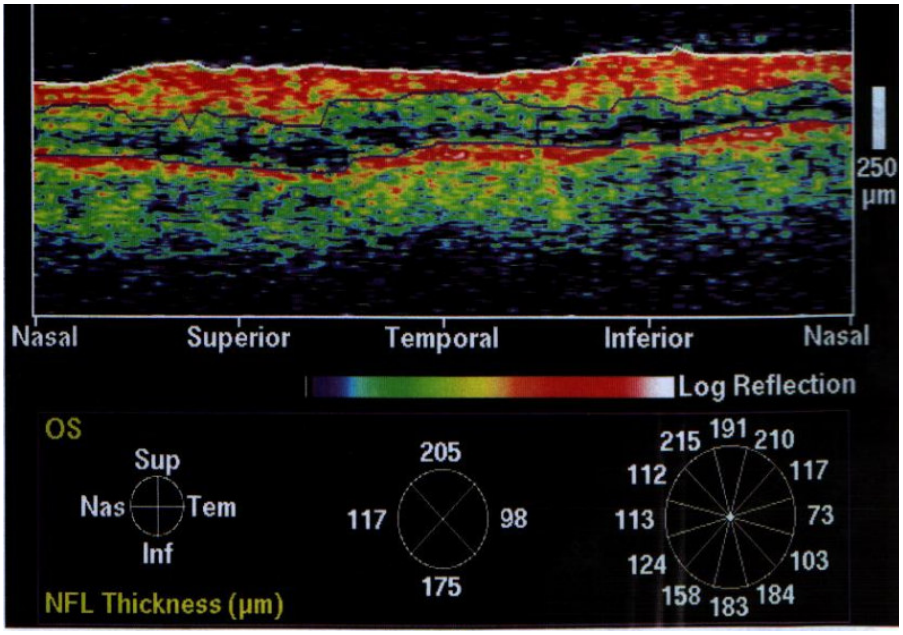


Figure 3.9 The optic nerve head RNFL thickness measurements by the OCT

3.4.7 MANAGEMENT OF GLAUCOMA

The aim of the management of glaucoma can be summarised as protection of the visual function of the patient in his/her suspected life time, without any restriction of his/her normal

daily activites, and without any or with minimum side effects of the medications (Figure 3-10, 3-11) (42).

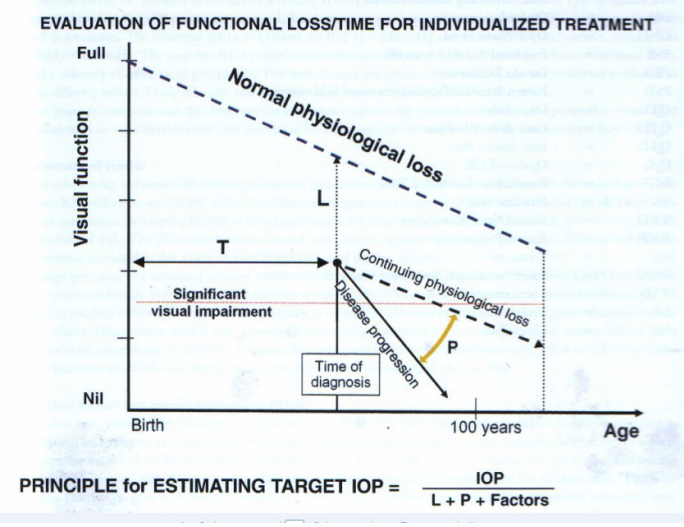


Figure 3.10 Evaluation of functional loss / time for individualized treatment

L: The difference of visual function between the normal for age and the function at the time for diagnosis

P: Angle between physiological loss and disease progression representing progression rate

T: Total functional loss at the time of diagnosis

Factors: Individual features influencing clinical management (i.e. corneal thickness, family history, gonioscopy, IOP range, life expectancy, pigment dispersion / pseudoexfoliation, stage of optic nerve damage, stage of visual field damage, systemic diseases)

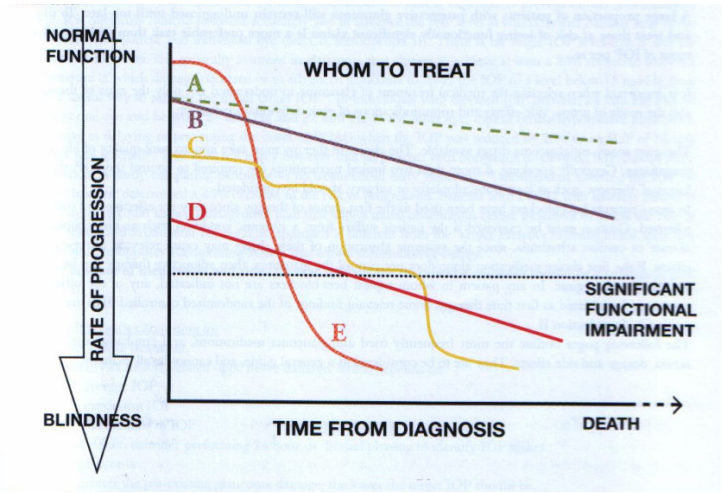


Figure 3.11 Whom to treat? curve for glaucoma

The ganglion cell loss and related functional distruption ratio are different in every patient and could vary even in the same eye with changing risk factors. For the protection of the life quality, patients should stay above the functional distruption threshold. The A curve above defines solely the effect of ageing on the visual function. The patients represented by C, D and E curves would pass under the important functional damage line and be handicapped by the visual dysfunction if they are not treated properly. However, the patient represented by B would not need medication although the disease progresses. Therefore, determination of the rate of progression of the disease is an important part of the management (43).

The management of glaucoma includes IOP control, improvement of the ocular blood flow and direct neuronal protection. Currently, the only treatment modality which is approved to protect the present visual function is IOP control (43). The “target pressure” determined for each patient is the estimated average IOP which would prevent further damage by glaucomatous progression. The management modalities for IOP reduction can be classified as medical treatment, laser treatment and surgical modalities, all of which are beyond the scope of this thesis.

4. CONTRAST SENSITIVITY FUNCTION

4.1 CONTRAST

The difference in lightness between the bright and dark areas represents the contrast of that specific context. **Contrast** is the relationship between the luminance of a brighter area of interest and that of an adjacent darker area. There are various mathematical definitions of luminance contrast.

Mathematically, the difference between the two luminances divided by the lower luminance is called the **Weber Contrast** (C_{Weber}).

$$C_{Weber} = (L_{max} - L_{min}) / L_{min} \quad (4.1)$$

L_{max}: Maximum luminance

L_{min}: Minimum luminance

Simple Contrast (C_{simple}) values are often used in photography, to specify the difference between bright and dark parts of the picture. This definition is not useful for real-world luminances, because of their much higher dynamic range and the logarithmic response characteristics of the human eye.

$$C_{simple} = L_{max} / L_{min} \quad (4.2.)$$

Peak-to-Peak Constrast (Michelson Contrast, Modulation) (CMichelson) is defined as the difference between the foreground and background intensities normalized by the sum:

$$C_{Michelson} = (L_{max} - L_{min}) / (L_{max} + L_{min}) \quad (4.3.)$$

Figure 4-1 shows a grating of low contrast and its luminance profile and a grating of high contrast but same spatial frequency. The dashed line across the luminance profiles represents the average luminance of the gratings (the average of the peaks and troughs). The average luminance (I_{ave}) for both gratings is the same; however, the grating on the bottom has

a greater difference between its peak and the average luminance value; thus, it has a higher contrast.

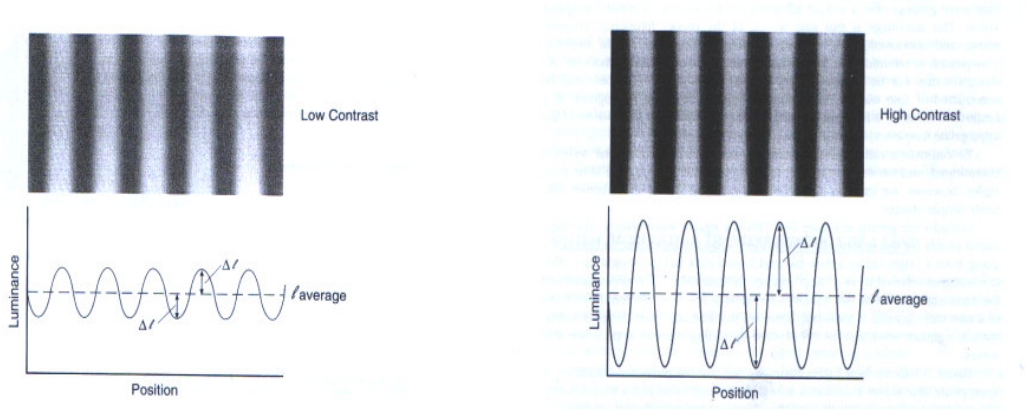


Figure 4.1 Contrast gratings and their luminance profiles

The contrast can also be defined as the ratio of the difference between the peak luminance and average luminance to the average luminance.

There are two common methods in vision research for expressing contrast. Michelson contrast usually applies to periodic patterns such as sine-wave gratings and is defined as the luminance of the brightest area minus the luminance of the dimmest area, divided by their sum (44, 45). For non-periodic patterns, such as letters on charts where dark targets are presented on spatially extended white backgrounds, contrast is typically defined as luminance of the background minus luminance of the letter, divided by the luminance of the background (46).

Contrast, however measured, is expressed as a percentage, from 0% to 100%. When contrast is 0%, there is no edge between the two adjacent areas-that is, no pattern is typically present. For any value greater than 0%, an edge exists though it may or may not be visible, depending on other image-processing capabilities of the detector. Contrast cannot be greater than 100% because of the physical impossibility of making the difference between the peak luminance and average luminance greater than the average luminance. (The trough of the luminance profile is at zero luminance when the difference luminance is equal to the average luminance. It is not possible to have less than zero luminance).

Temporal contrast refers to intensity modulation of a spatially uniform, flickering stimulus. **Spatial contrast** is a physical dimension referring to the light-dark transition of a border or an edge in an image that delineates the existence of a pattern or an object. There could be confusion over the difference between spatial contrast sensitivity and visual acuity. The contrast effect in a specific context affects the visual acuity; and high spatial contrast brings high visual acuity. **Visual acuity** is a measure of spatial-resolving ability of the visual system under conditions of very high contrast (at least 85%); all targets are presented at the same contrast, but their sizes vary during the test (46). Though contrast and acuity are associated with each other, they assess different aspects of spatial vision.

4.2 CONTRAST THRESHOLD AND CONTRAST SENSITIVITY

The amount of contrast a person needs to detect a target is called **contrast threshold**. Contrast threshold can be measured in several types of visual decision-making tasks, such as simple detection (is there something?), discrimination (are two things the same or different?), recognition (is something familiar?), or identification (what is the target?). Typically the detection threshold for a target is the lowest contrast threshold; though there can be exceptions when, for example, the thresholds for detecting and identifying a target are practically identical.

The contrast sensitivity is the measure of the ability of an individual to detect a difference in the luminance between two areas. If the areas occur sequentially in time, the ability to detect a difference in luminance is called **the temporal contrast sensitivity**. If the two areas are next to each other, the ability to detect a difference in luminance is called **the spatial contrast sensitivity**. Contrast sensitivity is a measure of the threshold contrast for seeing the target. Unlike visual acuity measurements, for contrast sensitivity testing; contrast is not kept the same during the test but is varied so that the minimum level of contrast for seeing a target can be determined.

In clinical research or patient care settings, contrast threshold is usually expressed as contrast sensitivity, where sensitivity is simply the reciprocal of threshold. Thus, subjects with low thresholds are said to have high sensitivity, and those with high thresholds have low

sensitivity. Contrast threshold and contrast sensitivity are typically expressed on a logarithmic10 scale, as is the convention in visual sensory science (47). Thus, a contrast threshold of 0.01 (1%) is a log contrast threshold of –2, a contrast sensitivity of 100, and a log contrast sensitivity of 2.

4.3 CONTRAST SENSITIVITY TESTS

The CSF is tested commonly by the sine-wave gratings. Figure 4-2 shows examples of square-wave and sine-wave gratings.

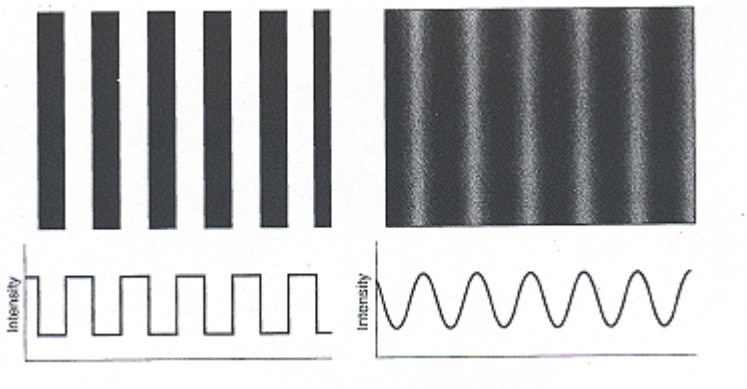


Figure 4.2 Square-wave and sine-wave gratings

In a sine-wave grating, the transition between the bright and dark regions is a gradual transition; indicated by the corresponding luminance profile of the stimulus. However, this gradual transition is perceived as bright and dark bands at the junction of the bright and dark regions. These perceived bands, which do not actually exist, are referred to as **"Mach bands"** (Figure 4-3). The Mach Band effect is another effect that can be explained by the lateral inhibition. Although the intensity is uniform over the width of each bar; the visual appearance is that each strip is darker at its right side than its left. Mach bands could be explained by assuming that the visual system performs a Fourier analysis of the stimulus. The gradual transition between the bright and dark regions consists of low spatial frequencies. As the CSF manifests low sensitivity to low frequencies due to lateral inhibition within the retina, these low frequencies are not perceived. The result is a relative enhancement of high spatial

frequencies; and consequently perception of an enhanced boundary, represented by Mach bands, at the location of a gradual physical transition.

Figure 4.3 The Mach bands

The grating contrast sensitivity tests include targets that are vertically oriented sine-wave gratings, so-named because the luminance of the vertical bars varies sinusoidally over space. The bar gratings presented to the test subject cover a range of spatial frequencies, usually at least the range of 0.5 to 15 cycles per degree (cpd). Contrast sensitivity is determined for each test grating and plotted on log-log axes. For normally sighted observers, this plot, known as **the contrast-sensitivity function** (CSF), has its peak sensitivity at intermediate spatial frequencies (3-6 cpd) with a steep roll-off at high spatial frequencies and a more gradual roll-off at lower frequencies (Figure 4-4).

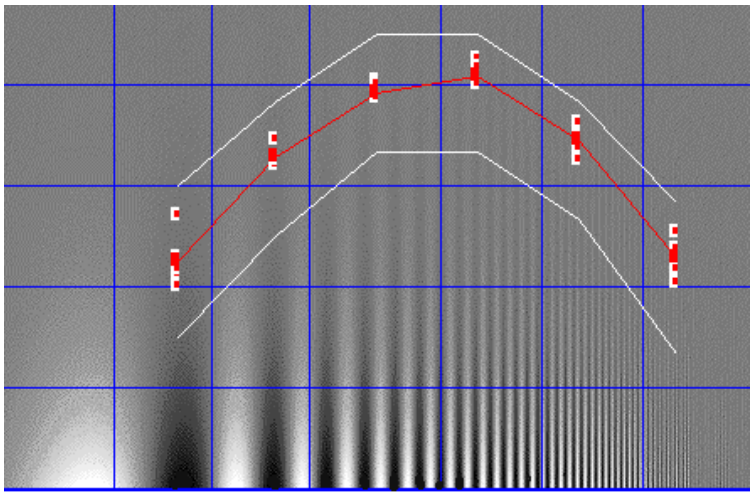


Figure 4.4 Demonstration of the contrast sensitivity function

Thus, the human CSF is a band-pass function. (48). The human visual system will detect a grating of frequency in the region of 4 cpd at lower contrast levels than it will detect gratings of low or high frequencies (Figure 4-5).

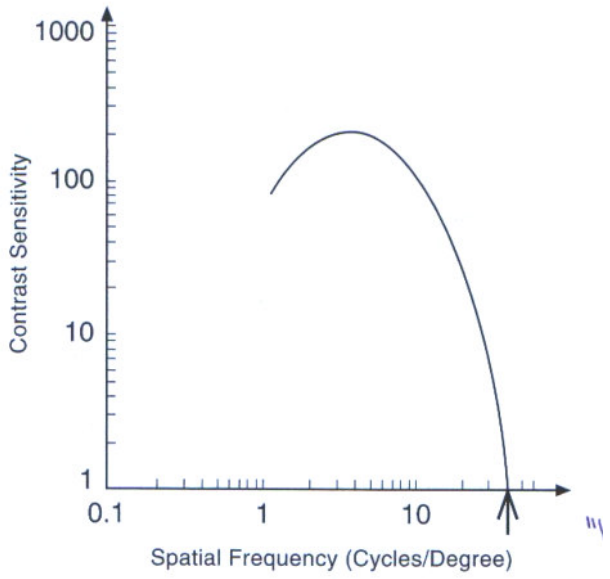


Figure 4.5 Typical human contrast sensitivity function for a normally sighted adult person, measured under photopic conditions.

The normal CSF shows a reduction in sensitivity for both low and high spatial frequencies. The high-frequency cutoff in sensitivity reveals that there is a finite limit to the visual system's ability to resolve detail. This limitation is equivalent to a visual acuity (resolution acuity) task. Even with a high-contrast eye chart, there is a limit to the patient's ability to see small (high-frequency) letters. The highest frequency point where the grating may no longer be resolved, even at 100% contrast is represented in the CSF curve by the point where the curve intercepts the abscissa. It should be noted that the abscissa represents 100% contrast.

The visual system has been thought to act as a Fourier analyzer; by breaking the visual world into its various spatial frequency components and reassemble the components to produce a perception. This is also referred to as **"linear system analysis"**. This view is supported by the existance of independent spatial frequency channels within the visual system (49). Rather than consisting of a single channel that is maximally sensitive to 4cpd, the CSF is

thought as forming an envelope that encompasses numerous narrower channels, each of which is presumably independent. Thus, the CSF forms an envelope for optotype (letters) of various contrast and size (Figure 4-6).

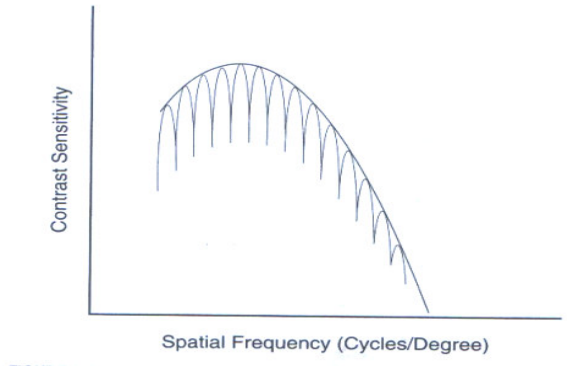


Figure 4.6 The CSF as an envelope for a large number of independent narrow spatial frequency channels

In order to determine the contrast sensitivity function (CSF), the subject is presented with a sine wave grating of a given spatial frequency. Initially this grating is below threshold, that the patient does not see a grating. Instead, the subject sees a screen of even luminance across its surface. The contrast of the grating is increased until a point is reached where the subject reports seeing the grating. The grating appears to emerge out of the background. This represents the contrast threshold for this grating. This procedure is repeated for a large number of different spatial frequencies. The result is a graph that shows contrast sensitivity as a function of spatial frequency (Figure 4-4).

The popularity of sine-wave gratings as test targets can be traced to two traditions. The modulation transfer function (MTF) is a standard way of characterizing the outputs of image-processing devices, especially optical systems. The MTF is the curve that defines the transmitted contrast as a function of changing spatial frequency and is typically determined through testing the system with bar gratings of varying spatial frequency (50, 51). In addition, human visual system could be characterized as multiple neural spatial filters, each with specifiable spatial-tuning characteristics, and the configuration of these filters could serve as the underpinnings of the CSF (52-56).

Initial contrast sensitivity tests in clinical practice and clinical research consisted of computer generated visual images as test targets and software-controlled threshold measurement procedure. The test targets typically were vertically oriented sine-wave gratings. Although computer-based devices are suitable for basic research; because of the perceived impracticability of using computer-controlled tests in the clinic (i.e., high cost, standardization of image calibration and procedures across sites and clinics, unavailability of the normative data, lengthy testing protocols), chart-based methods for assessing contrast sensitivity were developed beginning in the 1980s.

The Arden plates were the first commercially available printed contrast-sensitivity test implanted in the clinic (57). The Arden plates consist of a booklet of seven plates, with one sine-wave grating printed on each plate whose contrast varies from the top to bottom. Gratings range from 0.4 to 6.4cpd, at a test distance of 57cm. The test is administered plate by plate, whereby the examiner slowly uncovers the plate from low to high contrast until the patient notes the first appearance of the bars. The amount of plate uncovered is basically the threshold that is scaled arbitrarily with a score of 1 to 20. Scores are summed across plates to reveal a total contrast-sensitivity score. Arden plates were not without problems with respect to the testing methodology. Threshold is likely to be impacted by the rate by which the examiner uncovers the plates, by ambient lightning conditions, by decision-making criteria effects on the part of the patient, and by a high false-positive rate. Arden plates are not commercially available, today.

Two types of contrast-sensitivity tests are used today-grating tests and letter tests. The first grating test that could be mounted on the wall was **the VCTS** (also commonly called **the VisTech chart**), developed by Ginsburg (58) (Figure 4-7). The VCTS consists of six rows of sine-wave grating patches, each row displaying a grating of a different spatial frequency (1-24cpd). The first patch is a supra-threshold sample patch of the grating. The contrast of the subsequent 8 patches ranges from 0 to a contrast below or above threshold. Gratings are tilted in either of three orientations; supra-threshold examples of these orientations can be viewed at the bottom of the chart. The patient's task is to indicate whether each patch is blank or a grating is seen at a particular orientation. The test takes approximately 6 minutes.

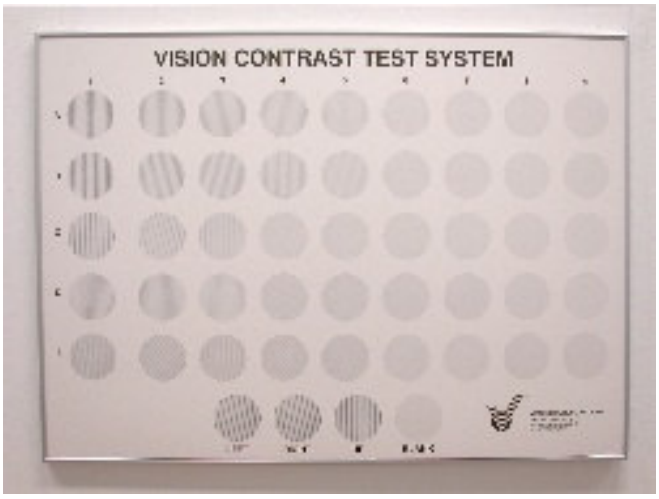


Figure 4.7 The VisTech contrast sensitivity chart

Another grating chart test is **the Sine-Wave Contrast Test**, or **SWCT** (Stereo Optical), which is almost identical to the VCTS. **The Functional Acuity Contrast Test**, or **FACT** (Vision Science Research Corporation), also developed by Ginsburg (59), is a further modification of the VCTS, including smoothing of the patch edges, a standard step size of 0.15 log in contrast change, and a larger patch size (Figure 4-8). In addition to the wall chart design of the VCTS, SCWT, and FACT, view-in designs are also commercially available.

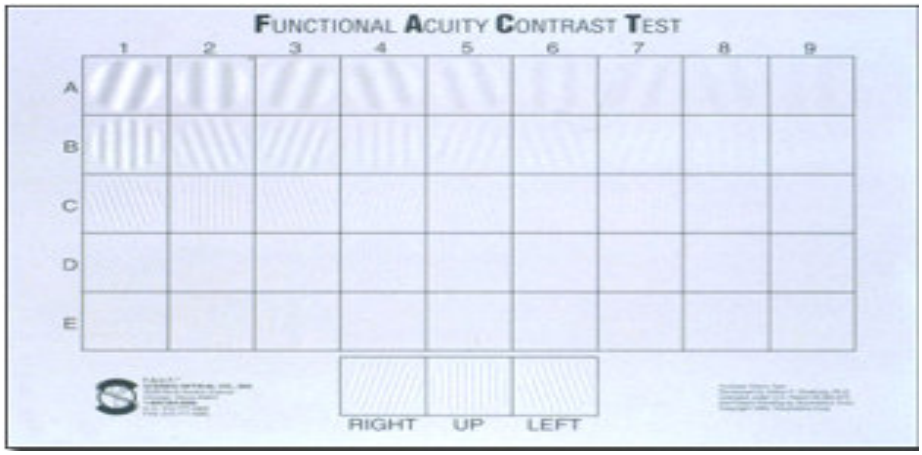


Figure 4.8 The Functional Acuity Contrast Test

The CSV-100 (Vectro Vision) is another grating-based chart. It has an internal retro-illumination system, is mounted on the wall or a stand, and has been used in a few published clinical studies on contrast sensitivity (60-62).

The most commonly used letter chart designed to assess contrast sensitivity is **the Pelli-Robson chart** (Haag-Streit) (63). It is a wall-mounted chart consisting of eight rows of letters with two triplets of letters per row (six letters in all per row). Each letter subtends a visual angle of 2.86° at a 1-m test distance. Contrast of the test letters decreases from nearly 100% at the top to less than 1% at the bottom of the bottom of the chart in 0.15-log unit sensitivity steps for each triplet of letters. The chart is printed on both sides so there is a separate chart with different letters for testing each eye. The patient's task is to start at the top reading the letters aloud and moving through the chart until he/she cannot read anymore. The original scoring system provides 0.15 credit per triplet if at least two of three letters are read correctly (64). A modified scoring system provides 0.05 credit per letter (65). Scores on the Pelli-Robson chart can range from 0 to 2.25 (corresponding to log contrast sensitivity). The Pelli-Robson score provides an estimate of the peak of the contrast-sensitivity function (66-68).

Other contrast-sensitivity tests have been discussed in the literature. **The edge contrast-sensitivity test** measures contrast threshold for an edge formed by a sharp luminance profile, similar to one cycle of a 0.4cpd square wave (69) (Figure 4-9). Developers of this test selected an edge as a target because edges are a naturally present and frequent aspect of our visual environment and thus have high ecologic validity. Edge detection is highly related to the peak of the contrast-sensitivity function. However, no validation data were presented on their specific edge test. This test is not commonly used today in clinical practice or research.

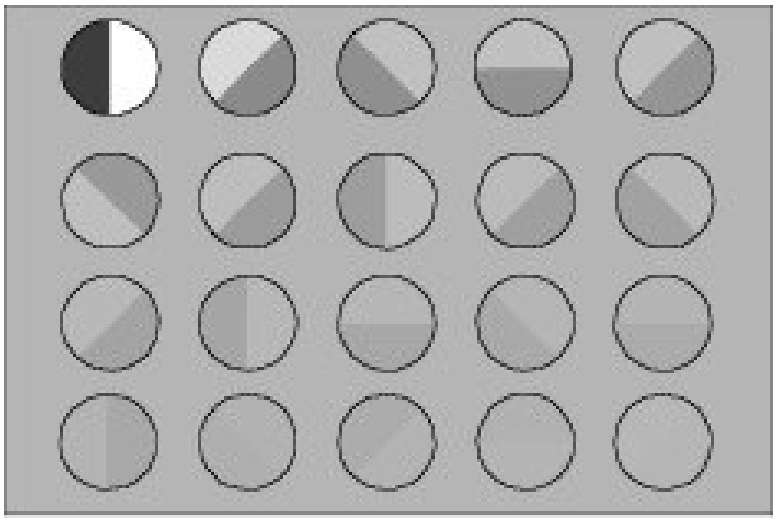


Figure 4.9 The edge contrast sensitivity test

Some charts measure low-contrast acuity, but they are not contrast-sensitivity tests though they are sometimes discussed as such. Some commonly used low-contrast acuity charts with good test-retest reliability include Regan charts (70, 71), the Bailey-Lovie chart (72), and the SKILL card (73). Those charts are designed like acuity charts, with letters decreasing in size down the chart. Low-contrast acuity is associated with contrast sensitivity but is not identical to it (correlation range, 0.3-0.5) (74, 75). It should be noticed that contrast-sensitivity charts and low-contrast acuity charts provide estimates of different visual constructs.

4.4 CONTRAST PERCEPTION IN GLAUCOMA

The optic nerve damage in glaucoma affects contrast sensitivity to a greater extent than visual acuity (76-78). Especially in the early stages of the chronic open angle glaucoma, contrast sensitivity changes are seen much earlier than visual field and optic nerve head changes (79). Both temporal and spatial contrast sensitivity are decreased in glaucomatous eyes. Temporal contrast was shown to decrease in earlier stages of glaucoma, but the clinical use of this fact has not yet been clarified. Additionally, the earlier stages of glaucoma are known to be characterized by loss of contrast sensitivity in low spatial frequencies (80, 81). However, this reduction in contrast sensitivity to stimuli which isolate the magnocellular pathway (low spatial and high temporal frequency) was not significantly different compared with the reduction in contrast sensitivity to stimuli that isolate the parvocellular pathway (82).

The changes in contrast sensitivity, measured by subjective tests like Arden gratings were shown to provide a sensitive means of evaluating patients with POAG (83); and with the use of electronic testing systems that present a wide range of spatial frequencies, abnormalities of contrast sensitivity have been shown (84).

Contrast sensitivity tests are also used in the follow-up of patients, in order to monitor the progression of glaucoma and the effects of treatment. Improvements in spatial and temporal contrast sensitivity after medical, laser or surgical treatment of glaucoma have been reported in various clinical studies (85-89). This improvement had been explained by the effect of the reduced IOP, improved ocular blood flow or neuroprotective effects of the medications.

5. OTHER TESTS FOR EVALUATION OF GLAUCOMA

5.1 COLOR PERCEPTION

The loss of S cones, sensitive to blue wavelength has been shown in glaucoma (90). Three tests are used in clinical practice to evaluate color perception, all of which show the blue color defect; Farnsworth-Munsell 100-Hue test, Farnsworth D-15 test and L'Anthony D-15 desaturated color vision test. Unfortunately, while the sensitivity of color vision tests for the detection of early glaucomatous abnormalities may be higher than that of conventional visual field testing, color tests lack specificity. Cataract, macular degeneration and optic nerve damage due to multiple sclerosis can also cause similar defects in color perception as glaucoma does.

5.2 ELECTROPHYSIOLOGICAL TESTS

The electrophysiological tests that can be done for the evaluation of the retinal nerve fiber layer pathologies include:

a. Electroretinography

b. Pattern Electroretinography

c. Visual Evoked Response

d. Electrooculography

These tests, however, are not routinely performed in clinical practice for the evaluation of glaucoma, but are only involved in visual research studies.

6. EXPERIMENT

6.1 THE GOAL OF THE EXPERIMENT

Based on the above clinical and theoretical information, we expect that the SLC effect diminishes in patients with glaucoma, compared with the normal subjects. Additionally, we expect that the normal enhancement of the contrast increments and decrements is deteriorated in glaucomatous patients. We expect the proposed supra-threshold contrast sensitivity test in this thesis to provide information about the defects in contrast sensitivity in glaucoma. This test is expected to be less prone to subjective errors made by the patient, compared with the visual field test at the threshold level of perception which requires high performance of the subject for a long time. We tested our hypotheses in the following experiments.

6.2 MATERIAL AND METHOD

6.2.1 SUBJECTS

Five normal subjects and five subjects with POAG were selected to be tested in the experiments. All patients with POAG had two or more of the following criteria for the diagnosis of glaucoma:

a. IOP equal to or greater than 21 mmHg on 2 or more occasions, without medication.

b. Visual field loss, which manifests itself as circumscribed paracentral defects, nasal steps, arcuate scotomas, sector shaped defects; or generalized depression of the retinal sensitivity, which manifests itself as decreased MD and PSD levels.

c. Pathological cupping of the optic disc with characteristic changes at the neuroretinal rim.

The demographic and clinical characteristics of the subjects are given in Table 5-1. The subjects were naïve as to the purpose of the experiment. The experiment adhered to NIH ethical guidelines for testing human subjects and an informed consent was obtained from each subject.

Table 6.1 Demographic and clinical characteristics of the subjects.

Number of Patients (Date of Birth)	Best Corrected Visual Acuity		Intraocular Pressure (mmHg); Medication		Cup / Disc Ratio		Pachymetry (µm)		Visual Field Defect Mean Deviation (MD), Pattern Standard Deviation (PSD)		Average Retinal Nerve Fiber Layer Thickness (µm)	
	Right Eye	Left Eye	Right Eye	Left Eye	Right Eye	Left Eye						
GLAUCOMA PATIENTS												
1 (1962)	20/20	20/33	22; Cosopt® 2x1	24; Cosopt® 2x1	0.5	0.6	596	597	MD: -3.31dB (p<2%), PSD: 1.95dB	MD: -6.11dB (p<0.5%), PSD: 2.22dB	115.12	92.75
2 (1981)	20/20	20/20	12; Carteol %2 Lp® 1x1	14; Carteol %2 Lp® 1x1	0.7	0.7	554	548	MD: -5.96dB (p<0.5%), PSD: 3.15 dB (p<5%)	MD: -4.89 dB (p<0.5%), PSD: 2.73 dB (p<10%)	98.30	85.81
3 (1939)	20/22	20/20	17; Carteol %2 Lp® 1x1	19; Carteol %2 Lp® 1x1	0.3	0.4	540	545	MD: -2.37dB (p<5%), PSD: 2.03 dB	MD: -3.05 dB (p<2%), PSD: 2.76 dB (p<10%)	103.30	107.74
4 (1969)	20/20	20/20	15; Carteol %2 Lp® 1x1	20; Carteol %2 Lp® 1x1	0.6	0.6	584	587	MD: -5.27dB (p<0.5%), PSD: 4<57dB (p>0.5%)	MD: -5.76 dB (p<0.5%), PSD: 4.12 dB (p<1%)	90.00	90.73
5 (1969)	20/20	20/20	23; Carteol 2%® 2x1	23; Carteol 2%® 2x1	0.6	0.5	543	545	MD: -8.28dB (p<0.5%), PSD: 5.57dB (p<0.5%)	MD: -3.23 dB (p<2%), PSD: 1.9 dB	104.82	105.87

Number of Patients (Date of Birth)	Best Corrected Visual Acuity		Intraocular Pressure (mmHg); No medication		c/d Ratio		Pachymetry (µm)	Visual Field Defect Mean Deviation (MD), Pattern Standard Deviation (PSD)	Average Retinal Nerve Fiber Layer Thickness (µm)
	Right Eye	Left Eye	Right Eye	Left Eye	Right Eye	Left Eye			
NORMAL SUBJECTS									
6 (1977)	20/20	20/20	13	13	0.2	0.3		Not measured	
7 (1979)	20/20	20/20	12	14	0.3	0.2		Not measured	
8 (1976)	20/20	20/20	15	15	0.2	0.2		Not measured	
9 (1958)	20/20	20/20	16	14	0.3	0.3		Not measured	
10 (1963)	20/20	20/20	11	13	0.2	0.2		Not measured	

Cosopt®: Topical fixed combination of ß-adrenergic receptor blocker and carbonic anhydrase inhibitor agents

Carteol®: Topical ß-adrenergic receptor blocker agent

6.2.2 APPARATUS AND STİMULİ

Twenty-one standard gray scale cards with edges measuring 4.6cm x 4.6 cm were prepared using the computer-graphics program CorelDRAWTM (Corel Inc., Dallas, TX). The cards had homogeneous lightness gray levels between 0% (white) and 100% (black) in program-specific 5% steps and were printed by a 600-dots/inch laser printer. A calibration curve for the standard cards was obtained using a lightmeter (Mannix DLM-1337, Lynbrook, NY) and is given in Figure 6-1.

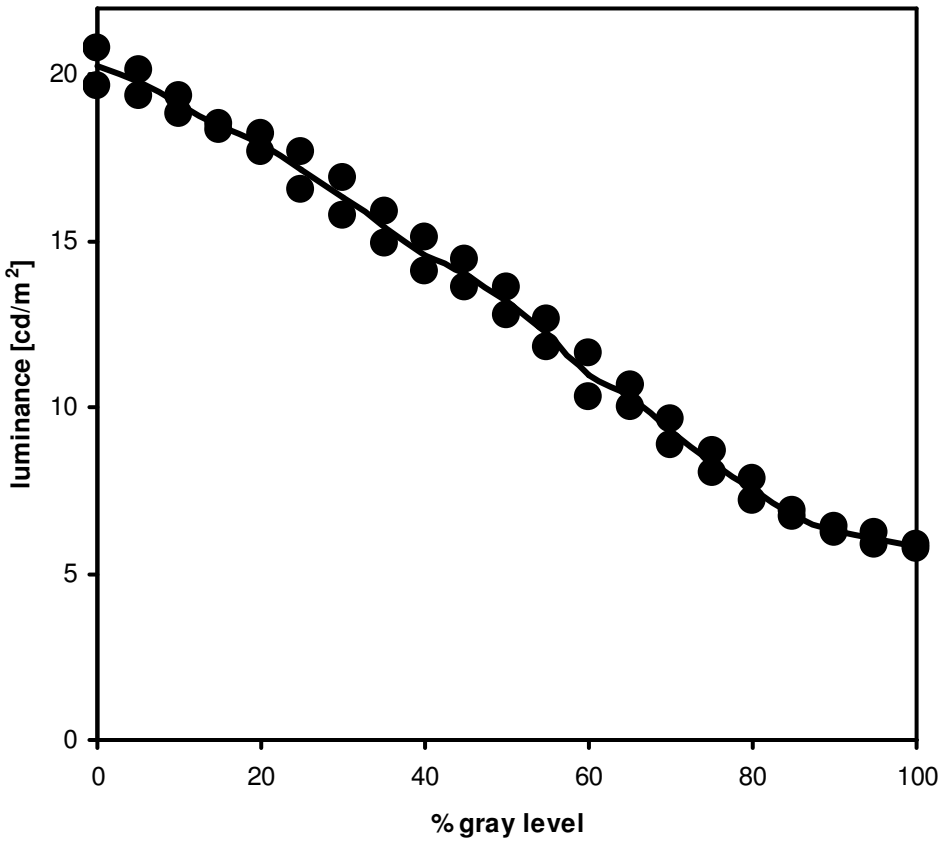


Figure 6.1 Calibration curve for the standard cards obtained from two measurements at each gray level.

The stimuli consisted of 36 cards with dimensions 11cm x 11cm with central gray colored circles, prepared using the same equipment as described above. Half of the cards had white background, whereas the other had black background. Six different circle sizes with the following diameters were used: 0.5, 2.5, 4.5, 6.5, 8.5, and 10.5 cm. The target gray level was either 25%, 50%, or 75%. A background surface was used for comparing the stimuli with the standard gray cards. This surface had a homogeneous 50% gray level with added Gaussian luminance noise. The spatial density of the noise was 35 pixel / mm^2.

The experiment was balanced with respect to the stimulus parameters and the subjects judged the gray level of the target circle in each condition by matching it to one of 21 standard

grays appearing on cards arranged by decreasing luminance. Matching errors were recorded and Michelson contrast values of perceived gray levels were calculated.

6.2.3 PROCEDURE AND DESİGN

The experiment was performed under constant ambient illumination. At the beginning of each experimental session, the stimuli cards were thoroughly shuffled. The 36 stimuli were randomly presented one at a time to the subject. The instructions were given to the subject describing the task, which was to select the standard gray card which has the closest lightness to the perceived lightness of the target circle on the stimuli. The subject made a comparison between the test and the 21 standard cards, which were arrayed on the background surface in order of reflectance; thus, all the standard cards were simultaneously visible. No time limit was imposed on the subject's decision. Each experimental session lasted about 30-60 min. A break was given in the middle of the session to prevent fatigue.

6.2.4 DATA ANALYSİS

Subjects' responses were recorded and the matching errors (subject's selected lightness match minus the veridical lightness level) were determined. Veridicality refers to the correct match as determined by the printed gray level. The errors were expressed as gray-level percentages.

To assess effects of practice, errors were plotted sequentially in the order that the subject gave their responses.

Following the Michelson contrast equation; the luminance contrast of each stimulus was defined as follows:

$$C_{input} = (L_{target} - L_{background}) / (L_{target} + L_{background}) \quad (6.1.)$$

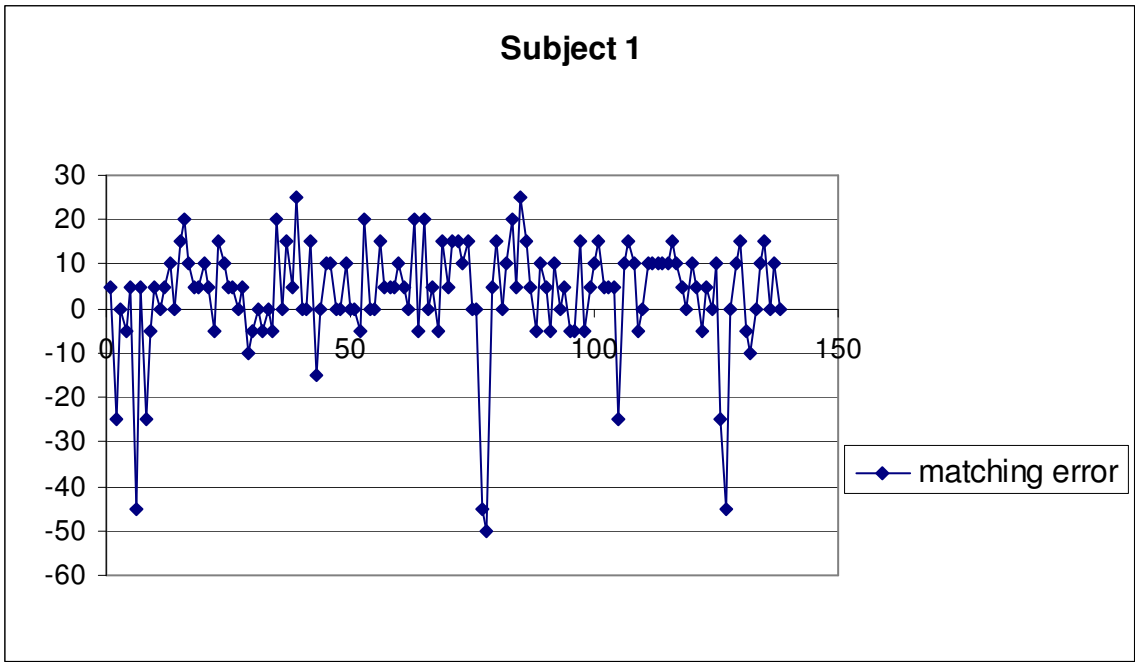
The lightness response of subjects for each stimulus was used to calculate the perceived contrast by using the below formula:

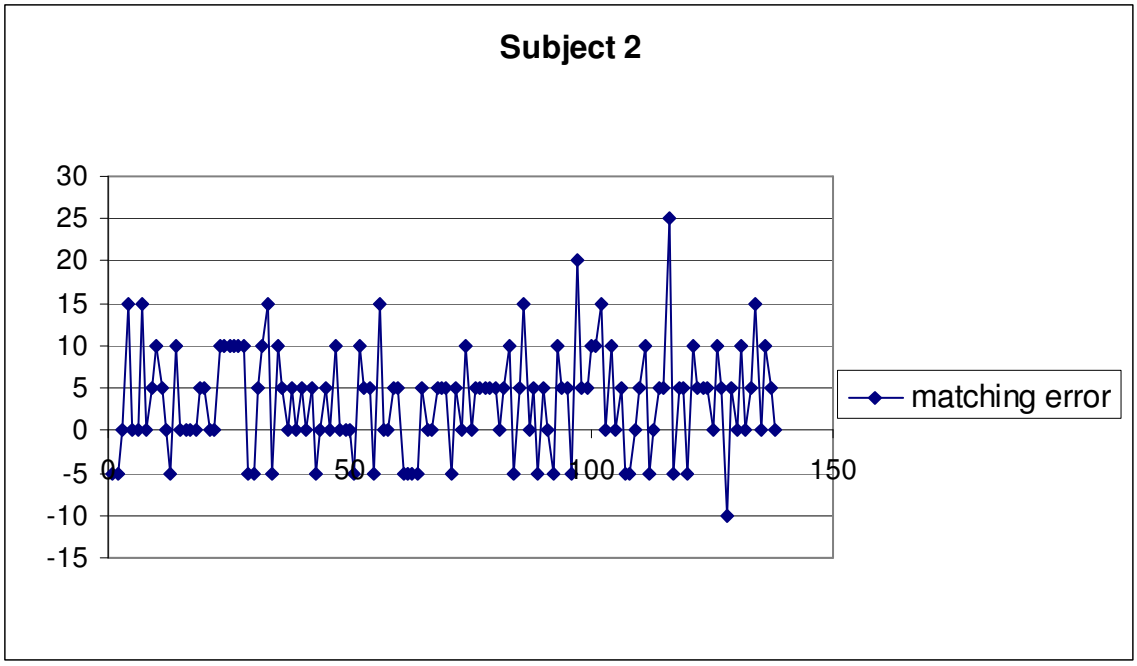
$$C_{output} = (L_{selected\ gray\ level} - L_{background}) / (L_{selected\ gray\ level} + L_{background}) \quad (6.2.)$$

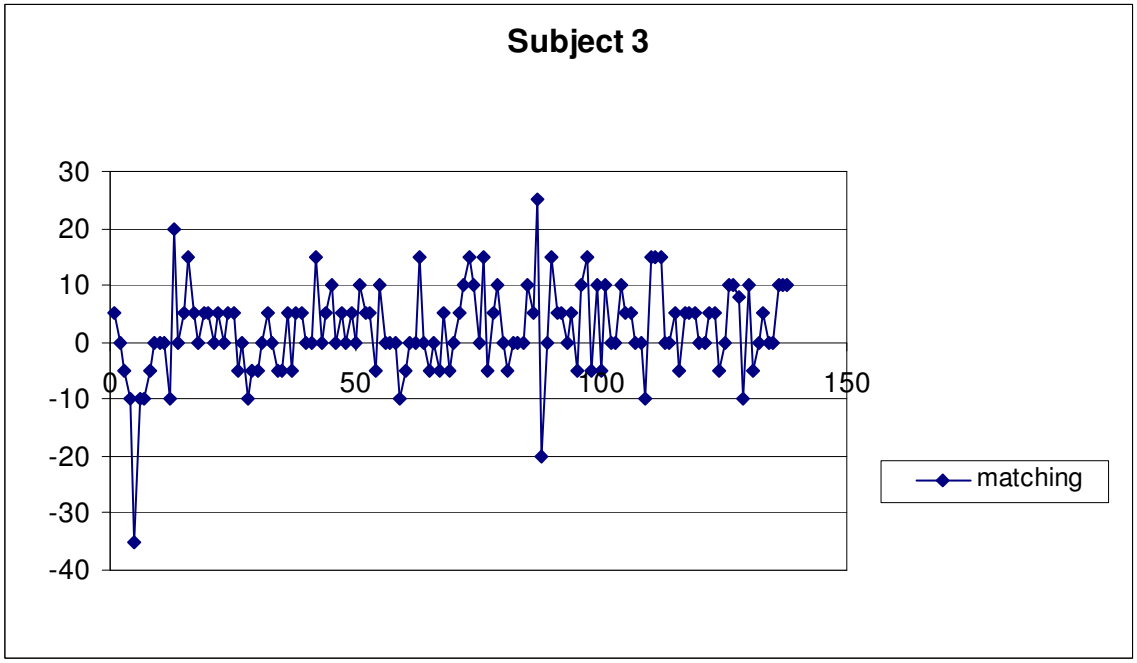
For the statistical analyses, Microsoft Excel Analyse-It toolbox (version 1.73) was used. Statistical analyses were made in order to compare the results from subject groups, with respect to size and luminance of the targets. The perceived contrast levels by the glaucomatous and normal patients were compared with each other and with the true luminance contrast levels by using independent samples t-test.

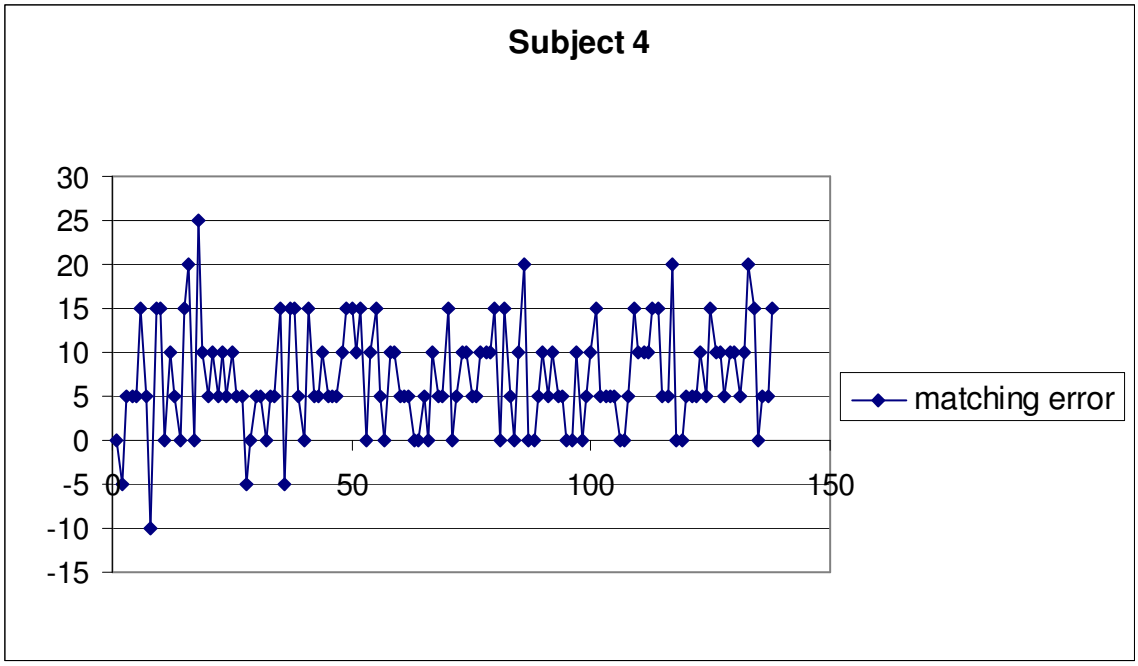
6.3 RESULTS

The errors of each patient were plotted sequentially in the order that the subject gave responses. The performance trend of each subject was close to constant, which shows no practice effects (Figure 6-2).




Subject 2
30
25
20
15
10
5
0
-5
-10
-15
0
50
100
150
matching error


Subject 3
30
20
10
0
-10
-20
-30
-40
0
50
100
150
matching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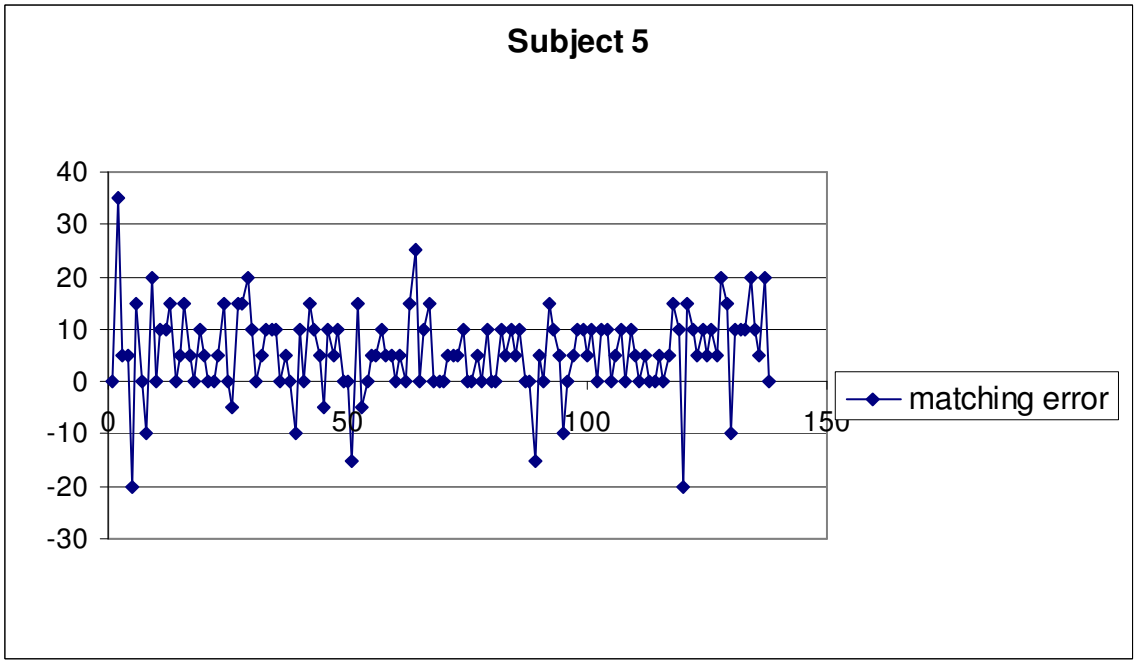
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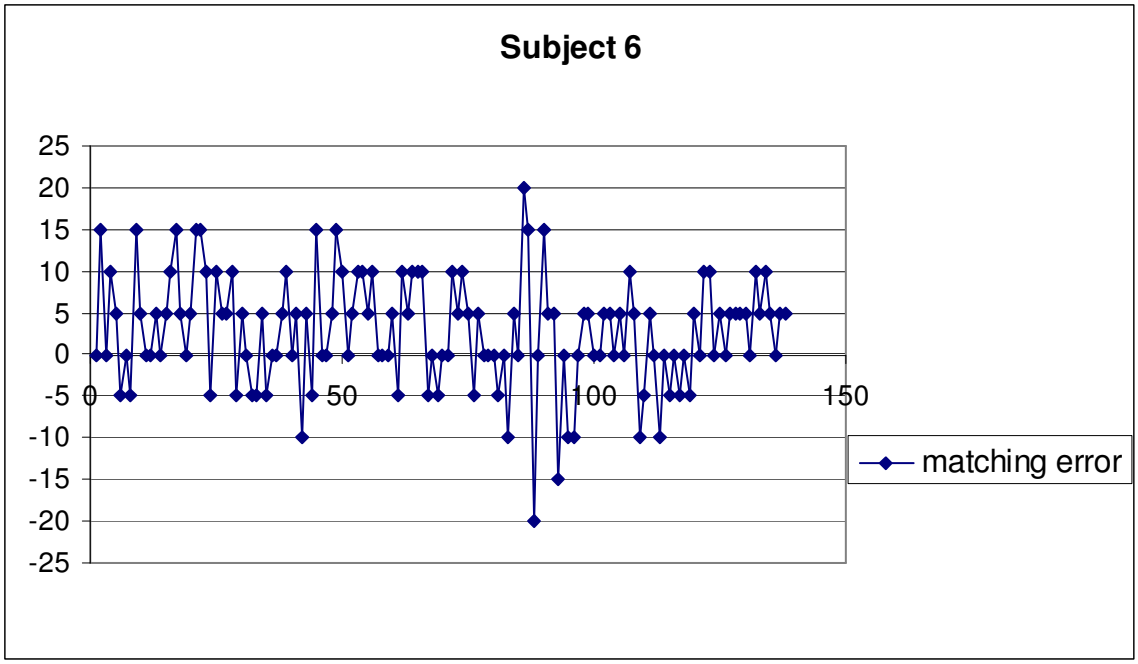
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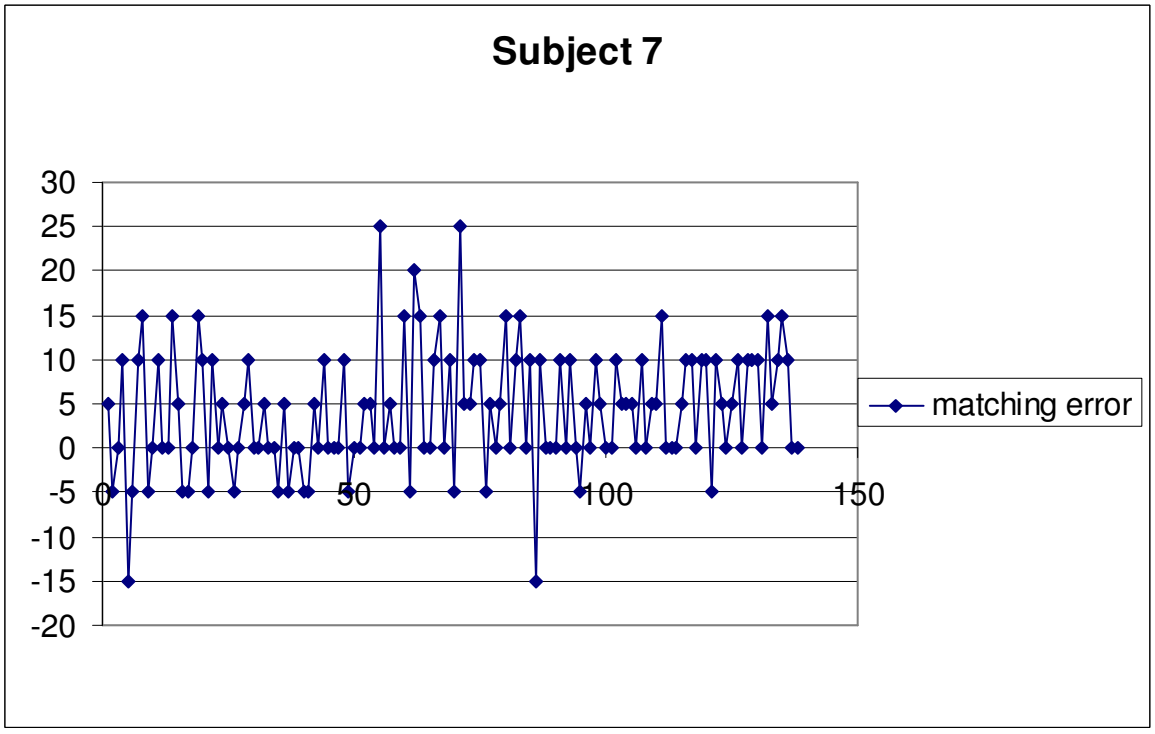
matching error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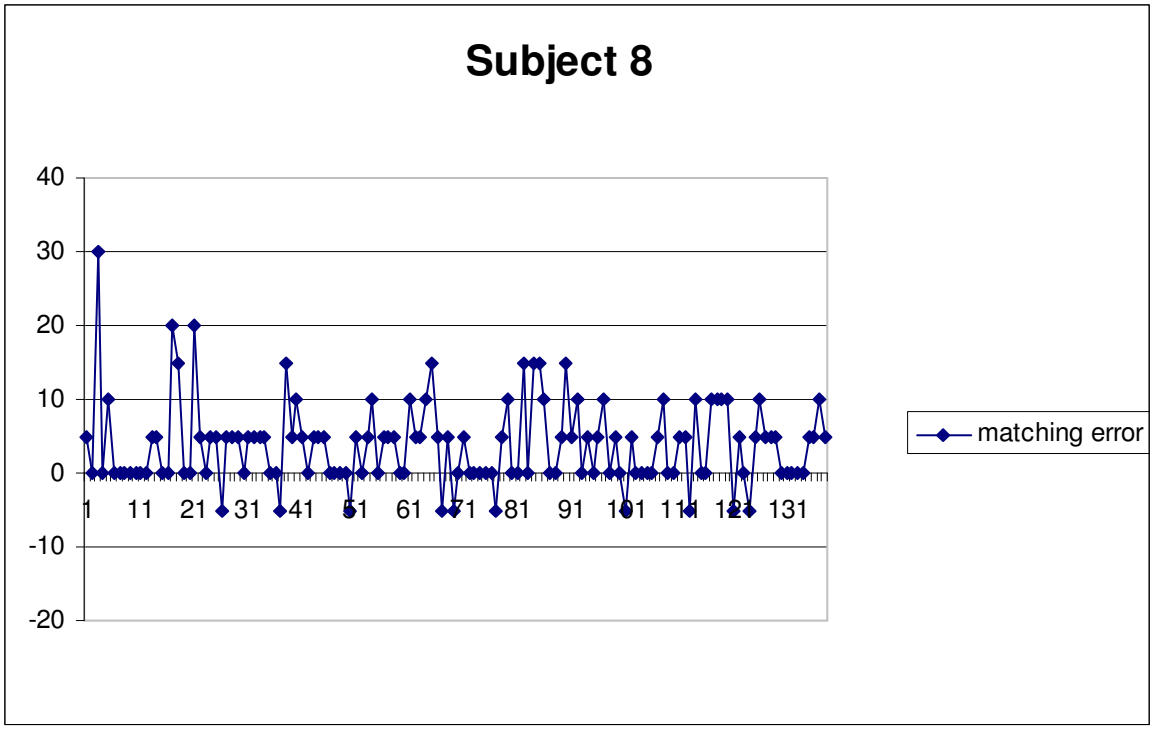
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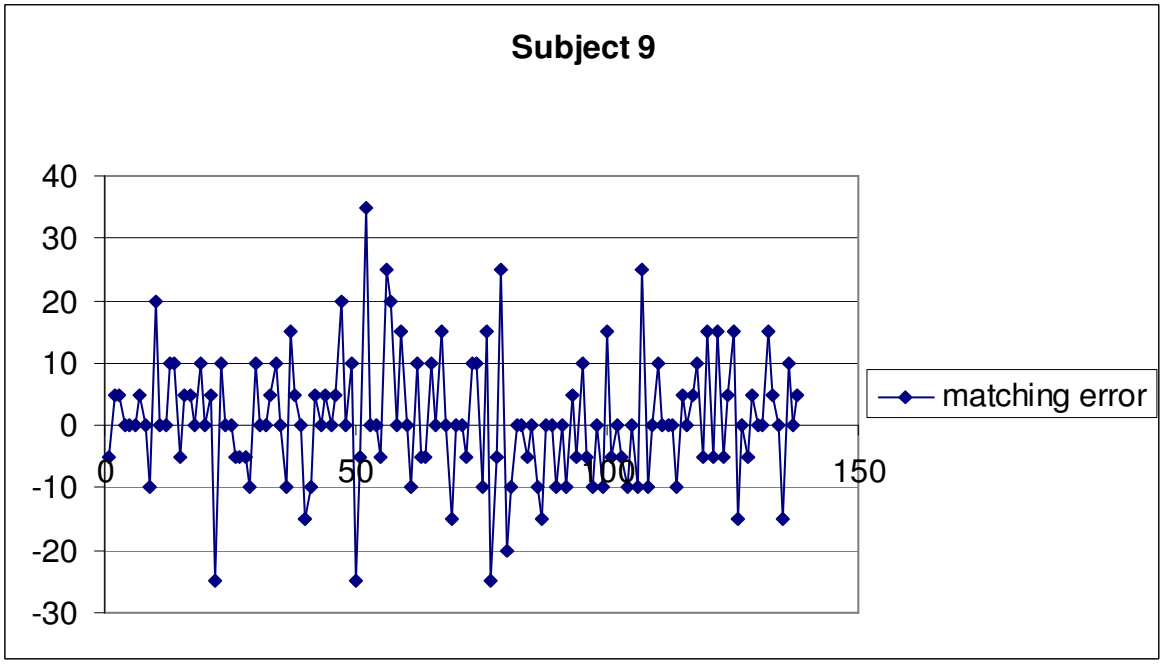
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matching error

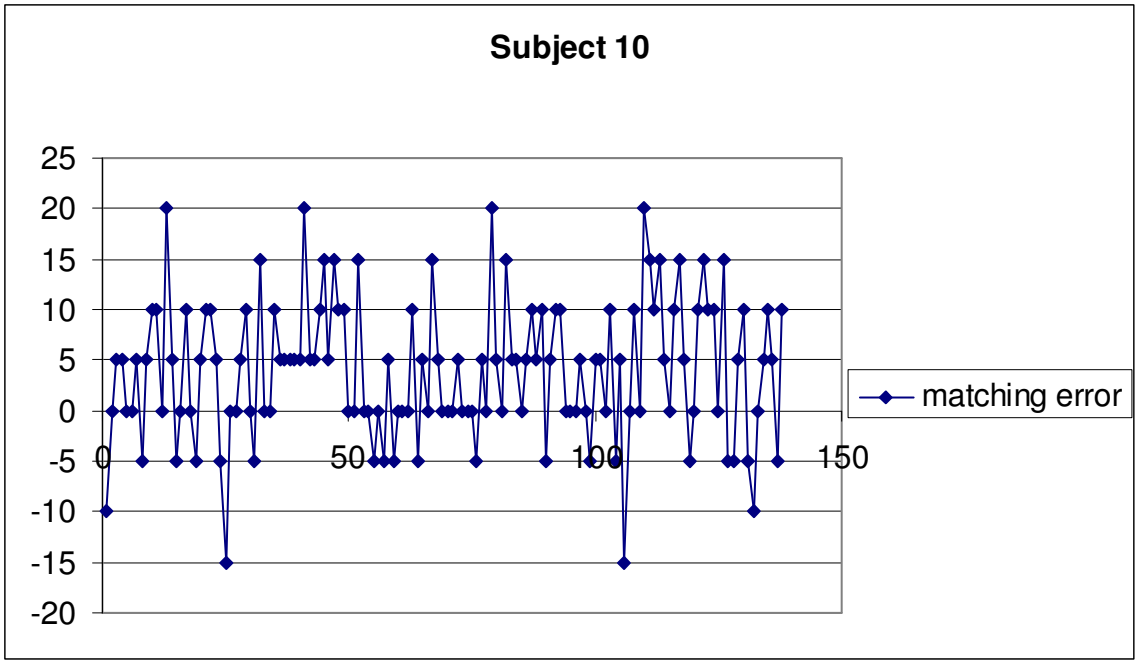

Figure 6.2 The sequential errors of each subject during the experiment

Two-factor ANOVA test with 5 replications showed no interaction between target size and luminance. Given the lack of interaction between target size and luminance on the magnitude of contrast effect, we compared the data for targets of different sizes and of different gray levels in normal and glaucomatous subject groups. The effects of target size were examined after pooling across data for the different gray levels; likewise, the contrast effects were examined after pooling across data for different sizes. The effect of target size on the matching errors and perceived contrast were analysed in pooled data in normal and glaucomatous subjects; as well as separately with 25%, 50% and 75% contrast targets in both groups.

6.3.1 Effects of target size

The error in the perceived lightness of the target is plotted as a function of target size, in all test cards as well as 75%, 50% and 25% target gray levels (Figure 6-3 to 6-10). There were no statistically significant difference between the results of normal and glaucomatous subjects, with respect to varying target sizes ($p>0.05$).

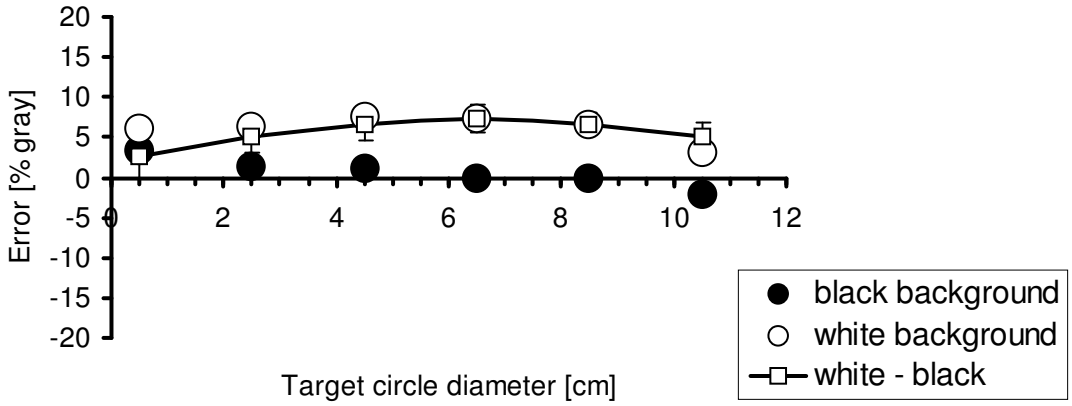

Figure 6.3 The errors of the glaucomatous subjects in the perceived lightness as a function of target size

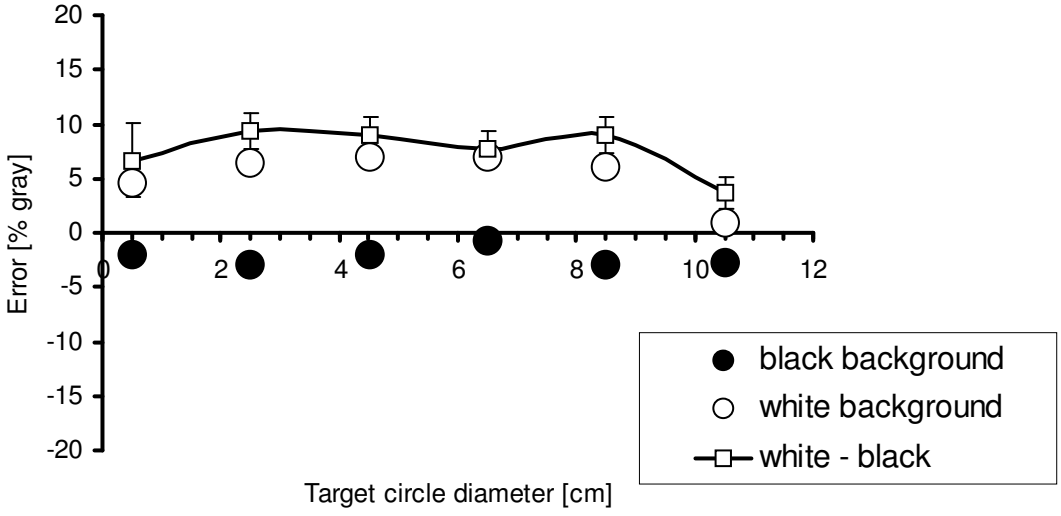

Figure 6.4 The errors of the normal subjects in the perceived lightness as a function of target size

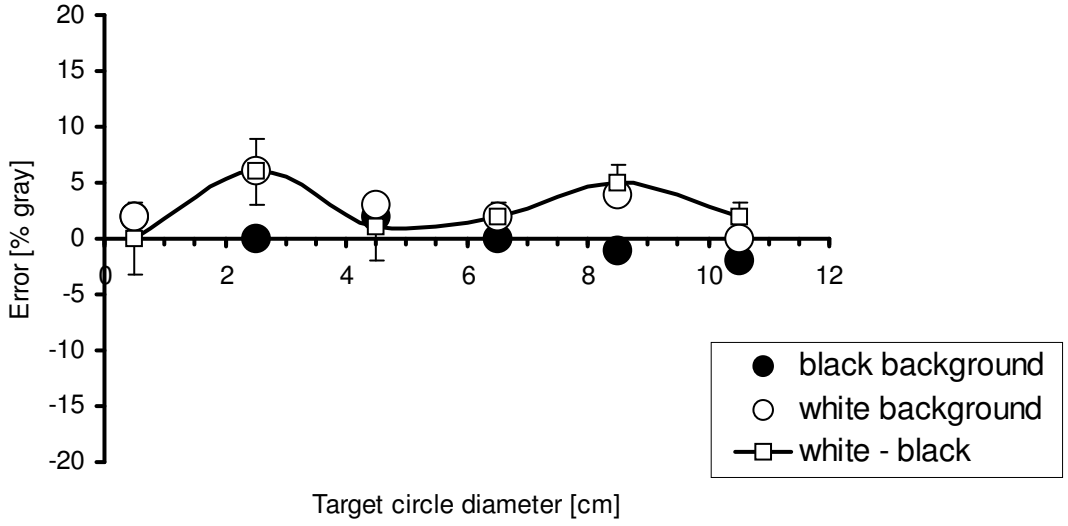

Figure 6.5 The errors of the glaucomatous subjects in the perceived lightness of 75% gray targets as a function of target size.

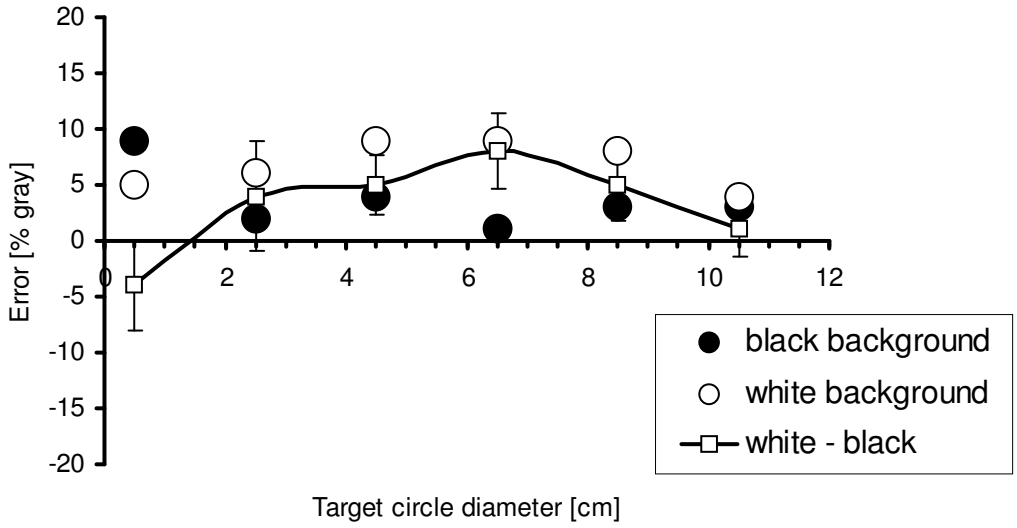

Figure 6.6 The errors of the glaucomatous subjects in the perceived lightness of 50% gray targets as a function of target size.

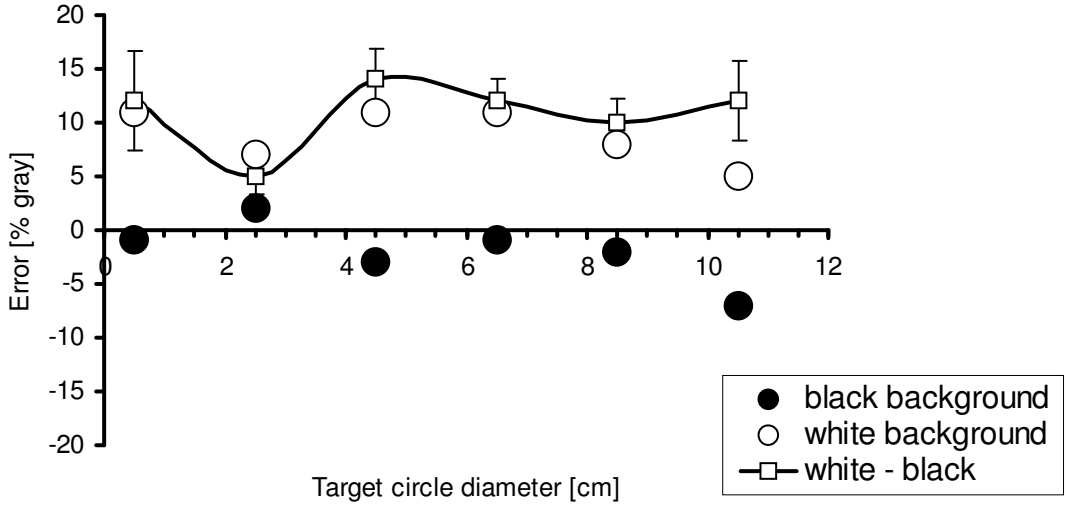

Figure 6.7 The errors of the glaucomatous subjects in the perceived lightness of 25% gray targets as a function of target size.

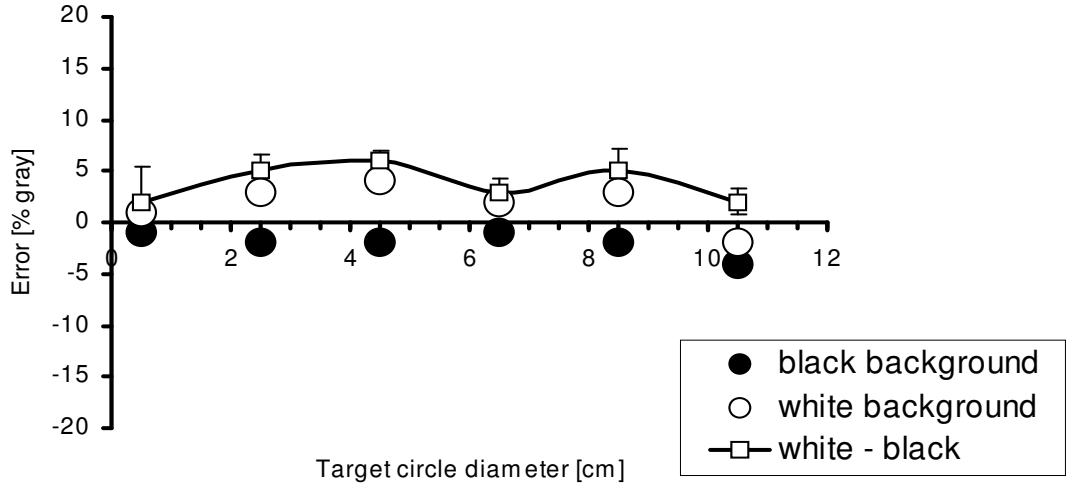

Figure 6.8 The errors of the normal subjects in the perceived lightness of 75% gray targets as a function of target size.

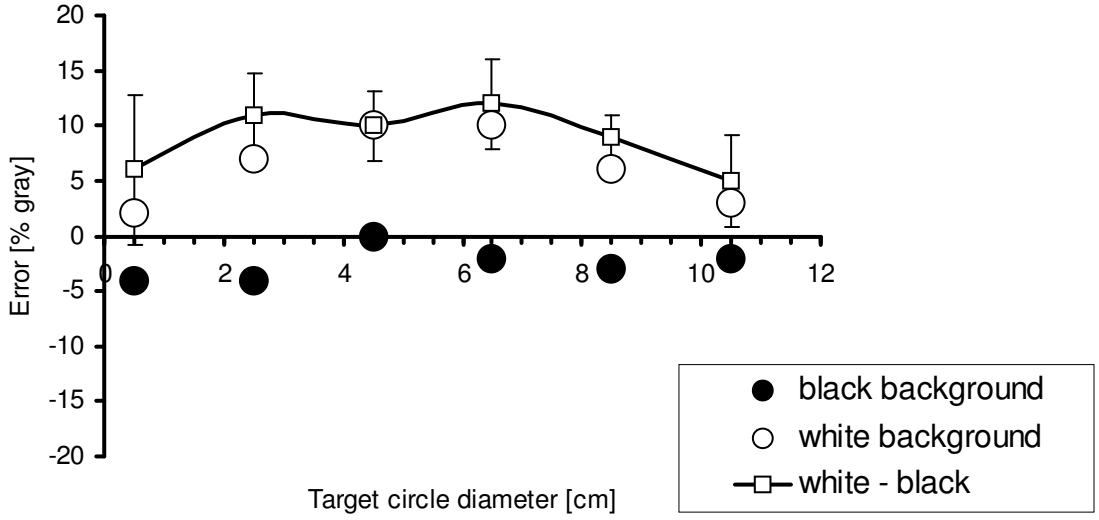

Figure 6.9 The errors of the normal subjects in the perceived lightness of 50% gray targets as a function of target size.

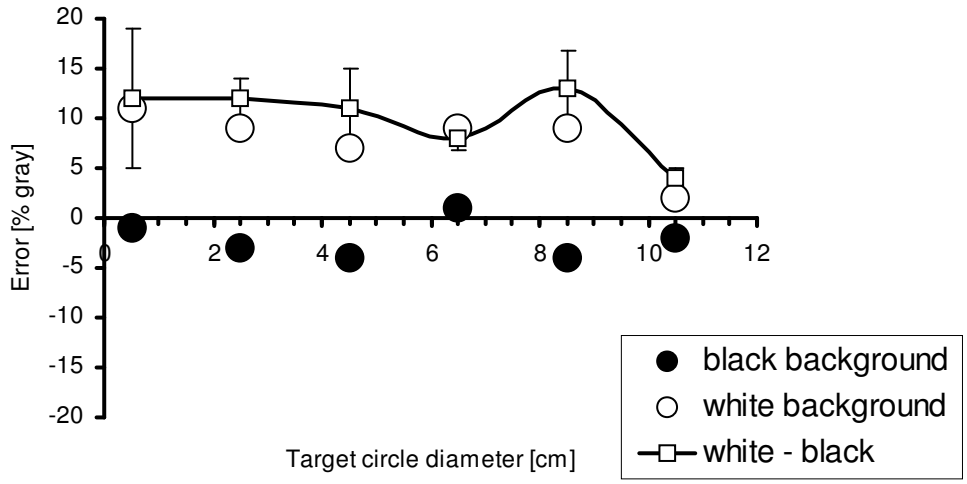

Figure 6.10 The errors of the normal subjects in the perceived lightness of 25% gray targets as a function of target size.

Table 6.2 The perceived contrast in normal and glaucomatous subjects as a function of target size

Diameter / background	Normal Subjects	Glaucoma Patients	p value
10.5 / black	0.370±0.124	0.360±0.134	0.8283
10.5 / white	-0.241±0.130	-0.257±0.133	0.7535
8.5 / black	0.368±0.133	0.348±0.135	0.6850
8.5 / white	-0.277±0.135	-0.283±0.139	0.8980
6.5 / black	0.358±0.131	0.351±0.139	0.8887
6.5 / white	-0.285±0.129	-0.285±0.125	0.9936
4.5 / black	0.363±0.132	0.340±0.150	0.6650
4.5 / white	-0.286±0.142	-0.289±0.129	0.9453
2.5 / black	0.368±0.133	0.344±0.137	0.6306
2.5 / white	-0.280±0.137	-0.281±0.151	0.9862
0.5 / black	0.359±0.137	0.324±0.146	0.5046
0.5 / white	-0.264±0.129	-0.275±0.132	0.8283

Table 6.3 The perceived contrast in normal subjects compared with the true contrast values as a function of target size

Diameter / background	Normal Subjects	Real Contrast	p value
10.5 / black	0.370±0.124	0.353±0.135	0.7216
10.5 / white	-0.241±0.130	-0.237±0.142	0.9236
8.5 / black	0.368±0.133	0.353±0.135	0.7636
8.5 / white	-0.277±0.135	-0.237±0.142	0.4314
6.5 / black	0.358±0.131	0.353±0.135	0.9307
6.5 / white	-0.285±0.129	-0.237±0.142	0.3377
4.5 / black	0.363±0.132	0.353±0.135	0.8502
4.5 / white	-0.286±0.142	-0.237±0.142	0.3533
2.5 / black	0.368±0.133	0.353±0.135	0.7678
2.5 / white	-0.280±0.137	-0.237±0.142	0.4014
0.5 / black	0.359±0.137	0.353±0.0348	0.9150
0.5 / white	-0.264±0.129	-0.237±0.142	0.5816

Table 6.4 The perceived contrast in glaucomatous subjects compared with the true contrast values as a function of target size

Diameter / background	Glaucoma Patients	Real Contrast	p value
10.5 / black	0.360±0.134	0.353±0.135	0.8927
10.5 / white	-0.257±0.133	-0.237±0.142	0.6922
8.5 / black	0.348±0.135	0.353±0.135	0.9170
8.5 / white	-0.283±0.139	-0.237±0.142	0.3689
6.5 / black	0.351±0.139	0.353±0.135	0.9574
6.5 / white	-0.285±0.125	-0.237±0.142	0.3269
4.5 / black	0.340±0.150	0.353±0.135	0.8005
4.5 / white	-0.289±0.129	-0.237±0.142	0.2995
2.5 / black	0.344±0.137	0.353±0.135	0.8513
2.5 / white	-0.281±0.151	-0.237±0.142	0.4158
0.5 / black	0.324±0.146	0.353±0.0348	0.5692
0.5 / white	-0.275±0.132	-0.237±0.142	0.4538

The contrast effects of the targets were also analyzed in normal and glaucoma groups, in different target sizes. The perceived contrast values at each target size and background were calculated in normal and glaucomatous groups; and compared between the two groups and between each group with the true contrast level (Table 6-2 to 6-4). The differences in the perceived contrasts between the two group of subjects were not statistically significant, in all of the target size subgroups ($p>0.05$). Additionally, the difference between the perceived contrast and the true contrast was not statistically significant in any of the groups, with respect to varying target sizes ($p>0.05$) (Figure 6-11)

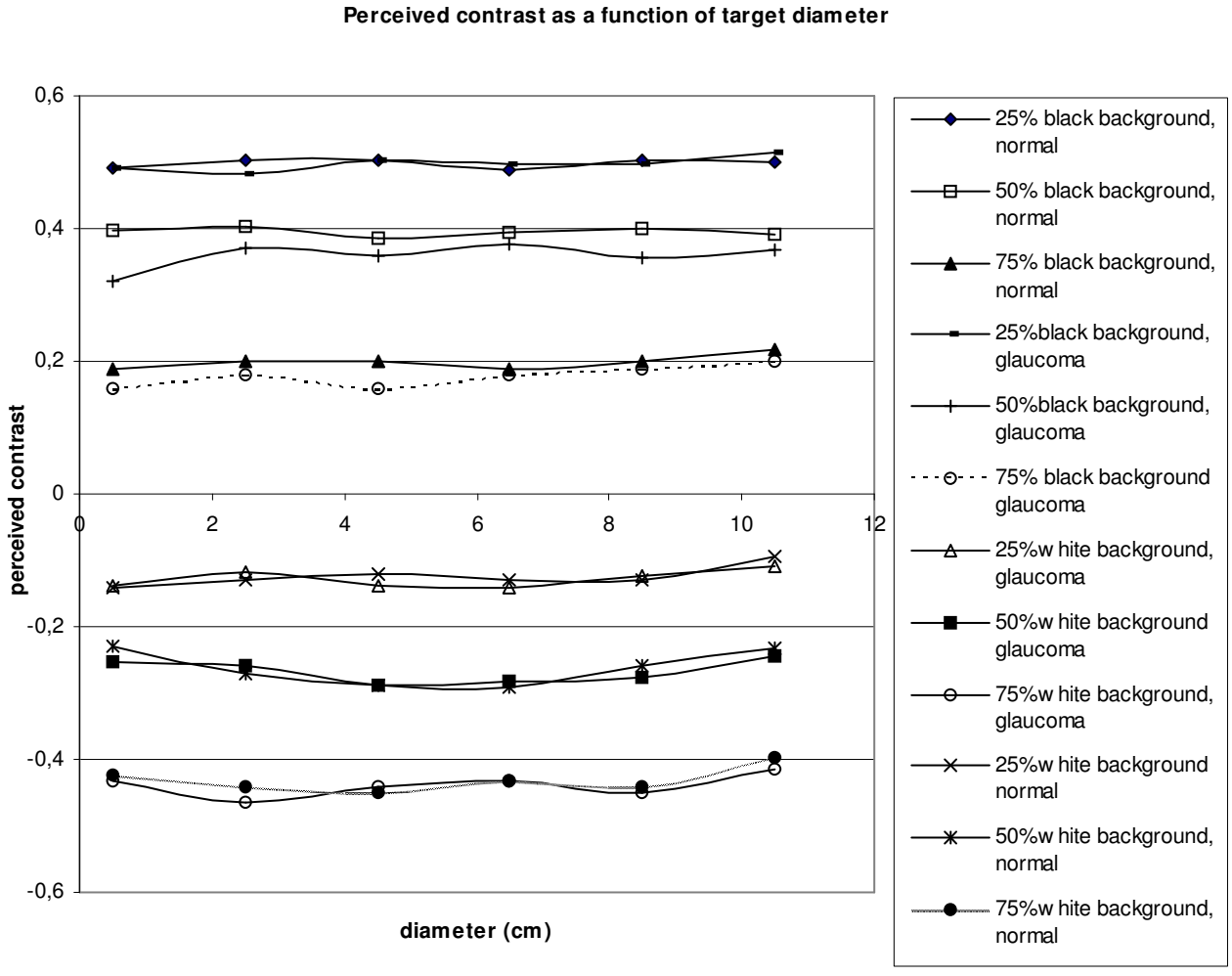

Figure 6.11 The perceived contrast as a function of target size

Therefore, no significant effect of target size was detected for either normal or glaucomatous subjects.

6.3.2 Effects of target luminance

When matching errors were directly compared, both normal and glaucomatous subjects perceived targets on white backgrounds as darker than the veridical gray level. Normal subjects perceived targets on a black background as lighter than veridical, but not fully symmetric with the effect on white background. However, glaucomatous subjects still matched darker than the veridical gray level to targets on black backgrounds, which suggest an assimilation effect. In every condition and for both subject groups, a robust simultaneous-lightness-contrast effect was observed overall, even though complementary test-stimuli with black and white backgrounds were not presented simultaneously (Figure 6-12, 6-13).

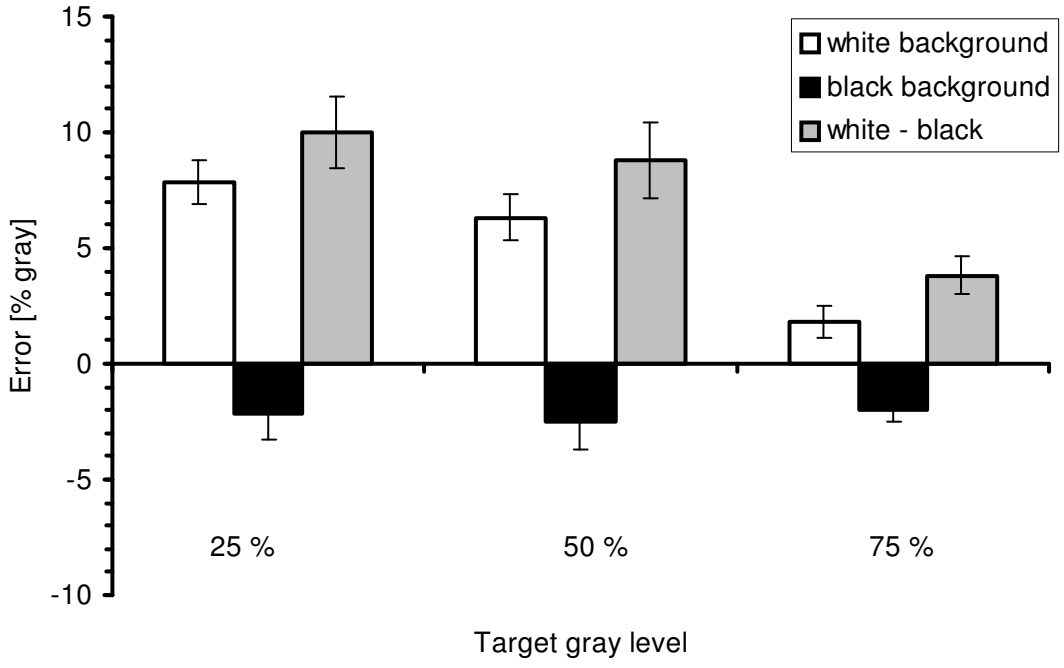

Figure 6.12 The errors of the normal subjects as a function of target gray level

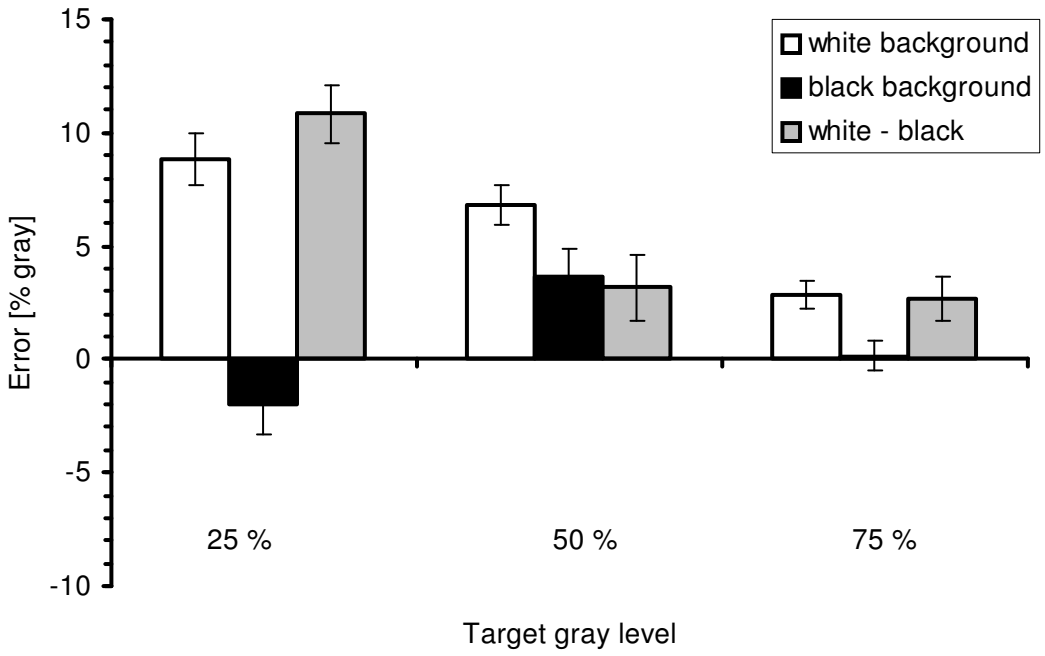

Figure 6.13 The errors of the glaucomatous subjects as a function of target gray level

The main effect of input contrast was significant, as expected. All subjects overestimated contrast decrements (black target on white background). Normal and glaucomatous subjects did not differ significantly in this perceived enhancement of contrast decrements (two-sample t-tests: $p > 0.28$). However, they did differ in their perception of contrast increments (two-sample t-tests: $p \leq 0.01$), except for the largest increment. Normal subjects enhanced contrast increments at 75% gray levels on black background (two-sample t-tests: $p = 0.0003$), whereas glaucomatous subjects showed no enhancement. Similarly, glaucomatous subjects showed no enhancement of contrast increments at 50% gray levels on black background and even displayed perception of contrast decrement (two-sample t-tests: $p = 0.0008$); whereas normal subjects showed enhancement, even though this enhancement was not statistically significant (Table 6-5 to 6-7, Figure 6-14 to 6-20).

Table 6.5 The perceived contrast in normal and glaucomatous subjects as a function of gray level and background color

Gray level / background	Normal Subjects	Glaucoma Patients	p value
25% / black	0.498±0.018	0.497±0.025	0.8274
25% / white	-0.124±0.029	-0.129±0.031	0.5351
50% / black	0.395±0.035	0.359±0.045	**0.001**
50% / white	-0.262±0.043	-0.267±0.039	0.6324
75% / black	0.199±0.028	0.177±0.038	**0.0147**
75% / white	-0.431±0.033	-0.439±0.028	0.2862

Table 6.6 The perceived contrast in normal subjects compared with the true contrast values as a function of gray level and background color

Gray level / background	Normal Subjects	Real Contrast	p value
25% / black	0.498±0.018	0.493	0.0975
25% / white	-0.124±0.029	-0.083	**<0.0001**
50% / black	0.395±0.035	0.388	0.2584
50% / white	-0.262±0.043	-0.211	**<0.0001**
75% / black	0.199±0.028	0.179	**0.0003**
75% / white	-0.431±0.033	-0.416	**0.0158**

Table 6.7 The perceived contrast in glaucomatous subjects compared with the true contrast values as a function of gray level and background color

Gray level / background	Glaucoma Patients	Real Contrast	p value
25% / black	0.497±0.025	0.493	0.3317
25% / white	-0.129±0.031	-0.083	**<0.0001**
50% / black	0.359±0.045	0.388	**0.0008**
50% / white	-0.267±0.039	-0.211	**<0.0001**
75% / black	0.177±0.038	0.179	0.7753
75% / white	-0.439±0.028	-0.416	**<0.0001**

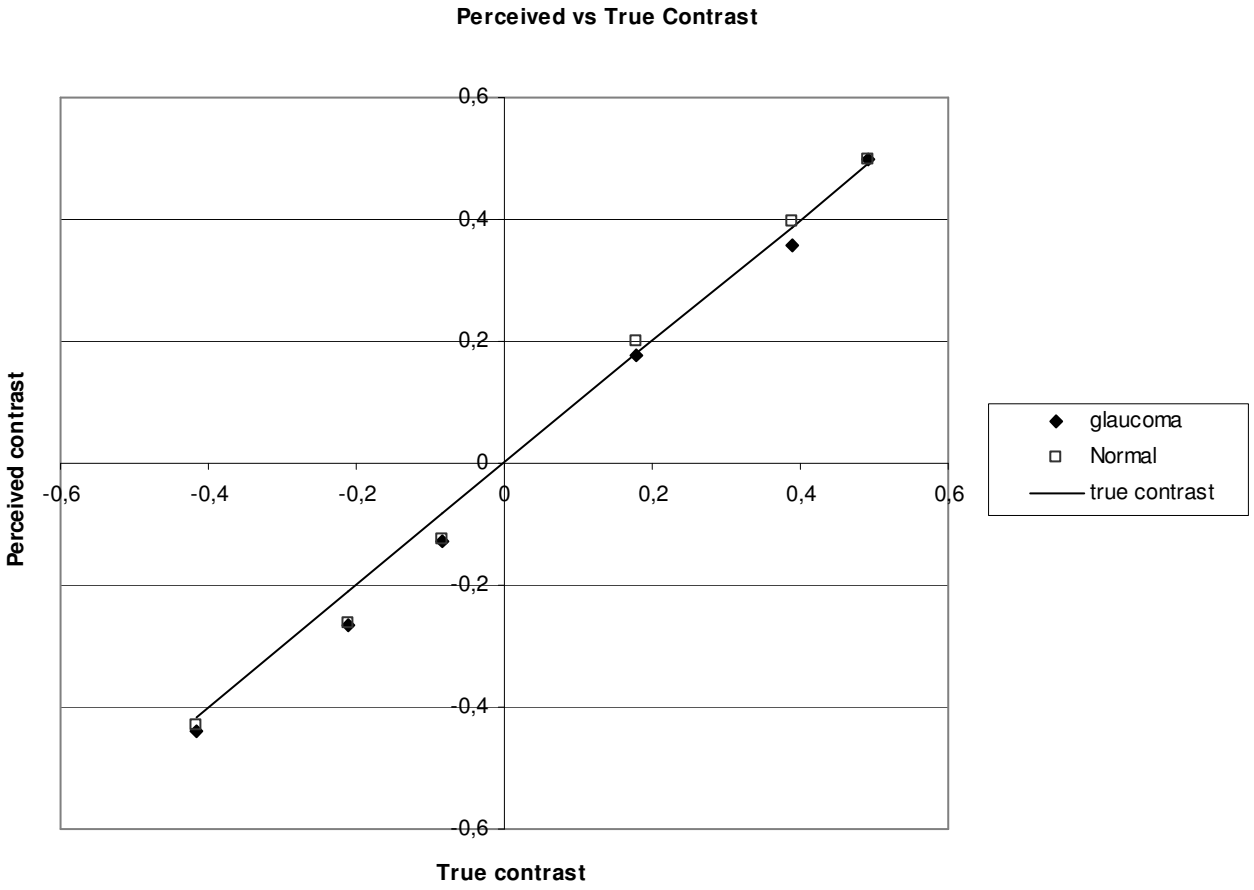

Figure 6.14 The perceived contrast as a function of true contrast

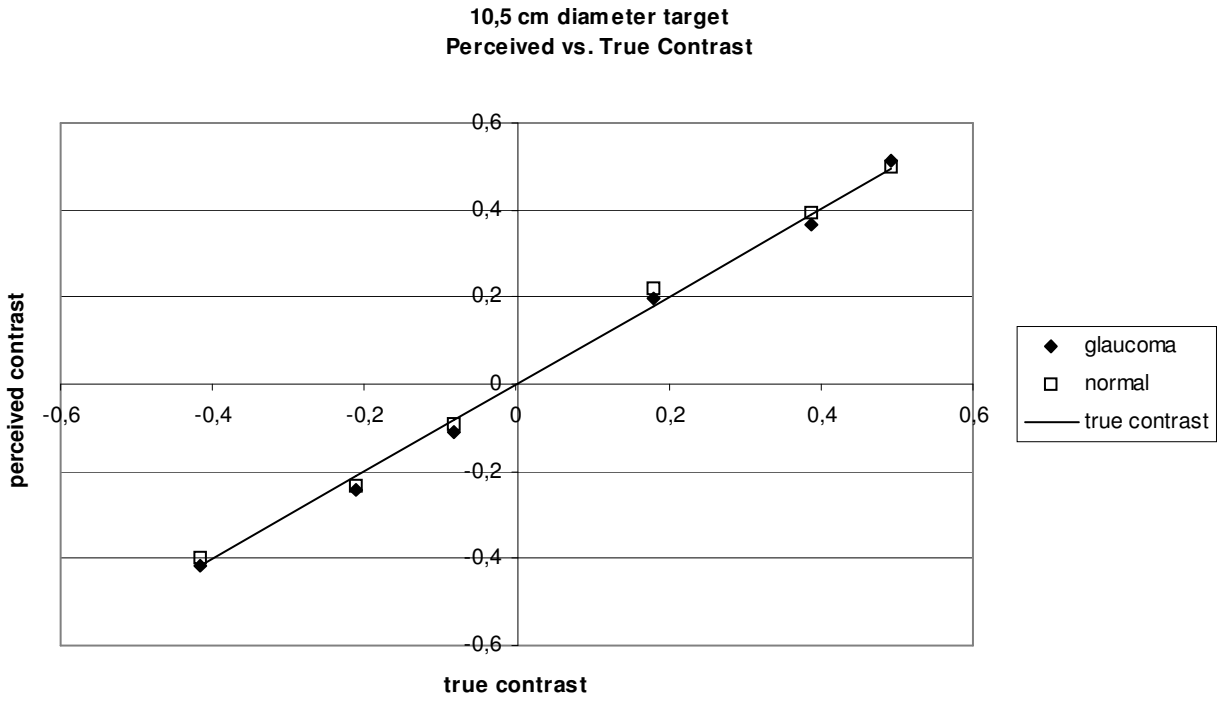

Figure 6.15 The perceived contrast as a function of true contrast in targets with 10,5cm diameter

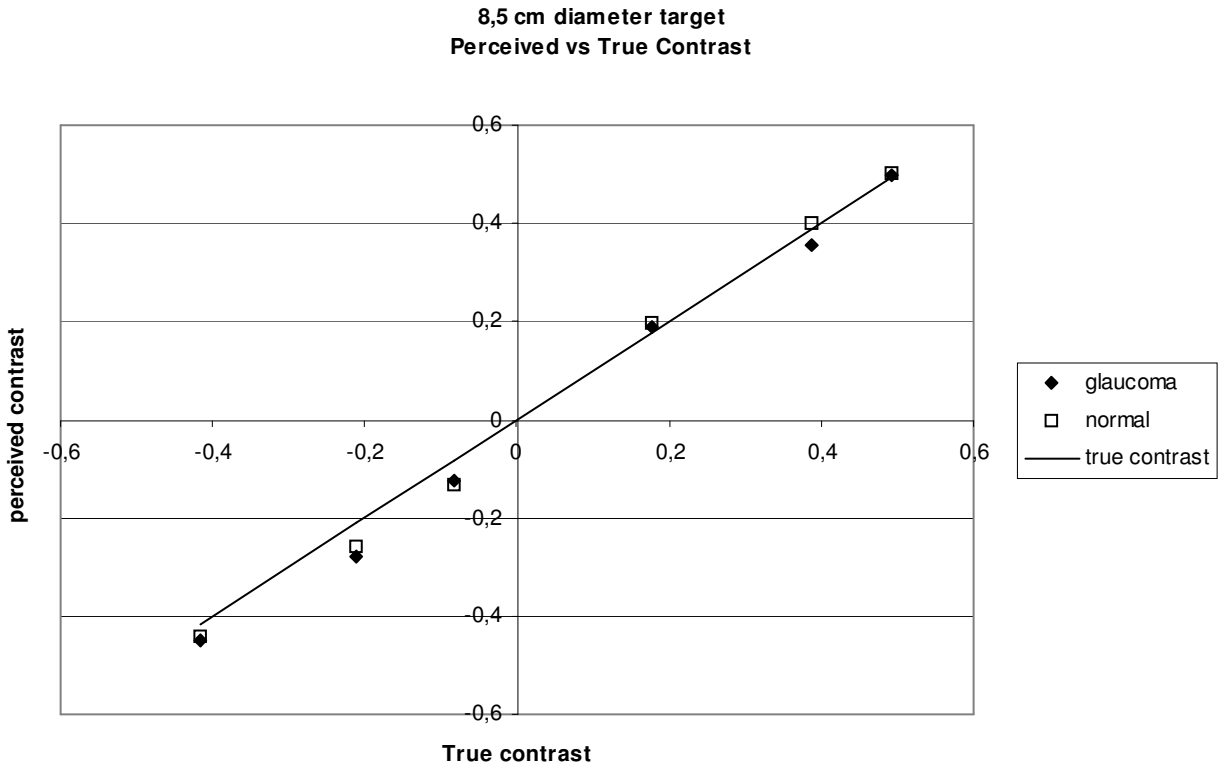

Figure 6.16 The perceived contrast as a function of true contrast in targets with 8,5cm diameter

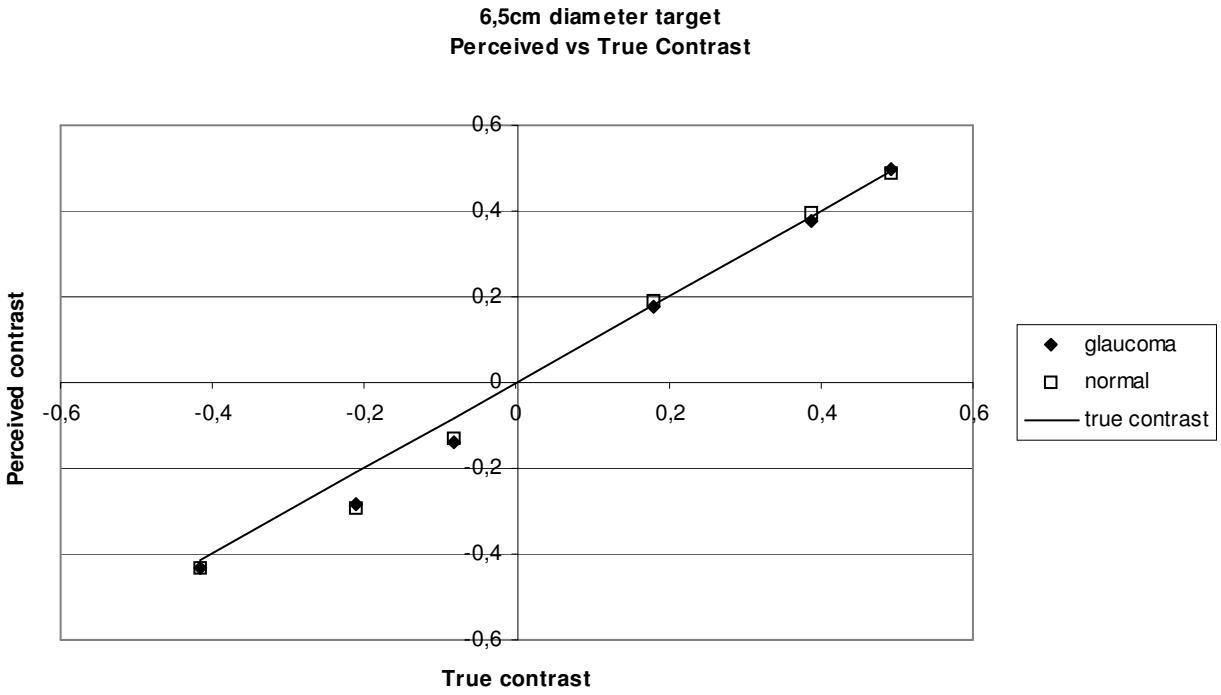

Figure 6.17 The perceived contrast as a function of true contrast in targets with 6,5cm diameter

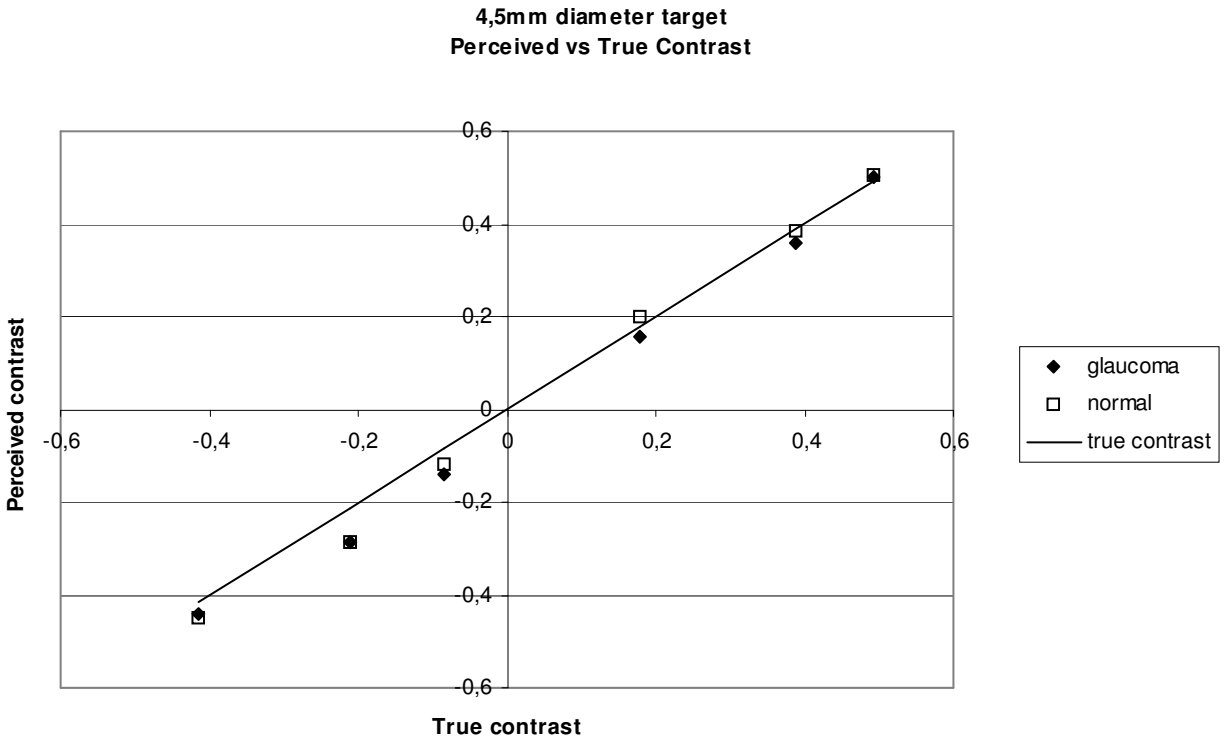

Figure 6.18 The perceived contrast as a function of true contrast in targets with 4,5cm diameter

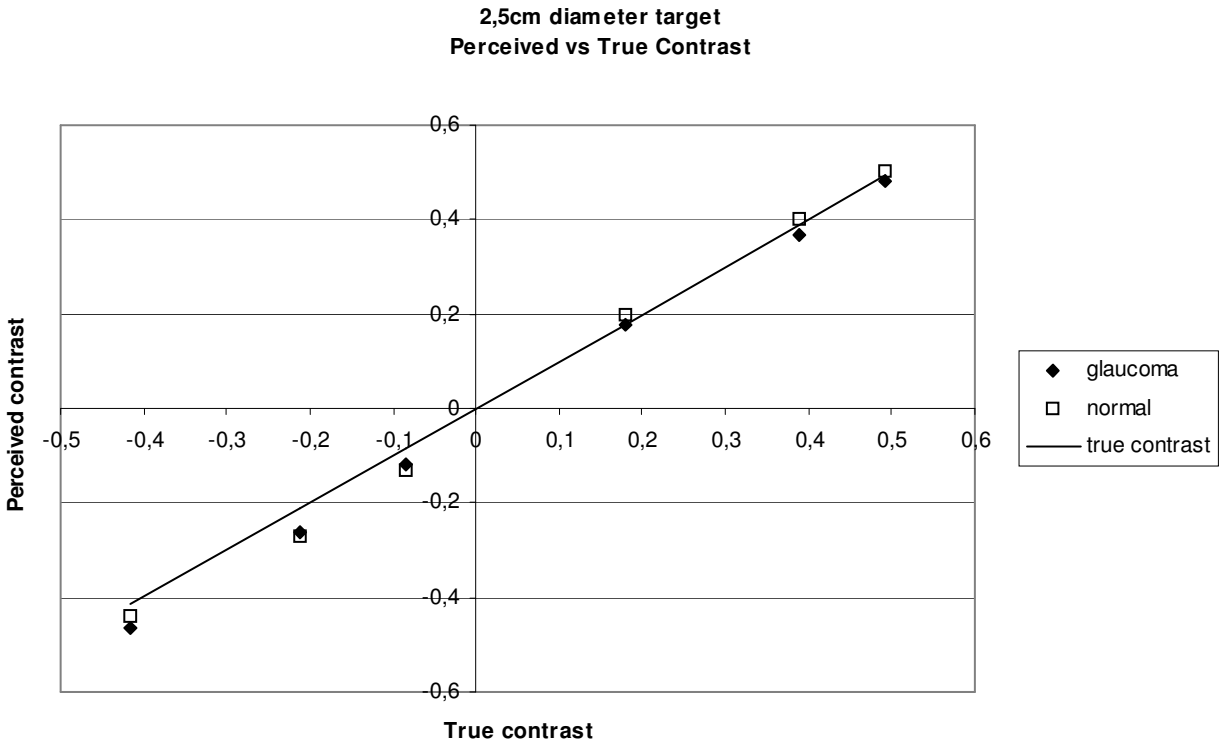

Figure 6.19 The perceived contrast as a function of true contrast in targets with 2,5cm diameter

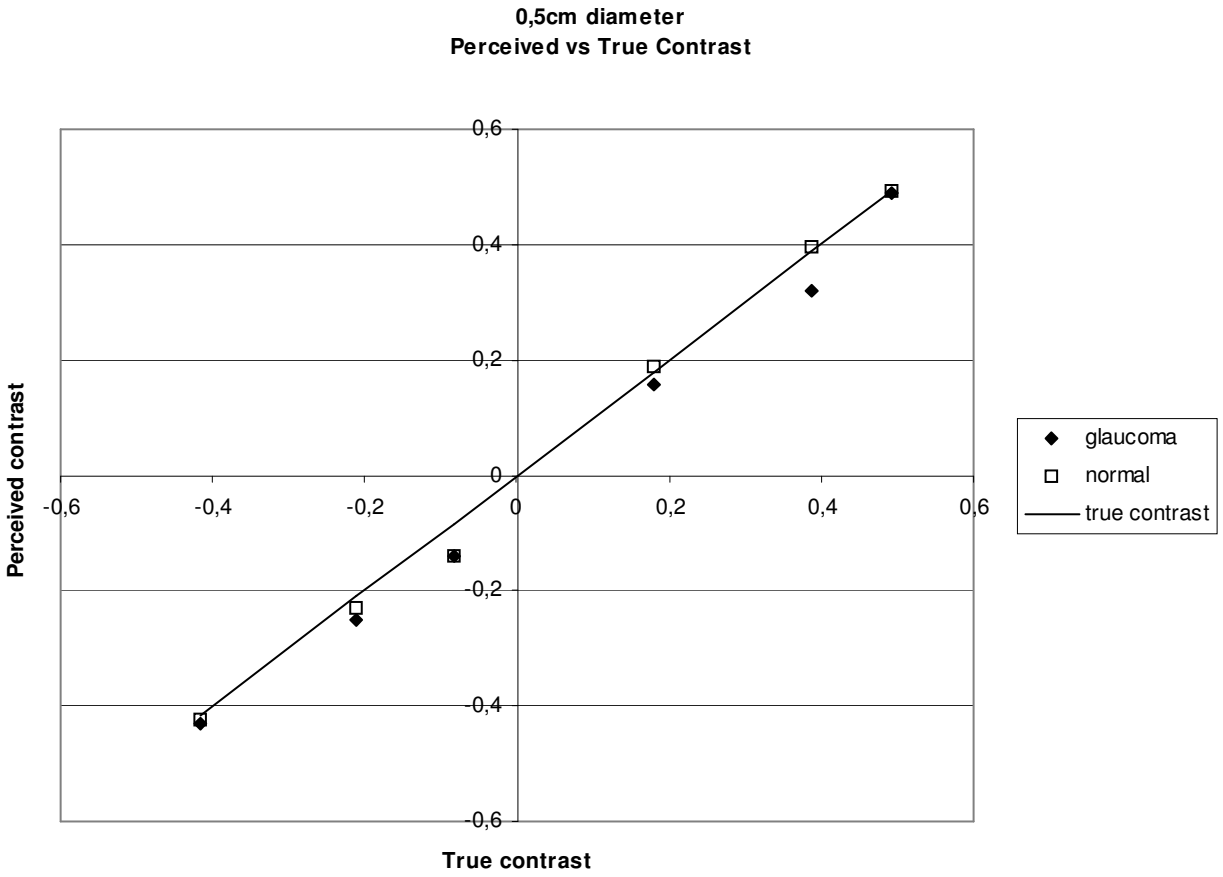

Figure 6.20 The perceived contrast as a function of true contrast in targets with 0,5cm diameter

7. DISCUSSION

Glaucoma is an ocular disease which damages normal functioning of the neurosensorial retina; so that normal contrast perception is disturbed and the visual field is narrowed, even though the high visual (resolution) acuity is maintained until the latest stages of the disease. The inner retina processes contrast and luminance perception, and a loss of sensitivity to these parameters is a known functional manifestation of glaucomatous disease (91-94). This decrease in the contrast sensitivity starts from the earliest stages of the disease, and become apparent much earlier than other defects in the visual system (79). Hawkins et al investigated the relationship between large-letter contrast sensitivity, high-contrast visual acuity, and visual field defects, in patients with glaucoma and 20/40 or better visual acuity. They reported that the reduced contrast sensitivity was significantly correlated with visual field losses; and concluded that compared with visual acuity the disease process preferentially affects contrast sensitivity (35).

Being an important tool for the early diagnosis of glaucoma, especially in the glaucoma suspect cases; if remains undetected, contrast sensitivity losses are proceeded with the other signs and symptoms of glaucoma, such as narrowing of the visual field and loss of resolution acuity at the late stages of the disease. Apart from the other ocular consequences of glaucoma; the contrast sensitivity loss by itself, leads to significant visual disturbances in the life quality of the patients. An experimental study on the impact of glaucomatous clinical vision changes on driving performance demonstrated that contrast sensitivity was the only variable significantly related to real-world accidents in patients with minimal visual field loss and normal or near-normal levels of visual acuity (95). Therefore, for all patients who are diagnosed as glaucomatous or glaucoma-suspect; an evaluation of the contrast sensitivity function should be done, for correct assessment of the clinical status and management of the disease.

The usefulness and benefit of contrast-sensitivity testing falls into three general categories.

The first category consists of those situations in which contrast sensitivity uncovers a hidden loss of vision-that is, it reveals the presence of visual dysfunction not apparent through other visual evaluations. The ophthalmic and neurological conditions whereby contrast sensitivity is impaired when acuity is normal include; glaucoma, cerebral lesions (96), optic neuritis related to multiple sclerosis (97), early stages of age-related cataract (98-100) and post-refractive surgery (101).

In some patients contrast-sensitivity impairment can contribute to the process of differential diagnosis, but there is little evidence that contrast sensitivity plays a significant enough role in diagnosis or screening to justify inclusion as a component of the general comprehensive eye examination. It does, however, help the clinician understand a patient's report of poor vision, particularly if acuity is normal or near normal. Furthermore, since the contrast-sensitivity impairment is closely linked to visual-task performance problems; clinicians realize better the disabling impact of the patient's eye condition for daily life.

The second category of benefit is that it provides another visual method to monitor the impact of treatment intervention. Visual acuity and visual field testing are the major functional outcomes in treatment evaluations in ophthalmology, but there are instances in which contrast sensitivity testing also reveals strong, positive effects of the treatment. These cases include, management of glaucoma by lowering the IOP with alpha-2 receptor agonists (102), photodynamic therapy with verteporfin for subfoveal choroidal neovascularization secondary to age-related macular-degeneration (103), cataract surgery (104), intravenous methylprednisolone treatment for optic neuritis (105).

Contrast sensitivity tests offer an easy method to detect the earliest ocular effects of glaucoma and monitor the effect of treatment and progression of the disease. It has been reported that improvements in spatial and temporal contrast sensitivity occur after medical, laser or surgical treatment of glaucoma (85-88, 102). Treatment related perfusion changes unrelated to IOP affect contrast sensitivity (106, 107). Blood velocity in the opththalmic artery was found to be highly correlated with changes in contrast sensitivity in normal tension glaucoma patients following nifedipine treatment (108). Alpha-2 type adrenergic agonists such

as brimonidine treatment in POAG has also been shown to improve the CSF; with a mechanism probably linked to the neuroprotective capabilities of the therapy.

Thirdly, contrast-sensitivity testing provides insights into the extent of patients' visual disability and functional performance problems. The contrast-sensitivity impairment and functional disability are related, a link that is independent of visual acuity loss and often stronger than the acuity-disability link. Contrast-sensitivity impairment is independently associated with an assortment of visual performance problems, including difficulties in mobility (109-111), driving (112, 113), reading (111, 114, 115), face recognition (111), and assortment of everyday tasks such as using tools and finding objects (111, 115, 116). Performance problems among visually impaired persons would not be adequately predicted nor their bases be understood if acuity tests alone were used to assess spatial vision. Therefore, in evaluating the effectiveness of treatment interventions to slow or reverse vision loss or to assess the impact of rehabilitation interventions to minimize the burden of vision impairment, contrast sensitivity is a logical choice for inclusion in monitoring patient outcomes.

In ophthalmology, visual acuity testing has been the standard examination method for determining the clarity or clearness of one's vision, a measure of how well a person sees. The word "acuity" comes from the Latin "acuitas," which means sharpness. Visual acuity is the spatial resolving capacity of the visual system. In terms of the CSF, visual acuity is defined as the highest spatial frequency just detectable when contrast is 100%. Standard visual acuity testing methods do not provide any information about the contrast sensitivity of the patient. Thus, visual acuity measurement by high-contrast targets (i.e. via Snellen chart) provides little or no information on many aspects of visual performance, such as the ability to function in low illumination or to detect low-contrast objects. For this reason, other tests have been developed for testing the contrast sensitivity function.

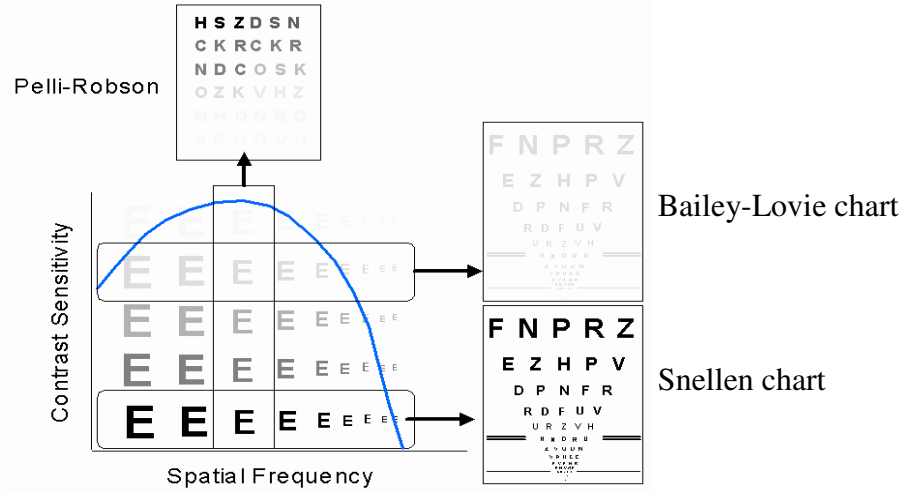

Figure 7.1 The relationship between the spatial frequency and contrast sensitivity.

Figure 7-1 demonstrates the commonly used visual acuity and contrast sensitivity tests, according their placement in the CSF curve. The commonly used resolution acuity charts (i.e., Snellen chart) consists of high-frequency optotypes, diminishing in size. The horizontal array of low-contrast optotypes of diminishing size, serve as the stimuli for the Bailey-Lovie chart. For the Pelli-Robson chart, all stimuli are the same size, but of diminishing contrast.

For the purpose of contrast sensitivity testing, computer-based devices that generate visual images, the Arden plates, grating tests and letter tests, edge contrast-sensitivity tests are used in the clinical setting. All these contrast sensitivity tests aim to find the minimum contrast level that the subject perceives. Thus, the contrast threshold is determined. These tests are prone to similar disadvantages as the visual field test. The contrast threshold levels are readily affected by the ocular media pathologies, such as cataract, cornea or vitreous opacities. Additionally, they are extremely vulnerable to cause misjudgments due to subjects' attention deficits. Furthermore, the effect of glaucoma on suppressing the supra-threshold firing rate of ganglion cells, besides and even at an earlier stage than increasing the threshold has been implemented by electrophysiological studies (117). Therefore, a supra-threshold contrast sensitivity test more likely provides information about the contrast sensitivity function of the subject earlier and with better accuracy.

Apart from the contrast sensitivity tests that detect the contrast threshold, the SLC effect can be used as a tool to monitor the contrast sensitivity function. SLC is a unique function of

the visual system, which operates to generate the perceived contrast with respect to the background.

The classical explanations of this illusion are:

1. A low level (physiological) effect: This effect originates from Hering's ideas of inhibitory processes in the visual system (118,119); and is based on low-level retinal mechanisms processing the local luminance contrast between the target and background.

This explanation involves the lateral inhibition mechanism, carried out by the horizontal and amacrine cells of the retina. The inhibitory signals are transmitted from one receptor to another laterally across the retina; and the firing rate of a receptor stimulated by a certain amount of light is diminished when the adjacent receptors are stimulated by the same illumination. Lateral inhibition models (119,120) explain the SLC effect by claiming that the receptors stimulated by background send inhibition to the receptors stimulated by the gray surface, causing its perceptual darkening. However, the receptors stimulated by dark background send little inhibition to nearby receptors, and, therefore, there is not a darkening effect. The induction of perceived lightness described by these models is also referred to as **local contrast**.

2. A high level (psychological) effect: As a result of **"misjudgment of illumination"**, as stated by Helmholtz (121), the lightness shift is caused by an "unconscious inference" about the illumination of the two parts of the display; ie., the white background is erroneously perceived as more illuminated than the black background (122).

It is generally believed that the two different mechanisms –Hering-type and Helmholtz-type-, both of which contribute into SLC (123). Hering-type mechanisms mainly contribute into classical SLC, grating induction, and other related lightness illusions (such as Mach bands, Herman grid), whereas Helmholtz-type mechanisms are mostly responsible for illusions such as Adelson's tile and snake lightness illusions (124).

Gestalt psychologists established that belongingness plays an important role in producing lightness illusions (125). **"The perceptual belongingness"** theory explains the

SLC effect, taking the higher-level processes into account. It was suggested that the perceived color of a surface is determined primarily by the global contrast between the surface and the other colored surfaces to which it perceptually belongs and not simply by low-level processes of local contrast involving lateral inhibition. The term perceptual belongingness refers to the result of a connection process that unifies the specific perceptual attributes arising from perceptual spatial articulation, which is the result of a perceptual organization process selecting specific physical spatial relationships of a visual pattern (126). Gilchrist showed that co-planarity of the test object with the inducing background was a crucial factor in producing the SLC effect and similar lightness illusions (127). Strength of the illusion is determined by an apparent illumination of a surface with which the test appears to be coplanar.

"The anchoring theory of lightness" says that a visual scene is divided into perceptual groups, or frameworks, on the basis of Gestalt grouping principles (128). For instance, the patches of different luminance are grouped together into frameworks; the lightness is then determined by the ratio of that patch's luminance to the luminance of the most luminous patch. It seems that objects can belong simultaneously to more than one group, with their lightness being influenced by every framework to which they belong (129). The anchoring effect (not a process), is experienced as a lightness shift induced by introducing a patch called **an anchor**. The presence of a particular stimulus arbitrarily selected as an "anchor" affects the shape of the psychophysical scale; it becomes steeper in the neighbourhood of the anchor. In lightness perception, the anchoring effect produced by the background on which the patches to be scaled are presented is sometimes referred to as **"the crispening effect"** (130,131). The lightness of any given surface is a weighted average of two lightness values, computed within two different frameworks: a local one and a global one. Within each framework, the role of the anchor is always assigned to the highest luminance, which is given a value of white, and all other regions will be perceived as shades of gray, depending on their luminance ratio to such white. Any area that takes up more than half of the visual field tends to lighten, and the larger it becomes the lighter it appears. The classical SLC and even SLC effect with double increments may be a result of the anchoring effect. (125,132). Anchoring effect is thought to be an error of judgment.

Finally, modern low-level theories of SLC (133-135) suggest that it arises as a result of functioning of a set of spatial-frequency filters at the early stage of the visual process. These filters constitute a sort of pre-processor through which all the retinal inputs have to come. Actually, the further parts of the visual system and the brain as a whole do not have an access to the proximal stimulus. The luminance distribution in the proximal stimulus remains directly unavailable for the brain; therefore, lightness can be derived only from the pre-processor's output rather than from luminance (or relative luminance, luminance contrast). There are some luminance patterns that are essentially altered by the pre-processor. When they differ, brightness illusions take place (e.g. the Mach bands, Hermann grid, and grating induction). Every brightness illusion results in a corresponding lightness illusion; however, not every lightness illusion is a result of discrepancy between the luminance and brightness distributions over space (e.g. Adelson's tile pattern).

The classical SLC display involves a gray test figure placed on a black background, and the same gray test figure on a white background. The SLC effect causes the subject to perceive the gray test figure lighter when placed on the black background, than when placed on the white background. The contrast increment and decrement are presented simultaneously; thus, the effect is called "the simultaneous lightness contrast".

A modified SLC test which aims to detect the changes in the perception of contrast increments and decrements seem to provide a helpful tool in detection of the earliest changes in the contrast perception due to diseases of the neurosensorial retina, as shown by this study. Both the contrast increments and contrast decrements are enhanced by subjects without any ocular disease. However, unlike the normal subjects, early stage glaucomatous subjects failed to enhance the contrast increments except for the largest increment. This change in perception of contrast increments could be explained by the damage to the low level processing of local contrast mechanisms, proposed by Hering. This defect could be the initial sign of the glaucomatous damage; and is probably followed by the defects in perception of greater contrast increments and contrast decrements. Thus, this test would help the clinician in his/her decision about the onset of medical therapy for the glaucoma-suspect cases, who have the signs of the disease but not at adequate levels to be detected by the visual field.

This modified SLC test has several superiorities over the classical contrast sensitivity tests and the visual field test.

The detection of the changes in contrast increments and decrements by a modified SLC test seem to be a more sensitive way to detect the contrast sensitivity changes in the early stages of the disease, compared with classical contrast sensitivity tests, which detect the contrast threshold. Since the suppression of supra-threshold firing rate of the ganglion cells has been demonstrated in glaucoma before the threshold is increased (117); supra-threshold testing strategy would prove to be more valuable in the early diagnosis of glaucoma-related defects in the neurosensorial retina. Additionally, this supra-threshold test is less prone to errors due to the subjects' attention deficit. It would be less affected by the environmental lightning, even though performing the test in a pre-determined and standardized constant ambient illumination seems to be mandatory for the comparison of different subjects' results and the results of a subject during the follow-up. Similarly, testing the contrast sensitivity function at the supra-threshold levels, the test seems to be less affected by the ocular media opacities, such as cataract, cornea and vitreous opacities. Therefore, supra-threshold contrast sensitivity tests seem to be more valuable in detecting the earliest changes in the contrast sensitivity function.

This modified SLC test could provide information about the functional changes in the visual system, earlier than the visual field test does. It is known that, especially in the early stages of the chronic open angle glaucoma, contrast sensitivity changes are seen before the visual field and optic nerve head changes appear. The late appearance of the visual field defects has been explained by the anatomical structure of the neurosensorial retina at the cellular level. It is known that, the density of ganglion cells is around 70-fold greater in the central 3° than that at 20° eccentricity where a nasal step visual field defect typically appears (96). This high density of retinal ganglion cells in central vision may result in over-sampling or visual redundancy, during most visual function investigations and a relatively late detection of defects in the central visual field. Although glaucomatous visual field loss can take many forms, it is typical for glaucomatous loss to be measurable first outside the fovea (136). However, contrast sensitivity changes could be detected by the tests using the central vision;

before the central visual field defects appear. It is well known that the diffuse glaucomatous damage, which seems to occur in the visual field prior to the onset of detectable focal perimetric defects, is reflected in global depressions of the central visual field, including functional deficits such as reduced contrast sensitivity (137).

It has been shown that structural damage occurs in the optic nerve head and retinal nerve fiber layer, before any functional visual loss is detectable in the visual field (138, 139). It has been shown that when detectable changes appear in the visual field test, the irreversible retinal damage had already been occurred and retinal axon loss of up to 50% rates could be present (138-140). Additionally, in the visual field areas where there is 5dB sensitivity loss, 20% neuroretinal cell loss is present; while in the visual field areas where there is 10dB sensitivity loss, 40% neuroretinal cell loss is present (141). Therefore, visual field testing is not a valuable diagnostic modality for the early diagnosis of glaucoma, especially for the management of the glaucoma-suspect cases; although it is still an important tool for the follow-up of disease progression, in later stages. Contrast sensitivity seems to be a more sensitive test for initial diagnosis of the disease, enabling subtle defects or improvements to be detected centrally in the early stages.

Besides having late onset behavior, the functional evaluation of glaucomatous damage on retinal nerve fiber layer by visual field testing is a threshold testing method; where the threshold luminance for retinal detection is being tried to be detected. This causes a significant amount of errors due to ocular media opacities and / or attention loss by the patient. The visual field test is a subjective test that requires the high performance of the patient for a long time. Therefore; a supra-threshold test which takes less time would be more appropriate. Being able to finish the test in approximately 30 minutes, this test provides an easier functional evaluation of the patients in early stage or suspect glaucoma. The task is easier to understand and even enjoyable for the pediatric patients. The test does not necessitate any expensive equipment; only the fixed and known lightning of the examining room is mandatory.

It should be noted that, the regions of contrast threshold elevations is the sensorineural retina, do not map onto the regions of visual field loss. This indicates that the contrast sensitivity testing (even at the suprathreshold level) cannot be considered as a substitute for

the visual field tests. While contrast sensitivity losses are indicative of glaucomatous damage to vision, they are providing a different assessment oof visual function from conventional visual field tests (142).

The visual concept shown in this study also carries essential importance in other means of visual assessment in the clinical setting. As an example, the Amsler chart for the evaluation of foveal involvement by the retinal degenerative diseases, like age-related macular degeneration; introduces vertically and horizontally aligned lines forming numerous squares, in the middle of which there is a bold fixation point. While fixating at that point with reading glasses on, patient reports whether those lines are properly aligned or not; i.e., whether the lines are parallel to each other and crossing the others perpendicularly, or not. If the patient has subfoveal chorioretinal degeneration, the lines seems undulated or wavy due to retinal photoreceptor misalignment. These charts were originally printed as white lines on black background in order to take the advantage of contrast increments. There are no regulatory rules in the production of commercially available Amsler charts, which are easily printed out from a computer. However in glaucomatous patients, inability to demonstrate contrast increment at low contrast should be taken into account in this process; and Amsler charts should be printed at higher contrast levels.

In short, in order to avoid evaluation errors, all subjective visual assessment tests should be carefully revised, by taking the information of contrast sensitivity loss in glaucomatous patients, into consideration. In order to get use of the contrast increment mechanism, highest possible contrast levels should be used.

8. CONCLUSIONS

The neurosensorial retina consists of three main neuron groups: the photoreceptors, bipolar cells and ganglion cells. The ON and OFF bipolar and ganglion cells have a center-surround organization: stimulation of the region surrounding their receptive fields elicit opposite responses due to the lateral inhibitory action of horizontal and amacrine cells. This lateral inhibition provides our visual system with a mean to emphasize areas of difference (contrast), i.e. it sharpens the boundary between objects of different luminance. Contrast is defined as the ratio of the difference in the luminance of two adjacent areas to the lower or higher of these luminance values. Spatial contrast is a physical dimension referring to the light-dark transition of a border or an edge in an image that delineates the existence of a pattern or an object. Contrast sensitivity is a measure of the threshold contrast for seeing the target; in this case, contrast is not kept constant during the test but is varied so that the minimum level of contrast for seeing a target can be determined. The usefulness and benefit of contrast-sensitivity testing include uncovering the hidden loss of vision not apparent through other visual evaluations, providing a visual method to monitor the impact of treatment intervention, and providing insights into the extent of patients' visual disability and functional performance problems. The visual acuity in terms of the contrast sensitivity function is defined as the highest spatial frequency just detectable when contrast is 100%. Especially in the early stages of the chronic open angle glaucoma, contrast sensitivity changes are seen much earlier that visual field and optic nerve head changes appear. Contrast sensitivity test could be used to detect the underlying visual dysfunction in glaucoma, as well as in follow-up of the patients with respect to progression of the disease and effects of the treatment. Both computer-based and chart-based devices are used for the assessment of the contrast sensitivity in clinical practice. The chart-based methods include; the Arden plates, the VisTech chart, the Functional Acuity Contrast test, The CSV-100 chart, Pelli-Robson chart.

The simultaneous lightness contrast (SLC) is a textbook illusion, which demonstrates that the lightness of an object depends on its immediate surround. A region seen against a dark background looks lighter than an identical region seen against a light background. The explanations of the illusion include a low level lateral inhibitory effect (proposed by Hering), a

high level psychological effect as a result of misjudgment of illumination (proposed by Helmholtz), the perceptual belongingness theory, the anchoring theory of lightness, and low-level spatial frequency filters. A modified SLC test was used to uncover the changes in the enhancement of contrast increments and decrements, due to deleterious effects of the glaucoma on neurosensorial retina. The test performed on glaucomatous patients and normal subjects revealed no significant effect of target size in either normal or glaucomatous subjects. When the effect of the input contrast was examined, both normal and glaucomatous subjects were found to overestimate contrast decrements (black target on white background) in a similar manner. However, they did differ in their perception of contrast increments, except for the largest increment.

This test detects the supra-threshold contrast sensitivity changes; which is a different concept from the threshold detection contrast sensitivity tests and the visual field defects. This test takes less time than the classical visual field tests; and is easier to understand and even enjoyable for the pediatric patients. It can be the first-line test in early stage glaucoma patients, as well as glaucoma suspects. Additionally, in order to avoid misjudgments, all subjective visual assessment tests should be carefully revised, considering the suprathreshold contrast sensitivity changes in glaucomatous patients. Other means of visual assessment (e.g. Amsler chart), can yield false-positive results if the test charts are not prepared in the highest contrast levels, which are not affected by the glaucomatous contrast changes.

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