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CLINICAL INVESTIGATIONS OF FIXATION STABILITY AND READING EYE MOVEMENTS

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ABSTRACT

Reading and writing plays a fundamental role in our culture. Compared with, e.g. speech, written language has an immense impact as it offers the possibility to share information over unprecedented distance in time and space. By observing how the eyes move while reading we can obtain knowledge of the recognition process. To enable reading, not only moving the eyes are required, but also a good quality of fixation is essential. This thesis presents findings from four eye movement studies performed with the Scanning Laser Ophthalmoscope (SLO) and Tobii Eye-tracker.

The aims were to 1) investigate the fixational pattern in healthy subjects using the microperimetry technique obtained with the SLO in order to learn more about normal fixational pattern. This is important since changes in fixational pattern, due to pathology, can occur prior to detectable changes in the macula or visual pathway; 2) use the SLO to map solar induced scotomas and evaluate the fixational pattern after such injury; 3) evaluate if the Tobii system could be used to evaluate reading performance despite its relatively low resolution and sampling frequency; and 4) evaluate if patients with neovascular AMD, treated with Lucentis, gain a better reading ability by using the Tobii Eye tracker.

The results from the SLO studies demonstrated that the fixational pattern in healthy subjects measured with the SLO had a mean centre of gravity located at a mean absolute distance of 0.27° from the fixation point (FP) and a directional predominance of the fixational pattern more frequently distributed vertically than horizontally. This means that computerized fixation control when performing microperimetry with the SLO provides information about the fixation pattern, which cannot be obtained with standard clinical perimetry techniques. The studies further showed that SLO microperimetry session with fixational mapping are useful in patients with unstable and/or extrafoveal fixation, which is a common situation in patients with a foveal lesion/injury.

The Tobii Eye tracker studies showed that the Tobii system, despite its relative low resolution and sampling frequency, is suitable for evaluation of reading performance in clinical settings. Furthermore, that texts used for studying reading performance must be chosen carefully since even texts of similar linguistic difficulty, due to the nature of the text content, can yield the differences found in reading performance.

When investigating AMD patients, the findings outlined that Lucentis treatment gave a significant better visual acuity, not necessarily connected with improved reading eye movements and reading ability. However, reading should be tested in order to fully understand a patient's complaints; however, as a direct measure of visual improvement after, for example Lucentis treatment, other tests should also be used.

Keywords: Scanning Laser Ophthalmoscope (SLO), Tobii Eye-tracker, reading speed, reading eye movements, fixation, regression, saccades, AMD, Lucentis.

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LIST OF ABBREVIATIONS

AMD	Age Related Macular Degeneration
ANOVA	Analyses of variance
ARM	Age Related Macular Degeneration
BCEA	Bivariate Contour Ellipse Area
CG	Center of Gravity
CNV	Choroidal Neovascularisation
CSF	Contrast Sensitivity Function
DLS	Differential light stimuli
DRP	Diabetic Retinopathy
ETDRS	Early Treatment Diabetic Retinopathy Study
LED	Liquid Crystal Display
LGN	Lateral Geniculate Nucleus
LIX	Läsbarhetsindex
NIR-LED	Near Infrared Light Emitting Diodes
OCT	Optical Coherence Tomography
RPE	Retinal Pigment Epithelium
SD	Standard Deviation
SLO	Scanning Laser Ophthalmoscopy
VA	Visual Acuity
VF	Visual Field
VOG	Video Oculography

1 INTRODUCTION

1.1 VISION

The complexity of human vision is tremendous and regarded as one of our most refined senses due to the proportion of the brain allocated to vision. The human eye, elegant in its details and design represents a gateway to the process we call vision. Light passes first through the transparent cornea, where it is refracted as it enters. Behind the cornea is the anterior chamber through which light passes on its way to the pupil. The pupil is a circular opening in the iris, which admits light into the middle of the eye. The amount of light admitted into the eye is controlled by varying the size of the pupil. Directly behind the iris and pupil is the lens. The ciliary muscles control the shape of the lens (i.e., the refractive power is changeable), all to make the incoming light focused onto the retina. Before the light reaches the retina it passes through the larger posterior (back) portion of the eye that is filled with a clear, jelly-like substance called the vitreous humour. All of the above structures, are crucial for our vision, but, with exception of the retina, will not be further discussed in this thesis. In the retina, we have the rod cells and cone cells which will be stimulated to set off a chain of split-second chemical reactions converting light to electrical impulses (Fig.1). It's not enough though, that the light reaches the retina correctly refracted by the cornea and lens to give us high quality vision. Slight movements of the eyes are essential for good visual perception (Yarbus 1959) and among these fixations play a fundamental role. Accurate and stable fixation is a result of a functional visual system and a failure to achieve this will result in decreased vision something that will impair for example our reading ability. The retinal area used for detailed vision and therefore also reading comprises only a few square millimetres. However, the importance of this area is indicated by its disproportionate overrepresentation in the visual brain: The central 10 degrees of the visual field, which account for approximately 2 % of the total visual field, utilise more than 50 % of the primary visual cortex (Trauzettel-Klosinski 2000). A number of diseases and anomalies can affect our fixation abilities and thereby our reading ability. It's therefore important for clinicians to be able to measure and test fixation.

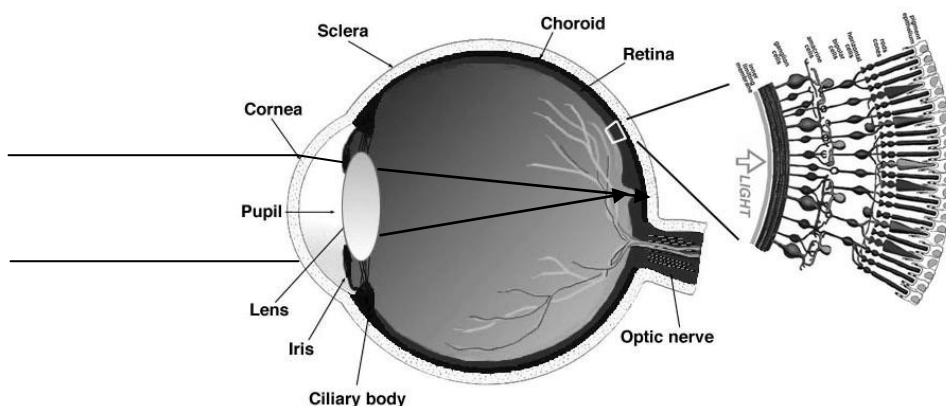


Fig. 1 A schematic section through the human eye with an enlargement of a sector of the retina.

(Picture from Webbvision and printed with permission from Prof. Helga Kolb Moran Eye Center Utah.)

1.2 THE RETINA

The retina is approximately 0.5 mm thick and lines the back of the eye. The cone cells (about 7 million in number) are located in greatest concentration in the small, central part of the retina called the macula. This area is responsible for producing sharp, detail vision and colour vision. The rod cells (numbering about 100 million) are found in the peripheral retina, away from the macula. These cells provide vision in dim light. The optic nerve contains the ganglion cell axons running to the brain and additionally, incoming blood vessels that come into the retina to vascularise the retinal layers and neurons. A transverse section of a portion of the retina reveals that the ganglion cells (the output neurons of the retina) lie innermost closest to the vitreous humor, and the photo sensors (the rods and cones) lie outermost in the retina against the pigment epithelium and choroid. Light must therefore pass through the thickness of the retina before striking and activating the rods and cones. Subsequently the absorption of photons by the visual pigment of the photoreceptors is translated into, first a biochemical message and then an electrical message that can stimulate all the succeeding neurons of the retina. The retinal message, concerning the photic input and some preliminary organization of the visual image into several forms of sensation, is transmitted to the brain from the spiking discharge pattern of the ganglion cells. If we look at a transverse section of the retina (Fig. 2), it becomes obvious that the retina is tremendously complex and contains many types of nerve cells. It is immediately obvious that there are many inter neurons packed into the central part of the section of retina intervening between the photoreceptors and the ganglion cells.

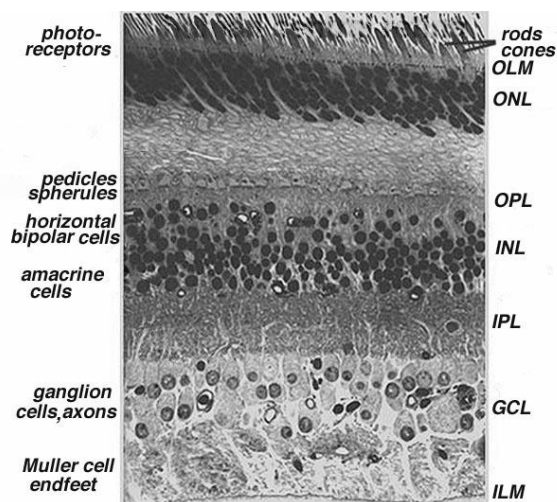


Fig. 2 Light micrograph of a transverse section through the human retina.

(Picture from Webbvision and printed with permission from Prof. Helga Kolb Moran Eye Center Utah.)

Rod and cone cells are connected to the bipolar cells, which connect to the ganglion cells. Lateral connections are made to cones and rods by horizontal and amacrine cells and Müller cells establish a link between neurons and vessels. Prior to any signals being sent to the brain from the retina, they are processed by different fundamental interactions between the neurons in retina. The lateral inhibition plays an important roll

in retina to increase spatial tuning of ganglion cells and hence sharpen the image (Cook & McReynolds 1998).

1.3 MACULA AND THE FOVEAL STRUCTURE

The macula (5.5 mm in diameter) is a highly specialized area of the retina and can be divided into the fovea (the central 1.5 mm) and the foveal pit (most central 0.35 mm). This region is responsible for high-resolution vision and contains xanthophyll, a yellow carotenoid, and layers of ganglion cells. The foveal pit is an area where cone photoreceptors are concentrated at maximum density and where rods are absent. Transverse sections of the foveal pit measure less than a quarter of a millimetre (200 microns). As described, the retina is a highly complex system, which is needed to provide the brain with signals so we can come to an understanding of the world around us.

1.4 THE OPTIC NERVE

The optic nerve (IInd cranial nerve) is a prolongation of the axons of the retinal ganglion cells. There are approximately 750,000 – 1,500 000 axons in each optic nerve (Curico & Allen 1990). The optic nerve, which acts like a cable connecting the eye with the brain, is actually more like brain tissue than nerve tissue. The ganglion cells, which are found in the central part of retina, have its highest concentration of density within the 16° visual field (VF) (Fig. 3).



Fig. 3 The optic nerve with parallel axons from ganglion cells (see arrow).

(Picture from Webbvision and printed with permission from Prof. Helga Kolb Moran Eye Center Utah.)

The optic nerve leaves the eye thru the optic foramen and the optic canal, running towards the chiasm where a partial crossing of fibres from nasal visual field of both

eyes can be seen. The nerve varies in diameters from 1.6 mm within the eye to 3.5 mm in the orbit and 4.5 mm in the cranial space.

1.5 THE VISUAL PATHWAY

Nearly all optic nerve axons end in the lateral geniculate nucleus (LGN). From here, signals about particular elements of the visual scene are passed on selected areas of the primary visual cortex, or V1, which curves around a deep fissure at the back of the brain (Fig. 3 & 4).

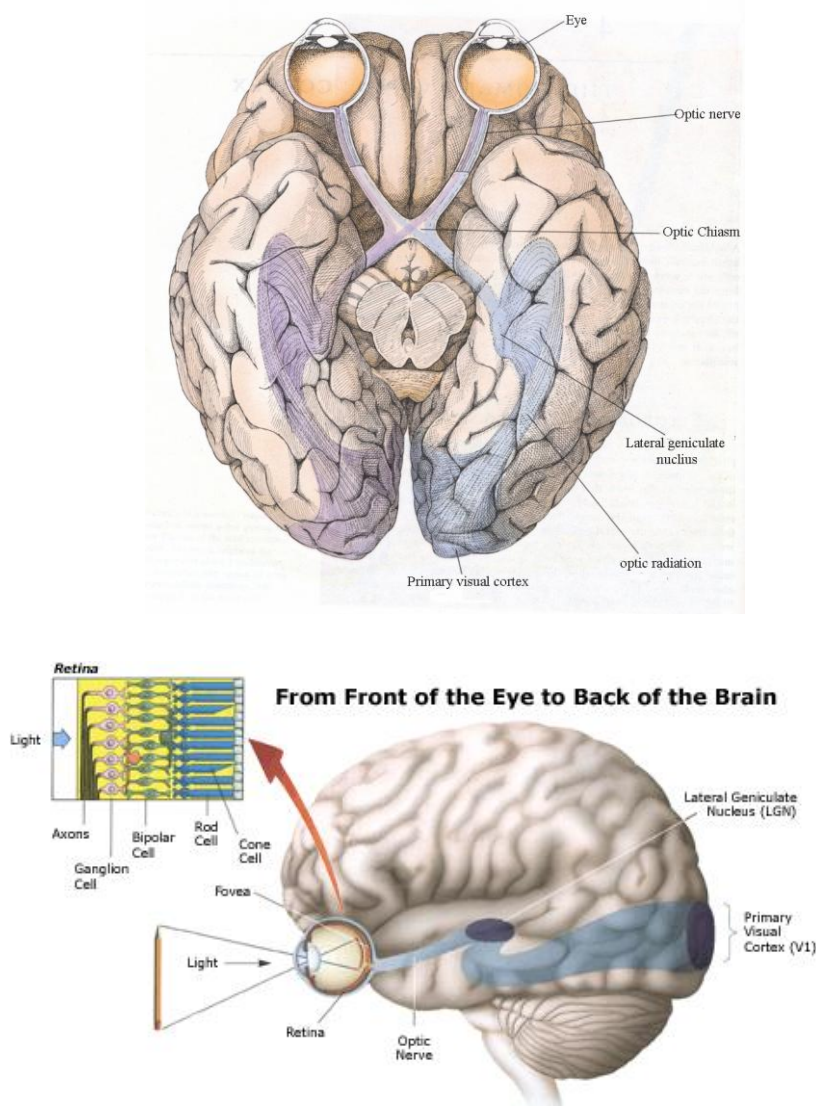


Fig. 4&5 The visual pathway from the eye to the back of the brain
(Pictures from Howard Hughes Medical Institute).

Visual information then flows through a cortical hierarchy. These areas include V2, V3, V4 and area MT (Fig 5). These secondary visual areas (collectively termed the extrastriate visual cortex) process a wide variety of visual primitives. Neurons in V1

and V2 respond selectively to bars of specific orientations, or combinations of bars. These are believed to support edge and corner detection. Similarly, basic information about colour, motion is processed here.

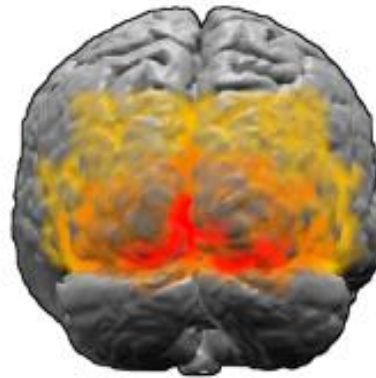


Fig. 6 Visual cortex V1, V2, V3, V4, V5 (also called MT).

(Picture printed under permission from the GNU Free Documentation License.)

1.6 AGING OF THE NORMAL EYE

As part of normal aging, vision decreases. Some important functional changes are loss of accommodation, i.e. the focusing capability, reduction in pupil size (Hammond et al. 2000), decreased transmission of the ocular media and decreased retinal sensitivity. Deceleration of dark adaptation probably attributed to delayed rhodopsin regeneration in retinal rod and cone cells, decreased colour vision and contrast sensitivity are other factors in the normal aging eye (Jackson et al. 1999, Nio et al. 2000). Neural and optical factors and their respective share to the decreased visual functions have been discussed and researchers have concluded that retinal sensitivity declined at medium and high spatial frequencies primarily due to retinal and neural changes (Elliot 1987, 1990). Others have shown that age related visual field changes were correlated to neural loss rather than optical alterations in the lens (Johnson et al. 1989). The amount of axons in the foetal human optical nerve is up to 3.5 times more at 17 weeks gestation than in the adult eye (Provis et al. 1985). A decreasing of rod and cone cells also occurs with increasing age and that the decrease seems to have more impact on rods with an approximately reduction of 30% between the age of 34 and 90 (Curcio et al. 1993). The fixational eye movement system shows no significant changes of age-related character when it comes to the overall stability (Kosnik et al. 1986, 1987). The range of fixation, however, especially for upward gaze, seems to decrease with advancing age (Chamberlain 1971). When examining vision and the eye's function and structure, it may be difficult to differentiate between changes due to normal aging and pathology. Loss and degeneration of cone and rod cells due to changes in the retinal pigment epithelium (RPE) is a cardinal cause to age related macular degeneration (ARM), expiration of neural tissue a crucial pathological change in glaucoma and hyperglycaemia associated with diabetes induce retinal neuro-degeneration.

1.7 VISUAL FUNCTIONS TESTING

Our visual world is composed of images of colours, textures, edges and contrasts. In addition, these images may be moving or flickering. The goal of visual testing is to quantify these functions. If correctly performed, a test of the visual function should together with other tests delineate the degree, location and possible cause of visual dysfunction. Visual acuity is commonly used as a measure of visual function. However, visual acuity says very little about the entire visual function and further tests, such as colour vision, contrast sensitivity, visual field and the ability to read, are needed in order to fully examine the patient's visual status. Common for all visual function tests are the necessity for central and stable fixation. One should bear in mind that factors such as fatigue, attention and motivation can influence the results. Furthermore, the difficulty of the task affects the variability of the test and increases the precariousness of the results. This can also be seen in both normal and abnormal vision.

1.7.1 Visual acuity

Visual acuity is defined as the clarity or sharpness of vision, which is the ability of the eye to see and distinguish fine details of high contrast. Visual acuity is an important factor for a variety of everyday tasks, including recognizing symbols, performing assembly work and reading text. To resolve details, the eye's optical system has to project a focused image onto the fovea. In scotopic vision, there is low resolution regardless of high sensitivity thereof, this due to the spatial summation of rods. Visual acuity (VA) is thus the capacity to discriminate the details of objects. The angle delimited by the detail at minimum acuity is the resolving power, and its reciprocal the visual acuity. There are various ways to measure visual acuity and in the optometric or ophthalmological clinical settings, the letter chart is most commonly used for measuring VA where letters are presented against a bright background with 100% contrast. In research, the (Early Treatment of Diabetic Retinopathy Study) chart, ETDRS is considered standard (Ferris et al. 1982). The chart, displayed with internal back illumination, contains a number of lines with five Sloan letters of equal difficulty with a patterned advance in letter size from line to line. Different charts are used for left and right eye respectively to avoid the effect of learning. People with age related macular disease often get unstable fixation and due to that thought to gain poor visual acuity. To test this, recent experiments have shown that the acuity was unaffected by even high levels of image instability. However, reading speed decreased with increased image instability (Falkenberg et al. 2007).

1.7.2 Colour vision

Colour vision is the ability to discern different wavelengths, or colours, of light and gives us more information for detecting and identifying objects than would be provided solely by black and white vision. Colour vision can be tested in several ways, either by identifying coloured plates with randomly appearing dots in colour and size. Within the pattern are dots, which form a number visible to those with normal colour vision and invisible, or difficult to see, for those with a colour vision defect. Other tests consist of sets of hue stimulus caps where the patient is supposed to discriminate between

approximately equal hue differences. Colour vision anomalies and colour aptitude are detected by a subject's ability to place the colour caps in hue order. Colour vision is important when testing vision but says very little about a patient's contrast sensitivity.

1.7.3 Contrast sensitivity

Contrast sensitivity is the visual ability to see objects that may not be outlined clearly or that do not stand out from their background. Contrast sensitivity tests measure the degree to which this ability has been lost. A contrast sensitivity test measures two variables, size and contrast. The ability to detect objects of different sizes at lower contrasts is expressed as a contrast sensitivity function (CSF). The test determines the person's contrast detection threshold, the lowest contrast at which a pattern can be seen. There are a substantial number of contrast sensitivity tests on the market for contrast sensitivity testing and they could differ in some degree but are all reliable. Contrast sensitivity testing is important when measuring vision, but cannot stand-alone. Another test that involves testing the ability to detect objects of different size of objects is visual field testing.

1.7.4 Visual field testing (Perimetry)

Several advanced methods for detecting disorders in the retina and the visual pathway have been developed over the years. One is visual field (VF) testing.

Visual field tests are designed to map a person's visual field, thus to document the central and peripheral vision. Visual field examinations provide important information about the diagnosis and follow-up of many ocular and visual pathway disorders (Federman et al. 1994). Thus, VF defect characteristics can be used for determination of the location of a lesion affecting the visual pathways. In retinal diseases, e.g., retinitis pigmentosa, VF examinations can be used to assess the extent of retinal involvement (Sunness et al. 1995). Visual field examinations in a clinical setting are usually performed with conventional techniques such as differential light stimuli (DLS). This could be unmanageable for a patient and the test-retest variability in DLS is very high (Artes et al. 2002). Tests like this are also time consuming and make the test less preferable in a psychophysical perspective. If the test involves presentation of stimuli above the average normal age threshold it also gives both lower variability and lower sensitivity for minor damage (Henson & Artes 2002). Two very common perimeters that use these techniques are the Goldman perimeter which is manually operated and in which the task is to detect a moving light coming in towards the central visual field from the periphery (kinetic perimetry) and the computerized Humphrey field analyzer in which the task is to respond (by pushing a button) each time a flash of light is perceived (static perimetry). In both kinetic and static perimetry, the subject is instructed to constantly fixate a target located straight ahead. Stable fixation is essential in perimetry since unstable fixation will make the results unreliable. Most instruments have therefore incorporated some sort of fixation control. Another fixation related source of error in perimetry is in subjects with eccentric viewing. With eccentric viewing, the resulting field will be compared with normative data of subjects with central fixation, i.e., there will be "mapping errors".

1.7.5 Mapping errors

A problem with conventional VF techniques, such as Goldman perimeter and Humphrey field analyzer, is that they rely on the assumption that the subject's fixation is kept foveal and stable during the examination (Whittaker et al. 1988, Fletcher et al. 1994, Schuchard & Raasch 1992, White & Bedell 1990). All modern perimeters, such as Humphrey field analyzer, have devices for control of fixation loss, but if the fixation is unstable and the eyes move significantly during testing, the size and location of a scotoma will be incorrectly plotted. In computerized DLS perimetry, fixation losses have been shown to be the most common cause of unreliability. In normal subjects fixation losses range from 9 to 16 %, depending on the technique used (Isayama & Tagani 1977). These conventional techniques are therefore inadequate for accurate evaluation of the VF in macular and retinal disorders where foveal vision can be compromised, and the patient often has unstable or extrafoveal fixation, i.e. eccentric viewing (Rohrschneider et al. 1995). If the fixation is not foveal, the VF will still be mapped as though fixation is in the centre of the field, and all tested points will be shifted relative to their true retinal location (Timberlake et al. 1982, Enoch et al. 1984, Schuchard et al. 1993, Guez et al. 1993). A way to compensate for this is to move the test chart according to the degree of extrafoveal fixation. The disadvantage of this strategy is the effect of cartographic deformation. However, with the Scanning Laser Ophthalmoscope (SLO) it is possible to evaluate retinal sensitivity in an investigator-determined location and the problems of mapping errors can therefore be avoided.

1.7.6 SLO: Perimetry and fixation pattern measurements

During the last decades, a scanning laser method has been used for perimetry, the Scanning Laser Ophthalmoscope (SLO) (Fig 4). SLO is a computerized technique for measuring the response to light stimuli in the central VF, which eliminates some of the earlier problems occurring during conventional techniques, such as unstable fixation (Timberlake et al. 1989). The use of SLO allows exact, repetitive measurements of the VF and the possibility to objectively map scotomas, i.e., scotometry/microperimetry and fixation/gaze measurements, to verify the location and stability of the fixation (Rohrschneider et al. 1995). Microperimetry performed with the SLO makes it possible to determine the sensitivity within 20° of the central retina (Henson et al. 1999). Other studies show that the results obtained with SLO microperimetry in normal subjects can be related to test results with another conventional perimetry technique, i.e., the Octopus M1 (macular) program (Andersen 1996). Regarding fixation stability, previous studies have shown that the fixation stability can be measured very exactly around the centre of the fixation point with the SLO (Fig 5) (Rohrschneider et al. 1998). The SLO may also be useful in evaluating fixation/gaze stability and sub clinical changes in retinal sensitivity surrounding laser scars after photocoagulation before subjective visual disturbance appears (Oshima et al. 1998). However, with all measurements of fixation stability it is difficult to find a model that truly displays the fixation pattern or area.



Fig. 7 The Scanning Laser ophthalmoscope (SLO).

(Picture from own production)



Fig. 8 Ocular fundus image from a SLO with fixation distribution overlay.

(Picture from own production)

1.7.7 Fixation area and earlier basis of calculation

When studying fixation, the area within which fixation is held, is of great interest to extract information about the fixation stability. To calculate this area, different methods have been used, such as quantifying fixation from video recordings (Möller & Bek 1998) or defining fixation as central if more than 50% of the fixation points are located in a predetermined area (Nilsson et al. 2008, Fujii et al. 2002). These methods give an appreciation of the area of interest, but no information about the fixational pattern. Another more common method is the Bivariate Contour Ellipse Area (BCEA) (Crossland et al. 2004). The method gives two orthogonal diameters describing the extent of the fixation distribution around a fixation mark, but relies on the assumption that the material studied, is normally distributed. This is often not the case in this kind of measurements and can therefore give misinterpretation of the data. We have developed a method called Centre of Gravity (CG). During each stimulus presentation, the location of fixation was saved in the SLO computer (in X and Y coordinates from the fixation cross-location). The mean of the X and Y coordinates in each subject was calculated to be used as a “centre of gravity” (CG) for the fixation locations. If the area within the fixation is held is calculated with the CG-method no consideration is necessary as to whether the material is normally distributed or not. We therefore consider the CG method more informative of fixational behaviour in both normal subjects as well as subsequent patients groups to be investigated.

1.8 READING AND THE NEED OF EYE MOVEMENTS

Reading is very important for most people in daily life. Reading can in a simplified manner be described as the combination of visual detection, eye movements and comprehension. A failure somewhere in this process like a retinal disease or a stroke can suddenly diminish the capability to read. Despite an increasing array of treatments to problems in our visual system, our knowledge of the different mechanisms within

the central nervous system involved in the process of reading is limited. Further knowledge of the reading process is still to be discovered, but by observing how the eyes move while reading we can obtain knowledge of the recognition process and observe changes in this process as ocular diseases are treated.

1.8.1 Eye movements in reading

Reading involves a number of fine tuned eye movements such as saccades, return-sweep saccades, regressions and fixations. Saccades are accurate, high-velocity, non-ballistic eye movements used to foveate objects of interest. Most saccades (~85%) are less than 15 degrees in amplitude (Rayner & Pollatsek 1989). Saccades in reading occur when the eyes move from one fixation point to another by left to right interfixation movements, and are in the order of 1 to 2 degrees (but could be as small as 0.5 and as large 4 degrees) (Tinker 1947). Return-sweep saccade refers to the large right-to-left saccadic eye-movement that shifts the eyes from near the end of one line to near the beginning of the next line in text and is normally between 12 – 20 degrees (Ciuffreda & Tannen 1995). Regressions are saccades that are directed from right to left by regressive movements during reading and typically reflect some text confusion or comprehension problem, but also a recheck or double check confirmation (Ciuffreda & Tannen 1995). Fixations refer to a number of eye stops or pauses of the eyes during reading (Tinker 1951). The more difficult the material, the more fixations one typically makes (Rayner 1998).

1.8.2 Linguistics

Linguistics is narrowly defined as the scientific approach to the study of language. From a linguistic viewpoint, readability is very interesting. Readability is typically referred to as the ease of “which the meaning of text can be comprehended” (Mills & Weldon 1987). This can perhaps be interpreted as a dim definition, but the appraisal of readability is bore upon a multitude of factors. An example of this is the many differences between texts that could be very comprehensive and well written and hence easy to read, while others can be more or less impossible to read. Furthermore there are also large differences between readers, where some are experienced and others illiterate. There could also be differences between reading situations, reading a scientific paper differs a lot from a fiction book while taking it easy at home. Finally, there could be discrepancy in presentation format, some novels are very comfortable to read on paper while on a flickering screen with bad contrast, it is very likely to be arduous. Readability of text is usually rated by using readability formulas, most quite simple, using combinations of word frequencies, word length and sentence length as basis for the results. In an attempt to give a scientific evaluation of readability, several approaches have been made to develop readability indexes (Björnsson 1968; Frey 1968; Klare 1975). Results from most of the calculations have given formulas referring to school grade levels, e.g. reading skills corresponding to grade 2, 5, 8, 11 (Duffelmyer 1985). A different approach though, is the Swedish LIX-formula (Björnsson 1968), which is not a regression-formula, as opposed to many others and hence does not consider grade levels. Still, the formula, in similar to the American ditto, is created of

one component corresponding to a syntactic level of difficulty and another component indicating the length of words, describing the semantic difficulty.

1.9 MEASUREMENTS OF EYE MOVEMENTS

1.9.1 Available techniques

Measurements of eye movements have been available for several decades. The first precise techniques were based on scleral search coils (which are still used today for certain applications) (Robinson 1963, van der Geest & Frens 2002, Ram-Tsur et al. 2006). Fixational eye movements have traditionally been measured by conventional methods such as the IR-reflection technique, scleral search coil or the VOG technique (Sherer et al. 1991, van der Geest & Frens 2002). In recent years, head-mounted and remote camera-based systems have been developed to allow more natural and less cumbersome methods of gaze tracking. However, video-based solutions have either required the use of helmet-mounted equipment or have struggled to deal with head movement. The today commonly used instrumentation for eye movement studies, also struggle with the fact of being time consuming and difficult to use in clinical settings and have primarily been used in experimental studies.

There has been a substantial amount of eye-movement research related to reading. Within this area, different research groups have investigated eye-movements in slightly different ways. Their aims have been to understand the mechanics of how the eyes move, often in relation to dyslexia and eye-movement anomalies (von Hoffsten & Rosander 1996, Ram-Tsur et al. 2006). This leaves very little written on the subject of the functional detection capability in for example eye diseases measured with these methods.

1.9.2 The Tobii Eye Tracker

Lately, a new technique for studying reading performance and eye-movements has been developed, the Tobii Eye-tracker (Tobii Technology Inc. 2008). Its primary advantage is its accessibility. In comparison to the video-based and head mounted solutions, the subject only has to sit in front of a computer screen. This ensures a reasonably natural environment for the subject, as long as working with computers can be assumed a natural environment, which provides the most realistic responses to different stimuli. Disadvantages with the system, compared with other eye movement apparatus is the relative low precision when it comes to resolution and sampling frequency. In several different applications, however, the Tobii systems accessibility seems to outweigh the lack of precision. The Tobii Eye Tracker 1750 (Tobii Technology, Inc. 2008) LCD computer screen has an integrated high-resolution camera with a large field-of-view, used to capture images of the patient required for eye tracking. During tracking, the Tobii Eye Tracker uses near infrared diodes (NIR-LEDs) to generate reflection patterns on the corneas of the eyes of the patients. The camera collects these reflection patterns, together with other visual information about the patients. Image processing algorithms in the software identify relevant features, including the eyes and the corneal reflection patterns. The position in space of each eyeball, and finally the gaze point on the screen, i.e., where the patient is looking is

calculated in the Tobii software system. The display is based on a unit with maximum resolution of 1280x1024 pixels. The field of view of the camera for the Tobii is 21 x 16 x 20 cm (width x height x depth) at 60 cm from the screen. The frame-rate is 50 Hz, i.e., 50 gaze data points per second. Each gaze data point is provided with a time stamp in milliseconds, and describes when each camera image of the eyes is taken. Since each image takes a certain amount of time for exposure, the time-stamp is set to the middle point of exposure. The time-stamp is accurate to about +/- 5 ms. In order to compensate for head movements in the calculation of eye movements, it is enough that one of the eyes are within the field of view. This grants an effective tolerance to head-motion of about 30 x 16 x 20 cm (width x height x depth) which is enough to compensate for head positions, which normally occur when sitting in front of a computer screen. The Tobii Eye Tracker recovers from a complete tracking failure in less than 100 ms, and can track eye gaze in angles up to +/- 40 degrees measured from the camera.

2 AIMS OF THE STUDIES

All studies aimed to evaluate fixation and eye movements in clinical settings. In the first and second studies, the SLO was used to investigate fixation/gaze stability during visual field testing in normal subjects and subjects with well-defined retinal damage due to viewing a solar eclipse. In the third and fourth studies the Tobii Eye Tracker was evaluated as a tool for studying fixation and reading eye movements in normal subjects and in subjects being treated with Lucentis for age related macular degeneration.

Paper I

To investigate the fixation pattern in healthy subjects using the microperimetry technique obtained with the SLO and to calculate the fixation pattern with the “centre of gravity” (CG) method using the x and y coordinates extracted from the SLO F00-files instead of the video grabbing technique commonly used.

Paper II

To assess patients' VA and subjective disturbance resulting from solar induced retinopathy and to perform ophthalmoscopic investigations of the fundus over a period of time. The study also aimed to use the SLO to map the solar induced scotomas and evaluate the fixation pattern after such injury.

Paper III

To investigate if the Tobii Eye Tracker could be used to evaluate reading performance despite its relatively low resolution and sampling frequency and to establish normal values for reading eye movements in healthy subjects.

Paper IV

To investigate the change in reading eye movements and visual acuity in patients with CNV before and after treatment with the anti vascular growth factor Lucentis.

3 MATERIAL AND METHODS

3.1 MATERIAL (PAPERS I AND II)

In paper I, the fixation pattern of 31, randomly selected, healthy adult eyes was investigated with the SLO, using the fixation control function in the microperimetry technique. The inclusion criteria were: best corrected visual acuity equal to or better than 20/20, no earlier or present eye disease and no ongoing medication. In paper II, 15 patients, who all had viewed a solar eclipse, were examined at the initial visit at the emergency ward and at follow up visits, at 3 (visit 2) and 12 month (visit 3) with subjective questioning of visual symptoms, testing of visual acuity, ophthalmoscopy and scanning laser ophthalmoscopy (SLO). Inclusion criteria were: visual disturbances such as reduced VA and central visual field loss resulting from watching an eclipse.

3.1.1 The Scanning laser procedure

Microperimetry was performed with the Rodenstock SLO-101 using previously described methods (Stürmer 1993, Timberlake et al. 1989, van de Velde et al. 1990ab, Weber 1990). The SLO obtains retinal images continuously with an infrared laser (780 nm) and scans/projects the stimuli on the retina with a modulated visible helium-neon laser (633 nm). Visual stimuli are produced in the laser beam raster by means of a microcomputer and graphics board connected to an acousto-optic modulator in the SLO. The acousto-optic modulator rapidly changes the intensity of the scanned laser beam in response to electronic signals from the graphics generator in the SLO computer. Any pattern produced by the SLO computer and projected onto the patient's retina is displayed simultaneously on a monitor. The SLO provides a 32° x 22° image of the fundus with a minimum resolution of 4 minutes of arc (20 µm) for measurement and positioning of the stimuli. The graphics capabilities allow the investigator to determine the retinal location of visual stimuli directly on the retinal image in real time. The variables used for manual static visual field testing were those used in conventional perimetry, i.e., background illumination: 10 cd/m², incremental test stimuli (brighter than background) of 7x7 arc min, which is approximately Goldman size 1. Stimulus duration was 200 msec. The helium-neon laser was also used as light source for background illumination and fixation aid. A fixation cross (0 dB) with a size of 36 x 36 arc min was used and the subjects were told to keep a steady fixation on the centre of the fixation cross. The stimulus was presented one at the time, and the patients were asked to react, by pressing a hand held button, in response to every stimulus seen. The experimenter chose a well-defined reference mark on the retina (i.e., a vascular branching point). This ensured a correct alignment of the stimuli position on the retina and rejection of data points where the stimulus was presented during a saccadic eye movement.

3.1.2 Data collection and data analyses

During each stimulus presentation, the location of the fixation was saved in the computer (in x and y coordinates from the location of the fixation cross). These fixation locations were used to calculate the fixation pattern in each subject. Each fixation point and its x and y coordinate is represented in relation to the fixation cross. The results presented were obtained by first calculating each fixation point during a measurement (obtained simultaneously as the stimuli is presented) in relation to the fixation cross, for each subject and then by taking the mean of the x and y coordinates for each subject to obtain the results for the whole group. The mean of the x and y coordinates in each subject were calculated to be used as a “centre of gravity” (CG) for the fixation locations. The distance and angular location of each CG relative to the fixation cross-location was calculated in all subjects.

3.1.3 Special proceedings

In paper I, we performed a radial presentation of stimulus in order to get an acceptable coverage of the central macular area of interest, similar to how the meridians in Goldman perimetry are presented. The peripheral stimuli were presented at different locations (0 to 15 degrees from centre) along the orthogonal (0, 90, 180 and 270 degrees) and oblique (45, 135, 225 and 315 degrees) meridians. In total between 30 and 90 stimuli were presented to each subject. The number of stimuli presented varied due to the ability of the subject to concentrate on the task.

In paper II, the patients looked into the SLO with the affected eye and in average 38 stimuli were presented in a radial grid pattern within an area of approximately 5 degrees radius from the foveola. We chose to present the stimulus in a radial grid pattern since this would allow more precise mapping of the most central retinal areas. To detect scotomas, three different sensitivities were used; 0 dB (if not seen, considered as a dense scotoma), 10 dB (relative scotoma) and 20 dB (minimal suprathreshold scotoma). A scotoma was defined as a negative response to a given stimulus presentation with the SLO.

3.1.4 Statistics

All calculations and plotting were performed in Origin Scientific Graphing and Analysis Software, version 7 (Microcal Inc.). One-way analyses of variance (ANOVA) were used for the statistical analysis.

3.2 MATERIAL (PAPERS III AND IV)

In paper III, 20 subjects participated in the experiment. Thirteen female and seven male were enrolled from the School of Optometry, Karolinska Institutet, Stockholm, Sweden. The mean age was 25.9 years (range 21 – 33). The inclusion criteria were (1) age 20- 40; (2) visual acuity (VA) EDTRS of 20/20 or better monocularly and binocularly; (3) refractive errors within ± 5 dioptres; (4) no symptoms related to binocular vision problems; (5) no symptoms or signs of ocular diseases; (6) no

premature birth or low birth weight; and (7) no diagnosed reading and writing deficiency. In paper IV, 20 subjects were enrolled from the Department of Vitreoretinal Diseases, 15 females and 5 males. Mean age was 81.8 (range 74 – 98). The inclusion criteria were (1) 50 year of age or older with subfoveal neovascular AMD who after clinical examination with fluorescein and ICG-angiography and coherence tomography (OCT) had VA 20/200 or better; (2) classic or predominantly classic neovascularisation (CNV); (3) occult CNV with an extension ≤ 4 disc areas with ongoing or a recent exposition of the disease. All participants were investigated with the Tobii 1750 eye tracker. In paper III they were examined once, and in paper IV before and three month after treatment with intravitreal ranibizumab (Lucentis) injections.

3.2.1 Apparatus

A Tobii 1750 eye tracker was used for the experiment (Tobii Technology Inc. 2008). Subjects were seated in comfortable chair approximately 60 cm from the screen. Before each recording the system was calibrated using a nine-point calibration pattern. Before the actual experiment each subject participated in a training session where they read single sentences in decreasing font sizes to make sure that they could clearly read text that was at least 60 % smaller than the font used for the experiment. Prior to measurements the system was individually calibrated. The texts were presented left justified in a 24-pt sans-serif font over six pages (Fig. 6).

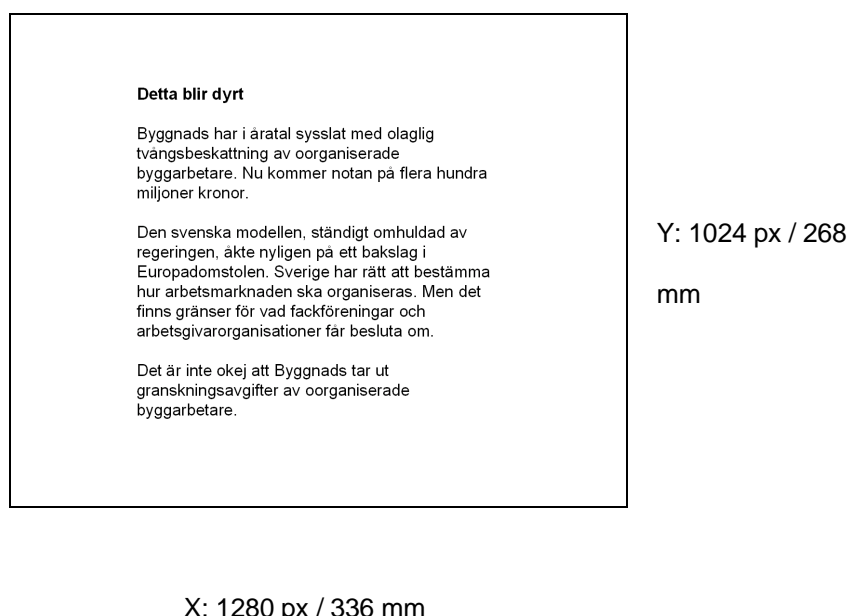


Fig. 9 Example of how a page was displayed with screen dimensions.

3.2.2 The texts used

Each subject read two texts, from now on called text A and B. Both were editorials from a Swedish newspaper of equal difficulty measured using LIX (Björnsson 1968) (see www.lix.se for a calculator) (LIX = 48). Each text was 35 sentences long and of similar word length (A=501, B=518) (Table 1).

	Text A	Text B
Sentences	35	35
Words	501	518
Long Words (>6 characters)	170	174
Average Sentence Length (ASL)	14.3	14.8
Long Word Ratio (LWR)	33.9 %	33.6 %
LIX (ASL + LWR)	48.2	48.4
Lexical Density (types/tokens)	55.9 %	55.8 %
Word Variation (log(types)/log(tokens))	90.6 %	91.3 %

Table 1 Text A and B word, sentence and LIX composition.

3.2.3 Procedure

Half of the subjects read text A before text B and vice versa. The subjects were instructed to read normally as they would in any everyday situation. They were informed that they would be asked questions about the text afterwards. After reading a text, the subject was asked five multiple-choice questions regarding the content. The questions were designed so that the options were ambiguous and could only be answered if one had read certain passages spread over the whole text. The complete experiment took approximately 15 minutes to perform.

3.2.4 Analysis

Reading speed was measured in words read per minute (wpm) from the onset of the first page to the conclusion of the last. Comprehension was enumerated as the ratio of correct answers (%). Eye movements were recorded as time stamped coordinates of how the eyes moved over the screen. The recordings were analysed in two steps. First fixations were detected; next the movements between fixations were categorized. Any period when the eye remained within 1.5 degrees from its centre of gravity for at least 100 ms was considered a fixation. During a fixation, the centre of gravity was continuously re-weighted to the horizontal and vertical mean position. In the event of larger movements or blinks the fixation was considered finished. Movements between fixations were categorized depending on amplitude and direction. Movements shorter than 6.3 degrees were classified as saccades if they were directed in a forward/downward direction (between 45 and 225 degrees); otherwise they were categorized as regressions. Movements larger than 6.3 degrees were categorized as forward/backward/down/up sweeps depending on orientation (Fig.7).

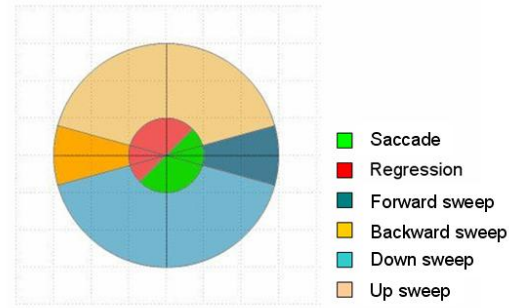


Fig.10 Categorization of eye movements depending on amplitude and orientation.

(Picture from own production)

Eye movements were independently analyzed for the left and right eye and the results were averaged over both eyes. The number of fixations, saccades, and regressions were normalised into occurrences per word. The duration of fixations, the amplitude of saccades and regressions, and the ratio between saccades and regressions were used as comparison measures for the statistical analysis.

3.2.5 Statistics

In paper III and IV, Wilcoxon signed-rank test was used for comprehension whereas paired Student's t-tests were used for all other measures. All tests were two-sided and the alpha level was set to 95 % ($p = .05$).

4 RESULTS

4.1 FIXATION AND GAZE-STABILITY (PAPERS I AND II)

In paper I, no correlation was found between the location of the presented stimuli and the fixation of each subject. In general, the fixation pattern varied between subjects. The mean distance of the CGs in relation to the fixation cross was found to be 0.27 degrees (SD 0.13; range 0.04-0.50; Fig. 8).

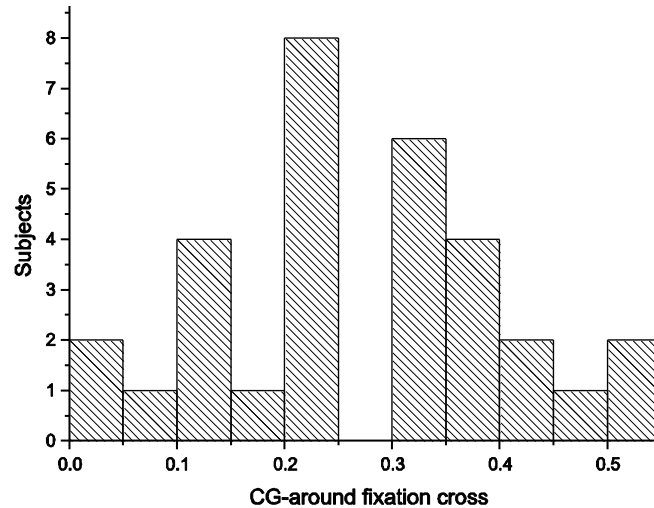


Fig. 11 Histogram showing the mean distance between the fixation cross and the centre of gravity (CG). Note that the CGs was distributed close to the fixation cross (mean 0.27 degs).

Also there was a slight tendency to have a directional preponderance of the CGs, more frequently distributed in the vertical sectors (70-110 and 250-290 degrees) than in the horizontal (340-320 and 160-200 degrees; Fig. 9), however, this tendency was not statistically significant.

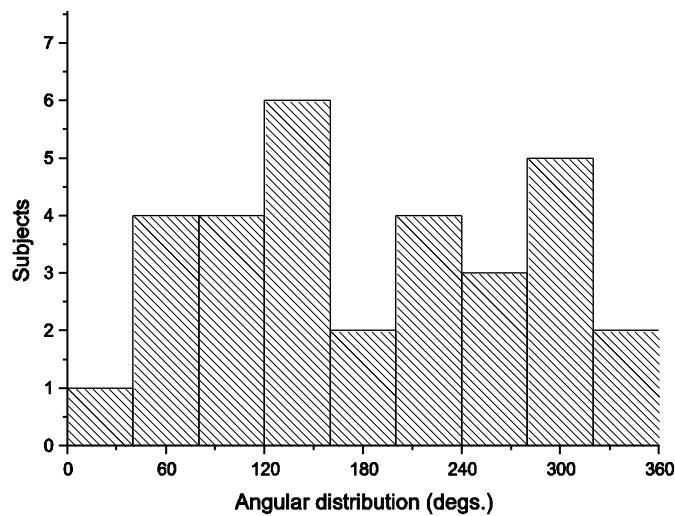


Fig. 12 Histogram showing the angular distribution of the CGs (centre of gravity) around the fixation crosses. Note a small directional preponderance in that more CGs is distributed in the vertical sectors (70-110 and 250-290 degs) than in the horizontal (340-320 and 160-200 degs).

On an individual basis, there were large differences in terms of fixation patterns. Some subjects showed a large area distribution of fixational locations, while others showed a much more concentrated distribution. The angular distribution of the fixations was also found to vary between subjects and some subjects showed a much more horizontal distribution of the fixation pattern than the more vertical distribution seen as the mean for the whole group. In paper II, the mean distance of the CGs in relation to the fixation cross was found to be 0.27 degrees (SD 0.10; range 0.13-0.46) at visit 2 and 0.36 degrees at visit 3 (SD 0.12; range 0.18-0.62). However, this difference was not significantly different ($p=0.174$). The fixation position in relation to the central scotoma was, at visit 2, predominately maintained inferior to the fovea, or inferior and nasal or shifting around the scotoma. At visit 3 fixations was predominately maintained inferior, nasal or temporal to the scotoma.

4.1.1 Subjective disturbance (Paper II)

The patients' subjective estimation of the disturbances from the scotoma showed that all patients (15) had a severe disturbance on the initial visit. At 3 months (visit 2), 8 had a severe disturbance, 5 had mild and 2 had no disturbance at all. At one year (visit 3), 6 had a mild disturbance and 9 had no disturbance at all.

4.1.2 Visual acuity (Paper II)

At visit 1 the patients' VA ranged between 0.25 – 1.2 (median 0.8). At visit 2 and 3 VA was between 0.4 – 1.6 (median 1.0) and 0.6 – 1.6 (median 1.0), respectively. Between visits 1 and 2, the average increase in VA was 0.25 (range 0-0.6) ($p < 0.001$) and between visit 2 and 3 the average increase was 0.09 (range 0-0.3) ($p < 0.221$). All but one patient showed an increased VA over the entire study period (Fig. 10).

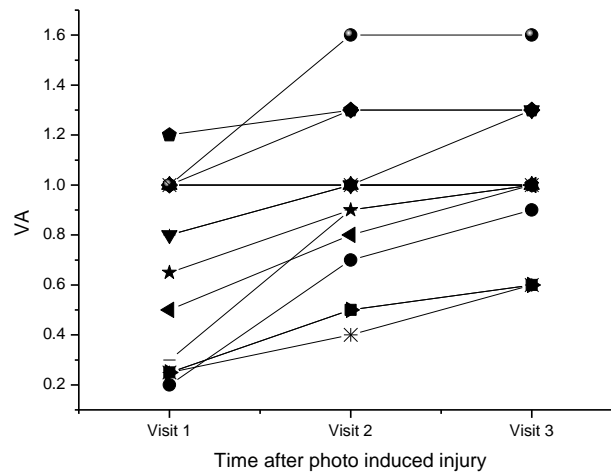


Fig 13 Visual acuity over time in all subjects. Note that VA increased in all patients except one.

A significant difference in VA ($p < 0.001$) could be seen between the initial visit and visit 2, and between the initial visit and visit 3 ($p < 0.05$), but not between visit 2 and 3 ($p = 0.221$). Large individual differences could be seen over time in the restoration of VA.

4.1.3 Fundoscopic findings (Paper II)

Foveal lesions such as oedema, lamellar macular holes and distinct retinal pigment epithelia (RPE) disturbance, could only be seen in 7 patients (47%) during the initial visit. The corresponding figures were four (27%) and two (13%) at visit 2 and 3, respectively.

4.1.4 Scotomas (Paper II)

A scotoma could be detected in all patients on every SLO examination. At visit 2 the size of the scotomas varied between 1 and 4 neighbouring stimulus presentations (corresponding roughly to 0.12 – 0.48 degrees, while at visit 3 the scotomas had a size of 1-3 stimulus presentation (corresponding approximately to 0.12 – 0.36 degrees) (Figure 11).

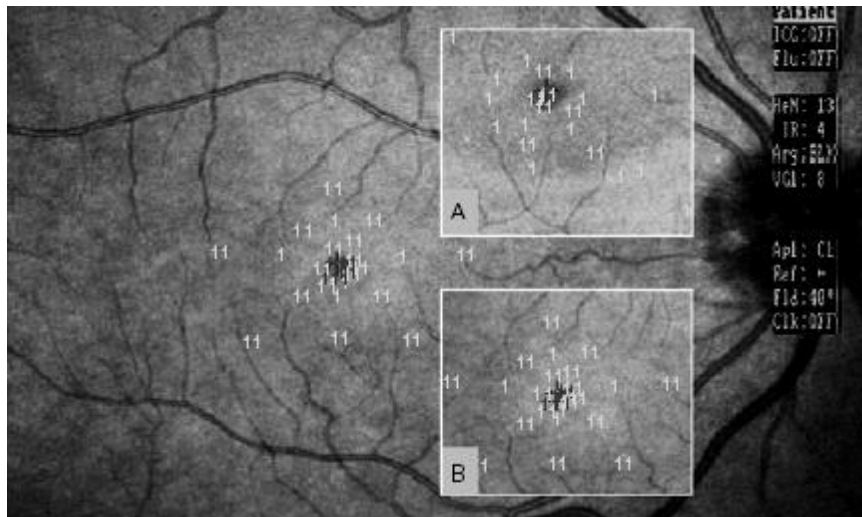


Fig 14 Fundus photograph from a representative subject showing the results of SLO investigation (large picture) with a microperimetry overlay showing non-response stimuli indicative of a scotoma (in black).

At visit 2, 11 patients showed a minimal suprathereshold (20 dB) and 4 a relative (10 dB) scotoma. At visit 3 a minimal suprathereshold scotoma could be seen in all patients, but no deeper defects. Since the radiation from the sun through the optical system of the eye was focused on the centre of the fovea, all scotomas also included the central fovea, which corresponds to the fixation mark.

4.2 TOBII EYE-TRACKER AND READING EYE MOVEMENTS (PAPER III AND IV)

In paper III, analysis of reading speed, comprehension and eye movements were done independently for text A and B and results from the two texts were compared. In paper IV, analysis of reading speed, comprehension and eye movements, texts A and B were regarded as one test which then was compared with the results of both texts after treatment.

4.2.1 Reading speed (Paper III)

In paper III, a significant difference in reading speed could be seen ($p < .001$). Text A was read significantly slower ($M = 184.6$ wpm, $SD = 61.2$) than text B ($M = 219.4$ wpm, $SD = 70.2$) (Table 2).

4.2.2 Comprehension (Paper III)

There was no significant difference in comprehension between the texts ($n_{s/r} = 14$, $p = .72$) (Table 2).

4.2.3 Fixations per word and duration (Paper III)

There was a significant difference in the number of fixations per word ($p < .001$). Text A was read with significantly more fixations per word ($M = 1.04$, $SD = 0.22$) than text B ($M = 0.92$ fpw, $SD = 0.18$). A significant difference in fixation duration ($p = .007$) was found. The fixation durations for Text A ($M = 285.1$ ms, $SD = 48.7$) were significantly longer than they were for text B ($M = 275.1$ ms, $SD = 44.0$) (Table 2).

4.2.4 Saccades per word and amplitude (Paper III)

Text A was read with significantly ($p < .001$) more saccades per word ($M = 0.66$, $SD = 0.18$) than text B ($M = 0.58$, $SD = 0.15$) and the saccade amplitudes for text A were significantly shorter ($M = 2.94^\circ$, $SD = 0.35$) than they were for text B ($M = 3.07^\circ$, $SD = 0.38$) (Table 2).

4.2.5 Regressions per word and amplitude (Paper III)

Text A was also read with significantly more regressions per word ($M = 0.11$, $SD = 0.08$) than text B ($M = 0.09$, $SD = 0.05$). The regression amplitudes for text A ($M = 2.49^\circ$, $SD = 0.38$) were shorter than they were for text B ($M = 2.59^\circ$, $SD = 0.27$) and there was no significant difference in regression amplitude ($p = .11$) (Table 2).

4.2.6 Saccadic and regression ration (Paper III)

Neither were there a significant difference in the saccade/regression ratio ($p = .61$). The ratio of saccades per regression was lower for text A ($M = 7.8$, $SD = 3.3$) than it was for text B ($M = 8.1$, $SD = 3.1$) (Table 2).

	Text A		Text B		
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>p</i>
Reading speed (wpm)	184.6	61.2	219.4	70.2	< .001 *
Comprehension (%)	63.0	20.8	62.0	15.8	.72
Fixations per word	1.04	0.22	0.92	0.18	< .001 *
Fixation duration (ms)	285.1	48.7	275.1	44.0	.07
Saccades per word	0.66	0.18	0.58	0.15	< .001 *
Saccade amplitude (°)	2.94	0.35	3.07	0.38	< .001 *
Regressions per word	0.11	0.08	0.09	0.05	.034 *
Regression amplitude (°)	2.49	0.38	2.59	0.27	.11
Saccade/regression ratio	7.8	3.3	8.1	3.1	.61

Table 2 Summary of eye movement variables for text A and B (Paper III).

4.2.7 Visual acuity (Paper IV)

On average there was a significant improvement in visual acuity ($p = .036$). The patients read significant more ETDRS letters after treatment with a mean (M) increase of 8.85 letters ($SD = 14.19$) (Table 3).

4.2.8 Reading speed and comprehension (Paper IV)

There was no significant difference in reading speed before and after treatment ($p = .25$) but a significant increase in comprehension of the texts before and after treatment ($p = .031$) (Table 3).

4.2.9 Eye movement parameters (Paper IV)

Concerning eye movements, in all parameters, except the number of regressions per word, there was no statistically significant difference when comparing the results from before and after treatment. However, there was a statistically significant increase in the number of regressions per word after treatment ($p = .046$) (Table 3).

All patients	Before treatment		After treatment		
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>p</i>
Reading speed (wpm)	181.2	34.2	171.5	41.2	.25
Comprehension (%)	50	20	60	22	.031*
Fixations per word	458.1	65.1	482.1	86.6	.194
Fixation duration (ms)	297.4	48.3	300	54.4	.817
Saccades per word	303.3	56.3	315.6	72.6	.384
Saccade amplitude (°)	117.8	16.5	116.6	15.6	.618
Regressions per word	62.4	32.3	70.2	39	.046*
Regression amplitude (°)	98.7	13.4	86.3	31.8	.069
Saccade/regression ratio					

Table 3 Reading speed, comprehension and eye movements for the whole group of patients

5 DISCUSSIONS

5.1 GENERAL DISCUSSION (PAPER I AND II)

Slight movements of the eyes are essential for good visual perception (Yarbus 1959). Three types of movements accompany fixation: drifts, tremor, and involuntary saccades (Ditchburn 1973, Huston 1982). Since the fixation in normal subjects is not kept stationary although efforts are made to fixate a stationary target, the term “fixation field” must be more appropriate.

5.1.1 Methodological considerations (Paper I and II)

Fixational eye movements have traditionally been measured by conventional methods such as the IR-reflection technique (Crossland & Rubin 2002), scleral search coil (Sherer et al. 1991) or the VOG technique (van der Geest et al 2002). However, the SLO microperimetry-technique is the only perimetry method that allows exact mapping of the fixation position simultaneously with stimulus presentation during perimetry. Therefore, the results from a fixational mapping during microperimetry performed with the SLO are important when measuring the central VF in patients with unstable and/or extra foveal fixation.

The similarity of our results concerning the area of central fixation pattern, with the ones obtained with conventional methods for fixational eye movements' analysis is interesting, considering the differences in static and dynamic measurements. The ability of an accurate measurement of the fixation pattern gives an estimate of the compliance during the perimetry. The fixation can be quantified from video recordings (Möller & Bek 1998) and defined as central if more than 50% of the fixation points were located in a predetermined area (Fujii et al. 2002). Others have used the Bivariate Contour Ellipse Area (BCEA) method for identifying the area used during fixation (Crossland et al. 2004). The BCEA method gives two orthogonal diameters describing the extent of the fixation distribution around a fixation mark. However, the CG method, as we have shown, can also give further information since the area around the fixation point is divided into eight sectors and the distribution of fixation points within these sectors can easily be calculated. The BCEA-method relies on the assumption that the material is normally distributed, which is often not the case in this kind of measurements, and can therefore give misinterpretation of the data. However, if calculated with the CG-method, no consideration is necessary to whether the material is normally distributed or not. We therefore consider the CG method more informative of fixational behaviour in both normal subjects as well as subsequent patient groups to be investigated. The CG method has, to our knowledge, not previously been performed with SLO. To our awareness no other study has addressed the question of angular distribution of fixations during testing. The explanation for the directional differences found in the study of normal subjects is not yet fully known. This may be correlated to the sensitivity orientation of the ganglion cells in that the responses of most cells, to high spatial frequencies, depend on grating orientation (Passaglia et al. 2002). This indicates that response fields could be described by an ellipse. However, an effect of higher visual pathways processing cannot be excluded.

5.1.2 Fixation/gaze-stability in normal vs. injured eye (Paper I and II)

The mean distance of the CGs in relation to the fixation cross corresponded well to each other in paper I and II (0.27°). However the mean distance of the CG increased over time in the patients in paper II, (0.36 at visit 3). The good fixation/gaze stability in most cases in paper II can probably be attributed to the resistance of the foveal cone cells to photochemical damage (Hope-Ross et al. 1993).

5.1.3 Funduscopy appearance, SLO and visual acuity (Paper I and II)

The results from paper II are consistent with other studies (Dhir et al 1981) which found no correlation between funduscopy appearance and VA. On the other hand, with SLO-microperimetry a clear correlation of this kind could be seen in all cases. Subjectively, a decrease of the visual disturbance occurred during the whole period, but 40 % of the patients experienced a mild disturbance after one year. The SLO results further showed presence of scotomas at visit 3, even when the patients did not experience any visual disturbance. The good visual prognosis in most cases can probably be attributed to the resistance of the foveal cone cells to photochemical damage (Hope-Ross et al. 1993).

5.2 GENERAL DISCUSSION (PAPER III AND IV)

Slight movements of the eyes are essential for fixation and a high level of visual perception. However, to enable reading, a good quality of fixation has to be combined with accurately controlled eye movements. With better knowledge about reading eye movements, researchers as well as practitioners, will gain better understanding of decreased reading ability in patients with various eye diseases.

5.2.1 Methodological considerations (Paper III and IV)

Measurements of eye movements have been available for several decades. The first precise techniques were based on scleral search coils (which are still used today) (Ram-Tsur et al. 2006). In recent years, head-mounted and remote camera-based systems have been developed to allow more natural and less cumbersome methods of gaze tracking, but have either required the use of helmet-mounted equipment or have struggled to deal with head movement. Even the today commonly used instrumentation for eye movement studies, also struggle with problems of being time consuming and difficult to use in clinical settings, and have primarily been used in experimental studies.

Tobii eye tracker is a novel technique for measuring eye movements. Its primary advantage is its accessibility, in comparison to the video-based and head mounted solutions, the subject only has to sit in front of a computer screen. This ensures a reasonably natural environment for the subject, which provides the most realistic responses to different stimuli. Disadvantages with the system, compared with other eye movement apparatus, are the relative low precision when it comes to resolution and sampling frequency. In several different applications, however, the Tobii system's

accessibility seems to outweigh the lack of precision. The results accounted for in this thesis show that the Tobii system, despite its relative low resolution and sampling frequency, is suitable for evaluation of reading eye movements. However, as a direct measure of visual improvement after, for example Lucentis treatment, other tests should preferably be used to get maximum understanding of the effect.

5.2.2 Visual acuity (Paper IV)

The treatment with intravitreal Lucentis was effective in significantly increasing mean BVCA for the majority of the patients, which is in accordance with recently published reports (Rosenfeld et al. 2006, Brown et al. 2006, Regillo et al. 2008, Rothenbuehler et al. 2009, Kiss et al. 2009, Bressler et al. 2009).

5.2.3 Reading speed (Paper III and IV)

For normal subjects, paper III, the average reading speed was found to be (184.6 and 219.4 wpm for text A and B respectively) which concurs well with reading speed found in other studies using text with similar difficulty (Tinker 1951, Björnsson 1968, Rayner & Pollak 1989, Ciuffreda & Tannen 1995). In paper IV, the values for reading speed were found to be ($M = 181.2$ wpm) before treatment and ($M = 171.5$ wpm) after, and gave no significant changes that could be explained by the treatment. Both before and after treatment our AMD patients on average read slower than was found examining normal subjects (Paper III).

The two texts chosen for these studies were linguistically matched and had the same LIX value (48). Despite this, reading speed was found to be statistically slower for text A compared with text B, a finding confirmed in paper IV as well, irrespectively of treatment or not. This finding shows the necessity of careful text selection when conducting reading studies, since both texts were chosen based on having an equal readability. Therefore, when conducting reading studies one should bear in mind that differences in reading speed and eye movements can occur even though the texts have a very similar rating of readability. Consequently, when analysing the effect of, e.g., treatment, the same text should be used both before and after treatment. This, however, does increase the risk of learning effects influencing the results.

5.2.4 Eye movements (Paper III and IV)

In paper III, the difference in reading speed between the two texts is reflected in the differences in eye movement patterns. Text A was found to have statistically longer fixations, a higher number of saccades per word, shorter saccade amplitudes and more regressions. The values for fixations, saccades per word and saccadic amplitude found were similar to previous findings (Findlay et al. 1995, Rayner 1998). The fact that the Tobii system could detect these differences in reading performance, despite its relative low resolution and sampling frequency implied that the system could be suitable for studies evaluating reading performance. In paper IV, for all eye movement parameters, except the number of regressions per word, there was no statistically significant difference when comparing the results from before and after treatment.

5.2.5 Comprehension (Paper III and IV)

In paper III, no difference in reading comprehension could be found. This implies that text A was probably read “more carefully” in order to understand the text. Although no improvement in reading speed could be found in paper IV, a significant improvement in comprehension could be seen from ($M = 50\%$) before treatment and ($M = 60\%$) after. The reason for this might be the increased visual acuity, but could also be a result of the strive to achieve as well since the patients were aware of the questionnaires they were about to get after the tests. The improved comprehension could also be a result of the learning effects since the same texts were read on both occasions. However, this is unlikely for two reasons, firstly since the texts were read three months apart and secondly since one would expect reading to be faster the second time if the patients recognized the texts.

5.2.6 Equals increased visual acuity increased reading ability (Paper IV)

When looking at individual data in paper IV, two distinct groups can be defined: (I) patients that had an increased visual acuity of 10 or more letters after treatment (i.e., equivalent to two lines or better on the chart); and (II) patients who did not achieve a 10 letter improvement. Within these groups ($I = n 5$, $II = n 9$), a clear difference in reading eye movement performance could be seen for those who had an increased visual acuity of 10 letters or more (Table 4). They displayed, not only as the whole group, a significant increased comprehension but also a significant slower reading speed ($p = .003$), which could be explained with a more in-depth reading when also having an increased visual acuity. Furthermore, a significant number of more fixations per word could be seen ($p = .029$), this is also probably due to a more thorough reading since a higher level of VA allows more rechecks or double check confirmation (Ciuffreda & Tannen 1995) without “getting lost” in the text. Naively one would expect that increased or stable (i.e., not further reduced) visual acuity after Lucentis treatment would result in an ability to read faster and make fewer eye movements. However, this seems not to be the case. On the other hand, comprehension improved after treatment, something that might indicate that reading becomes easier even though it is not directly related to the reading speed. Other research groups have similar findings when trying to develop computerised reading aids for dyslexia. When making reading easier, the reading speed become slower (Goldstein et al. 2006).

Patients with ≤10 letters increased visual acuity	Before treatment		After treatment		
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>p</i>
Reading speed (wpm)	174.2	31	148.2	23.3	.003*
Comprehension (%)	44	15	64	22	.031*
Fixations per word	473.5	58.7	516.5	52.7	.029*
Fixation duration (ms)	309.2	55.6	325.3	59.2	.609
Saccades per word	297.4	24.8	325.2	48.4	.055
Saccade amplitude (°)	116.31	14.3	113.8	16.3	.350
Regressions per word	83.9	40.4	91.6	51.8	.273
Regression amplitude (°)	95.2	10.5	95.9	14.5	.696
Saccade/regression ratio					

Table 4 Reading speed, comprehension and eye movements for the group of patients with an increased visual acuity of 10 letters or more. (Students T-test was used for all parameters except comprehension, in which Wilcoxon matched-pairs signed-ranks test were used).

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