Aspects on Function in Age-Related Macular Degeneration

Christina Winther

UNIVERSITY OF GOTHENBURG

Department of Clinical Neuroscience and Rehabilitation
Institute of Neuroscience and Physiology
The Sahlgrenska Academy at University of Gothenburg
Gothenburg, Sweden
2016

Aspects on Function in Age-Related Macular Degeneration
© Christina Winther 2016

ISBN 978-91-628-9676-8 (PRINT)
ISBN 978-91-628-9677-5 (PDF)
http:// hdl.handle.net/2077/40885

The cover picture was designed by Lars Frisén.
Published articles have been reprinted with permission of the copyright holder.

Printed by INEKO AB, Gothenburg, Sweden.

Abstract

Age-related macular degeneration (AMD) is one of the leading causes of severe visual loss among persons ≥ 60 years. AMD can be categorized in one of three stages: early, intermediate, or late. In early AMD visual symptoms are inconspicuous whereas, in the late stage, severe loss of vision is common. Late AMD has dry and wet forms. Wet AMD is a chronic disease with episodes of exacerbation, with varying intervals between relapses. The sooner a new episode of disease activity is discovered and treated the better for the visual outcome while delayed treatment often leads to irreversible loss of visual function. Providing timely diagnosis and treatment poses a difficult challenge for ophthalmology clinics today.

Measurement of visual resolution by using conventional distance acuity charts is inadequate for the detection of early functional changes in AMD and also for monitoring the progression in the disease. A key problem is associated with the optotype test targets and their information overload. Optotypes are many times larger than the retinal functional units, the receptive fields, and viewing time is usually unrestricted. There is a need for new sensitive tests of vision to uncover low degrees of visual impairment in AMD and for allowing self-testing of vision in patients treated for wet AMD. There is also a need for simplified and standardized reading tests to gain insight into an important task of daily life, reading performance. The aims of this thesis was to evaluate new vision tests designed for the detection and grading of lesions in the macula and to study if these tests are suitable for self-testing of vision. Further, a new abbreviated and standardized reading test was studied.

Methods: In prospective studies on AMD patients and normal subjects new tests of vision were evaluated. The tests in paper I-III are based on Rarebit testing which is able to detect gaps in the receptive fields, using bright microdots on a dark background. The tests were gradually refined from mini data projectors and personal computers to a unique application for smartphone, including the possibility of self-testing of vision and transmission of results. The reading test evaluated in paper IV was also in the form of a smartphone application.

Results: The new tests of vision evaluated in paper I-III capture macular deficits hidden to conventional acuity tests. The new reading test evaluated in paper IV measures basic reading abilities at least as good as conventional and more time-consuming

Conclusions: By using new more sensitive tests which appear to have good potential for effective self-testing of vision in AMD, some currently performed hospital-based controls may be replaced with self-tests at home. This may contribute to a more effective use of healthcare resources. The new reading test demonstrates a new approach towards meaningful and time-efficient assessment of reading ability.

Key words: age-related macular degeneration, macula, macular oedema, rarebit, reading test, reading speed, self-test, smartphone application, vision test, visual acuity

List of Papers

This thesis is based on the following four papers, which will be referred to in the text by their Roman numerals.

I. Christina Winther, Lars Frisén: A compact rarebit test for macular diseases. Br J Ophthalmol 2010; 94: 324-327.

II. Christina Winther, Lars Frisén: New rarebit vision test captures macular deficits hidden to acuity tests. Acta Ophthalmol 2015; 93: 481-485.

III. Christina Winther, Lars Frisén: Self-Testing of Vision in Age-Related Macula Degeneration: A Longitudinal Pilot Study Using a Smartphone-Based Rarebit Test. J Ophthalmol 2015 June 1. doi: 10.1155/2015/285463.

IV. Christina Winther, Lars Frisén: Assessment of spot reading capacity in patients with age-related macular degeneration using printed charts and a new smartphone-based reading test. Manuscript.

Contents

Introduction **1**

Background **1**

Age-related macular degeneration (AMD) 4
  Dry AMD 5
  Wet AMD 5
Diagnostic tools and AMD 7
  Angiography 7
  Optical Coherence Tomography 8
Symptoms in AMD 9

Clinical tests **11**

Visual Acuity 11
Near word acuity 13
Reading speed 13
Low-contrast visual acuity 14
Dysmetropsia and Metamorphopsia tests 15
Preferential hyperacuity 17
Photostress test 18
RareBit probing 18

Aims of the Thesis **22**

Materials, Methods and Results **23**
Paper I........ 23
Paper II 25
Paper III........ 29
Paper IV........ 32

Discussion **37**
Paper I........ 37
Paper II 39
Paper III........ 41
Paper IV........ 42

Conclusions **45**

Future Perspectives **46**

Svensk sammanfattning/ Summary in Swedish........ **48**

Acknowledgements **51**

References........ **53**

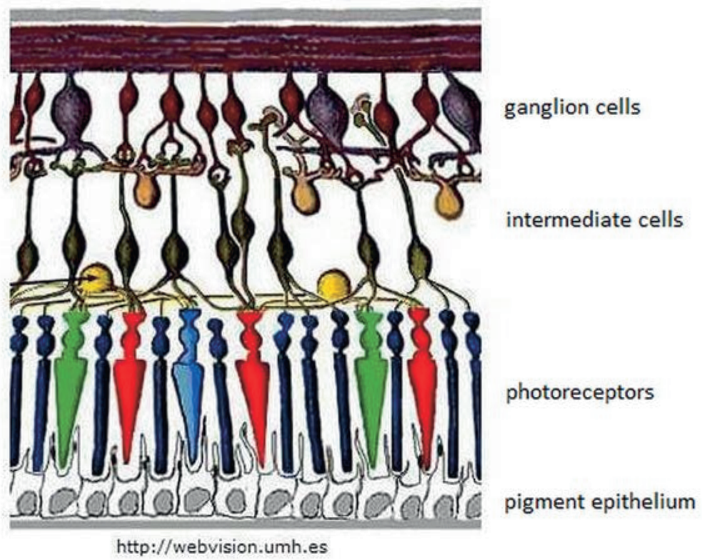
Introduction

Human visual function can be analysed and measured in many different ways, some more complicated than others. The most simple and widespread of all visual tests is the measurement of visual acuity using a letter chart. This type of test has been used for more than 150 years and measures resolution, i.e. the ability to discriminate two high-contrast points in space. By using letters, or optotypes, on a chart, the test is made simple and understandable, at least for literate persons. Acuity tests measures function only in a very restricted part of the retina, the so-called macula lutea, or macula for short. This is the part of the retina in which the photoreceptors are most densely packed. It is also the site for a disease called age-related macular degeneration, which is the most common cause of irreversible visual loss in the Western World today. Thus, it may seem that visual acuity tests would be ideal for detecting and following this disease. Unfortunately, and in spite of their popularity, visual acuity tests are not very sensitive to early changes in macular function. It has been shown that approximately 40 per cent of the photoreceptor matrix in the macula can be lost before visual acuity drops below 1.0 [1], which is often accepted as normal value. With the advent of new and more effective treatment regimes for age-related macular degeneration there is a need for better diagnostic tools. The general aim of this thesis is to try to find such tools.

Background

The back wall of the eye (the posterior segment) contains three distinct structures, innermost the retina, in the middle the choroid and outermost the sclera. The fibrous white sclera acts as a tough outer coat that protects the delicate interior structures of the eye. The choroid is a vascular tissue with the highest blood flow in the entire body. It supports the retina with nutrients and transports waste products.

The retina lines the interior surface of the back of the eye. The retina´s function is to capture light and to process the resultant stimuli. These stimuli are then transmitted to the visual cortex in the brain for interpretation and creation of a visual perception. If flatted out the retina is a circular area of between 30 and 40 mm in diameter and 0.5 mm thick. The retina contains distinct layers (Figure 1).The output neurons (ganglion cells) lie innermost in the retina, closest to the pupil and the input neurons (photoreceptors), lie outermost in the retina, closest to the sclera. Thus, light must travel through the entire retina before activating the light sensitive photoreceptors, rods and cones. The photoreceptors and ganglion cells build functional units called receptive fields. A receptive field is defined as that aggregate of receptors that transmits information to the same ganglion cell. The ratio between the number of photoreceptors and ganglion cells increases with the distance from the centre of the macula [2].



http://webvision.umh.es

Figure 1. Schematic outline of retinal neural elements and pigment epithelium.

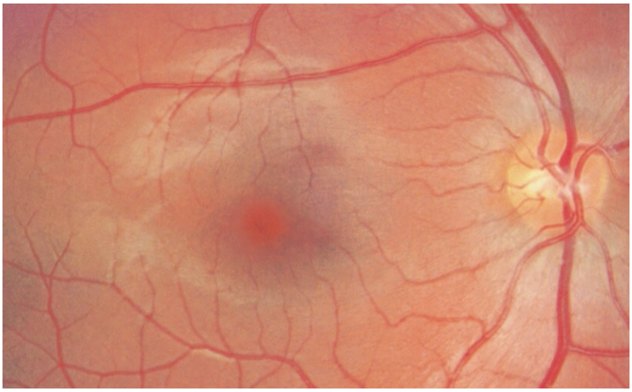


Figure 2. Normal macula.

The average retina contains approximately 100 million rods and 5 million cones [3]. Rods are responsible for dark-adapted vision and they dominate peripheral retina. The central part of the retina, the macula, is a region of approximately 5.5 mm in diameter and corresponds to approximately 15-20° of the visual field (Figure 2). Because of its content of yellow pigment (xanthophyll) the macula is often called “the yellow spot”. The central 1.5 mm of the macula is called the fovea and corresponds to approximately 5° of the visual field. This is a cone dominated area responsible for high-resolution vision and colour vision. In this area the ratio between photoreceptors and ganglion cells in the receptive fields is approximately 1:2-2.5, i.e. each cone connects to more than one ganglion cell. In the central part of the fovea is a region devoid of retinal vessels, known as the foveal avascular zone. Within the centre of the fovea is the foveola, a 0.35 mm area where cones are especially slender and densely packed allowing the foveola to have the highest spatial resolution in the eye. Surrounding the fovea is the thickest part of the retina, a 0.5 mm diameter rod-dominated zone, the parafovea. Surrounding this is a transition zone towards the peripheral retina, the perifovea, and in this zone the relation of ganglion cells to photoreceptors gradually falls from approximately 1:1 to 2:1.

Adjacent to the photoreceptor layer is a single layer of cells, the retinal pigment epithelium (RPE). These cells are intimately related to the photoreceptors and they ingest and digest the constantly destructed outer segments of the photoreceptors. The RPE also works as a light absorber, it supplies the photoreceptors with nutrients, maintain ion balance, eliminates water, and secretes a number of so-called neurotransmittors. Last but not the least the RPE forms a barrier that separates the inner space of the eye from the outer blood stream thus forming a separate- and from the outer blood stream disconnected - immune space.

As years pass the capacity to digest material from the photoreceptors is impaired and undigested material is stored within the RPE cells. This storage of waste products has a negative impact on cell metabolism and the digestive capacity is further impaired. Eventually the cell structure of RPE cells change and the cells are enlarged. With age there is also a reduction of the number of RPE cells resulting in increased demands on the remaining cells.

Waste material from the RPE is continuously transported to the choroid, a five layered structure rich in vascular tissue. The choroid has the highest blood flow in the entire body and provides the retina with essential nutrients. The innermost part of the choroid is called Bruch´s membrane. Throughout life lipids are built up within this layer and the membrane becomes both thicker and more hydrophobic as we get older.

Age-related macular degeneration (AMD)

Age-related macular degeneration is the most common cause of severe loss of central vision among people ≥ 60 years in the Western World [4, 5]. In Framingham , USA, a city founded in 1700 and located by the very first north American trail leading westbound from the Atlantic, a nowadays often cited study on the prevalence of AMD was conducted during 1973-1975.The study population had been under investigation for coronary disease risk factors since 1948. Members of the study population who were 52 to 85 years-of-age, were offered an eye examination. The study revealed that AMD affected about 2% of those aged 52-64 years, 11% of those aged 64-74 years and 28% of those 75 years or older [4]. With an aging population, not only in the Western World, but also globally, AMD will become an increasingly prevalent and important disease worldwide [6].

There are several classification schemes of AMD. In 2013 members of the Beckman Initiative for Macular Research Classification Committee proposed a 5-stage AMD classification scale [7]. This classification system start from “no apparent aging changes” to “normal aging changes” further to “early-” and “intermediate AMD” and finally “late AMD”. However, in daily work AMD is most often referred to as “dry or wet”.

Dry AMD

Degenerative changes in the RPE and Bruch´s membrane are called dry AMD. One of the hallmarks of dry AMD is drusen (Figure 3). These are round, yellow-white lipid- and collagen-containing lesions located between the RPE cells and Bruch´s membrane. Drusen are mainly classified according to size, distribution and confluence [8]. Another sign of dry AMD is hyper- and hypopigmented areas in the macula. This is due to the degeneration of RPE cells eventually causing death of photoreceptors. When RPE cell reduction is profound, large map-like areas are formed. These so-called geographic atrophies are transparent areas revealing underlying choroidal vessels and represent the most advanced form of dry AMD (Figure 3). Currently, there are no treatments for dry AMD

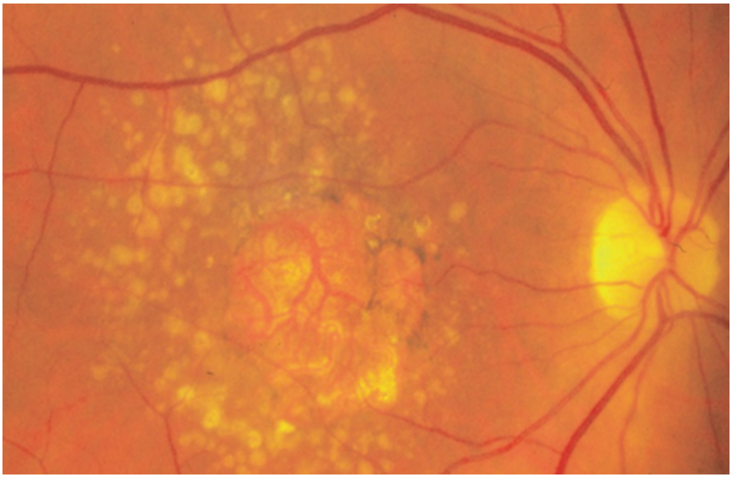


Figure 3. Drusen and geographic atrophy.

Wet AMD

As Bruch´s membrane becomes thicker and more hydrophobic the transportation of liquids from the retina to the choroid is impaired. This may lead to a serous detachment of the RPE, so-called pigment epithelial detachment. A detachment of the RPE may also emerge if abnormal choroidal vessels are formed. These so-called choroidal neovascular vessels (CNV) are the hallmarks of wet AMD. The cells forming the abnormal vessels lack barrier functions which cause an extensive leakage of fluid, proteins and lipids both underneath and into the retina resulting in swelling (oedema) (Figure 4). This is devastating for the photoreceptors and if untreated, eventually causes cell death. A fibrous scar is formed and visual acuity is severely impaired**.** The exact trigger mechanisms of wet AMD are unknown but a cascade of interacting intrinsic and extrinsic cellular factors precede the CNV formation. Among these factors the vascular endothelial growth factor (VEGF) is the most well-known.

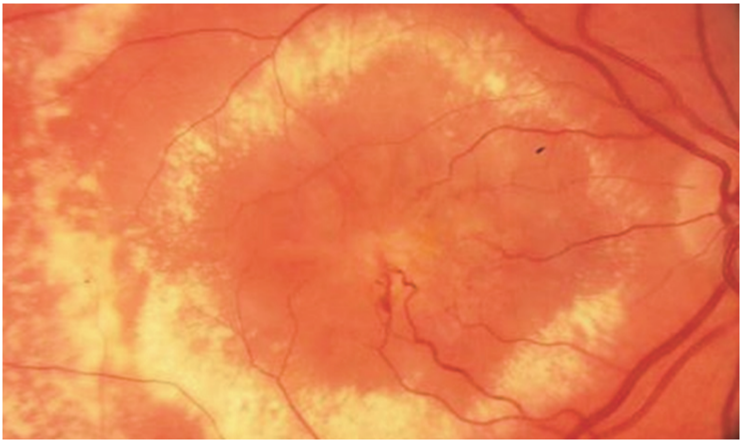


Figure 4. Wet AMD. Leakage of fluid and lipids/proteinaceous material (yellow-white).

Until recent years no effective treatment against wet AMD have been available and advanced AMD has been a leading cause of severe visual loss among elderly in developed countries. In 2006 the first effective treatment against wet AMD was introduced, ranibizumab (Lucentis®), a drug inhibiting the action of VEGF [9, 10]. Injected into the eye under sterile conditions this drug significantly slows the progression rate of wet AMD [11-13]. Previously the ophthalmologist´s main task, after thorough examination, was to refer the visually handicapped patient suffering from advanced wet AMD, to a low vision care centre. Today wet AMD is considered a chronic disease with episodes of exacerbation, although the interval of relapses are unknown and varies both intra- and inter-individually. Patients suffering of wet AMD are therefore scheduled for regular ophthalmological examinations to reveal signs of disease activity. The sooner a new episode of disease activity is discovered and treated the better for the visual outcome. Delayed treatment often leads to irreversible loss of visual function and providing timely diagnosis and treatment poses a difficult challenge for ophthalmology clinics today [14-17].

Diagnostic tools and AMD

To improve diagnosis of wet AMD the use of different imaging techniques have become increasingly important. Most common of these diagnostic tools are fluorescein angiography (FA), indocyanine green angiography (ICG) and optical coherence tomography (OCT).

Angiography

In 1959 junior medical student Harold Novotny and senior medical student David Alvis, Indiana School of Medicine, performed the very first fluorescein angiographies on each other. The two worked on a small project sponsored by the American Air Force to determine the oxygen saturation of circulating blood through retinal veins. One day they came up with the idea of photographing fluorescence in blood as it circulated in the retinal vessels. This was before 1964 and the Declaration of Helsinki so after some library searches they tried it out on themselves, with success. After performing the medical experiment on fellow students and patients they submitted a paper on their work to the American Journal of Ophthalmology. The paper was rejected. In fact, getting the medical society interested in their work was not easy at all. At last, the chairman of Novotny´s and Alvis´ medical school finally managed to convince the editor of Circulation to publish their work [18].

Fluorescein angiography requires a fundus camera equipped with one excitation and one barrier filter. Fluorescein is injected intravenously and when reaching the retinal circulation pictures are taken. White light from the camera flash passes through a blue excitation filter and the blue light entering is absorbed by fluorescein molecules. When the molecules fluoresce they emit light in the yellow-green spectrum. A barrier filter selectively blocks light so only light emitted from the fluorescein is captured on the photographs. Pictures are taken immediately after fluorescein injection and continues for at least ten minutes.

Indocyanine green (ICG) angiography was approved in 1959 for the use in medicine. Initially it was used to visualize circulation in the liver and the heart and from 1969 also for ophthalmological purposes [19]. ICG is also a fluorescent dye but it operates in the near infrared spectrum (approximately

800nm) in which tissues are more translucent and thus enable visualization of structures beneath the retina. The principle of performing ICG is similar to FA but with different camera filters. Pictures are taken up to 20-30 minutes after injecting the dye, depending on the diagnosis.

Optical Coherence Tomography

Optical Coherence Tomography (OCT) is a newly invented non-invasive technique for performing high-resolution cross-sectional images of internal structures in biological tissues by measuring their optical reflections (Figure 5-6). OCT was first described in 1991 [20]. To simplify, OCT is analogous to ultrasound but instead of sound waves it uses low-coherence (broadband) light. An optical probe directs the light beam at the target tissue and captures light that is back-scattered from that tissue. Different tissues have different qualities that influence the back-reflectance (the degree of intensity which that tissue reflects light). These qualities then allow the OCT image to differentiate layers of tissue based on the relative differences in the back-reflectance of the tissue composites. Owing to its powerful resolution it provides images of retinal structures on a micrometric scale. Today the OCT techniques have successively improved and the technique is able to visualize retinal and recently also subretinal structures in a three-dimensional manner.

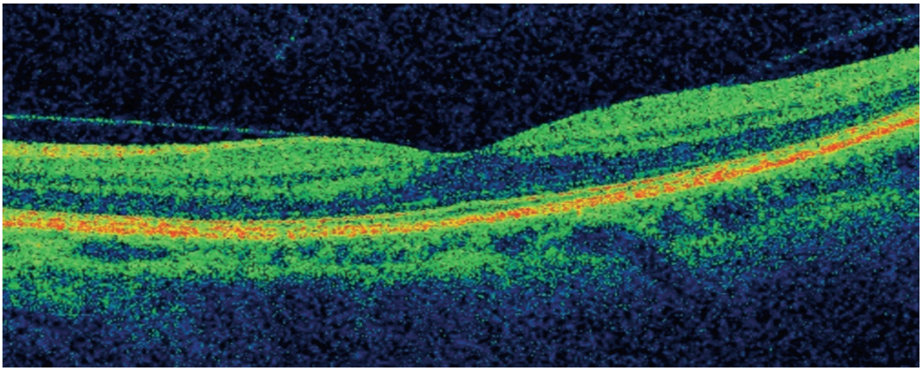


Figure 5. OCT - normal macula.

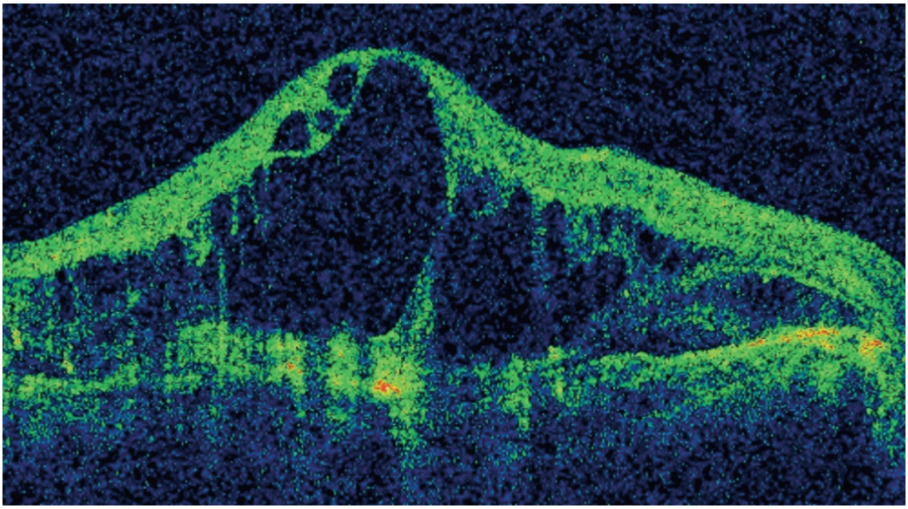


Figure 6. OCT - macular oedema.

Symptoms in AMD

During examination of a patient suffering from AMD a common opening remark is “I can´t see anything”. When the ophthalmologist ask the patient to explain a bit more the answer is often “I can´t read” and after a while, “well, it´s difficult to read. Newspaper print seems grey and words are difficult to distinguish. I can´t see the small print sizes, letters vanish or sometimes scramble around and I need much more light, but the right sort of light otherwise I become blinded. And people believe I´ve become arrogant since I don´t greet them when we meet downtown. It is so difficult to recognize faces some distance away. And by the way, if it is a very bright and sunny day, I seldom go downtown at all, I just can´t see a thing. And driving my car when it is dark outside has become a nightmare” (informal observations).

When there is a general decrease in the number of photoreceptors in the macula the acuteness of vision decreases, that is, the resolving ability of the visual system is impaired.

A more localized loss of photoreceptors in the macula results in the absence of retinal input from that area to the visual cortex. When the damaged area is surrounded by areas with remaining function a so-called scotoma is formed.

When scotomas are small, single letters may vanish during reading. This can sometimes be compensated by pure guessing. However, deciphering groups of digits is often a more difficult task because of the need of close scrutiny and here guessing is less helpful. Another adaptive strategy is scanning or sweeping along a word using functioning photoreceptors adjacent to the scotoma. This slows down reading speed and to read a text letter by letter reduces the joy of reading. As scotomas enlarge also larger objects may become difficult to see.

Metamorphopsia means that the true shape of an object is distorted. Straight lines seem to be curved or a viewed object seems tilted. During the progress of structural changes in the macula, still functioning photoreceptors become dislocated. Dislocated photoreceptors will start to sample new retinal images previously reported by other photoreceptors. Since there is no way for the brain to recognize and adjust the changed retinotopy, incoming visual information will appear to be in disarray.

Dysmetropsia means that the true size of an object seems to be changed and this is due to spatially displacement of photoreceptors. The most common example of this is during macular oedema when an object seems to appear smaller than its true size, so-called micropsia.

When exposed to very bright or very dim conditions there is always a recovery time of vision but in AMD this recovery time is significantly prolonged. Driving through a tunnel at daytime or viewing oncoming headlights when driving at night can be devastating.

Contrast refers to the border of an image or an object and the transition of light-dark. When contrast sensitivity is impaired, as in AMD, images and texts seem washed out. In daily life, for example, this increases the risk of falling when stepping down from the curb onto a similarly coloured pavement.

Different colours of the same lightness can be characterized by their hues and saturations. Defects in colour vision can usually be characterized by subnormal discrimination of hue and/or saturation. This is perceived by an afflicted patient as a washed-out appearance of colours. Generally blue-yellow defects occur in acquired retinal diseases, macular degeneration included.

Clinical tests

Visual Acuity

In the middle of the 19th century there was a growing interest in measuring visual function. In 1861 the Dutch ophthalmologist Fransiscus Cornelis Donders introduced the term “visual acuity” to describe the spatial-resolving ability of the visual system, i.e. the sharpness of vision [21]. Donders defined a functional reference standard as the ability of an eye to recognize letters subtending a visual angle of 5 minutes of arc. He then compared the performance of patients´ eyes to that reference standard. Comparing the letter size recognized by the patient to the reference standard gave the magnification requirement needed to bring that patient to the same performance as a standard eye.

In 1862 his fellow countryman and co-worker Herman Snellen, introduced the Snellen optotype test chart [22]. Snellen´s work was based on the original ideas generated by Donders. He was also inspired by the work of the English astronomer Robert Hook, who had found that the human eye can separate double stars when they are 1 minute of arc apart. The stylized letters were designed on a 5x5 grid and were called optotypes. Snellen calibrated his optotypes based on an external standard. The size of a letter was defined from a stroke width of 1 minute of arc. In Snellen fraction, the numerator was the test distance (the distance between the subject and the letter chart), and the denominator was the distance at which the optotype should be positioned in order to subtend an angle of 5 minutes of arc. The critical gap that needed to be resolved was 1/5 this value, i.e. 1 minute of arc (1 minute of arc = 1/60 of a degree) **(**Figure 7). A result represented as 20/100 means that the test distance was 20 feet and that the subject being tested could not read letters smaller than those that a normal individual should be able to read at 100 feet. The Snellen notation can be converted into decimal notation by regarding the slash as a division sign, 20/100 then becomes 0.2. The reciprocal of the Snellen notation equals the angle (in minutes of arc) which the strokes of the letter subtend at the subject´s eye. This angle is called the Minimum Angle of Resolution (MAR).

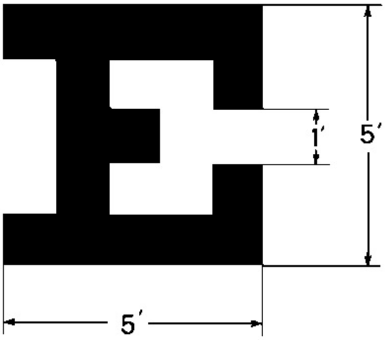


Figure 7. Example of an optotype

Each line on Snellen´s rectangular acuity chart held a variable number of letters and the progression of letter sizes on Snellen´s acuity charts were irregular. 1868 a former co-worker of Donders and Snellen, John Green, proposed a revision of the Snellen chart, replacing Snellen´s non-uniform steps with a fixed geometric progression of each line and also a proportional spacing of letters [23]. However, time was not ready for new ideas.

It would take until 1976, when the Bailey-Lovie log-MAR acuity chart [24] was introduced and the logarithmic scaling became generally accepted for visual acuity measurement. Visual acuity was by Bailey and Lovie expressed as the logarithm of the Minimum Angle of Resolution (MAR). The layout was changed to five proportionally spaced letters on each line giving a triangular appearance of the chart. In 1982 the logMAR Early Treatment Diabetic Retinopathy Study visual acuity chart (ETDRS) was introduced [25] and this chart is nowadays worldwide accepted as the standard for visual acuity measurement.

However, conventional acuity tests are tolerant to various forms of damage to the visual system and they may fail to identify lesions involving up to 40% of the receptive fields in the fovea [1]. A key problem is associated with the optotype test targets and their information overload. The test targets are many times larger than the receptive fields and substantial fractions of an optotype may be removed without markedly affecting resolution threshold [26, 27]. Another form of information overload is the often unrestricted viewing time of optotypes allowing scanning eye movements to be used to gather test target information. Measurement of visual acuity is also a poor indicator of visual abilities in daily life [28].

Near word acuity

A common way to measure near acuity is not by using single letters but by using words. However, reading a word is a much more complex task and requires not only resolution of letters by the visual system but also correct eye movements, language and word encoding, comprehension and memory [29-35]. Near word acuity is often measured in ophthalmology practice by using printed paper charts with short paragraphs in different print size and a common clinical approach is recording the smallest legible font size. The print sizes are set in the non-intuitively interpreted unit points (pt or p). Point is a unit measure used in typography but to complicate things there are two different point systems, the French-European and the British-American. The French-European point (p) originates from the French royal foot (French word for foot is pied) and 1 point= 1/864 royal French foot=0.376 mm. The British-American point (pt) originates from the US inch and 1 point is 1/72 inch=0.352 mm. As an example in daily life, Swedish newspaper articles are often typed in print size 8.8 French-European points. When performing the near word acuity test, the patient is asked to start reading at the top of the chart where the paragraphs are printed in large print sizes and then continue to read downwards as far as possible where paragraph print size successively become smaller. In clinical praxis there is often a lack of standardization in the use of the test. For example, time limits are not defined, scanning words back and forth is possible, the amount of incorrect read words are not noted, pure guessing can mask visual impairment and so on. The reading charts are also quite artificial compared to common texts in daily life. In everyday work, the interpretation of the presented test results is often in the eye of the beholding ophthalmologist.

Reading speed

An important question to be asked before investigating reading performance is what should actually be measured with the reading test [36]. Adding the perspective of time may provide the interpreter of a performed reading test with valuable information which could be related to daily life activities. The required reading speed differs depending on different reading tasks. Reading speed can of course be measured and the result presented as the number of correctly read words per minute (wpm) [37, 38]. Several studies have examined the reading speed in normal subjects and a speed of at least 200 wpm is considered as normal [39, 40]. In patients suffering from AMD, information of reading speed could help the clinician to a better understanding not only of visual function but also of visual function in daily life [41]. However, to measure reading speed is time consuming and seldom possible to perform in a daily clinical practice. The reason for this is the overhead cost. Keeping track on reading time and at the same time taking correct notes on reading errors needs either extra staff during the test or recording the test for later analysis.

Low-contrast visual acuity

Contrast sensitivity is a measure of the threshold contrast for seeing an object i.e. the ability to distinguish between finer and finer increments of light versus dark. Contrast sensitivity varies between individuals but is often severely impaired in patients with AMD [42]. In ordinary clinical examinations visual acuity charts with high contrast between the optotypes and the background are used. However, in situations in daily life with low light or fog, contrast between objects and their background is reduced. There are several ways to measure contrast sensitivity, but clinically so-called low-contrast visual acuity charts are often used. A commonly used chart is the Pelli Robson contrast sensitivity chart (Figure 8) [43]. The chart consists of capital letters on horizontal lines. Instead of decreasing the size of the letters on each successive line, the contrast of the letters, relative to the chart background, decreases. For each three letters, contrast is decreased from left to right and from the top towards the bottom on the chart. The lowest contrast where 2 out of 3 letters in a group are correctly read determines a logarithmic contrast sensitivity score.

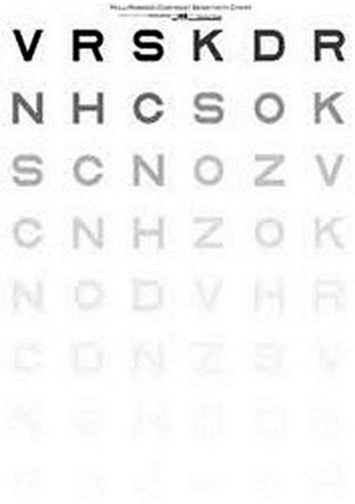


Figure 8. Pelli-Robson Contrast Sensitivity Chart

Dysmetropsia and Metamorphopsia tests

To test and analyse metamorphopsia may not today seem as a question aimed for philosophic discussions. But in the 17th and 18th century transformation of physical reality into internal perception was a central theme of philosophical debate. Philosopher George Berkeley (who is well- known for his question concerning whether a tree that falls in the forest has truly fallen if it is not seen or heard) discussed in his first major work the limitation of human vision and that proper objects of sight are not material objects but light and colour [44]. In 1764 the Scottish philosopher Thomas Reid describes his own distortion of vision (after observing the pathway of Venus through a telescope) in a remarkably modern way. "… that a straight line, in some circumstances, appears to the right eye to have a curvature in it. Thus, when I look upon a music book, and, shutting my left eye, direct the right eye to a point of the middle line of the five which compose the staff of music, the middle line appears dim indeed at the point to which the eye is directed, but straight; at the same time, the two lines above it and the two below it appear to be bent outwards, and to be more distant from each other, and from the middle line, than at other parts of the staff to which the eye is not directed … Although I have repeated this experiment innumerable times within these 16 months, I do not find that custom and experience takes away this appearance of curvature in straight lines." [45, 46].

In 1862 German ophthalmologist Richard Förster published a medical illustration of metamorphopsia showing a square grid of lines with distortions. A decade later Förster continues his work on metamorphopsia tests by publishing a set of parallel test lines with a central fixation spot [47].

The Amsler grid

In 1947 the Swiss ophthalmologist Marc Amsler published a set of test cards with a grid of horizontal and vertical lines and in the centre of the grid a small dark dot. The grid was not a new idea but Amsler was interested in how to monitor macular symptoms. He constructed the test cards in a practical format and at a low cost. Perhaps most important, Amsler urged for the use of the cards not only in the ophthalmological office but also as a self-test for the patients at home [48].

When using an Amsler grid the chart should be viewed at reading distance (approximately 30 cm). One eye at the time is examined (the other eye being covered by the patient´s hand). The patient should fixate the dot in the centre and a set of standard questions should be asked the patient. For example: Do you see the black spot in the centre of the squared chart? Do you see all lines, horizontal and vertical, straight and parallel? Do you see any blur, hole, or distortion? If metamorphopsia occurs the lines may appear wavy or bent or some squares may differ in size or shape from the others.

Amsler cards are often found in ophthalmological practice and are also recommended as a home testing device to detect symptoms of AMD such as a central scotoma or metamorphopsia.

However, the use of an Amsler grid as a diagnostic tool has been questioned [49-51]. A main problem concerns the huge amount of false negative results, as concluded in one study "Absence of evidence is not evidence of absence" [50]. The most compelling explanation for false negative results is the "filling-in" phenomenon. When there is an absence of neural input, as in a scotoma, there is not a distinct visible "hole", instead visual features are perceived on the basis of the surrounding features, by filling-in. Defects may be hidden between the horizontal and vertical lines and thus circumvents detection. Patients may also forget to fixate the centre dot and instead start to scan the grid for misalignments. There are also difficulties in quantification, documentation and storage of test results.

The M-Charts

This test is a set of charts with 19 dotted lines with dot intervals of between 0.2° to 2.0° visual angles. In the centre of the lines is a fixation mark. To start, a vertical straight line (0°) is shown to the patient. If the patient recognizes this line as straight test score is 0. If the line is considered irregular, charts with dotted lines where interval changes from fine to coarse are shown to the patients one after another. When finally a dotted line is considered as straight this dotted line´s visual angle will be the test score. The charts are then rotated 90° and the same test is performed again [52, 53].

The MacuFlow test

This test is created in computer graphics and attempts to null spatially extensive dysmetropsias. A grey grid is presented on a white background. When viewed at 0.3m the test area subtend approximately 20°. The grid sweeps at 1°/s centripetally and seamless in an optic flow manner. When a viewed area is recognized as distorted, the patient by tapping the computer keyboard restores this area to a straight pattern and nulling the dysmetropsia [54].

Preferential hyperacuity

Hyperacuity is the ability to perceive a misalignment of line segments [55]. Integration of information over multiple photoreceptors makes perception possible of line objects smaller than one single photoreceptor. Hyperacuity thresholds are typically in the magnitude of 5 seconds of arc, 5-10 times smaller than the threshold for two-point discrimination (visual acuity).

Recently a new preferential hyperacuity self-test was presented, the Foresee Preferential Hyperacuity Perimeter (Foresee PHP) [56, 57]. This is a stand-alone device connected to a power outlet and a phone line. In the test, a distorted pattern is briefly displayed on a screen and patients use a computer mouse to indicate the location of the distortion.

Another recently developed hyperacuity self-test is the shape discrimination test my Vision Track (mVT) [58]. The test is based on an earlier desktop test [59] but adapted as an application for mobile touch screen devices. The test presents three visual stimuli (2 circles and 1 radially distorted circular shape) simultaneously and asks the patient to identify the distorted shape by a touch.

Photostress test

The photostress test is also known as the glare recovery test. In this test the retina is exposed to a controlled glare source and the time course for return of retinal sensitivity in terms of predefined visual tasks (for example visual acuity or contrast discrimination) is measured. When the retina is exposed to intense light, visual pigments in the photoreceptors are bleached, resulting in a transient state of insensitivity. The recovery of visual function is believed to be largely due to regeneration of photosensitive pigments. Patients with AMD often have a delay in recovery time in this test compared with normal subjects.

RareBit probing

This technique was developed to detect subtle defects in the neural visual system [60] and has been exploited in studies investigating early signs of neuro-visual damage [61-70] .

In a normal eye the receptive fields that build the retinal architecture are complete without overlaps or gaps. The Rarebit test principle probes the integrity of these receptive fields with simple checks for the presence of function. This means that individual variation in the number of receptive fields does not influence the test. Instead the test probes presence or absence of function in the receptive fields and thus the completeness of the neural matrix.

Test targets are called Rarebits due to their reduced information content. Rarebits are briefly (200 ms) exposed microdots (one-half of normal minimum angle of resolution) presented on a dark background.

RareBit Perimetry and the RareBit Fovea Test

Conventional perimetry operates in a threshold domain by asking the visual system: “How well do you see here?” Rarebit perimetry operates with simple checks for the presence of function by asking the visual system: "Is there a receptive field here?”

Rarebit Perimetry is implemented in computer graphics. The test is performed on a personal computer with a liquid crystal display and test distance is 1 m in the standard setting (Figure 9). The test evaluates the central 30° x 20° of the visual field which is further divided into 24 areas. There is also a possibility to test flanking regions between 30°-60°.

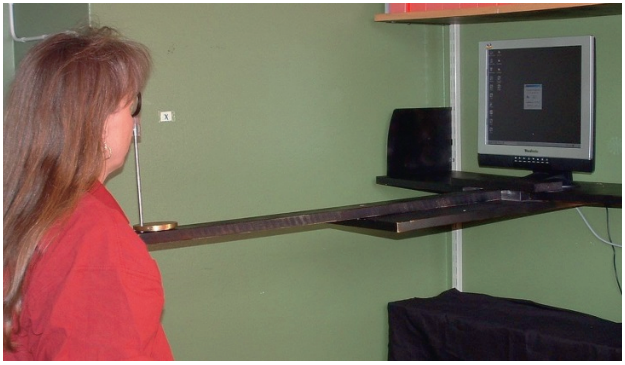


Figure 9. RareBit Perimetry

Using high contrast, rarebits probe for the presence of vision. The size of the rarebit stimuli ranges from 0.5 to 6 minutes of arc depending on the location of the tested area. The test presents pairs of dots separated by 4°. For control purpose, ten percent of presentations contain one dot or no dot at all. For each presentation, the subject has to indicate whether he or she saw 1 dot, 2 dots, or none at all. This is done by clicking, double-clicking, or not clicking on the computer mouse and when doing so the test provides both visually and audible feedback. As the test is completed results are plotted in a grey-scale format. The more dark rectangles are plotted, the more widespread the damage and the darker the rectangles are, the more severe is the damage (Figure 10).

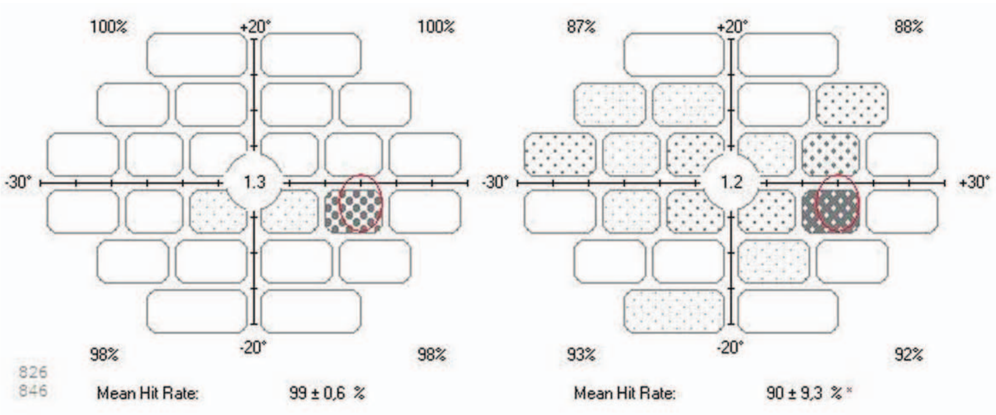


Figure 10. Example of test result in RareBit Perimetry

In the Rarebit Fovea Test the central 4° of the visual field is tested. This central field is divided into 10 squared areas, each subtending approximately 1.5° x 1.5°. Test stimuli presentation and responding by mouse-clicking is similar to the Rarebit Perimetry Test although the presented dots are separated by 1°.

The Rarebit Fovea Test has been evaluated for the detection of early changes in macular function [71]. It has shown potentials to serve as a sensitive diagnostic tool.

In summary, there is a wide range of tests for analysing and measuring visual function in AMD. Some tests may detect subtle alterations in macular function but are difficult to perform. Others require only a simple set-up but are less sensitive to early signs of functional damage.

Another aspect on tests deals with the immense width of normal limits. Inter-individual differences are due to numerous factors, including true anatomical differences (as the number of cones in the macula).

However, given an optimal test of visual function, such a test has to be performed repeatedly on a regular basis if early detection of visual damage is desirable, as in wet AMD. Currently, patients are encouraged to self-monitor vision between follow-up appointments and to contact their clinic if changes are detected. However, the tests used for self-monitoring are neither sensitive nor specific.

There is a need of better diagnostic tools. These tests should be simple to perform. Further, they should crisply define normality and detect early signs of visual deterioration. Finally, they should be available in the format of a self-test for the assessment and monitoring of visual function over time.

Aims of the Thesis

This thesis deals with various aspects of vision in patients with age-related macular degeneration (AMD).

The general aims were to evaluate

- new vision tests, for the detection and grading of lesions in the macula.

- if self-testing of vision is feasible

- reading abilities by abbreviated tests

The specific aims were to evaluate

- sensitivity and specificity of a new compact rarebit test for macular diseases, the MacuBit test (**Paper I)**

- sensitivity and specificity of a new personal computer based vision test, which depends on a new type of rarebit test targets (segmented digits), the DigitStep test (**Paper II).**

- sensitivity and specificity of a new smartphone application of the DigitStep test named the MultiBit test and to investigate whether this test has the potential to serve effective long-term monitoring by self-testing (**Paper III)**

- whether so-called spot reading ability can be efficiently assessed using printed texts and a new smartphone-based test named Celego (**Paper IV)**

Materials, Methods and Results

Paper I

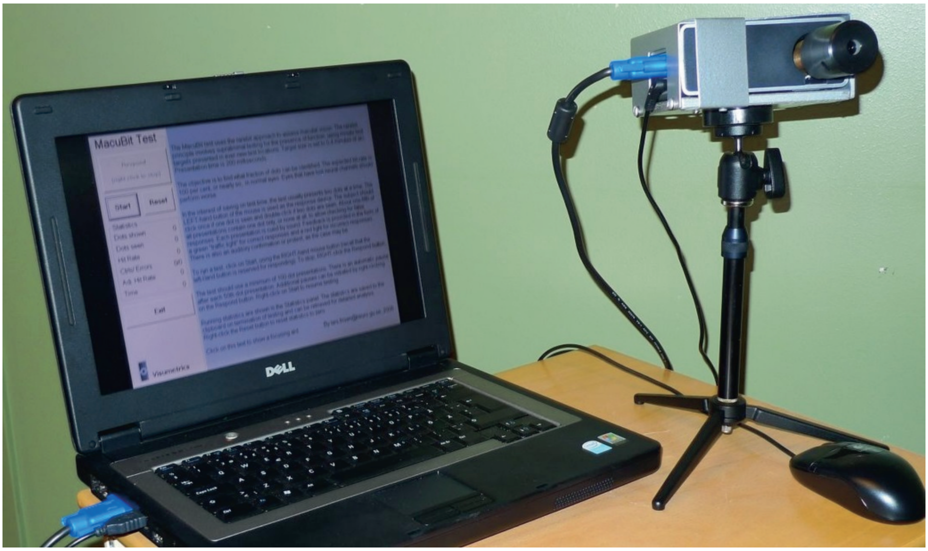


Figure 11. The MacuBit test

The MacuBit test (MBT) (Figure 11) was a new rarebit test specifically devised for testing macular vision under more practicable conditions than those used in the predecessor, the Rarebit Fovea Test.

The MacuBit device contained a presentation unit controlled by a laptop computer using a purpose written software. The test target presentation unit was a modified miniature data projector although the original optical system was replaced by an adjustable ocular that allowed direct viewing of the test. The subject´s field of view was a dark circular area with a diameter of 500 pixels, subtending 5.3°. Each pixel subtended 0.6 min of arc at the subject´s eye. The test targets, rarebits, were computer generated by turning on one or two pixels for 200 ms, in ever-new locations, probing the test area for functional locations. Subjects were told that each presentation involved one or two bright dots, or sometimes none at all, and they were asked to indicate the number of dots seen by clicking the computer mouse once, twice or not at all. A complete test contained a total of 50 dot-pair presentations. Results were expressed as hit rates, i.e. the percentage of targets seen relative to the number of targets shown. Since receptive fields are seamlessly tiled together without holes or overlaps, expected hit rate for normal subjects was 100%, or nearly so.

Fifty-three normal subjects were recruited. Each normal subject contributed test results from one eye only.

12 patients with bilateral advanced age-related macular degeneration (AMD) were enrolled from an ongoing study of the effect of unilateral laser treatment. These patients contributed results from their non-treated control eyes.

Visual acuity was assessed using a standard printed acuity chart. The percentage of correctly read letters on each line was recorded.

Results

All 53 normal subjects took part in the vision test. Two elderly subjects were unable to master the computer mouse as needed to complete the MBT and another two could not remember the instructions; these subjects were excluded.

In the remaining 49 normal subjects mean age was 60 ± 8 years (range 50 – 78). In the AMD group four subjects had immeasurably low central vision and had to be excluded. The remaining eight subjects had a mean age 81 ± 6 years.

Mean decimal visual acuity in the normal subjects was 1.43 ± 0.18 and MBT hit rate was 90.9 ± 7.5% (median 93%, range 68-100). In contrast to acuity, hit rates decreased with increasing age. The AMD group obtained poorer results. Mean visual acuity was 0.66 ± 0.13 and average MBT hit rate was 40 ± 25% (median 39, range 11 – 80). Both results differed significantly from those of the normal subjects (t test: $p<0.001$). Since the differences in MBT test results between the normal and AMD groups may in part be attributable to differences in age, the eight AMD patients were compared to the eight oldest normal subjects. These normal subjects had a mean age of 74 ± 3 years and a mean hit rate of 81 ± 8.3%. The difference in hit rate remained significant ($p<0.002$).

Paper II

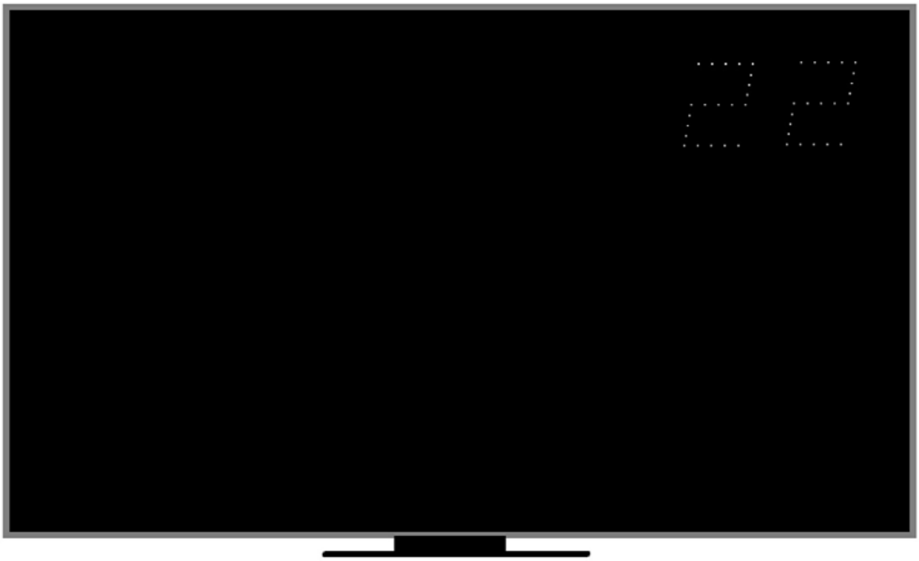


Figure 12. The DigitStep test

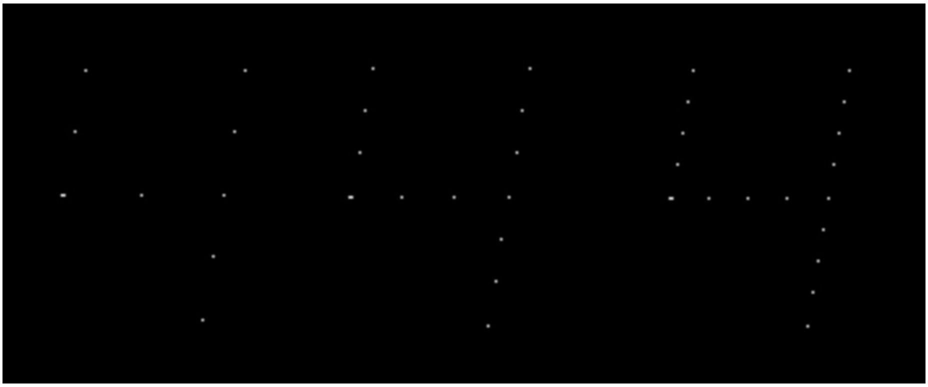


Figure 13. Examples of segmented digits defined by different numbers of rarebits per segment (RPS), from left to right 3, 4, and 5 RPS.

The DigitStep test (Figure 12) was a personal computer based vision test aimed for assessment of macular conditions like age-related macular degeneration. In this test, multiple rarebits were combined to meaningful patterns, segmented digits. Three rarebits suffice to fully define a segment and digits defined by three RPS are recognized by most normal subjects.

Digits were generated under personal computer control on a 17´´ liquid-crystal display in a dark room. The test area subtended 4.6° x 3.5° at the 4 m viewing distance. The test digits subtended 40 x 50´, equivalent to 0.1 decimal optotypes. The number of rarebits building each digit segment (rarebits per segment, RPS) was preset at 3,4,5,6,8,10,16,30,60,90 and 128 (Figure 13). Presented against a dark background each rarebit had the visual appearance of a dot about 0.5´ diameter.

Digits were presented in pairs with identical RPS numbers. Pair members were selected at random and presented in a left-to-right sequence in randomly selected screen locations. There was no fixation mark. Digits were presented for 150 ms each, with a 150 ms blank interval between. Digit pairs were separated by a time interval of 2.5 s providing time for verbal responses.

The test task was to call out any digits seen. The examiner´s task was to find the lowest RPS number for which the subject could read minimum three digits in maximum three paired presentations.

Thirty-seven AMD patients and twenty-five normal subjects were recruited to the study. Based on the results of biomicroscopy, ocular coherence tomography and retinal angiography the macular lesions were classified as drusen (10) dry AMD (16) or wet AMD (35). Patients who had the same type of lesion in both eyes contributed results from the least involved eye only whereas those who had different types of lesions contributed results from both eyes.

Visual acuity was assessed with an ETDRS chart. Each correctly read letter provided a score of 1, for a maximum of 100.

Results

The three patient groups were closely similar in age (77 ± 5, 76 ± 9 and 75 ± 8 (SD) years) whereas the control subjects were somewhat younger, 65 ± 10 years.

All normal controls and all patients in the drusen and dry AMD groups completed the DigitStep test without difficulty. However, in the wet AMD group nine of 35 eyes (26%) failed to see the strongest stimulus. These subjects had significantly lower mean ETRDS scores than those who completed the DigitStep test (51 ± 10 versus 71 ± 9, p=0.0002) and were excluded from further analysis. Twenty-four of the 25 normal subjects needed no more than three RPS. Forty-six of the 51 AMD results fell outside the normal limit.

Analysis of variance indicated no significant difference between the AMD-groups for ETDRS (p = 0.21) whereas the opposite was true for DigitStep test (p<0.0002). A post hoc analysis of the latter showed a significant difference between the dry and wet groups (median values 5 and 30, respectively; p=0.02). The corresponding ETDRS values were 76 and 72 (p=0.47). Inspection of the DST score distributions suggested that RPS results > 16 indicated the presence of oedema.

A Receiver Operating Characteristic curve (ROC curve) is a plot of the true positive rate (sensitivity) against the false positive rate (1-specificity) for the different possible cut-points of a diagnostic test. It shows the trade-off between sensitivity and specificity. The closer the curve follows the left-hand and the top border of the ROC space, the more accurate the test. The closer the curve comes to the 45-degree diagonal of the ROC space, the less accurate the test. The accuracy of a test depends on how well the test separates the group being tested into those with and without the disease in question. Accuracy is measured by the area under the ROC curve (AUC). An area of 1 represents a perfect test and an area of 0.5 represents a worthless test.

Combining all observations, the ETDRS and DigitStep analyses generated AUC values of 0.86 and 0.95 respectively (Figure 14). The difference was statistically significant (p<0.01). At 90% specificity, estimated sensitivity was 75% (95% confidence interval (CI): 63-87) for ETRDS (criterion ≤ 81) and 91% (CI: 76-94) for DigitStep (criterion > 3).

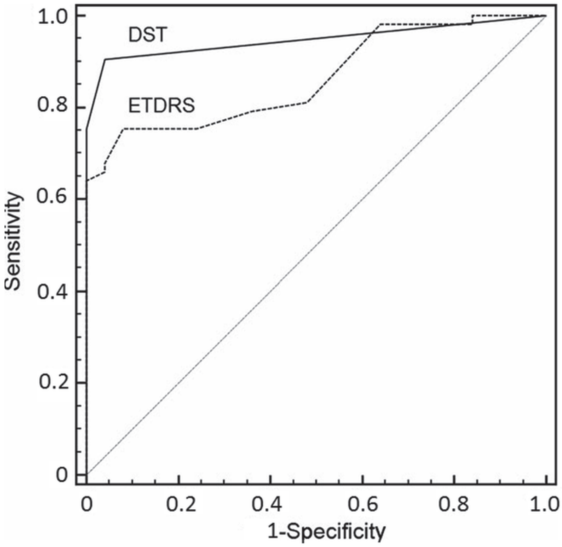


Figure 14. ROC curves for the DigitStep and ETDRS tests. The diagonal represents lack of discrimination.

Separate analysis of the abilities of ETDRS and DigitStep to discriminate dry and wet AMD generated AUC values of 0.57 and 0.71 respectively. The ETDRS result was not significantly different from 0.5 (p=0.51), indicating poor discrimination. For DigitStep, the difference was significant (p=0.01). However, at a specificity of 90% estimated sensitivity was modest (64%, CI: 34-83, criterion > 10).

Paper III

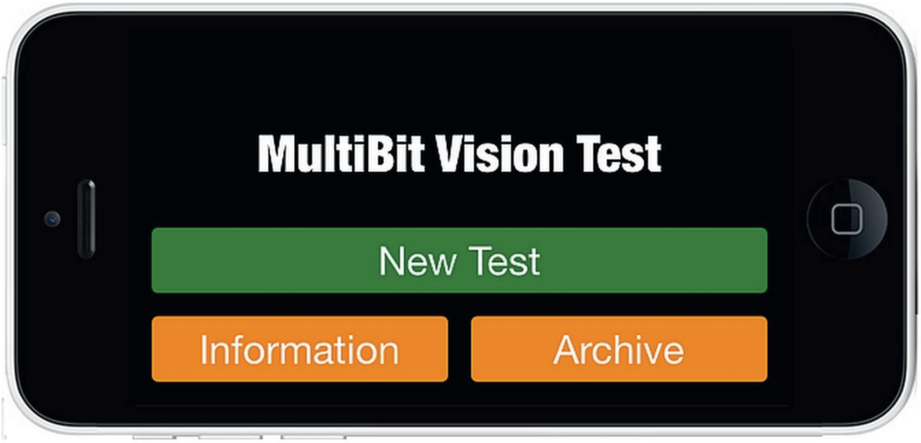


Figure 15. The MultiBit Test

The MultiBit test (Figure 15) is a rarebit vision test in the form of a tablet/smartphone application. Apple's iPhone/iPod Retina Screen platform was used since it meets the rarebit specification (pixel subtend <1′) at a practicable test distance.

The test is aimed for longitudinal self-testing of macular function in patients with AMD.

As described in the DigitStep test, the MultiBit test cycles segmented digits in carefully worked-out sequences (3, 4, 5, 6, and 7 RPS in test level 1 and 8, 10, 16, 30, and 60 RPS in test level 2). The test is performed monocularly in a dark room.

Digits are presented in pairs with identical RPS numbers. Pair members are selected at random and presented in a left-to-right sequence in randomly selected screen locations. There are no fixation demands.

Digits are presented for 150ms each, with a 150 ms blank interval in between. The test task is to spell out all digits seen. An interval of 4 sec between successive digit pairs provide the time for verbal response. The responses are automatically recorded in an internal audio file. A complete MultiBit test comprises 3 presentations of the 5 RPS settings in the user-selected test level.

When all 15 digit pairs have been shown, the test enters a scoring mode. Here, the digits shown during testing are presented in an easily read format. The subject checks these digits against the recorded responses and tap the appropriate "hit" or "miss" button. Finally, the percent correctly read digits is automatically calculated and presented as the test score. Inbuilt instructions guide the user throughout the test.

The MultiBit test devices were provided on loan and study participants were asked to perform the test at least twice a week at home. Patients with access to wifi could send test results by email. Otherwise, stored test results were downloaded during clinical appointments.

Visual acuity was assessed at all visits to the eye clinic using an ETDRS chart. Each correctly read letter provided a score of 1, for a maximum of 100.

Twenty-eight patients from a wet AMD treatment programme were recruited to the study. Those who had the same type of AMD lesion in both eyes (active or inactive) provided results from the least involved eye only whereas those with different types of lesions provided results from both eyes. A total of 36 eyes qualified for the study. Examination intervals were decided on an individual basis depending on current disease activity, as judged from a thorough examination and response to any previous treatment against wet AMD.

Twenty control subjects were recruited and examined once in the same way as the patients, angiography excluded.

Results

Mean age of the 28 patients was 76 ± 7 years and for the 20 normal subjects 68 ± 7 years. At study entry, 26 eyes had some degree of macular oedema whereas 10 had no oedema.

The patients returned for renewed clinical evaluations at mean intervals of 63 days. At each follow-up visit, results were compared with those of the nearest preceding visit. In all, 144 inter-visit intervals, or epochs, were available for analysis.

Twenty-six epochs were clinically judged to show worsening, 50 epochs were judged to show improvement and 68 epochs were judged stable. The patient group made a total of 1203 MBT self-tests during periods averaging 39 weeks in length. All MultiBit results were carefully evaluated by subjective inspection, epoch by epoch. Epochs showing trends of decreasing scores, increasing variation, or both were rated worse. Epochs showing increasing test scores were rated better. All other epochs were rated stable. ETDRS results were rated similarly, using direct numerical comparisons of scores. The outcomes of the clinical examinations were summarized as worse, better or stable. A numerical assessment of agreement between clinical- and ETDRS results and between clinical- and MultiBit results was obtained by calculating kappa statistics. This is a statistical tool aimed for calculating the degree of agreement among judgers. In cases of perfect agreement, kappa equals 1 and a kappa of 0 indicate chance agreement. For ETDRS, kappa equalled 0.03 (95% confidence interval -0.09-0.15) and for MultiBit 0.41 (confidence interval 0.29-0.53). Notably, the ETDRS confidence interval included 0 whereas the MultiBit interval neither included 0 nor overlapped the ETDRS interval.

Paper IV

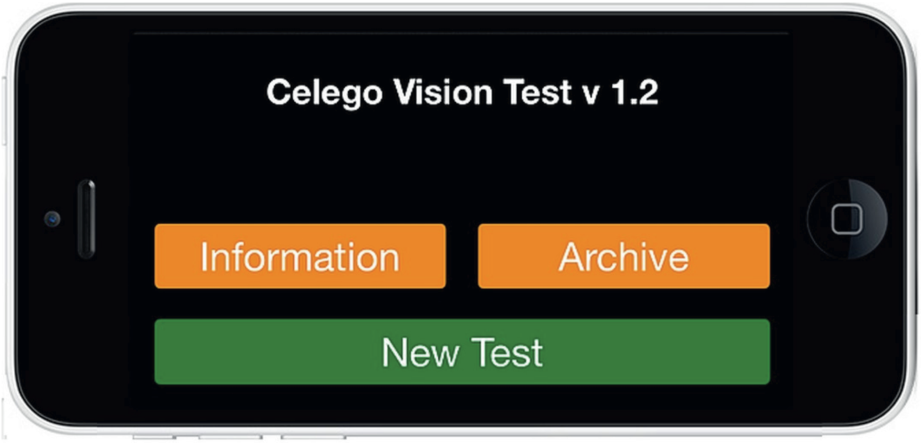


Figure 16. The Celego test

The Celego test (C test) (Figure 16) is a new smartphone-based reading test. The name Celego refers to the Latin words “Celer” which means “quick” and “Lego” which means “to read”. The test offers a possibility of rapid assessment of reading capacity. The ability to read fluent text may be the best indicator of both severity of disease and performance in daily life [72]. Arranging for meaningful testing of the ability to read fluent is quite difficult.

In this study a set of traditional printed reading charts [73] (T test) and the C test were used for assessing the smallest font size allowing a reading speed of 40 words per minute (wpm), so-called spot reading. A new scoring of test results was also suggested.

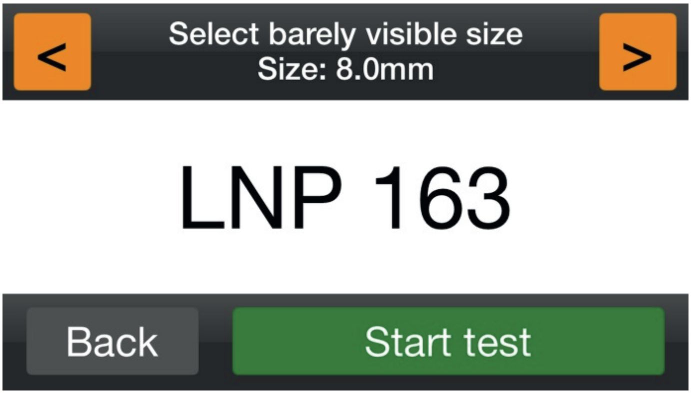
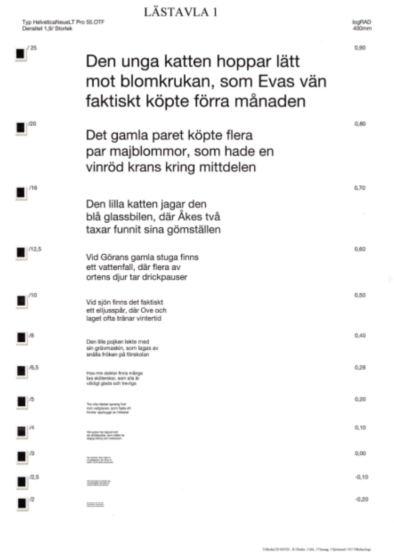


Figure 17. Example from the smartphone-based reading app, Celego.

The C test displays three letters combined with three digits in ever-new combinations (Figure 17).

The test task is to spell out all letters and digits seen. Fourteen font sizes are used, ranging from 12.5 to 0.7 mm in height. Test targets are exposed for 2 s followed by a blank interval of 4 s, providing time for verbal responses. In total 12 targets (24 words) are exposed during 24 s, corresponding to 60 wpm. A complete test comprises 3 presentations of 4 adjacent target sizes. A suitable range of target sizes is shown in a short pre-test trial. The responses are automatically recorded in an internal audio file. Once the 12 target combinations had been shown, the test enters scoring mode. Here the same test target combinations are displayed are presented in an easily read format and the audio file is played back. Scoring is performed by comparing targets actually shown to the recorded responses and by tapping the appropriate “hit” or “miss” button. The number of correct responses is automatically calculated at the end of the test.



LÄSTAVLA 1

Typ HelveticaNeueLT Pro 55.OTF
Densitet 1,9/ Storlek

logRAD
400mm

Storlek		logRAD
/25	Den unga katten hoppar lätt mot blomkrukan, som Evas vän faktiskt köpte förra månaden	0,90
/20	Det gamla paret köpte flera par majblommor, som hade en vinröd krans kring mittdelen	0,80
/16	Den lilla katten jagar den blå glassbilen, där Åkes två taxar funnit sina gömställen	0,70
/12,5	Vid Görans gamla stuga finns ett vattenfall, där flera av ortens djur tar drickpauser	0,60
/10	Vid sjön finns det faktiskt ett elljusspår, där Ove och laget ofta tränar vintertid	0,50
/8	Den lille pojken lekte med sin grävmaskin, som lagas av snälla fröken på förskolan	0,40
/6,5	Hos min doktor finns många bra sköterskor, som alla är väldigt glada och trevliga	0,28
/5	[illegible]	0,20
/4	[illegible]	0,10
/3	[illegible]	0,00
/2,5	[illegible]	-0,10
/2	[illegible]	-0,20

Figure 18. Example from the printed reading test.

In the T test each chart contains 12 sentences comprising 14 words distributed over 3 rows (Figure 18).

Letter size on the reading charts is expressed in so-called point size numbers. This is a conventional terms used in professions dealing with typography. One point equals 0.35 mm. Letter sizes in the printed charts ranged from text No. 1, point size 25 (8.75 mm) to text No. 12, point size 2 (0.7 mm). After a brief instruction each subject was asked to start reading the first sentence on the chart and continue as far as possible. A smartphone was used for audio recordings. In a later stage, the recorded files were played back and documentation of reading errors and reading time was performed.

For the C test scoring of results was performed by introducing a new index of reading capacity. In this index results are expressed on a scale ranging from 0 to 100 (as in the ETDRS test). A score of 0 corresponds to an inability of reading the largest test targets and a score of 100 means that the smallest test text is read correctly.

In the T test, each of the 12 font sizes was assigned a value of 8.3 (100/12).

The C test comprised 14 font sizes and 3 presentations per size, a total of 42 possible presentations. Each presentation was assigned a value of 2.38 (100/42). In reality, all 42 presentations were not used. Starting with the barely legible font size, the test made 3 presentations each of 4 adjacent font sizes. For example, if the subject selected size number 6 as barely legible, the test would display target sizes 4, 5, 6, and 7. Sizes 8-14 were never actually shown but were assumed to have been read correctly had they been shown.

Forty-three patients with AMD were recruited to the study. Based on the results of biomicroscopy, optical coherence tomography and retinal angiography, macular lesions were classified in three groups. Among the eligible eyes (48) eleven had 11 dry AMD, 15 currently inactive wet AMD and 22 had currently active wet AMD.

20 control subjects were examined in the same way as the patients, excluding angiography.

Distance visual acuity was assessed with an ETDRS chart. Each correctly read letter provided a score of 1, for a maximum of 100.

Results

All subjects completed the ETDRS test. Among the 43 initially recruited patients, two failed the C test and one of these subjects also failed the T test. Failure was attributable to large central atrophies in the macula. These two patients were excluded from further analysis.

The AMD patient´s mean age was 76 ± 7 years and the normal subject´s mean age was 74 ± 13 years.

AMD patients performed significantly worse than control subjects in both tests. Average VA in the AMD group was 76 ± 12 and in the control group 88 ± 5 ($p<0.0001$). Mean T test score was 61 ± 17 in AMD patients versus 79 ± 7 in normal subjects ($p<0.0001$). Mean C test score was 67 ± 18 in AMD patients versus 86 ± 9 in control subjects ($p<0.0001$). Results of the T test and the C test correlated strongly, the correlation coefficient equalled 0.84 ($p<0.0001$).

Actual test times were closely similar in the two tests, mean 89 ± 19s in the T test versus a fixed test time of 72 s in the C test. Overhead time needed for scoring after the actual tests were completed was approximately 5 min for the T test and 0.5 min for the C test.

Discussion

Rarebit testing is a model in which single receptive fields are stimulated. The question of whether the image of the rarebit on the retina matches the receptive field size or if it perhaps is larger is difficult to settle. However, clinical studies indicate that rarebit probing does work and does provide good sensitivity and specificity [66, 67, 69, 70].

Retinal receptive fields are normally seamlessly tiled together. The expected outcome from the new tests was that most rarebits should be seen by normal subjects and that signs of receptive field damage (“holes” in the neural matrix) would cause a proportionate reduction in test hit rates.

Wet AMD is a chronic disorder with relapses occurring at unknown intervals. Treatment with anti-VEGF drugs significantly slows the progression rate of the disease, provided that treatment is administrated at the optimum point in time. Thus, the sooner a new episode disease activity is discovered and treated, the better for the visual outcome.

However, since new patients are constantly being diagnosed and very few already treated patients are discharged from regular check-ups, the management of AMD patients poses a major logistic challenge. By involving patients themselves in self-testing of vision, management might be facilitated.

Paper I

An important aspect of most vision tests is the immense width of normal limits [74]. Inter-individual variation is caused by numerous factors ranging from anatomical differences in the number of photoreceptors and the surface area of the visual cortex to psychological factors as maturity and degree of attention. For example an average normal subject having a conventionally measured decimal visual acuity of 1.3 may lose a substantial proportion of the neural substrate before passing through the lower normal bound. To accept the clinically established acuity of 1.0 (or 0.0 in logMAR charts like the ETDRS) as normal, does not facilitate the early recognition of visual impairment.

Conventional tests of visual acuity use test targets holding a huge excess of information in both space and time. In studies using fragmented optotypes, substantial fractions of the optotypes could be removed without markedly affecting resolution thresholds [27] [75, 76]. Further, the unlimited viewing times of optotypes in most clinical tests encourage subjects to perform scanning eye movements for collection of test target information. Finally, acuity tests only measure function in and close by the fixation point or the preferred locus of fixation [77]. All in all, the information overload in acuity tests mean that some 40% of neural elements must be lost before the injury is detected by the actual test [1].

In AMD, a condition affecting the entire macular area, early detection of disease progress is highly desirable.

In this study a new vision test for macular diseases, the MacuBit test, was evaluated. The test depended on minute stimuli, so-called rarebits, with limited exposure time. In a circular area subtending 5.3°, test targets made simple checks, in ever-new locations, for the presence of visual function. The conventional acuity test principle, gauging the density of functional units was replaced by a simple probing for holes in the receptive field matrix.

The difference in test principles was also reflected by the weak correlation between the two tests. On first sight this might seem odd, but since the acuity test reflects the spatial density of receptive fields and the MacuBit probes the matrix for functional units and its completeness (and reported a proportion) poor correlation was actually desired.

Normal subjects showed hit rates as expected (mean hit rate 90.9 ± 7.5%) and in contrast to acuity, hit rates also decreased with increasing age. The AMD patients obtained significantly poorer results (mean hit rate 40 ± 25%).

Some of the differences between normal subjects and AMD subjects may be attributable to the difference in age between groups. Regrettably subjects were not exactly age-matched. Motor skills decrease with age and one might also question the use of a computer mouse to indicate the number of test targets seen. Two elderly subjects in the normal group were indeed excluded from the study due to inability to use the computer mouse correctly. Since the present case material did not allow exact age-matching, an interim solution was to compare the small group of eight AMD patients with the eight oldest normal subjects. The difference in test performance (hit rate) remained significant (p=0.002).

Four of the twelve initially recruited AMD patients were, due to immeasurable low central vision, unable to perform both the acuity- and the MacuBit tests and had to be excluded. The MacuBit test may be less well suited for assessing more advanced stages of disease. This is because waiting times between seen probes may be so long, that attention waver.

The study was not successful in recruiting patients with early signs of AMD. All patients suffered from rather advanced macular illness and one of the main issues, i.e. if the new test would capture signs of minor damage, could not be evaluated in the study. However, the study results encouraged the planning of further studies employing rarebit testing [68].

Paper II

Rarebit testing is a conceptual model in which single receptive fields are stimulated. The question whether the optical image of the rarebit on the retina match the receptive field size or if it may be larger is difficult to settle because of the quality of the optics in the individual eye. However, clinical studies indicate that rarebit probing does work and does provide good sensitivity and specificity. The MacuBit test, presented in paper I , has been shown to have high sensitivity for functional deterioration due to early AMD [68].

The MacuBit test used a specially designed device. The increased access of improved computer technology at reasonable costs, favoured a further development of new vision tests using rarebit test targets.

In the DigitStep test, evaluated in this study, test targets were generated under ordinary personal computer control on a 17´´ liquid-crystal display. The software was available free of charge on the Internet in the form of a Java applet named DigitStep. These circumstances facilitated access to the new test for interested clinicians and researchers.

The specific aim of the new test was to uncover low degree visual damage. As in the previous MacuBit study, the DigitStep employed the rarebit test principles; a reduction of test target information to a minimum and to assess function over an extended area.

In the DigitStep test, single rarebits were combined to meaningful patterns, segmented digits. Such digits are familiar and easily recognizable since they often occur in daily life, from the use in alarm clocks to queue number displays.

A weakness in the former MacuBit test, was its limited suitability when testing subjects suffering from more pronounced visual impairment. The possibility to increase the number of RPS building a segmented digit expanded the usability of the new test.

Normal eyes are expected to see all rarebit probes, or nearly so. In this study twenty-four of the 25 normal subjects needed no more than 3 RPS for correct digit identification and 46 of the 51 AMD patients fell outside this limit. These results support the theoretical model of rarebit testing where test targets probe the completeness of receptive fields in the macula and search for gaps. Furthermore, the DigitStep seems to define a narrow limit for normal function whereas the range of normal test results in conventional acuity tests is wide.

When inspecting the low RPS results, one subject in the normal group needed 4 RPS. It is understandable that single normal subjects may need 4 RPS due to age-related losses of receptive fields or variations in psychological functions. In subjects with drusen, 7 cases of 10 fell outside the normal limit. Only three subjects passed the 3 RPS level. Regrettably, a grading of drusen in size and type was not performed. It is possible that repeated test measurements, followed by the calculation of an average test result, combined with drusen subtype analysis would offer an explanation of these results.

Analysis of DigitStep results in the AMD group indicated a significant difference between the dry and the wet subgroups. No such differences were found in the analysis of ETDRS results. On the contrary, considerable overlaps between AMD subgroups were seen. Median ETDRS acuity in the dry and wet AMD subgroups was quite similar whereas median RPS results differed markedly. On further inspection of DigitStep score distribution, RPS results over 16 pointed to a high likelihood of the presence of oedema. This may be due to oedema-mediated tilting of macular cones. It is known that cones capture light more efficiently on truly axial input than on oblique input, known as the Stiles-Crawford effect. Abnormal Stiles-Crawford effects have previously been demonstrated in AMD [78].

As pointed out in previous studies, the results above likewise indicate that conventional acuity tests fail to detect early functional damage [79-82]. Rarebit test targets, on the other hand, appear to be less blunt and seem to capture more subtle impacts on visual function due to different structural changes.

Several patients in the present study suffering from wet AMD, hit the preset ceiling of 128 RPS. This test characteristic is a limitation, as in the MacuBit test, although this problem may be overcome in a revised test using larger symbol sizes containing larger number of dots.

According to the results in this study, the DigitStep test appears to capture deficits in macular function hidden to conventional acuity tests.

Paper III

Management of AMD patients is well known to pose a major logistic problem. By involving patients themselves, management might be optimized. The rapid improvement of technology in electronic tablets and smartphones and their wide availability, points to a practicable technical platform for self-testing. The DigitStep test showed promising good results, including a particular sensitivity to macular oedema. By transforming the DigitStep test to a smartphone application (app) format, the MultiBit self-test was created.

The thought of a self-test is not new [51, 83]. There is a wide variety of smartphone applications, e.g. conventional acuity tests converted into an app format [84]. These tests offer little in terms of new sensitive test principles.

There are though two new self-tests aimed for remote monitoring of patients suffering from AMD.

One is the recently presented myVision Track (mVT), a forced-choice shape discrimination test with automatically scored results transmitted for remote monitoring [58]. Test results have shown that the mVT is capable of discriminating groups of subjects with different stages of AMD. The next test is the Foresee Preferential Hyperacuity Perimeter (Foresee PHP) [56, 57, 85, 86]. This test is also based on the principle of detecting visual distortion. When used as a tool for longitudinal self-testing of vision, the outcome for patients with AMD was significantly better compared to patients under ordinary clinical care. However, the capacity of identifying changes over time in individual cases, have not been published for these two tests.

The results in this study indicate that the MultiBit test is capable of capturing gradual changes in decease activity in individual cases. Analysis of test results was not performed by a computerized statistical tool but by subjective grading.

This is a limitation of the study. However, the authors independently evaluated the test plots visually and their evaluations agreed in 141 out of the 144 epochs.

Comparing test results and clinical ratings the standard ETDRS acuity test showed close to chance agreement. These findings were consistent with the results in our previous rarebit studies and did not surprise. The MultiBit test showed a better agreement although not a perfect match.

A question discussed also in our previous papers concerns the usability of the test in patients suffering from more advanced AMD damage. Due to the maximum 60 RPS in MBT targets, the test excludes subjects with acuities below approximately ETDRS 50 (0.2 decimal) which is a limitation. Another aspect concerns the low RPS end. There is probably a transition zone between 3 and 4 RPS where subtle changes of visual function may hide. As suggested for the DigitStep test, this limitation may be overcome by repeated measurements followed by the calculation of an average test result.

An important matter concerns whether elderly subjects are capable of managing a smartphone based test. This study included both subjects with and without previous experience in smartphone usage and most subjects rather easily grasped the test task. An elderly person can keep up with modern technology. Annually performed studies inventing access of IT technology in the population, point out that the number of retired persons who regularly use computers and internet continue to rise each year [87].

Many patients often request a possibility to get involved in the evaluation of their state of health and the planning of different interventions. In this study, many subjects expressed a feeling of being in control of their disease when assessing their visual function at home with the MultiBit.

A large-scale multicenter study of patients suffering from recurring macular oedema has recently started. If data collected from this study may result in a computerized analytical tool for automated evaluation of transmitted test results, the MultiBit test may in the future contribute to a more effective use of healthcare resources which would benefit the patients.

Paper IV

The tradition of expressing visual function in terms of distance visual acuity is well-established in patients suffering from AMD [88]. The effect of a given treatment is often evaluated as the number of letters gained or lost on an ETDRS chart. This is understandable, since these tests are standardized and moderately time consuming.

However, a recent study on patients with wet AMD showed significant improvements in measured reading speed after successful treatment. Further, when matters concerning quality of life was analysed, reading ability at near showed the greatest improvement [72]. When discussing visual performance and outcomes after treatment with patients themselves impact on reading capability is often emphasized [89-91].

The main approaches to assess reading ability are reading speed, text comprehension and smallest legible letter size [36, 40, 92-94]. The latter is used in ordinary clinical check-ups.

During these clinical appointments, printed reading charts are used in a non-standardized fashion. Test results are expressed as a typographical point number and the interpretation of this information often lies in the eye of the beholder, since criteria for acceptable reading speed and text comprehension never have been formalized.

Another aspect is that digits are not included in the tests. Deciphering groups of digits is probably the most demanding reading task because of the need of particularly close scrutiny. A wrong guess may have unwanted consequences.

In this study two types of simplified reading tests were evaluated, one in the form of a set of traditional printed reading charts [73], and the other in the form of a new smartphone application. Using these tests, the smallest font size allowing a reading speed of 40 wpm, so-called spot reading, was measured. This speed allows the reading of short messages like addresses and receipts. The ability of spot reading has a direct bearing on important activities in daily life for visually handicapped subjects. Assessment of the smallest legible letter size for spot reading could offer concise information of visual performance.

Measurement of spot reading was possible with both tests. Both tests also revealed that critical letter size differed markedly between normal subjects and patients with AMD and the results correlated strongly. The two tests correlated moderate with distance visual acuity. Reading single letters on an acuity chart is a less complex task than reading words, which includes a variety of visual- and psychological factors [93].

The two tests differ in many aspects. The smartphone reading test contains both digits and letters, presented in ever new combinations. Test targets thus become less predictable and the user´s native language is less important. The test presents a fixed number of characters in each target, not reflecting how words are constructed in reality. The printed charts contain 2-9 letter words but no digits. The use of sentences reflects real life, but after repeated usage sentences may be memorized. Both test present targets with high contrast not mimicking the wash-out appearance hold by many prints in daily life.

Both tests offer the possibility of measuring reading speed. In the C test, speed is automatically set and easily measured. A minor revision of the software would probably also result in a number of selectable speeds. The printed charts allow calculation of individual reading speeds, although this is not easily done during ordinary clinical appointments. In this study reading performance was recorded and analysed in a later session, a time consuming work. This was an important practical difference between the tests.

In this study a new format is used for the description of test results. The score scale ranges from 0 to 100. A subject capable of reading the mid-size test targets, but not the next smaller size, would be assigned a score of 50. The use of a simple test score facilitates the comparison of results over time. It is probably also more understandable to patients, compared to results expressed as the number of correctly read words per minute at a given font size.

This study demonstrates a new approach towards a meaningful and time-efficient assessment of reading speed, useful as a reproducible and standardized tool in the everyday clinical work. The new smartphone test also contains a number of other practical aspects as self-testing, self-scoring, storing and transmission of results.

Conclusions

General conclusions

The new rarebit vision tests appear well suited for the detection and grading of lesions in age-related macular degeneration.

Self-testing of vision is feasible.

Reading abilities can be evaluated by abbreviated tests.

Specific conclusions

The MacuBit test allows portable rarebit testing for neuro-macular damage. It is useful for the screening of age-related macular degeneration.

The DigitStep test appears as a useful tool for early detection of macular dysfunction and allows detailed assessment of more severe degrees of visual loss.

The MultiBit smartphone test appears to have a good potential for effective self-testing of vision in age-related macular degeneration and may contribute to an effective longitudinal monitoring of patients treated for macular oedema.

The Celego smartphone based test allows efficient assessment of spot reading ability.

Future Perspectives

With an aging population, not only in the Western World but also globally, prevalence of AMD will increase worldwide. In persons with established AMD, lifelong follow-up is recommended to detect vision change early and to prevent permanent loss of visual function through timely treatment.

Current AMD care is based on repeated clinical controls where patients and caregivers meet face to face. Evaluation of visual function is based on assessment of visual acuity using conventional tests which often fail to recognize early signs of damage. Evaluation of macular anatomy is based on high technology imaging techniques capable of detecting subtle anatomical change [95], sometimes of questionable clinical relevance [96].

New tests of vision based on rarebit testing show promising results in detecting early functional damage and offer a possibility of self-testing and remote control.

For an effective remote control process of an increasingly number of patients performing self-tests, automated evaluation of test results is highly desirable. To perform this, appropriate analytical tools are needed. These tools must be tested against new and larger data sets and this is one of the goals in a recently started large-scale multicentre study. In this study, also patients with other types of macular conditions are included.

Development of new imaging techniques may lead to a better understanding of the pathophysiology and the morphological changes in macular diseases. Imaging with adaptive optics instruments already allows visualization of individual photoreceptor elements [97, 98]. Today, these instruments are exclusive but as technology moves forward they will probably be available in regular ophthalmic care in the future. Tedious examinations like angiography may be replaced. A direct correlation between the outcomes of functional tests and morphological changes in macular anatomy is desirable. This would facilitate the evaluation of clinically significant changes and perhaps promote the development of targeted treatments [99, 100].

However, the vast majority of investigational drugs and treatments in pipeline, are planned to be administered via intravitreal injections [100]. Unlike local or oral treatment on a daily basis intravitreal injections are often administered only after signs of disease activity. Close monitoring of visual function and structural macular changes is therefore essential and poses a difficult challenge for eye clinics today. In the future, self-administered vision tests whose results could be automatically analysed and linked to patient administrative systems could free resources and allow timely treatment of AMD, reducing visual handicap and improving quality of life for these patients.

Svensk sammanfattning/ Summary in Swedish

Åldersrelaterade förändringar i ögats gula fläck (s.k. makuladegeneration) är en dominerande orsak till allvarlig synförlust hos personer över 60 år. Sjukdomen skadar funktionen i det centrala synfältet och därmed drabbas bl. a. läsförmåga och detaljseende. I ett tidigt skede av sjukdomen är förändringarna subtila medan i slutskedet är gula fläcken omvandlad till ett ärr vilket ofta medför permanent synhandikapp.

För några år sedan kom det första läkemedlet som kan bromsa en försämring av synen, i vissa fall av makuladegeneration (den våta varianten). Läkemedlet ges som en injektion i ögat i samband med ett enklare operativt ingrepp under sterila förhållanden. Därmed inleddes en ny era som innebar att förhållningssättet till diagnostik av makulasjukdom helt förändrades. Sjukdomen är nu att betrakta som kroniskt förlöpande med återkommande skov, som kräver förnyad behandling. Därmed ställs helt nya krav på sjukvårdsresurser för diagnostik och behandling av dessa tillstånd.

Det viktiga för all framgångsrik behandling är att förändringarna i gula fläcken upptäcks i ett tidigt skede, innan någon permanent skada på syncellerna uppstått. I dagsläget råder en kösituation till sjukvården för dessa patienter och under kötiden riskerar en drabbad person att förlora synfunktion som inte går att återställa.

Det finns således ett behov av nya metoder för att tidigt upptäcka skador i syncellerna, helst på ett sådant sätt att patienterna själva ska kunna testa sin synfunktion.

Ett stort problem i klinisk diagnostik är att de syntester som används idag har mycket begränsad känslighet. Den vanligaste undersökningen är synskärpemätning på en syntavla. Sådan synskärpetest är inte idealisk för att upptäcka tidig skada. Orsaken är att testbokstäverna innehåller ett stort överskott av information. Ett skadat öga kan ofta prestera ett normalt resultat genom att patienten scannar av syntavlan flera gånger. Det är också lätt att gissa rätt även om man bara ser delar av en bokstav.

Ett annat test som används i diagnostiken av makulasjukdomar är läsning av en text på läsavstånd. En patient med makulasjukdom läser ofta långsammare och har svårare att läsa en text som är tryckt med mindre textstorlek. Siffror är ofta extra svåra att tyda på grund av att de oftast förekommer i ett mer oförutsägbart sammanhang. Ett problem vid utvärdering av läsförmågan är dock att de lästester som används idag är svåra att utföra på ett standardiserat sätt och att de är svåra att tolka.

En målsättning med denna avhandling är att skapa ett syntest som är bättre på att upptäcka tidiga skador i gula fläcken än de tester som används idag. Om ett sådant test ska bli riktigt användbart bör det kunna användas av patienten själv i sin hemmiljö. En annan målsättning är att skapa ett lättanvänt lästest som är bättre standardiserat och snabbare än de test som används idag.

Frågeställning

Kan nya typer av syntester påvisa funktionsnedsättning i gula fläcken tidigare än konventionella syntester? Kan dessa syntester också medge självtestning av synfunktionen?

Kan nya standardiserade lästester mäta funktion lika bra som nuvarande traditionella, mer tidsödande och svårtolkade tester?

Metodik

Studier på AMD-patienter och kontrollpersoner hos vilka helt nya syntester utvärderats. Syntesterna har i delarbetena 1-3 successivt förfinats, från mini-dataprojektorer (MacuBit test) och persondatorer (DigitStep test) till en unik applikation för smartphone (MultiBit test) med möjlighet till självtest av synfunktionen i hemmiljö och insändande av resultat till ögonkliniken.

Det nya lästestet som utvärderats i delarbete 4 är utformat som en applikation för smartphone (Celego test). Förutom bokstäver innehåller testet även siffror. Det nya lästestet medger även självtester i hemmiljö och insändande av resultat till kliniken.

Resultat

De nya syntester som utvärderats i delarbete 1-3 kan fånga tecken på funktionsnedsättning i gula fläcken som nuvarande konventionella syntester kan avslöja först i ett sent stadium av sjukdomen.

Det nya lästest som utvärderats i delarbete 4 kan mäta basal läsfunktion minst lika bra som dagens mer tidsödande tester.

Slutsats

De nya känsligare syntesterna har potential för självtest av synfunktion i hemmiljö. De skulle därför kunna ersätta en del av de kliniska kontroller som görs idag. På så sätt skulle sjukvårdsresurser kunna frigöras och användas för att minska skadliga väntetider för patienter med makulasjukdomar.

Det nya lästestet har potential att på ett standarsiserat och tidsbesparande sätt ge en god uppfattning om patientens basala läsförmåga.

Acknowledgements

The making of this thesis would not have been possible without the contributions of many people to whom I am immensely grateful. In particular wish to express my sincere gratitude to:

Lars Frisén, "Il Vulcano Scientifico", my supervisor and friend who shared with me his brilliant knowledge. With genuine interest, never-ending patience and joy he enthusiastically taught me how to make research.

Bertil Lindblom, my supervisor and friend, for all his support, constructive criticism and kindness.

Maria Egardt and **Eva Byhr,** two beautiful minds, my closest colleagues and true friends, for their endless support, tender love and care.

Ulf Stenevi, a wise man, for all his good advice and kind support.

Lena Bond Taylor, a skilled co-worker and dear friend, for all the hard work and happy moments building the AMD-team.

Dragana Skiljic, a superb organizer, for good advice, helpful planning and good spirits, all crucial for getting my dissertation finished.

Inger Almgren and **Elisabeth Ståhlberg,** for their excellent administrative support and kindness.

Kerstin Norrsell, a wise woman, for all the years teaching me what is important and what is not.

Johan Sjöstrand, Zoran Popovic and Jörgen Thaung, dedicated researchers, for interesting discussions and inviting me into the world of Adaptive Optics.

Richard Grenmark, Petra Vånder, Mats Johanson and Charlotte Chalfen, dear friends and skilful colleagues, for interesting discussions and many laughs.

All my colleagues at the Eye Clinic, Sahlgrenska University Hospital, especially **Gunnar Jakobsson, Lena Sjödell, Tommy Andersson**, **Kristina Stenberg and Gun Lindgren** for creating a friendly atmosphere, sharing your knowledge and important thoughts with me.

All the staff at the Eye Clinic, Sahlgrenska University Hospital, especially the ones always doing their utmost for our AMD-patients, your work is admirable.

All the staff, former and present, at the Eye Clinic, Skaraborgs Hospital/ Lidköping, for excellent work and always choosing to focus on possibilities, not problems.

All the staff at Guldhedskliniken, for sharing your eminent work wrapped in pure joy.

Oliver, Markus, Carl, Christer, Ingrid, Gunnar, Ingrid,
Claes and Ewa May, my loved ones.

The work in this thesis has been funded by De Blindas Vänner, Forskningsfonden vid Skaraborg Sjukhus, Beth och David Dahlin Stiftelse, Stiftelsen Handlaren Herman Svenssons fond för blinda och synsvaga, Dr Reinhard Marcuses fond.

References

1. Frisén L, Quigley H: Visual acuity in optic atrophy. A quantitative clinicopathological stydy. Graefes Arch Clin Exp Ophthalmol 1984 222:71-74.
2. Sjöstrand J, Popovic Z, Conradi N, Marshall J: Morphometric study of the displacement of retinal ganglion cells subserving cones within the human fovea. Graefes Arch Clin Exp Ophthalmol 1999 237:1014-1023.
3. Curcio CA, Sloan KR, Kalina RE, Hendrickson AE: Human photoreceptor topography. J of Comp Neurol 1990 292(4):497-523.
4. Leibowitz HM, Krueger DE, Maunder LR, Milton RC, Kini MM, Kahn HA, Nickerson RJ, Pool J, Colton TL, Ganley JP *et al*: The Framingham Eye Study monograph: An ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973-1975. Surv Ophthalmol 1980 24(Suppl):335-610.
5. Klein R, Klein BE, Jensen SC, Meuer SM: The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. Ophthalmology 1997 104(1):7-21.
6. Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY, Wong TY: Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. The Lancet Global Health 2014 2(2):e106-116.
7. Ferris FL, 3rd, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, Sadda SR, Beckman Initiative for Macular Research Classification C: Clinical classification of age-related macular degeneration. Ophthalmology 2013 120(4):844-851.
8. Suzuki M ST, Spaide RF: Pseudodrusen subtypes as delinated by multimodal imaging of the fundus. Am J Ophthalmol 2014 157:1005-1012.
9. Narayanan R, Kuppermann BD, Jones C, Kirkpatrick P: Ranibizumab. Nat Rev Drug Discov 2006 5(10):815-816.
10. Ferrana N, Damico L, Shams N, Lowman H, Kim R: Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration Retina 2006 26:859-870.
11. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY; MARINA Study Group: Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006 355:1419-1431.

12. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S, Group AS: Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006 355(14):1432-1444.
13. Bloch SB, Larsen M, Munch IC: Incidence of legal blindness from age-related macular degeneration in denmark: year 2000 to 2010. Am J Ophthalmol 2012 153(2):209-213 e202.
14. Muether PS, Hoerster R, Hermann MM, Kirchhof B, Fauser S: Long-term effects of ranibizumab treatment delay in neovascular age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2013 251(2):453-458.
15. Massamba N, Dirani A, Knoeri J, Pasquier B, Ingram A, Soubrane G: Evaluating the impact of summer vacation on the visual acuity of AMD patients treated with ranibizumab. Eye (Lond) 2015 29(11):1453-1457.
16. Butt T, Lee A, Lee C, Tufail A et.al.: The cost-effectiveness of initiating ranibizumab therapy in eyes with neovascular AMD with good vision: an economic model using real-world outcomes. BMJ Open 2015 5:e006535.
17. Muether P, Hermann M, Koch K, Fauser S: Delay between medical indication to anti-VEGF treatment in age-related macular degeneration can result in a loss of visual acuity. Graefes Arch Clin Exp Ophthalmol 2011 249:633-637.
18. Novotny HR, Alvis DL: A method of photographing fluorescence in circulating blood in the human retina. Circulation 1961 24:82-86.
19. Alander JT, Kaartinen I, Laakso A, Patila T, Spillmann T, Tuchin VV, Venermo M, Valisuo P: A review of indocyanine green fluorescent imaging in surgery. Int J Biomed Imaging 2012 2012:940585.
20. Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, Hee MR, Flotte T, Gregory K, Puliafito CA *et al*: Optical coherence tomography. Science 1991 254(5035):1178-1181.
21. Donders F: On the Anomalies of Accommodation and Refraction. 1864.
22. Snellen H: Letterproeven tot Bepaling der Gezichtsscherpte. 1862.
23. Green J: On a new series of test-letters for determining the acuteness of vision. Transact Amer Opth Soc Meeting 1868:68-71.
24. Bailey I, Lovie J: New Design Principles for Visual Acuity Letter Charts. Am J Optom and Physiol Opt 1976 53:740-745.
25. Ferris FL, 3rd, Kassoff A, Bresnick GH, Bailey I: New visual acuity charts for clinical research. Am J Ophthalmol 1982 94(1):91-96.
26. Frisen L: The neurology of visual acuity. Brain 1980 103(3):639-670.
27. Seiple W, Holopigian K, Szlyk JP, Greenstein VC: The effects of random element loss on letter identification: implications for visual

acuity loss in patients with retinitis pigmentosa. Vision Res 1995 35(14):2057-2066.

28. Rubin GS, Muñoz B, Bandeen-Roche K, West SK: Monocular versus binocular visual acuity as measures of vision impairment and predictors of visual disability. Invest Ophthalm Vis Sci 2000 41:3327-3334.
29. Bouma H de Voogd AH: On the control of eye saccades in reading. Vision Res 1974 14:273.
30. Leigh RS, Thurston SE, Tomsak RL, Grossman GE, Lanska DJ: Effect on monocular visual loss upon stability of gaze. Invest Ophthalm Vis Sci 1989 30:288S.
31. Morrisson RE RK: Retinal image size and the perceptual span in reading. Eye movements in reading: perceptual and language process. 1983:31-40.
32. O´Regan JK: The control of saccade size and fixation duration in reading: The limits of linguistic control. Percept Psychophys 1980 28:112-117.
33. Taft M: Recognition of affixed words and the word frequency effect. Mem Cognit 1979 7:263-272.
34. Thorndyke P: Cognitive structures in comprehension and memory of narrative discourse. Cogn Psychol 1977 9:77-110.
35. Just MA, Carpenter PA: A theory of reading: From eye fixations to comprehension. Psychol Rev 1980 87:329-354.
36. Rubin GS: Measuring reading performance. Vision Res 2013 90:43-51.
37. Mansfield JS, Ahn SJ, Legge GE, Luebker A: A new reading-acuity chart for normal and low vision. Ophthal Vis Opt 1993 3:232-235.
38. Mansfield JS, Legge GE, Bane MC: Psychophysics of reading. XV: Font effects in normal and low vision. Invest Ophthalmol Vis Sci 1996 37(8):1492-1501.
39. Whittaker SG, Lovie-Kitchin J: Visual requirements for reading. Optom Vis Sci 1993 70(1):54-65.
40. Carver RP: Reading rate: Theory, research and practical implications. J Reading 1992 36(2):84-95.
41. Colenbrander A: Assessment of functional vision and its rehabilitation. Acta Ophthalmol 2010 88(2):163-173.
42. Sjöstrand J, Frisen L: Contrast sensitivity in macular disease. A preliminary report. Acta Ophthalmol (Copenh) 1977 55(3):507-514.
43. Pelli D, Robson J, Wilkins A: The design of a new letter chart for measuring contrast sensitivity. Clin Vis Sci 1988 2:187-199.
44. Berkeley G: A Essay towards a New Theory of Vision. 1709.
45. Reid T: An Inquiry into the human mind, on the principles of common sense. 1764:114-131.

46. Marmor M: A brief history of macular grids: from Thomas Reid to Edvard Munch and Marc Amsler. Surv Ophthalmol 2000 44(4):343-353S.
47. Förster R: Metamorphopsie. Ein Symptom partieller Schrumpfung der Retina (Retinitis circumscripta). 1862.
48. Amsler M: Earliest symptoms of diseases of the macula. Br Journal Ophthalmol 1953 37:521-537.
49. Schuchard R: Validity and interpretation of amsler grid reports. Arch Ophthalmol 1993 111(776-780).
50. Crosslands M RG: The Amsler chart: absence of evidence is not evidence of absence. Br J Ophthalmol 2007 91(3):391-393.
51. Trevino R: Recent progress in macular function self-assessment. Ophthalmic Physiol Opt 2008 28(3):183-192.
52. Matsumoto C, Arimura E, Okuyama S,Takada S, Hashimoto S, Shimomura Y: Quantification of metamorphopsia in patients with epiretinal membranes. Invest Ophthalmol Sci 2003 44:4012.
53. Arimura E, Matsumoto C, Nomoto H, Hashimoto S, Takada S, Okuyama S , Shimomura Y: Subjective Perception of Metamorphopsia and Metamorphopsia Score Using M–chartsTM in Patients With Macular Diseases. Invest Ophthalmol Vis Sci 2006 47:5644.
54. Frisén L: The Amsler grid in modern clothes. Br J Ophthalmol 2009 93:714-716.
55. Westheimer G: The spatial sense of the eye. Proctor lecture. Invest Ophthalmol Vis Sci 1979 18:893-912.
56. Loewenstein A, Malach R, Goldstein M, Leibovitch I, Barak A, Baruch E, Alster Y, Rafaeli O, Avni I, Yassur Y: Replacing the Amsler grid: a new method for monitoring patients with age-related macular degeneration. Ophthalmology 2003 110(5):966-970.
57. Loewenstein A: Use of home device for early detection of neovascular age-related macular degeneration. Ophthalmic Res 2012 48:11-15.
58. Kaiser P, Wang Y, He Y, Weisberger A, Wolf S, Smith C: Feasibility of a novel remote daily monitoring system for age-related macular degeneration using mobile handheld devices: results of a pilot study. Retina 2013 33:1863-1870.
59. Wang YZ, Wilson E, Locke KG, Edwards AO: Shape discrimination in age-related macular degeneration. Invest Ophthalmol Vis Sci 2002 43(6):2055-2062.
60. Frisén L: New, sensitive window on abnormal spatial vision: rarebit probing. Vision Res 2002 42:1931-1939.
61. Corallo G, Iester M, Scotto R, Calabria G, Traverso CE: Rarebit perimetry and frequency doubling technology in patients with ocular hypertension. Eur J Ophthalmol 2008 18(2):205-211.

62. Brusini P, Salvetat ML, Parisi L, Zeppieri M: Probing glaucoma visual damage by rarebit perimetry. Br J Ophthalmol 2005 89(2):180-184.
63. Jacobson L, Flodmark O, Martin L: Visual field defects in prematurely born patients with white matter damage of immaturity: a multiple-case study. Acta Ophthalmol 2006 84(3):357-362.
64. Nilsson M, von Wendt G, Wanger P: Early detection of macular changes in patients with diabetes using rarebit fovea test and optical coherence tomography. Br j Ophthalmol 2007 91:1596-1598.
65. Salvetat M, Zeppieri M, Parisi L, Brusini P: Rarebit perimetry in normal subjects: test-retest variability, learning effect, normative range, influence of optical defocus, and cataract extraction. Invest Ophthalmol Vis Sci 2007 48:5320-5331.
66. Hackett DA, Anderson AJ: Determining mechanisms of visual loss in glaucoma using rarebit perimetry. Optometry and vision science : official publication of the American Academy of Optometry 2010 88:48-55.
67. Vislisel JM DC, Johnson CA, Wall M: Variability of rarebit and standard perimetry sizes I and III in normals. Optom Vis Sci: 2011 88:635-639.
68. de Kinkelder R, van Leeuwen TG, Verbraak FD: Detection of early-stage age related macular degeneration with a compact rarebit test. Br J Ophthalmol 2012 96(10):1354-1355.
69. Frisén L: Performance of a rapid rarebit central-vision test with optic neuropathies. Optom Vis Sci: 2012 89:1192-1195.
70. Frisén L: Rapid assessment of neuro-visual integrity using multiple rarebits. Opthalmology 2013 120:1756-1760.
71. Nilsson M: The rarebit fovea test. Ph D Thesis, Karolinska Institute 2008.
72. Frennesson C, Nilsson UL, Peebo BB, Nilsson SE: Significant improvements in near vision, reading speed, central visual field and related quality of life after ranibizumab treatment of wet age-related macular degeneration. Acta Ophthalmol 2010 88(4):420-425.
73. Thaung J, Olseke K, Ahl J, Sjostrand J: Reliability of a standardized test in Swedish for evaluation of reading performance in healthy eyes. Interchart and test-retest analyses. Acta Ophthalmol 2014 92(6):557-562.
74. Frisén L, Frisén M: How good is normal visual acuity? A study of letter acuity thresholds as a function of age. Graefes Arch Clin Exp Ophthalmol 1981 215:149-157.
75. Evans DW, Wang Y, Haggerty KM, Thibos LN: Effect of sampling array irregularity and window size on the discrimination of sampled gratings. Vision Res 2010 50:20-30.

76. Frisen L: Scope of super-resolution in central vision. Br J Ophthalmol 2010 94(1):97-100.
77. Eisenbarth W, Mackeben M, Poggel DA, Strasburger H: Characteristics of dynamic processing in the visual field of patients with age-related maculopathy. Graefes Arch Clin Exp Ophthalmol 2008 246(1):27-37.
78. Smith V, Pokorny J, Diddle K: Color matching and the Stiles-Crawford affect in observers with early age-related macular changes. J Opt Soc Am 1988 5:2113-2121.
79. Klein R, Wang Q, Klein B: The relationship of age-related maculopathy, cataract, and glaocoma to visual acuity. Invest Ophthalmol Vis Sci 1995 36:182-191.
80. Rosser D, Cousens S, Murdoch I, Fitzke F, Laidlaw D: How sensitive to clinical change are ETDRS logMAR visual acuity measurements. Invest Ophthalmol Vis Sci 2003 44:3278-3281.
81. Arditi A, Cagenello R: On the statistical reliability of letter-chart visual acuity measurements. Invest Ophthalmol Vis Sci 1993 34(1):120-129.
82. Lovie-Kitchin J, Brown B: Repeatability and intercorrelations os standard vision tests as a function of age. Optom Vis Sci: 2000 77:412-420.
83. Kuchenbecker J, Lindner H: Visual function tests on the Internet-sense or nonsense? Strabismus 2004 12:97-102.
84. Tofigh S, Shortridge E, Elkeeb A, Godley BF: Effectiveness of a smartphone application for testing near visual acuity. Eye (Lond) 2015 29(11):1464-1468.
85. Loewenstein A, Ferencz J, Lang Y, Yeshurun I, A P, Siegal R, Lifshitz T, Karp J, Roth D, Bronner G *et.al*: Toward earlier detection of choroidal neovascularization secondary to age-related macular degeneration: multicenter evaluation of a preferential hyperacuity perimeter designed as a home device. Retina 2010 30:1058-1064.
86. Chew E, Clemons T, Bressler S: Randomized trial of a home monitoring system for early detection of chooroidal neovascularization home monitoring of the eye (HOME) STUDY. Ophthalmology 2014 121:535-544.
87. www.internetstatistik.se.
88. Munk MR, Kiss C, Huf W, Sulzbacher F, Roberts P, Mittermuller TJ, Sacu S, Simader C, Schmidt-Erfurth U: One year follow-up of functional recovery in neovascular AMD during monthly anti-VEGF treatment. Am J Ophthalmol 2013 156(4):633-643.
89. Mitchell J, Bradley C: Quality of life in age-related macular degeneration: a review of the literature. Health Qual Life Outcomes 2006 4(97).

90. Munk M, Kiss C, Huf W, Sulzbacher F, Bolz M, Sayegh R, Eisenkölbl S, Simader C, Schmidt-Erfurth U: Therapeutic interventions for macular diseases show characteristic effects on near and distance visual function. Retina 2013 33(9):1915-1922.

91. Yuzawa M, Fujita K, Tanaka E, Wang EC: Assessing quality of life in the treatment of patients with age-related macular degeneration: clinical research findings and recommendations for clinical practice. Clin Ophthalmol 2013 7:1325-1332.

92. Legge GE, Rubin GS, Pelli DG, Schleske MM: Psychophysics of reading--II. Low vision. Vision Res 1985 25(2):253-265.

93. Legge GE, Ross JA, Isenberg LM, LaMay JM: Psychophysics of reading. Clinical predictors of low-vision reading speed. Invest Ophthalmol Vis Sci 1992 33(3):677-687.

94. Legge G: Psychophysics of Readings in Normal and Low vision; 2007.

95. Vujosevic S, Varano M, Egan C, Sivaprasad S, Menon G, Erginay A, Verbraak F, Lund-Andersen H, Martinez J, Jürgens I *et al*: Relevance of retinal thickness changes in the OCT inner and outer rings to predict progression to clinical macular edema: An attempt of composite grading of macular edema. Opthalmic Res 2015 55:19-25.

96. Hunter A, Chin EK, Telander DG: Macular edema in the era of spectral-domain optical coherence tomography. Clin Ophthalmol 2013 7:2085-2089.

97. Thaung J, Knutsson P, Popovic Z, Owner-Petersen M: Dual-conjugate adaptive optics for wide-field high-resolution retinal imaging. Opt Express 2009 17:4454-4467.

98. Popovic Z, Knutsson P, Thaung J, Owner-Petersen M, Sjöstrand J: Noninvasive imaging of human foveal capillary network using dual-conjugate adaptive optics. Invest Ophthalmol Vis Sci 2011 52:2649-2655.

99. Delplace V, Payne S, Shoichet M: Delivery strategies for treatment of age-related ocular diseases: From a biological understanding to biomaterial solutions. J Control Release 2015 219:652-668.

100. Ishikawa M, Jin D, Sawada Y, Abe S, Yoshitomi T: Future therapies of wet age-related macular degeneration. J Ophthalmol 2015 2015:138070.