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de Kinkelder, R.

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CHAPTER SEVEN

DETECTION OF EARLY-STAGE AGE RELATED MACULAR DEGENERATION WITH A COMPACT RAREBIT TEST

Abstract

Early detection of age related macular degeneration (AMD) is very important to start treatment and prevent further loss of vision. Technological developments have made it possible to transform a so-called rarebit test to a compact, self contained device that can probe the neuro-visual system by briefly presenting small stimuli on the retina. This device, the Macubit has been tested on 12 patients suffering from AMD in an early stage, but still with good vision, and a healthy control group.

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R. de Kinkelder, T.G. van Leeuwen, F.D. Verbraak
CHAPTER 7

7.1 INTRODUCTION

Detection of eye diseases, like AMD, in an early stage is indispensable to prevent further loss of vision. The main challenge in these diseases is to diagnose and monitor the loss and dysfunction of the receptive units in the retina. The most frequently used method for testing this foveal function is a visual acuity (VA) measurement using letter charts. Here, VA is tested by requiring the patient to identify letters on a chart from a set distance. However, with less than two thirds of the optic nerve axons a decimal VA of 20/20 can still be achieved (1). Therefore, this test cannot be regarded as sensitive to low-degree degradation of the foveal function. Furthermore, the test targets that are used are many times larger than the retinal receptive units (2). Studies have shown that a large majority of elements in a VA test can be removed without degrading normal performance (3, 4).

To address this shortcoming a so-called rarebit test has been developed (2). In this test, microdot stimuli that match the size of the receptive units (~20 µm) of the retina, are briefly presented (200 ms), and may therefore be more sensitive to detect early damage at the level of these receptive fields (2). The microdots are presented on a LCD monitor connected to a personal computer. These tests can be applied in the central and peripheral vision. They describe the functional state of the neural matrix of the retina. Rarebit fovea testing has diagnostic potential in conditions like age related macular degeneration (AMD). A disadvantage of the original rarebit test is that it requires a calibrated darkroom and a large measuring distance of approximately two meters.

A new device has been recently introduced to overcome this disadvantage: the Macubit test (5). The device is compact, self-contained, and can be used in lighted environments. In a previous study by Winther et al. (5) the device has been tested on a group of patients suffering from AMD in a progressed stage and already with loss of vision. Although the results look very promising Macubit would be more valuable if it detects functional loss of the retina before patients have deteriorated vision.

This pilot study is set up to prove the validity of the Macubit to test for early functional and structural loss in the central 4 degrees of the macula in patients at risk for developing manifest AMD. Since there is a need in clinical practice for efficient tools for screening for and monitoring early AMD (6, 7) the device will be tested on a group of patients with signs of early AMD and a group of healthy volunteers. The results will be compared by the results from the study by Winther and Frisénén.
7.2 MATERIALS AND METHODS

For patients and healthy subjects to participate in the study we defined inclusion and exclusion criteria:

The inclusion criteria for this study were:

- Age > 45 years
- Visual acuity $\geq 20/32$
- Clear ocular media
- Willing to read, and sign the informed consent.
- Refraction between S+3 and S-5

Exclusion criteria were:

- Diabetes Mellitus
- Other eye disease, like glaucoma, uveitis, known or identifiable at screening

7.2.1 PATIENTS AND HEALTHY CONTROLS

Twelve patients (mean age: 74.9±11.1 years) with signs of early AMD i.e. having drusen and pigment epithelium alterations, and normal visual acuity were measured. Only one eye was measured and used for data analysis. In addition the right eyes of 23 healthy patients (mean age: 59.8±9.7 years), i.e. without ocular pathology and clear ocular media, were measured as controls. Following the signing of an informed consent, all participants underwent a visual acuity test using a letter chart, the Macubit Test, and fundus photography. Diagnosis of the early signs of AMD was done by an ophthalmologist in the outpatient clinic of our department of ophthalmology.

7.2.2 MACUBIT TESTING

The Macubit device (displayed in Figure 7-1) is a modified projector (Mitsubishi PK10, Irvine, CA) using light emitting diodes (LED). The MacuBit test dots are generated and projected with the aid of a Digital Micromirror Device (DMD) unit. The core is an 11 x 8 millimeters matrix containing 800 x 600 tiltable micromirrors. The mirror array is illuminated by three LEDs and the intensity of light reflected from each mirror is determined by its tilt angle. By precisely phasing color and tilt angles for the 480,000 mirrors, the Macubit behaves like a miniature computer screen. Each pixel subtended 0.6 minutes of arc at the subject’s eye, closely similar
to a foveal cone. Target and background luminances were set to 200 and 5cd/m², respectively.

Figure 7-1: The Macubit device is a compact self contained device that can measure the state of the neural matrix of the retina. The test is based on the principle of rarebit testing in which microdot stimuli that match the size of the receptive units (~20 µm) of the retina are briefly presented (200 ms). The patient has to indicate how many dots are seen (zero, one or two).

The Macubit device was controlled by a personal computer running at the same resolution (600x800), to create similar output on the computer screen (which can only be seen by the experienced operator) and the Macubit device (only seen by the patient). The Macubit was provided with an internal mask that limited the subject’s field of view to 5.3°. Prior to testing, the non-tested eye was patched. The Macubit was adjusted in height and the subject was able to adjust the focus by turning the ocular. The test field was shown after adjustment of height and focus and consisted of a dark screen and a faintly luminous rim circle that aided alignment. During the test there was no fixation mark to prevent fading and the influence on lateral eye motions on the test results.

The stimuli (zero, one or two with each measurement) were generated by turning on one or two pixels for 200 ms. The dot location was different for every measurement and was controlled by a semi-random algorithm that provided a spatially uniform distribution across the test area, without overlapping. Each measurement (i.e. dot presentation) was accompanied by a beep sound. 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. Visual and auditory feedback was provided after each presentation. The interval between the measurements was automatically adapted to the current reaction time of the subject. When two dots were shown the separation between the dots was 30' in both vertical and horizontal direction. To check false responses by the patient sometimes one or no dots were shown. When the patient was comfortable with the measurement procedure a total of 50 dot pairs were shown, randomly alternated with one or zero dots. The percentage of seen dots versus shown dots (or hit rate) expressed the test results. Responses to control presentations were recorded separately and the hit rate was adjusted.
accordingly. Because normal eyes hold seamless and non-overlapping arrays of receptive fields, the expected result is a hit rate of 78 to 100%, whereas eyes which have lost receptive fields, or component parts of receptive fields, should score poorer (<78%), in proportion to the loss of neural elements.

### 7.2.3 Visual Acuity Test

Visual acuity was assessed using a standard printed acuity chart with a background luminance of 200 cd/m². The percentage of correctly read letters was recorded for each line. Probit analysis provided 50% correct thresholds, in minutes of arc. Conversion to the clinically preferred decimal format was done by inversion. A VA higher than 1.15 is considered normal.

### 7.3 Results

Macubit Test results expressed in hit rate are displayed in Figure 7-2 versus visual acuity. As anticipated, visual acuity of almost all subjects was 1.15 or higher. In the healthy control group the mean Macubit hit rate was 92.5% (standard deviation (SD): 7.7 %), similar to the results found by Winther and Frisén. The results from their paper are presented in Figure 7-3.

![Figure 7-2: Scatter plot displaying the Macubit hit rate versus the corrected VA thresholds. The closed dots (●) display the results of the healthy group and the open dots (○) display the results of the patients suffering from early AMD](image)

Macubit hit rates above the threshold of 78% are considered normal. In the patient group the mean Macubit hit rate was 52.3% (SD: 22.4%). Despite the normal VA, all patients had a hit rate below 80%. Comparison of the means by an independent t-test showed a significant difference (p<0.001) in Macubit hit rate between both groups (92% versus 52%), while the VA was not different (1.52 ± 0.34 versus 1.34 ± 0.22, p=0.122). Reflecting the early stage of AMD, our patients’ hit rates were better than those reported for severe AMD, 40% ± 25.
In the study by Winther and Frisén the normal subjects obtained a mean hit rate of 90.9±7.5% (median 93%, range 68-100). The acuity thresholds averaged 1.43±0.18 (Snellen 20/14). The AMD patients (age 81±6 years) had an average decimal acuity threshold of 0.66±0.13 (median 0.64=Snellen 20/31) and an average hit rate of 40±25% (median 39, range 11-80); both results differed significantly from those of the normals (t test: p<0.001 for both variables).

7.4 DISCUSSION

We tested the Macubit on patients with good vision but with early signs of AMD and on a group of healthy volunteers. We found a statistically significant difference between the two tested groups indicating that Macubit can discriminate patients with early AMD from healthy subjects using psychophysical testing (i.e. the test is based on the relation between stimulus, here the Macubit, and sensation or response by the patient).

We tested the MacuBit against a VA letter chart test, the gold standard to test visual function. There are some differences between the two methods: VA tests reflect the spatial density of functional receptive fields. The Macubit test, however, probes the photoreceptive field for functionality and returns a hit rate percentage. Another important difference concerns the size of the used test targets. Studies by Geller and Sieple have indicated that test targets can still be identified even when the targets are broken down into smaller elements. This indicates that the used VA tests are not sensitive enough to detect AMD in an early stage. Rarebit testing uses test targets as big as the receptive units. Retinal vessels can be probed instead of the receptive units inducing erroneous test results. To overcome this problem Macubit is restricted to the a-vascular zone in the retina.

The computer mouse is used as the response device and the results are stored to a computer. In this test the subject should click once if one dot is seen and double-
click if two dots are seen. Since AMD is an age related disease and some of the subjects never worked with a computer mouse, the patients sometimes find it difficult to use the mouse as a response device, especially the principle of double-clicking. To overcome this, the test was only started when the subject practiced several times and after approval of the operator.

7.5 **CONCLUSION**

In conclusion, compared to a healthy control group, the Macubit hit rate was significantly lower for the patient group with signs of early AMD (p<0.001), while the visual acuity was not different. Consequently, the Macubit device can detect functional losses that cannot be detected by a visual acuity chart and could therefore be an efficient tool to detect early AMD and monitor treatment effects in that stage.

7.6 **REFERENCES**