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A simple video-based system for examining irregularities in very slow, smooth-pursuit eye movements in cancer patients

Ein einfaches Videosystem zur Untersuchung der Irregularitäten langsamer Augenfolgebewegungen bei Krebspatienten

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Abstract

Subjective observations made during routine examination of eye movement functions (orthoptic status) reveal that very slow, smooth-pursuit eye movements in cancer patients are irregular. To objectively measure such movements, a video-based system was built to allow analysis of very slow, smooth-pursuit eye movements (1.8°/s). Analysis involves quantification of drift and jerk-like gaze movements that cause deviations in gaze direction from the predicted trajectory. Gaze deviations observed in cancer patients are compared to those for the normal population. Our results show that deviations are more important in cancer patients than in the normal population. The difference is statistically significant ($p<0.05$) for deviations ranging between 0.75° and 1.75°. In the future, the system may possibly be used in the diagnosis of cancer.

Keywords: cancer; smooth-pursuit eye movements; video oculography.

Zusammenfassung

Aufgrund orthoptischer Untersuchungen besteht die Vermutung, dass bei Krebspatienten Unregelmäßigkeiten in langsamen Augenfolgebewegungen auftreten, die bei einer Normalpopulation nicht oder nur geringfügig zu beobachten sind. Um die Vermutung mit objektiven Methoden zu untersuchen, wurde ein Videosystem entwickelt, mit dem langsame Augenfolgebewegungen (1.8°/s) registriert und bezüglich Unregelmässigkeiten ausgewertet werden können. Die Auswertung betrifft im Wesentlichen die Quantifizierung von Abweichungen der Blickrichtung zur vorhergesagten Blickrichtung bei langsamen Augenfolgebewegungen. Untersuchungen mit dem entwickelten System zeigen, dass Abweichungen zwischen 0,75° und 1,75° bei Krebspatienten signifikant ($p<0{,}05$) häufiger auftreten als bei der Normalpopulation. Das System könnte in Zukunft für die Diagnose von Krebs von Bedeutung sein.

Schlüsselwörter: Augenfolgebewegungen; Krebs; Video-Okulographie.

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Introduction

Eye movements are studied in many fields, ranging from more applied issues, such as marketing, to basic science aimed at understanding processes in the brain [2, 3].

Four types of eye movement are known: smooth pursuit, saccades, vergence and vestibulo-ocular reflex movements. Smooth-pursuit eye movements are found when an observer visually tracks a smoothly travelling object in a fronto-parallel plane. The velocity of the eye movement during smooth pursuit increases linearly with the target velocity. For velocities between 10 and 90°/s, the smooth-pursuit velocity follows the target velocity with a slope of 0.9 and reaches a maximum velocity of approximately 100°/s [10]. When there is a need to resolve small details, the eye must be oriented to focus details onto the fovea. Since the acquisition of visual information requires some time, in a first approximation the detail must be kept stationary on the fovea. This process is called fixation. Reading or scanning a scene is accomplished by a series of fixations followed by a rapid dislocation of fixation, a so-called saccade. The maximum speed of horizontal saccades can be modelled as an asymptotic exponential function with a peak at 520°/s [1]. Vergence movements are conjugated or disconjugated eye movements used to change fixation in depth. The maximum velocity of vergence eye movements is approximately 200°/s [5]. Eye movements may be triggered or synchronised with visual and vestibular input (vestibular-ocular reflex) to stabilise the retinal image. For instance, optokinetic nystagmus occurs when gazing at stripes on a rotating cylinder.

During prolonged fixation the eye is not at complete rest, but performs small saccades, so-called microsaccades, and drift movements. As cited elsewhere [6, 12], microsaccades were reported as early as 1950 by Ratliff and Riggs. The amplitude of microsaccades varies with the experimental set-up, among other factors. An amplitude of approximately 0.2–1.1° with a typical frequency of ~0.1–5 Hz [12] is observed when the subject's head is fixed using a forehead and chin rest. When a bite bar is used, the amplitude recorded is two- to four-fold smaller [12]. Microsaccades have been studied using a fixed target. It is unclear whether the properties of microsaccades depend on the motion of the target.

Interestingly, little is known about very slow, smooth-pursuit eye movements. During assessment of orthoptic status, very slow, smooth-pursuit eye movements are stimulated by sweeping a finger at a speed of approximately 1–10°/s across the fronto-parallel field of gaze. An orthoptic examination also involves approximate detection of loss of fixation. Thus, two types of loss of fixation are of interest. In the first type, the patient is not able to fixate the target beyond a given range in the field of gaze. In the second type, fixation is lost only for a short period of time and correct fixation then returns. To catch up with the target, the eye performs a small saccade. Alternatively, the gaze varies in speed to re-establish proper fixation. The first type of fixation loss is easy to observe by eye. In contrast, detection of the second type of fixation loss depends on the experience of the examiner.

Given their wide range in speed and amplitude, different methods are required to investigate different types of eye movements. To the best of our knowledge, methods for studying very slow (1.8°/s) smooth-pursuit eye movements in humans have not been reported in the literature. In particular, we were not able to find any reports on the properties of very slow, smooth-pursuit eye movements in cancer patients.

Recording of slow, smooth eye movements in clinical practice was a major challenge 30 years ago. At that time, electro-oculography (EOG) was frequently used to record eye movements in clinical practice. Since EOG is an AC coupled method with a time constant of 1.5–2 s [11], determination of the exact position of fixation is a problem in very slow, smooth-pursuit eye movements. More adequate methods for this purpose are the scleral search coil (a coil placed on the eyeball) or video-based techniques, which have been shown to be equivalent in terms of precision [4]. The scleral coil method is not suitable for routine orthoptic examination since it is too obtrusive. Commercial video systems are thus more appropriate for recording slow, smooth-pursuit eye movements in patients. Digital camcorders, which are widely available and are inexpensive, can record video images digitally or/and transmit recorded signals digitally, making PC hardware for digitising analogue video signals superfluous. However, there is still a lack of methods for analysing video records to extract information about irregularities in slow, smooth-pursuit eye movements.

A recent attempt to detect slow eye movements (SEMs) was reported for a sleep research study. SEMs are defined, among other criteria, as sinusoidal excursions of 0.2–0.6 Hz lasting more than 1 s [7]. SEMs are detected by eye using a plot of recorded eye movements. The procedure is time-consuming and susceptible to important inter- and intra-scorer errors [7]. A wavelet-based technique may be used to overcome this problem in the future [7].

We developed a video-based system to assess gaze deviations from a predicted trajectory for very slow, smooth-pursuit eye movements (1.8°/s). The system requires a unit that generates a moving target, a video-based device for recording the pupil, a method for computing the gaze direction using video records of the pupil, and a method for quantifying gaze deviation from the predicted trajectory. The system was used to compare deviations for cancer patients with deviations for the normal population. This allows objective investigation of differences in deviation between normal subjects and patients.

Materials and methods

Slow-moving fixation target

The configuration used to produce a slow-moving fixation target is shown in Figure 1. The target was generated by projecting the beam of a red (670 nm) laser (Laser Modul 670 nm, LAS67/01-L, Conrad Elektronik AG, Wollerau, Switzerland) on a white wall using a scanner mirror (LSK 120E; Laser Scanning Kaiser AG, Stallikon, Switzerland). The scanning mirror is driven by a triangular wave with a period length of 55.2±0.55 s and was positioned 495 cm from the wall. The length of the trajectory (see a in Figure 1) of the red dot produced on the wall was 1.45±0.03 m. The observer viewed the red dot at a distance of 153 cm from the wall. The observer's head was fixed with a forehead and chin rest. The target appears to travel at a mean speed of approximately 1.8°/s. Since the dot travels in a fronto-parallel plane and the scanning mirror is driven at a constant angular velocity, the angular velocity perceived by the observer varies, depending on the position of the dot. Differences in the perceived speed of the dot in the sagittal plane and in the outermost position of the dot were computed by means of trigonometric calculations. The perceived speed varied by less than 22% and can therefore be neglected in this context.

Video recording unit

Gaze was recorded by tracking the pupils of the observer using video cameras placed slightly below the observer's

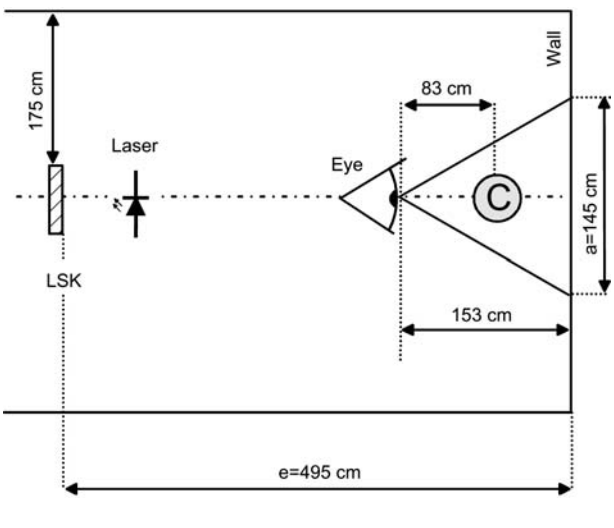

Figure 1 Experimental set-up for recording slow smooth-pursuit eye movements showing the position of the scanning mirror, the laser, the wall, the position of the observer's eye and the two cameras (C) used to record the pupils of the observer.

Frankfurt [8] plane at 83 cm from the eye. Two digital video camera recorders were used for this purpose. Video images of the left and right eyes were recorded using Sony DCR-PC100 and DCR-TRV125E cameras (Eschenmoser AG, Zurich, Switzerland), respectively. Separation between the two centres of the camera lenses was approximately 10 cm. By zooming, the image pane was adjusted to cover the full eye of the observer. Video recordings (25 frames/s) were stored digitally on the camera tape. After measurement, data were transferred via a digital-to-digital connection (iDV or IEEE1394) to a PC and stored in AVI format at a resolution of 768×576 pixels. The resolution was adapted to the total number of pixels of the charge-coupled device (CCD) of the cameras (690,000 for the PC100 and 400,000 for the TRV125E).

As reported below, calibration revealed a resolution of 0.5°/pixel. As previously shown [9], momentum analyses of the image of the pupil improve the resolution of the gaze direction recorded. We previously used a CCD of 500×582 pixels to record images of the pupil, with the unit optics configured to record changes in gaze of 40° in the horizontal direction [9], representing optical resolution of approximately 0.08°/pixel. We also showed that for a pupil of 3 mm and one of 6 mm in diameter, momentum analysis improves the resolution to approximately 0.027° and 0.013°, respectively [9]. We can therefore assume that momentum analysis improves the resolution by a factor of three or more, depending on the number of pixels forming the area of the pupil. Thus, we assume that the method reported here allows for a resolution of 0.17° (per pixel) or better.

A halogen illumination source with two fibre optic light guides was used to illuminate the two eyes. To minimise glare, the visible spectrum of the illuminating light was reduced using an RG 630 edge filter with a cut-off at 630 nm (Schott, Mainz, Germany).

Determination of gaze direction by analysing video records

Videos recorded of the pupil were first stored digitally on tape then processed by computing the first momentum of the pupil using a purpose-built program. To reduce artefacts produced by this program, some parameters used by the program require manual adjustment, which represents a drawback in automatic analysis. However, adjustment of the parameters allows the system to cope with varying measurement conditions. In our case, for instance, recordings of smooth-pursuit eye movements were carried out in a room partially illuminated by varying daylight. The quality of the pupil image therefore varied, depending on the amount of daylight and on the amount of bright objects reflected in the patient's eye. Parameters requiring manual adjustment include the contrast enhancement of the red channel, the threshold luminance for pupil detection and the number of passes for recursive computation of the momentum, as explained below.

Since the eye is illuminated by red light, the contrast of the pupil image is enhanced by giving the red channel an advantage over the green and blue channel. Amplification of the red channel is manually selected by visually comparing the resulting pupil image with the original. Amplification values of 3 (70%), 2 (7.5%) and 1 (22.5% of cases) were used in the present study.

Threshold luminance refers to the luminance *Y*, which is computed according to the National Television System Committee (NTSC) standards for the transformation of *RGB* to *YUV* coordinates, by weighting the *RGB* values as follows:

$$Y=0.299\times R+0.587\times G+0.144\times B.$$

The image of the pupil is converted into a 1-bit image using the threshold luminance *Y*. Conversion involves setting to 1 the value for pixels darker than or equal to the threshold and setting to 0 the value for pixels brighter than the threshold. The momentum of resulting 1-bit image is computed for the *x* and *y* coordinates.

In the case of ideal pupil detection, the number of pixels with a value of 1 is proportional to the area of the pupil. This relation is used in recursive computation of the first momentum to reduce artefacts resulting from dark spots appearing outside the pupil. The initial estimate of the first momentum is used as the centre of a square. The edge of the square is set to twice the diameter of a circle with an area corresponding to the number of pixels with a value equal to 1. The first momentum of the image is re-computed after discarding pixels outside the square. The number of passes for which this procedure is repeated is manually selected. Except for one case, the number of passes was set to 1 for all evaluations reported below.

Finally, a cross is plotted within the original image of the pupil at the position found for the first momentum. Single images including the cross are concatenated and saved as a movie that can be visually checked for possible artefacts.

Quantification of deviations in fixation

The program used to determine the gaze direction analyses the video frame by frame and generates a file that includes the frame number, the *x* and *y* coordinates of the first momentum of the pupil in each frame, and the total number of pixels below the threshold in each frame. In a few frames, momentum detection fails and an artefact is produced. For instance, when the eyelid is shut, the pupil is not detected. In such a case, the computed first momentum deviates significantly from the momentum detected in the previous frame. To eliminate such artefacts, the change in gaze direction is limited to 50° per frame, corresponding to 1250°/s if a rate of 25 frames/s is considered. Outliers are replaced using the coordinates of the first momentum detected in the previous frame. Replacing an outlier using the average for neighbouring frames was considered inadequate because this method would fail in the case of two consecutive outliers.

The method for detecting deviations in fixation is based on two subjective observations made during patient examination. First, the eye may cease centrally fixating the smooth travelling target for a short time and then resume normal fixation. Second, loss of fixation appears to be caused by drift movements and microsaccades. We estimate that under such circumstances a velocity criterion would fail to detect small deviations in gaze from the predicted position. Therefore, we detected deviations by comparing the actual gaze direction with the gaze direction resulting from linear fitting of the data. If the absolute difference between the actual gaze direction and the predicted direction is greater than or equal to the threshold, then the actual direction is classified as departing from the fitted direction. The total number of frames in which gaze is found to depart from the fitted direction is taken as a measure of gaze deviation during the smooth-pursuit eye movement task. Data were analysed using different thresholds ranging from 0.25° to 2.25° in steps of 0.25°.

A moving window was used for linear fitting of recorded data. This technique has two advantages compared to fitting of the whole pursuit in one direction using a straight line. First, geometric distortions of the trajectory of the fixation target are better taken into account by a moving window compared to linear fitting of the whole pursuit in one direction. Second, there is no need to identify points of reversal during pursuit.

In proximity to points of reversal during pursuit, the linear fitting method generates a bias. It can be shown that in proximity to points of reversal, the slope for smoothed data is half the value of the slope for the original data in a first-order approximation. Therefore, the bias increases with time at a speed of half the slope of the original data. Assuming a slope for the original data of 1.8°/s, a given size of the moving window and a given threshold for classifying data as departing from the predicted trajectory (see above), we can compute the number of frames in which data are classified as departing from the predicted trajectory due to bias. The results in Table 1 are based on the first-order approximation described above and the exact number of frames is lower than the values reported in Table 1.

Experimental procedure and calibration

Before eye movements were recorded, subjects underwent a standard vision test including acuity, stereopsis and amplitude of accommodation, as well as a standard assessment of the orthoptic status. This included examination of near and far binocular fixation, assessment of the near point of binocular fixation and further checks of binocular motility.

After these tests, the subject's head was fixed in the forehead and chin rest. A bite board was considered too obtrusive in our circumstances. Subjects were instructed to fixate on the red dot on the wall as precisely as possible. In the first step, the instrumentation was calibrated. For this purpose the dot was displaced between the two end points of the trajectory by means of a rectangular function.

After calibration, the dot was moved using a triangular function. Subjects were asked to continue fixating on the dot. When the dot approached one of the endpoints of the trajectory, subjects are alerted that measurement was going to start. The examiner signalled the start of the measurement verbally as soon as the dot appeared at the corresponding endpoint of the trajectory. After approximately 56 s (one period) the dot appeared again at the endpoint of the trajectory and the experimenter signalled the end of the measurement.

To determine conversion between the coordinate of the first momentum of the pupil image, which is expressed in pixels, and the gaze direction, expressed in degrees, momentum values assessed during the calibration were analysed statistically. For this purpose, a histogram of the coordinate of the first momentum was plotted for each

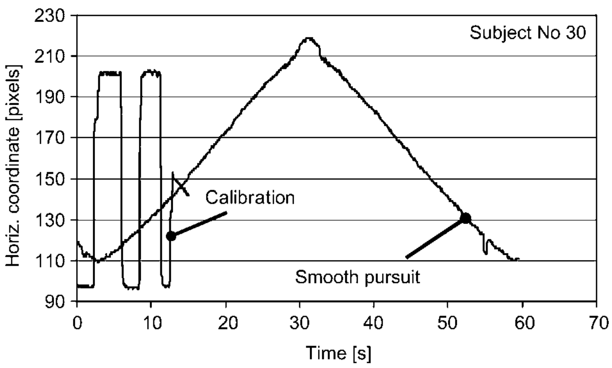

Figure 2 Horizontal direction of gaze during calibration (rectangular function) and during smooth-pursuit eye movements (triangular function).
The gaze direction is expressed in pixels as a function of time. Pixels refer to the horizontal coordinate of the first momentum, which was computed using the pupil image.

Table 1 First-order approximation of the effect of the moving window size on the number of frames in which the first momentum departs from the correct position by a given amount (threshold).

Moving window size (s)	Number of frames								
	Threshold								
	0.25°	0.5°	0.75°	1.0°	1.25°	1.5°	1.75°	2.0°	2.25°
0.25	0	0	0	0	0	0	0	0	0
0.5	11	0	0	0	0	0	0	0	0
1	36	22	8	0	0	0	0	0	0
2	86	72	58	44	31	17	3	0	0
4	186	172	158	144	131	117	103	89	75
8	386	372	358	344	331	317	303	289	275

The correct number of frames is less than the number reported in the Table. Data denote the number of frames in which the deviation is at least as large as the threshold for a gaze speed of 1.8°/s.

calibration record. The two most frequent coordinates were identified as corresponding to the gaze direction when fixated on the red dot while at the left and right endpoints (see Figure 2). Conversion was computed by taking the ratio between the amplitude of the red dot as seen from the observer's position in degrees and the difference between the two most frequent coordinates in pixels.

Subjects

Subjects were recruited from patients and personnel of Glarus Hospital and their acquaintances. Subjects were informed about the purpose and risks of the study and on the anonymous data management involved. After being told that they were free to leave the study at any time without personal consequences, subjects were asked to give informed consent to participate in the study. Subjects were not rewarded.

A total of 40 subjects took part in the experiment, 16 of whom (8 females) were patients with a diagnosis of cancer. Details of the cancers are listed in Table 2. Patients were selected based on organisational criteria. Among the patients there were six carcinomas of the gastrointestinal tract, four breast carcinomas, two lymphomas, two lung carcinomas, one ovarian carcinoma and one prostate carcinoma.

The patient age ranged from 27 to 75 years, with a median of 50 years and quartiles of 45 and 57 years. Binocular decimal acuity (Landolt ring, 5 m) in this group ranged from 0.4 to 2.0, with a median of 1.0 and quartiles of 0.7 and 1.4, respectively. The normal population consisted of 24 subjects (12 females) who were hospital staff members or acquaintances of the patients or staff who declared that they were healthy. The age of these healthy subjects ranged from 18 to 79 years, with a median of 51 years and quartiles of 43 and 59 years. Binocular decimal acuity in this population ranged from 0.5 to 2.0, with a median of 1.26 and quartiles of 0.89 and 1.44, respectively. A Mann-Whitney U-test revealed no significant difference between the two groups for either age ($p=0.881$) or binocular acuity ($p=0.503$). Further details of the vision testing and orthoptic status will be reported elsewhere.

Table 2 Pathological background and age of the cancer patients.

Case	Cancer	Age (years)
1	Breast carcinoma	39
2	Breast carcinoma	46
3	Colon carcinoma	50
4	Breast carcinoma	63
5	Colon carcinoma	63
6	Carcinoma of the ovaries	53
7	Non-Hodgkin's lymphoma	54
8	Breast carcinoma	46
9	Carcinoma of the lung	27
10	Colon carcinoma	55
11	Carcinoma of the lung	75
12	Carcinoma of the oesophagus	50
13	Carcinoma of the rectum	58
14	Prostate carcinoma	43
15	Colon carcinoma	47
16	Hodgkin lymphoma	45

Results

Since sound was always recorded on the video tape and since the experimenter verbally commented on all steps during measurements, manual extraction of single sequences for calibration and measurement was easily accomplished. Figure 2 shows a plot of the horizontal gaze direction for one subject recorded during calibration and during measurement. The vertical shift in range between the calibration and the measurement data is due to an offset produced by the function generator used to drive the mirror scanning the red spot on the wall.

The mean duration of the sequences analysed for our 40 subjects was 57.9 ± 5.1 s, which is approximately 2 s longer as the mean trajectory of the red dot.

Individual data on gaze direction as a function of time were plotted and visually inspected. For some of the data, the gaze direction appeared to be constant. By comparing the computed gaze direction with the video, we were able to identify this phenomenon as an artefact. Data sets for which the gaze direction appeared to be constant (slope = 0) for more than 5% of the duration of the analysed sequence were rejected. Thus, three data sets for the right eye (subjects 3, 17 and 25) and five sets for the left eye (subjects 11, 12, 16, 28, 32) were discarded.

As reported above, in frames in which the first momentum could not be detected, the first momentum was taken from the previous frame. In our data this occurred for 100 frames, representing an average of 1.25 frames per eye. The number of frames that could not be detected in patients and healthy subjects were compared by Mann-Whitney U-test: there was no significant difference in the number of frames not detected between the two groups ($p=0.469$).

In a first step, we will compare the amount of detected deviations in our two groups based on data fitted using a 2-s moving window.

The number of frames in which the actual gaze direction departed from the fitted direction is plotted in Figure 3 as function of the threshold (0.75° to 2.25°) determining the deviation for the left and right eye separately.

For each threshold, median numbers of frames detected in the two groups were compared using the Mann-Whitney U-test. The results are listed in Table 3. It is evident from Table 3 that the number of frames above the threshold differed significantly ($p<0.05$) between patients and healthy subjects for thresholds between 0.75° and 1.75°. We can therefore state that deviations in gaze direction from the predicted trajectory in very slow, smooth-pursuit eye movements are more frequent in patients than in healthy subjects.

Comparing median values in Figure 3 with bias computed generated due to the moving window fitting technique (see Table 1, first order approximation of number of frames above threshold due to bias) we can conclude that in healthy subjects, deviations approach the size of

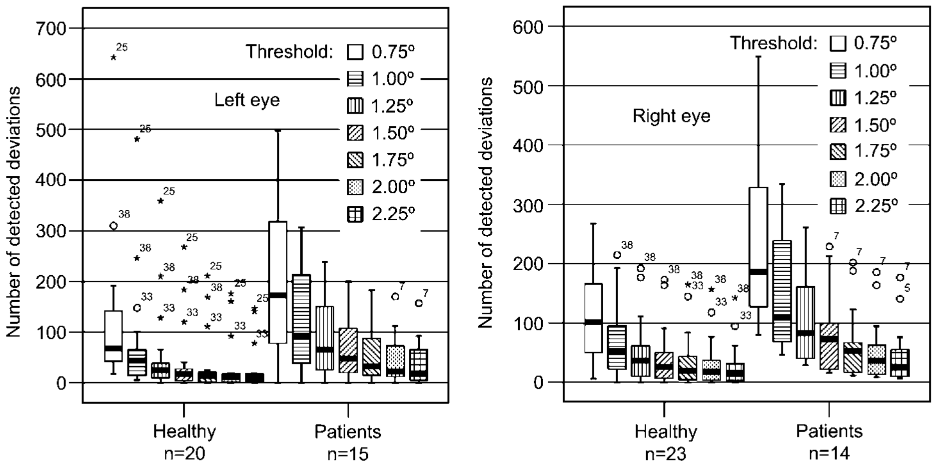

Figure 3 Boxplot representation of the number of frames in which deviations of actual gaze direction from the fitted direction were detected.
The left panel refers to the left and the right panel to the right eye. The left-hand group in each panel refers to data for healthy subjects. Circles and asterisks denote outliers and are labelled with the number of the subject. Medians (bold line within the box) for healthy subjects and patients differ significantly for thresholds between 0.75° and 1.75° (see Table 3).

Table 3 Mann-Whitney U-test results for comparison between healthy subjects and patients of the number of frames above the threshold for deviation of gaze direction from the predicted trajectory.

	Healthy subjects (n)	Patients (n)	Probability p						
			Threshold						
			0.75°	1.00°	1.25°	1.50°	1.75°	2.00°	2.25°
Right eye	23	14	0.002	0.002	0.005	0.010	0.022	0.057	0.088
Left eye	20	15	0.043	0.055	0.033	0.036	0.033	0.074	0.158

the bias. In contrast, deviations in patients are about twice as important as the bias.

The evaluation reported above was also carried out for data fitted using moving windows of 8 s, 4 s and 1 s. The number of deviations detected differed significantly between the two groups for all thresholds (0.75°–2.25°) when using the 8-s and 4-s windows. For the 1-s window, significant differences were only found for thresholds of 0.75° and 1°. We therefore believe that in our case a window size of 2 s is optimal for fitting data on very slow, smooth-pursuit eye movements.

Discussion

As shown experimentally, we developed a method to allow objective quantification of a phenomenon reported for cancer patients performing very slow, smooth-pursuit eye movements.

The correlation of the phenomenon with the illness raises the question as to whether the phenomenon is due to medication, to hospitalisation in general or is more directly related to the illness. If the latter is true, analysis of very slow, smooth-pursuit eye movements might contribute to cancer diagnosis. A small amount of equipment is required to perform measurements: a video camera, a forehead and chin rest, a light source used to improve pupil illumination, and a device used to generate a smooth-travelling fixation target. If the room illumination can be controlled, a light source to illuminate the pupil is not required. The fixation target can be produced by video projection of a computer-generated target. Therefore, the equipment required can be reduced to a video camera, a forehead and chin rest, a PC and a beam, all of which are easily available at a moderate price. It is possible to record both eyes using a single video camera, which again reduces the complexity of the system. Recording of both eyes is not even necessary, as it has been shown that differences between healthy subjects and patients are statistically significant for each eye separately for a threshold between 0.75° and 1.75° (Table 3).

Subject perturbation by the instrumentation is considered to be small, which is an advantage over other methods used to investigate eye movements objectively. The advantage is a particular benefit for patients exposed to frequent clinical tests involving technical equipment.

To reduce artefacts due to variations in illumination settings, manual adjustment of only three parameters of the video analysis software is required. Since the effect of such adjustments is displayed online, the adjustment procedure is fast and easy.

Some assumptions have been made for predicting the trajectory of smooth eye movements. In particular, the size of the moving window for smoothing is a factor that controls the experimental outcome. By varying the size of the window and considering a speed of 1.8°/s, we were able to determine an optimal window size of 2 s.

It is hoped that further research work will confirm that the method can be used as a tool in early cancer diagnosis.

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