SACCADES OF THE EYE AND EYELID;

CLINICAL APPLICATIONS

SACCADES VAN HET OOG EN OOGLID;

KLINISCHE TOEPASSINGEN

PROEFSCHRIFT

ter verkrijging van de graad van Doctor
aan de Erasmus Universiteit Rotterdam op gezag van de
Rector Magnificus, Prof.dr.ir. J.H. van Bemmel

en volgens besluit van het College voor Promoties
de openbare verdediging zal plaatsvinden op
woensdag 28 november 2001 om 11.45 uur

door

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geboren te Tilburg

Promotiecommissie

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Zoals de omslag symbolisch weergeeft is wetenschap bedrijven als het aanvangen van een reis, waarvan je weet dat hij eens eindigen zal maar niet weet hoe en waar. Het is vergelijkbaar met de ontdekkingstochten van weleer. Met de sextant wordt de koers uitgezet.

Aan Monique
Aan Julius, Anoushka, Emely
Aan mijn ouders

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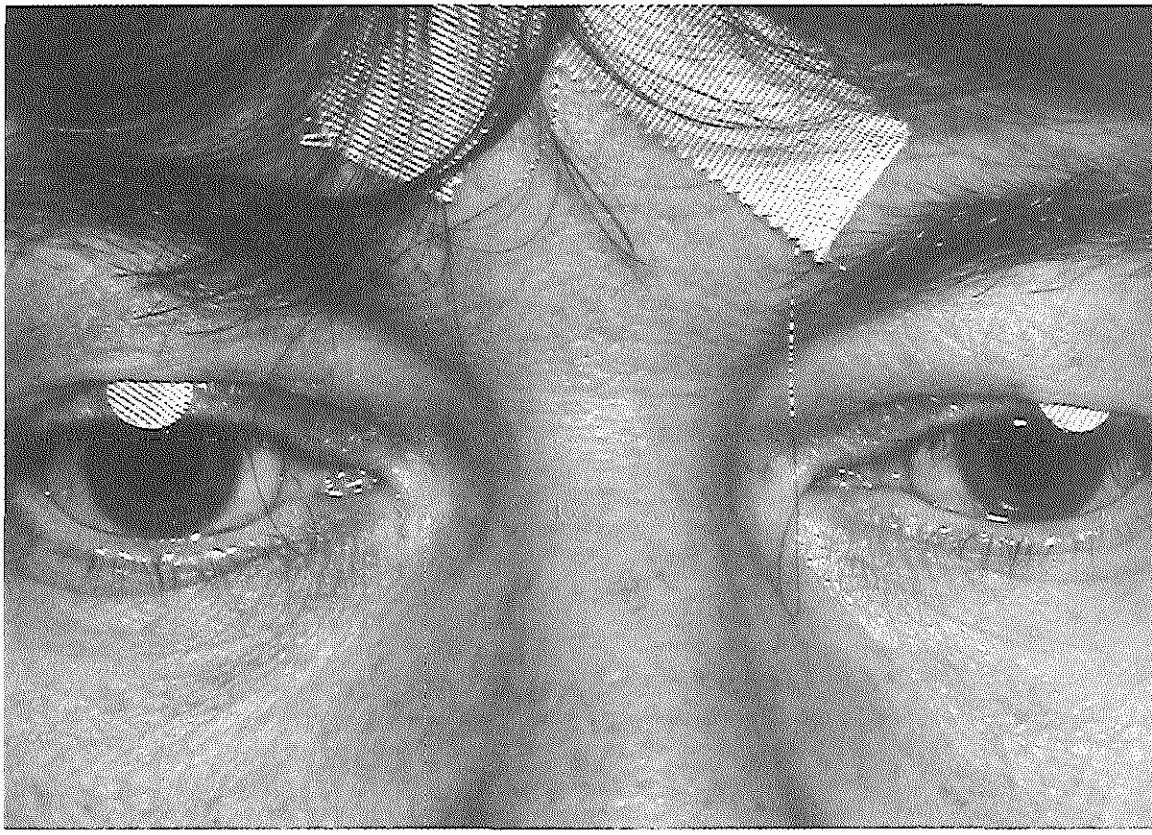
CHAPTER 1

INTRODUCTION



1.1 Saccades of eye and eyelid

The word "saccade" originally related only to the rapid eye movements which serve to direct gaze from one visual target to the other. Saccades are, therefore, refixation movements that place a new object of interest on the fovea. Becker and Fuchs *(1988)* coined the term "lid saccades" for eyelid movements that accompany vertical eye saccades, because of the similarities in metrics between eye and eyelid saccades. For upward saccades, such closely related movements might have been expected because the levator palpebrae muscle is derived embryologically from the superior rectus muscle *(Gilbert, 1957)*. Both muscles share a common sheath, and are innervated through the superior division of the oculomotor nerve *(Miller, 1985)*. There is a basic difference, however, between the control of saccadic movements of the eye and the eyelid. Whereas each external eye muscle has an antagonist, it seems that the levator palpebrae muscle acts independently during vertical gaze shifts *(Becker and Fuchs, 1988; Evinger et al., 1984; Evinger et al., 1991)*. Since the levator palpebrae muscle has no actively contracting antagonist, downward lid saccades are thougt to result from passive forces in the surrounding tissues, i.e., the canthal ligaments, and the orbicularis oculi muscle, assisted by the rotating eye *(Kennard and Smyth, 1963; Sibony et al., 1991; Guitton et al., 1991)*. Gravity is not necessary for downward lid displacement because the lid also closes when subjects are standing on their heads *(Sewall, 1933)*. EMG studies of the orbicularis oculi muscle have failed to document any signs of activity during downward directed lid saccades *(Evinger et al., 1984; Niida et al., 1987)*. Furthermore, lid saccades in patients with impaired orbicularis oculi function, as in facial nerve palsy, appeared normal *(Sibony et al., 1991)*. Yet, it is difficult to explain the existence of downward lid movements with saccadic dynamics if they were invoked only by passive elastic forces. The mechanical coupling between the globe and the lid on downward gaze probably plays a small role, if any, in the lid metrics. Taping the lid away from the globe had no effect on saccadic eye velocity *(Collewijn et al., 1985)*.

1.1.1 Velocity

It is known from the literature that eye saccades have remarkably stereotyped characteristics. *(Boghen et al., 1974; Bahill et al., 1975; Collewijn et al., 1988a, b)* They are fast, accurate, follow a main sequence *(Bahill et al., 1975)*, and show good conjugacy *(Lemij and Collewijn, 1991, Kapoula et al., 1989)*. The main sequence provides a consistent relationship between the peak velocity and the size of the movement. It was first described by Bahill et al. *(1975)* and shows that the velocity increases in relation to the distance travelled. However, if the target amplitude increases beyond approximately 40°, saccadic peak velocity saturates. Eye saccadic peak velocity in normal subjects falls within a relatively limited range, whith values up to 600°/sec. *(Westheimer, 1954; Boghen et al., 1974; Bahill et al., 1975; Baloh et al., 1975; Collewijn et al., 1988a, b; Yee et al., 1985)*. Most of these data relate to horizontal saccades only *(Boghen et al., 1974; Bahill et al., 1975; Baloh et al., 1975)*. Less is known about the peak velocity amplitude relationships of vertical

saccades *(Collewijn et al., 1988b)*. This difference is primarily due to the inability of commonly used eye movement recording techniques, such as electrooculography (EOG), and infrared limbus tracking methods (IR), to accurately record vertical eye movements. Electrooculography is particularly questionable for vertical movements of the eyes because of the effects of the concomitant movements of the lids: upward saccades have peaked, overshooting trajectories *(Ford, 1959)*. In vertical recordings with the infrared limbus tracking method, on the other hand, the eyelashes can obscure the limbus superiorly and inferiorly. Yee and his colleagues *(1985)* applied the search coil method, which proved the most accurate recording method in their study for vertical saccades, compared to the other two, i.e., EOG and IR, methods.

Becker and Fuchs *(1988)* investigated lid-eye coordination with the search coil method. Concurrent lid and eye saccades in the downward direction had similar velocities, but lid saccades were slower than eye saccades in the upward direction. Evinger et al. *(1991)* similarly found that, for most amplitudes, downward lid saccades tended to be faster than upward lid saccades, although at large amplitudes, the reverse appeared to be true, probably due to the saturation of lid saccadic peak velocity. Guitton et al. *(1991)* provided a database of the kinematics of lid saccades. Lid velocities in the up and down direction were similar and increased nonlinearly with amplitude, saturating at approximately 450°/sec.

Starting lid position can be quite different between two successive recordings *(Becker and Fuchs, 1988)*, and have an effect on lid saccadic peak velocity. In blinks, by contrast, maximum velocity was independent of the starting lid position *(Guitton et al., 1991)*. Evinger et al. *(1991)*, observed that downward lid saccades frequently overshoot their target. Many blinks tend to occur preferentially during saccades *(Evinger et al., 1984)*. The probability that a blink occurs increases with the size of the gaze shift *(von Cranach et al., 1969; Watanabe et al., 1980; Evinger et al., 1991)* For blinks of equal size, the maximum velocity of the down phase is slightly more than twice as high as the maximum velocity of the up phase. For example, a 30° down-phase typically achieves a maximum velocity of 840°/sec and the same amplitude up-phase attains a maximum speed of 400°/sec *(Evinger et al., 1991)*. In our recordings, *(Wouters et al., 1995)* transient overshoots of the eyelids were observed mostly in downward saccades and more frequently at larger target amplitudes. In the analysis of downward lid measurements one difficulty is the potential confusion between saccade-related lid movements and blinks. Blinks are accompanied by characteristic horizontal converging eye movements *(Collewijn et al., 1985)*. In chapter 2 we show that during the transient overshoots of the eyelids, such disjunctive horizontal eye movements were not observed *(Wouters et al., 1995)*. If, in the analysis of lid saccadic recordings, blinks are mistaken for an integral part of the lid saccade, i.e., the transient overshoot, downward lid velocities are overestimated. In our analysis the software was adjusted to interpret the recordings correctly.

1.1.2 Conjugacy

To maintain binocular fixation, saccades of the two eyes are well yoked, within limits. In other words, they are conjugate *(Lemij and Collewijn, 1991, Kapoula et al., 1989)*, following Hering's classical law of equal innervation *(Hering, 1868)*. In horizontal saccades, the abducting eye initially achieves a higher velocity than the adducting eye, which leads to a transient intrasaccadic divergence. During vertical saccades, which are virtually identical in the two eyes, disjunctive horizontal components were systematically present *(Collewijn et al., 1988b)*. The saccadic size differences were, on average, about 0.1° (SD = 0.5°) for horizontal saccades and about 0.1° (SD = 0.3°) for vertical saccades *(Lemij and Collewijn, 1991)*. Similarly, such almost perfect yoking has been found in normal subjects by Collewijn et al. *(1988b, c)*.

There is limited information regarding the symmetry of movement of the two eyelids. Conjugacy of eyelid movement would ensure protection of both eyes when the trigeminal pathway from either eye is stimulated, as in the blink reflex. Findings in several clinical conditions indicate the existence of bilateral coordination of eyelid movements *(Gay et al., 1967; Schechter, 1978)*. Neuroanatomic studies in primates have shown that the motor neuronal pool for both levator palpebrae muscles lies within the unpaired central caudal oculomotor nucleus *(Fuchs et al., 1992; Warwick, 1953; Porter et al., 1989)*. Stava et al. *(1994)* provided quantitative data on the conjugacy of spontaneous blinks. Becker and Fuchs *(1988)* reported similarities in the main sequences for the two eyelids, but furnished little detailed information on the conjugacy of lid saccades. In Chapter 2 we provide insight into this conjugacy of lid saccades. They were less conjugate than eye saccades. Nonconjugacy of lid saccades averaged approximately 8% of the target amplitude. This quantitatively large nonconjugacy of lid saccades excludes the use of bilaterally recording lid saccades to investigate a unilateral disease, as was done by Sibony et al., *(1991)*. In their study on patients with a unilateral facial paralysis, the lid saccades in the affected eyelid were consistently smaller and showed a lower velocity compared with the contralateral unaffected eyelid, which occurred idiosyncratically among subjects in our study *(Wouters et al., 1995; Chapter 4)*.

1.2 Method for recording saccades of the eye

The measurement of eye movements has evolved from rather insensitive methods, such as photoelectric viewing, to the current state-of-the-art method used in our experiments, i.e., electromagnetic recording. An ideal system would be able to measure rotations of the globe, yet be completely insensitive to translational movements. The device must not interfere with vision, and must not require the attachment of anything to the eyeball. It must either be unaffected by movements of the head. Sensitivity to head movements arises because of the marked curvature of the cornea: if it were replaced with a plane reflecting surface, it would become

essentially insensitive to small translations. In practice this means fitting the eye with a contact lens assembly that has a small plane mirror mounted on it – a technique first attempted by De La Barre in 1898. The use of contact lenses can cause some discomfort to the subject. Any attachment to the human eye adheres by surface tension to the mucous conjunctiva. Relatively little slip occurs when the attached device is used to measure small movements of an open eye, but a lid artifact of unknown amplitude may occur when the upper lid sweeps down over it during a blink. And a normal blink will also destabilize an eye tracker when first the lashes and then the upper lids occlude the infrared beam that is used to plot the eye movements. Barlow *(1963)* has shown that the scleral-fitting contact lens allows appreciable slip even when the subject is trying to hold his eye steady. The Yarbus-type lens *(Yarbus, 1967)*, which is held to the eye by suction, reduced slippage by a factor of four or five. When larger movements of the eyes are executed, quite large errors can develop as backlash, for example, some 6° of lag after a 9° saccade *(Byford, 1962)*. It seems probable that individual variations in the fitting and use of contact lenses produce significant differences in their adhesions to the eye. Contact lens methods therefore seem unsuitable for the accurate measurement of eye movements when saccades of a natural extent are permitted.

No system has yet been devised that meets all above conditions, and the experimenter must choose the method that is most appropriate for the kind of investigation that he or she wishes to make. I will describe in some detail the electromagnetic recording method we used to record the movements of both the eye and eyelid.

1.2.1 Electromagnetic recording

A uniform alternating magnetic field induces an alternating voltage in an eye coil, the amplitude of which is proportional to the sine of the angle between the plane of the eye coil and the direction of the magnetic field. This signal can be amplified and then phase-detected with respect to the magnetic field, and after low-pass filtering, will provide a signal that corresponds to movements of the eye in the horizontal plane. With two alternating fields at right angles to each other, employed simultaneously, one being directed horizontally and the other vertically, the induced voltage is composed of the inductions by each magnetic field. If these magnetic fields are also 90° out of phase with each other, it is possible to break the alternating current potential recorded from the sensor coil down to its horizontal and vertical components. It is therefore possible to measure vertical and horizontal eye movements simultaneously. The eye coil can either be fixed surgically to the eye for chronic recording in animals *(Fuchs and Robinson, 1966)*, or be attached to a contact lens *(Robinson, 1963)*. Collewijn et al. *(1975)* fitted the coil in a soft scleral ring. This provides less inertia than a contact lens, however, a rise in intraocular pressure that may occur, after positioning, limits the period of time for which it may be safely worn. The method gives accurate and precise responses to eye movements. It is insensitive to translation, as long as the field is adequately uniform in space. The main source of error probably arises in the leads joining the eye coil to the amplifier, since they are liable to spurious induction. This error can be reduced by twisting the leads tightly together.

1.3 Method for recording saccades of the eyelid

Many different techniques have been used to measure the eyelid movements (blinks, saccades). In some, eyelid motion was transformed into the motion of an external device by a mechanical attachment (lever arm) between the eyelid and the device.These methods include the following systems: lever arm to potentiometer *(Kennard and Glaser, 1964)*; lever arm to moving light-emitting diode and photosensitive position detector *(Evinger et al., 1984)*; lever arm to search coil in magnetic field *(Collewijn et al., 1985)*. In other studies, the eyelid was not attached to an external device. These methods include: high-speed cinephotography *(Doane, 1980)*; changes in overall reflected light measured by a photocell *(Franks and Whithers, 1955)*. These techniques are cumbersome and difficult to use, particularly in a clinical environment. Becker and Fuchs *(1988)* employed a much more convenient technique. Eyelid motion was measured with a search coil in a magnetic field technique *(Robinson, 1963)*. The authors mentioned in passing that their technique was well suited to recording eyelid positions, although this was not demonstrated explicitly. In parallel studies published *(Evinger et al., 1991; Guitton et al., 1991)* the same technique was used. We applied their method, but first we validated the technique *(Wouters et al., 1995; Chapter 2)* which indeed turned out to be appropriate. This highly precise method, requiring no mechanical links between the eyelid and an external device, is simple to install, calibrate, and use. Lid saccades were recorded with handmade round search coils. Every such coil consisted of 50 turns of insulated copper wire (diameter 0.05 mm). A typical coil had an outer diameter of approximately 4 mm, weighed 15 mg, and was less than 0.5 mm thick. To reduce spurious induction, the leads of the coil were twisted together tightly. The coils were fixed on the lower part of the eyelid right above the pupil with a round piece of adhesive tape (diameter 6.5 mm). The magnetic search coil method is innocuous to patients, and the tiny coil causes virtually no restrictions to eyelid movement. This method offers an advantage over approaches that attach a lever arm to the eyelid to measure vertical lid motion *(Evinger et al., 1984; Kennard and Glaser, 1964; Snow and Firth, 1989; Kennard and Smyth, 1963)*. Unless placed with extreme care, lever arm systems can slightly impede eyelid movement. The advantages of the magnetic search coil over high-speed photography to measure lid movement *(Doane, 1980)*, are that a larger amount of data can be collected and rapidly analyzed for individual patients and that its temporal resolution is superior. Reflection techniques of monitoring lid movement measure neither rotation nor translation of the lid, but rather the area of the exposed eye or lid *(Holder et al., 1987; Niida et al., 1987)*. Calibration of these systems requires photographic analysis, and the results are not directly comparable to either rotation or vertical motion measures. Thus the eyelid coil method, which we validated and applied in our recordings, appears to be the best procedure for quantitatively examining saccadic lid movements.

1.4 Outline of the present thesis

This thesis describes the results of several experiments regarding eye and eyelid movements. The applied electromagnetic search coil method enabled us to investigate concomitant saccades of the eye and eyelid. Eye saccades have stereotyped characteristics, such as its conjugacy *(Lemij and Collewijn, 1991; Collewijn et al., 1988b, c)*, and its main sequence relationship, i.e., the relatively fixed relationship between saccadic amplitude and its peak velocity *(Bahill, 1975)*. Becker and Fuchs *(1988)* noted metrical similarities between the movements of the eye and upper eyelid. They therefore coined the term lid saccades. In addition, they assumed conjugacy of lid saccades based on main sequence similarities. However, concomitant lid saccades of each upper eyelid were not mutually compared.

In Chapter 2 we questioned the assumed conjugacy of lid saccades. Lid saccades were recorded bilaterally with a modification of the electromagnetic search coil technique. Several investigators *(Becker and Fuchs, 1988; Stava et al., 1994; Evinger et al., 1991; Guitton et al., 1991; Sibony et al., 1991)* applied the same technique, however, they never explicitly validated the method. We therefore validated the method (Chapter 2), which indeed turned out to be appropriate. Subjects hardly noticed the tiny coils on the upper eyelid, upward lid movements were probably not impeded by the lid coil, but most importantly, a linear relationship existed between eyelid position and recorded voltage in the measured range of the centrally positioned lid coil. In addition, we explored the effect of lid coil position on lid saccadic amplitude. The position of the lid coil turned out to be critical. We also investigated the conjugacy of lid saccades. Lid saccades proved to be considerably less conjugate than the associated, simultaneously recorded, eye saccades. Lid saccades turn into glissades more often than do eye saccades *(Becker and Fuchs, 1988)*, which might affect the accurate determination of the ending of a lid saccade. A glissade is a rather slow terminal movement and is the result of the eyelid settling to a new steady level of excitation. It arises from a mismatch between the pulse, which drives the eyelid to the new position, and the step, which will hold it there.

To avoid the possibly confounding effects of blinks made during vertical gaze shifts, we carefully monitored any horizontal eye movements. Blinks are accompanied by converging eye movements *(Collewijn et al., 1985)*. The differentation is important because the downphase of a 30° blink typically achieves a maximum velocity of 840°/sec *(Evinger et al., 1991)*, whereas downward lid saccades achieve a peak velocity of approximately 420°/sec *(Wouters et al., 2001; Chapter 4)*. With the adopted criteria for saccadic detection and analysis we proved in Chapter 2 that saccades of the two eyelids had similar durations and had their onset almost simultaneously. However, lid saccades were not as conjugate as eye saccades. Nonconjugacy averaged approximately 8% of the target amplitude.

Eye saccades are normally highly conjugate. In Chapter 3, we examined the conjugacy of eye saccades in patients with Graves' disease. One of the signs most consistently observed in Graves' disease is a restrictive myopathy of the rectus muscles *(Trokel and Jakobiec, 1981; Wiersinga et al., 1989; Hay, 1984; Jacobson and Gorman, 1984)*. Either rectus muscle of each eye may be affected, although the inflammatory changes are usually most severe in the inferior rectus muscle. If yoked muscles of the two eyes are unequally affected, this would probably change eye motility and more specifically, the conjugacy of eye saccades. However, under such conditions of muscular asymmetry, asymmetrical adaptive changes may occur in the oculomotor system to retain nonconflicting visual information to both eyes *(Viirre et al., 1988)*. Wouters et al. *(1998; Chapter 3)* showed the occurrence of nonconjugate saccades in patients with Graves' disease. We do not know whether adaptive mechanisms in the oculomotor system, as described by Viirre et al. *(1988)*, were active in this condition. The average value of nonconjugacy discriminated insufficiently between saccades in Graves' disease and control subjects. We improved the discriminating power considerably by including the maximum main sequence (V_{max}) velocity in the analysis. Patients with Graves' disease made saccades with a significantly lower V_{max} ($P < 0.05$) than the control subjects. Moreover, we found a rather large variability among patients with Graves' disease between the degree of saccadic conjugacy and the main sequence; either or both of these could be abnormal.

In Chapter 4, we investigated the metrics of lid saccades in blepharoptosis to distinguish any differences in the dynamics of eyelid movements in relation to the cause of blepharoptosis, and to aging. Distinctive differences in the metrics of lid saccades were found between the various forms of blepharoptosis. Age, however, did not play a significant role in dynamics of lid saccades.

In Chapter 5, we investigated the eye saccades in patients with Parkinson's disease. Characteristically, eye saccades in these patients frequently reach their target in multiple steps rather than in one or two *(Terävänen and Calne, 1980)*. In this study we explored the possibilities of discriminating patients with Parkinson's disease from controls by quantifying the phenomenon of saccadic multistepping in a newly derived multistepping index (MSI). We also used this MSI to monitor the effect of l-dopa substitution therapy in these patients. The MSI was found to discriminate well between patients and control subjects. In addition, a significant decrease in MSI occurred in patients with Parkinson's disease after the introduction of l-dopa therapy. However, the obtained MSI values were still higher than those of control subjects.

Finally, in Chapter 6 a summary of this thesis is presented.

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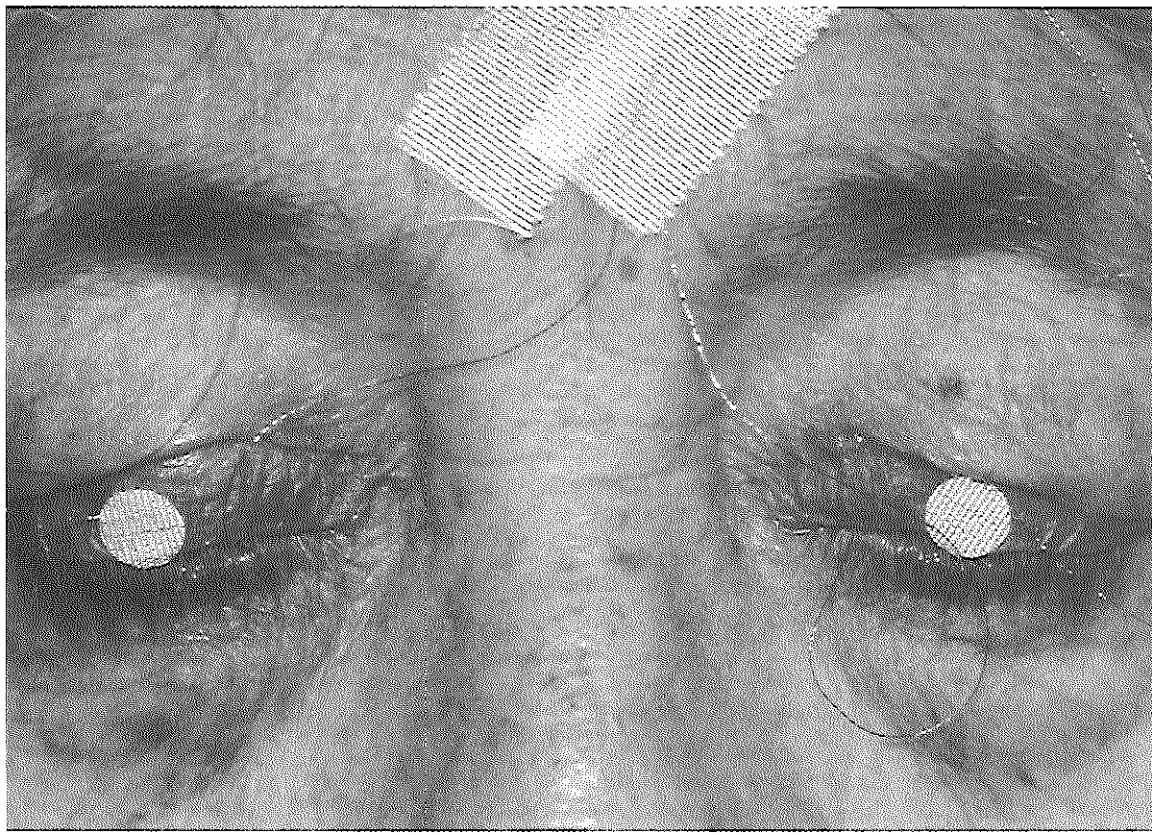
CHAPTER 2

CONJUGACY OF EYELID MOVEMENTS IN VERTICAL EYE SACCADES

INVEST OPHTHALMOL VIS SCI. 1995;36:2686-2694.



2.1 Abstract

Purpose.

To examine the conjugacy of lid saccades in normal subjects.

Methods.

Saccades of both upper eyelids were recorded simultaneously by means of small, lightweight, magnetic search coils, fixed on each lid. Subjects then made vertical eye saccades between fixed targets. The associated eye saccades were recorded simultaneously by means of magnetic search coils. The authors further examined whether the position of the lid coils affected the recordings.

Results.

Lid saccades were not as conjugate as their associated eye saccades. Nonconjugacy of lid saccades averaged approximately 8% of the target amplitude, irrespective of saccadic direction. By contrast, nonconjugacy of the associated eye saccades averaged approximately 1% of the target amplitude. Coil position significantly ($P < 0.05$) affected the recordings.

Conclusions.

Lid saccades are not as conjugate as their associated eye saccades. Coil position is critical for the recordings of lid saccades.

2.2 Introduction

Becker and Fuchs *(1988)* introduced the term lid saccades for eyelid movements accompanying vertical eye saccades because of the similarities in metrics between eye and lid saccades. However, some differences were observed. First, lid saccades turned into glissades more often than did eye saccades. Second, the lid position was not as stable as the eye position before and after a saccade. Third, lid saccades in the upward direction were often smaller and slower than the accompanying eye saccades *(Becker and Fuchs, 1988)*. In addition, Niida et al. *(1987)* found that the duration of upward lid saccades was approximately 70 msec longer than that of eye saccades.

Similarities between vertical eye and eyelid saccades can be related to their close anatomic and physiological relationships. The levator palpebrae muscle, involved in movements of the upper eyelid, is derived embryologically from the superior rectus muscle *(Gilbert, 1957)* involved in vertical eye movements. They share a common sheath, and both muscles are innervated through the superior division of the oculomotor nerve *(Miller, 1985)*. Furthermore, the premotor saccadic signals presumably come from a common source because the discharge patterns of levator and superior rectus motoneurons are similar *(Fuchs et al., 1992)*. This common source is considered to be located in the mesencephalic rostral interstitial nucleus of the medial longitudinal fasciculus *(Schmidtke and*

Buttner-Ennever, 1992). Neuroanatomic studies in primates have shown that the motor neuronal pool for both levator palpebrae muscles lies within the unpaired central caudal nucleus *(Fuchs et al., 1992; Warwick, 1953; Porter et al., 1989)*, which is an integral part of the oculomotor nucleus. There is a basic difference, however, in the control of sacccadic movements between the eye and eyelid: Whereas each external eye muscle has an antagonist, it seems that the levator palpebrae muscle acts independently during vertical gaze shifts *(Becker and Fuchs, 1988; Evinger et al., 1984; Evinger et al., 1991)*. In blinks, however, the levator muscle has an actively contracting antagonist: the orbicularis oculi muscle *(Evinger et al., 1984; Evinger et al., 1991)*.

Becker and Fuchs *(1988)* recorded upper eyelid movements by means of electromagnetic search coils. They fixed a lightweight magnetic search coil to one or both upper eyelids just above the eyelashes. This apparently did not influence the dynamics of the eyelid movements. The authors mentioned in passing that their technique was well suited to recording eyelid positions, although this was not demonstrated explicitly. We therefore validated their technique, which indeed turned out to be appropriate. We also assessed whether coil position on the upper eyelid affected the recordings and found that the positioning of the coils was critical.

Vertical eye saccades are conjugate *(Collewijn et al., 1988b; Lemij and Collewijn, 1991a)*. Saccadic size differences average approximately 0.1° (SD = 0.3°) *(Lemij and Collewijn, 1991a)*. Spontaneous blinks are also conjugate *(Stava et al., 1994)*. To our knowledge, however, the conjugacy of lid saccades has not been investigated in detail. Becker and Fuchs *(1988)* reported similarities in the main sequences for the saccades of the two eyelids in 2 of their 3 subjects. The main sequence relates to the relatively fixed relationship between amplitude, duration, and peak velocity *(Bahill et al., 1975)*. Based on these findings, Evinger et al. *(1991)* assumed a good conjugacy and restricted their recordings of eyelid movements to one upper eyelid. Sibony et al. *(1991)*, also implicitly assuming conjugacy in normal subjects, compared lid saccades between affected and unaffected eyelids in patients with a unilateral, isolated facial paralysis. The affected eyelid consistently made smaller saccades than the fellow eyelid. Guitton et al., *(1991)* recorded only one upper eyelid to provide normative data on main sequence relationships. We would argue, however, that similarities in main sequences for the two eyelids provide little detailed information on their conjugacy. Insight into this conjugacy may increase our understanding in the control of eyelid movements. We have studied this conjugacy by comparing the metrics of associated lid saccades between the two eyelids. Lid saccades were less conjugate than eye saccades.

2.3 Materials and Methods

Three experiments were conducted. In the first experiment, the eyelid recording technique was validated. In the second experiment, we examined the

effect of coil position on upper eyelid recordings. The conjugacy of vertical lid saccades was assessed in our third experiment.

The investigations adhered to the tenets of the Declaration of Helsinki and were approved by the institutional human experimentation committee. Informed consent was obtained from each subject after the nature of the procedures had been explained fully.

Recording technique and calibration

Eye and lid saccades were both recorded by the magnetic search coil technique *(Becker and Fuchs, 1988; Robinson, 1963; Collewijn et al., 1975)*. Lid saccades were recorded with handmade round search coils. Every such coil consisted of 50 turns of insulated copper wire (diameter, 0.05 mm). A typical coil had an outer diameter of approximately 4 mm, weighed 15 mg, and was less than 0.5 mm thick. To reduce spurious induction, the leads of the coil were twisted together tightly. The coils were fixed on the lower part of the eyelid right above the pupil with a round piece of adhesive tape (diameter 6.5 mm). Once the coils were attached, the subjects hardly noticed them. An impression of the lid coil on the lower part of the eyelid was noticed in all subjects after the experiment had ended. This was not observed in the skin fold. Eye movements were recorded with commercially available search coils (Skalar Medical B.V., Delft, The Netherlands).

The field frequency was 20 kHz. All recordings were amplified to a ±10V range, low-pass filtered at 120 Hz (-3 dB), digitized with 12-bit precision, and sampled at a frequency of 250 Hz. The recordings were stored on disk for off-line analysis. Signal noise level was less than 1.8 min arc. The recording equipment and search coils were calibrated before each recording session. Any misalignment of the coils was adjusted later, i.e., off line, by software. The accuracy of the calibration procedure was better than 0.5%.

Experimental procedures

Experiment 1: Validation of Eyelid Recording Technique. This validation experiment addressed the principles of the recording technique. Search coils only record rotations, not translations. The voltage induced in them is proportional to the angle of rotation, relative to the direction of the magnetic field. Therefore, if eyelid movements were perfect rotations, the position of the eyelid, as projected onto a frontal plane, would relate linearly to the recorded potential from an eyelid-fixed coil in case of a vertical magnetic field.

Eight subjects, three men and five women, between 26 and 32 years of age, participated in this experiment. During the experiment, the subjects were seated facing a stimulus screen, containing red light emitting diodes (LEDs), at a viewing distance of 40 cm. Head movements were restricted by a chinrest and forehead support. A ruler mounted in a frontal plane next to the upper eyelid concerned served as a calibration measure. The positions of the nine LEDs, along the mid-sagittal meridian, ranged between 35° above and 55° below the straight-ahead position. Subjects fixed the lit LEDs, one at a time, for 4 seconds, during which time eyelid positions (i.e., coils output voltage) were recorded. At the same

time, close-up photographs of the involved upper eyelid were taken in each position. These photographs were later projected with a 10-fold magnification. Eyelid position, relative to the ruler-scale, was then measured with a reproducibility of 0.1 mm.

Experiment 2: Effect of coil position. Five subjects, three men and two women, between 24 and 36 years of age, participated in this second experiment. None of them had any history of upper eyelid disease.

Three coils were mounted on the lower part of the left upper eyelid of all subjects. One coil was fixed right above the center of the pupil, and the other two were fixed on either side. At any time, all signals of the three lid coils were recorded simultaneously. Subjects faced a different stimulus screen than the one used in experiment 1. The LEDs were positioned along a mid-sagittal meridian, 10°, 20°, 30°, or 40° apart, symmetrically around the straight-ahead position. Head movements were restricted by a chin rest and forehead support. The viewing distance to the LED in the straight-ahead position was 1 m. Subjects were asked to alternate their gaze, on the mark of an electronically generated tone, at a frequency of 1 Hz between two lit LEDs. The four target amplitudes were presented in a randomized order. Each trial lasted 16 seconds. Before each trial, subjects could practise briefly.

Experiment 3: Conjugacy of Eyelid Movements. Ten subjects, four men and six women, between 20 and 46 years of age, served as subjects in our third experiment. Visual acuities were 20/20 or better for each eye in all subjects. None of them had any history of upper eyelid, ocular, or oculomotor pathology. To ascertain that binocular vision was present, stereopsis was assessed in these subjects, by means of the Titmus stereo test (inclusion criterion: 1 min arc or better). The experimental procedures were similar to those in experiment 2, but this time only one coil was attached to the lower part of each upper eyelid, right above the center of the pupil with straight-ahead gaze. To record the associated eye saccades, search coils were mounted on both eyes. Viewing was binocular at all times.

Data analysis

A computer program analyzed all recordings. Identical criteria were adopted for the detection of eye and lid saccades. Saccadic onset was detected if the acceleration exceeded 1000°/second^2 and the velocity exceeded 25°/second. Saccadic offset was detected by a deceleration of less than 1000°/second^2 and a velocity of less than 50°/second. Furthermore, lid saccades were included only if they occurred in conjunction with an eye saccade. For each detected eye and lid saccade, peak velocity, amplitude, and duration were determined. These data were analyzed further with a statistical software package, SPSS-X. Only primary eye saccades and the associated lid saccades were selected for analysis by an eye amplitude criterion (set at 75% of the target amplitude). Multivariate analysis of variance was used to test any observed differences between the fellow eyelids or

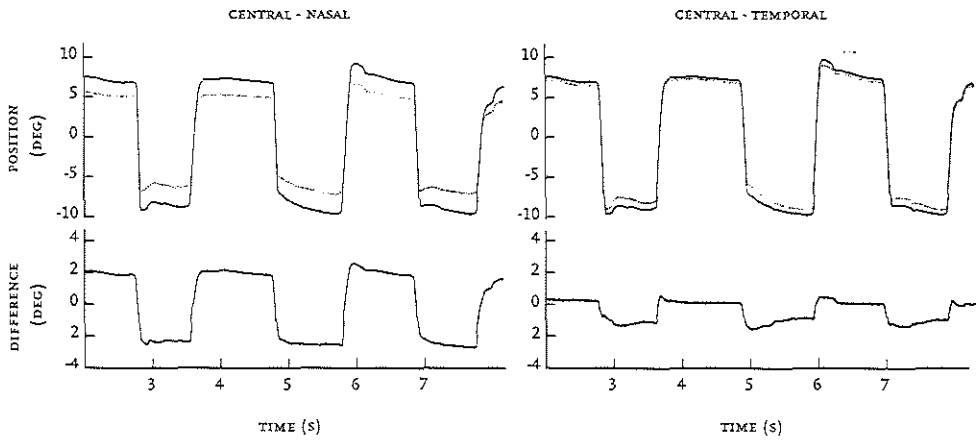
fellow eyes. Subjects were taken as a random factor in the analyses. All interactions between fixed factors were checked on statistical significance and retained in the model if significant. To meet the requirements of normal distributions and homogeneous variances for this test, the amplitudes, durations, and peak velocities of eye and lid saccades were transformed into their logarithmic values. To describe the magnitude of the effects, means and standard deviations of the nontransformed variables are given.

2.4 Results

Validation of Eyelid Recording Technique

In all subjects, a linear relationship existed between eyelid position and recorded voltage in the centrally positioned lid coil. The correlation coefficient (Pearson's r) was larger than 0.96 in every subject. Therefore, eyelid movements can be considered to be virtually perfect rotations, which justifies the use of lid coils for their registration.

Figure 1. Simultaneous recordings of lid saccades in three adjacent lid coils on one eyelid (target amplitude, 20°; subject GW.) The left panel shows the relations between the lid coils positioned centrally (C, solid line), and nasally (N, dotted line). The right panel shows the centrally and temporally (T, dotted line) positioned lid coils. The lower panels show the corresponding differential signals between the central coil minus either the nasal (left) or the temporal (right) coil.



Effect of Coil Position

Coil position affected the recordings of the lid saccades ($P < 0.05$). Figure 1 (Sub GW) shows the simultaneous recordings made with three adjacent lid coils on one eyelid, for typical eye saccades of approximately 20°. Their difference signals have been included. In subject GW (Fig. 1), lid saccades as recorded by the central coil were larger than those recorded with the coils either on the nasal or the temporal side. Amplitude differences between the central and the nasal lid coil averaged approximately 4.5° (SD = 0.3°; range, 4.1° to 5.3°) for these 20° saccades. Smaller differences were found between the central and the temporal lid coil; approximately 1.2° (SD = 0.4°; range 0.1° to 1.6°) for the same target amplitude.

The displacement recorded by the central coil was not the largest in each case; the distribution of magnitudes showed idiosyncratic differences among subjects and could vary even with saccadic amplitude within a single subject.

For all five subjects together, the recorded amplitude difference between the central and the nasal lid coil averaged approximately 0.8° (SD = 0.7°) for 10° saccades and increased with the target amplitude to approximately 3.0° (SD = 1.7°) for 40° saccades. The recorded amplitude difference between the central and the temporal lid coil also increased with the target amplitude but was smaller; approximately 0.8° (SD = 0.5°) and 2.1° (SD = 1.2°), respectively.

Linearity of the central coil, though not explicitly tested as in experiment one, was nevertheless thought to be present in this experiment; the central coil matched the recordings made with one coil on the lid within one individual.

These results demonstrated that the position of the lid coils is critical for reliably recording the conjugacy of lid saccades. We therefore positioned the lid coils as symmetrically as possible, right above the pupils with straight-ahead gaze, in the following experiment.

Conjugacy of Eyelid Movements

Saccadic Amplitudes. Lid saccades were not as conjugate as their associated eye saccades ($P < 0.05$). Figure 2 shows the eye and eyelid recordings of a typical subject (Sub AS). Vergence traces have been added (vergence is defined as: the position of the left eye(lid) minus the position of the right eye(lid)). The nonconjugacy (defined as: amplitude differences between the two eyelids or between the two eyes) averaged approximately 0.5° (SD = 0.3°; range: 0° to 1.2°) for his 10° lid saccades and increased with the target amplitude to 2.0° (SD =0.9°; range: -0.5° to 5.3°) for his 30° lid saccades. By contrast, his associated eye saccades (Fig. 2) were very conjugate: the nonconjugacy averaged approximately 0.2° (SD = 0.1°; range: 0° to 0.4°) for both 10° and 30° saccades.

In the group as a whole, the nonconjugacies of lid saccades increased with the target amplitude ($P < 0.05$) and were approximately 8% of the target amplitude. Those nonconjugacies averaged, in ascending order for our four target amplitudes, approximately 0.7° (SD = 0.5°), 1.7° (SD = 1.5°), 2.1° (SD = 1.6°), and 3.4° (SD = 2.6°), respectively. Nonconjugacy of the lid saccades was similar for the two directions, upward and downward ($P > 0.05$). By contrast, the nonconjugacies of the associated eye saccades were only approximately 1% of the target amplitude

(P > 0.05) and were similar for the two directions, upward and downward (P > 0.05). Figure 3 shows this nonconjugacy in separated scatterplots of lid and eye saccades for each direction, either upward or downward. The scatter is much larger for lid saccades than for eye saccades.

Figure 2. Simultaneous recordings of left and right eye saccades (left) and their associated lid saccades (subject AS; right). Vergence traces have been added. Vergence is defined as the position of the left eye(lid) minus the position of the right eye(lid). Note the variability in magnitude of 10° lid saccades. (solid line) Left eye(lid). (dotted line) Right eye(lid).

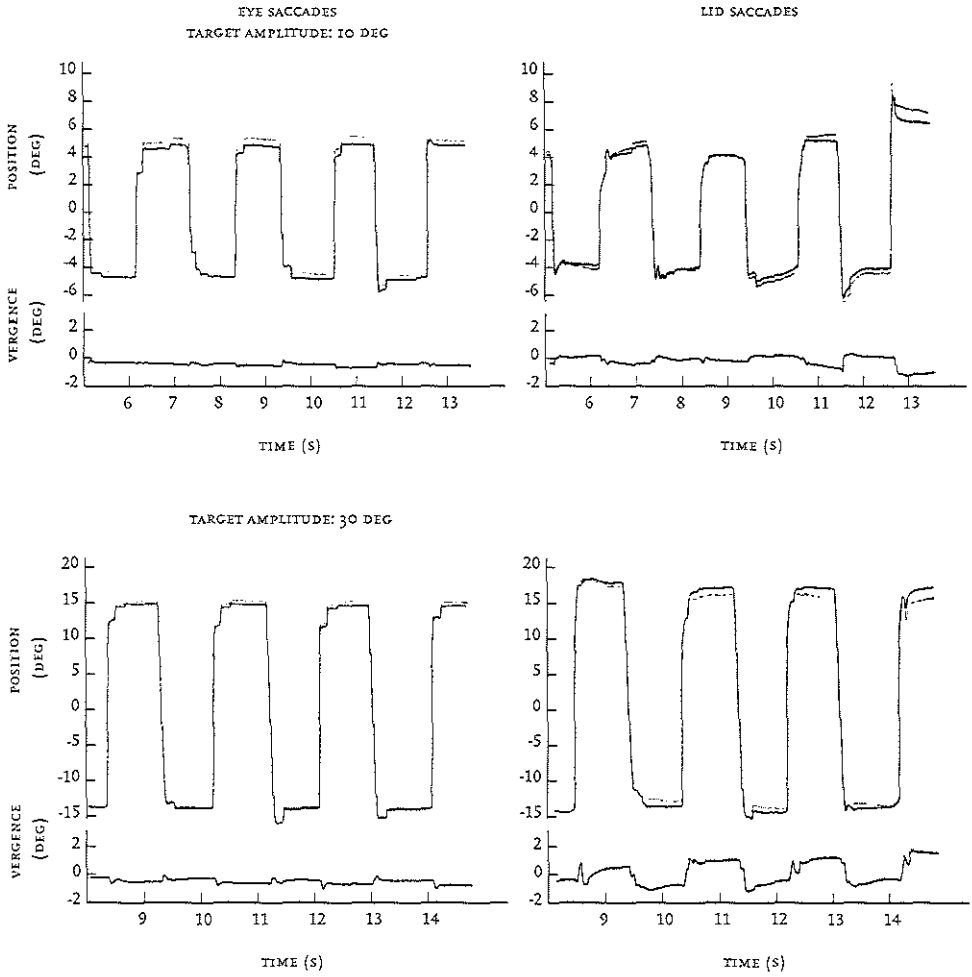
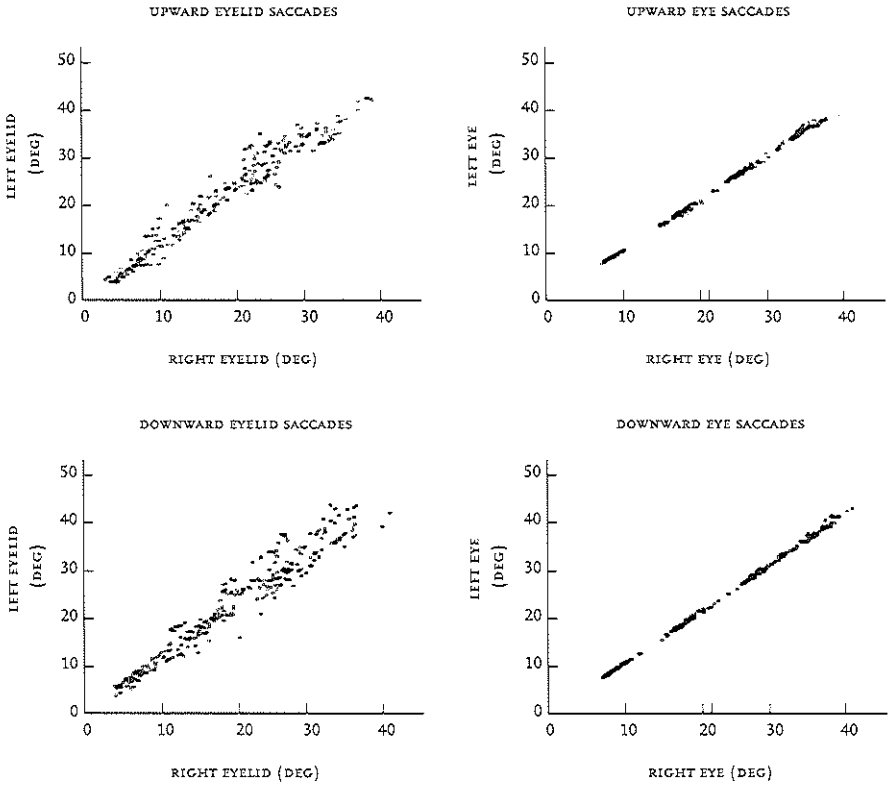
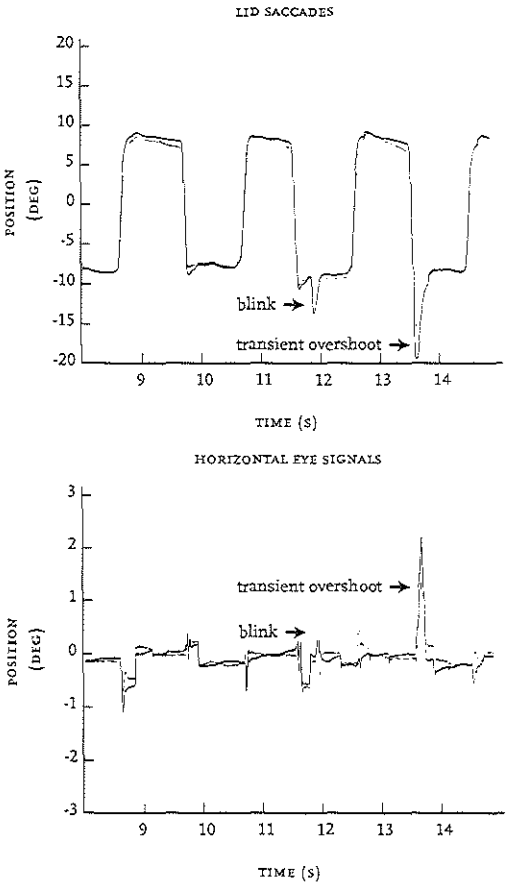


Figure 3. Scatterplot of saccadic size of individual eye(lid) saccades of the right eye(lid) versus saccadic size (degrees) of the left eye(lid) at the four target amplitudes in our group (n=10). Saccades of the lids and eyes are separated and have been pooled for each direction, either upward or downward. Correlation coefficients (Pearson's r) were 0.97 for the lid saccades, and 0.99 for the associated eye saccades.



In subject AS (Fig. 2), lid saccades of the right eyelid were larger than those of the left eyelid for 10° lid saccades. By contrast, at 30° saccades, the left eyelid made larger saccades than the right eyelid, except in one upward saccade. The associated eye saccades were always larger on the right side. Similar variations in nonconjugate lid saccades both within one target amplitude and between target amplitudes were observed in seven other subjects. In two subjects, it was always the same eyelid (the left) that made the larger saccades.

Figure 4. Typical example of a transient overshoot of lid saccades (upper panel). Recordings of the associated horizontal eye signals are included (lower panel).



Another observation in all subjects was that the eyelids often showed transient overshoots at all four target amplitudes. Figure 4 shows a typical example of such a transient overshoot. Recordings of the associated horizontal eye movements have been included. The transient overshoots were observed mostly in downward saccades. The returning phase was either fast, as in blinks, or slow, as in glissades. Such transient overshoots occurred more frequently at larger target amplitudes. There was no consistent relationship between the target amplitude and the magnitude of the transient overshoot or its appearance. The transient overshoots of the eyelids were sometimes similar to those of the eyes commonly observed in downward saccades. However, they occurred considerably more frequently in the lids than in the eyes. In addition, transient overshoots of lid and eye saccades occurred independently of one another.

To discriminate between transient overshoots of the eyelids and voluntary blinks, we analyzed the horizontal components of the associated eye movements. Blinks are accompanied by converging eye movements (Collewijn et al., 1985). A typical example is presented in Figure 4. By contrast, during the transient overshoots of the eyelids, such disjunctive horizontal eye movements were not observed (Fig. 4).

In addition, lid saccades varied more in amplitude within one subject and had larger intersubject variabilities for those amplitudes than the associated eye saccades. For 10° lid saccades, the standard deviation was approximately 2.2° (mean amplitude, 7.3°), and for 40° lid saccades, it was 4.8° (mean amplitude, 32.0°). The associated eye saccades had a standard deviation of approximately 1.0° (mean amplitude, 9.2°) and 2.1° (mean amplitude, 36.2°), respectively.

Downward lid saccades were larger than upward lid saccades ($P < 0.05$) in our group, irrespective of the target amplitude. The difference between downward and upward lid saccades averaged approximately 1.1° (SD =2.1°) for 10° saccades and increased to 2.3° (SD = 4.8°) for 40° saccades. A similar effect was found for the associated eye saccades ($P < 0.05$). Downward eye saccades were, on average, approximately 0.3° (SD = 1.0°) for 10° saccades and 1.4° (SD = 2.1°) for 40° saccades larger than upward eye saccades.

In all subjects, the position of the eyelid showed more intersaccadic instabilities (Fig. 2) than that of the eye, irrespective of saccadic direction at all target amplitudes. This confirms earlier reports by Becker and Fuchs (1988).

Saccadic duration. The duration of lid saccades was the same ($P > 0.05$) for the two eyelids, irrespective of saccadic direction at all target amplitudes. In our group, the duration was approximately 104 msec (SD = 43.8 msec) for 10° saccades and increased with the target amplitude to 193.5 msec (SD = 48.2 msec) for 40° saccades. Saccades of the left and right eye also had similar durations ($P > 0.05$) that increased with the target amplitude from approximately 92 msec (SD = 13 msec) for 10° saccades up to 183.8 msec (SD = 38.7 msec) for 40° saccades. The equality of duration in the two eyes was irrespective of saccadic direction and present at all target amplitudes. In addition, the duration of upward and downward lid saccades was similar for the two directions ($P > 0.05$), at similar target amplitudes, as was the duration of the associated eye saccades.

Saccadic onset of the two eyelids was almost simultaneous: within 1.9 msec (SD = 2.2 msec; range, 0.0 msec to 8.0 msec) for 10° saccades and within 3.0 msec (SD = 5.0 msec; range, 0.0 msec to 16.0 msec) for 40° saccades, irrespective of saccadic direction. Saccadic onset occurred just as often first in the left eyelid as in the right eyelid (paired sample t-test; $P > 0.05$). For comparison, eye saccades had their saccadic onset within approximately 0.6 msec (SD = 2.0 msec; range, 0.0 msec to 8.0 msec) of one another.

Lid Eye Coordination. Durations of lid saccades were similar to those of the associated eye saccades only at the 10° target amplitude (paired sample t-test; $P > 0.05$). At the other target amplitudes, on average, lid saccades had longer

durations (paired sample t-test; $P < 0.05$) than their associated eye saccades in the two directions; these differences were in the downward direction approximately 6.6 msec (SD = 23.9 msec) for 20° saccades, 8.0 msec (SD = 21.6 msec) for 30° saccades, and 9.3 msec (SD = 21.7 msec) for 40° saccades. In the upward direction, the durations differed more: on average, approximately 15.3 msec (SD = 30.8 msec), 18.1 msec (SD = 37 msec), and 10.1 msec (SD = 23.1 msec), respectively.

Lid saccades had their saccadic onset, on average, approximately 6 msec (SD = 4.1 msec; range, 0 msec to 20 msec) later than their associated eye saccades (paired sample t-test; $P < 0.05$) in downward and upward direction at all target amplitudes.

Saccadic Peak Velocities. Saccadic peak velocities were, on average, higher in the left eyelid than in the fellow eyelid ($P < 0.05$), irrespective of saccadic direction at all target amplitudes. However, the eyelid, left or right, in which the higher peak velocity occurred, varied inconsistently within and between trials in one subject.

In the group as a whole, the differences in peak velocities increased with the target amplitude and averaged, for downward lid saccades, approximately 20.6°/sec (SD = 23.8°/sec) for 10° saccades, 45.6°/sec (SD = 55.8°/sec) for 20° saccades, 50.3°/sec (SD = 45.5°/sec) for 30° saccades, and 65.8°/sec (SD = 66.3°/sec) for 40° saccades. Upward lid saccades differed less in their peak velocities: on average, approximately 12.8°/sec (SD = 12.1°/sec), 36.9°/sec (SD = 29.3°/sec), 47.5°/sec (SD = 35.0°/sec), and 61.8°/sec (SD = 42.5°/sec), respectively. By contrast, the peak velocities between the two associated eye saccades were similar ($P > 0.05$) in both directions and at all target amplitudes.

By examining the amplitudes, the peak velocities, and duration of individual saccades of the two eyelids, we found that, compared to its counterpart, the larger lid saccade could be associated with a lower peak velocity and a longer duration, a larger peak velocity and a shorter duration, and equal peak velocities but a longer duration. These different combinations varied inconsistently.

Downward lid saccades had higher peak velocities than upward lid saccades ($P < 0.05$) by approximately 46°/sec (SD = 14°/sec), on average, at the four target amplitudes. By contrast, for the associated eye saccades, the peak velocities were similar in the two directions ($P > 0.05$).

2.5 Discussion

Several authors *(Becker and Fuchs, 1988; Evinger et al., 1991; Sibony et al., 1991; Guitton et al., 1991)* have recorded eyelid movements with magnetic search coils without explicitly validating the technique. We found that vertical lid movements were virtually perfect rotations as recorded with a centrally positioned search coil. This observation does not in itself justify the use of search coils for

recording vertical lid movements: If the coils considerably affected the movements proper, the coils still would not be suitable. We consider that the low weight of the coils (approximately 15 mg) only minimally affects the movements because a change in position requires a force of as much as 10 g/mm *(Evinger et al., 1984)*. In addition, the small size of the lid coil (diameter approximately 4 mm) permits it to be positioned entirely over the tarsal plate, the dense fibrous skeleton of the upper eyelid. Normally, the connective tissue between the tarsal plate and its overlying skin may allow little movement between the two *(Anderson and Beard, 1977)*. Only if the fairly rigid coils were to exceed the tarsal plate might they impinge on the softer tissues superior to it and possibly hamper their movements. In that case, the movement of the entire eyelid might be affected. We also think the coils were too thin (less than 0.5 mm) to restrain considerably the lid movements when touched by the skin fold over the eyelid. Furthermore, the subjects did not find the lid coils to be uncomfortable. On the whole, we consider lid coils to be suitable for recording lid movements.

Moreover, we found that the recordings of lid saccades were affected by the positioning of the coils. If the upper eyelid rotated around a single rotational axis, comparable to a visor, each point of the upper eyelid would, in principle, rotate equally. Our findings therefore imply that the various parts of the upper eyelid have different rotational axes. We propose several possible causes for this multitude of axes. The tarsal plate, largely consisting of dense fibrous tissue, is flexible and gives shape to the upper eyelid. During lid movements, it may closely follow the shape of the underlying structures, notably the sclera and the cornea. Because the cornea has a smaller radius than the sclera, the part of the eyelid overlying the cornea also might be more curved than the part overlying the sclera. As a result, those parts of the eyelid sliding over the nasal and temporal parts of the cornea will diverge more (i.e., relative to each other) than if the same parts slid over the sclera. What is more, the movements of the various parts of the upper eyelid relative to each other will depend on the gaze position. As a result, the effect of the cornea will probably be smaller with lid saccades than with blinks because the eye and the lid move comparably in lid saccades, whereas in blinks, the lid totally covers the converging eye *(Collewijn et al., 1985)*. There may be another reason for the different recordings we found for the various parts of the upper eyelid. The nasal and temporal parts of the upper eyelid are qualitatively differently attached. Briefly, the nasal attachment is firm, whereas the temporal one is fairly loose *(Anderson and Beard, 1977)*. As a result, the axes of rotation of the temporal part of the upper eyelid may have a wider range in space than those of the more nasal parts of the eyelid. In studies such as ours into the conjugacy of upper eyelid movements, all these variations within a single eyelid may best be avoided by mounting lid coils as symmetrically as possible, e.g., right above the center of the pupil in primary gaze position.

The conjugacy of normal lid saccades, the main topic of this article, has not been studied previously in great detail. Several clinical studies suggest that Hering's law of equal innervation may apply to lid movements *(Gay et al., 1967;*

Schechter, 1978). Becker and Fuchs *(1988)* compared the main sequences of the two eyelids and found that they were similar. From these data, they inferred good conjugacy. Main sequences, however, are curves that are fitted to several data at the expense of detail. Individual saccades show certain deviations (scatter) from the fitted line that need not be equal for the two lids. For eye saccades, this scatter appears to be conjugate *(Bains et al., 1992)*. We found that vertical lid saccades indeed were considerably less conjugate than the associated eye saccades. There were large variations in amplitude between paired saccades of the two eyelids, but also inconsistent variations in the duration and the peak velocities. These inconsistencies indicate that main sequences do not reflect accurately the metrics of individual lid saccades and are of little value when the conjugacy of movements is assessed.

A good conjugacy of lid saccades is to be expected because their premotor saccadic control is shared with that of eye saccades *(Fuchs et al., 1992)*, which are conjugate. In both movements, the same motor nucleus is involved *(Fuchs et al., 1992; Warwick, 1953; Porter et al., 1989)*. Discharge patterns of levator and superior rectus motoneurons are similar, though levator motoneurons discharge at lower firing rates than do superior rectus motoneurons *(Fuchs et al., 1992)*. Our data agree with a shared control of both eye and lid saccades: We found that lid saccades always had their onset shortly after that of the eyes. The interval between the two varied little. For both kinds, upward saccades were smaller than downward saccades. In addition, saccades of the two eyelids had similar durations and had their onset almost simultaneously. However, the amplitudes and peak velocities of lid saccades varied considerably between the two sides. This variation reflects a control of lid saccades far less refined than of eye saccades. Obviously, there is no functional need for a control of lid saccadic conjugacy as tight as of eye saccadic conjugacy. The good conjugacy of eye saccades serves to foveate binocularly a newly selected visual target and thus prevents diplopia. Several stimuli that disrupt the functional yoking of eye saccades have been shown to cause adaptive changes that restore this functional yoking *(Lemij and Collewijn, 1991a; Kommerell et al., 1976; Erkelens et al., 1989; Lemij and Collewijn, 1991b; Schor et al., 1990; Oohira et al., 1991)*. These adaptive changes are known as nonconjugate adaptations. In case of lid saccades, the movements do not have to be conjugate as long as the lids do not prevent each eye from seeing. We do not know whether nonconjugate adaptation of the eyelids may also occur. Carefully examining patients with unilateral ptosis may provide us with an answer. Our data will then serve as normal values.

We found that transient, downward overshoots frequently occurred. Surprisingly, they have been reported only by Evinger et al. *(1991)*. Our first impression of these overshoots was that they were blinks made during downward saccades. However, because they were not associated with converging eye movements, typical of blinks *(Collewijn et al., 1985)*, we feel that they are separate entities. Evinger et al. *(1991)* found weak bursts of electromyographic activity in the orbicularis muscle during large saccades, but not during small saccades.

This confirms similar reports *(Niida et al., 1987)*. We found that the transient overshoots occurred in saccades of any magnitude, and we therefore question the role of the orbicularis oculi muscle in the genesis of transient overshoots.

We also found that there were bigger velocity differences between the two eyelids in downward than in upward lid saccades. Because downward lid saccades result from the relaxation of the levator and passive downward forces whereas upward ones result from its activation, this is not surprising.

The principal finding of our experiments was that lid saccades are not as well yoked as eye saccades. Obviously, there is no functional need for such a good conjugacy in lid saccades. To what extent this poor yoking of lid saccades may be affected by disease, aging and imposed adaptive stimuli remains to be seen.

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CHAPTER 3

SACCADIC EYE MOVEMENTS IN GRAVES' DISEASE

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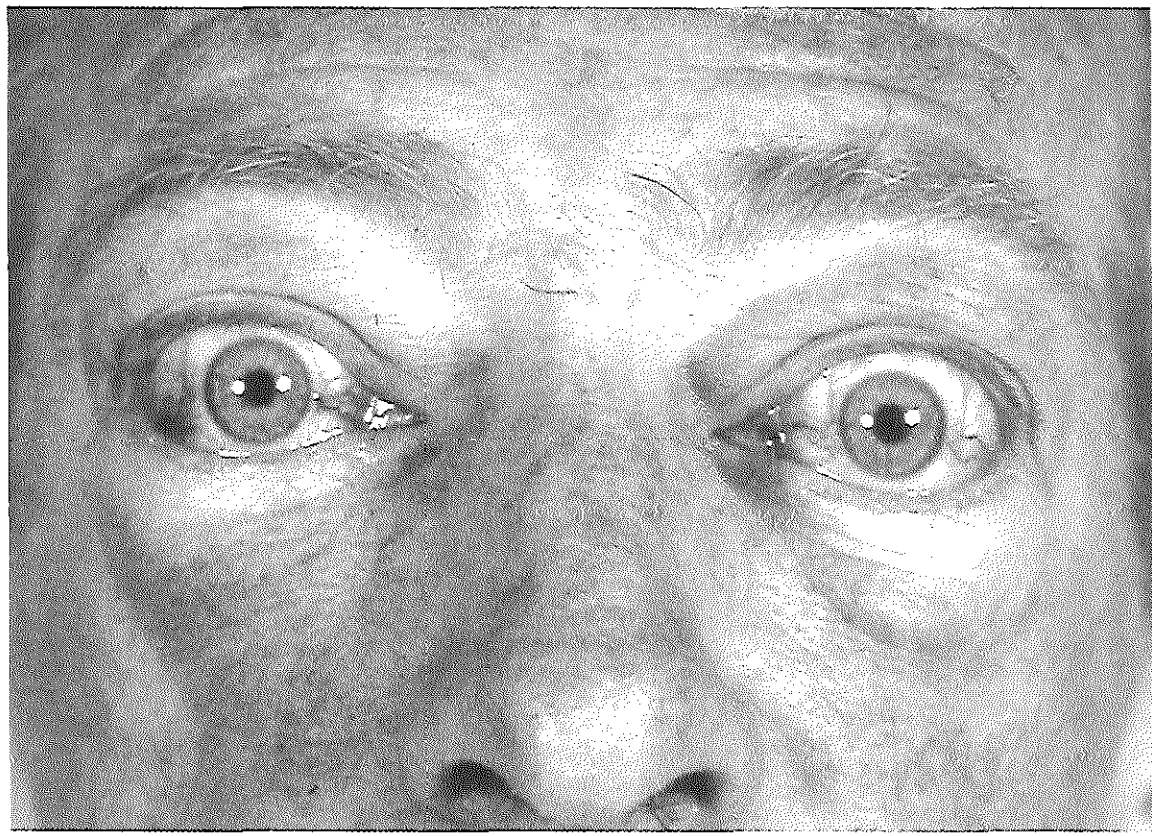


3.1 Abstract

Purpose

To describe the saccades made by patients with Graves' disease (GD) patients and to attempt to distinguish these objectively and quantitatively from the saccades in control subjects.

Methods

In 12 euthyroid patients with GD, the saccades of both eyes were recorded simultaneously with electromagnetic search coils. Subjects were asked to alternate their gazes between two fixed targets that were 10°, 20°, 30° or 40° apart along each horizontal or vertical meridian. The data from the patients with GD and those from the similarly recorded group of 12 control subjects were examined in two ways. First, the difference in saccadic sizes between the two eyes was assessed. Second, the saccadic dynamics – that is, the maximum velocity and the saturation constant of the main sequence – were determined for each eye. Repeated measurement analysis of variance was used to test observed differences between the two groups. Finally, through exact logistic regression analysis, classification of the saccades as those of a patient with GD or of a control subject was carried out.

Results

The saccades of patients with GD were generally less conjugate than those of control subjects ($P < 0.05$). On average, the maximum main sequence velocities in patients with GD were lower than in control subjects ($P < 0.05$). The saccades of patients with GD were well differentiated from those of control subjects.

Conclusions

The saccades in GD may differ markedly from normal saccades, and the two can be reliably distinguished.

3.2 Introduction

Graves' disease (GD) comprises a variety of ocular signs and symptoms, ranging from mild abnormalities, such as upper eyelid retraction and conjunctival edema, to severe sight-threatening and disfiguring manifestations. Not all signs and symptoms need be apparent simultaneously. At times, this presents the clinician with a diagnostic dilemma, especially when only mild abnormalities merely indicative of GD are present.

Restrictive myopathy of the rectus muscles is one of the signs most consistently observed in patients with GD *(Trokel and Jakobiec, 1981; Wiersinga et al., 1989; Hay, 1984; Jacobson and Gorman, 1984)*. The principal cause of this dysfunction is an inflammatory reaction of the rectus muscles related to progressive muscle enlargement, which ultimately develops into restrictive fibrosis and is caused by lymphocytic infiltration, perimysial fibroblast proliferation, and

edema *(Jensen, 1971; Schultz et al., 1960)*. This restrictive effect of the affected muscles has been demonstrated by electromyography, saccadic velocity tests, and isometric active force measurements *(Jensen, 1971; Schultz et al., 1960; Feldon and Unsöld, 1982; Metz, 1977; Miller et al., 1965; Igarashi et al., 1994)*. In some cases of GD, however, inferior rectus paresis may exist without fibrosis of the affected muscles *(Hermann, 1983)*.

All four rectus muscles of each eye may be affected simultaneously in GD, although the inflammatory changes are usually most severe in the inferior rectus muscle, followed in decreasing order of severity and frequency by inflammation of the medial, superior and lateral muscles *(Wiersinga et al., 1989; Enzmann et al., 1979)*. Computed tomographic scans reveal bilateral, symmetrical rectus muscle enlargement in most patients with GD, but asymmetrical enlargement is also relatively common *(Wiersinga et al., 1989; Enzmann et al., 1979)*.

Orthoptic testing, routinely performed in patients with GD to assess eye motility, provides information only about the static range of the rectus muscles. In one study on dynamics, investigators demonstrated that the horizontal saccades in patients with GD indicate abnormally quick fatigue, although there were no visible structural changes of the muscles on computed tomographic scanning *(Mauri et al., 1984)*. Other investigators have suggested that examining eye movement dynamics in GD, rather than muscular structure, may provide useful information *(Feldon and Unsöld, 1982; Feldon et al., 1990)*. Unfortunately, the recording technique used to examine saccades may have been somewhat inaccurate.

Saccades are the fast movements of the eyes that bring a new part of the visual field to the foveal region. To maintain binocular foveation, saccades of the two eyes are well yoked, within limits-that is, they are conjugate *(Lemij and Collewijn, 1991a; Kapoula et al., 1989)*. To preserve saccadic conjugacy in the presence of some degree of asymmetrical rectus muscle dysfunction, selective adaptation (i.e., a change in the innervation of one eye only, independent of that of the other eye) occurs in the saccadic system *(Snow et al., 1985; Viire et al., 1988)*. Selective adaptation may also take place in the absence of rectus muscle dysfunction: the wearing of anisometropic eyeglasses compels the saccadic system to make nonconjugate saccades selectively *(Lemij and Collewijn, 1991a; Erkelens et al., 1989; Schor et al., 1990; Oohira et al., 1991)*. Thus, several mechanisms may be at work to maintain the functional conjugacy of the eye movements-that is, to make saccades that achieve binocular fixation of the same target. In the present experiments, we investigated whether the saccades in patients with GD remain conjugate. Any nonconjugacy may occur through changes in the viscoelastic properties caused by the inflammatory processes that are different in the two orbits, if those changes exceed the critical limits of selective adaptation. To our knowledge, there are no studies to date in which this subject has been examined.

Furthermore, we investigated the dynamics of the saccades made by patients with GD. In normal saccades *(Baloh et al., 1975)* and in those made in the presence of myasthenia (Barton et al., 1994), saccadic amplitudes and peak velocities form a fairly tight, exponential pattern known as the main sequence

(Bahill et al., 1975). Beyond critical limits, any inflammatory change of the orbital plant in patients with GD will probably affect the dynamic properties of their eye movements. In patients with GD the saccadic peak velocities can be abnormally low *(Feldon et al., 1990)*. Because the associated saccadic amplitudes were not measured, it remains unclear whether the main sequence applies.

Our main interest was to describe the saccades made by patients with GD by determining saccadic conjugacy and saccadic dynamics. In addition, we attempted to distinguish the saccades of patients with GD from normal saccades. We found that many patients with GD made nonconjugate saccades and that the average maximum main sequence velocities in patients with GD were lower than in control subjects. Nonconjugacy per se could not reliably distinguish between normal saccades and those seen in patients with GD. By also taking the saccadic dynamics into account, we greatly improved the power of distinction.

3.3 Materials and Methods

The investigations adhered to the tenets of the Declaration of Helsinki and were approved by the institutional human experimentation committee. Informed consent was obtained from each subject after the experiments were fully explained.

Patients and Control Subjects

Twelve patients with GD (11 women and 1 man), aged between 34 and 74 years, participated in the experiment. Each patient had a medical history of thyrotoxicosis, confirmed by laboratory investigations (increased T_4 level, low thyroid-stimulating hormone level), in conjunction with a diffuse goiter, and each was euthyroid at the time of admission to the study. They all showed several clinical signs of GD, such as lid lag, lid retraction, a swollen caruncle, conjunctival edema, or conjunctival hyperaemia over the muscle insertions. The patients had not previously undergone eye or eyelid surgery, retrobulbar irradiation, or immunosuppressive therapy. Patients were excluded if diplopia existed in any secondary gaze position, whether horizontal or vertical, during routine orthoptic testing. In some, the ductions were not full, notably in upward gaze, but were symmetrical for the two eyes. None of the patients had a history of other ocular or oculomotor disease. The visual acuity of each eye was 20/25 or better.

A group of 12 control subjects (6 women and 6 men), aged between 21 and 78 years, also took part in the experiment. No restricted eye movements were observed during routine orthoptic testing of this group. None of the control subjects had a history of ocular or oculomotor disease or showed signs or symptoms of GD. The visual acuity of each of the control eyes was 20/20 or better.

Recording Technique and Calibration

The eye movements of both eyes were recorded simultaneously by means of the electromagnetic search coil technique, with commercially available search coils (Skalar Medical, Delft, The Netherlands) (Robinson, 1963; Collewijn et al.,

1975). The field frequency used was 20 kHz. The recordings were amplified to a ±5V range, low-pass filtered at 120 Hz (-3 dB), digitized with 12-bit precision, and sampled at a frequency of 250 Hz. The recordings were stored on disk for off-line analysis. Signal noise level was less than 1.8 min arc. The recording equipment and the search coils were calibrated objectively before each recording session, with the coils mounted on a calibration device. Any misalignment of the coils on the eyes, determined when the subjects monocularly fixated a light-emitting diode (LED) display in the primary position of gaze, was later adjusted by software. The accuracy of the calibration procedure was better than 0.5%.

Experimental Procedure

A search coil was attached to each eye of each subject following instillation of a topical anaesthetic (Oxybuprocaine 0.4%). Subjects were then seated, with their heads centred in a cubic coil frame in which an alternating horizontal and vertical electromagnetic field was generated. Head movements were restricted by a chinrest and forehead support. The subjects faced a stimulus screen, containing red light-emitting diodes (LEDs), at a viewing distance of 1 m. The LEDs were positioned symmetrically around the straight forward position on the horizontal and vertical meridians, 10, 20, 30 and 40° apart. The subjects were asked to shift their gaze from one lit LED to the other on hearing an electronically generated tone, at a pace of 1 per second. The four target ranges on each meridian were tested in a randomized sequence. Each trial lasted 16 seconds, in which typically eight saccades in each saccadic direction were made. Before each trial, subjects could practise briefly.

Data analysis

A computer program analyzed the recorded data. The criteria adopted for the detection of saccadic onset were acceleration exceeding 1000°/second^2 and velocity exceeding 25°/second. Saccadic offset was detected by a deceleration of less than 1000°/second^2 and a velocity of less than 50°0/second. The amplitude and peak velocity of each detected saccade were determined. The data were analyzed further with statistical analysis software (SPSS-X; SPSS, Chicago IL). Only primary saccades were selected for analysis, provided their amplitude exceeded 50% of the target amplitude. The absolute amplitude difference between the saccades of the two eyes was taken as a measure of conjugacy. Nonlinear regression analysis was used to analyse the saccadic dynamics of the two eyes separately for each saccadic direction. The main sequence (Bahill et al., 1975) was modeled as $PV = V_{max}(1\text{-}e^{-A/C})$, where PV = peak velocity (in degrees), V_{max} = maximum main sequence velocity (per second), A = saccadic amplitude (in degrees), and C is the saturation constant (Baloh et al., 1975). Given the observed values for PV and A, the parameters V_{max} and C in the above model were estimated for each eye in each subject, by means of nonlinear regression analysis. In the analysis, a weighting factor (WT = 1/A) was used, because the intrasubject variability of saccadic peak velocity increased with the target amplitude. Repeated measurement analysis of variance was used to test observed differences in the

degree of nonconjugacy or in the V_{max} between patients with GD and control subjects.

Finally, we classified the saccades of a single person as either those of a patient with GD or of a control subject. For this purpose, we applied an exact logistic regression analysis (Altman, 1992; LogXact, 1992). If P is the probability of having GD disease, then the logit is defined as ln(P/1 - P). In logistic regression analysis, this logit is specified as a linear function for the explanatory variables $X_1, \ldots X_p$: $\ln(P/1 - P) = ß_0 + ß_1X_1 + \ldots ß_pX_p$. The coefficients $ß_0, ß_1, \ldots ß_p$ were estimated by an exact logistic regression analysis (LogXact, 1992) for each eye separately. Through backward elimination, the relevant explanatory variables were selected. The analysis started with a potential set of 12 explanatory variables. For each saccadic direction, there was the average degree of saccadic conjugacy, pooled for the four target amplitudes, the maximum main sequence velocity (V_{max}), and the main sequence's saturation constant (C). Saccades were considered abnormal if the estimated probability was larger than 0.52.

3.4 Results

The saccades made by patients with GD were less conjugate and had a lower V_{max} than those made by control subjects ($P < 0.05$), regardless of the saccadic direction. Saccadic nonconjugacy of patients with GD exceeded the nonconjugacy of control subjects by $0.7 \pm 0.2°$. The difference in saccadic nonconjugacy was somewhat larger for vertical saccades than for horizontal saccades. Within each group, there was no significant difference in saccadic nonconjugacy between upward and downward saccades. The V_{max} of patients with GD was approximately $70 \pm 22.8°$/sec lower than the V_{max} in control subjects in either eye. Within each group, there was no difference in V_{max} between horizontal and vertical saccades.

The saccades made by patients with GD could be distinguished from those made by control subjects. The table shows the probability for each subject to be classified as a patient with GD or as a control subject. The values of the relevant explanatory variables (V_{max} and the average conjugacy) for each eye have been added. The regression equation for the model used to determine the magnitude of the logit(P) for the left eye was

$$\text{logit}(P) = 10.25 - 0.0305 * V_{max} + 7.0721 * \text{nonconjugacy} \quad (1)$$

and equalled for the right eye

$$\text{logit}(P) = 11.0897 - 0.0308 * V_{max} + 5.738 * \text{nonconjugacy} \quad (2)$$

With our applied exact logistic regression analysis, 11 of 12 patients with GD and as many control subjects were correctly classified. The incorrectly classified control subject was considered to have GD in both eyes (Table 1).

No distinguishing features were noted between the two incorrectly classified subjects and their associated fellow group members.

Omitting either of these explanatory variables resulted in a loss of the recognizability of the two types of saccades (i.e., GD versus control). If the average degree of conjugacy was used alone, only 9 of 12 patients with GD and 10 of 12 control subjects were correctly diagnosed. The recognizability was even worse, on average, if only the main sequence parameters were used.

Table 1. The probability of having GD with the values of the relevant explanatory variables

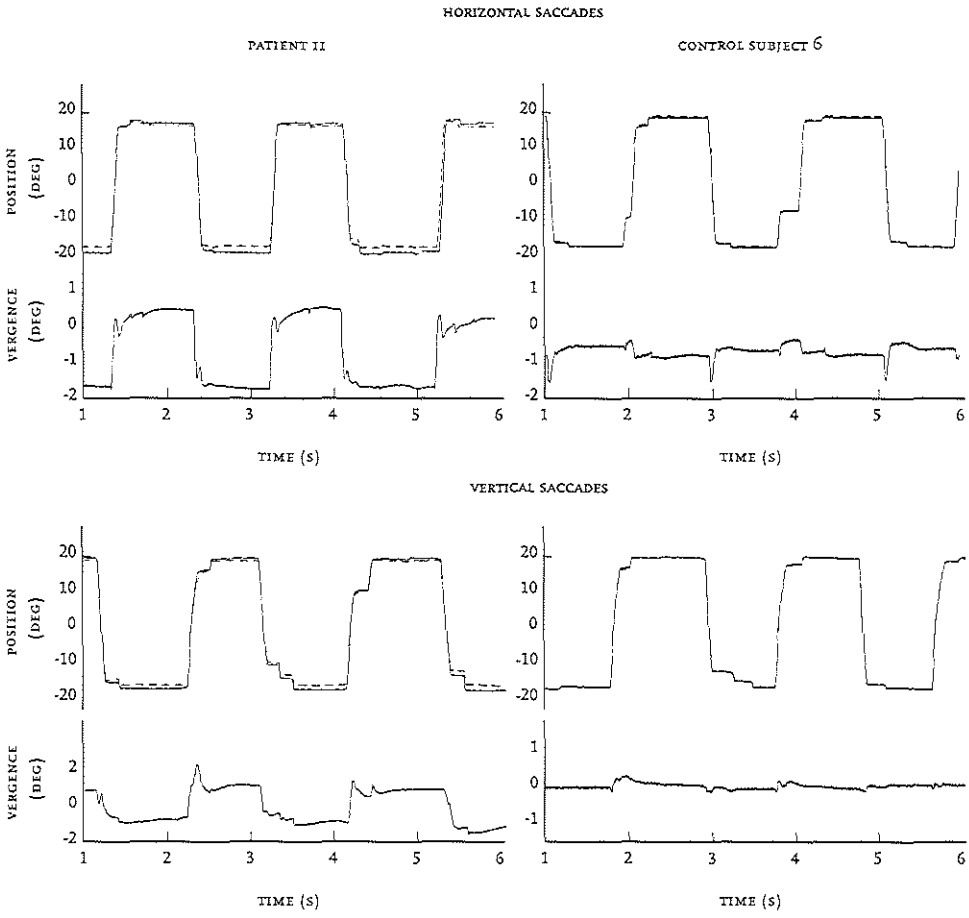
GD, Graves' disease; V_{max}, maximum main sequence velocity.

* Values in parentheses are SE.

† Values in parentheses are SD.

	EXPLANATORY VARIABLES			PROBABILITY / PREDICTED GROUP	
PATIENTS	V_{max} (LEFT EYE)* degrees/s	V_{max} (RIGHT EYE)* degrees/s	NONCONJUGACY † degrees	LEFT EYE	RIGHT EYE
1	372 (20.5)	331 (33.4)	1.5 (1.0)	0.99 GD	0.99 GD
2	470 (32.5)	506 (28.9)	1.9 (2.6)	0.99 GD	0.99 GD
3	496 (16.5)	478 (16.5)	0.9 (0.6)	0.77 GD	0.79 GD
4	400 (9.5)	419 (10.7)	0.3 (0.2)	0.28 NORMAL	0.27 NORMAL
5	397 (11.3)	419 (10.8)	0.4 (0.4)	0.69 GD	0.59 GD
6	359 (5.1)	371 (5.6)	0.3 (0.1)	0.79 GD	0.79 GD
7	411 (5.5)	433 (7.4)	0.4 (0.2)	0.66 GD	0.54 GD
8	409 (12.2)	440 (13.6)	2.4 (1.5)	0.99 GD	0.99 GD
9	296 (3.3)	306 (3.5)	0.3 (0.2)	0.97 GD	0.97 GD
10	434 (39.1)	372 (25.1)	1.2 (0.5)	0.99 GD	0.99 GD
11	554 (14.5)	511 (11.8)	1.2 (0.5)	0.85 GD	0.89 GD
12	387 (4.7)	383 (3.8)	0.5 (0.2)	0.90 GD	0.91 GD
CONTROL SUBJECTS					
1	379 (10.4)	396 (9.6)	0.5 (0.3)	0.92 GD	0.87 GD
2	546 (10.6)	564 (11.5)	0.2 (0.2)	0.01 NORMAL	0.01 NORMAL
3	592 (14.1)	582 (13.6)	0.4 (0.3)	0.01 NORMAL	0.01 NORMAL
4	447 (24.3)	438 (24.4)	0.4 (0.2)	0.40 NORMAL	0.51 NORMAL
5	494 (23.2)	494 (21.9)	0.2 (0.1)	0.03 NORMAL	0.04 NORMAL
6	465 (9.5)	475 (11.8)	0.3 (0.1)	0.07 NORMAL	0.08 NORMAL
7	570 (10.5)	586 (9.8)	0.5 (0.3)	0.03 NORMAL	0.02 NORMAL
8	540 (10.8)	536 (11.1)	0.3 (0.2)	0.02 NORMAL	0.02 NORMAL
9	473 (12.3)	496 (11.6)	0.3 (0.3)	0.06 NORMAL	0.05 NORMAL
10	465 (8.2)	456 (6.2)	0.3 (0.1)	0.15 NORMAL	0.23 NORMAL
11	393 (2.5)	398 (2.6)	0.3 (0.2)	0.45 NORMAL	0.52 NORMAL
12	580 (9.3)	561 (6.6)	0.4 (0.1)	0.01 NORMAL	0.02 NORMAL

Figure 1. Simultaneous recordings of left and right eye 40° saccades along both meridians in patient 11 (left), and control subject 6 (right). Left eye: solid line; right eye: dotted line. Traces for vergence (position of the left eye minus the position of the right eye) have been added. The saccades of the patient with GD were markedly nonconjugate along both meridians.



Conjugacy of Saccades

Nine of 12 patients with GD made significantly fewer ($P < 0.05$) conjugate saccades than did the control subjects along one or both meridians. In individual patients, the degree of saccadic conjugacy varied inconsistently. Highly conjugate saccades along one meridian occurred with nonconjugate saccades along the orthogonal meridian. In addition, idiosyncratic inconsistencies even in the degree of saccadic conjugacy were seen between opposite directions along a single meridian.

The saccadic nonconjugacy of the nine patients with GD averaged 1.1 ± 0.7° for rightward saccades and 1.3 ± 1.4° for upward saccades. In contrast, good conjugacy was found along both meridians in 10 control subjects. Their pooled conjugacy averaged only 0.3 ± 0.1°, regardless of the saccadic direction. The recordings of patient 11 and those of control subject 6, a typical control subject, for 40° horizontal and vertical saccades are shown in Figure 1. Vergence traces (showing the position of the left eye minus the position of the right eye) have been added to each figure. Patient 11 made nonconjugate saccades along both meridians (Table 1; Fig. 1). Her 40° rightward saccades of the left eye were a mean of 1.5 ± 0.2° larger than those of the right eye. Her 40° leftward saccades revealed larger differences between the two eyes (mean, 2.2 ± 0.2°). In her 40° vertical saccades, the nonconjugacy averaged 1.7 ± 0.3° for downward saccades and 2.1 ± 0.6° for upward saccades. Regardless of the saccadic direction, her left eye always made larger saccades than her right eye. By contrast, the saccades of control subject 6 (Fig. 1) were highly conjugate along both meridians, typical for all control subjects. The conjugacy along both meridians averaged 0.3 ± 0.1° for his 40° saccades and is shown by the small deflections in the vergence trace (Fig. 1).

Main sequence

Nine of 12 patients with GD had a main sequence in both eyes that was markedly different from those shown by most control subjects. In the control group, such a distinctive main sequence was detected in two subjects in both eyes, with another two subjects showing a deviant main sequence only in the right eye. Figures 2 and 3 show the main sequence of individual patients with GD (patients 9 and 10, respectively) and are each compared with the main sequence of all control subjects (n = 12). The saccades have been pooled for each eye and for each meridian. The V_{max} of patient 9 (Fig. 2) was lower ($P < 0.05$) in each eye than the mean V_{max} of the control group as a whole. Her V_{max} averaged 326.3°/sec (C = 9.1) for saccades along the horizontal meridian, averaged 392.1°/sec (C = 13.2) along the vertical meridian and were similar for both eyes along each meridian. In addition, no differences were found in her V_{max} between upward and downward saccades. Nevertheless, her downward saccades were somewhat larger than her upward saccades. For example, during upward 40° saccades, her left eye reached a mean saccadic amplitude of 35.3 ± 1.6°, whereas during her downward 40° saccades, the mean amplitude was 36.8 ± 1.6°. In the control group as a whole, the average V_{max} was also similar for both eyes along both meridians. However, upward saccades achieved a higher V_{max} than did downward saccades. Nevertheless, the latter were larger. For example in upward 400 saccades, the average saccadic amplitude for both eyes was 35.5 ± 1.8°, whereas in downward 40° saccades, the mean saccadic amplitude was 36.7 ± 2.4°. Although patient 9 showed a lower V_{max} than the average V_{max} of the control subjects, saccadic amplitudes were similar at all target amplitudes.

The average V_{max} of patients with GD correctly classified was 394 ± 40.7°/sec (C = 12.5). The correctly classified control subjects had an average V_{max} of 478 ± 5.2°/sec (C = 14.4). Control subjects considered to have a markedly

different main sequence had an average V_{max} of approximately 421 ± 7.0°/s (C = 12.1), compared with the average V_{max} of 468 ± 8.9°/s (C = 14.1) of patients with GD considered to have a main sequence similar to those of most control subjects.

No simple correlation was discerned between the degree of saccadic conjugacy and the main sequence in the patients; either or both could be abnormal. For example, the eyes of patient 10 had markedly different main sequences (Fig. 3) and nonconjugate saccades along both meridians. In addition, her right eye saccades, in contrast to those of patient 9 (Fig. 2), were markedly smaller than the saccades in the control subjects. The corresponding saccadic amplitude for 40° downward saccades of her right eye was 29.3 ± 1° and for 40° upward saccades was 30.0 ± 0.9° (Fig. 3). Another patient with GD (patient 11) showed a normal main sequence in both eyes, although nonconjugate saccades were made.

Figure 2. The main sequence of patient 9 (triangles) compared with the main sequence of all control subjects (n = 12; circles). Each triangle represents a single saccade, and each circle represents the average value of the saccades made by one control subject at each target amplitude. The saccades have been pooled for each eye and for each meridian.

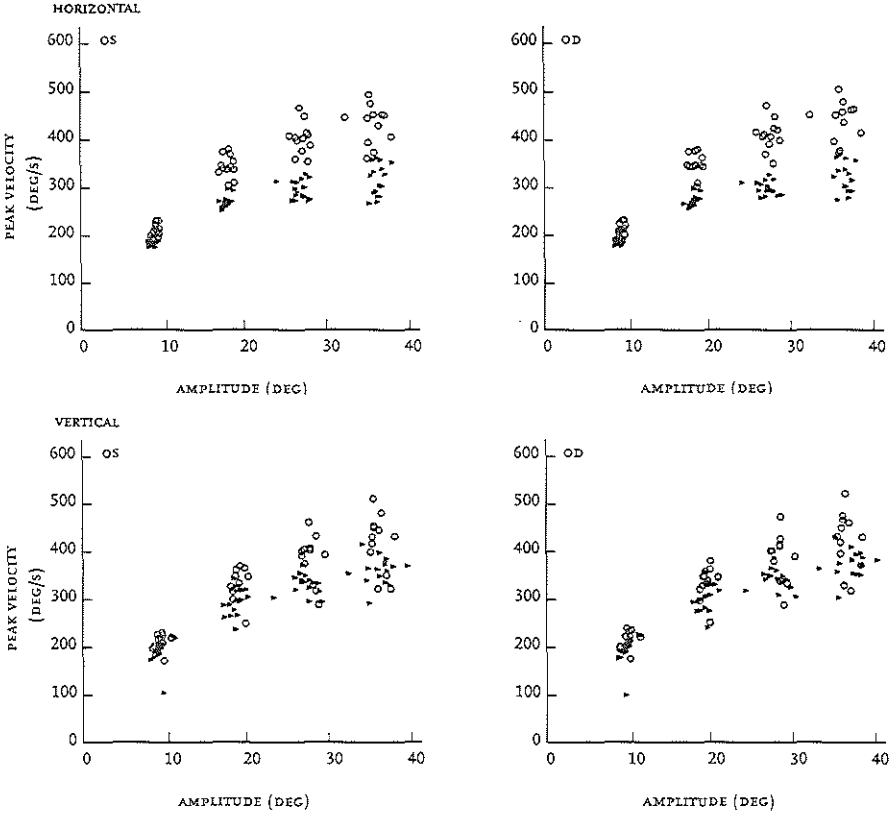
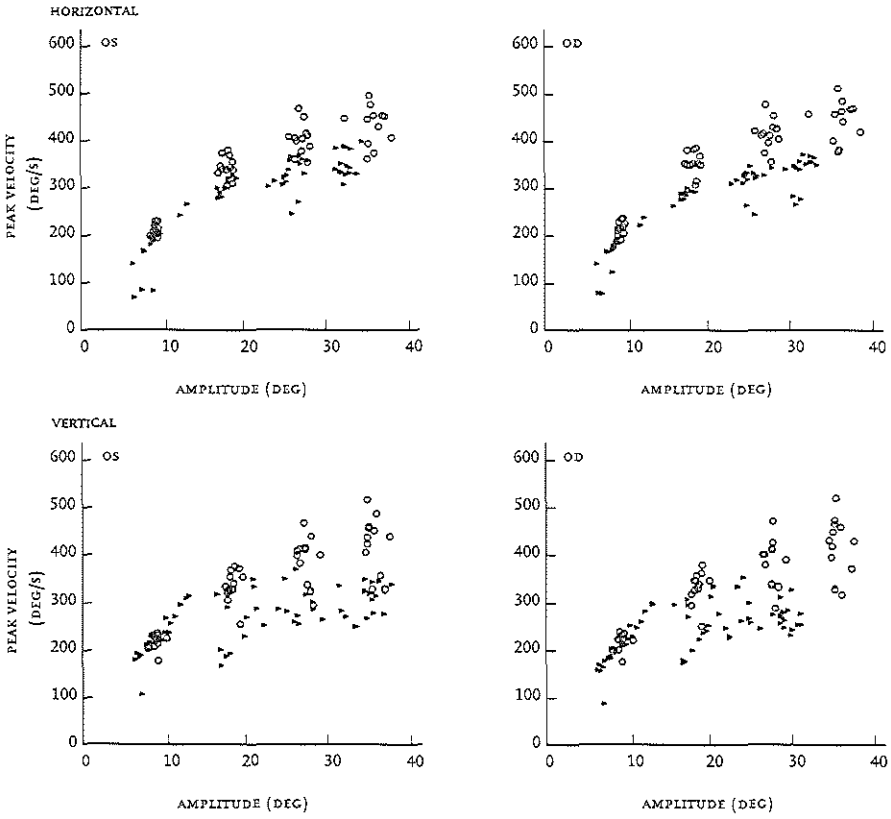


Figure 3. The main sequence of patient 10 (triangles) compared with the main sequence of all control subjects (n = 12; circles). Each triangle represents a single saccade, and each circle represents the average value of the saccades made by one control subject at each target amplitude. The saccades have been pooled for each eye and for each meridian.



3.5 Discussion

This is the first study to demonstrate that the saccades made by patients with GD without diplopia can be reliably distinguished from those made by control subjects. The distinction made in this study was founded on two saccadic characteristics, saccadic conjugacy and saccadic dynamics. The latter was expressed by the saccadic main sequence's V_{max} and saturation constant C. The individual characteristics proved to be inadequate to uphold such a differentiation, although saccadic conjugacy was the most important one. To our knowledge, the conjugacy of the saccades made by patients with GD has not been

examined previously, but the dynamics of the saccades have *(Feldon and Unsöld, 1982; Metz, 1977; Mauri et al., 1984; Feldon et al., 1990)*. Feldon et al. *(1982; 1990)* noted reduced saccadic peak velocities in patients severely affected by GD, but not in those with only mild or moderate signs. Metz *(1977)* made use of electrooculography to study vertical saccades. He observed that the peak velocities of 40° vertical saccades were within normal limits. Considering our results, with significant differences in V_{max} between patients with GD and control subjects, we query whether Metz's recording technique was sufficiently sensitive to detect deviations from normal in the saccadic peak velocities. Mauri et al. *(1984)* investigated in patients with GD the conventional saccadic parameters: amplitude, duration, and peak velocity. The values they obtained did not differ from those in control subjects, except in patients severely affected clinically, whose saccadic duration was slightly longer. They also demonstrated that, as time passes, the variability in the saccadic peak velocity increases, which was attributed to fatigue. Our present results do not confirm this finding.

The research conducted by several investigators *(Feldon and Unsöld, 1982; Mauri et al., 1984; Feldon et al., 1990)* was limited to horizontal saccades. We contend that vertical saccades are potentially of greater significance, because in GD, the inferior rectus muscle is the one most commonly and severely affected. Our data clearly show a markedly larger saccadic nonconjugacy in vertical saccades than in the horizontal ones in several subjects. In some other patients, it was primarily the horizontal meridian that yielded saccadic nonconjugacy, whereas in others, both meridians were clearly affected. By assessing saccades along only one meridian, important information may be lost.

Differences in the degree of saccadic nonconjugacy between downward and upward saccades are likely to occur, because the inferior rectus muscle is more often affected and usually more severely, than the superior rectus muscle. We did not, however, find such a difference between downward and upward saccades. This may be because of the limited number of patients in our experiments or of the selective adaptation of the oculomotor system. Nonconjugate saccades in one direction presumably compel the saccadic system to make equally nonconjugate saccades in the opposite direction, to retain as much binocular foveation as possible. We noted nonconjugacies of as much as 2° in the patients with GD. They did not experience diplopia, presumably because the nonconjugacies were well within the limits of Panum's fusional area *(Erkelens and Collewijn, 1985; Schor and Tyler, 1981)*.

Under normal circumstances, saccades are highly conjugate *(Lemij and Collewijn, 1991a; Kapoula et al., 1989)*, but this state may be disrupted by physical impairment that differs for each of the two orbits, as occurs in unilateral tenotomy *(Viire et al., 1988)*. It has been demonstrated *(Snow et al., 1985; Viire et al., 1988)* that selective adaptation subsequently takes place in an effort to restore the saccadic conjugacy. We hypothesized that any physical impairment differently affecting the viscoelastic properties of the two orbits would lead a priori to saccadic

nonconjugacy and thus would give rise to subsequent selective adaptation. Only when the latter process was insufficient would a degree of saccadic nonconjugacy remain. The range of saccadic adaptation to compensate for differences in the two eyes is limited *(Viire et al., 1988; Lemij and Collewijn, 1991b)*, and we therefore examined the conjugacy of the saccades in the patients with GD. Several made normally conjugate saccades, but most others had poor saccadic yoking.
We assume that normal conjugacy can occur only when either both orbits are equally impaired or any selective adaptation process is complete. Good conjugacy in our patients with GD was frequently accompanied by similar, abnormal main sequences-that is, abnormally low V_{max} in both eyes. These abnormalities do not seem to favor either of the two mechanisms leading to good saccadic conjugacy. Most other patients with GD exhibited poor saccadic conjugacy. We assume that in these patients, the impairment of the two orbits was dissimilar and that the selective adaptation process must have been incomplete to compensate fully for the differences. It remains to be seen whether better selective adaptation occurs with passing time. In case of anisometropia, the process may be complete in as little as 1 hour *(Lemij and Collewijn, 1991b)*. Unilateral tenotomies in monkeys, however, were followed by conjugacy restoration times of 24 hours *(Viire et al., 1988)* to 58 days *(Snow et al., 1985)*. Surely, there is no physical impairment of the orbital plant in case of anisometropia.

We speculated that the saccadic nonconjugacy and diminished peak velocities were caused by changes in the viscoelastic properties of the oculomotor plant, because GD is associated with restrictive fibrosis of the extraocular muscles. Damage to individual muscle fibres might also contribute to the noted sacccadic abnormalities. Our technique, however, could not discriminate between the two possible causes, nor could it show their concerted action, if present.

Our method proved to be effective in distinguishing between the saccades of normal subjects and those made by patients with GD. This may hold promise for future clinical use. At present, the treatment of patients with GD is largely symptomatic, and to our knowledge there is no treatment to prevent full-blown ophthalmopathy. Furthermore, early treatment with radioiodine to suppress hyperthyroidism may actually exacerbate ophthalmopathy *(Bartalena et al., 1989)*. Severe ophthalmopathy eventually develops in approximately 3% to 5% of people with diffuse goiter and hyperthyroidism *(Jacobson and Gorman, 1984)*. If an adequate treatment existed, early detection and treatment in a subclinical stage could prevent serious future signs and symptoms. Assessing saccades in everyone with diffuse goiter and hyperthyroidism might then be of use in detecting those at risk of development of ophthalmopathy. We do not know whether saccadic abnormalities rightly predict the eventual severity of the disease. More long-term studies are required to substantiate this. For now, we think the clinical use of our technique may be of little value. We emphasize that we were only able to distinguish normal saccades from abnormal ones. It is uncertain whether our method will also prove reliable in distinguishing saccades made in GD from those in other disorders that affect the orbital plant. Further research is needed to investigate this question.

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CHAPTER 4

UPPER EYELID MOTILITY IN BLEPHAROPTOSIS AND IN THE AGING EYELID

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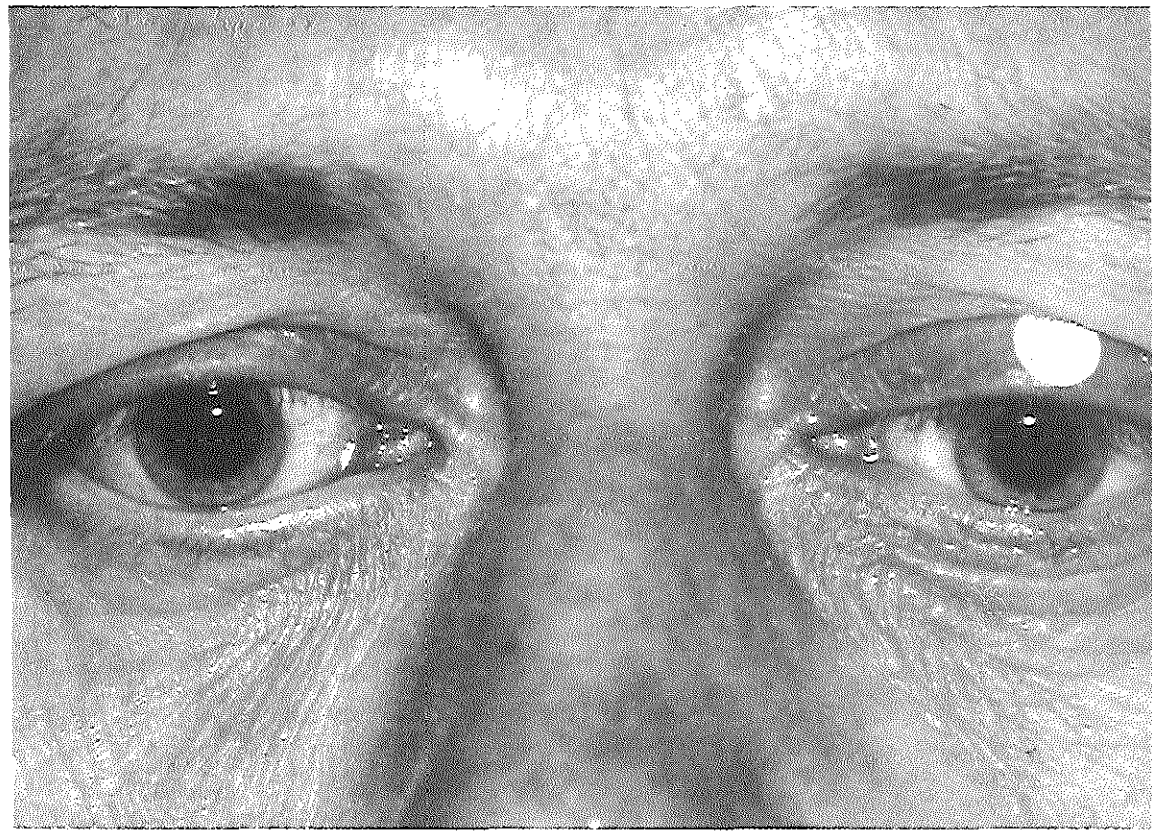


4.1 Abstract

Purpose

To study the metrics of lid saccades in blepharoptosis and to distinguish any differences in the dynamics of eyelid movements that are related to the cause of blepharoptosis, and to aging.

Methods

The lid and vertical eye saccades of 7 patients with congenital blepharoptosis and those of 18 patients with aponeurogenic blepharoptosis, either involutional or rigid-contact-lens-induced, were recorded with electromagnetic search coils. For each saccade, two parameters were assessed: amplitude and peak velocity. Two age-matched control groups were assessed in the same manner. Repeated measures analysis of variance was used to investigate any observed differences between the included groups.

Results

Congenital and rigid-contact-lens-induced blepharoptosis were readily distinguishable from one another, as well as from the age-matched control group in both lid saccadic amplitude and peak velocity. For example, 40° downward lid saccades in the congenital blepharoptosis group averaged 22.9° ± 4.0° (SD), whereas 30.0° ± 4.7° lid saccades were made by the age-matched control group. The subjects in the two groups with aponeurogenic blepharoptosis also made lid saccades that were distinctive for their group ($P < 0.02$), in both amplitude and peak velocity. For 40° downward saccades in involutional and rigid-contact-lens-induced blepharoptosis, lid saccadic amplitude averaged 32.7° ± 4.3° and 40.3° ± 3.5°, respectively. Lid saccadic peak velocity declined significantly with age. Lid saccadic peak velocity for 40° upward saccades in the younger control group averaged 401.7 ± 11.4°/sec, whereas the older control group achieved an average peak velocity of 360.7 ± 60.4°/sec. The lid saccadic dynamics in the involutional blepharoptosis group proved to be similar ($P > 0.05$) in saccadic amplitude and peak velocity, to those of age-matched controls.

Conclusions

In different forms of blepharoptosis, distinctive metrics of lid saccades occur. The current data suggest that involutional blepharoptosis is not a consequence of normal age-related changes in eyelid function.

4.2 Introduction

There are several known causes of blepharoptosis, such as a diseased levator palpebrae muscle or its aponeurosis and neurologic and mechanical disorders *(Frueh, 1980)*. Various types of blepharoptosis may be identified by proper assessment of established clinical parameters such as levator function, a commonly used parameter of the functional integrity of the levator palpebrae

muscle. Levator function has been defined as the maximum eyelid amplitude (in millimeters), measured from downgaze to upgaze *(Berke, 1952; Kersten et al., 1995)*. Another measure of levator function is the so-called levator force, which is infrequently used, because no clinically useful device is currently available *(Frueh and Musch, 1996)*. Other parameters, such as the position of the upper eyelid crease, the interpalpebral fissure height, upper eyelid margin-corneal reflex distance, fatigue with sustained upgaze, and ocular motility may provide additional information toward establishing the correct diagnosis. Nevertheless, the cause of the blepharoptosis may remain obscure *(Kersten et al., 1995; Frueh and Musch, 1996)*, whereas a correct diagnosis facilitates its adequate management.

Aponeurogenic blepharoptosis is caused by disinsertion, or thinning, of the levator muscle aponeurosis *(Paris and Quickert, 1976; Older, 1978; Anderson and Dixon, 1979)*. Typically, the levator function is good *(Beard, 1976)*, and a high eyelid crease is usually found. In the elderly it is most often an involutional disorder *(Frueh and Musch, 1996; Older, 1983)*. In the younger population, a period of rigid contact lens wear is frequently the only identifiable cause *(Kersten et al., 1995; van den Bosch and Lemij, 1992)*. In aponeurogenic blepharoptosis it is clinically difficult to discriminate between the possible causes - that is, involutional or contact lens wear. Only history and the age of occurrence can currently be used to differentiate between the two. Intraocular surgery, postoperative edema, ocular inflammation, and topically applied steroids are other factors related to aponeurogenic blepharoptosis *(Frueh, 1980; Anderson and Dixon, 1979)*.

In congenital myogenic blepharoptosis, the levator function is typically diminished, and the eyelid shows a lag during downgaze. Upper eyelid crease position is unaffected. Although most congenital blepharoptoses are myogenic *(Beard, 1976)*, some are caused by a neurologic abnormality *(Callahan and Beard, 1990)*, an aponeurotic defect *(Frueh and Musch, 1996)*, or a mechanical distortion of the upper eyelid, as with neurofibroma *(Gayton et al., 1993)*. During clinical examination, such other causes of congenital blepharoptosis are readily distinguished from the myogenic ones. Genetic linkage has recently been established for at least some cases of congenital blepharoptosis *(Engle et al., 1997)*.

Few studies have described the metrics of lid saccades in normal subjects *(Wouters et al., 1995; Evinger et al., 1991; Becker and Fuchs, 1988; Guitton et al., 1991)*. Concurrent lid and eye saccades have repeatedly been shown to have similar amplitudes and peak velocities *(Becker and Fuchs, 1988)*. Several investigators *(Wouters et al., 1995; Evinger et al., 1991; Guitton et al., 1991)* have found higher peak velocities in downward lid saccades than in upward ones. In one study *(Becker and Fuchs, 1988)*, however, the opposite was found, possibly because of the small number of subjects included in that study.

In the present experiments, we compared the metrics of lid saccades among several forms of blepharoptosis and in age-matched control groups.

4-3 Materials and Methods

The investigations adhered to the tenets of the Declaration of Helsinki and were approved by the institutional human experimentation committee. Informed consent was obtained from each subject after the experiments were fully explained.

Patients and Control Subjects

We included seven patients with congenital blepharoptosis (CB; age range, 22-70 years). Each patient had a history of unilateral or bilateral blepharoptosis since birth. For inclusion, the maximum eyelid amplitude had to be less than 8 mm at clinical examination, with lid lag during downgaze. In addition, 18 patients with the clinical signs of aponeurogenic blepharoptosis, either attributed to involutional changes (IB; n = 13; age range, 68-87 years), or secondary to rigid contact lens wear (CLB; n = 5; age range, 21-46 years) were included. For inclusion, the maximum eyelid amplitude had to be 10 mm or more, and a high upper eyelid crease had to be present. They had a history of gradually progressive unilateral or bilateral blepharoptosis.

If each upper eyelid showed blepharoptosis, the most affected upper eyelid was included for analysis, although both eyelids were simultaneously recorded. Blepharoptosis was defined as an interpalpebral fissure height of 7 mm or less, measured between the lower and the upper eyelid margin *(van den Bosch and Lemij, 1992)*, or an asymmetry between the two upper eyelids of more than 2 mm. Maximum eyelid amplitude was measured from downgaze to upgaze while the additional action of the frontalis muscle was blocked by digital pressure on the eyebrow on the orbital rim. Patients were excluded if they had previously undergone eye or eyelid surgery or if they had a systemic disease that might affect upper eyelid position or motility, such as Graves' disease or a generalised neuromuscular disease. In addition, patients were excluded if they showed any progression of blepharoptosis after sustained upgaze, jaw-winking, or a visible lid twitch.

Two groups of normal control subjects, young control subjects (YC; n = 10; age range, 25-51 years), or older control subjects (OC; n = 16; age range, 64-84 years) took part in our experiments as age-matched control groups. All normal subjects had a vertical eyelid fissure of 8 mm or more, and each had a levator function of 10 mm or more. None of the subjects in the control groups had any history of ocular or oculomotor disease. We randomly included the measurements of one upper eyelid and the associated eye of each normal subject.

Recording Technique and Calibration

Lid and eye saccades were recorded simultaneously by means of the electromagnetic search coil technique *(Wouters et al., 1995; Becker and Fuchs, 1988; Robinson, 1963; Collewijn et al., 1975)*. Lid saccades were recorded with handmade search coils. Every such coil consisted of 50 turns of insulated copper wire *(diameter, 0.05 mm)*. A typical coil had an outer diameter of approximately 4 mm, weighed 15 mg, and was less than 0.5 mm thick. To reduce spurious induction,

the leads of the coil were tightly twisted together. The coils were fixed on the lower part of the eyelid, just above the eyelid margin and right above the center of the pupil with a piece of adhesive tape *(diameter, 6.5 mm)*. Once the coils were attached, the subjects hardly noticed them. Eye saccades were recorded with commercially available search coils *(Skalar Delft, The Netherlands)*.

The field frequency used was 20 kHz. The recordings were amplified to a ±5 V range, low-pass filtered at 120 Hz (-3 dB), digitized with 12-bit precision, and sampled at a frequency of 250 Hz. The recordings were stored on disk for off-line analysis. Signal noise level was less than 1.8 min of arc. Both the recording equipment and the search coils were calibrated objectively before each recording session, with the coils mounted on a calibration device. Any misalignment of the coils on the eyes, determined when the subjects monocularly fixed a lit LED in the primary position of gaze, was later adjusted by software. The accuracy of the calibration procedure was better than 0.5%.

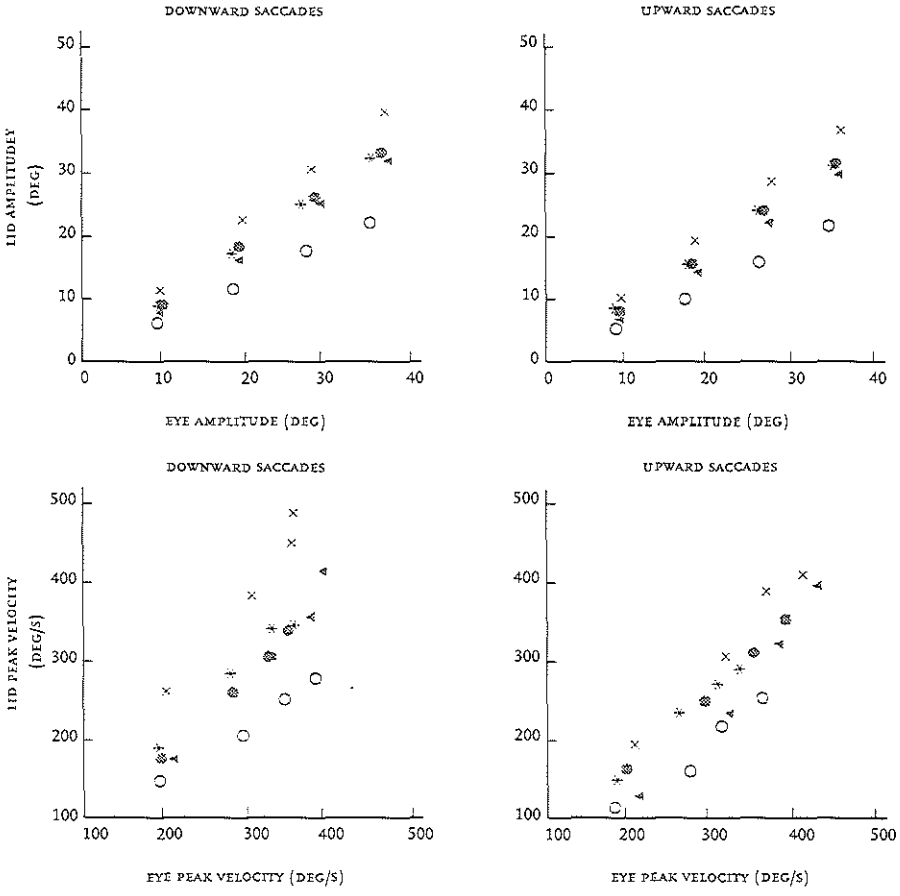
One search coil was attached to the upper eyelid, and a scleral search coil was placed on the ipsilateral eye under topical anaesthesia (0.4% oxybuprocaine; Novesine; Chauvin, Düsseldorf, Germany). Subjects were then seated, with their heads centered in a cubic coil frame in which an alternating horizontal and vertical electromagnetic field was generated. Head movements were restricted by a chinrest and forehead support. The subjects faced a stimulus screen, containing red LEDs at a viewing distance of 1 m. The LEDs were positioned symmetrically around the straight-ahead position along the midvertical meridian, 10°, 20°, 30°, and 40° apart. The subjects were asked to shift their gazes from one lit LED to the other after hearing an electronically generated tone, at a pace of 1 per second. The four target ranges were tested in a randomized sequence. Each trial lasted 16 seconds, in which, typically, eight saccades in each saccadic direction were made. Before each trial, subjects were allowed to practice briefly.

Data Analysis

The recorded data were analyzed with a previously devised computer program *(Wouters et al., 1995)*. The criteria adopted for observer-independent detection of saccadic onset were acceleration exceeding 1000°/second^2 and velocity exceeding 25°/sec. Saccadic offset was detected by a deceleration of less than 1000°/second^2 and a velocity of less than 500/sec. The amplitude and peak velocity of each detected saccade were determined. Only primary eye saccades and the associated lid saccades were selected for analysis, by an eye amplitude criterion (set at 50% of the target amplitude). Repeated measures analysis of variance (mixed-model ANOVA) *(Verbeke and Molenberghs, 1997)* was used to investigate any observed differences among the included groups. Two outcome (dependent) variables were defined: the difference in saccadic amplitude between lid and eye (in degrees) and the difference in saccadic peak velocity between lid and eye (in degrees per second). Each outcome variable was analyzed separately in a linear model with random coefficients and with the following independent variables: patient group (five groups), saccadic direction (up and down), and target amplitude (10°, 20°, 30°, and 40°). Also interactions between group and target amplitude

and between group and direction were tested. Amplitude squared was included to test for curvilinearity. The fitted linear model provided estimates for the mean coefficients. Pairwise comparisons were used to test whether these mean coefficients differed between groups.

Figure 1. Lid sacadic amplitude (in degrees) and peak velocity (in degrees per second) with those of the eye in all five groups, pooled for saccadic direction.



4.4 Results

Assessing the dynamics of eyelid saccades was valuable as a means of differentiating between two clinically similar forms – involutional and contact-lens-induced – of aponeurogenic blepharoptosis. Moreover, large differences were found in the amplitudes and peak velocities of the eyelid saccades made by patients with congenital blepharoptosis on the one hand and by those with the aponeurogenic condition on the other. For example, in the group with congenital blepharoptosis the lid saccadic amplitude for 40° saccades averaged 23.6° (average peak velocity 278°/sec), whereas the contact lens group achieved an average of 38.8° (average peak velocity 450.8°/sec). Lid saccadic peak velocity was affected by age, averaging 410.0°/sec for the younger control group and 352.2°/sec for the older control group for 40° saccades. Lid saccadic dynamics in the involutional blepharoptosis group were closely similar to those of the age-matched control group.

Both the amplitude and the peak velocity of the eyelid saccades increased with those of the eye in all five groups (Fig. 1). The eye saccadic amplitudes of the group of patients with congenital blepharoptosis were significantly smaller ($P < 0.05$; independent samples t-test) from those of the age-matched control group. No differences in eye saccadic amplitude ($P > 0.05$; independent samples t-test) were found between the other groups. However, eye saccadic peak velocities differed significantly between all groups ($P < 0.05$; independent samples t-test). To counteract possible effects of eye motility variation on the lid motility metrics, we subtracted eye saccadic amplitude and peak velocity from those of the concomitant lid saccade. This approach enabled us to differentiate clearly between the various groups of patients with blepharoptosis. We also found age-related differences in normal subjects.

Figures 2 and 3 show the various regression lines for the estimated linear relationships of the saccadic amplitude (lid-eye) and the peak velocity (lid-eye) as a function of the target amplitude. Each regression line represents one group. The statistical differences between these lines are presented in Table 1. The estimates for mean intercepts and mean slopes for saccadic amplitude and peak velocity are given in Tables 2 and 3, respectively. Saccadic amplitudes *(lid-eye; Fig. 2)*, yielded significantly different linear slopes and intercepts across the five groups ($P = 0.0001$ and $P = 0.0163$, respectively). Peak velocities *(lid-eye; Fig. 3)* only differed significantly in their linear slopes between the five groups ($P = 0.0197$), not in their intercepts.

Figure 2. Regression lines for the estimated linear relationship of the saccadic amplitude (lid-eye; in degrees), as a function of the target amplitude for each group.

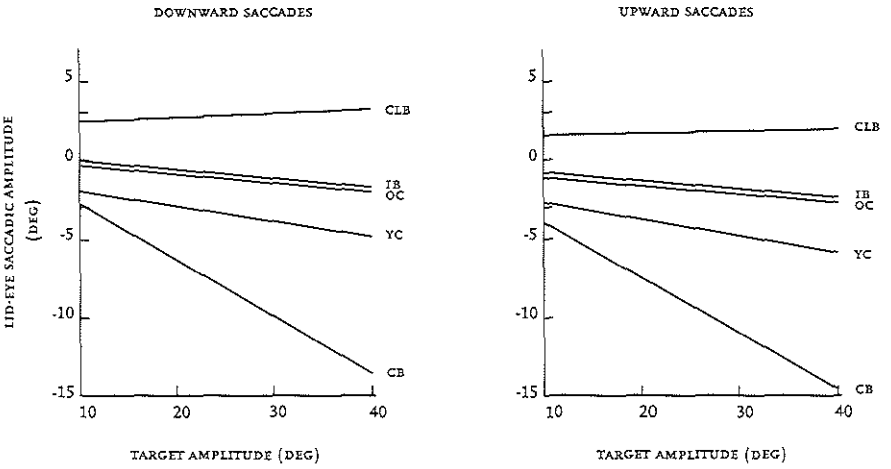
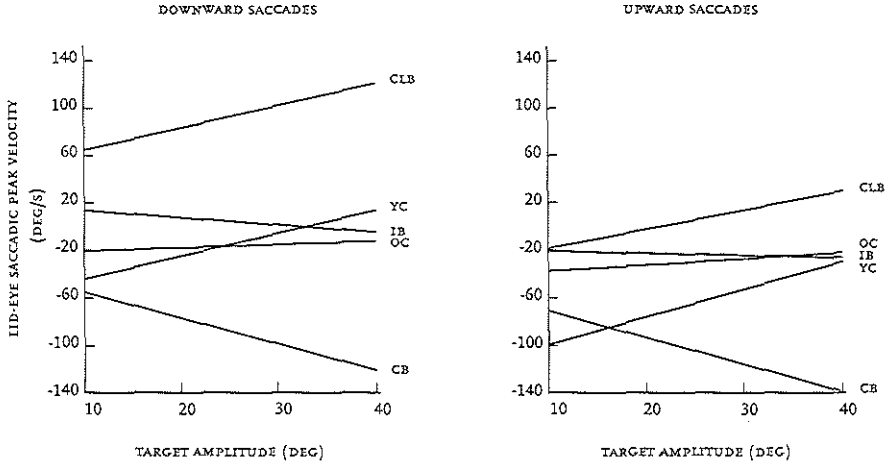


Figure 3. Regression lines for the estimated linear relationship of the saccadic peak velocity (lid-eye; in degrees per second), as a function of the target amplitude for each group.



CB = congenital blepharoptosis;

IB = involutional aponeurogenic blepharoptosis;

CLB = contact lens induced aponeurogenic blepharoptosis;

YC = younger control group;

OC = older control group.

Table 1: P-values for testing the null hypothesis that the regression lines of two groups coincide.

Comparison between groups	Lid-eye saccadic amplitude (deg)	Lid-eye saccadic peak velocity (deg/s)
YC versus OC	0.0663	0.0368 *
IB versus OC	0.8674	0.5675
CLB versus YC	0.0001 *	0.0012 *
CB versus YC	0.0001 *	0.0115 *
CB versus CLB	0.0001 *	0.0001 *
IB versus CLB	0.0177 *	0.0107 *

CB = congenital blepharoptosis;

IB = involutional aponeurogenic blepharoptosis;

CLB = contact lens induced aponeurogenic blepharoptosis;

YC = younger control group;

OC = older control group.

* Statistically significant difference at $P < 0.05$

Table 2: Estimated linear relationships of the difference in saccadic amplitude. Target amplitudes ranged from 10 to 40°, for the five groups and two saccadic directions considered. Data are mean degrees and values in parentheses are SE.

group	mean intercept (SE)		mean slope (SE)
	downward saccades	upward saccades	
CB	0.892 (0.712)	0.013 (0.757)	- 0.366 (0.040)
IB	0.755 (0.492)	- 0.124 (0.560)	- 0.060 (0.028)
CLB	2.445 (0.772)	1.566 (0.817)	0.013 (0.044)
YC	- 0.746 (0.550)	- 1.625 (0.611)	- 0.100 (0.031)
OC	0.450 (0.438)	- 0.429 (0.513)	- 0.063 (0.025)

Table 3: Estimated linear relationships of the difference in saccadic peak velocity. Target amplitudes ranged from 10 to 40° for the five groups and two saccadic directions considered. Data are mean degrees per second and values in parentheses are SE.

group	mean intercept (SE)		mean slope (SE)
	downward saccades	upward saccades	
CB	- 32.56 (25.99)	- 50.34 (27.19)	- 2.186 (1.087)
IB	12.17 (18.37)	- 17.81 (18.86)	- 0.512 (0.741)
CLB	52.13 (29.16)	- 39.77 (29.49)	1.644 (1.178)
YC	- 65.31 (20.67)	-116.99 (20.97)	1.971 (0.835)
OC	- 22.45 (16.40)	- 42.02 (16.71)	0.209 (0.661)

Table 4: Amplitude and peak velocity for 40° downward and upward lid and eye saccades. Amplitude is expressed as mean degrees; peak velocity is expressed as mean degrees per second. Values in parentheses are SD.

group	amplitude (deg)				peak velocity (deg/s)			
	downward saccades		upward saccades		downward saccades		upward saccades	
	lid	eye	lid	eye	lid	eye	lid	eye
CB	24.3 (5.2)	35.2 (2.6)	22.9 (4.0)	34.7 (1.8)	291.1 (45.2)	395.3 (84.6)	264.7 (72.3)	385.5 (62.6)
IB	32.7 (4.3)	34.8 (2.5)	31.3 (4.0)	34.5 (2.1)	348.9 (72.9)	361.1 (70.3)	295.6 (78.7)	341.1 (70.6)
CLB	40.3 (3.5)	36.4 (1.7)	37.3 (3.5)	35.7 (2.4)	490.5 (152.4)	358.2 (70.5)	411.1 (104.6)	408.9 (83.3)
YC	32.3 (5.4)	36.9 (2.4)	30.0 (4.7)	35.4 (1.7)	419.7 (143.7)	395.7 (94.7)	401.7 (11.4)	431.8 (83.3)
OC	33.7 (5.3)	35.9 (2.1)	31.8 (4.3)	35.0 (2.1)	343.7 (72.6)	352.5 (65.1)	360.7 (60.4)	395.7 (57.4)

Comparisons between Groups

Table 4 shows the mean amplitude *(in degrees)* and peak velocity *(in degrees per second)* for 40° lid and eye saccades *(upward and downward)* for all groups.

YC Versus OC

Lid saccades in the YC group could be readily distinguished from those of the OC group by saccadic peak velocity, but not by saccadic amplitude *(Table 1)*. The lid saccades in the OC group were, on average, slightly larger *(Table 4)* than those in the YC group. By contrast, the amplitudes of the associated eye saccades in the OC group were, on average, smaller than those in the YC group. In both control groups, eye saccades were larger than those of the lid *(Table 4)*. The YC group had, on average, higher peak velocities of both types of saccades, lid and eye, regardless of saccadic direction *(Table 4)*.

IB Versus OC

The lid saccades in the IB group could not be clearly distinguished from those in the age-matched control group by any lid saccadic parameter *(amplitude or peak velocity; Table 1)*, although, on average, slightly smaller lid saccades were made in the IB group *(Table 4)*. Both groups made lid saccades that were smaller than the associated eye saccades *(Table 4)*. In addition, the differences in saccadic amplitude between lid and eye saccades were somewhat smaller, on average, in the IB group than in the age-matched control group. In the IB group, lid saccadic peak velocity was affected by saccadic direction. Saccadic peak velocity was higher in downward than in upward saccades. By contrast, the peak velocities of downward and upward associated eye saccades were similar *(Table 4)*.

CLB Versus YC

Lid saccades in the CLB group could be readily distinguished from those in the YC group by saccadic amplitude and by peak velocity *(Table 1)*. Lid saccadic

amplitudes were, on average, larger in the CLB group than in the YC group *(Table 4)*. In both groups, downward lid saccades were larger than upward ones. In addition, lid saccades were larger than the associated eye saccades in the CLB group *(Table 4)*, whereas in the YC group the opposite was found: larger eye saccades than lid saccades. The difference between lid and eye saccades *(lid minus eye)* in the CLB group was largest for downward saccades and averaged 3.9° ± 3.3° for 40° saccades, and -4.6° ± 3.9° in the YC group. In the CLB group, downward lid saccades had, on average, higher peak velocities than upward ones (Table 4). The associated eye saccades showed contrary results: Saccadic peak velocities were higher in upward than in downward saccades. In addition, the eye saccadic peak velocities were similar for the two groups (Table 4).

CB Versus YC

Lid saccades made in the CB group were markedly smaller and had lower peak velocities than those of the YC group (Table 1). On average, downward lid saccades were slightly larger than upward ones in the CB group (Table 4). Lid saccades made in the CB group were significantly smaller than the associated eye saccades (Table 4). The difference between lid and eye saccades (lid minus eye) averaged 10.9° ± 3.5° for 40° downward saccades, and 11.8° ± 3.6° for 40° upward saccades. The amplitudes of eye saccades in the CB group were significantly smaller than those in the YC group (Table 4). Downward lid saccades had higher peak velocities than upward ones in the CB group. By contrast, the peak velocities of the associated eye saccades were similar for the two directions (Table 4).

CB Versus CLB

The CB group could be readily distinguished from the CLB group by lid saccadic amplitude and by its peak velocity (Table 1). On average, only slight differences in the amplitudes and peak velocities of the associated eye saccades were noted (Table 4).

IB Versus CLB

Significant differences in lid saccadic amplitude and its peak velocity were found between the two aponeurogenic blepharoptosis groups (Table 1). The lid saccades in the CLB group were, on average, larger and had higher peak velocities (Table 4).

4.5 Discussion

Our data, obtained through search coil registration, showed clear differences in the eyelid metrics of patients with either congenital or aponeurogenic blepharoptosis. In addition, marked differences were found between the two forms of aponeurogenic blepharoptosis (involutional and contact-lens-induced).

Aging affects the metrics of spontaneous blinks *(Sun et al., 1997)* and

vertical eye saccades *(Huaman and Sharpe, 1993)*. Our data confirmed aging's effects on vertical eye saccades: reduced amplitudes with significantly lower peak velocities. Lid saccades also displayed a reduced peak velocity with age, albeit, with an increased amplitude. We may speculate that changes in the elastic properties of the levator muscle, its aponeurosis and the eyelid tissues, contribute to these effects of aging, because the elastic fibers become fewer and thinner with age *(Stasior et al., 1993)*.

Because age-related *(involutional)* aponeurogenic blepharoptosis is assumed to be caused by disinsertion or laxity of the levator muscle aponeurosis *(Frueh, 1980; Anderson and Dixon, 1979)*, we expected to find a different amplitude and peak velocity in such patients with blepharoptosis, compared with the age-matched control group. However, no differences between the two groups were found, which suggests that either the anatomic changes that cause aponeurogenic blepharoptosis do not affect eyelid motility proper, or they are compensated for, or our recording method may have been too insensitive to detect any differences in eyelid motility. This result partially concurs with a previous study by Frueh and Musch *(1996)* who measured levator force and established no difference between patients with aponeurogenic blepharoptosis and the control group. There apparently is no muscular degeneration in aponeurogenic blepharoptosis *(Berke et al., 1995)*. Therefore, the integrity and motility of the levator neuromuscular system probably remains unaffected, despite a lower lid position with a higher lid crease in some older subjects.

The blepharoptosis associated with contact lens wear is clinically similar to that in patients with age-related aponeurogenic blepharoptosis, which suggests a similar pathogenesis. Of interest, our patients with CLB showed markedly different motility, which was not age-related. The amplitude and peak velocity they produced were significantly larger, suggesting that either the cause of the blepharoptosis was different, or that the compensatory oculomotor mechanisms of the two groups were different. Such mechanisms may vary with age.

Eyelid excursion relates to the number of functioning sarcomeres in a myofibril *(Faulkner et al., 1982)*. Muscle force, however, does not depend on this number but on the cross-sectional area of functioning muscle fibers *(Knuttgen, 1976)*. Maxwell et al. *(1981)*, in their study on a chronically stretched masseter muscle found an increased sarcomeres count, without any change in the cross-sectional fiber area. We therefore propose that repetitive stretching of an eyelid, such as may occur when removing a contact lens, might similarly increase the sarcomeres count and eyelid excursion. Lengthening of the levator muscle may occur, yielding a lower eyelid position. Such an explanation is corroborated by the finding of a strong correlation between levator function and exophthalmometer readings in Graves' disease *(Frueh, 1984)*. Muscle strength, however, is unaffected by stretching, as was demonstrated by Frueh and Musch *(1996)*.

Patients with congenital myogenic blepharoptosis clinically show a smaller eyelid amplitude, supposedly because of the poor development of the levator palpebrae muscle proper. We also found smaller eyelid amplitudes. Moreover,

saccadic peak velocity was disproportionately lower. Possibly, this was due to the absence of myofibrils and to changes in the elastic tissues of the levator muscle. Apparently, search coil registration can differentiate reliably between congenital myogenic blepharoptosis and aponeurogenic blepharoptosis.

In patients with bilateral blepharoptosis, the most ptotic upper eyelid was included for analysis, although the two were simultaneously recorded. Several clinical studies suggest that Hering's law of equal innervation of the extraocular muscles may apply to lid movements *(Schechter, 1978; Gay, 1967)*, which may lead to overelevation of an eyelid contralateral to a ptotic eyelid. Neuroanatomic studies in primates have shown that the motor neuronal pool for both levator palpebrae muscles lies within the unpaired central caudal nucleus *(Warwick, 1953; Porter et al., 1989; Fuchs et al., 1992)*. However, in eye movements Hering's law probably results from nonconjugate adaptation to the effects of aging and disease *(Fuchs et al., 1992; Lemij and Collewijn, 1991a; Lemij and Collewijn, 1991b; Lemij and Collewijn, 1992; Schor et al., 1990)*. The bilateral control of lid saccades is much less conjugate than that of eye saccades *(Wouters et al., 1995)*. Probably, adaptation occurs only if a functional need arises, (e.g., to retain sight in both eyes). It is unclear from our study to what extent, if any, an equal innervation of the lid movements, similar to Hering's law, affected our measurements.

We have demonstrated that search coil registration is of additional value in the examination of patients with blepharoptosis. However, we have not yet established its full clinical potential, notably on an individual level. The assessment of eyelid motility in other kinds of blepharoptosis would be of further interest.

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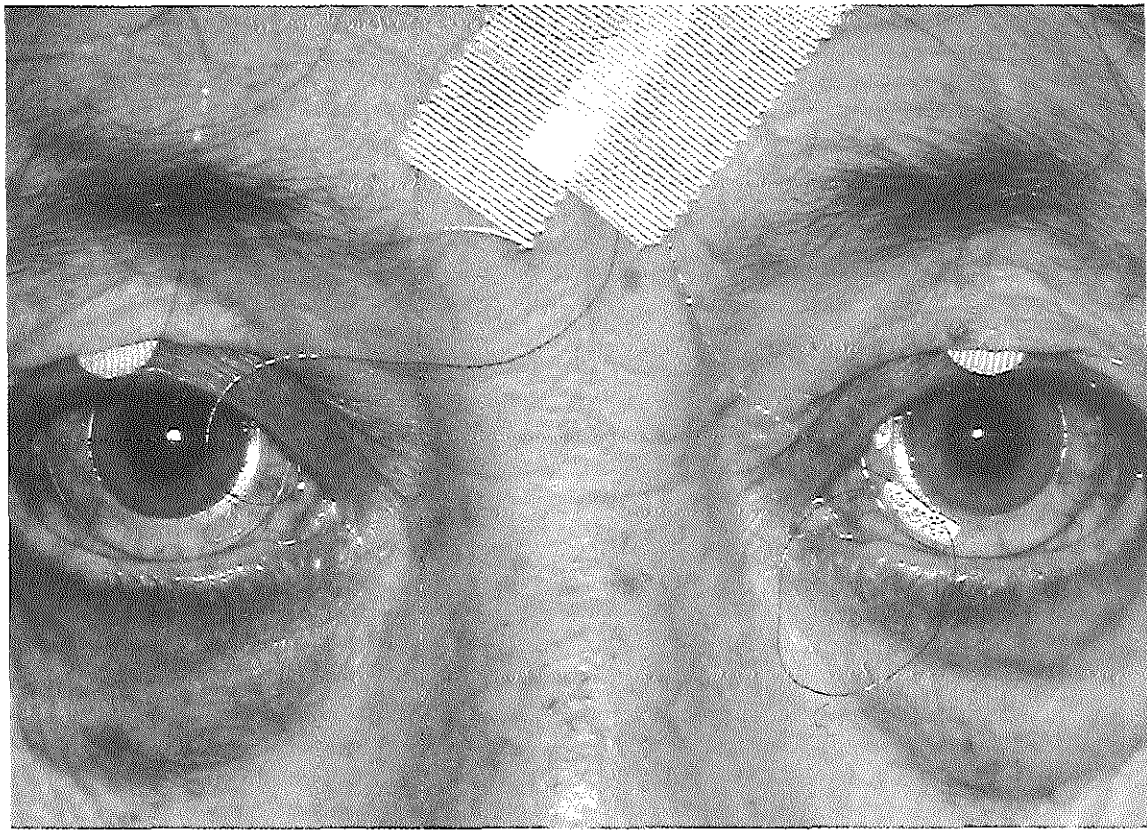
CHAPTER 5

SACCADIC MULTISTEPPING IN PARKINSON'S DISEASE AND THE EFFECT OF L-DOPA



5.1 Abstract

Purpose

A known phenomenon in patients with Parkinson's disease is called saccadic multistepping. In this pilot study we explored the possibilities of discriminating patients with Parkinson's disease from controls by quantifying saccadic multistepping into the newly derived multistepping index (MSI). We also used this MSI to monitor the effect of l-dopa substitution therapy. Furthermore we investigated saccadic conjugacy of Parkinsonian saccades.

Methods

Horizontal and vertical eye saccades of 12 patients (mean age 70.2 years) with ideopathic Parkinson's disease were recorded with the magnetic search coil technique. Nine patients were tested before l-dopa substitution therapy. Of these, 6 patients could be tested again 3 months after introduction of l-dopa therapy, in addition to 3 patients who where already using l-dopa therapy. Results were compared with those of 15 age matched controls (mean age 72.0 years). The MSI was defined as the number of accessory saccades per gaze shift. Saccadic (dis)conjugacy was defined as the relative disconjugacy (RD), being the difference of the saccadic amplitude between OS and OD divided by the target amplitude.

Results

The mean MSI in untreated patients (2.34; SD = 0.95) was significantly higher than in control subjects (0.76; SD = 0.50; $P < 0.001$). The mean MSI in treated patients (1.72; SD = 0.80) was significantly lower than in untreated patients ($P = 0.022$). If only the 6 patients measured before and after introduction of treatment were considered, there was a significant decrease in mean MSI by, on average, 0.50 (range 0.08-0.86; $P = 0.012$), reflecting an improvement in oculomotor function. The RD of patients (1.94%) did not differ significantly from that of controls (1.82%).

Conclusions

Saccadic multistepping was observed in our patients and was quantified into the newly derived multistepping index (MSI). The MSI is highest in patients with Parkinson's disease, and discriminates well between patients and controls. The MSI is highest in upward saccades and in saccades of large amplitudes. There is a significant decrease in MSI after introduction of l-dopa therapy, however, the effect is confounded with time. A randomized trial is required to properly investigate the effect of therapy. The MSI may then be a useful tool for research into Parkinson's disease where a quantitative approach is needed, or where quantitative treatment monitoring of patients with Parkinson's disease is required.

5.2 Introduction

Parkinson's disease is a syndrome caused by degeneration of dopamine producing neurons in the substantia nigra of the brain, resulting in a disordered motor performance, clinically characterized by tremor, rigidity, and bradykinesia. Eye movements may also be affected. Of these, rapid volitional eye movements are fragmented into multiple saccades *(Walsh and Hoyt's, 1985)*.

Saccadic eye movements enable us to quickly shift our gaze from one object to another. Many saccadic parameters have also been investigated in patients with Parkinson's disease *(White et al., 1983; Bronstein and Kennard, 1985; Gibson and Kennard, 1987; Rascol et al., 1989)*. To our knowledge, however, there is no saccadic parameter that distinguishes between normal and abnormal saccades in a simple and unambiguous way.

The effect of l-dopa substitution therapy on oculomotor function is somewhat unclear. Corin et al. *(1972)*, found no overall improvement of oculomotor performance on a semi-quantitative scale: only 2 out of 29 patients improved. Gibson et al. *(1987)*, found an improvement of saccadic accuracy and peak velocity, and Rascol et al. *(1989)*, reported an improvement in saccadic accuracy but not in saccadic latency or in peak velocity. It was the aim of our study to devise a parameter that would discriminate between normal and Parkinsonian saccades, and to investigate the effect of l-dopa on oculomotor function.

A phenomenon observed in patients with Parkinson's disease is called multistepping *(Teräväinen and Calne, 1980)*, in which a saccade reaches its target in multiple steps rather than in one or two *(typically, a large, so called, primary saccade is followed by one or a few secondary saccades, also called corrective saccades)*. Crawford et al. *(1989)*, reported a higher incidence of multiple saccades in Parkinsonian patients who were taking their normal medication. Lueck et al. *(1992)*, mentioned that Parkinsonian patients showed greater evidence of multistepping than control subjects, but these results failed to reach statistical significance. Multistepping has not yet been investigated in a quantitative approach, nor has the effect of l-dopa therapy on multistepping been previously described.

In this pilot study, we explored the possibilities of using the multistepping phenomenon to discriminate patients with Parkinson's disease from healthy controls, and to determine the effect of l-dopa on saccadic multistepping. We recorded saccades of patients before, and during l-dopa therapy and compared the results with those of age matched controls. To quantitate saccadic multistepping, we defined a multistepping index (MSI) that distinguished very well between patients and controls. Also, we showed a decrease in the MSI in patients taking l-dopa. Finally, we showed that saccadic conjugacy in Parkinsonian saccades is unimpaired.

5.3 Materials and Methods

Patients / Control Subjects

Twelve patients (6 men and 6 women; mean age 70.2 years) with ideopathic Parkinson's disease participated in the study. Each patient with Parkinson's disease was analysed and scaled by the participating Neurologist according to the New York rating scale devised by Hoehn and Yahr and modified by Lieberman *(1974)*. All patients were mildly to moderately affected (stage I - II) on this rating scale. Clinical data of patients are shown in Table 1. Patients showed no clinical evidence of dementia.

Nine newly diagnosed patients (mean age 70.1 years) had their eye movements recorded before initiating l-dopa substitution therapy. Of these, six patients (mean age 71.3 years) could be recorded again after 3 months of medication. In addition, we recorded eye movements of 3 patients (mean age 70.3 years) who were already using l-dopa substitution therapy for a period of 3-15 weeks. This resulted in 9 patients recorded before medication and 9 patients recorded during treatment; 6 patients were in both groups. Fifteen age-matched controls (8 men and 7 women; mean age 72.0 years) recruited from hospital staff members and spouses of patients served as controls.

All investigations adhered to the tenets of the Declaration of Helsinki and were approved by the institutional human experimentation committee. Informed consent was obtained from each subject after the nature of the procedure had been fully explained.

Table 1. Of all 12 patients, age (years), stage of disease (Lieberman), and the mean multistepping index (MSI) are presented before and after introduction of l-dopa treatment. Patients 7, 8 and 9 were only measured before treatment, MSI during treatment is not available (n/a). Patients 10, 11 and 12 were only measured after treatment had been initiated, MSI before treatment is not available (n/a).

Clinical patient data

		before treatment		during treatment	
Patient	Age (years)	Stage	mean MSI (SD)	Stage	mean MSI (SD)
1	65	IR0T0B1G1D0	2.99 (1.11)	IR0T0B0G0D0	2.12 (0.83)
2	74	IIA3R2T0B2G1D2	2.75 (0.90)	IIR1T0B1G1D1	2.19 (0.69)
3	76	IIR2T2B2G1D1	2.48 (1.0)	IIR1T0B1G0D0	2.25 (0.98)
4	65	IR2T2B0G0D0	1.94 (0.58)	IR1T1B0G0D0	1.23 (0.40)
5	73	IIR2T0B2G1D0	1.90 (0.93)	IIR1T0B1-2G0-1D0	1.89 (0.70)
6	75	IIR0T0B1G1D0	1.42 (0.60)	0R0T0B0G0B0	0.86 (0.39)
7	64	IR2T2B1G1D0	2.63 (0.74)	IR1T0B0G0D0	N/A
8	75	IIR1T1B2G1D0	2.98 (0.65)	0R0T0B0G0D0	N/A
9	64	IIR2T2B1G1D0	2.00 (0.58)	IIR0T0B1G0D0	N/A
10	66	IR1T2B1G1D0	N/A	IR1T1B0G0D0	1.34 (0.74)
11	78	IIR2T0B1G1D0	N/A	IIR1T0B0G0D0	2.11 (0.39)
12	67	IIR2T0B2G2D0	N/A	0R0T0B0G0D0	1.49 (0.56)

Recording Technique

We recorded eye movements with the magnetic search coil technique *(Robinson, 1963; Collewijn et al., 1975)* using commercially available search coils (Skalar Medical, Delft, The Netherlands). The procedure used in our hospital has been described in detail elsewhere *(Wouters et al., 1995)*. In short, the subjects were seated facing a stimulus screen containing light emitting diodes (LEDs), at a viewing distance of 1.0 m. De LEDs were positioned 10°, 20°, 30°, and 40° apart, symmetrically around the straight-ahead position, along both the horizontal and the vertical meridian. Head movements were restricted by a chin rest and forehead support. All recordings were amplified, low-pass filtered at 120 Hz, digitized with 12-bit precision, sampled at 250 Hz and stored for off-line analysis.

Measurement Procedure

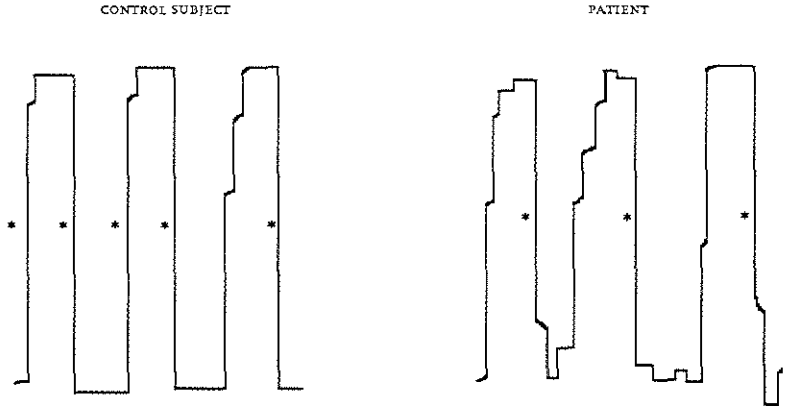
Subjects were asked to alternate their gaze, on the mark of an electronically generated tone, between two constantly lit LEDs, thus making so-called volitional saccades *(Lueck et al., 1992)*. Presentation order of amplitudes and meridians was randomized. The amount of time where the subject had to make saccades of one amplitude and in one meridian was called a trial; each trial was preceded by a period for the subjects to practise saccades in this particular meridian and of this amplitude. Trials for controls lasted 16 seconds and had the tone generator set to 1.0 Hz. Patients needed more time to shift their gaze from one lit LED to the other so they had the generator set to 0.5 Hz in 32 seconds lasting trails.

A computer program was used for automated and observer indepedent saccade detection and analysis. Saccadic onset was detected if the acceleration exceeded 1000°/second^2 and the velocity exceeded 25°/second. Saccadic offset was defined by a deceleration more than 1000°/second^2 and a velocity less than 50°/second.

Multistepping Index (MSI)

Depending on when they occur in time, saccades are usually divided into primary and secondary (or corrective) saccades. To quantitate multistepping, however, we classified saccades on the basis of their magnitude instead of their occurrence in time. Therefore, we distinguished main saccades and accessory saccades. A saccade was a main one if its amplitude reached 70% or more of the target amplitude. All other saccades were called accessory, whether they occurred before, after or without any main saccade. The multistepping index (MSI) was defined as the number of accessory saccades divided by the number of gaze shifts. This is illustrated in Fig. 1 (see also results section: a typical subject). The MSI was initially calculated separately for both eyes. Because of the high saccadic conjugacy and the strong correlation between the MSI for the right eye and the MSI for the left eye (Pearsons correlation coefficient = 0.9998), the MSI for both eyes was averaged per trial. A mean MSI for every subject was obtained by pooling all MSI values for all 4 amplitudes and all 4 directions.

Figure 1. An example of how the multistepping index (MSI) was calculated for a typical control subject and for a typical patient with Parkinson's disease, for 20° vertical eye saccades. Main saccades are marked with an asterisk; all other saccades are accessory.



	control subject	patient
total no. of saccades detected	10	16
total no. of main saccades	5	3
total no. of accessory saccades	5	13
total no. of gaze shifts	6	6
Multistepping Index	0.83	2.17

Saccadic Conjugacy

To investigate saccadic conjugacy, the relative disconjugacy (RD) was computed by dividing the difference of the amplitude of the main saccade between OS and OD by the target amplitude. In this way, a low RD reflects a high saccadic conjugacy. The RD was pooled over all amplitudes and directions resulting in the mean RD per patient. Differences in saccadic conjugacy between groups were tested by comparing mean RD values.

Statistics

Differences in mean MSI and mean RD values between groups were tested for statistical significance with a student's t-test. The statistical significance of the decrease in MSI of the six patients that were recorded before and after starting therapy was tested with a paired student's t-test.

A (rm ANOVA) model repeated measures analysis of variance for untreated patients and controls was used to test wether the MSI, and the difference in MSI between the two groups, varied by saccadic direction and/or

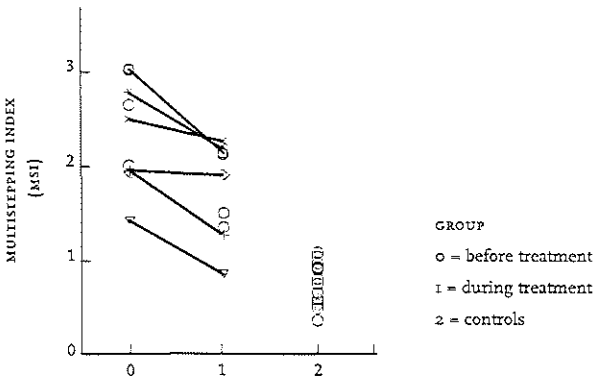
by saccadic amplitude. The same was done in a model for patients before and during treatment. Imbalance of data (not all patients were measured before and during treatment) was accounted for by the 'maximum likelihood method' in the 'mixed procedure' of the SAS statistical package. The level of statistical significance was set at a = 0.05.

5.4 Results

A typical subject

Figure 1 shows the recordings made by a 74 year old control subject, and those of a 73 year old patient with Parkinson's disease, both for 20° vertical eye saccades. Saccades of the control subject consisted mainly of a primary saccade sometimes followed by a secondary or corrective saccade. In the present context, we distinguish a main saccade, sometimes followed by an accessory saccade. In the patient, however, many hypometric accessory saccades preceded or followed the main saccade; occasionally, a main saccade could not even be identified. In this example, 5 accessory saccades were detected in the tracings of the control subject and 13 in the tracings of the patient. Six gaze shifts are displayed for both subjects, resulting in a mean MSI of 0.83 (5/6) for the control subject vs. 2.17 (13/6) for the patient.

Figure 2. Shows the mean MSI values for the Parkinson patients before treatment, during treatment, and for the age-matched control group. The mean MSI values of the six Parkinson patients who had been measured twice, before and during treatment, have been connected.



MSI of patients vs. controls and the effect of l-dopa

For all saccadic directions and amplitudes the MSI was pooled together and called mean MSI (Table 1). Figure 2 shows the mean MSI for each investigated group of patients and those of the age matched control group. The mean MSI in untreated patients (2.34; SD = 0.95) was higher than in control subjects (0.76; SD = 0.50; P < 0.001; Fig. 2). There was no overlap between groups. The mean MSI in treated patients (1.72; SD = 0.80) was significantly lower than in untreated patients (P = 0.022). If only the 6 patients measured before and after treatment were considered, there was a significant decrease in mean MSI by, on average, 0.50 (range 0.08-0.86; P = 0.012).

Table 2. The MSI is modelled by a rm ANOVA as a function of saccadic amplitude (A). The slope (amplitude effect) differs between patients before treatment and controls. The intercept depends on saccadic direction. In the final column the two functions are substracted, and yield the difference in MSI between the group of untreated patients and the control group.

Effect of saccadic amplitude and direction on MSI in patients before treatment and controls.

	MSI for:		Difference in MSI between:
Saccadic direction	patients before treatment	controls	untreated patients and controls
UP	2.40+0.025*A	0.75+0.011*A	1.65+0.014*A
DOWN	1.42+0.025*A	0.16+0.011*A	1.26+0.014*A
RIGHT	1.59+0.025*A	0.52+0.011*A	1.07+0.014*A
LEFT	1.37+0.025*A	0.50+0.011*A	0.87+0.014*A

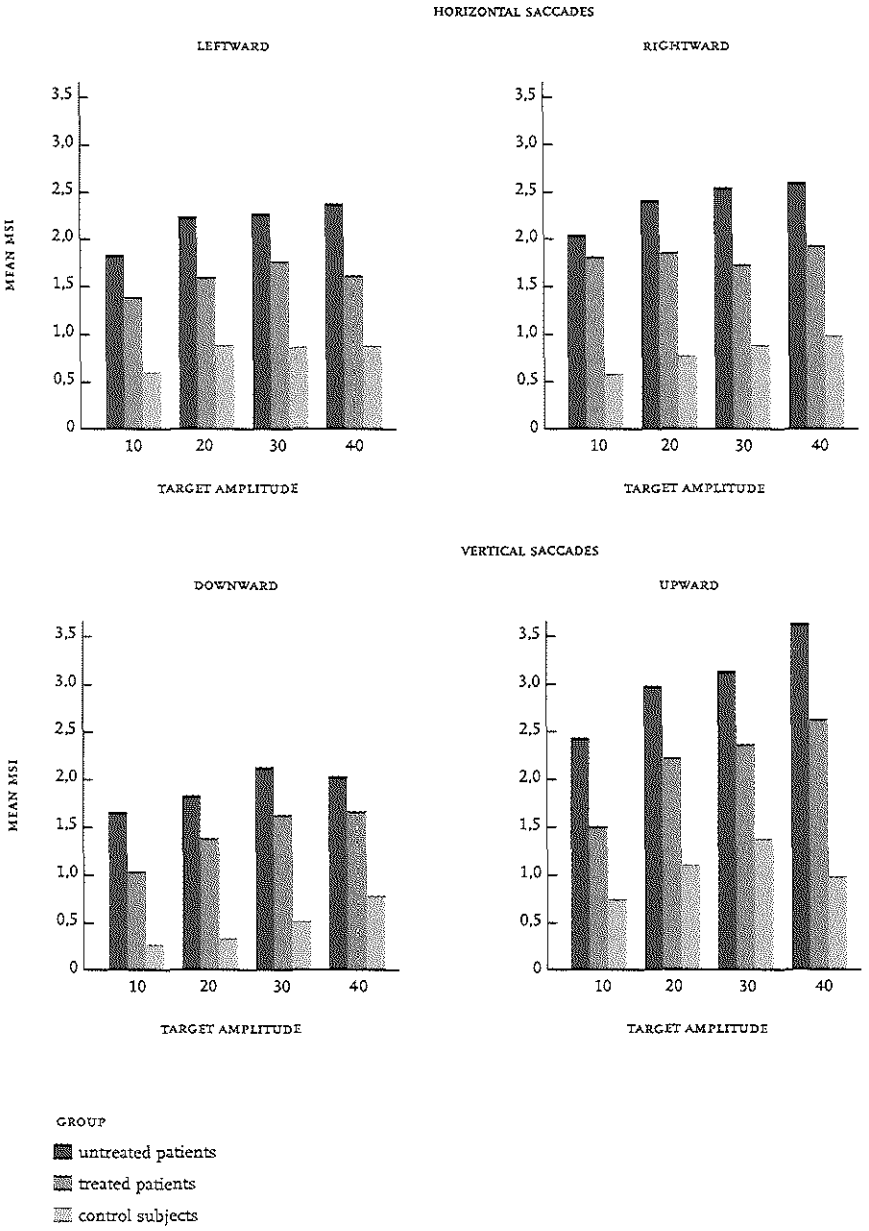
rm ANOVA model for untreated patients vs. controls

The effect of saccadic amplitude and direction in this model has been summarized in Table 2. The MSI is modelled as a linear function of amplitude, with an intercept depending on saccadic direction; the intercepts and slopes differed between untreated patients and controls. The slope represents the amount of MSI increase per degree amplitude increase. There was no evidence of non-linearity in the effect of amplitude.

1. Amplitude effect (slope)

The MSI linearly increased as the saccadic target amplitude increased, irrespective of saccadic direction (Fig. 3). This amplitude effect was statistically significant (P = 0.0001); the slope was 0.011 for controls and 0.025 in untreated patients. The difference between these two slopes was also significant (P = 0.011).

Figure 3. The average MSI for the group of Parkinson patients before and during treatment and for the age-matched control group in each saccadic direction and for each target amplitude (deg) are presented.



2. **Direction effect (intercept)**

The direction effect was significant in the control group (P = 0.0002). The intercepts for all directions have also been prestented in Table 2. For untreated patients and for controls the MSI was highest in upward saccades (intercept 2.40 and 0.75, respectively). For example, 30° upward saccades would, on average, yield an MSI of 3.15 in treated patients, and 1.08 in controls.

Also presented in Table 2 is the difference in MSI between untreated patients and controls; this difference is highest where the intercept is highest (1.65 in upward saccades), and where saccadic amplitude is high (e.g. 40°).

Table 3. The MSI is modelled by a rm ANOVA as a function of saccadic amplitude (A). The slope (amplitude effect) differs between patients before and during treatment. The intercept depends on saccadic direction. In the final column the two functions are substracted, and yield the difference in MSI between the group of patients before and during treatment.

Effect of saccadic amplitude and direction on MSI in patients before and during treatment.

	MSI for patients:		Difference in MSI between patients:
Saccadic direction	before treatment	during treatment	before and during treatment
UP	2.48+0.020*A	1.66+0.020*A	0.82
DOWN	1.50+0.020*A	0.94+0.020*A	0.56
RIGHT	1.67+0.020*A	1.35+0.020*A	0.32
LEFT	1.49+0.020*A	1.14+0.020*A	0.35

rm ANOVA model for patients before and after treatment

The effect of saccadic amplitude and direction in this model has been summarized in Table 3. Again, the MSI is modelled as a linear function of amplitude, with an intercept depending on saccadic direction; the intercepts differed between patients before and during treatment.

1. **Amplitude effect (slope)**

The MSI linearly increased as the saccadic target amplitude increased (Fig. 3). This amplitude effect was significant (P = 0.0002); the slope was 0.015 in treated patients and 0.025 in untreated patients. This difference, however, was not significant (P = 0.10). From here on the statistical model assumed a common slope of 0.020.

2. **Direction effect (intercept)**

The direction effect was significant in patients before treatment

(P = 0.0001) and significantly different from that in patients during treatment (P = 0.0001). The intercepts for all directions have also been presented in Table 3. For untreated patients and treated patients the MSI was highest in upward saccades *(intercept 2.48 an 1.66, respectively)*. For example, 30° upward saccades would, on average, yield an MSI of 3.08 in patients before treatment, and 2.26 in patients during treatment. Due to the imbalance in our data, the estimates for the intercept for patients before treatment were not identical in both models.

Also presented in Table 3 is the difference in MSI between untreated patients and treated patients; this difference is highest in upward saccades (intercept = 0.82).

Saccadic Conjugacy

Saccadic conjugacy as we defined it, was not impaired in Parkinson's disease. The relative disconjugacy (RD), reflecting the difference in saccadic amplitude of main saccades between left and right eye expressed as a percentage of target amplitude, was 1.94% (SD = 1.21) for untreated patients, 1.94% (SD = 0.74) for treated patients and 1.82% (SD = 0.85) for controls. These differences were not significant.

5.5 Discussion

The main finding of our study is that saccadic multistepping can be objectively quantified in the newly devised multistepping index (MSI), discriminating well between patients with Parkinson's disease and controls. The lowest mean MSI value in untreated patients was 1.42; the highest mean MSI value in controls was 1.08, indicating high sensitivity and specificity. In addition, we conclude that there is a decrease in MSI after the introduction of l-dopa therapy. A randomized trial is required to properly investigate the effect of therapy.

Although past studies on Parkinsonian saccades differ greatly in research design and outcome, they all conclude that Parkinsonian saccades are hypometric (i.e., have low saccadic amplitudes compared to target amplitude) *(White et al., 1983; Rascol et al., 1989; Crawford et al., 1989; Lueck et al., 1992; DeJong, 1971; Melvill Jones and DeJong, 1971; Gibson et al., 1987; Lueck et al., 1990; Ventre et al., 1992)*. This is in agreement with the high prevalence of accessory saccades (that are hypometric) found in our patients. However, as pointed out by Crawford *(1991)*, earlier eye movement research had concentrated mainly on single individual saccades, thus overlooking the fact that saccades can appear as continuous sequences, as in Parkinson's disease. This continuous sequence has now been quantified in our multistepping index.

Multistepping in Parkinsonian saccades has been mentioned several times after it was first reported by Teräväinen et al., 1980; Crawford et al., 1989; Lueck et al., 1992. The study by Crawford et al. *(1989)* was the only one to demonstrate significant differences in multistepping between patients and controls. Our results

also show that multistepping was a specific feature of Parkinsonian saccades. In addition to Crawford's study, where multistepping was either present or absent, we devised the MSI, a continuous parameter probably allowing more subtle distinction as compared to a dichotomous scale. To our knowledge, this is also the first study that assessed multistepping in untreated patients, and the effect of l-dopa. In our group of patients, that was relatively small, the MSI discriminated well between normal and Parkinsonian saccades, and improved significantly after the introduction of l-dopa therapy, indicating improvement of oculomotor performance, however, the effect is confounded with time. It would be interesting to see whether the MSI has the same high sensitivity and specificity in a larger group of patients, and whether the MSI correlates with clinical signs and symptoms.

To our knowledge, there are no studies to date that have investigated voluntary vertical saccades in untreated Parkinson's disease. Corin et al. *(1972)* reported that 75% of patients had abnormal vertical saccades. However, his observations consisted of clinical assessments of saccades on a semi quantitative scale. Tanyeri et al. *(1989)*, who used search coils for their measurements, found that vertical (reflex) saccades were unaffected in patients with Parkinson's disease who were taking their normal (dopaminergic) medication. Interestingly, our results show that the MSI of vertical saccades is not only abnormal in patients, but that upward saccades are even most affected. We also showed that the MSI of vertical saccades decreased after the introduction of l-dopa therapy.

The MSI provides quantitative data that is objective and easy to obtain. It seems to quantitate a characteristic part of Parkinsonian saccades and might thus be useful for basic research regarding pathophysiology of the disease. Upward saccades of large amplitudes seem to be most useful since they are relatively most affected in Parkinson's disease. The MSI also holds potential to monitor effectiveness of any new Anti-Parkinsonian drugs; upward saccades of any amplitude seem to be most useful for this purpose. Whether the MSI will be of use in a clinical setting, remains to be seen.

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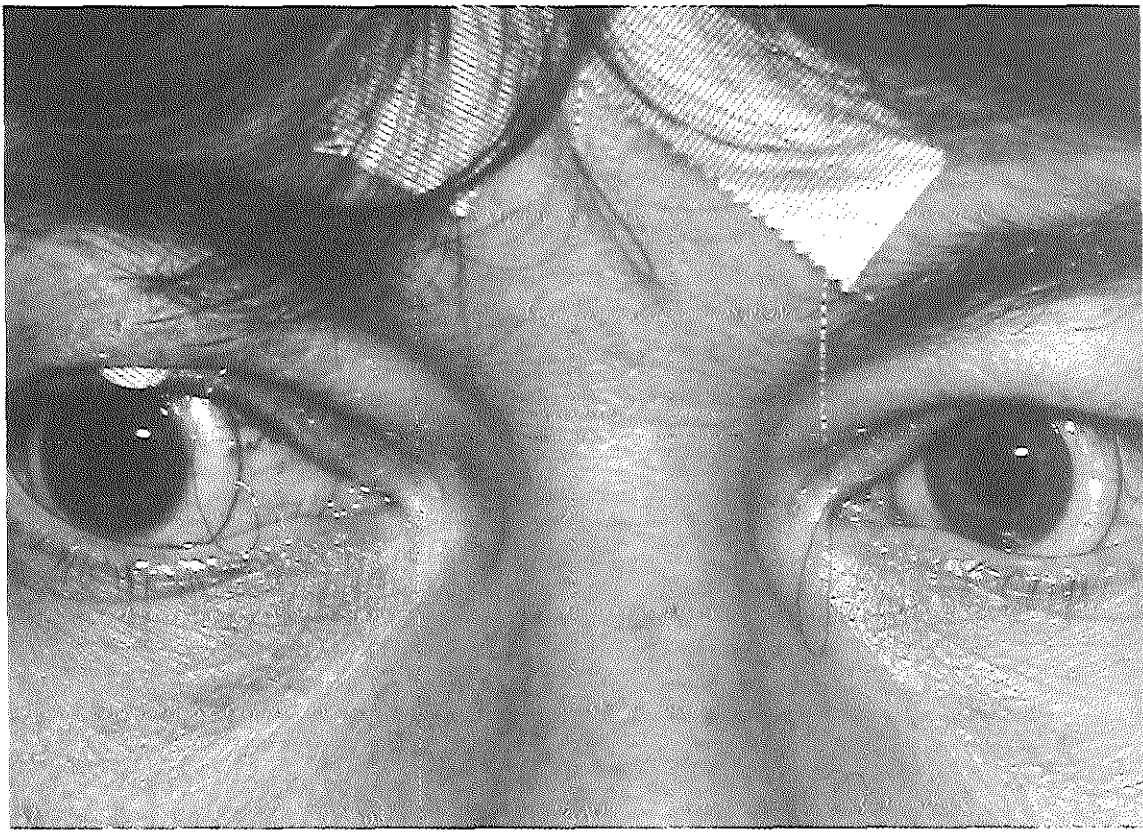
CHAPTER 6

SUMMARY

SAMENVATTING



Summary

As the central issue of this thesis we investigated the motility of the eye, the eyelid and their mutual relations in vertical movements. Eye movements were recorded with magnetic induction coils. Through a modification of the search coils we could apply the same recording method to record the eyelid movements. The eye and lid movements of interest were saccades. Saccades are fast eye movements which serve to direct gaze from one object of interest to another. Becker and Fuchs *(1988)* discovered characteristic similarities in motility between saccades of the eye and eyelid which led them to call the eyelid movements associated with vertical eye saccades "lid saccades". In this thesis we therefore speak of eye and lid saccades.

The dual recording technique enabled us to analyse simultaneous eye and lid movements and correlate lid motility directly with those of the concomitant eye movements. Therefore, we could exclude from the analysis any lid movements that occurred in between two eye saccades. In addition, we could exclude blinks from the analysis. Blinks are accompanied by converging eye movements *(Collewijn et al., 1985)* which were detected because of the dual recording method. The advantage of dual registration is emphasized again in Chapter 4 were we analysed lid motility in various groups of patients with blephaptosis. In the data analysis we could counteract possible side effects of eye motility variation on the lid motility metrics.

Chapter 2 contains an appraisal of the use of induction coils on eyelids. A linear correlation is found between the rotation of the eyelid and its vertical displacement. Our findings show that using induction coils on eyelids for the purpose of scientific research, such as conducted previously by, for example, Becker and Fuchs *(1988)*; Evinger et al. *(1991)* and Guitton et al. *(1991)*, is indeed justified. We also assessed whether the actual position of the coil on the eyelid affects the recordings and thereby indirectly influences the results of the measurements. The positioning proved to have a significant effect on the measured amplitude of the eyelid's rotation. Of foremost importance in Chapter 2, however, is the experiment to assess the conjugacy of the eyelids. Lid saccades were expected to show good conjugacy, as the eyelids share their premotor saccadic control with the eye saccades, that are conjugate. Yet lid saccades were found to be considerably less conjugate than the concomitant eye saccades. Our results do confirm the notion of a control shared by both eye and lid saccades. The onset of the latter invariably takes place shortly after that of the former. Moreover, the saccades of the two eyelids were found to be similar in duration and their onset to be virtually simultaneous.

In Chapter 3, we examine whether the eye saccades produced by patients suffering from Graves' disease are essentially different from those recorded in normal subjects. While Graves' disease is primarily a thyroid condition, patients present with deteriorating soft eye parts that possibly indicate an immune system failure. The condition is characterized by restrictive myopathy, in which the

muscles of the eyes may be affected in equal measures but asymmetric muscle enlargement is also frequently found, the asymmetry possibly being reflected in the nonconjugacy of the saccades. Additional to this parameter, the main sequence of the saccades was taken into account in the analysis. The main sequence denotes the relationship between the amplitude and the velocity of the saccade. Feldon et al. *(1990)* demonstrated an abnormally low saccadic velocity in Graves' disease patients. The two saccadic parameters we applied for the purposes of this work, i.e. conjugacy and velocity, allowed the saccades produced by patients suffering from Graves' disease to be distinguished from those made by normal subjects. No simple correlation could be established between the patients' degree of saccadic nonconjugacy and their main sequence; either one or both could be abnormal. The saccades produced by those at risk of developing this ophthalmopathy may also be affected, although further research is needed to substantiate such a possibility.

Chapter 4 deals with blepharoptosis. Specifically, we evaluate the possibility of differentiating between the various causes of the condition through an analysis of eyelid saccades. The vertical eyelid aperture, i.e. the distance between the lower eyelid and the upper eyelid, is reduced in blepharoptosis, which may be congenital or develop at any moment in time. The congenital variant may be easily distinguished, clinically, from its developed, aponeurogenic counterpart. The latter may be divided into two categories, one being caused by wearing contact lenses and the other being age-related and involutional. Two groups of normal subjects, each with an average age equal to that of the group of patients, were analysed in an identical fashion. The eyelid saccades recorded were shown to be distinct, both in amplitude and in velocity, for each group of patients researched. For example, 40° downward lid saccades in the congenital blepharoptosis group averaged 22.9° ± 4.0° (SD), whereas in involutional and rigid-contact-lens-induced blepharoptosis, lid saccadic amplitude averaged 32.7° ± 4.3° and 40.3° ± 3.5°, respectively. The difference in the dynamics of the saccades produced by the two, clinically indistinguishable, forms of aponeurogenic blepharoptosis, was remarkable. Although lid saccades display a peak velocity reducing with age, the age difference between the two groups could not explain the variations in saccadic amplitude and velocity we established. In further research, for example into congenital blepharoptosis, it would be of interest to determine whether eyelid metrics may be correlated with the severity of the condition and the necessary recession of the levator aponeurosis, with a view to achieving optimum results from surgical intervention.

Chapter 5 contains an analysis of the saccades produced by patients suffering from Parkinson's disease. A recognized symptom of this condition is the production of hypometric saccades, that is to say that several saccades (multistepping) are required to train the eyes onto the intended target, whereas normal subjects usually require a single corrective or accessory saccade, apart from the primary one. The number of corrective saccades per gaze shift was expressed in a multistepping index (MSI). The saccades produced by patients suffering from

Parkinson's disease achieved a significantly higher MSI rating than those made by normal subjects. Treating the patients with l-dopa brought about a positive effect on the MSI rating, indeed a significant improvement was found. The analysis of saccades therefore provides a useful method for quantifying Parkinson's disease and for assessing the benefits of l-dopa treatment.

Samenvatting

Centraal in dit proefschrift staat de motiliteit van het oog, het ooglid en de onderlinge interactie bij verticale bewegingen. De bewegingen van het oog werden vastgelegd met magnetische inductiespoelen. Door de hierbij gebruikte search coils te modificeren kon dezelfde registratiemethode worden gebruikt om de bewegingen van het ooglid vast te leggen. De onderzochte bewegingen van zowel het oog als het ooglid waren saccades. Saccades zijn snelle oogbewegingen die dienen voor refixatie. Becker en Fuchs *(1988)* vonden karakteristieke overeenkomsten in motiliteit tussen saccades van het oog en ooglid en noemden de geassocieerde bewegingen van het ooglid bij verticale oogsaccades 'lid saccades'. In dit proefschrift wordt daarom gesproken over oog dan wel lid saccades.

Door de gelijktijdige registratie van zowel oog als lid saccades kon de motiliteit van het ooglid direkt gecorreleerd worden aan die van het oog. Hierdoor konden bewegingen van het ooglid die optraden tussen twee oog saccades in uit de analyse worden gehaald. Evenzo konden knipperbewegingen buiten de analyse gehouden worden. Knipperbewegingen gaan gepaard met convergerende oogbewegingen *(Collewijn et al., 1985)* die door de gelijktijdige registratie van oog en ooglid bewegingen werden ontdekt. Het voordeel van gelijktijdige registratie wordt nog eens benadrukt in hoofdstuk 4 waar de motiliteit van het ooglid bij verschillende groepen patiënten met ptosis werd geanalyseerd. In de analyse kon het effect van de oogbeweging op de beweging van het ooglid worden geneutraliseerd.

In hoofdstuk 2 werd het gebruik van de inductiespoelen op de oogleden geëvalueerd. Een lineair verband werd aangetoond tussen de rotatie en de verticale veplaatsing van het ooglid. Het gebruik van de inductiespoelen op de oogleden voor wetenschappelijk onderzoek zoals al eerder uitgevoerd door onder andere Becker en Fuchs *(1988)*; Evinger et al. *(1991)* en Guitton et al. *(1991)* bleek op basis van onze bevindingen gerechtvaardigd. Wij beoordeelden tevens of de positie van de inductiespoel op de oogleden een effect had op de registraties en daarmee indirect op de uitkomst van het onderzoek. De positionering bleek een significant effect te hebben op de gemeten rotatie grootte van het ooglid. Het belangrijkste experiment in hoofdstuk 2 bestond uit het beoordelen van het conjugaat zijn van lid saccades. Conjugatie kon worden verwacht daar de premotore aansturing wordt gedeeld met de aansturing van de oog saccades die conjugaat bewegen. De lid saccades bleken echter opmerkelijk minder conjugaat dan de oog saccades. De data pleiten echter toch voor een gezamenlijke en gedeelde premotore aansturing van oog en lid saccades. Het begin van de lid saccades lag altijd kort achter dat van

de oog saccades. Daarnaast duurden de lid saccades van beide oogleden nagenoeg evenlang en lag het beginpunt van beide lid saccades ongeveer gelijktijdig.

In hoofdstuk 3 werd getoetst of de oogsaccades van patiënten met de ziekte van Graves wezenlijk verschilden ten opzichte van saccades bij normale proefpersonen. De ziekte van Graves is primair een schildklier aandoening waarbij aanwijzingen bestaan voor een immuungerelateerde aantasting van de weke delen van het oog. De ziekte wordt gekenmerkt door een restrictieve myopathie waarbij de oogspieren in meer of mindere mate kunnen zijn aangedaan. Beide ogen kunnen in gelijke mate zijn aangetast, maar asymmetrische spiervergroting komt ook veelvuldig voor. Deze asymmetrie zou mogelijk zijn terug te vinden in het niet conjugaat zijn van de saccades. Naast deze parameter werd ook de main sequence van de saccades in de analyse betrokken. De main sequence beschrijft de relatie tussen de amplitude en de snelheid van de saccade. Feldon et al. *(1990)* toonde aan dat de saccade snelheid abnormaal laag kan zijn bij patiënten met de ziekte van Graves. Met de twee door ons gehanteerde saccadische parameters, het conjugaat zijn en de snelheid, bleek differentiatie tussen de saccades van patiënten met de ziekte van Graves en normale proefpersonen mogelijk. Geen eenduidig verband kon worden gevonden tussen de twee gebruikte saccadische parameters. Bij individuele patiënten was of de ene saccadische parameter afwijkend, of de andere of beiden. Saccades bij patiënten met het risico om de orbitopathie te ontwikkelen kunnen mogelijk al afwijkend zijn. Aanvullend onderzoek bij deze specifieke groep patiënten kan dit eventueel aantonen en leiden tot vroegtijdige interventie.

In hoofdstuk 4 werd getoetst of differentiatie tussen de verschillende oorzaken van blepharoptosis mogelijk was door de saccades van de oogleden te analyseren. Bij blepharoptosis is er sprake van een afgenomen verticale lidspleet, de afstand tussen het onderste ooglid en het bovenooglid. Blepharoptosis kan aangeboren zijn of op een later tijdstip ontstaan. De aangeboren congenitale vorm laat zich klinisch gemakkelijk onderscheiden van de ontstane aponeurogene blepharoptosis. Binnen de aponeurogene vorm zijn twee subgroepen te onderscheiden; de blepharoptosis is ontstaan door het dragen van contactlenzen of is een leeftijdsgerelateerde involutionele vorm. Twee groepen van normale proefpersonen waarvan de gemiddelde leeftijden gelijk zijn aan die van de patiënten werden op gelijke wijze geanalyseerd. Aangetoond werd dat de saccades van de oogleden van iedere onderzochte groep patiënten wezenlijk verschilden in zowel de grootte als in de snelheid van de saccades. Bijvoorbeeld, neerwaartse lid saccades van 40° in de congenitale ptosis groep bedroegen gemiddeld 22.9° ± 4.0° (SD), terwijl in de involutionele en contactlens geinduceerde ptosis groep, de amplitudes van de lid saccades gemiddeld, respectievelijk, 32.7° ± 4.3° en 40.3° ± 3.5° bedroegen. Opmerkelijk was het verschil in de dynamiek van de saccades tussen de twee, klinisch niet te onderscheiden, vormen van aponeurogene ptosis. Het leeftijdsverschil tussen beide groepen kon de gevonden verschillen in grootte en snelheid van de saccades niet verklaren, alhoewel

saccades van de oogleden met een toename van de leeftijd minder snel werden. Het is interessant om te evalueren of de motiliteit van de oogleden gecorreleerd kan worden aan de mate van de ptosis en de daarmee gepaard gaande recessie van de levatoraponeurose in bijvoorbeeld congenitale ptosis, zodat een optimaal chirurgisch resultaat kan worden behaald.

In hoofdstuk 5 werden saccades van de ogen bij patiënten met de ziekte van Parkinson geanalyseerd. Bij dit ziektebeeld is bekend dat de saccades hypometrisch zijn, hetgeen inhoudt dat meerdere saccades (multistepping) nodig zijn om de ogen op het beoogde einddoel te krijgen. Gezonde proefpersonen hebben naast een primaire saccade meestal slechts één correctie (accessory) saccade nodig om het einddoel te bereiken. Het aantal correctie saccades per blikverandering (gaze shift) werd uitgedrukt in een multistepping index (MSI). Saccades van patiënten met de ziekte van Parkinson bleken een significant hogere MSI te hebben dan controle personen. De MSI werd positief beïnvloed door patiënten met l-dopa te behandelen; een significante verbetering van de MSI werd gevonden. De ziekte van Parkinson kan door de analyse van saccades worden gekwantificeerd en de behandeling met l-dopa getoetst.

Dankwoord

Dit proefschrift is tot stand gekomen dankzij de inzet van velen. Vooraf was de doelstelling om minimaal één, mogelijk twee wetenschappelijke publicaties in een gerenommeerd tijdschrift te plaatsen. Dankzij de inspirerende en onophoudelijke aandacht van Dr. H.G. Lemij, mijn co-promotor, en Dr. W.A. van den Bosch voor mijn werkzaamheden kon uiteindelijk dit proefschrift gerealiseerd worden. De wijze waarop jullie mij begeleid hebben roept enorme bewondering op.

Beste Hans, je was nauw betrokken bij mijn aanstelling voor dit onderzoek en had vertrouwen in mijn kwaliteiten als wetenschapper. Je begeleiding bestond voornamelijk uit het stimuleren van vertrouwen in eigen kunnen, hetgeen naast de structurele opbouwende kritiek, nu terugblikkend, als bijzonder prettig is ervaren. Jouw gave om ingewikkelde materie helder te formuleren zullen mij altijd bijblijven. Hans, ontzettend bedankt.

Beste Willem, ik heb je leren kennen als een groot analyticus, hetgeen in combinatie met je wetenschappelijke kennis en taalgevoel tot een voor mij ideale combinatie leidde. Jij sprak mij ook regelmatig aan op mijn voortgang, hetgeen op dat moment weleens als een onheuse bejegening werd ervaren, maar toch mede leidde tot de afronding van dit proefschrift. Door je onophoudelijke inzet voor mij naast je andere werkzaamheden heb ik veel waardering voor je gekregen. Ik ben zeer verheugd dat je als 'deskundige' in de promotiecommissie hebt willen plaatsnemen.

Prof.dr. H. Collewijn. Han bedankt dat je mijn Promotor wilt zijn. Het enthousiasme waarmee je mij begeleid en steunt bij het afronden van het proefschrift is prijzenswaardig.

Prof.dr. G. van Rij, Prof.dr. C.J. Erkelens, Dr. J. van der Steen, Prof.dr. P.J. Koudstaal, en Prof.dr. H.J. Simonsz. Bedankt voor het kritisch doornemen van mijn proefschrift en voor uw bereidheid zitting te nemen in de promotiecommissie.

Dhr. A. Slingerland. André, dit onderzoek werd mede door jouw technisch inzicht voortvarend gestart. De meetopstelling werd gezamenlijk gebouwd en analyse software, toegespits op de uit te voeren onderzoeken, geïntegreerd. Jouw inzet en bereidheid tot hulp in de avonduren, nadat je je carrière elders voortzette, zijn enorm belangrijk geweest voor de afronding van dit proefschrift. Beste André, bedankt voor al je hulp.

Dhr. P.G.H. Mulder. Paul, jouw hulp bij de analyse van de data waren onontbeerlijk voor de afronding van de individuele hoofdstukken in dit proefschrift. Je enthousiasme, maar meer nog je gedrevenheid om tot een goede analyse te komen zullen mij altijd bijblijven. Paul bedankt.

De medische staf van het Oogziekenhuis Rotterdam wil ik bedanken voor het feit dat ik als junior staflid verbonden kon blijven aan het Oogziekenhuis om mijn proefschrift af te ronden.

Dr. C. Bulens. Carel, bedankt voor je medewerking bij het tot stand komen van het vijfde hoofdstuk.

Drs. T. Colen. Thomas, bedankt voor je hulp bij het tot stand komen van het vijfde hoofdstuk. Je hulp bij de registraties en opzet van het artikel worden gewaardeerd. Succes met je op stapel zijnde eigen promotie.

Mevr. M.C.W.M. Wouters. Milli, ondanks je drukbezette leven wilde en kon je toch tijd vrijmaken om daar waar nodig je kennis van de Engelse taal met mij te delen. Milli, ontzettend bedankt.

Dr. M.J. Tjon-Fo-Sang en Dr. S. Tabak. Martha en Sylvia, bedankt voor de vele gezellige momenten samen en het feit dat jullie mijn paranymphae willen zijn.

Verder ook dank aan alle medewerkers van de afdeling electro-diagnostiek voor de leuke tijd die ik er gehad heb.

Natuurlijk wil ik ook mijn ouders bedanken voor alle steun die ik altijd van ze heb mogen ontvangen.

Tot slot wil ik Monique, mijn echtgenote, bedanken voor de onvoorwaardelijke steun gedurende de periode dat ik haar nu ken. Monique, door jouw begrip en de gezellige tijd samen kon ik mijn opleiding afronden en dit proefschrift realiseren. Bedankt!

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'under revision for Vision Research'

Curriculum Vitae

De auteur werd op 9 november 1963 geboren in Tilburg. In 1984 behaalde hij het eindexamen VWO op het Sint Laurenscollege te Rotterdam-Hillegersberg. Aansluitend studeerde hij Geneeskunde aan de Erasmus Universiteit te Rotterdam. In 1992 slaagde hij voor het artsexamen. Daarna was hij een jaar werkzaam als arts-assistent Neurologie in het St. Franciscus Gasthuis te Rotterdam. Op 1 oktober 1993 werd hij aangesteld als arts-onderzoeker in het Oogziekenhuis Rotterdam. Tijdens deze aanstelling verrichtte hij het onderzoek beschreven in dit proefschrift onder leiding van Dr. H.G. Lemij, Dr. W.A. van den Bosch en Prof.dr. H. Collewijn in het Oogziekenhuis. In oktober 1995 werd de auteur aangesteld als assistent geneeskundige niet in opleiding (AGNIO). Vanaf 1 januari 1997 tot en met 31 december 2000 werkte hij als assistent geneeskundige in opleiding (AGIO) tot oogarts in het Oogziekenhuis Rotterdam (opleider: Drs. G.S. Baarsma). In deze opleidingsperiode werd het wetenschappelijk onderzoek voortgezet. Vanaf januari 2001 is de auteur werkzaam als oogarts.

The only limit to our realization of tomorrow will be our doubt of today

President Franklin D. Roosevelt *(1882-1945)*

Met dank aan:

Stichting Wetenschappelijk Onderzoek
Het Oogziekenhuis
Prof.dr. H.J. Flieringa Stichting
Rotterdamse Vereniging Blindenbelangen
Allergan
Laméris Ootech B.V.
Alcon Nederland B.V.
Tramedico
Bournonville Pharma B.V.
Novartis Ophthalmics
Ursapharm Nederland B.V.
Pharmacia B.V.

Niek de Bruijn (ontwerp en opmaak)