令和２年度学位論文

Utilizing eye gaze analysis using an eye tracker for clinical research on strabismus

アイトラッカーによる視線解析の斜視臨床研究への応用

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CONTENTS

ABSTRACT

Purpose: This study aimed to analyze the gaze of strabismus observed in patients with diseases, such as myasthenia gravis (MG) and intermittent exotropia (XT), as gaze analysis may be effective for this condition.

Methods: All participants without dyscoria could clearly observe the visual target 40 cm away. To record eye movements easily and continuously, a video eye-tracker which is non-invasive, quantifiable, high temporal and spatial resolution was used. The following 3 experiments were conducted. Experiment 1: Twenty-one normal subjects, 5 MG patients with diplopia, 5 MG patients without diplopia, and 6 superior oblique (SO) palsy patients were included. Subjects fixated on a target in the upward direction for 1 min. The horizontal (X) and vertical (Y) eye positions were recorded. Fixation stability was first quantified using the bivariate contour ellipse areas (BCEAs) of fixation points as an index of whole stability. Then, the standard deviations (SDs) of the X and Y eye positions (SDXs and SDYs, respectively) were quantified as indices of directional stability, with the data divided into three 20-s fractions to detect temporal fixation fluctuation. Experiment 2: Horizontal saccades (15° rightward and 15° leftward) of monocular vision were recorded under monocular viewing in 18 patients with exotropia and 20 normal subjects. All patients were examined using the same method after strabismus surgery (resection and recession). Experiment 3: The smooth pursuit of nine

patients with intermittent exotropia was recorded before and after strabismus surgery (1 week, and 1, 3, and 6 months). They were asked to track a step-ramp target moving at ± 6.1°/s horizontally as accurately as possible under binocular viewing. The differences in gain (eye velocity divided by target velocity) and amplitude of smooth pursuit between the right and left eyes were compared between the pre- and post-surgical data. In addition, the correlation of pre- and postsurgical changes in the differences in gain and amplitude with pre- and postsurgical changes in the ocular deviation were analyzed.

Result: Experiment 1: BCEAs were larger in MG patients (both with and without diplopia) than normal subjects and SO palsy patients, without significant differences among the three 20-s fractions. Compared with normal subjects, SDXs were larger only in MG patients with diplopia; SDYs were larger in both MG patients with and without diplopia. In addition, SDYs in MG patients with diplopia were larger than those in MG patients without diplopia and SO palsy patients. Furthermore, a significant difference among the three 20-s fractions was detected for SDYs in MG patients with diplopia. Experiment 2: The PVs of adduction and abduction in the patients were higher than those in the normal subjects. Following the surgery, the PVs of abduction of the surgical eye (non-dominant eye) decreased to the level of the normal subjects. However, there were no correlations between changes in the PVs and the extent of surgery. Experiment 3: The difference in gain and amplitude between the left and right eyes in patients with intermittent XT were improved at 1 week after surgery and maintain improvement for 6 months after surgery; however, the ocular deviations regressed to 30 % of deviation in

pre-surgery by 6 months after surgery. The correlations between ocular deviation and difference in gain and amplitude between the left and right eye were significant. However, There were no correlations between pre-post surgical changes in the amount of ocular deviation and pre-post surgical changes in difference in gain and amplitude between the left and right eye.

Conclusions: Patients with MG, especially those with diplopia, exhibit fixation instability in the upward gaze. Quantification of fixation stability with an eye tracker is useful for precisely identifying MG-specific fatigue characteristics. Surgical correction of ocular alignment normalized the patient's increased PV in the operated eye for abduction of horizontal saccade. Furthermore, surgical correction of ocular alignment improved binocular coordination of smooth pursuit in intermittent exotropia. In the long term, the improvement of the binocular coordination of smooth pursuit tended to remain, although the eye position partially reverted to the presurgical state. The eye movements recorded by an eye tracker were fully usable in clinical research. The gaze analysis is possible to add the evaluation for the dynamic indexes of eye movements in the current strabismus diagnosis and treatment. This suggests that it is possible to observe "eye movement" of the pathological condition of strabismus, which is originally a dynamic abnormality, and obtain data on the mechanism of strabismus development.

1. INTRODUCTION

Strabismus is a misalignment of the visual axes between the eyes. It can be congenital, or acquired from eye movement disorders caused by defect in the nerve, neuromuscular junction, or extraocular muscles, such as paralysis, inflammation, degeneration, or trauma. However, most of pediatric cases of strabismus are not caused by these defects. Patients with strabismus have abnormal binocular vision and cannot accurately determine the distance of the visual target because of diplopia or suppression of deviated eye by the central nervous system. Before treatment planning, strabismus is evaluated by measuring the ocular deviation angle, range of ocular motility, and binocular vision function. However, clinically, the current examinations cannot evaluate unmeasurable symptoms, such as the fluctuation of gaze; currently, the ocular alignment is recorded at only one data point (ocular position). Therefore, detailed constantly moving eye, such as the accuracy of eye movement and conjugacy of both eyes cannot be examined. In addition, only a few studies have examined the pathological condition of strabismus from the viewpoint of gaze analysis because of the complexity of eye movement recording. Therefore, to record eye movements easily and continuously in clinical practice, I focused on gaze analysis using an eye-tracking system that is non-invasive, quantifiable, and has sufficient temporal and spatial resolutions for eye movement velocity.

1)Anatomy of eye movements

Extraocular muscules

The eye movements are controlled by three pairs of muscles, shown in Figure 1: (1) the medial and lateral rectus muscles, (2) the superior and inferior rectus muscles, (3) the superior and inferior oblique muscles. The medial and lateral rectus muscles contract to move the eyes from side to side (adduction of abduction). The superior and inferior rectus muscles contract to move the eyes upward or downward. The oblique muscles function mainly to rotate the eyeballs to keep the visual fields in the upright position.[1)]

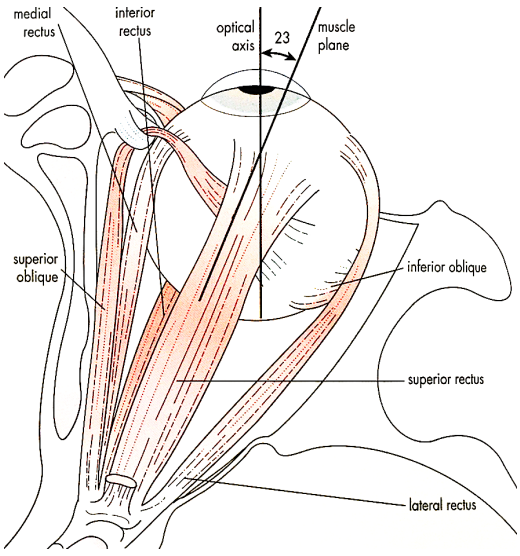

Figure 1. The extraocular muscles of the right eyeball in central gaze, seen from above.[2)]

Neural pathways for control of eye movements

The extraocular muscles are innervated by lower motor neurons that form three cranial nerves: the abducens, the trochlear, and the oculomotor. The abducens nerve (cranial

nerve VI) exits the brainstem from the pons-medullary junction and innervates the lateral rectus muscle. The trochlear nerve (IV) exits from the caudal portion of the midbrain and supplies the superior oblique muscle. In distinction to all other cranial nerves, the trochlear nerve exits from the dorsal surface of the brainstem and crosses the midline to innervate the superior oblique muscle on the contralateral side. The oculomotor nerve (III), which exits from the rostral midbrain near the cerebral peduncle, supplies all the rest of the extraocular muscles. Although the oculomotor nerve governs several different muscles, each receives its innervation from a separate group of lower motor neurons within the third nerve nucleus.[3]

2) Eye movement

Saccadic eye movement

The function of saccadic eye movements is to place the object of interest on the fovea rapidly or to move the eyes from one object to another. This can be performed voluntarily or occur as a reflex triggered by the presence of an object in the peripheral visual field. The peak velocity (PV) of saccade is an important parameter for saccade evaluation. The PV correlates with the amplitude of the saccade, and the normal range of the PV has been determined.[4][5] The PV of horizontal saccades reportedly reaches adult values by the age of 4.5 years.[6]

Smooth pursuit

The smooth pursuit system is an oculomotor control mechanism that facilitates smooth movement of the eyes when following a moving target to stabilize the retinal image. The system has usually been characterized as a negative feedback controller, where the motion of the retinal image is the stimulus that drives the smooth eye movement. Because an image must be both still on the retina and near the fovea for highest acuity, both the velocity and position of the retinal image must be controlled when the subject visually tracks a moving target.[7]

Vestibular reflex

The function of vestibular reflexes is to maintain eye position with respect to changes in the head and body as a whole.

Convergence / Divergence

Vergences are eye movements that turn the eyes in opposite directions so that images of objects fall on the corresponding retinal points. Convergence is the ability of the two eyes to turn inwards, and divergence is their ability to turn outwards from a convergent position. Three major stimuli are known to elicit vergence: (1) retinal disparity that leads to fusional vergence; (2) retinal blur that evokes accommodative vergences; and (3) motion inducing both disparity and accommodative vergence.[8]

Optokinetic nystagmus

Optokinetic nystagmus (OKN) is a smooth pursuit movement interspersed with

saccades invoked to compensate for the retinal movement of the target. The smooth pursuit component of the OKN appears in the slow phase of the signal.[9]

Fixating eye movement

Fixation is eye movement that stabilizes the retina over a stationary object of the insert. Fixations are characterized by miniature eye movements: tremor, drift, and microsaccades (Figure 2). Microsaccades are eye movement signals that are more or less spatially random varying over 1 to 2 min of arc in amplitude.[9]

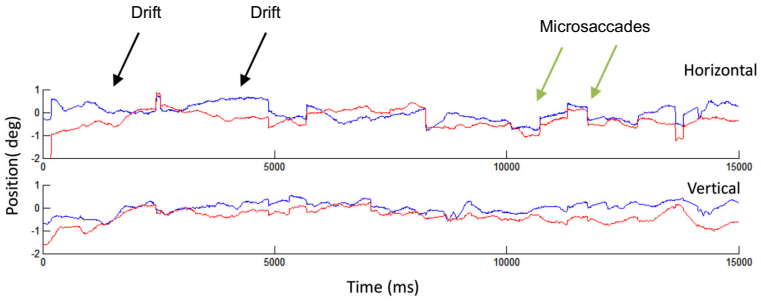

Figure 2. Human fixation eye movement [10]

3) Strabismus

Strabismus is a misalignment of the visual axes that initially results in confusion, diplopia, or suppression (i.e., to ignore the image of the misaligned eye and see only the image from the straight or better-seeing eye) (Figure 3). A tropia is a manifest visual axis deviation that can be constant or intermittent (also known as strabismus or squint). A phoria is a latent ocular deviation that is controlled by a person's fusional ability. Heterotropia describes the misalignment of the eyes with regard to the axes of Fick: X, Y, and Z. The X-axis passes through the equator of the eye horizontally; the Y axis

passes through the pupil horizontally; and the Z axis passes through the equator vertically (Figure 4). Heterotropia can be classified according to direction of the deviation. Horizontal tropia is esotropia (eyes deviating in) or exotropia (eyes deviating out). Vertical tropia is hypertropia (one eye is higher than the other) or hypotropia (one eye is lower than the other). Cyclotropia (rotational tropia) is excyclotropia or incyclotropia (Figure 5).[11][12]

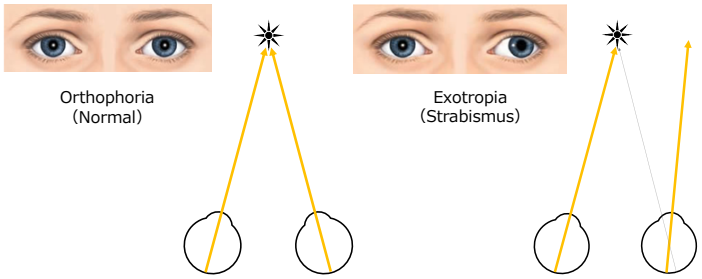

Figure 3. Orthophoria and exotropia (modified from http://dranandraut.com/services.aspx)

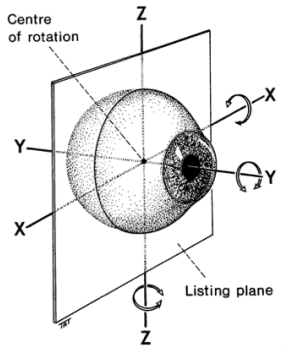

Figure 4. Axes of Flick; X, Y, and Z[12]

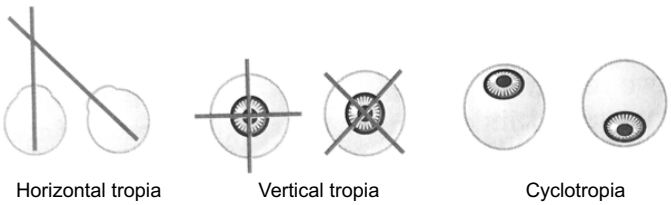

Figure 5. Basic type of strabismus [1]

Binocular vision function

Simultaneous perception is ability to see two images, one on each retina (superimposed, unblended). Fusion is simultaneous perception of two similar images blended as one. Stereopsis is the relative ordering of visual objects in depth. It arises when horizontally disparate retinal elements are stimulated simultaneously (Figure 6). The fusion of such disparate images results in a single visual impression perceived in depth. A solid object is seen stereoscopically because each eye sees a slightly different aspect of the object.[13]

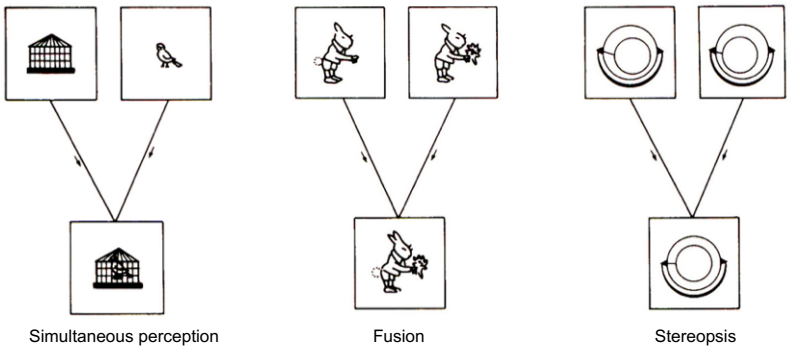

Figure 6. Binocular vision function[12]

With normal vision, both eyes aim at the same location. The brain then combines the two pictures into a single, three-dimensional image, which provides depth perception. When one eye is misaligned, two different pictures are sent to the brain. In a young child, the brain learns to ignore the image of the misaligned eye and sees only the image from the straight or better-seeing eye (suppression). The child then loses depth perception. Adults who develop strabismus often have double vision because their brains have already learned to receive images from both eyes and cannot ignore the image from the turned eye.

4) Clinical examination of strabismus

Evaluation of ocular deviation

- Cover–uncover test (Figure 7, left) [11][12]

Cover tests allow the examiner to differentiate between a tropia and a phoria, to assess the degree of control of deviation, and to note the fixation preference and strength of fixation for each eye. To perform the cover test, one eye is covered, and watching the other eye is observed. If the uncovered eye moves, tropia exists. This should be performed separately for each eye. When tropia exists, the fixating eye should be determined. If either eye shifts centrally when covering the other, the patient can alternate fixation. If only one eye shifts centrally and the other is not affected, then the non–moving eye is the fixating eye. If the uncovered eye is stable, but the covered eye moves under cover, the patient is diagnosed with phoria.

- Alternate cover test (Figure 7, left) [11][12]

The alternate cover test interrupts binocular fusion mechanisms and reveals the total deviation (tropia and phoria). One eye is covered for about 2 seconds; the cover in then quickly shifted to the opposite eye. It is performed by covering each eye alternately, not allowing fusion to be re-established when switching from one eye to another eye. This test reveals either tropia or phoria. If no movement occurs, the patient is orthophoric.

- Alternative prism cover test (Figure 7, right) [11]

The alternative prism cover test (APCT) measures combined phoria and tropia. It is performed in the same manner as the alternate cover test, but prisms of increasing power are placed in front of either eye until the eyes stop shifting.

Figure 7. Cover test (Left) and prism cover test (Right) test [12]

Evaluation of binocular vision function

- Titmus stereo test (Figure 8)

The Titmus test utilizes a three-dimensional polaroid vectograph consisting of two plates in the form of a booklet, which are viewed through polaroid spectacles. On the right, there is a large housefly, and on the left, there are series of circles and cartoons. The fly is a test of gross stereopsis (3000″). Children are often tested by asking them to hold one of the wings of the fly, which they will do above the plate if it is seen stereoscopically. The other vectograms of the test provide finer tests for stereoscopic acuity. In the circle test, the degree of disparity ranges from 800″ to 40″ and in the animal test from 400″ to 100″.[9]

Figure 8. Titmus stereo test [15]

Evaluation of eye movement (mobility range)

- Hess test (Figure 9)

The Hess test is a dissimilar image test used in patients with paretic deviations. The patient wears red-green filter goggles with the red filter initially in front of the right eye. Subsequently, the patient holds a green light projection while the examiner holds a red one. The examiner projects the red light onto the screen and asks the patient to superimpose the patient's green light on to the red light. In normal circumstances, the two pointers should almost be superimposed in all nine positions of gaze. The goggles are then reversed so that the red filter is in front of the patient's left eye, and the procedure was repeated. [12]

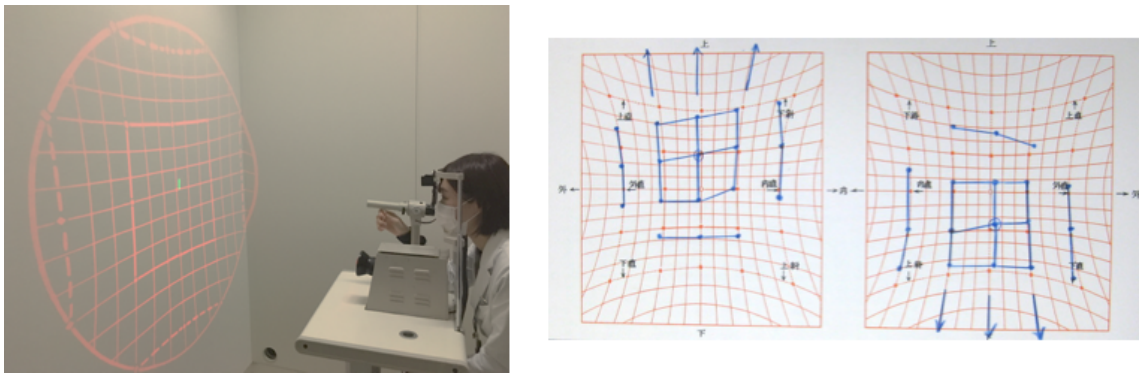

Figure 9. (Left) Hess test, (Right) Hess chart (left superior oblique muscle palsy)

5) Recording methods for eye movement

Electrooculography

The simplest method for measuring human eye movement is based on the electric dipole nature of the human eye. Because of its easy operation, electrooculography (EOG) is the standard technique used for recording eye movements in clinical practice. The resolution and accuracy of EOG signals are limited by electromagnetic field noise in the environment, thermal noise generated by the input resistance of the amplifier and contact resistance of the skin electrodes, and capacitive noise due to electrical activities of the muscles and neurons. [8]

Scleral search coil technique

The scleral search coil (SSC) technique is the current gold standard for accurate recording of eye movements. This system measures voltages in one or two coils induced by two or three rapidly oscillating magnetic fields. This technique has high temporal (>500 Hz) and spatial (<0.1°) resolutions and low noise. However, the SSC technique is a very expensive, complex, and uncomfortable, requiring the subject to wear a contact annulus to the eye ball (Figure 10) with a risk of corneal abrasion. Therefore, it is not suitable for clinical practice.[8]

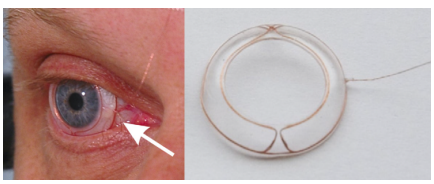

Figure 10. Subject wearing a scleral search coil (Left); a scleral search coil (right) [16]

Video eye-tracker

Eye–tracking systems are used in psychology, marketing research, sports, and other fields. Using infrared light and high-speed CCD camera (Figure 11, left), these systems monitor the center of the pupil and corneal reflection (Figure 11, right), recording the eye gaze over time easily and non-invasively. In addition, this technique has reasonably high temporal (> 200 Hz) and spatial (0.1°– 0.5°) resolutions.[8]

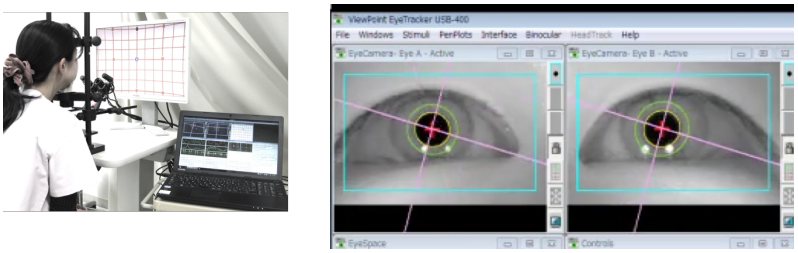

Figure 11. Video–eye tracker system

6) Myasthenia gravis

Ocular symptoms of myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disease that targets neuromuscular junctions. Involvement of extra-ocular muscles, causing ptosis and diplopia are frequent presenting and persistent features. Approximately 60% of patients with MG have diplopia at the time of diagnosis.[17] Therefore, the majority of patients with MG with diplopia are first examined by an ophthalmologist. Zambelis et al.[18] reported that 38% of patients with isolated ptosis and/or diplopia who are referred for electrophysiological

evaluation have MG. Furthermore, they stated that the presence of both diplopia and ptosis was more likely due to MG than any other disease.

Diagnosis of myasthenia gravis

If MG is suspected, additional examinations are needed to obtain a definitive MG diagnosis. These examinations include ptosis evaluation before and after an edrophonium test and an ice pack test.[19] Additionally, the presence of acetylcholine receptor antibodies or muscle-specific receptor tyrosine kinase antibodies in the serum, 'waning' during repetitive nerve stimulation and 'increased jitter' on a single-fibre electromyography can confirm the presence of MG.[19]

Evaluation of "fatigability" in myasthenia gravis

A quantitative MG score and an MG composite scale are used to evaluate disease severity. For these measures, diplopia is evaluated by asking the patient to gaze in one direction. The time from gaze to subjectively determined diplopia appearance is measured.[20][21] The 1 min upper gaze test is used to identify ptosis and diplopia and to determine whether the MG fatigue phenomenon is present.[22] However, these evaluations are subjective with the patient condition determined using physician observation or patient symptom reporting. In clinical observation, ophthalmologists infer the presence of diplopia and its severity by measuring ocular alignment and motion using the APCT and the Hess test, respectively.[23] These tests, however, are not objective and have poor reproducibility in patients with MG because ocular alignment is quantified using only

one data point (ocular position). This is problematic because ocular alignment and range of ocular motion change over time in patients with MG[23] because their muscles easily fatigue which is a characteristic of MG. Therefore, objective and reproducible evaluations of gaze instability caused by fatigability in patients with MG are needed and should include sequential eye position data obtained with a reasonably high sampling frequency (more than 200 Hz).[24-26] There are several studies that have examined saccadic eye movements of patients with MG using electro-oculography or infrared scleral reflection or scleral search coil [27-30] and reported that the peak velocity of saccade in patients with MG was similar to or greater than that of normal subjects.[27][28] These studies, however, did not evaluate gaze stability of patients with MG by measuring fixation position, although fixation methods are more widely used and meaningful clinical tests (e.g., the Quantitative MG score, MG composite scale) for the gaze stability of patients with MG. An eye tracker is capable of measuring ocular position continuously for a long enough period with relatively high time resolution. Upward is the most sensitive gaze direction for detecting the ocular MG symptoms (i.e., diplopia and ptosis) because extraocular muscle weakness is known to appear most prominently in the elevator muscles of patients with MG.[22][31][32]

7) Intermittent exotropia

Intermittent exotropia (XT) is a classic example of intermittent ocular deviation. The patient exerts a fusional reserve to keep the eyes straight, temporarily. Environmental

factors, such as fatigue, illness, and certain medications, may impair this fusional ability, manifesting as tropia. Ocular motility restriction does not exist. Intermittent XT is a type of comitant strabismus. Most previous studies on intermittent XT evaluated the deviation angle and binocular vision function. Moreover, normal binocular function is maintained by heterophoria or orthophoria.

8) Previous studies on saccades and smooth pursuit in strabismus

Saccade in strabismus

A previous study reported no difference in the mean velocity of horizontal SEM between patients with horizontal strabismus and normal subjects.[33] However, few studies have compared saccade velocities before and after strabismus surgery.[33][34] Bucci et al. observed that the PV of horizontal saccades significantly decreased in some patients after undergoing surgery for horizontal strabismus.[34] They suggested that strabismus surgery improved the velocities of convergence and divergence.[33] However, these previous studies investigated the effects of correcting the eye position on conjugate eye movements in mixed subject populations, including different types of strabismus and some operative methods.

Smooth pursuit in strabismus

Lions and colleagues[35] reported that the binocular coordination of smooth pursuit in children with strabismus (early onset or acquired esotropia, intermittent or constant XT)

was worse than that in normal-seeing children and children with vergence deficits having binocular vision. In addition, they found that binocular coordination of smooth pursuit in children with vergence deficits was abnormal. They concluded that binocular vision plays an important role in improving binocular coordination of pursuit. Von Noorden and colleagues[36] reported that the smooth sinusoidal eye position profiles were superseded by quick saccadic jumps at lower pursuit frequencies in patients with strabismic amblyopia. In previous studies on smooth pursuit related to strabismus, an abnormal saccadic substitution response appeared to be related to the presence of amblyopia rather than strabismus.[36][37] A different study reported that binocular vision function could be required to maintain binocular coordination of smooth pursuit.[35] On the other hand, Ono and colleagues[38] suggested that monkeys with strabismus retained the ability to produce conjugate adaptation of smooth pursuit and that a single central representation of retinal motion information in the viewing eye drove adaptation for both eyes equally. An experimental study involving 2 monkeys with XT showed that changes in smooth pursuit gain immediately after surgery returned to the preoperative levels by 6 months postoperatively.[39] However, longitudinal changes in smooth pursuit following strabismus surgery have not been studied in humans.

2. PURPOSE

Ocular alignment and range of ocular motion change over time in patients with MG. Therefore, objective and reproducible evaluations of gaze instability caused by fatigability in patients with MG are needed. Eye movements, such as saccade and smooth pursuit in patients with intermittent XT were not well known detail, although Intermittent exotropia (XT) is a common and classic example of intermittent ocular deviation. The purpose of this study was to investigate whether or not clinical research of strabismus using an eye tracker is useful for some strabismus types in which gaze analysis is considered effective to elucidate the pathology of strabismus.
The contents of this research have already been published in three papers.[40)-42)]

1) Fixation stability of the upward gaze was quantified in patients with MG using an eye tracker (Experiment 1).[40)]

2) Horizontal saccades were recorded using an eye–tracker in patients with only XT to compare the PVs, before and after undergoing strabismus surgery of the same type (unilateral resection and recession) (Experiment 2).[41)]

3) To observe changes in the horizontal smooth pursuit in patients with intermittent XT before and after strabismus surgery (Experiment 3).[42)]

3. METHODS

The present study was approved by the Institutional Review Board of the University of Toyama (approval # 27-159) and conformed to all local laws and to the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant after the experimental procedure was fully explained.

Set-up for eye position monitorin

The horizontal (X) and vertical (Y) positions of each eye were recorded using the ViewPoint EyeTracker® system (Arrington Research, Scottsdale, AZ) at a sampling rate of 220 Hz (in experiment 1 and 2), or 350Hz (in experiment 3), as was previously done by Crossland et al.[24-26] The system consisted of 2 infrared CCD cameras mounted on the head positioner. The eye tracker determined eye position using the dark pupil technique and eye-tracking data were stored on a hard disk for offline data analysis. A computer monitor (Diamondcrysta®, RDT222WM-S, Mitsubishi, Tokyo) displaying the target was located at 40 cm from the participant's eye. The monitor luminance was 190 cd/m^2, the resolution was 1,680 ×1,050 pixels, and the refresh rate was 60 Hz. Each subject sat in a chair facing the display set at a distance of 40 cm from the subject, with horizontal eye level even with the centre of the display, the primary position (figure 15). The subject's head was stabilized against a head and chin rest. Prior to testing, a calibration and a subsequent validation procedure were performed for each subject using the software

supplied by the eye-tracker manufacturer (ViewPoint EyeTracker Software User Guide). All statistical analyses were performed using the JMP Pro software package (V.11.2.0, SAS Institute, Cary, NC, USA). P value less than 0.05 was considered statistically significant.

1) Fixation stability of the upward gaze in patients with myasthenia gravis

Participants

Four groups of volunteers (normal subjects, patients with MG with diplopia, patients with MG without diplopia and patients with superior oblique (SO) palsy) were recruited for the study; the SO palsy group was included to determine whether the presence of diplopia itself affects the fixation stability. The diagnosis of MG was made based on clinical (fluctuating symptoms with easy fatigability and recovery after rest), immunological and neurophysiological findings.[19] Diagnostic tests included anti-acetylcholine receptor antibodies, anti-muscle-specific tyrosine kinase antibodies, edrophonium test and decremental muscle response to a train of low-frequency repetitive nerve stimuli. Participants in all groups did not have dyscoria and could clearly watch the target when vision was uncorrected or corrected using soft contact lenses. Patients whose best corrected decimal visual acuity was less than 1.0 (Snellen: 20/20) were not included because of the possible disturbance in visual fixation caused

by lowered visual acuity. Patients were not excluded because of age, MG type or disease duration, except for those who could not fixate the target of upward from the beginning.

Assessment of fixation stability

The fixation target consisted of a red inner circle (0.2° in diameter) superimposed at the centre of a black circle (1.5° in diameter) and a white cross was located in the centre of the circular target (Figure 12), as previously reported by Thaler et al.[43] The target was positioned 20° above each subject's horizontal plane (primary position) to induce an upward gaze and was displayed on a computer monitor. Subjects were instructed to keep their gaze fixed on the target for 1 min with both eyes. During examinations, patients with ptosis were examined with their eyelids mildly lifted using a surgical tape (to the extent that eyes did not dry) so that the eye tracker could detect the pupil of the subject even when gazing at 20° upward, and therefore, the eyelid descent itself was not a problem.

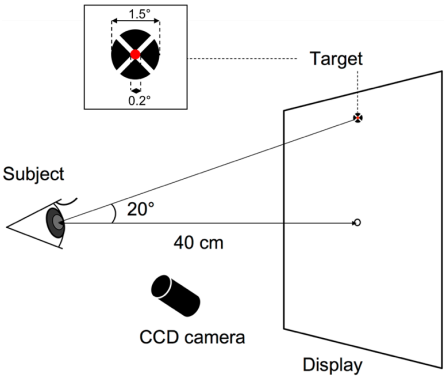

Figure 12. The fixation target was positioned 20° above each subject's horizontal plane (primary position) to induce an upward gaze and was displayed on a computer monitor at a distance of 40cm. CCD, charge-coupled device.

Data obtained immediately after initiating target presentation were discarded because these data included saccadic eye movements related to beginning fixations. As this period of eye movements varied from subject to subject, the data that accompanied the eye movements were discarded manually by visual inspection of the eye position chart in each subject. Data that contained artefact noise, related to blinking or erroneous pupil image capture, were also excluded after manual confirmation of artefact presence using stored data. For blinks and erroneous pupil image capture, the data obtained 100 ms before and after the onset of these events were removed from analysis.[44] Data were selected on the dominant eye in all patients. The dominant eye was determined using the Hole-in-Card test.[45] Approximately 5% of the overall data were excluded due to blinks and noisy recording. Fixation stability was first quantified using bivariate contour ellipse areas (BCEA) encompassing fixation points as an index of whole fixation stability, with the data divided into three 20 s fractions (ie, 0–20 s, 20–40 s and 40–60 s). The BCEA was calculated using the following formula[24]:

$$BCEA = 2k\pi\sigma_H\sigma_V (1-\varrho^2)^{1/2} \quad (1)$$

where σ_H and σ_V are the SDs of the horizontal and vertical eye positions, respectively, and ϱ is their Pearson product-moment correlation. The k is dependent on the probability area chosen and is calculated using the following equation:

$$P = 1 - e^{-k} \quad (2)$$

where e is the base of the natural logarithm. For this study, fixation data were calculated using P values of 0.68 (i.e., 1 SD), which led to k values of 1.14. Then the SDs of the X and Y eye positions were calculated as indices of detailed (individual direction) stability

with the data divided into the three 20 s fractions. Although BCEA and SDs are not independent measures, both parameters were used, because BCEA is presently one of the standard indexes for evaluation of whole fixation stability as described in previous studies.[24)26)46)] A repeated measure analysis of variance (ANOVA) was performed for the data on 68% BCEA and SDs with groups as a between-subjects variable and the 20 s fractions as a within-subjects variable. If a significant difference was identified, pairwise comparisons were performed using a two-tailed t-test with Bonferroni correction.

2) Horizontal saccadic velocity in patients with exotropia

Participants

Twenty normal healthy adults (mean age: 29.9 years, range: 8–81 years, 8 women) and 18 patients with XT (mean age: 26.8 years, range: 6–80 years, 8 women) volunteered to participate in the study. All participants without dyscoria could clearly observe the visual target 40 cm away, with either the naked eye or soft contact lenses (corrected visual acuity of 1.0 or greater). All patients underwent surgery (resection of medial rectus muscle and recession of lateral rectus muscle) on their nondominant eyes, performed by 2 surgeons (MM and KF). The deviation angles near (30 cm) and far (5 m) were measured using the alternate prism cover test. The dominant eye was determined using the hole-in-card test.[45)] Patients with constant XT (acquired, concomitance, not consecutive) were considered eligible if exophoria (or orthophoria)

and stereopsis, based on the Titmus stereo test, were achieved after the surgery. All patients were examined before and again 6–12 weeks after surgery.

Stimulus presentation and examination paradigm

The target consisted of a red inner circle (0.2° in diameter) superimposed at the center of a black circle (1.5° in diameter) and a white cross, in accordance with the study by Thaler et al.[43] They were examined under the following two conditions: monocular viewing with the dominant eye and monocular viewing with the nondominant eye; the other, nonviewing eye covered by an infrared filter (IR-76®, Fujifilm, Tokyo, Japan). They were instructed to fixate their gaze on a target located in the center at the beginning of the test trial, to fixate on the new target as rapidly as possible when it appeared at either 15° rightward or 15° leftward randomly, and finally to return their gaze to the original, center location when the latter target disappeared (Figure 13). Each subject performed five trials in each direction (adduction and abduction), with exclusion of saccade trials that included blinks or incorrect responses. A limited number of trials were used, as patients were examined during consultation hours and some participants were young children.

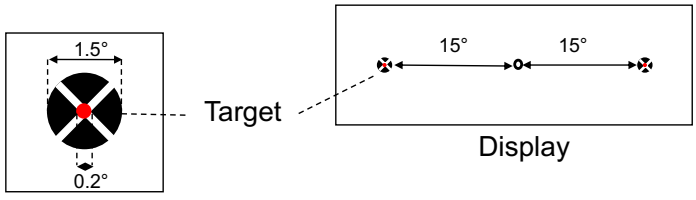

Figure 13. The fixation target was presented t either 15° rightward or 15° leftward randomly.

Data analysis and statistics

In the present study, only primary saccades, and not corrective saccades, were analyzed. The maximum value of the velocity waveform obtained from the primary differential values of the eye position in a saccade was defined as the PV. The onset of a primary saccade was defined as the time when the eye velocity exceeded 5% of the saccadic PV; the offset was set to when the eye velocity dropped below 10°/s, as is the previously reported standard.[11)33)] Data of eye movements that were in the wrong direction or that were contaminated with blinks were discarded. For each participant, the PVs (mean of 5 trials) for adduction and abduction of each eye were calculated. The Mann–Whitney U test was used to compare the PVs for each dominant and nondominant eye between normal subjects and patients with XT, pre-surgically. The Wilcoxon signed-rank nonparametric test for paired samples was used to compare the PVs between pre and postsurgical parameters in patients with XT. For patients with XT, Spearman's rank-correlation between changes in the PV in the operated (nondominant) eye and the amount of surgery (resection or recession) was calculated.

3) Binocular coordination of smooth pursuit in patients with intermittent exotropia

Participants

Patients at least 5 years of age with intermittent exotropia who were scheduled to undergo strabismus surgery were recruited to participate in the study. All patients

underwent surgery (unilateral resection of the medial rectus muscle and recession of the lateral rectus muscle in the nondominant eye, or bilateral lateral rectus muscle recession). All surgical procedures were performed by the same surgeon (MM). The control of the intermittent exotropia was determined clinically using the monocular cover-uncover test. Control was deemed poor if exotropia manifested spontaneously or if there was any disruption of fusion without recovery after the cover-uncover testing. Good control was defined as exotropia manifested only after the cover testing and resumed fusion immediately with or without blinking or refixation. The deviation angles at near (30 cm) and distance (5 m) were measured using the alternate prism cover test. Stereopsis was evaluated using the Titmus stereo test; a break point of >5 cm from the nose was considered poor convergence.[47] Patients were included if there was an exodeviation angle of ≧15 prism diopters (PD) at near and at distance on APCT. Furthermore, patients with constant exotropia (acquired, concomitant, not consecutive) were eligible for inclusion if the eye position indicated heterophoria or orthophoria after surgery and the Titmus stereo test confirmed stereopsis of 400″. All participants without dyscoria could clearly observe the visual target 40 cm away with either the naked eye or using soft contact lenses (corrected visual acuity of at least 1.0). Patients with other eye diseases, a neurologic or systemic disease, or eye movement disorders were excluded. All patients were examined before surgery and 1 week, and 1, 3, and 6 months after surgery.

Stimulus presentation and examination paradigm

The visual motion target was a white Gaussian spot with a diameter of 0.5° and luminance of 117 cd/m^2, presented on a uniform gray background (70 cd/m^2) in accordance with the method used by Ke and colleagues[48] (Figure 14). Examination took place under binocular viewing conditions. Each trial started with central fixation. Participants were asked to track as accurately as possible a step-ramp target moving at 6.1°/s horizontally. The step-ramp method was used to prevent early saccades in smooth pursuit, as described by Rashbass[49] and Sakuma and colleagues.[50] The step amplitude was 0.85°. The motion target was initially displaced in the direction opposite to the target's velocity step before moving back across the fovea ramp. The motion target moved from the center to either 18.3° leftward or 18.3° rightward. The direction was randomized across trials. Each subject performed 5 trials in each direction. Smooth pursuit trials that included blinks, saccades (with the exclusion of catch-up saccades), or incorrect responses were excluded. A limited number of trials were performed because the patients were examined during consultation hours, and some of the study participants were young children.

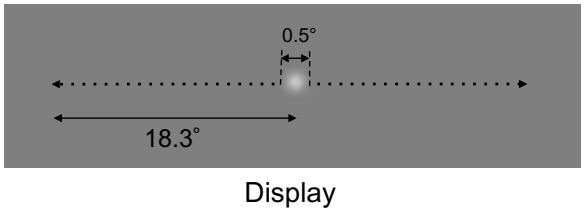

Figure 14. The motion target moved from center to either 18.3° rightward or 18.3° leftward randomly at 6.1° /s.

Data analysis and statistics

The means of the differences between the left and right eyes in the gain, that is, eye velocity divided by target velocity ($Diff_{L-R}$ gain), and amplitude ($Diff_{L-R}$ amplitude) of smooth pursuit across 5 trials in each trial type (leftward and rightward pursuit) were calculated for each participant. The Friedman test was performed to detect the effects before surgery and 1 week, and 1, 3, and 6 months after strabismus surgery. If the difference was significant, pairwise comparisons were performed using a Wilcoxon signed-rank test with Bonferroni correction. The correlations of $Diff_{L-R}$ gain and $Diff_{L-R}$ amplitude values with the ocular deviation at near using all pre- and post-surgery data were analyzed. I also analyzed the correlation of pre- and postsurgical changes in $Diff_{L-R}$ gain and $Diff_{L-R}$ amplitude with pre- and postoperative changes in the ocular deviation at near (in this analysis, only values of each parameter 6 months after surgery were used as postoperative data). Spearman's rank correlation was used for these correlation analyses. The Friedman test was performed using IBM SPSS for Windows statistics (version 21.0, IBM Corp, Armonk, NY).

4. RESULTS

1) Fixation stability of the upward gaze in patients with myasthenia gravis

Study subjects

A total of 21 normal, healthy subjects (mean age: 48.9 ± 18.6 years, 9 women) who had no strabismus or oculomotor abnormalities were included in the study as a control group. The MG group consisted of 10 patients with MG (mean age: 54.7 ± 16.5 years, 6 females) with diplopia (n = 5) and without diplopia (n = 5) at disease presentation (Table 1). These patients were diagnosed with MG based on the presence of antibodies in their serum (8 patients were acetylcholine receptor antibody positive, one was muscle-specific kinase antibody positive and one was seronegative), edrophonium test results (8 of 9 patients tested positive and one patient was not tested) and repetitive nerve stimulation results (5 of 8 patients tested positive and 2 patients were not tested). The primary ocular deviations of the patients with MG without diplopia measured by APCT were orthophoria or slightly exophoria. In the patients with MG with diplopia, two patients exhibited XT: one was 45 PD exotropic, the other was both 20 PD exotropic and 3 PD left hypertropic. Another patient exhibited 14 PD right hypertropia, one exhibited 16 PD exophoria and one was orthophoric but presented with disturbances of adduction and abduction in his right eye. The SO palsy group consisted

of 6 patients with SO palsy with diplopia (mean age: 53.5 ± 16.3 years, 4 women). Patients with SO palsy in this study were unilateral palsy. This group consisted of patients with acquired SO palsy and patients with decompensated congenital SO palsy. They had awareness of diplopia in the upward gaze. Their ocular deviation measured by the synoptophore in the upward gaze was 3.5 ± 5.22° of the horizontal deviation, 4.83 ± 5.24° of the vertical deviation and 3.17 ± 3.44° of the cyclodeviation. There were no statistically significant differences in subject ages among groups (ANOVA; $F_{(3,33)} = 0.4$, $P = 0.75$).

No.	Age	Sex	MGFA Clinical classification	Diplopia
1	28	F	IIa	-
2	38	F	IIa	-
3	61	M	IIa	+
4	71	M	I	+
5	40	F	IIa	+
6	49	M	IIb	-
7	76	M	IIb	+
8	65	F	IIa	-
9	47	F	IIa	+
10	72	F	IIb	-

Table 1. Characteristics of myasthenia gravis patients.
MGFA: Myasthenia Gravis Foundation of America, M: male, F: female

Upward gaze stability based on the measure of BCEAs

A repeated measures ANOVA test revealed that there was a significant main effect of study groups for the 68% BCEA ($F_{(3,33)} = 1.46$, $P < 0.0001$). The 68% BCEA was significantly larger in the MG groups (both with diplopia and without diplopia) than in the normal group (two-tailed t-test with Bonferroni correction: $Ps < 0.05$; Figure 15). In contrast, there were no significant main effects of 20 s fractions or interaction of groups

× fractions ($F_{(2,66)} = 1.32$, $P = 0.27$ or $F_{(6,66)} = 1.02$, $P = 0.42$, respectively; Table 1). Typical fixation scatter plots are shown for each group in Figure 16. By observation, the variation in the normal group was smaller (Figure 16A) than in all other groups (Figure 16B–E). Individual variation was markedly greater in the MG group (Figure 16B, C) than in other groups, particularly in the vertical direction. A patient with MG with diplopia was examined before and after MG treatment, which was accompanied with amelioration of the disease state as observed in the clinical symptoms, such as diplopia and ptosis. After the treatment, the BCEAs were markedly decreased from those of the pretreatment values (Figure 19E).

Upward gaze stability based on the measure of vertical and horizontal SDs

A repeated measures ANOVA test revealed that there was a significant main effect of study groups for SD in both the X and Y eye positions (for X, $F_{(3,33)} = 8.90$, $P = 0.0002$; for Y, $F_{(3,33)} = 17.1$, $P < 0.0001$). The SD of X position was significantly larger in the MG with diplopia group than in the normal group (two-tailed t-test with Bonferroni correction, $P < 0.05$; Figure 15). The SD of Y position was significantly larger in the MG with diplopia group than the other groups including the MG without diplopia group (two-tailed t-test with Bonferroni correction, all $Ps < 0.05$); the SD of Y position in the MG without diplopia group was also significantly larger than the normal group (two-tailed t-test with Bonferroni correction, $P < 0.05$; Figure 15). For the SDs of X position, there was a main effect of fractions ($F_{(2,66)} = 4.81$, $P = 0.011$) but no interaction of groups × fractions ($F_{(6,66)} = 1.64$, $P = 0.15$; Table 1). For the SD of Y eye position, there were

both main effect of fractions and interaction of groups × fractions ($F_{(2,66)}$ =7.88, P = 0.0009 and $F_{(6,66)}$ = 5.52, P = 0.0001, respectively; Table 2). The SD of Y eye position in the MG with diplopia group was significantly larger during the first 20 s period than that in the third 20 s period (two-tailed t-test with Bonferroni correction, $P < 0.05$; Table 2).

		68%BCEA (° ^ 2)			
		Normal (N=21)	MG Diplopia- (N=5)	MG Diplopia+ (N=5)	SO palsy (N=6)
Time from fixation start	0-20 s	3.21 ± 2.89	3.9 ± 1.78	13.97 ± 8.56	6.67 ± 4.49
	20-40 s	2.14 ± 1.54	4.12 ± 2.67	10.2 ± 3.75	5.92 ± 4.96
	40-60 s	2.02 ± 2.18	4.7 ± 4.19	7.11 ± 7.95	7.06 ± 8.99

		SD (°)							
		Normal (N=21)		MG Diplopia(-) (N=5)		MG Diplopia(+)(N=5)		SO palsy (N=6)	
		X	Y	X	Y	X	Y	X	Y
Time from fixation start	0-20 s	0.49±0.27	1.02±0.62	0.5±0.22	1.22±0.29	1.21±0.61	4.87±3.16	0.74±0.28	1.58±0.98
	20-40 s	0.41±0.22	0.82±0.34	0.43±0.25	1.59±0.62	0.78±0.4	2.41±0.36 *	0.69±0.31	1.41±0.64
	40-60 s	0.36±0.19	0.73±0.34	0.47±0.25	1.31±0.67	0.68±0.32	1.65±0.83	0.71±0.22	1.49±1.25

Table 2. Temporal fixation stability. Values are mean ± standard deviation (SD) of the 68% bivariate contour ellipse areas (BCEA: the upper table), the horizontal (X) and vertical (Y) fluctuations (the lower table) in the normal subjects (Normal) , patients with myasthenia gravis (MG) without diplopia (MG diplopia-), patients with MG with diplopia (MG diplopia+) and superior oblique palsy (SO) groups during the first (0-20 s), second (20-40 s) and third (40-60 s) fractions in the fixation period. * Indicates 2-tailed t-test with Bonferroni-correction $P < 0.05$.

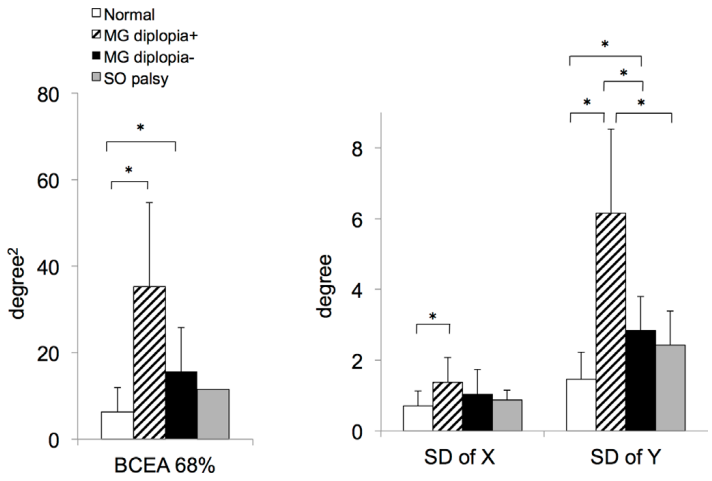

Figure 15. Results of 1 min fixation stability testing for normal subjects (white bars), patients with myasthenia gravis (MG) with diplopia (hatched bars), patients with MG without diplopia (black bars) and patients with superior oblique palsy (SO) (grey bars). Means are shown and error bars indicate SDs. The asterisk (*) indicates $P < 0.05$. SD; standard deviation, BCEA; bivariate contour ellipse area, MG; myasthenia gravis, SO; superior oblique palsy.

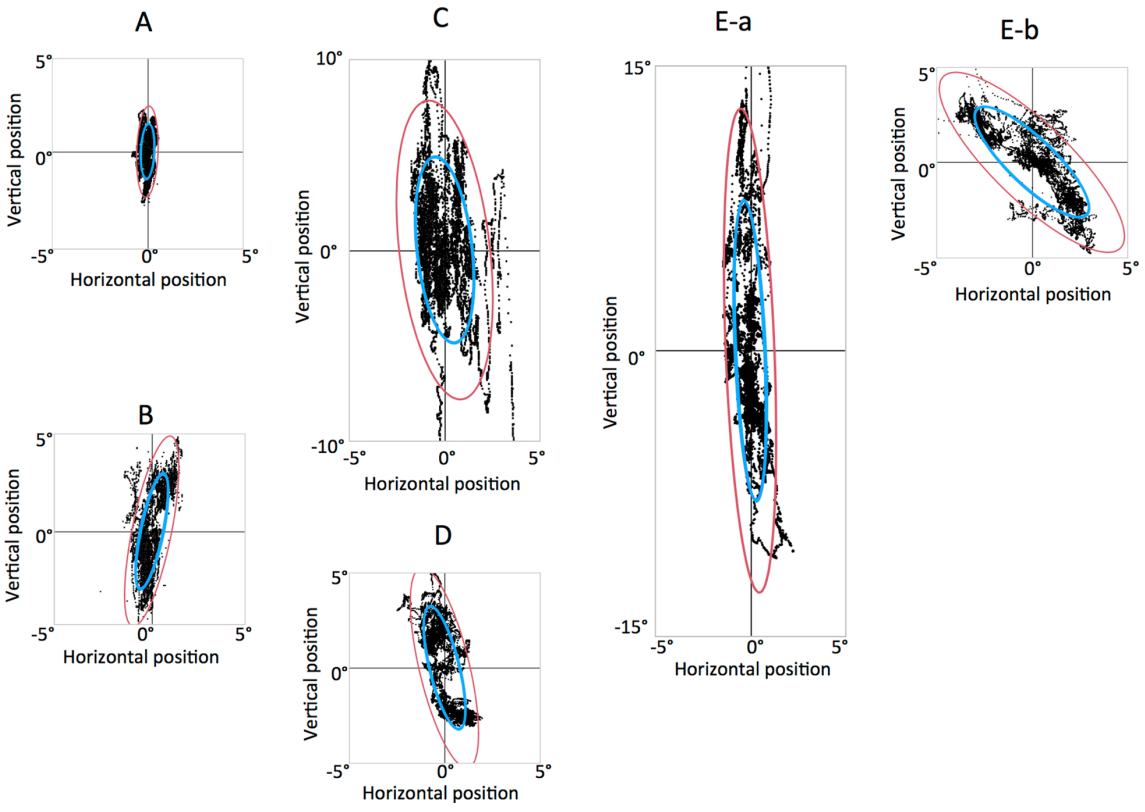

Figure 16. Typical fixation testing results in a normal subject (A), a patient with myasthenia gravis (MG) without diplopia (B), a patient with MG with diplopia (C) and a patient with superior oblique (SO) palsy (D). Results are also compared in a patient with MG before (E-a) and 2 months after (E-b) initiating MG treatment. Each dot on all plots represents eye position, as measured by the eye tracker. Blue and red ellipses represent the 68% and 95%, respectively, of the bivariate contour ellipse areas (BCEA) encompassing the fixation points.

2) Horizontal saccadic velocity in patients with exotropia

The presurgical exodeviation angle (mean ± SD) near and far were 45.9 ± 17.2 PD (range: 16 PD to 95 PD) and 40.3 ± 18.1 PD (range: 14 PD to 87 PD), respectively. The surgical doses for the lateral rectus muscle and medial rectus muscle were 5.9 ± 1.4mm (range: 4–8 mm) and 5.9 ± 1mm (range: 4–8 mm), respectively. The postsurgical deviation angle (mean ± SD) near and far were 7.6 ± 10.0 PD (range: -10 PD to 30 PD) and 4.1 ± 5.1 PD (range: -10 PD to 18 PD), respectively. All the patients presented orthophoria or exophoria after surgery. No patient presented disturbance of adduction or abduction post-surgically. All patients showed stereopsis on the Titmus stereo test (Table 3).

No.	Age	Sex	Dominant eye	Surgical dose (mm)	Deviation angle at near (PD)		Deviation angle at far (PD)		Stereopsis (second)	
					Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery
1	27	M	LE	RE: MR4.0 LR4.0	30	16	14	4	40	40
2	31	M	LE	RE: MR6.5 LR6.5	57	0	72	0	100	60
3	35	F	LE	RE: MR7.0 LR7.5	40	6	50	8	400	100
4	21	M	LE	RE: MR5.5 LR4.5	45	12	40	2	RE sup	3000
5	70	F	LE	RE: MR6.0 LR5.5	58	0	42	−2	RE sup	100
6	6	M	LE	RE: MR6.0 LR6.0	45	16	35	10	50	50
7	22	F	LE	RE: MR6.0 LR7.0	59	−1	51	0	50	40
8	13	M	RE	LE: MR5.0 LR4.5	35	−10	25	−2	40	40
9	11	M	RE	LE: MR4.5 LR4.5	35	6	25	6	40	40
10	8	F	RE	LE: MR6.5 LR6.5	40	2	35	4	100	40
11	13	M	RE	LE: MR4.5 LR4.5	16	2	20	1	40	40
12	37	F	RE	LE: MR7.0 LR6.5	59	8	40	4	LE sup	3000
13	13	M	RE	LE: MR6.5 LR8.0	50	20	45	8	100	40
14	80	F	RE	LE: MR6.5 LR8.0	55	18	60	8	LE sup	200
15	53	M	RE	LE: MR8.0 LR8.0	95	30	87	18	50	50
16	20	F	RE	LE: MR5.5 LR4.0	52	20	30	10	40	40
17	10	M	LE	RE: MR6.0 LR6.5	30	−8	30	−10	40	40
18	12	F	RE	LE: MR5.0 LR4.5	25	0	25	4	140	50

M : male; F : female; RE : right eye; LE : left eye; MR: medial rectus; LR: lateral rectus; PD: prism diopter; sup: suppression.

Table 3. Summary of patients with exotropia

Comparison of the PVs between normal subjects and patients with XT

Figure 17 shows monocular recordings of typical sequences of horizontal saccades for a normal subject (gray symbols) and a patient with XT before surgery (black symbols). The shape of the primary saccade was smooth for most subjects in both groups, although some patients with XT sometimes exhibited overshoot Figure 17B. The number of cases in which the saccades overshoot their targets was one for adduction and 5 for abduction in the normal group. In patients with XT before surgery, overshoot was noted in 6 cases for adduction and 8 for abduction. The corrective saccade, which appeared 180 ms after the end of the primary saccade, facilitated an eye position that could reach the target (15° rightward). The PV was significantly higher in the XT group than in the normal group, in either movement direction, for both eyes (Figure 18; in the dominant eye, $P = 0.032$ for adduction and $P = 0.049$ for abduction; in the nondominant eye, $P = 0.016$ for adduction and $P = 0.037$ for abduction).

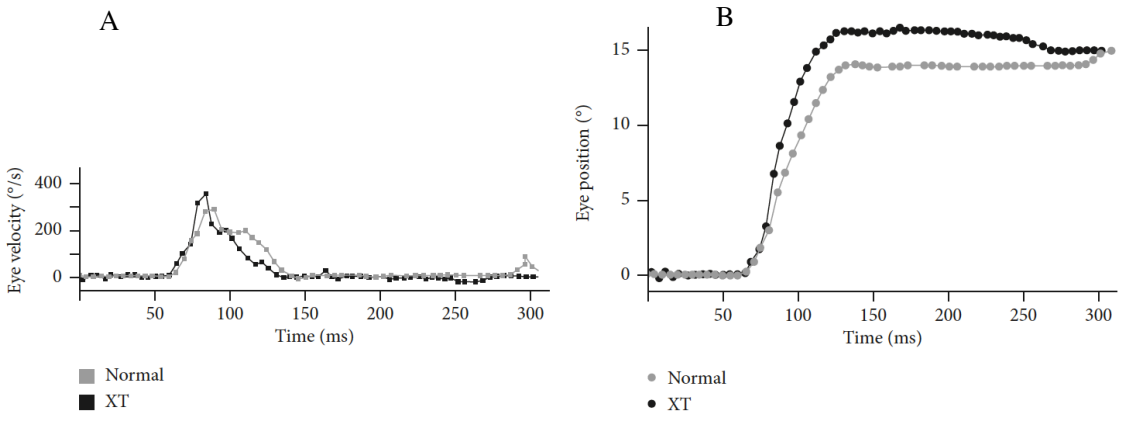

Figure 17. Typical example of an abducting saccade for right eye: eye velocity waveform (A) and primary differential value of eye position (B) for a normal subject (gray symbols) and a patients with exotropia (XT), before surgery (black symbols).

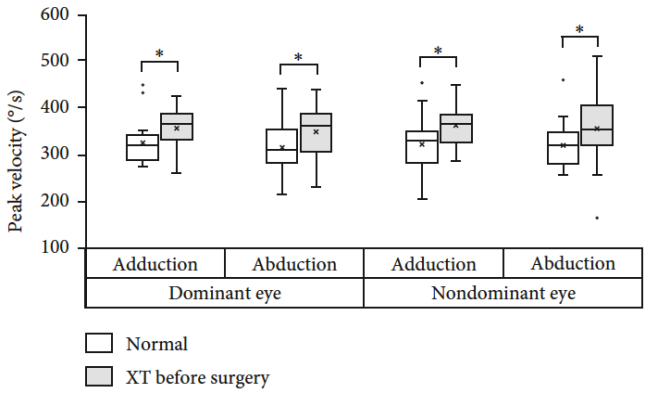

Figure 18. Comparison of horizontal saccadic velocity in normal subjects (white box) and presurgical patients with exotropia (XT, light gray box). In dominant eye, the peak velocity (PV) was significantly higher in the XT group than in the normal group for both adduction and abduction. In the nondominant eye, the PV was similar to that of the dominant eye. The asterisk (*) indicates $P < 0.05$.

Changes in patients with XT after surgery

PVs in adduction and abduction

For adduction, the PVs in the dominant eye tended to reduce after the surgery, although the difference did not reach statistical significance ($P = 0.55$). No significant changes were observed in the nondominant eye ($P = 0.21$) (Figure 19). For abduction, there were no significant changes in the PVs in the dominant eye after the surgery ($P = 0.39$). The PVs in the nondominant eye clearly decreased after the surgery ($P = 0.016$), such that the mean PV value approached that of normal subjects (Figure 19). There was no significant difference between the normal subjects and the patients with XT after surgery for abduction in the nondominant eye ($P = 0.55$).

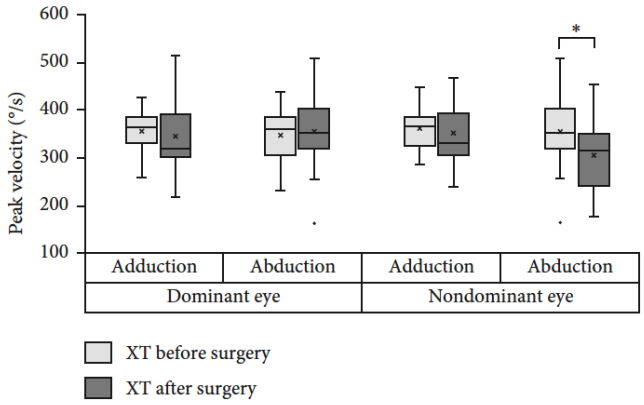

Figure 19. Comparison of presurgery (light gray box) and postsurgery (gray box) horizontal saccadic velocity in patients with exotropia (XT). In the abduction of the nondominant eye (operated eye), the postsurgery peak velocity (PV) was significantly lower than the presurgery PV. The asterisk (*) indicates $P < 0.05$.

Relationship between changes in PVs and extent of surgery

There was no correlation between changes in the PVs and the extent of the surgery in the operated, nondominant eyes (adduction: $rs = -0.006$, $P = 0.98$; abduction: $rs = -0.36$, $P = 0.14$) (Figure 20).

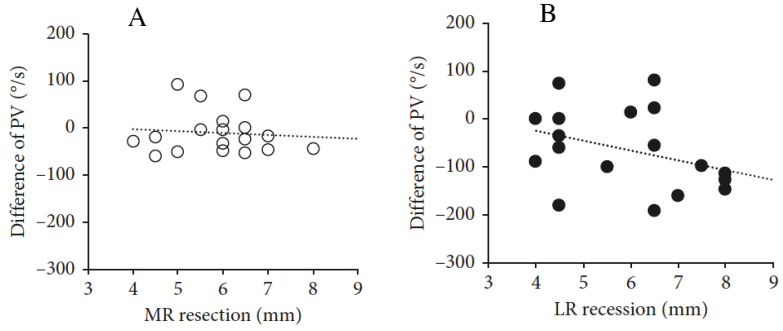

Figure 20. Relationships between changes in peak velocities (PVs) and extent o surgery. There was no correlation between changes in the PV and the extent of surgery in the operated, nondominant eyes (A: adduction and resection; B: abduction and recession). MR: medial rectus, LR: lateral rectus.

3) Binocular coordination of smooth pursuit in patients with intermittent exotropia

A total of 9 patients (mean age: 22.2 ± 13.9 years, 10-45 years, 7 females) were included (Table 4).

Longitudinal changes in ocular deviation and sensory outcome

One patient (patient 9) had constant XT (poor control of the intermittent XT) at preoperative examinations. The other 8 patients had non-constant XT. Patient 2 had good control of the intermittent XT for the entire duration of the preoperative examination. Seven patients sometimes had constant XT during the examination but did achieve refusion by blinking or refixation. The preoperative mean exodeviation angles (mean and SD) at near was 59.1 ± 34.7 PD ranging 18–113 PD; at distance, 50 ± 19.5 PD ranging 25–80 PD (Table 4). One week after surgery, the mean deviation at near was 5.9 ± 10.5 PD ranging -14 –18 PD; at distance, 1.8 ± 6.4D ranging -10D–12D. However, the ocular deviations at near and distance regressed to 18.9 ± 17.5 PD ranging 2–57 PD and 14.8 ± 15.5 PD ranging 2–50 PD, respectively, by 6 months after surgery (Table 4, Figure 21). Before surgery stereopsis at near varied from 40 to nil (>3000″). Four of 9 patients had good stereopsis (≦ 60″). After surgery, the stereopsis of all patients was improved or equal to before surgery. Seven patients had good stereopsis (≦ 60″). A patient who had no stereopsis before surgery had stereopsis of 400″ postoperatively. Fusion was examined using synoptophore preoperatively, but not

postoperatively. Four patients (4, 6, 7, and 9) did not have fusion before surgery. Other patients had a wide range of fusion, except for patient 5, who had a narrow range of fusion before surgery (Table 4).

No.	Age, years	Sex	Surgery, mm	Deviation at near, PD[a]			Deviation at distance, PD[a]			Convergence		Stereopsis, (")		Fusion range, (°)
				Pre	1W	6M	Pre	1W	6M	Before	After	Before	After	Pre
1	12	M	LE MR 6.5, LR 6.5	40	6	20	40	8	16	Good	Good	40	40	−15 to +10
2	12	F	BE LR 5.0	18	4	6	35	2	4	Good	Good	40	40	−13 to +40
3	29	F	RE MR 5.5, LR 5.5	80	16	10	60	6	6	Good	Good	80	40	−15 to +22
4	10	F	RE MR 6.5, LR 6.5	45	−1	8	45	−1	4	Good	Good	140	40	—
5	10	M	RE MR 6.5, LR 6.0	30	−14	2	30	−10	2	Poor	Good	40	40	−2 to +9
6	31	F	LE MR 6.5, LR 8.0	86	6	20	63	2	20	Good	Good	3000	100	—
7	12	F	LE MR 5.0, LR 4.5	25	0	12	25	−2	6	Good	Good	140	50	—
8	39	F	RE MR 7.0, LR 8.0	113	18	57	72	12	50	Good	Good	50	40	−25 to +30
9	45	F	RE MR 8.0, LR 9.0	95	18	35	80	−1	25	Poor	Good	>3000	400	—

BE, both eyes; *LE*, left eye; *LR*, lateral rectus muscle; *MR*, medial rectus muscle; *RE*, right eye; *PD*, prism diopter.
[a]*Pre-*, before surgery; *1W*, 1 week after surgery; *6M*, 6 months after surgery.

Table 4. Summary of patients with exotropia

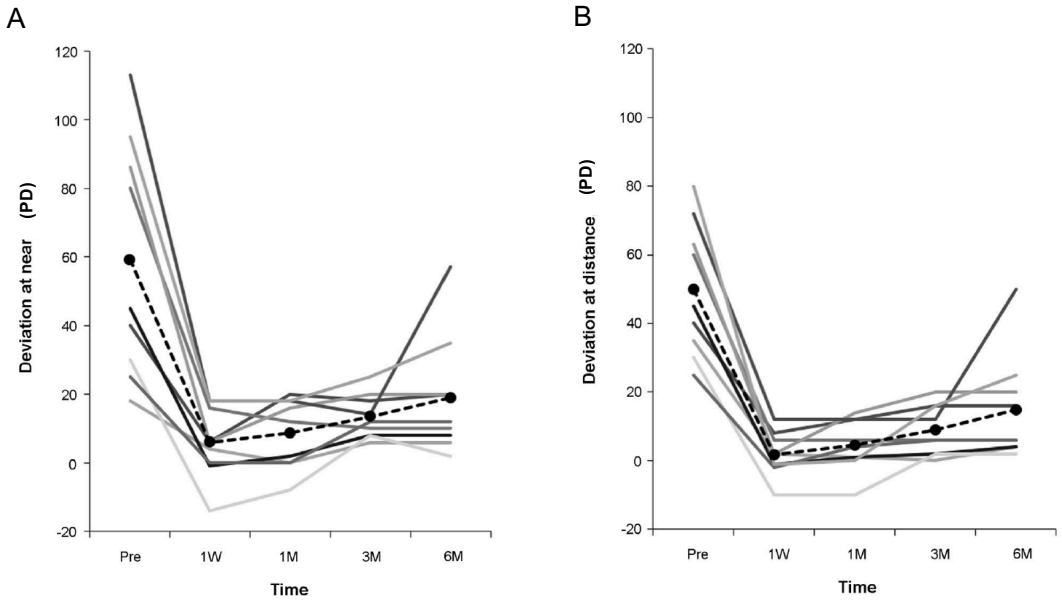

Figure 21. Binocular alignment at near (A) and distance (B) for each patient. Solid lines indicate each individual; mean for all patients is indicated by the dashed line with solid circles. The time points are before surgery (Pre) and 1 week (1W), and 1, 3, and 6 months (1M, 3M, and 6M) after surgery.

Longitudinal changes in smooth pursuit

In the presurgical data, mean $Diff_{L-R}$ gain was 0.23 ± 0.1; the mean $Diff_{L-R}$ amplitude, 3.0 ± 3.7°. These values were improved at 1 week after surgery (gain, 0.08 ± 0.06; amplitude, 0.9 ± 0.65°) and remained improved for 6 months postoperatively. The values of $Diff_{L-R}$ gain were significantly improved at 3 and 6 months postoperatively (Friedman test, $\chi^2 = 11.64$; $df = 4$; $P = 0.013$; Wilcoxon signed-rank test with Bonferroni correction at 1 week and 1, 3, and 6 months, $P = 0.15$, $P = 0.08$, $P = 0.016$, $P = 0.016$, respectively; Figure 22A), although the values of $Diff_{L-R}$ amplitude did not reach statistical significance at any assessment time after surgery (Friedman test, $\chi^2 = 8.0$; $df = 4$; $P = 0.09$; Figure 22B). Figure 26A show a trajectory of both eye positions for patient 1, with intermittent XT before and after surgery. Although the smooth pursuit for the patient initially showed good binocular coordination, disconjugacy of pursuit was revealed midway during smooth pursuit due to expression of XT (Figure 23A-a, small arrows). Because the patient remained orthophoric during smooth pursuit after surgery, binocular coordination of smooth pursuit was improved; however, his binocular coordination of catch-up saccades during smooth pursuit was fine even before surgery. Patient 2 consistently had good control of the exodeviation at near before and after surgery. Her binocular coordination of smooth pursuit was good during the pursuit examination before surgery (Figure 23B-a). After surgery, her good binocular coordination of smooth pursuit was maintained and her pursuit eye movement was smoother than before surgery because of a decreasing number of large catch-up

saccades (Figure 23B-b). Patient 9 had constant XT at near and distance before surgery but good control of the exodeviation after surgery. Before surgery, there was a marked difference in pursuit amplitude between both eyes, because she fixed her left eye to the target and her right eye deviated outward (Figure 23C-a, b).

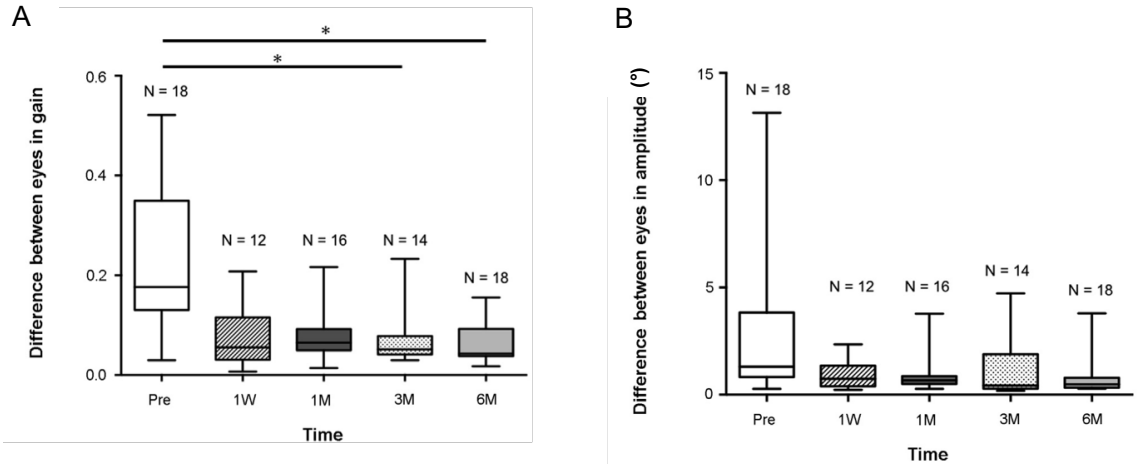

Figure 22. Comparison of differences in gain (A) and amplitude (B) between eyes. The white box indicates the preoperative difference. The shaded box indicates the difference at 1 week postoperatively; the gray box, at 1 month; the dotted box, at 3 months; and the light gray box, at 6 months. Horizontal black lines within each box indicate median values. Boxes extend from the 25th to the 75th percentile of each period; upper and lower lines indicate maximum and minimum values. The asterisk (*) indicates $P < 0.05$.

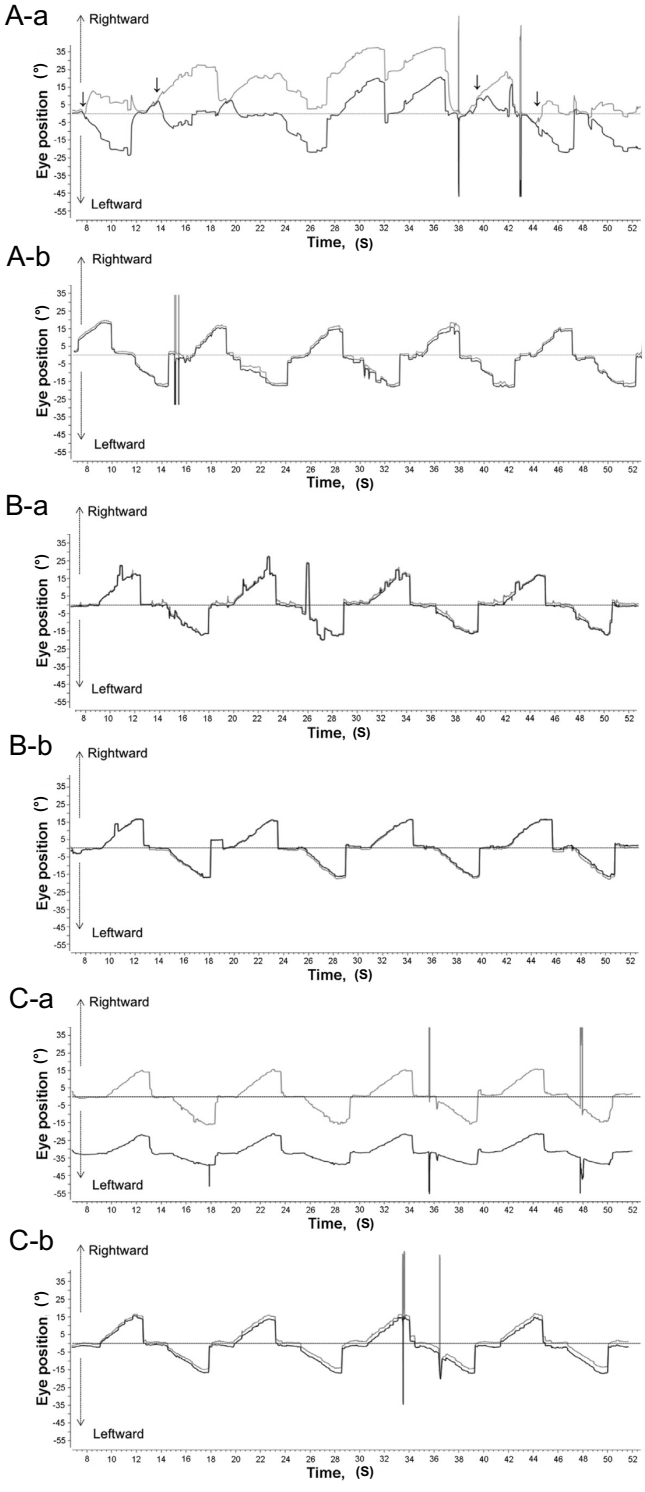

Figure 23. Typical examples (patients 1, 2, and 9) of smooth pursuit for the right eye (solid light gray line) and left eye (solid gray line) waveform. Eye position during smooth pursuit before surgery (patients 1 [A-a], 2 [B-a], and 9 [C-a]) and 1 month after surgery (patients 1 [A-b], 2 [B-b], and 9 [C-b]). The small arrow (A-a) indicates the beginning of the time that disconjugacy of pursuit was evident.

Relationships between smooth pursuit and ocular alignment

As shown in Figure 24, the correlations between ocular deviation and $Diff_{L-R}$ gain (A) and $Diff_{L-R}$ amplitude (B) were significant (ocular deviation vs $Diff_{L-R}$ amplitude, $\varrho = 0.47$ and $P < 0.05$; ocular deviation vs $Diff_{L-R}$ gain, $\varrho = 0.6$ and $P < 0.05$). There were no correlations between pre- and postoperative changes in the amount of ocular deviation and pre- and postoperative changes in $Diff_{L-R}$ amplitude or those in $Diff_{L-R}$ gain ($Diff_{L-R}$ amplitude vs. ocular deviation, $\varrho = 0.046$ and $P = 0.86$; $Diff_{L-R}$ gain vs ocular deviation, $\varrho = -0.311$ and $P = 0.21$).

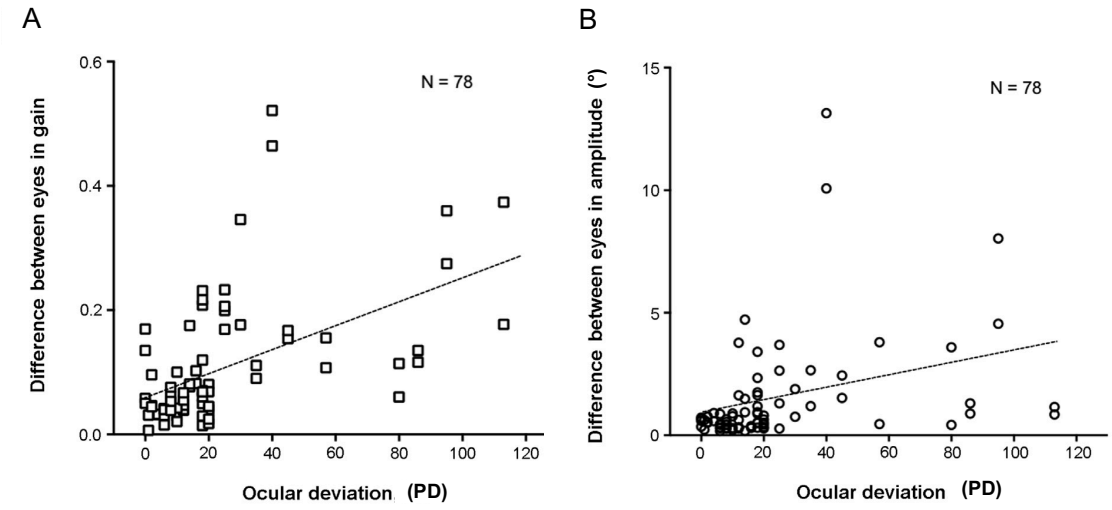

Figure 24. Relationships between difference in gain and ocular deviation (A) and between difference in amplitude and ocular deviation (B).

5. DISCUSSION

1) Fixation stability in patients with myasthenia gravis

Directional selectivity of fixation stability during the upward gaze

The study of fixation stability in MG showed that fixation fluctuation during the upward gaze was larger in the vertical direction than in the horizontal direction in all subjects. The upper gaze was used in the current study because it has been shown to be suitable for detecting the MG fatigue phenomenon.[22] To the best of our knowledge, this is the first study to examine upward gaze stability in healthy subjects and patients with MG. Therefore, the difference in fixation stability between the vertical and horizontal directions observed in the present study could be related to the direction of the gaze. The directional selectivity of fixation stability observed in the present study may stem from the peripheral mechanism needed to maintain the upward gaze. Anatomical factors could play a role: muscle bulk is greater for the superior rectus (SR) muscle than for the other recti[51]; the SR muscle load is greater than for the other vertically acting muscle in rabbits[52]; the SR has fewer muscle spindles than the other recti.[53] During upward fixation, the SR and the inferior oblique (IO) contract. Persistent contraction of the SR and the IO may produce fatigue in these extraocular muscles, which could lead to larger fluctuation of eye position in the vertical direction. Indeed, this speculation is consistent

with the present observation that the fluctuation in vertical direction was much larger in patients with MG than normal subjects.

Fixation instability in subjects with myasthenia gravis

This study showed that the upward gaze in patients with MG was more unstable in the vertical position than in normal subjects or patients with SO palsy. Vertical position instability was especially high in the MG with diplopia group. Cleary et al. have demonstrated that in patients with MG, weakness of the elevator muscles (i.e., the SR and the IO) is significantly greater than that of other extraocular muscles.[31] Almog et al. also showed that the IO was involved more often than any other extraocular muscle in patients with MG.[32] Such a trend of extraocular muscle dysfunction (more severe and frequent impairment of the elevator muscles) in patients with MG, which was the reason for using upward gaze in the present testing, may underlie the fixation instability of patients with MG in upward gaze. In spite of the well-known ocular symptoms of patients with MG, no reports on gaze stability in patients with MG were identified in the academic literature. However, some studies that evaluated central fixation stability using BCEAs in patients with amblyopia and macular degeneration found that visual fixation was unstable in eyes with visual impairments.[24][26][46] Patients with strabismus have unstable fixation in the deviated eye.[54] Diplopia may also have unstable fixation because of retinal image fusion attempts. However, diplopia is not the underlying cause of the fixation instability observed here in MG subjects because SO palsy subjects (who also had diplopia) did not have the same degree of instability. In addition, the fixation in

patients with MG without diplopia was more stable than that in patients with MG with diplopia, but not similar to normal subject. Therefore, it is likely that the marked fixation fluctuation in MG subjects with diplopia was caused by MG fatigability and not by diplopia. The present study showed no significant changes in BCEA and SD of Y over time (determined by comparing three consecutive 20 s periods) in normal subjects, in MG subjects without diplopia and in SO palsy subjects. In contrast, patients with MG with diplopia tended to show increased BCEA and SD of Y during the first 20 s period in MG subjects with diplopia. This result was surprising because in the present study it was initially expected that easily fatigued muscles in MG subjects would cause fixation to become more unstable over time. Not yet fully understood, but it may be that extraocular muscles, which at least partially functioned during the first 20 s period, attempted to correct eye position drift towards the upward gaze. However, as muscles became fatigued, ocular position corrections would have become smaller and less frequent, resulting in a smaller fluctuation of eye positions during the second and third 20 s periods compared with those during the first 20 s period. That is, the unexpected result may have been caused by the decrease in eye position correction ability of the patients with MG with diplopia along with the lapse of time. In support of this theory, Feldon et al.[55] have reported that patients with MG exhibit commonly substantial instability of eye positions immediately after saccadic movements (they called this 'wavering fixation'). They commented that wavering fixation was the expression of varying levels of tonic innervation to agonist and antagonist resulting from fatigue that caused the eye to drift. Also, in the present study, the vertical eye position in some of

the participants of MG group drifted from the target position (data not shown). Furthermore, the vertical SD value of this group further decreased from the second 20 s period (2.41) to the third 20 s period (1.65), although this did not reach the level of the statistical significance.

Usefulness of eye tracking in evaluating fixation stability in patients with myasthenia gravis

Current clinical evaluations of ocular symptoms in patients with MG with diplopia (initial diplopia and residual diplopia following treatment) are subjective. A published report on the diagnosis and evaluation of MG-associated diplopia describes methods for confirming acquired strabismus caused by MG. These include comparing ocular deviation in the Hess screen test before and after edrophonium infusion.[23] Electromyography demonstrates the fatigue phenomena electrophysiologically and the edrophonium test shows the pharmacological condition of the fatigue phenomenon. However, these tests are diagnostic invasive methods (i.e., electromyography is painful[56]; edrophonium has an effect on cardiovascular system[57]), and therefore, ophthalmologists avoid repeated use of these tests if alternative, non-invasive methods are available. The ice pack test, which involves cooling the orbital cavity through the application of ice over closed eyelids for 2 min, is less invasive for diagnosing myasthenic ptosis.[58] In contrast, the ice pack test for diagnosing myasthenic diplopia is more invasive because it requires a 5 min or longer cooling time because extraocular muscles are located in the deeper portion of the orbital cavity.[59][60] Unfortunately, the ice

pack test becomes increasingly uncomfortable for the patient when cooling times are longer than 2 min.[58] Compared with these clinical tests, the present quantification method using the eye-tracking system can non-invasively evaluate gaze stability in patients with MG almost without discomforts. As an improvement in gaze stability indicates an improvement in the MG disease state[19)-22)], eye tracking is especially suitable for evaluating treatment efficacy in patients with MG. Ocular symptoms associated with MG strongly contribute to the quality of life decline observed in patients with MG.[61] Therefore, evaluating diplopia is important, even after treatment has been initiated. The currently used Hess screen and APCT measure ocular motility and position at only one time point. Therefore, they do not accurately evaluate fatigability over time. Evaluating gaze stability using an eye-tracking system is beneficial to diagnosis and evaluation of treatment efficacy in patients with MG because it is non-invasive, quantitative and accurately measures eye position over a long enough period of time to evaluate the muscle fatigability that is characteristic of MG.

2) Horizontal saccadic velocity in patients with exotropia

The effect of strabismus surgery on saccade velocity in patients with XT

The PV of horizontal saccades in normal subjects was almost the same as that previously reported,[40)5)] while that in patients with XT was higher than that of the normal subjects, for both the dominant and nondominant eyes. It is presumed that the PVs were influenced by the accuracy of saccades (especially when overshoot saccades occurred),

since the amplitude of saccades in patients with XT was larger than in the normal subjects (data not shown). On the contrary, it is necessary to consider the cause due to the difference in the viewing condition. In a study by Niechwiej-Szwedo et al.[62], there was no significant difference in the PV of saccades between binocular viewing and monocular viewing in patients with horizontal strabismus without stereopsis, whereas in normal subjects and strabismus patients with stereopsis, the PV was lower during monocular viewing than during binocular viewing. Alternatively, as reported by Niechwiej-Szwedo et al.[62], the saccadic velocity in the normal subjects in the present study might have been decreased due to monocular viewing, because this was an unusual viewing condition for them. Conversely, the saccadic velocity of patients with XT, who were eligible for surgery, might not have been decreased because they had adapted to using monocular viewing over a long period of time. Difference of saccadic velocities between normal subjects and patients with XT could be caused by differences in both saccade accuracy and viewing condition. Reduced tension of the extraocular muscles, which is the aim of strabismus surgery, may have resulted in changes of the PV. In the present study, however, there was no correlation between the changes in PVs after the surgery and the extent of resection/recession. In addition, the PV in adduction of the operated eye did not change after surgery. Kushner performed a posterior fixation of the medial rectus in seven patients with convergence excess esotropia.[63] They observed that postoperative saccadic velocity testing did not reveal the expected decrease in saccadic velocity, as the eye moved increasingly into the field of action of the operated muscle.[63] Surgical effects on saccadic velocity are likely to be different

between the lateral rectus muscle and the medial rectus muscle. Bucci et al.[33] observed that the PV of horizontal saccades was significantly decreased after surgery for horizontal strabismus in three of eight patients. However, the directions of horizontal saccades were not reported in their result. Therefore, mechanisms other than extraocular (peripheral) factors are necessary to explain the change in the PV after surgery.

Effect of strabismus surgery on the neural mechanism

It has been reported that, in macaques with strabismus, the firing rate of neurons in the paramedian pontine reticular formation, the motor center for horizontal saccades, differed from that of normal monkeys.[64] Additionally, abnormal activities are observed in the abducens nucleus of macaques with strabismus.[65] Therefore, the patients in our study might have had some abnormal activities in these oculomotor centers before surgery. Orthophoria or exophoria achieved by strabismus surgery could have influenced and improved the central sensory-motor mechanisms within a few months after the surgery, since binocular viewing became easier as a result of the corrected primary eye position. This would have resulted in reduced PV in abduction. Although the present study does not provide direct evidence for this speculation, both peripheral and central sensory-motor mechanisms may be involved in the changes in the PV of horizontal saccades, both of which could result from the improvement of the primary eye position. On the other hand, Pullela et al.[39], in their study using two monkeys with strabismus, reported that the immediate changes in ocular alignment, saccades, and smooth pursuit after strabismus surgery gradually reverted to presurgical levels by six

months after surgery. They concluded that immediate improvement in misalignment and changes in eye movement gains are likely due to contractility changes in the extraocular muscle, whereas longer-term effects are likely a combination of neural and muscle adaptation.[39]

3) Binocular coordination of smooth pursuit in patients with intermittent exotropia

In our patient cohort, the $Diff_{L-R}$ gain and $Diff_{L-R}$ amplitude were significantly decreased after strabismus surgery; that is, the binocular coordination of smooth pursuit improved postoperatively. Moreover, the improvement tended to persist for at least 6 months. Some aspects of the surgical outcomes, including changes in ocular deviation and binocular visual function, may be involved in this improvement.

Relation between binocular coordination of smooth pursuit and exodeviation angle

As a result of the postoperative improvement in deviation angle, which leads to a mechanically balanced position of the left and right eyes, binocular coordination of smooth pursuit (i.e., $Diff_{L-R}$ gain and $Diff_{L-R}$ amplitude) seems to be improved. It is known that intermittent XT in humans recurs frequently in the long term after strabismus surgery.[66][67] Consistent with this, in many of our patients, the ocular deviation angle more or less reverted toward the presurgical level during the 6 months after surgery, while the improvement in binocular coordination of smooth pursuit tended to persist during this

period. The value of the $Diff_{L-R}$ gain and $Diff_{L-R}$ amplitude, which are decreased immediately after surgery, should increase as the deviation angle returns to the preoperative level. Therefore, the improvement of deviation angle may be less important for maintaining binocular coordination of smooth pursuit in the long term.

Relation between binocular coordination of smooth pursuit and ability to maintain heterophoria and binocular vision

I hypothesize that binocular coordination of smooth pursuit is determined by the patient's ability to maintain heterophoria and binocular vision during examination of smooth pursuit. Pullela and colleagues[39] reported that the changes in smooth pursuit gain noted immediately after surgery returned to preoperative levels by 6 months after surgery in monkeys with XT. Their experiment used 2 monkeys that had no binocular vision function because of artificial XT induced by prism goggles in infancy (the sensitive period of binocular vision development). In contrast, in the present study, most patients showed an increased ability to maintain periods of orthophoria after surgery. This indicates, in agreement with the findings of Lions and colleagues[35], that the maintenance of orthophoria during smooth pursuit and improvement in binocular vision function could influence the improvement in binocular coordination of smooth pursuit. Although the exodeviation angle reverted postoperatively over the long term, the maintenance of orthophoria during smooth pursuit and normal binocular vision could lead to continued improvement in binocular coordination of smooth pursuit. To support

this hypothesis, cases of infantile XT (or infantile esotropia) without normal binocular vision must be compared before and after strabismus surgery.

In this study, $Diff_{L\text{-}R}$ amplitude and $Diff_{L\text{-}R}$ gain were correlated with the ocular deviation angle. The $Diff_{L\text{-}R}$ amplitude and $Diff_{L\text{-}R}$ gain were proportional to the exodeviation angle measured by alternate prism cover testing, when some patients showed XT during examination of smooth pursuit (e.g., Figure 23A-a [patient 1], C-a [patient 9]). However, the $Diff_{L\text{-}R}$ amplitude and $Diff_{L\text{-}R}$ gain were small when the patient showed orthophoria during examination of smooth pursuit, as seen in patient 2 (Figure 23B-a), even if the patient showed a large exodeviation. It is likely that a large deviation angle made it difficult to maintain orthophoria during smooth pursuit, as in patient 1 (Figure 23A-a). Therefore, it is likely that the $Diff_{L\text{-}R}$ amplitude and $Diff_{L\text{-}R}$ gain are correlated with the ocular deviation angle indirectly via the duration of orthophoria.

The changes in $Diff_{L\text{-}R}$ amplitude and $Diff_{L\text{-}R}$ gain achieved by strabismus surgery were not correlated with the extent of improvement in deviation angle. These outcomes might be attributable to the influence of the data from patients with good binocular vision function despite large ocular deviation angles before surgery (patients 3 and 8). The values of the $Diff_{L\text{-}R}$ amplitude and $Diff_{L\text{-}R}$ gain before surgery were small in these patients, that is, binocular coordination in smooth pursuit was good, because they maintained orthophoria during smooth pursuit. Therefore, the changes in $Diff_{L\text{-}R}$ amplitude and $Diff_{L\text{-}R}$ gain achieved by surgery may not have been proportional to the

extent of improvement in deviation angle. Furthermore, the small number of data on the change in $Diff_{L-R}$ amplitude and $Diff_{L-R}$ gain before and after surgery (i.e., before vs. 6 months after surgery) may have weakened the statistical power of the study to detect a significant correlation. Studies that include these examinations in a larger number of subjects will be needed to obtain solid evidence on this correlation.

Limitation

Experimant 1: The difference in fixation stability between the vertical and horizontal directions observed in the present study could be related to the direction of the gaze, although, to get solid evidence for this relation, additional tests using gazes in left and right directions are necessary. To confirm the present finding, it was necessary to further investigate by increasing the number of cases of MG. Although all the patients met the diagnostic criteria of MG in the present study, not all patients have undergone all tests. This is one of the limitations of this study, making it impossible to further analyze relationships between the degree of fixation instability of the patients with MG and their disease states.

Experiment 2: Longitudinal evaluation of saccades after strabismus surgery in humans will need to include investigation of neural responses after peripheral remodeling, since the data obtained a few months after strabismus surgery in the present study indicated that PVs change during the process of remodeling of extraocular muscles that have undergone resection and recession surgery.

Experiment 3: The limitations of this study include the wide range of patient ages and the small number of cases. Furthermore, the patients included had varying ocular deviation angles. Therefore, our conclusions are offered with caution.

Future prospects

It will be needed to obtain solid evidence on these studies as following; It is important to analyze the changes in gaze stability before and after treatment in the same MG patients, and to correlate gaze stability with other laboratory findings, rather than grouping by presence or absence of diplopia. Collecting the data of large number of MG patients may enable to set the cutoff value of the BCEAs in MG patients to distinguish from other patients with diplopia. The relationship between the change in saccade PVs and smooth pursuit after surgery and the changes in ocular deviation angle and binocular vision function after surgery must be monitored for more than 6 months to determine whether or not improvement of binocular coordination and normalizing saccade PVs persists.

For understanding the pathological mechanism of strabismus, it is essential to research not only to the static condition, namely, ocular deviation, but also the dynamic condition, that is, eye movement. Therefore, I continue detailed analysis of eye movement in strabismus patients to reveal valuable information regarding the pathological mechanism and the effects of ocular alignment correction. Moreover, for

obtaining data on the mechanism of strabismus development, I plan to clarify the growth of eye movements in infants and young children.

6. CONCLUSIONS

1) Gaze instability caused by fatigability associated with MG can be more accurately evaluated by quantifying fixation with eye tracking and considering how fixation changes over time.

2) Strabismus surgery normalized the patient's with XT increased PV in the operated eye for abduction of horizontal saccade.

3) Surgical correction of ocular alignment improved binocular coordination of smooth pursuit in intermittent exotropia. In the long term, the improvement of the binocular coordination of smooth pursuit tended to remain, although the eye position partially reverted to the presurgical state.

These results suggested that the eye tracking system was useful as diagnosis and treatment index for patients with strabismus.

Conflicts of Interest

The author declares that they have no conflicts of interest.

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