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# Quantitative Analysis of Eyeball Rotation During Lateral Gaze in Intermittent Exotropia: A Magnetic Resonance Imaging Study

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**Purpose:** To evaluate the eyeball rotation during lateral gaze in patients with intermittent exotropia (IXT) using three-dimensional magnetic resonance imaging (MRI).

**Methods:** In this prospective observational study, patients with IXT ($n = 29$) underwent orbital MRI during central, right, and left gazes. Fixation targets were placed at a 40° angle for lateral gaze. After acquisition of MR images, the position of the static tissues other than the eyeball in the MR images were matched three-dimensionally. The optical axis was defined as the perpendicular line to its lens passing through the corneal vertex. The rotation angle was measured as the angle between optical axes in central gaze and lateral gaze using ImageJ. A difference of 3° or more in the rotational angle between both eyes was considered a significant difference.

**Results:** Eight patients (26.7%) had a larger adduction angle than the abduction angle of the fellow eye and six patients (20.0%) showed a smaller adduction angle during lateral gaze on at least one side. There was no significant factor associated with the pattern of rotation.

**Conclusions:** Almost one-half of the patients with IXT had significant difference in the rotation angle between both eyes during lateral gaze. Measurement of the rotation angle during lateral gaze using MRI showed that IXT is not a perfectly comitant disturbance of gaze in some subjects.

**Translational Relevance:** Quantitative analysis for eye movements using MRI can provide useful information for physiologic mechanism and proper surgical planning in patients with IXT.

## Introduction

Intermittent exotropia (IXT) is the most common form of comitant strabismus in the Asian population.[1,2] Most previous studies have focused on the clinical characteristics of IXT, such as clinical diagnosis and management. However few studies have assessed eye movements in IXT, which is necessary to understand the pathophysiology of the disease.[3,4] To understand the mechanism of mechanical and innervational abnormalities in IXT, obtaining an objective and quantitative measurement of eye movement produced by motor nuclei activity is desirable.

To evaluate the patients' eye movements, most strabismologists rely on the direct observation and manual examination such as the prism and alternate cover test (PACT). Although the PACT is a very simple and cost-effective way of measuring the deviation, it has some limitations in accuracy and interobserver reliability.[5,6] Duction and version testing is also a subjective and semiquantitative method.


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Therefore, objective, quantitative, and recordable methods have been induced in research or clinical practice.[7,8] One of the objective methods used for the analysis of eye movements is magnetic resonance imaging (MRI). With the recent technical advancements in MRI, eye position and movement can be studied noninvasively and in detail.[9,10] MRI provides high soft tissue contrast along with high spatial resolution in multiple planes, enabling detailed visualization of the anatomical structure of the orbit.[11] In addition, three-dimensional eye movement during visual gaze can be analyzed by digitally reconstructing magnetic resonance (MR) images.[12]

Therefore, in this study we aimed to investigate eye movements in patients with IXT by measuring the rotation angle during lateral gaze using three-dimensional MRI. We focused on the difference in the rotation angle between both eyes during lateral gaze to identify the pattern of eyeball rotation during binocular conjugate movements (versions).

## Methods

This cross-sectional observational study was approved by the Institutional Review Board of Hanyang University Hospital and the study protocol was in accordance with the principles of the Declaration of Helsinki for biomedical research. The purpose of the study was completely explained to all participants, and informed consent was obtained before their inclusion in the study.

### Study Patients

Patients with IXT who were included from July 2016 to December 2019 were studied prospectively. All patients underwent a comprehensive ophthalmologic examination, including best-corrected visual acuity measurement, tonometry, refraction, slit-lamp examination, funduscopic examination, and ocular motility testing. Ocular motility testing included the duction and version test and the PACT. The binocular fixation preference test was used for ocular dominance.

The exclusion criteria were as follows: (1) previous strabismus or intraocular surgery, (2) significant ocular disease affecting visual acuity, and (3) a history of systemic or neurological disorders affecting the eye movement.

### MR Image Acquisition Procedures

The orbital MRI protocol was described in our previous study.[13] T2-weighted orbital MRI (repetition time = 2500 ms; echo time = 248 ms; flip angle = 90°; section thickness = 0.6 mm; field of view = 180 × 180 mm; matrix = 256 × 256; voxel size = 0.7 × 0.7 × 0.6) was performed using a 3.0 T whole-body scanner) (Achieva 3.0T; Philips Medical Systems, Best, the Netherlands) with a 32-channel head coil. Sets of 67 contiguous, 0.6 mm-thick quasitransverse images were obtained, occupying a 40.2-mm field of view.

The patients were placed in the supine position and their heads were stabilized. The patients could gaze at targets through an opening in the head coil mask. Fixation targets were secured on the inside of the scanner bore. The diameter of the bore was 60 cm; the distance between the target and patient's eyes was approximately 30 cm. The target for the central gaze was positioned in the exact midline of scanner bore, and the targets for lateral gaze were placed at 40° angle of the gaze. As the scanner bore was always in the same position during imaging, the fixation target points were presented in an identical manner to all patients.

To secure the monofixation and manifested exodeviation in each scanning, the eye not fixated on a target remained occluded with a thin patch during the scanning. Scanning was repeated when patients were looking at the appropriate fixation target for each gaze—central or left gaze with left eye fixation and central or right gaze with right eye fixation. All orbital MRI were performed using the same imaging design, quasitransverse imaging planes, fixation targets, and gaze directions. To minimize errors in evaluating eyeball position, the position of the static tissues other than the eyeball in the MR images for all gazes was matched three-dimensionally. Digital MR images were converted into a DICOM file format and images were processed using custom analysis programs in Visual C++ using Visual Studio Community (version 2015; Microsoft, Redmond, WA). Subsequently, MR images were reconstructed three-dimensionally using our program. Our software was designed to ensure accurate superimposition. MR images of horizontal gaze with each eye fixation were adjusted based on the position of the static tissues in the MR image of the primary position with the same eye fixation (Fig. 1). Two authors (Y.M. and H.W.L.) independently checked the axial, sagittal, and coronal images to observe the correct alignment and check whether any structures other than the eyeball showed movement between the images. When the adjustment was failed, we excluded the MRI images from the image analysis.

### Image Analysis

MR image analysis was performed using ImageJ 64 (version 1.51; National Institutes of Health, Rockville,

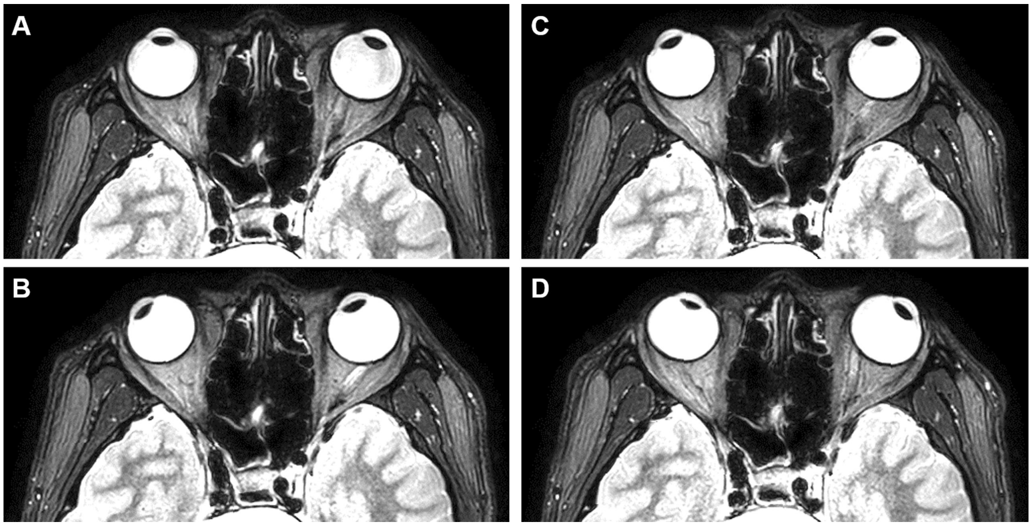


**Figure 1.** Magnetic resonance (MR) images after three-dimensional reconstruction and superimposition of static tissues. It should be noted that the axial plane in this program is inverted left and right compared to the original MR image. Scanning for the patients with IXT was conducted in (**A**) central gaze with left eye fixation, (**B**) left gaze with left eye fixation, (**C**) central gaze with right eye fixation, and (**D**) right gaze with right eye fixation. MR images of horizontal gaze with each eye fixation were adjusted based on the position of the static tissues in the MR image of the central gaze with the same eye fixation. We confirmed that only the eyeball and adjacent structures showed movement and the static tissues such as brain and skull were in the same position in each MR images.

MD; available at http://rsb.info.nih.gov/ij/index.html). First, we identified the reference line that connects both equators of the lens. Then, the optical axis of each eye was defined as the perpendicular line to the reference line passing through the corneal vertex, which is the most anterior point of the surface of the cornea. The optical axis was determined in the axial MR image with the largest cross section of eyeball. The rotation angle was defined the angle between the optical axes in central gaze and lateral gaze (Fig. 2). The axial length was also measured as the distance between the anterior and posterior end of the eye on the optical axis and it was measured in MR image when the eye gazed the central target. All measurements were performed twice by a single examiner (Y.M.) independently, and the mean values were obtained. The intraclass coefficient value of the parameters was 0.939.

The rotation angle was compared between both eyes during lateral gaze: the abduction angle of left eye versus the adduction angle of right eye during left gaze and the adduction angle of left eye versus abduction angle of the right eye during right gaze. The lateral incomitance in IXT was defined as a decrease in the deviation by 5 or more prism diopters (PD) during lateral gaze in several previous studies.[5,14] Therefore, the difference of 3° or more in the rotation angle between both eyes during lateral gaze was considered a significant difference.

## Statistics

We used SPSS (version 23.0; SPSS Inc., Chicago, IL) for all our analyses. The Wilcoxon signed-rank test was used for comparisons of deviation angle in the central gaze between right and left eye or dominant and nondominant eye fixation. The Kruskal-Wallis test and the $\chi^2$ test were performed to identify the clinical factors correlated with the angle change. A $P$ value of 0.05 or less was considered statistically significant. All data were presented as mean ± standard deviation.

# Results

In total, 29 patients with IXT were included in this study. The mean angle of deviation in the PACT was 48.14 ± 15.59 PD (range, 30–85 PD) at a distance and 46.07 ± 14.82 PD (range, 25–80 PD) at near. Baseline demographics and clinical characteristics of all patients are presented in Table 1. Of the total patients, 15 (51.7%) (group 1) showed no significant difference in rotation angle between both eyes.

The other eight patients (27.6%) (group 2) showed a larger adduction angle of one eye than the abduction angle of fellow eye. Of them, two patients showed a significant difference in the rotation angle between both eyes when they gazed to the ocular dominance side. Further, two patients had a significant

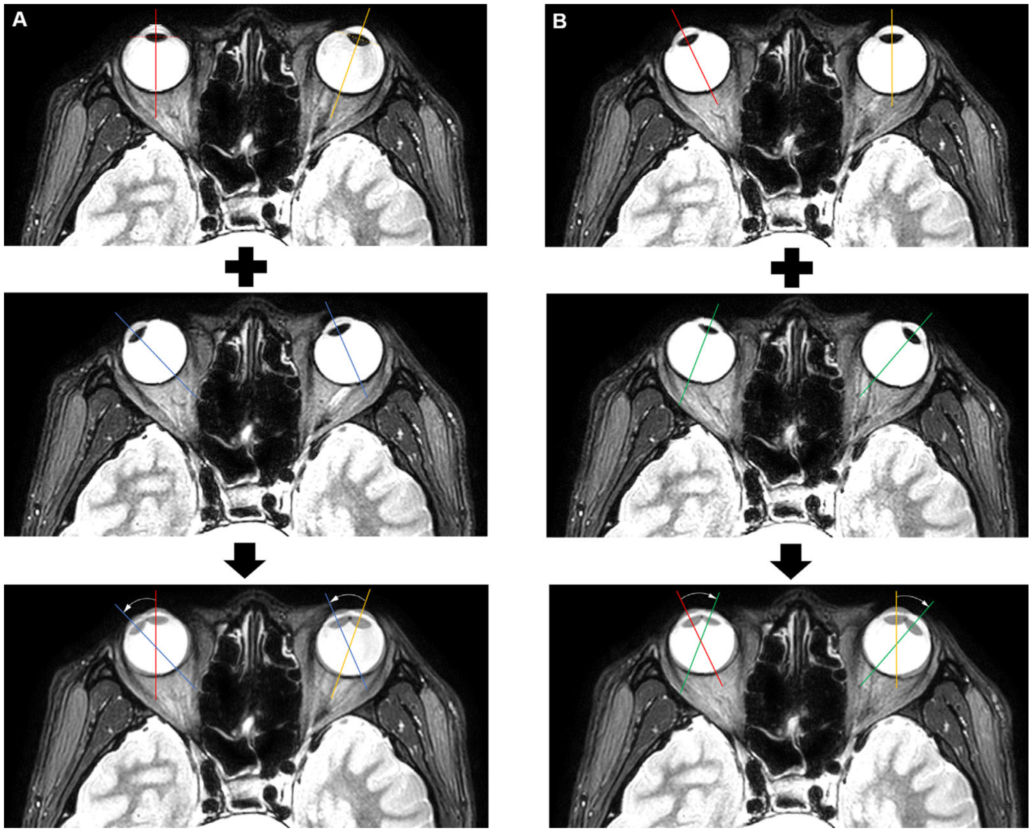


**Figure 2.** Measurement of rotation angle in MR images. (**A**) In the MR images of central gaze with left eye fixation, the dotted lines indicate the reference line connecting both equators of the lens (*red line* for left eye and *orange line* for right eye). The optical axis of each eye is defined as the perpendicular line to the reference line passing through the corneal vertex, which is the most anterior point of the surface of the cornea. The *blue lines* indicate the optical axes of both eyes in the MR images of left gaze. Abduction angle of left eye is defined as the angle between the optical axes in central gaze and in left gaze. Adduction angle of right eye is defined as the angle between the optical axes in central gaze and in right gaze. Additionally, axial length is also measured as the distance between two *short white lines*, which indicate the anterior and posterior end of the eye on the optical axis when the eye gazes the central target. (**B**) The *green lines* indicate the optical axes of both eyes in right gaze. In the same way mentioned, the adduction angle of left eye and the abduction angle of right eye are presented.

difference in the rotation angle when they gazed to the opposite side form the ocular dominance. In the remaining four patients, adduction angle of one eye was larger than the abduction angle of fellow eye by 3° or more during lateral gaze in both sides (Table 2, Fig. 3).

Six patients (20.7%) (group 3) showed a smaller adduction angle during lateral gaze in at least one side. Of them, one had a smaller adduction angle during lateral gaze in both sides. Among the remaining five patients, three showed a smaller adduction angle when they gazed to the ocular dominance side, and two showed when they gazed to the opposite side from the ocular dominance. (Table 3, Fig. 4)

There was no significant difference in clinical characteristics among three groups according to the pattern of rotation (Table 4).

## Discussion

In this study, about one-half of the patients with IXT showed a significant difference in the rotation angle between both eyes during lateral gaze, with one-quarter of the patients having a larger adduction angle and the other one-quarter of patients having a smaller adduction angle. The difference in the rotation angle between both eyes makes the changes in the deviation angle of exotropia in the lateral gaze. Therefore, this result showed that the comitancy, which means that the angle of strabismus is consistent in all direction of gazes, is not applied to all patients with IXT. Furthermore, some patients showed increased exodeviation in lateral gaze in contrast with the lateral incomitance, which has been discussed in previous studies for IXT from the 1960s.[15,16]

**Table 1.** Baseline Demographic and Clinical Characteristics of the Study Population ($n = 29$)

| | Mean ± Standard Deviation | Range |
|---|---|---|
| Age (years) | 33.4 ± 18.2 | 9.4 to 66.0 |
| Sex (M:F)* | 17:12 | |
| Best-corrected visual acuity (logMAR) | | |
| Right eye | 0.05 ± 0.06 | 0.0 to 0.2 |
| Left eye | 0.06 ± 0.08 | 0.0 to 0.3 |
| Spherical refractive error (D) | | |
| Right eye | −2.62 ± 2.58 | −11.75 to 0.13 |
| Left eye | −2.38 ± 3.25 | −11.75 to 2.88 |
| Axial length (mm) | | |
| Right eye | 24.6 ± 1.2 | 22.9 to 28.0 |
| Left eye | 24.7 ± 1.3 | 22.6 to 27.7 |
| Angle of deviation in PACT (PD) | | |
| At Distance | 48.1 ± 15.6 (25.3 ± 6.8°) | 30 to 85 (16.7 to 40.4°) |
| At Near | 46.1 ± 14.8 (25.2 ± 7.2°) | 25 to 80 (14.0 to 38.7°) |
| Subtype of IXT (basic:DE:CI)* | 17:6:6 | |

*Values are presented as the ratio of the numbers of patients.

CI, convergence insufficiency; D, diopter; DE, divergence excess; logMAR, logarithm of the minimum angle of resolution.

**Table 2.** Details on Eight Patients Who Had Larger Adduction Angle during Lateral Gaze (Group 2; $n = 8$)

| | | MRI Analysis (°) | | | |
|---|---|---|---|---|---|
| | | Left Gaze | | Right Gaze | |
| Patient | Ocular Dominance | Abduction Angle of Left Eye | Adduction Angle of Right Eye | Adduction Angle of Left Eye | Abduction Angle of Right Eye |
| 1 | Left | 51.01 | 53.56 | **59.48** | **50.60** |
| 2 | Right | **44.94** | **54.57** | **42.64** | **37.26** |
| 3 | Left | **36.75** | **41.47** | 36.06 | 34.19 |
| 4 | Right | **32.83** | **38.10** | **50.01** | **40.44** |
| 5 | Right | 40.83 | 38.54 | **56.28** | **49.20** |
| 6 | Left | **37.01** | **43.79** | **48.34** | **39.71** |
| 7 | Right | **36.84** | **45.49** | **47.04** | **38.63** |
| 8 | Right | **35.36** | **41.68** | 48.94 | 50.68 |

Numbers in bold indicate that the adduction angle of one eye is ≥3° larger than the abduction angle of the fellow eye.

In patients with IXT, decreased exodeviation during lateral gaze compared with the primary position indicates lateral incomitance. Although the cause of lateral incomitance is unclear, mechanical and innervational factors such as pulley instability, oblique muscle dysfunction, and impaired vergence facility are suggested mechanisms for lateral incomitance.[5,14,16] Moore[16] reported a series of 500 patients with exodeviations, of which 21.6% had significant lateral incomitance. However, Repka et al.[5] reported that only 9% of patients with IXT had true incomitance of more than 5 PD. Furthermore, the authors concluded that lateral incomitance could be induced by improperly positioning the neutralizing prism. The accuracy is more compromised in diagnostic positions other than the primary position, especially in extreme side gaze. In our study, the measurement errors induced by the position of the prism were eliminated using MR images and not the PACT. Further, 27.6% patients had a larger adduction angle (≥3°) than the abduction angle of the fellow eye, which induced lateral incomitance, comparable with the result reported by Moore.[16] Although the clinical implications of lateral incomitance have been controversial,[14,16–18] it should be considered in a significant number of patients with IXT.

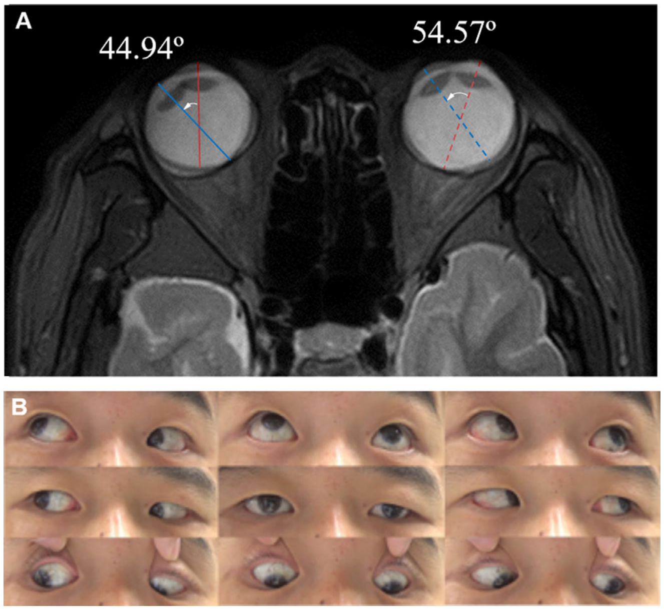


**Figure 3.** Measurement of the rotation angle during left gaze when patient 2 fixed his left eye on the target. (**A**) Superimposed image composed of axial MR images of central and left gazes. This figure shows that the static tissues such as brain and skull are well-aligned (**B**). Clinical images in the nine-cardinal positions of patient 2. In the image of left gaze photograph, the right eye is fully adducted.

In our study, six patients (20.7%) had a smaller adduction angle; therefore, they showed increased exodeviation during lateral gaze compared with central gaze. One of the causes for the smaller adduction is the difference in convergence between central gaze and lateral gaze. The experimental conditions, such as patient's alertness, target size, the distance between the target and patient's eye, and monocular patching, were similar during MRI in the central and lateral gazes. Therefore, various convergence mechanisms including tonic, accommodative, proximal, and fusional convergence would function similarly during both central and lateral gazes. However, in reviewing the MR images, we found that the convergence was stronger during central gaze than during lateral gaze, indicating that lateral gaze could disrupt convergence, which in turn could affect the measurement of exodeviation in two patients (patients 12 and 14). Therefore, clinicians should consider this difference of convergence effect according to the eye position.

Adduction deficit should be considered as the cause of the smaller adduction angle. Conjugate adduction in horizontal version is controlled by neural impulses from the horizontal gaze center and the saccade-related exodeviation is produced by a normal delay in conducting an adduction signal over interneurons, from the abducens nuclear of the pons to the medial rectus subnucleus of the midbrain.[19,20] Furthermore, a previous study had reported that Schwann cell degeneration of the tendon proprioceptors in the medial rectus muscle possibly induces the degeneration of proprioceptors in patients with exotropia.[21] Therefore, abnormalities of neural impulse or innervation to the medial rectus muscle may cause the weakness in adduction. Several studies have the evaluated interventions of exotropia; some studies have reported that bilateral lateral rectus recession provides more stable results,[17,22,23] whereas others have reported that unilateral recession–resection has a higher rate of successful outcomes.[24–26] Thus, the best surgical intervention for the treatment of exotropia is controversial. Considering the conjugate adduction deficit, which supports the functional impairment of the medial rectus muscle, surgical intervention to strengthen the medial recuts muscle may be more effective in treating exotropia when the adduction angle is smaller and the exodeviation is aggravated during lateral gaze. Further studies are needed to assess the effect of the difference in

**Table 3.** Details on Six Patients Who Had Smaller Adduction Angle During Lateral Gaze (Group 3; $n = 6$)

| | | MRI Analysis (°) | | | |
|---|---|---|---|---|---|
| | | Left Gaze | | Right Gaze | |
| Patient | Ocular Dominance | Abduction Angle of Left Eye | Adduction Angle of Right Eye | Adduction Angle of Left Eye | Abduction Angle of Right Eye |
| 9 | Left | **32.4** | **28.09** | 38.47 | 39.87 |
| 10 | Right | 50.09 | 47.64 | **32.55** | **38.51** |
| 11 | Right | 32.46 | 32.40 | **29.54** | **34.00** |
| 12 | Right | **35.15** | **29.91** | 38.10 | 35.68 |
| 13 | Left | 53.52 | 51.12 | **42.15** | **52.33** |
| 14 | Left | **47.53** | **31.63** | **31.86** | **51.09** |

Numbers in bold indicate that the adduction angle of one eye is ≥3° smaller than the abduction angle of fellow eye.

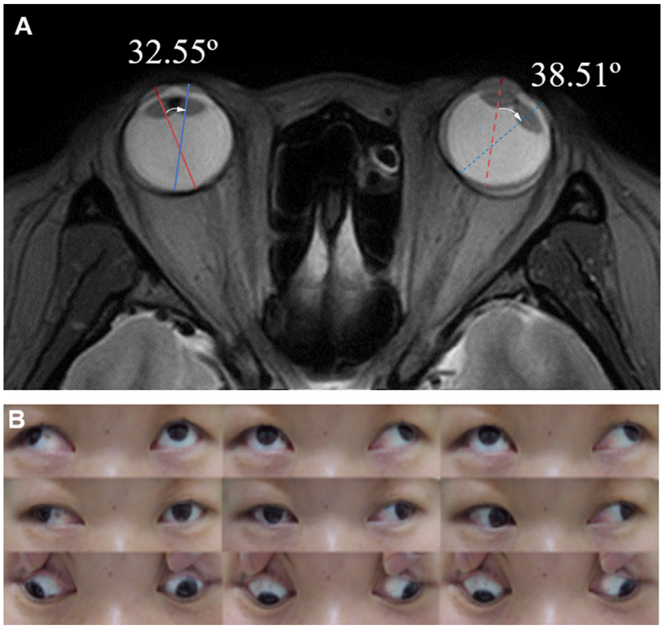


**Figure 4.** Measurement of the rotation angle during right gaze when patient 9 fixed her right eye on the target. (**A**) Superimposed image composed of axial MR images of central and right gazes. This figure shows that the static tissues such as the brain and skull are well aligned. Adduction angle of the right eye is larger than abduction angle of the left eye. (**B**) Clinical images in the nine-cardinal positions of patient 9. In the image of right gaze photograph, the left eye is not fully adducted and does not cross the midline.

the rotation angle between both eyes on the surgical outcomes after lateral rectus recession or medical rectus resection.

Unilateral surgery for IXT is usually performed in the nondominant eye.[27] Ocular dominance can be classified into sighting, sensory, and motor dominance, and the ocular sighting dominance was measured in our study.[28] The side of ocular dominance was not completely accordant with the side of gaze where the significant difference in rotation angle was found. Of the aforementioned six patients who had a smaller adduction angle during lateral gaze, three showed angle changes when they gazed to the side of dominance, and another patient showed angle changes in both sides. The other two patients had smaller adduction angle when they gazed to the side of nondominance. Therefore, the choice of the eye for unilateral surgery in IXT should be based on both the sighting dominance and the pattern of rotation angle that could reflect the oculomotor characteristics of strabismus.

Unfortunately, we were not able to identify the clinical factors associated with the pattern of rotation. Physical factors such as pupillary distance and axial length were not correlated with the angle change pattern. Therefore, further studies, including neuronal and muscular factors, should be conducted to suggest the mechanism of the angle change.

This study has several limitations. First, the accuracy of measurement for rotation angle in MRI is yet unknown. Although we confirmed that the position of participant and targets were correct before each scan, the head could move slightly during scanning causing the difference in the target's position for each eye. In addition, although we set the threshold for

**Table 4.** Clinical Characteristics of the Three Groups According to the Pattern of Rotation

| | Group 1 ($n = 15$) | Group 2 ($n = 8$) | Group 3 ($n = 6$) | *P* Value |
|---|---|---|---|---|
| Age (years) | 35.8 ± 20.7 | 33.3 ± 18.7 | 27.8 ± 10.4 | 0.870 |
| Sex (M:F)* | 8:7 | 6:2 | 3:3 | 0.606 |
| Axial length (mm) | | | | |
| Dominant eye | 24.3 ± 1.0 | 25.0 ± 1.3 | 24.5 ± 1.6 | 0.388 |
| Nondominant eye | 24.6 ± 1.1 | 25.2 ± 1.5 | 24.7 ± 1.7 | 0.736 |
| Interpupillary distance (mm) | 64.8 ± 3.1 | 66.0 ± 4.3 | 62.7 ± 3.8 | 0.252 |
| Angle of deviation in PACT (PD) | | | | |
| At Distance | 44.4 ± 14.0 | 53.1 ± 17.7 | 50.84 ± 16.9 | 0.359 |
| At Near | 44.7 ± 15.8 | 55.4 ± 15.2 | 46.7 ± 17.8 | 0.317 |
| Subtype of IXT (basic:DE:CI)* | 9:2:4 | 3:3:2 | 5:1:0 | 0.442 |

*Values are presented as the ratio of the numbers of patients.

Group 1 includes patients who showed no significant difference in rotation angle between both eyes during lateral gaze.

Group 2 includes patients who showed larger adduction angle than abduction angle of fellow eye during lateral gaze at least one side.

Group 3 includes patients who showed smaller adduction angle than abduction angle of fellow eye during lateral gaze at least on side.

CI, convergence insufficiency; DE, divergence excess.

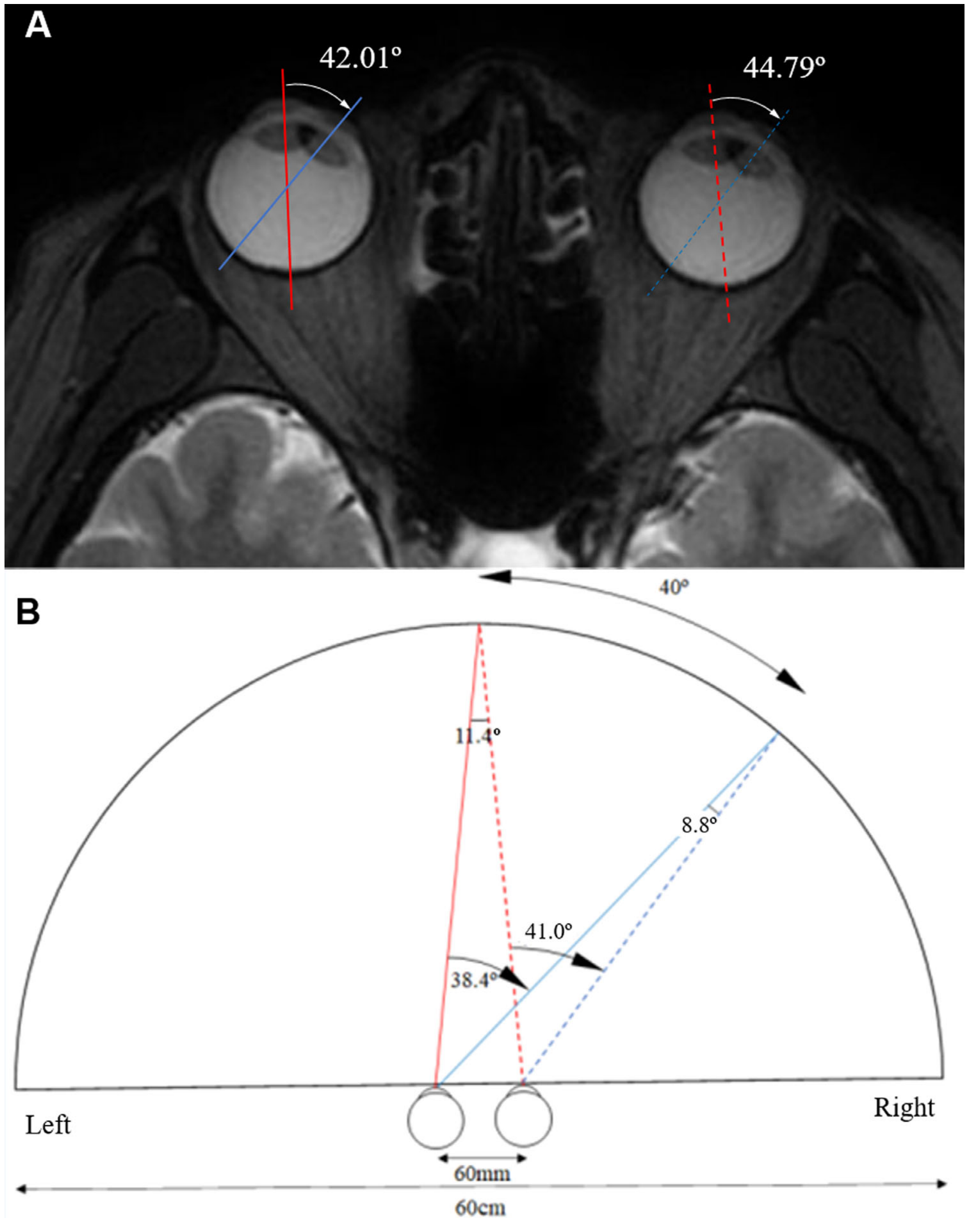


**Figure 5.** (**A**) Superimposed axial MR image of a healthy individual during central and 40° right gazes. *Red lines* (*solid line* for the left eye and *dotted line* for the right eye) indicated the optical axes of both eyes in central gaze with right eye fixation and *blue lines* (*solid line* for the left eye and *dotted line* for the right eye) in right gaze. Adduction angle of the left eye is 2.78° smaller than the abduction angle of the right eye. (**B**) Schematic figure showing change in the angle of deviation during lateral gaze when the eyes were fixated at a near target at 30 cm. The visual axes during central gaze are represented by *red lines*, and the visual axes during lateral gaze are represented by *blue lines*. When the interpupillary distance is 60 mm, the angle between both visual axes is 11.4° during central gaze and 8.8° during lateral gaze at 40°. The range of eyeball rotation is 38.4° in adduction and 41.0° in abduction.

the significant difference in this study as 3°, it should be validated whether the difference in rotation angle between two eyes is within 3° in healthy subjects during lateral gaze. Second, we only included patients who underwent MRI. Further, 24 participants (82.8%) had large-angle exotropia and their angle of deviation in the PACT was 40 PD or more at distance and/or near. Therefore, the selection bias should be considered when interpreting our results. Last, in our study, because the distance between the target and patient's eyes was approximately 30 cm, ocular vergence could occur when the participant gazed at the target. Although fusional convergence was controlled using monocular patching, there could be other mechanisms of convergence and convergence could affect the actual angle of deviation during horizontal gaze. In a healthy individual with an interpupillary distance of 60 mm, the abduction angle of right eye is 41.0° and adduction angle of 38.4° during right gaze at 40°, theoretically (Fig. 5). Although this discrepancy induced by convergence is less than 3°, which was set as a criterion for the significant difference in our study, it should be considered. To overcome this limitation, a comparison of the angle change between the patient with strabismus and normal control may be helpful to elucidate more clearly the angle changes in lateral gaze. Furthermore, the pupillary distance should be considered for the ideal experiment, although their effects would be minimal. In our cohort, interpupillary distance ranged from 58 mm to 70 mm, and in an individual with an interpupillary distance of 70 mm the difference in rotation angle between both eyes is 3.0° using the same method in Figure 5.

Despite these limitations, to the best of our knowledge, this report is the first to document the rotation angle during lateral gaze using three-dimensionally reconstructed MR images. By reconstructing three-dimensional MR images and adjusting the alignment of superimposed images, we were able to obtain high-quality images for analysis of rotation angle.

In conclusion, this study investigated the eyeball rotation and quantitative measurement of eye movements during lateral gazing in IXT using three-dimensional MRI. In this study, almost one-half of the patients with IXT had significant difference in rotation angle between both eyes in lateral gaze. Of them, one-half of the patients showed larger adduction angle during lateral gaze and the other half showed smaller angle. The fact that IXT is not a perfectly comitant disturbance of gaze in some subjects may help to improve our understanding of the neurophysiological mechanism of exotropia provide useful information for proper surgical planning in patients with IXT.

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