Cross-Coupled Eye Movement Supports Neural Origin of Pattern Strabismus

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Submitted: January 1, 2015

Accepted: April 1, 2015

Citation: Ghasia FF, Shaikh AG, Jacobs J, Walker MF. Cross-coupled eye movement supports neural origin of pattern strabismus. *Invest Ophthalmol Vis Sci*. 2015;56:2855–2866. DOI:10.1167/iops.15-16371

PURPOSE. Pattern strabismus describes vertically incomitant horizontal strabismus. Conventional theories emphasized the role of orbital etiologies, such as abnormal fundus torsion and misaligned orbital pulleys as a cause of the pattern strabismus. Experiments in animal models, however, suggested the role of abnormal cross-connections between the neural circuits. We quantitatively assessed eye movements in patients with pattern strabismus with a goal to delineate the role of neural circuits versus orbital etiologies.

METHODS. We measured saccadic eye movements with high-precision video-oculography in 14 subjects with pattern strabismus, 5 with comitant strabismus, and 15 healthy controls. We assessed change in eye position in the direction orthogonal to that of the desired eye movement (cross-coupled responses). We used fundus photography to quantify the fundus torsion.

RESULTS. We found cross-coupling of saccades in all patients with pattern strabismus. The cross-coupled responses were in the same direction in both eyes, but larger in the nonviewing eye. All patients had clinically apparent inferior oblique overaction with abnormal excyclotorsion. There was no correlation between the amount of the fundus torsion or the grade of oblique overaction and the severity of cross-coupling. The disconjugacy in the saccade direction and amplitude in pattern strabismus did not have characteristics predicted by clinically apparent inferior oblique overaction.

CONCLUSIONS. Our results validated primate models of pattern strabismus in human patients. We found no correlation between ocular torsion or oblique overaction and cross-coupling. Therefore, we could not ascribe cross-coupling exclusively to the orbital etiology. Patients with pattern strabismus could have abnormalities in the saccade generators.

Keywords: saccades, pattern strabismus, fundus torsion, cross-coupling

Pattern strabismus describes horizontal strabismus that is vertically incomitant. Historically, pattern strabismus is attributed to the oblique muscle dysfunction.¹ Little is known about the etiology of isolated primary oblique overaction. Clinical observations have suggested that a torsional offset due to loss of fusion might alter the direction of the recti muscle action, hence causing the pattern strabismus.^{2,3} For example, excyclotorsion of the globe will result in medial rectus becoming a partial elevator leading to overelevation during adduction, and inferior rectus becoming a partial adductor and superior rectus a partial abductor causing a V-pattern. Correlation between the fundus torsion and static eye fixation in patients with pattern strabismus further supported the viewpoint emphasizing altered recti pull.⁴ Subsequent studies suggested that oblique overaction is a clinical description rather than an actual mechanism of the pattern strabismus.⁵ Static malposition or dynamic instability of the extraocular muscle pulleys in patients with craniofacial dysmorphism causes pattern strabismus.⁶ Neurophysiology experiments in nonhuman primates reared with alternate monocular occlusion suggested a neural basis for pattern strabismus.⁷⁻⁹ These

animals had cross-axis eye movements; for example, intended horizontal saccades were associated with cross-axis vertical eye movement and vice versa. Neural recordings from ocular motor neurons have shown that horizontal cross-coupled movement corresponds to increased firing rate of horizontal motor neurons, whereas vertical cross-coupled movement corresponds to increased firing rate of vertical motor neurons. The presence of the neural correlate of cross-coupled movements in animal models suggested that abnormal central innervations might cause the pattern strabismus.⁷⁻⁹ These principles describing the pathophysiology of pattern strabismus are based on subjective clinical impression, orbital imaging, and neurophysiology in animal models. There is a paucity of investigations of objective eye movement assessments in human patients with pattern strabismus. We aimed to quantify eye movements and fundus torsion in patients with infantile and late onset pattern strabismus without craniofacial abnormalities.

We hypothesized that overaction of the oblique muscles, as previously predicted in pattern strabismus, should be reflected in the static misalignment as well as dynamic disconjugacy of saccades. For example, inferior oblique overaction should

cause an upward deviation of the adducting eye during a horizontal saccade, and the oblique upward saccade would have greater amplitude in the adducting than the abducting eye.

It is unknown whether patients with pattern strabismus have cross-coupling of the eye movement, as described in the nonhuman primate model. If, indeed, animal models are analogous to the patients with pattern strabismus, we should also see cross-coupled eye movements in these patients. We quantitatively assessed the presence of cross-coupling of saccades in patients with pattern strabismus. There are several possible explanations for cross-coupled responses. Mechanical factors, such as an abnormal fundus torsion or inappropriate innervations, and consequent cross-talk between horizontal and vertical saccade generators, can result in cross-coupling. The torsion hypothesis predicts a correlation between the severity of cross-coupled saccades and the static fundus torsion. According to the torsion hypothesis, patients with greater static torsion will have larger cross-coupling of saccades. The absence of such a correlation would suggest that abnormal static torsion is not the exclusive cause of pattern strabismus.

METHODS

Subjects

We measured eye movements in 14 patients with V-pattern strabismus and clinically apparent inferior oblique overaction. Clinically significant V-pattern was defined as a change in the horizontal eye alignment of at least 15 prism diopters with an outward movement from down- to upgaze.¹⁰ The exclusion criteria were coexisting craniofacial dysmorphism, orbital connective tissue disorders, extraocular muscle palsy, anterior or posterior segment structural pathology, and manifest or latent dissociated vertical deviation. We ruled out ophthalmoplegia by confirming normal horizontal and vertical peak saccadic velocities to amplitude relationship (Supplementary Fig. S1). We clinically graded inferior oblique overaction with +0.5 as a trace and +4 as maximal. We divided our comparison group into disease control that comprised five patients with comitant strabismus without oblique muscle overaction or dissociated vertical deviation, and 10 healthy controls. The experiment protocols complied with the tenets of the Declaration of Helsinki and were approved by the Cleveland Clinic Institutional review board. All subjects provided written informed consent before participation.

Eye Movement Measurements

We used video oculography (EyeLink 1000; SR Research, Ontario, Canada) simultaneously to measure horizontal and vertical eye positions of both eyes at 500 Hz sampling frequency. The subjects supported their head on a chin-rest 55 cm away from the liquid crystal display (LCD) screen. The subjects fixed their gaze on a circular red visual target of 0.5° visual angle presented on the LCD screen.

We used an infrared permissive filter to capture binocular eye positions in monocular viewing conditions. Such filter allowed infrared waves used to capture eye position in video oculography, but blocked visible light, hence, preventing vision through the covered eye. Each eye was calibrated under monocular viewing conditions with best-corrected vision of the viewing eye as the subjects fixated on targets at known horizontal and vertical eccentricities. Although monocular viewing was allowed, we simultaneously measured position of both eyes. Amblyopic subjects always viewed with the better-

seeing eye. We randomly assigned right or left eye as the viewing eye for the subjects without amblyopia.

Experimental Paradigms

Eye movements were first measured during sustained gaze holding for six seconds at the center position and target eccentricities of 5° and 10° to the left, right, up, and down. Then, we recorded a sequence of visually guided saccades from the center position to one of 14 eccentric locations and back. Eccentric target locations were 5°, 10°, and 15° to the right and left; 5° and 10° up and down, and in oblique directions (combinations of 10° to the right or left and up or down). Each trial was performed twice, hence making a total of 72 visually guided saccades (24 horizontal, 16 vertical, and 32 oblique). We obtained fundus photos in straight-ahead gaze to quantitatively determine static ocular torsion.

Data Analysis

We assessed periods of gaze holding for latent fixation nystagmus that was defined as a nasally directed drift followed by a refoveating, temporally directed saccade. Visually guided saccades were identified with a velocity threshold of 50° per second. The saccades were further confirmed by visual inspection in the interactive data analysis program. We separately analyzed horizontal, vertical, and oblique saccades. We measured the absolute difference between starting and ending eye positions to determine saccade amplitude. We also recorded the peak saccadic velocity.

Analysis of Dynamic Incomitancy During Saccades.

We separately analyzed horizontal and vertical components of intended pure horizontal and pure vertical saccades. This analysis was aimed to quantitatively assess the dynamic incomitancy in pattern strabismus. We defined a cross-coupled response as the change in eye position along the orthogonal direction of the desired eye movement, expressed as a percentage of the position change in the primary direction. For example, for an intended pure vertical saccade the cross-coupling Index (CCI) was calculated as follows:

$$CCI = 100 * \text{absolute} (\Delta H / \Delta V)$$

In this equation, ΔH is the change in horizontal eye position and ΔV is the change in vertical eye position. The direction of cross-coupled response might vary for a given direction of visually guided saccades. Therefore, we considered the absolute values to allow the comparison of magnitudes in different saccadic directions. The cross-coupling index was calculated separately for the viewing and nonviewing eyes of all patients.

We measured oblique saccades to assess whether disconjugacy increased in the field of apparent inferior oblique overaction. We compared the amplitude of the angular vector and its polar direction during the oblique saccade of the viewing and nonviewing eyes. We preferred analysis of vectorial saccadic amplitude rather than decomposing the saccade into horizontal and vertical components. Such consideration was in light of the caveat that directional decomposition might confound amplitude and directional disconjugacy.¹¹ The prediction was that for upward oblique saccades, the upward directional shift as well as the amplitude would be greater in the adducting nonviewing eye, as it moved into the field of overacting inferior oblique. For each patient, the data were obtained only under one eye viewing condition. The assignment of the viewing eye was determined randomly for nonamblyopic subjects with comparable visual acuity of both eyes. The amblyopic subjects

TABLE 1. Clinical Features and Demographics of Patients With Pattern Comitant Strabismus

Patient	Age, y	Sex	Onset	Strabismus Type	Strabismus		Latent	VA OD	VA OS	RE OD	RE OS
					Angle, PD	Amblyopia	Nystagmus				
Pattern strabismus											
1	42	Female	Infantile	Consecutive exotropia	35	Yes	Yes	20/80	20/20	Plano	0.5
2	12	Female	Late	Intermittent exotropia	0	No	No	20/20	20/20	−0.5	−0.5
3	6	Female	Late	Accomodative esotropia	4	Yes	No	20/25	20/40	+2.00	+2.25
4	13	Female	Infantile	Consecutive exotropia	20	Yes	Yes	20/50	20/20	Plano	Plano
5	13	Female	Late	Residual exotropia	20	No	No	20/20	20/20	−0.5	−0.5
6	12	Female	Late	Intermittent exotropia	35	No	No	20/20	20/20	−2.75	−1.75
7	4	Female	Infantile	Residual exotropia	35	No	Yes	20/25	20/25	+0.75	+0.75
8	11	Male	Infantile	Consecutive exotropia	12	No	Yes	20/20	20/20	+6.25	+6
9	5	Female	Late	Intermittent exotropia	30	Yes	No	20/40	20/20	+4.0	+2.25
10	18	Male	Late	Intermittent exotropia	50	No	No	20/20	20/20	−0.25	−0.25
11	10	Male	Infantile	Intermittent exotropia	12	Yes	Yes	20/20	20/50	−4.75	−9.0
12	14	Female	Late	Residual exotropia	4	No	No	20/20	20/20	−1.5	−2.25
13	50	Female	Infantile	Consecutive exotropia	12	Yes	Yes	20/15	20/80	+2.25	+2.5
14	8	Male		Residual exotropia	0	No	No	20/15	20/15	+0.5	+0.5
Comitant strabismus											
1	7	Female	Infantile	Constant exotropia	25	No	Yes	20/25	20/25	+1.25	+1.25
2	60	Male	Late	Basic esotropia	25	No	No	20/20	20/20	−3.25	−3.5
3	57	Male	Late	Basic exotropia	45	No	No	20/20	20/20	−1	−0.75
4	9	Female	Late	Accomodative esotropia	45	No	No	20/20	20/20	+3.25	+3.25
5	9	Female	Infantile	Constant exotropia	30	No	Yes	20/20	20/20	+1.25	+1.25

VA, visual acuity; RE, refractive error; OD, right eye; OS, left eye.

always viewed with the good eye. To distinguish the adducting and abducting saccades we separately analyzed right- and left-eye viewing conditions.

Ocular Torsion. We used two techniques to assess ocular torsion quantitatively. The traditional method determined the relationship of the center of the optic disc and fovea with the horizontal meridian,¹² while the contemporary technique determined the tilt of the retinal vascular arcade.¹³ The measured ocular torsion by these two methods had a good correlation, and we took the average values for further analysis.

Statistical Analysis

We used Matlab (Mathworks, Natick, MA, USA) and GraphPad Prism 5 (La Jolla, CA, USA) for statistical analysis. A Shapiro-Wilk normality test was used to determine if the cross-coupled responses and the saccadic disconjugacy were normally distributed. A 1-way ANOVA was used to compare saccadic disconjugacy, whereas Kruskal-Wallis ANOVA was used to compare the mean cross-coupled response elicited during saccades between the three groups. Mann-Whitney *U* test was used to compare the vectorial saccadic disconjugacy between the viewing and nonviewing eyes in the subjects with pattern strabismus. Spearman rank correlation coefficient was used to measure statistical dependence between cross-coupled responses and other parameters including primary strabismus angle, saccade size, inferior oblique overaction, eye-in-orbit position dependence, and the fundus torsion.

RESULTS

Clinical Features

We measured eye movements in 14 subjects with pattern strabismus, 5 with comitant strabismus, and 10 healthy controls. Six of 14 pattern strabismus subjects had amblyopia after correction for refractive error using age-appropriate

testing methods. The mean age of pattern strabismus subjects was 15.6 ± 13.5 years, while of comitant strabismus it was 28.4 ± 27.5 years, and of healthy controls it was 18.0 ± 11 years. Table 1 summarizes the clinical features.

FIGURE 1. An example of horizontal and vertical eye position traces of the viewing (black and blue trace, respectively) and nonviewing eye (gray and cyan trace, respectively) during horizontal saccade in a pattern strabismic (PS7) patient. Notice the cross-coupled responses were seen in the viewing and nonviewing eyes during the actual saccade. The postsaccadic drift and the vergence response were more prominent in the horizontal and vertical eye traces in the nonviewing eye. Positive values represent rightward and upward movements, whereas negative values represent leftward and downward movements.

FIGURE 2. (A–C) Representative horizontal and vertical eye position traces of the viewing (*black* and *blue* trace, respectively) and nonviewing (*gray* and *cyan* trace, respectively) eye during horizontal saccade under conditions of right eye viewing in healthy control (HC), comitant strabismic (CS), and pattern strabismic (PS) patient. Positive values represent rightward and upward movements whereas negative values represent leftward and downward movements. In the healthy control and comitant strabismic patient (A, B), no CC responses were seen. In the pattern strabismic patient, cross-coupled responses were seen in the orthogonal upward direction during adducting saccade (C). (D–F) Representative horizontal and vertical eye position traces of the viewing and nonviewing eye during a vertical saccade under conditions of right eye viewing in HC, CS, and PS patient. Positive values represent rightward and upward movements, whereas negative values represent leftward and downward movements. In the healthy control and comitant strabismic patient (A, B), no cross-coupled responses were seen. In the pattern strabismic patient, cross-coupled responses were seen in the orthogonal rightward direction during a downward saccade (F).

FIGURE 3. Summary of the cross-couple index in the viewing and nonviewing eye while adducting and abducting saccades (defined per the nonviewing eye) in HC, SC, and PS. Each column represents mean. Error bars represent 95% confidence interval. ★Statistical significance with 1-way ANOVA ($P < 0.05$).

Cross-Coupling of Horizontal and Vertical Saccades

Figure 1 shows an example of a cross-coupled vertical eye movement during intended pure horizontal saccade in the viewing and nonviewing eye. The cross-coupled responses differ from the immediate postsaccadic drift comprising 160 ms after the end of the saccade and the divergence movement that influences the final static eye position.¹⁴ The cross-coupled responses also were present during corrective saccades (Fig. 1). We did not analyze cross-coupling of corrective saccades because of their small amplitude (approximately 10% of the main axis component of the corrective movement).

We compared cross-coupling index in the viewing and nonviewing eye during horizontal and vertical saccades in healthy controls, comitant, and pattern strabismus subjects. Figures 2A to 2C depict an example of a leftward saccade from one subject from each group. The cross-coupling index in the example of a healthy subject depicted in Figure 2A was 0.5% in the nonviewing eye, while it was 0.4% in the viewing eye. In the illustrated example of comitant strabismus subject, the cross-coupling index was 0.5% in the nonviewing eye and 0.7% in the viewing eye (Fig. 2B). The cross-coupling index in the illustrated example of pattern strabismus was higher in the nonviewing eye (17%) compared to the viewing eye (7%, Fig. 2C). In addition, the cross-coupling was in the same direction in both eyes in case of the pattern strabismus subject.

Figures 2D through 2F illustrate an example of horizontal cross-coupling during intended pure vertical saccade from one subject from each group. The cross-coupling index during

vertical saccade in the example of a healthy subject was 1.1% in the nonviewing eye and 1.8% in the viewing eye (Fig. 2D). In subjects with comitant strabismus, the cross-coupling index was 2% in the nonviewing eye and 0.7% in the viewing eye (Fig. 2E). The cross-coupling index in the example of pattern strabismus was 26% in nonviewing eye, while it was 6% in the viewing eye (Fig. 2F). The cross-coupling during vertical saccade in pattern strabismus was present in the same direction in both eyes with greater amplitude in the nonviewing eye.

We then compared the cross-coupling index collectively for all three groups during all horizontal (Fig. 3) and vertical (Fig. 4) saccades. The mean (and standard deviation) of cross-coupling index in healthy subjects during abduction of the viewing eye was $4.7\% \pm 4.5\%$ and adduction of the nonviewing eye was $4.8\% \pm 4.4\%$ (Figs. 3A, 3B). The mean cross-coupling index in patients with comitant strabismus during abduction of the viewing eye was $4.2\% \pm 3.1\%$ and simultaneous adduction of the nonviewing eye was $4.6\% \pm 3.4\%$ (Figs. 3A, 3B). In the patients with pattern strabismus the mean cross-coupling index during simultaneous abduction of the viewing eye and adduction of the nonviewing eye was $7.8\% \pm 6.7\%$ and $12.8\% \pm 9.5\%$, respectively (Figs. 3A, 3B). These responses were greater than the corresponding responses in patients with comitant strabismus (Figs. 3A, 3B). The difference was statistically significant ($P < 0.001$, Kruskal-Wallis test) in viewing and nonviewing eyes. The mean cross-coupling index elicited during simultaneous adduction of the viewing eye, and abduction of the non-

FIGURE 4. Representation of the cross-couple index in the viewing and nonviewing eye during upward and downward saccades in HC, CS, and PS. Each column represents mean. Error bars represent 95% confidence interval. ★Represents statistical significance with 1-way ANOVA $P < 0.05$.

viewing eye in healthy controls was $4.2\% \pm 3.6\%$ and $4.0\% \pm 3.2\%$, respectively, and that in comitant strabismus patients was $5.4\% \pm 4.1\%$ and $6.8\% \pm 4.8\%$, respectively. The mean cross-coupling index elicited during simultaneous adduction of the viewing eye, and abduction of the nonviewing eye in pattern strabismus was $7.2\% \pm 6.3\%$ and $8.7\% \pm 9.1\%$, respectively (Figs. 3C, 3D). These values also were higher compared to healthy controls and comitant strabismic patients (Figs. 3C, 3D). The difference was statistically significant ($P < 0.001$, Kruskal-Wallis test) in viewing and nonviewing eyes.

The mean cross-coupling index during upward saccades in healthy subjects was $5.2\% \pm 4.5\%$ for the viewing eye and $5.2\% \pm 4.2\%$ for the nonviewing eye. The mean cross-coupling index in patients with comitant strabismus in the viewing eye was $2.2\% \pm 1.9\%$ and in the nonviewing eye was $8.7\% \pm 4.5\%$. The mean cross-coupling index during upward saccades in pattern strabismus subjects in the viewing eye was $9.4\% \pm$

7.7% and in the nonviewing eye was $16.2\% \pm 13.5\%$ (Figs. 4A, 4B). The amount of cross-coupling of the intended upward saccade was larger in subjects with pattern strabismus compared to healthy and comitant strabismus subjects (Figs. 4A, 4B). The difference was statistically significant ($P < 0.001$) in the viewing and nonviewing eyes. The mean cross-coupling index elicited during downward saccade of the viewing and nonviewing eyes in healthy controls was $4.2\% \pm 3.1\%$ and $5.4\% \pm 4.2\%$, and in comitant strabismus it was $6.7\% \pm 3.9\%$ and $5.0\% \pm 5.6\%$, respectively (Figs. 4C, 4D). The mean cross-coupling index elicited during downward saccade of the viewing and nonviewing eyes in pattern strabismus subjects were $8.8\% \pm 8.4\%$ and $13.4\% \pm 10.7\%$, respectively (Figs. 4C, 4D). The severity of cross-coupling in pattern strabismus subjects was significantly higher compared to healthy controls and comitant strabismics. The difference was statistically significant ($P < 0.001$, Kruskal-Wallis test) for both conditions. In addition, the cross-coupled responses were in the same

TABLE 2. Direction of Cross-Coupling in Viewing and Nonviewing Eye During Horizontal and Vertical Saccades

Direction	Horizontal Saccades			Vertical Saccades		
	Downward OU	Upward OU	Disconjugate	Adduction	Abduction	Disconjugate
Abduction	33%	32%	35%			
Adduction	22%	54%	24%			
Upward				20%	43%	37%
Downward				46%	22%	32%

OU, both eyes.

FIGURE 5. Illustration of the lack of correlation between the orbital eye position and the cross-coupling index measured in the viewing and nonviewing eye during adduction, abduction, upward, and downward saccades.

direction in the viewing and the nonviewing eyes during 65% of abducting and 76% of adducting saccades of the nonviewing eye, 63% of upward and 68% of downward saccades (Table 2).

We investigated whether there was a correlation between the amounts of cross-coupled response with the saccadic amplitude. There was no systematic change in the cross-coupled response as a function of amplitude of horizontal and

vertical saccades in individual and collectively as a group in pattern strabismus subjects (Spearman correlation, $P < 0.05$). We then investigated whether there was a change in the amount of cross-coupled response as a function of strabismus angle in the primary position. We performed linear regression analysis to determine the correlation between cross-coupled responses elicited during horizontal and vertical saccades in

FIGURE 6. The polar plot of the saccadic movements of the viewing (filled triangles) and nonviewing eye (open triangles) in four cardinal and four oblique directions in PS patients. (A) The directional vectors during right eye viewing; (B) the directional vectors during left eye viewing conditions. Laterality of the viewing eye determined the direction of the saccade; for example, during right eye viewing 0° = adducting, 180° = abducting, 90° = upward, and 270° = downward saccades of the nonviewing eye, whereas during left eye viewing 0° = abducting, 180° = adducting, 90° = upward, and 270° = downward saccades of the nonviewing eye.

the viewing and nonviewing eyes of pattern strabismus subjects to strabismus angle in the primary position. We found a modest correlation between cross-coupled responses elicited in the nonviewing eye during adducting saccades and upward saccades with the strabismus angle in the primary position ($r = 0.5$, $P = 0.04$ and $r = 0.5$, $P = 0.04$, respectively).

Inferior oblique overaction due to muscle length adaptation or orbital mechanical factors can also cause cross-coupling. In such a case, the cross-coupling should correlate with the eye-in-orbit position, for example, more eccentric eye-in-orbit positions during adduction would lead to increased cross-coupling. Figure 5 depicts a correlation between eye-in-orbit position and cross-coupling index measured in the viewing and nonviewing eye in all pattern strabismus subjects. There was no correlation between eye-in-orbit and cross-coupling index during horizontal and vertical saccades in pattern strabismus subjects ($r \leq 0.3$, Spearman correlation). Similar analysis on individual subjects did not reveal any correlation between these two parameters.

Saccadic Disconjugacy

The amplitude disconjugacy was present in pattern and comitant strabismus subjects with horizontal saccades being the most disconjugate. The amount of amplitude disconjugacy seen in pattern strabismus patients was $13.4\% \pm 13.1\%$, $9.4\% \pm 9.3\%$, $8.6\% \pm 7.3\%$ for horizontal, oblique and vertical saccades, respectively. The disconjugacy in pattern strabismus was comparable to patients with comitant strabismus (horizontal, $14.7\% \pm 14.3\%$; oblique, $10.2\% \pm 10.1\%$; vertical, $6.1\% \pm 2.1\%$). The saccades in strabismic patients were more disconjugate compared to healthy subjects (horizontal, $5.1\% \pm 6.2\%$; oblique, $5.1\% \pm 4.8\%$; vertical, $4.8\% \pm 3.6\%$). The difference was statistically significant (1-way ANOVA, $P < 0.0001$).

We then investigated the vectorial amplitude and directional disconjugacy of saccades. We separately analyzed right-eye-viewing and left-eye-viewing conditions. An upward deviation of the nonviewing eye during adducting and adducting/

upward saccades with increased disconjugacy would be expected if the inferior oblique muscle in the nonviewing eye were overacting. Figures 6A and 6B (right- and left-eye viewing, respectively) depict a polar plot of average saccade displacements of the viewing (filled arrows) and nonviewing (open arrows) eyes in the four cardinal and four oblique directions in pattern strabismus patients. The vectorial amplitude of the nonviewing eye movement was not higher during pure adducting and adducting plus upward saccades of the nonviewing eye (Mann-Whitney U test right-eye viewing adduction, $P = 0.5$; adduction and upward, $P = 0.5$; left-eye viewing adduction, $P = 0.2$; adduction and upward, $P = 0.3$). Of particular importance to the question of inferior oblique overaction is whether there is a disconjugacy in saccade direction. An overacting inferior oblique would be expected to cause an upward deviation of the nonviewing eye relative to the viewing eye during horizontal and oblique saccades when the nonviewing eye adducts. There was no relative upward shift of the nonviewing eye during adducting horizontal saccades or adducting and upward oblique saccades (Mann-Whitney test right-eye viewing adduction, $P = 0.19$, adduction and upward, $P = 0.16$). During left eye viewing condition, there was in fact a downward vectorial shift of the nonviewing eye during adduction with no significant difference between viewing and nonviewing eye during adducting and upward saccades (Mann-Whitney U test right-eye viewing adduction, $P = 0.2$; adduction and upward, $P = 0.5$).

Fundus Torsion

Ocular torsion was measured in 9 of 14 pattern strabismus patients using fundus photography. We were unable to obtain reliable fundus photographs in 5 patients due to lack of cooperation. The mean excyclotorsion calculated using the retinal vascular tilt method in pattern strabismus was greater ($23.7^\circ \pm 9.1^\circ$) compared to comitant strabismus ($15.3^\circ \pm 2.8^\circ$) and healthy control ($9^\circ \pm 1.8^\circ$). The mean excyclotorsion of both eyes collectively calculated using the fovea-optic disc center relationship method gave similar results with greater

FIGURE 7. Linear regression of the cross-coupling index and fundus torsion elicited in the viewing (A) and nonviewing (B) eyes during abduction, adduction, upward, and downward saccades. The *solid lines* represent linear regression during horizontal saccades, whereas the *dashed lines* represent linear regression during vertical saccades.

torsion measured in pattern strabismus ($28.7^\circ \pm 10.2^\circ$) compared to comitant strabismus ($21.1^\circ \pm 1.5^\circ$) and healthy controls ($14.5^\circ \pm 3^\circ$). There was a strong correlation between the fovea–optic disc center method and the tilt of vascular arcade method for measurement of ocular torsion using fundus photography ($r^2 = 0.89$). The ocular torsion measured using the foveo–optic disc method was greater than the tilt of retinal vascular arcade method (Bland–Altman analysis, bias = 7; 95% limits of agreement, 16 to –2).

We then examined whether the cross-coupling index correlated with ocular torsion in pattern strabismus patients. We performed linear regression analysis to assess the correlation between cross-coupling index in the viewing and nonviewing eyes, and average ocular torsion measured by two methods. Figure 7 summarizes the results for each patient during different directions of the eye movements in the viewing (Fig. 7A) and nonviewing (Fig. 7B) eye. There was no correlation between the cross-coupling index in the viewing and nonviewing eyes and the ocular torsion in pattern strabismus patients (Figs. 7A, 7B). We then looked for the correlation between cross-coupling index in the viewing and nonviewing eyes and grade of inferior oblique overaction. Figure 8 summarizes the results for each patient during different directions of the eye movements in the viewing (Fig. 8A) and nonviewing (Fig. 8B) eyes. There was no

correlation between the cross-coupling index in the viewing and nonviewing eyes and the severity of inferior oblique overaction (Spearman correlation, $P > 0.05$).

DISCUSSION

We assessed eye movements in 14 patients with V-pattern strabismus and compared them to those in comitant strabismus patients and healthy subjects. We found cross-coupling of saccadic eye movements supporting the hypothesis for cross-talk in the supranuclear saccade generators in pattern strabismus.^{7–9} Consistent with previous reports, our patients with V-pattern strabismus also had clinically apparent inferior oblique overaction with abnormal excyclotorsion.^{2,3} However, we could not ascribe cross-coupling to abnormally increased ocular torsion. Our conclusions were based on following key findings in patients with pattern strabismus. Cross-coupled saccades in the orthogonal axis were present during intended pure horizontal and pure vertical saccades. The cross-coupled eye movements were present in the same direction in viewing and nonviewing eyes, but were larger in the nonviewing eye. Abnormal static fundus torsion was present in pattern strabismus, but there was no correlation between the amount of the fundus torsion and cross-coupled saccades. Hence, we could not ascribe cross-coupling of saccades to abnormal

FIGURE 8. Lack of correlation of the CCI and inferior oblique overaction elicited in the viewing (A) and nonviewing (B) eyes during abduction, adduction, upward, and downward saccades. Note that all of our patients with pattern strabismus had grade 2 or greater clinically observed inferior oblique overaction.

ocular torsion. Actual inferior oblique overaction can lead to increased disconjugacy of upward and oblique saccades in the nonviewing eye with consistent upward shift of the saccade vector. However, this was not the case in patients with pattern strabismus. There was no correlation between the severity of clinically apparent inferior oblique overaction and the cross-coupling index. The direction and amplitude disconjugacy of saccades in pattern strabismus was not consistent with the pattern explained by clinically apparent inferior oblique muscle overaction.

It is well known that strabismic have disconjugate horizontal saccades.^{14–18} We found disconjugacy in horizontal, vertical, and oblique saccades in pattern strabismus. Nonhuman primate models of pattern strabismus also had disconjugate vertical and oblique saccades.¹¹ As we found in humans with pattern strabismus, the macaque models also lacked the correlation between the amount of disconjugacy and the patterns expected based on inferior oblique overactions.¹¹ These results further support the notion that oblique muscle “over-action” is a clinical description of the appearance of the eyes, rather than an actual mechanism for the pattern strabismus.⁵

Orbital imaging studies in subjects with pattern strabismus and cranial dysmorphism provided further evidence for non-torsion hypothesis.⁵ For example, temporally elevated inclination of the palpebral fissure was associated with A-pattern, whereas its downward inclination was associated with V-

pattern.^{19,20} Heterotopy of orbital pulleys and instability of the horizontal recti are proposed mechanisms of pattern strabismus in patients with craniofacial dysmorphism or connective tissue disorders.^{21–23} It is, however, noteworthy that not all patients with pattern strabismus have abnormal orbital structure, neither do the monkeys with sensory induced strabismus.²⁴ Thus, orbital anomalies are unlikely to be the cause of pattern strabismus in all cases. In the present study, we did not perform orbital imaging. However, we excluded patients with learning disability, mental retardation, neurologic abnormality on clinical examination, craniofacial dysmorphism, or connective tissue disorders.

Nonhuman primates with disruption of binocular fusion during critical periods of visual development develop a pattern strabismus with cross-coupled saccades in the non-viewing eye.^{9,25} Two putative sources of such cross-coupling in macaque models of pattern strabismus were identified.⁹ One, the inappropriate plane of action of the extraocular muscles in the nonviewing eye due to abnormal static torsion can cause cross-coupling of saccades. Alternatively, the lack of calibration in neuronal responses in the premotor circuits that independently control horizontal and vertical eye movements leading to inappropriate synaptic weighing between horizontal and vertical burst generators can cause cross-coupling. The neuronal responses from horizontal medial rectus motor neurons and vertical ocular motor neurons in strabismic monkeys have shown a direct

correlation between the firing rates of the nuclear motoneurons with the state of horizontal patterns.^{7,8} Such neuronal signature supported the central origin of pattern strabismus. Disruption in the premotor vestibular inputs to the extraocular muscles subnuclei is one of the putative mechanisms for pattern strabismus.²⁶ Our patients, however, did not have vestibular deficits during clinical examination. The test of vestibular hypothesis and its correlation with the cross-coupled ocular motility will justify the need for future investigations directed at measuring the gain of vestibular ocular reflex evoked by stimulation in specific semicircular canal plane and its objective comparison with ocular motor cross-coupling.

Recent investigations have suggested that premotor supraoculomotor area carry strabismus angle information.²⁷ The premotor neurons from the supraoculomotor area project to the medial rectus motoneurons and receive input from vertical and torsional neural integrators.²⁷ In addition, anatomical studies have shown direct projections from vertical and torsional eye movement structures to medial rectus motoneurons.²⁸ We predict that connections between the vertical and torsional areas and the horizontal recti motoneurons might be the source of cross-axis eye movements in macaque models and patients with pattern strabismus. Cross-innervation is a known property of saccadic burst generators. Horizontal saccade commands trigger not only activity of horizontal burst generators, but also the vertical burst neurons.^{29,30} The activity in orthogonal (vertical) burst neuron must be actively suppressed to produce a pure horizontal saccade. The proof for such active modulation comes from adaptation experiments that induced the horizontal visual drift after vertical saccades.³¹ Synaptic plasticity along with readjustment of the balance between the opposing signals determines the active elimination of cross-coupled orthogonal movements.³¹ The cerebellar cortex has an important role in driving such plastic responses, preventing cross-coupled signals, and correctly directing saccade in a desired direction. Despite optimal performance up to 5% to 10% crosstalk has been reported in control nonstrabismic macaque monkeys during horizontal and vertical optokinetic responses.³² In our healthy controls, we saw a similar degree of cross-axis movements during horizontal and vertical saccades in the viewing and nonviewing eye. Such cross-coupling was significantly larger in subjects with pattern strabismus.

We found cross-coupling in the viewing and nonviewing eye during horizontal and vertical saccades. The cross-coupling index was not dependent on orbital position of the eye. Therefore, cross-coupling could not be attributed to mechanical factors, such as muscle length adaptation or displacement of orbital pulley. The amount of cross-coupling did not correlate with static fundus torsion. Lack of measurement of dynamic torsion is a limitation of our study. Reliable measurement of dynamic torsion warrants the use of scleral search coil technique. Most of our patients were in the pediatric age group. Most institutional regulations (including ours) do not allow the use of search coil in this age group. Nevertheless, we were able to measure static torsion reliably using well-described and used fundus photography techniques.^{3,4,33}

We interpreted our results in light of the neurophysiological findings from the macaque models of pattern strabismus. Contraction of vertical rectus in presence of abnormal static eye torsion muscles could cause an inappropriate horizontal movement, and contraction of horizontal rectus muscles could result in a cross-coupled vertical eye movement. In such instance, the activity of vertical motor neurons should correlate with the horizontal component of the cross-axis movements and vice versa. The neuronal activities in

strabismus monkeys lack such characteristics.^{7,8} Instead, the activity of horizontal motor neurons correlated with the horizontal cross-coupled component during intended vertical saccades and vertical motor neurons discharge correlated with the vertical component of intended horizontal saccades.^{8,27} These results support central origin of cross-coupling in pattern strabismus.

In summary, we found cross-coupling of saccades in the viewing and nonviewing eyes of patients with V-pattern strabismus. Although these patients had the common findings of excess static excyclotorsion and apparent inferior oblique overaction, saccadic cross-coupling did not correlate with either of these clinical findings. Our results suggestive of cross-coupling in saccades are in agreement with data from nonhuman primates. These findings suggested a possibility that supranuclear circuits responsible for the saccadic pulse command could be abnormal in subjects with pattern strabismus and may contribute to the development of the static misalignment. Future studies should determine whether such cross-coupling is unique to saccades or whether it also occurs during slow eye movements, like pursuit or vestibulo-ocular reflex.

Acknowledgments

We thank R. John Leigh, MD (RJL), for providing technical equipment.

Supported by National Institutes of Health (NIH; Bethesda, MD, USA) Grant EY06717 (RJL); grants from Knights Templar Research Foundation (FG) and Fight for Sight Foundation (FG); RPB Unrestricted Grant CCLCM-CWRU; and a Dystonia Medical Research Foundation fellowship award (AS). Some resources used for these experiments were supported by NIH Grant R01 EY06717.

Disclosure: F.F. Ghasia, None; A.G. Shaikh, None; J. Jacobs, None; M.F. Walker, None

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