Vertical and Oblique Saccade Disconjugacy in Strabismus

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PURPOSE. Previous studies have shown that horizontal saccades are disconjugate in humans and monkeys with strabismus. The present study was designed to extend these results to vertical and oblique saccades. A major goal was to assess the conjugacy in terms of both amplitude and direction.

METHODS. Saccadic eye movements were recorded binocularly in three adult monkeys. One had normal eye alignment, one had exotropia resulting from a bilateral medial rectus tenotomy in the first week of life, and one had esotropia resulting from prism rearing during the first 3 months of life. We assessed the conjugacy of saccades in various directions by comparing both amplitude and direction.

RESULTS. Saccades in the strabismic monkeys were disconjugate in terms of both amplitude and direction. These effects were as large for vertical and oblique saccades as for horizontal ones. However, the pattern of disconjugacy often varied as a function of saccade direction. In some cases, saccades that appeared to be conjugate in terms of amplitude differed substantially when direction was taken into account.

CONCLUSIONS. These data indicate that the assessment of saccade disconjugacy in strabismus may yield misleading results if direction is not considered. The complex pattern of disconjugacy suggests that strabismus is associated with substantial abnormalities within the circuitry controlling saccades. Neurophysiological studies are needed to identify the specific neural substrates for these behavioral effects.

Keywords: saccade, strabismus, exotropia, esotropia, eye movement

In primates, normal visual perception depends upon maintaining a close alignment of the eyes so that fixated targets activate both foveae. Accordingly, much of the visual system is binocular, with individual neurons responsive to signals originating from either eye. Disruption of binocular vision during a critical period of postnatal development often causes a lasting misalignment of the eyes, impaired motion perception, and amblyopia.1-4

Infantile strabismus is a disorder of eye alignment affecting at least 3% of children. In addition to the visual impairments mentioned above, various oculomotor abnormalities have been reported, including asymmetrical smooth pursuit gain,5-9 an absence of disparity vergence,10 and latent nystagmus.8,11,12 Several studies have also reported that horizontal saccades are disconjugate in both humans13-16 and monkeys with strabismus.17 To our knowledge, however, there are no published quantitative analyses of vertical or oblique saccades in strabismus. This gap in our knowledge is unfortunate, since primates make these movements almost constantly to explore their visual environment. The primary goal of the present study, therefore, was to determine whether horizontal and vertical saccade disconjugacy is influenced by the orthogonal component.

METHODS

Subjects and Surgical Procedures

Three rhesus monkeys (Macaca mulatta) served as subjects. One (monkey N1) has normal eye alignment. Monkey XT1 has incomitant exotropia (25°) resulting from a bilateral medial rectus tenotomy performed during the first week of life. The muscles were not cut during this procedure. Monkey ET1 has incomitant esotropia (15°) resulting from prism rearing. Following eye muscle surgery or prism rearing, monkeys ET1 and XT1 were allowed to grow without further manipulation until after they had reached maturity (7 years of age for monkey XT1; 5 years for monkey ET1), at which time additional procedures were performed to prepare for neurophysiological experiments. All surgical procedures were performed in compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. All protocols were approved by the Institutional Animal Care and Use Committee (IACUC) at the Washington National Primate Research Center. Aseptic surgeries were performed in a dedicated facility using isoflurane anesthesia (1.25%-2.5%). Detailed descriptions of the procedures can be

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found in Mustari et al.\textsuperscript{18} and Ono and Mustari.\textsuperscript{19} Briefly, a titanium post (Crist Instruments Co., Inc., Hagerstown, MD) was affixed to the skull with bone screws so that the head could be immobilized during experiments. In the same surgery, a search coil was implanted under the conjunctiva of one eye to measure eye position (CNC Engineering, Seattle, WA).\textsuperscript{20,21} Following surgery, analgesic (buprenorphine, 0.01 mg/kg, intramuscular) and anti-inflammatory (bunamine, 1.0 mg/kg, intramuscular) treatments were delivered every 6 hours for several days. Following recovery, animals were trained to perform a variety of fixation and oculomotor tasks. Once they were proficient (generally 2–3 months), an additional surgery was performed to implant a search coil in the other eye.

**Behavioral Tasks and Visual Display**

During experiments, monkeys sat in a specially designed primate chair, positioned in the center of a 1.5-m magnetic coil frame. Animals’ heads were kept restrained for the duration of each experimental session. The eye coil signals from each eye were calibrated under monocular viewing conditions while the animal fixated targets that stepped from $-20^\circ$ to $20^\circ$ horizontally and vertically. Eye and target position signals were passed through an antialiasing 6-pole Bessel filter (200 Hz). CED-Power1401 hardware (Cambridge Electronic Designs, Cambridge, England) was used to digitize signals at 1 kHz with 16-bit precision.

Visual targets consisted of a 0.25° laser spot backprojected onto a tangent screen, 57 cm from the animal. Monkeys were rewarded every 300 ms whenever at least one of the eyes was directed to a location within $5^\circ$ of the target. Every 1.5 to 5 seconds, the target stepped to a new location, eliciting a saccade to reacquire the target. Possible target locations were chosen randomly from a set of Cartesian coordinates ($0^\circ$, $2^\circ$, $4^\circ$, $6^\circ$, $8^\circ$, $10^\circ$, $12^\circ$, $15^\circ$, $20^\circ$ left, right, up, or down). Thus, saccades of up to $40^\circ$ could be elicited with this task. Monkey ET1 wore a set of goggles that permitted binocular viewing, or monocular viewing with either eye. Under binocular viewing conditions the animal alternated her fixating eye but showed a clear preference for the right eye. Due to the large exotropia, monkey XT1 always used the right eye to view targets more than $10^\circ$ to the right, and the left eye to view targets to the left of $0^\circ$ (straight ahead). Between these two points, the animal alternated but showed a clear preference for the left eye.

Visual acuity was tested in monkeys N1 and ET1 using sinusoidal gratings presented at various locations, $5^\circ$ away from a central fixation point. Animals indicated that they could see the stimulus by making a saccade. The percent contrast was manipulated over a range of 15% to 50%, and spatial frequency ranged from 5 to 9 c/deg. Contrast sensitivity functions were then computed.

**Data Analysis**

Spike 2 was used for data acquisition and preliminary offline analyses. Data were then imported into MATLAB (Mathworks, Natick, MA) and analyzed further using custom software. To avoid contamination by post-saccadic drifts, saccade onsets and offsets were measured using a combination of velocity and acceleration criteria. Saccade offset was defined as the first offset was measured using a combination of velocity and acceleration criteria. Saccade offset was defined as the first point in time at which either of two conditions was met: (1) the eye velocity dropped below $50^\circ$/s or (2) eye velocity dropped below $100^\circ$/s and the absolute value of acceleration dropped below $10,000^\circ$/s/s. This algorithm successfully detected the occasional large post-saccadic drift that reaccelerated the eye before the velocity dipped below the $50^\circ$/s threshold. For each eye, saccade onsets and offsets were measured separately for the horizontal and vertical components. The amplitudes and durations of each component were defined with respect to these time points. The conjugacy of the horizontal and vertical components was quantified using the following equation:

$$Amp\ Ratio = \frac{C_{A_{left}}}{C_{A_{right}}},$$

where $C_A$ represents component amplitude. The difference in saccade direction for the two eyes was computed as:

$$Direction\ Difference = Polar\ Direction_{LeftEye} - Polar\ Direction_{RightEye}.$$
For both monkeys, the position of the nonfixating eye tended to be more stable if that was the dominant eye. This can be seen most clearly for monkey ET1 (Figs. 1A, 1B). When given a choice, this animal showed a clear bias in favor of fixating the target with the right eye. Note the large variability in the left eye position when the right eye was tracking the target (Fig. 1B).

Figure 2 shows 8 seconds of raw saccade data from each of the three animals. In the normal animal (Fig. 2A), the saccades are almost perfectly conjugate. In contrast, saccades in monkeys ET1 (Fig. 2B) and XT1 (Fig. 2C) are often disconjugate, with arrows indicating several of the more blatant examples. For the strabismic animals, when the saccade had a large vertical component, the horizontal component was sometimes monocular, or even in opposite directions for the two eyes. In Figures 2B and 2C, note the large postsaccadic drifts visible after some saccades.

**Saccade Amplitude Disconjugacy**

Because microsaccades have relatively low accelerations and peak velocities, we were not able to reliably measure their amplitudes. Also, for these movements, small disconjugacies could lead to very large (or very small) amplitude ratios that would dominate the mean values we report below. For these reasons, all analyses of disconjugacy (Figs. 3–8) were based only on saccades with vectorial amplitudes of at least 5°. Disconjugate microsaccades were frequently observed in the strabismic animals, but we were not able to analyze them quantitatively.

Figure 3 plots the horizontal amplitude ratio (see Methods) for saccades in 10 different directions. Note that a ratio of 1 represents a conjugate saccade; values > 1 indicate that the left eye made the larger saccade, and values < 1 indicate that the right eye made the larger saccade. For monkey N1, a two-way ANOVA revealed a significant effect of direction ($P = 0.0006$) but not of fixating eye ($P = 0.12$). For the strabismic animals, significant effects were found for direction ($P < 0.001$ for both strabismic animals) and fixating eye ($P < 0.001$ for both strabismic animals). A comparison of the left and right columns of Figure 3, however, shows that the effect of fixing eye tended to be small in all three animals.

In monkey N1 (Figs. 3A, 3B), the amplitude ratio for the horizontal component was close to 1 for saccades in all
FIGURE 2. Eight seconds of raw data from each of the three monkeys. Horizontal and vertical positions of the right eye are shown in red, the left eye in blue. In the normal animal (A), saccades in all directions were highly conjugate. For both of the strabismic animals (B, C), saccades were often highly disconjugate. Arrows indicate some of the most egregious examples.
FIGURE 3. Comparison of horizontal saccade amplitudes for the left and right eye for saccades in 10 different directions. Each arrow represents the average value of this ratio for a particular direction bin. Data are separated depending on whether the left eye (left column) or right eye (right column) was fixating the target. For the normal animal (A, B), the horizontal amplitudes were highly similar (though not necessarily identical) for every direction tested. For the esotropic (C, D) and the exotropic (E, F) monkeys, horizontal saccade amplitude often differed markedly between the two eyes. This effect clearly depended upon the amplitude of the vertical component. Note, however, that it made little difference which eye was fixating the target.
FIGURE 4. Comparison of vertical saccade amplitudes for the left and right eye for saccades in 10 different directions. All conventions are the same as for Figure 3. As was the case for horizontal amplitude, for the normal monkey the vertical amplitudes were highly similar for the two eyes for every direction tested (A, B). For the esotropic monkey (C, D), the vertical amplitude tended to be slightly greater for the right eye when the saccade had an upward component but slightly larger for the left eye when there was a downward component. For the exotropic monkey (E, F), left eye vertical amplitude was much greater for saccades directed toward 150° (up-left) and 330° (down-right). For up-right and down-left, however, the vertical amplitudes were much greater in the right eye.
Comparison of vectorial saccade amplitudes for the left and right eye for saccades in 12 different directions. The disconjugacies were small for some directions. In the interest of clarity, therefore, we have used a different gain scale from that in Figures 3 and 4. All other conventions are the same. Comparing vectorial saccade amplitudes removes the potentially confounding effect of saccade direction. (A, B) Data from monkey N1. For monkey ET1 (C, D), the left eye made the larger saccade for most directions. For up-left saccades, however, the reverse was true. For monkey XT1 (E, F), saccade amplitudes were larger for the right eye for most directions. The left eye amplitudes were not significantly larger for any direction.
Figure 6. Comparison of averaged vectors for horizontal and vertical saccades. Left eye, blue; right eye, red. For all data in this figure, the vectorial amplitude for the fixating eye was between 8° and 12°. For monkey N1 (A, B), both the amplitudes and directions were highly similar for the two eyes. For monkeys ET1 (C, D) and XT1 (E, F), differences were observed for both amplitude and direction. With the data plotted in this way, one can see that comparing only the amplitudes of the horizontal or vertical component may be misleading because the directional differences can be substantial.
Figure 7. Comparison of averaged vectors for horizontal and vertical saccades for four direction bins that are not shown in Figure 6. All conventions are the same as for Figure 6. (A, B) Monkey N1; (C, D) monkey ET1; (E, F) monkey XT1.
Figure 8. Comparison of averaged vectors for horizontal and vertical saccades for four direction bins not shown in Figures 6 and 7. All conventions are the same as for Figure 6. (A, B) Monkey N1. In Figures 6 through 8, note that for monkey ET1 (C, D), clear directional differences were found for upward saccades and up-right saccades, regardless of which eye was fixating. For monkey XT1 (E, F), note that the left eye’s saccade was deviated in the clockwise direction for every bin, regardless of which eye was fixating.
directions. Nonetheless, paired groups *t*-tests revealed significant differences between the two eyes for some directions. For both of the strabismic animals, it is clear that the horizontal amplitude disconjugacy was often much greater and that it varied more widely according to the direction of the saccade. For saccades within 15° of 120° (up-left), the horizontal component was dramatically smaller in the left eye (Figs. 3C–F). For 60° (up-right), the horizontal component was much larger in the left eye. For monkeys XT1 and ET1, therefore, the horizontal component could be approximately the same in both eyes, larger for the left eye, or larger for the right eye, depending on the direction. For monkey XT1, the pattern of horizontal disconjugacy was quite orderly. For saccades with a rightward component, the horizontal amplitude ratio increased steadily as the direction became more upward. For saccades with a leftward component in this animal, the reverse was true.

Figure 4 shows the vertical amplitude ratio for saccades in 10 different directions. For monkey N1, a two-way ANOVA revealed a significant effect of direction (*P* < 0.0006) but not of fixating eye (*P* = 0.40). For monkey ET1, significant effects were found for both direction (*P* < 0.0001) and fixating eye (*P* = 0.02). For monkey XT1, significant effects were found for both direction (*P* < 0.0001) and fixating eye (*P* < 0.0001). As was the case for horizontal amplitude ratio, the effect of fixating eye tended to be small for all three animals (compare the left and right columns of Fig. 4).

For monkey N1, the ratios were close to 1 for all directions. However, there was a tendency for vertical amplitude to be larger in the left eye, a result that often reached significance. For monkey ET1 (Figs. 4C, 4D), left eye vertical amplitude tended to be smaller for directions involving an upward component (arrows fall short of 1) and equal or larger for directions involving a downward component (many arrows extend beyond 1). While modest, these effects reached significance for a majority of directions, particularly when the right eye was attending. A more complex pattern was observed for monkey XT1. The left eye vertical component was notably larger for 150° and 330° but much smaller for all up–right and down–left directions. These effects reached significance for all conditions except 90° with the left eye fixating and 120° with the right eye fixating. Overall, however, the pattern was highly similar regardless of which eye was fixating the target (compare left and right columns of Fig. 4).

Another way to view Figures 3 and 4 is to consider how these patterns of horizontal and vertical amplitude disconjugacy would relate to “A” and “V” patterns. For monkey XT1, the horizontal amplitude is higher for the left eye for up–right saccades and higher for the right eye for up–left saccades. This will result in decreased exotropia on up gaze. The horizontal amplitude is higher for the left eye for down–left saccades and higher for the right eye for down–right saccades, resulting in increased exotropia on down gaze. Similarly, in Figure 4, we see that leftward saccades will tend to increase the vertical deviation, while rightward saccades will decrease it. Thus, the pattern of saccade disconjugacy is consistent with this animal’s “A” pattern of static fixation. These cross-axis effects were less consistent in monkey ET1, perhaps because this animal’s “V” pattern was weaker and post-saccadic drift sometimes influenced the final static eye position. Nonetheless, the cross-axis effects can be seen for this animal also. In Figure 3, the pattern of horizontal disconjugacy for directions involving an upward component will result in increased esotropia on up gaze, consistent with the slight “V” pattern shown in Figure 1.

Quantifying disconjugacy in terms of component amplitude makes sense in light of the decomposition of vectorial saccadic commands into separate horizontal and vertical signals in brainstem. A limitation of this approach, however, is the danger of confounding amplitude and direction. Suppose, for example, that the attending eye makes a purely horizontal saccade while the fellow eye makes an oblique saccade of the same vectorial amplitude. In the above analysis this would appear to be a “horizontal amplitude disconjugacy” when it should properly be described as a difference of direction. To address this concern, the above analysis was repeated using vectorial instead of component amplitude. The results are shown in Figure 5. For monkey N1, a two-way ANOVA revealed a significant effect of direction (*P* < 0.0001) but not of fixating eye (*P* = 0.82). For monkey ET1, highly significant effects were found for both direction (*P* < 0.0001) and fixating eye (*P* < 0.0001). For monkey XT1, a significant effect was found for direction (*P* < 0.0001) but not for fixating eye (*P* = 0.25).

For monkey N1 (Figs. 5A, 5B), significant disconjugacies were found for some directions (particularly up-left), but these differences were quite small. For the strabismic animals, amplitude disconjugacies were larger and more consistent. For monkey ET1 (Figs. 5C, 5D), the left eye made larger saccades for most directions. For up–left saccades, however, the right eye amplitude was larger. These effects were significant for all conditions in this animal, with the exception of 90° (upward) saccades initiated with the right eye fixating. For monkey XT1, saccade amplitudes were significantly larger in the right eye for most directions for both fixation conditions. When the left eye was fixating, however, there was no significant difference for down–right and up–left saccades. With the right eye fixating, amplitude differences were significant for all but 120° and 300°. The very small amplitude ratio for upward saccades initiated with the right eye fixating is a consequence of the large dissociated vertical deviation which brought the left eye closer to the orbital limit. These data confirm that saccade amplitudes for these strabismic monkeys differ for the two eyes, independent of differences in direction.

**Saccade Direction**

As above, a complete description of saccade disconjugacy must take into account direction as well as amplitude. Figures 6, 7, and 8 show averaged vectors for saccades in which the vectorial amplitude in the fixating eye is between 8° and 12°. These data are shown in three separate figures in the interest of clarity. Plotted in this way, one can appreciate the complexities of saccade disconjugacy in strabismus. For example, in Figure 6E it appears that downward saccades in monkey XT1 are conjugate when the left eye fixates, yet Figure 5E suggests that this is not the case. In Figure 6E we see that the apparent inconsistency is accounted for by a large difference in saccade direction. Similarly, what appears to be a huge amplitude disconjugacy for 60° saccades in Figure 5D is partly a consequence of the fact that the directions are quite different in the two eyes (Fig. 8D). These data show that quantifying the amplitude disconjugacy of horizontal or vertical saccades is a complex issue because the direction in the nonfixating eye may be oblique.

A one-way ANOVA was used to test the hypothesis that the direction difference between the two eyes (see Methods) was unrelated to fixating eye. No significant effect was found for monkeys N1 and XT1 (*P* = 0.33 and *P* = 0.35, respectively). For monkey ET1, a significant effect was found (*P* < 0.0001).

For monkey N1, no significant difference in saccade direction was found between the two eyes for any of the 12 directions tested (Watson-Williams test). For monkey ET1, with the right eye fixating, the directions for the two eyes differed
significantly for horizontal directions and all directions with an upward component. No significant differences were found for directions with a downward component. Results were similar when the left eye was fixating, except that no significant difference was found for 120° and a significant difference was found for 300°. For monkey XT1, saccade directions were quite different between the two eyes for every direction tested (typically approximately 15°–25°). Regardless of which eye was fixating the target, the left eye saccade was always deviated clockwise, relative to the right eye's saccade direction. These effects were highly significant for all 12 directions with either eye fixating.

Figure 9 summarizes the saccade disconjugacy for the three monkeys for saccades in all 12 direction bins. Figures 9A and 9B show the vectorial amplitude ratios, and Figures 9C and 9D show the differences in saccade direction (in degrees). While the amplitude disconjugacy clearly tends to be greater for the strabismic animals, the most obvious abnormality can be seen with respect to saccade direction. In the normal animal, saccade directions were always highly similar for the two eyes, but for the strabismic animals the directions often differed by 10° to 20° or more.

Main Sequences
A proper comparison of the main sequences for the two eyes requires that the directions be the same, which, as discussed above, is often not the case for individual saccades. To address this, main sequences were computed for each eye, based on trials in which saccade direction for that eye was no more than 15° away from the desired direction (up, down, left, or right). This meant that the data sets were somewhat different for the two eyes, but it removed the potential confounding influence of directional differences. Main sequences were computed separately for rightward, leftward, upward, and downward saccades.

Figure 10 shows the main sequences for downward saccades. For all three animals, the prediction bands for the two eyes almost completely overlapped over much of the range of amplitudes tested. Similar results were obtained for upward saccades (data not shown).

In spite of the overall similarity of the main sequences for the two eyes, there were clear differences for certain amplitudes. The most robust example is shown in Figure 11 (a subset of the data shown in Figs. 10E, 10F). Since the main sequence was linear over this narrow range, we fit these data with linear regressions. For small downward saccades in monkey XT1 (Fig. 11), both the slopes (Tstat = 5.32) and the y-intercepts (Tstat = −17.48) differed significantly between the two eyes. No significant differences were found for upward saccades in monkey XT1 (slopes: Tstat = 1.01; y-intercepts: Tstat = −0.94). For upward saccades in monkey ET1, a significant difference was found for the y-intercepts (Tstat = −0.46, y-intercepts: Tstat = −2.17). For monkey N1, no significant differences were found for downward saccades (y-intercept Tstat = −2.06; slopes Tstat = 0.86). For upward saccades, no significant difference was found for the slopes
(Tstat = 1.28), but a small difference was found for the y-intercepts (Tstat = -4.69).

In Figure 10 one can see that the strabismic monkeys made fewer large vertical saccades. When the vertical target step was large, these animals sometimes switched the fixating eye (which introduced a horizontal component that caused the trial to be excluded from this analysis). Additionally, although both strabismic animals were capable of fixating targets that
were far up and far down, they seemed to dislike doing so. Nonetheless, for all three animals, we were able to elicit at least a few large vertical saccades.

**DISCUSSION**

To understand the abnormalities of saccades in strabismic monkeys, one must first determine the conjugacy of these movements in normal animals. In monkey N1, small disconjugacies can be observed for some directions (Figs. 3–5). A close examination of the literature suggests that saccades are not always perfectly conjugate in normal humans and monkeys. For example, Zhou and King23 reported small-amplitude disconjugacies in awake monkeys (see Figs. 1A and 4 in their study). They reported a mean conjugacy index of 0.05 for the vertical component in awake monkeys. In their study the conjugacy index was computed as $\frac{\text{LeftEyeAmp}}{\text{RightEyeAmp} + \text{LeftEyeAmp}}$. Thus, if the amplitudes were 10.5 and 9.5 for the left and right eye, respectively, this would yield a value of 0.05. In our data this would equate to an amplitude ratio of 1.105, which is greater than the typical disconjugacy we found for monkey N1 (see Fig. 4). Similarly, Kapoula et al.15 reported a small intrasaccadic divergence (<1°) in their normal human subjects (see Fig. 2 of their study). Figure 3 of the present study shows that there was a tendency for the left eye amplitude to be slightly smaller for rightward saccades and slightly larger for leftward saccades. This resulted in a small intrasaccadic divergence, with amplitude ratios typically ranging from 0.9 to 1.15. Overall, therefore, the disconjugacy observed for the normal animal in the present study is fairly comparable to what has been reported in the literature. It should be emphasized, however, that the saccade disconjugacy was clearly larger and more consistent for both of our strabismic animals.

A major conclusion of this study is that a complete description of saccade disconjugacy in strabismus must take into account both amplitude and direction. When the difference in direction is substantial, these two factors become confounded if one considers only horizontal or vertical amplitude. It is particularly noteworthy that both aspects of disconjugacy were observed for some directions and not others. It is difficult to account for this complex pattern of abnormalities solely in terms of abnormal action of a particular set of muscles. Clinically, inferior oblique overaction typically results in an overelevation in adduction.24 In Figures 6E and 6F, one can see that the overelevation occurred for the abducting eye. For monkey ET1, there was very little directional difference for abducting or adducting horizontal saccades (Figs. 6C, 6D). Bilateral superior oblique overaction most often results in a “lambda” pattern and a downshoot for the adducting eye.24 Unilateral superior oblique overaction results in a hyperdeviation that increases for contralateral gaze positions. The saccade disconjugacy we observed did not cleanly fit any of these patterns. In monkey ET1, for example, the directions are notably different only for upward and up–right saccades, manifested as an increased esotropia. This does not fit the “Y” pattern that typically results from inferior oblique overaction (i.e., divergence in up gaze). In monkey XT1, there is a downshoot of the adducting eye but no evidence of a lambda pattern (see Figs. 6E, 6F; Figs. 7E, 7F; Figs. 8E, 8F). Also, the right eye’s amplitude is larger for most directions, which would not be expected if the only abnormality was a superior oblique overaction. Nonetheless, it is quite possible that abnormal signals are sent to the oblique muscles in these animals, which could partially explain the directional effects.

In monkey XT1 we performed a bilateral medial rectus tenotomy during the first week of life. This demands consideration of the possible influence of weakened eye muscles on this animal’s saccade behavior. If normal neural signals were sent to weakened medial rectus muscles, the abducting eye should always make the larger saccade. This was the case for rightward saccades in this animal. For leftward saccades, however, the amplitude was consistently larger in the right (adducting) eye (Fig. 5) even though that required the use of the muscle that received the tenotomy. Moreover, the disconjugacy was just as severe for vertical saccades. It is also important to emphasize that we never performed eye muscle surgery on monkey ET1. Although we cannot eliminate the possibility that eye muscle abnormalities may have influenced
the conjugacy of saccades in our strabismic animals, the above observations strongly suggest that the neural signals are disordered.

Saccade disconjugacy could result from changes in the density of innervation within the eye muscles and/or (for monkey XT1) differences in the sites of reattachment of the medial rectus muscles to the two eyes. For example, it is possible that relative weakness of an eye muscle early in life is compensated for by changes in the density of innervation of that muscle and/or the antagonist. However, microstimulation of three sites in the right abducens nucleus of monkey XT1 always caused the contralateral (left) eye to move much faster than the ipsilateral (right) eye. This never occurred for any of six sites in the normal animal and nine sites in monkey ET1. This implies that any changes at the level of eye muscles or innervation density favor the left eye (for rightward saccades). However, for visually guided saccades in the same direction, it is the right eye that makes the larger movement. Therefore, while there could easily be abnormalities of the eye muscles and/or the innervation density in this animal, this is unlikely to be the sole explanation for the present results.

If the data cannot be accounted for solely in terms of muscle and/or plant abnormalities, then the two eyes must be receiving different commands. One possibility is that a disordered vergence system might be contributing an inappropriate signal. Indeed, it is known that strabismus is associated with a loss of disparity vergence. Neurophysiological studies have shown that the firing rates of neurons in the supraoculomotor area (SOA) are correlated with the angle of strabismus. In normal animals, some SOA neurons carry vergence velocity commands. If these neurons modulate their activity during saccades in strabismus, the effect would be a difference in the horizontal amplitudes for the two eyes. It is not clear, however, how this explanation could completely account for the present data. Consider, for example, that horizontal saccades have a smaller amplitude in the left eye for monkey XT1. This would require a divergence signal for saccades to the right and a convergence signal for saccades to the left. It is not clear why this would happen. It is also unclear how this would account for vertical amplitude disconjugacy. Nonetheless, it is possible that abnormal activity in SOA could be a contributing factor.

It is also possible that the saccadic system itself may be outputting a disconjugate signal, which implies that the circuitry is at least partially separate for the two eyes. It has been noted that this is the case in the normal animals. But this idea has been highly controversial. m is binocular in normal primates, however, this might not be the case in strabismus. If individual brainstem saccadic neurons preferentially drive one eye, then the potential exists for the two eyes to receive different commands. This may be the explanation for the observation (Fig. 11) that small downward saccades were faster for the right eye in monkey XT1. In a recent study we applied microstimulation to the paramedian pontine reticular formation (PPRF) in the same two strabismic monkeys used for the present report. For most sites the evoked movements were notably disconjugate, in terms of both velocity and direction. In contrast, stimulation in a normal control animal evoked conjugate movements. Since PPRF stimulation should not have activated areas of the brain involved in vergence eye movements, these results suggest that the brainstem saccadic circuitry is abnormal in strabismus. Of course, this does not eliminate the possibility that abnormal vergence signals might contribute to saccade disconjugacy. As noted above, there is evidence that the static angle of strabismus is related to the tonic firing rates of neurons in SOA. It is entirely plausible that inappropriate vergence velocity signals could be present, even during saccades between targets at the same viewing distance.

Although significant effects of fixating eye were often found, the actual differences were generally small. Perhaps the desired displacement is determined for one eye but used as the input to the saccade generators for both eyes. Indeed, this is consistent with the well-known concept of visual suppression. If this is the case, it may not matter very much which eye saw the target; the disconjugacy would result from improper implementation of this command by brainstem saccade circuitry. According to control systems models, however, saccade amplitude is governed by a local feedback loop that dynamically compares desired displacement with an estimate of current displacement. If both eyes receive the same desired displacement command and the amplitudes still differ, then there may be abnormalities within the brainstem saccade generator that interfere with the functioning of the local feedback loop.

The relationship between saccade disconjugacy and static strabismus angle also deserves some comment. According to most control systems models, saccade velocity commands in PPRF and the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) are integrated to produce the tonic eye position signal for the motoneurons. If saccadic commands differ for the two eyes, this should influence the static angle of strabismus. A defining characteristic of pattern strabismus is that the horizontal and vertical deviations vary with eye position along the orthogonal axis. Although the neural basis for this is probably complex, it might be partially attributable to abnormal tuning of premotor saccadic burst neurons. For example, if monocular neurons in PPRF carry abnormal vertical signals, this would cause the static horizontal strabismus angle to be influenced by the vertical saccade amplitude.

In summary, the present data suggest that an early loss of binocular vision leads to a complex pattern of abnormalities within the circuitry driving saccades. From a clinical standpoint it may be that the chances of developing normal ocular motor behavior depend upon restoring binocular vision before these circuits progress too far along an abnormal developmental trajectory. Unfortunately, little is known about the neurophysiological development of the oculomotor system early in life. It is safe to say, however, that proper dynamic and static coordination of the eyes depends upon proper sensorimotor transformations and precisely calibrated ocular motor circuitry, balanced with the strength of eye muscles and the characteristics of the plant. Further neurophysiological studies will be needed to identify the specific abnormalities that contribute to abnormal ocular motor behavior in strabismus.

Acknowledgments

The authors thank Bob Cent, Greg Anderson, Bob Smith, Renae Koenke, and Kun Qian for technical assistance.

Supported by National Institutes of Health Grants EY06069 and EY019266, Office of Research Infrastructure Programs (ORIP) Grant P51OD010425, and Research to Prevent Blindness.

Disclosure: M.M.G. Walton, None; S. Ono, None; M. Mustari, None

References


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