Stimulation of Pontine Reticular Formation in Monkeys With Strabismus

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Saccade disconjugacy in strabismus could result from any of a number of factors, including abnormalities of eye muscles, the plant, motoneurons, near response cells, or atypical tuning of neurons in saccade-related areas of the brain. This study was designed to investigate the possibility that saccade disconjugacy in strabismus is associated with abnormalities in paramedian pontine reticular formation (PPRF).

METHODS. We applied microstimulation to 22 sites in PPRF and 20 sites in abducens nucleus in three rhesus macaque monkeys (one normal, one esotrope, and one exotrope).

RESULTS. When mean velocity was compared between the two eyes, a slight difference was found for 1/5 sites in the normal animal. Significant differences were found for 5/6 sites in an esotrope and 10/11 sites in an exotrope. For five sites in the strabismic monkeys, the directions of evoked movements differed by more than 40° between the two eyes. When stimulation was applied to abducens nucleus (20 sites), the ipsilateral eye moved faster for 4/6 sites in the normal animal and all nine sites in the esotrope. For the exotrope, however, the left eye always moved faster, even for three sites on the right side. For the strabismic animals, stimulation of abducens nucleus often caused a different eye to move faster than stimulation of PPRF.

CONCLUSIONS. These data suggest that PPRF is organized at least partly monocularly in strabismus and that disconjugate saccades are at least partly a consequence of unbalanced saccadic commands being sent to the two eyes.

Keywords: strabismus, exotropia, esotropia, saccadic eye movements, PPRF
PPRF Stimulation in Strabismus

The saccadic system could conceivably produce unequal eye movements if the inputs differ.

If either of these explanations entirely account for saccadic disconjugacy in strabismus, microstimulation of PPRF should bypass the abnormality. Evoked movements, therefore, should be conjugate. However, it also is possible that disconjugacy may be due to abnormalities at the level of eye muscles, the pulleys, motoneurons, and/or PPRF. If this is the case, stimulation of PPRF should evoke disconjugate movements.

The present study, therefore, was designed to determine whether saccadic disconjugacy in strabismus is attributable, at least in part, to abnormalities in PPRF.

**Methods**

**Subjects and Surgical Procedures**

Three female macaque monkeys (*Macaca mulatta*) were used as subjects. One (subject N1) had normal eye alignment while two (subjects ET1 and XT1) had strabismus. Monkey ET1 wore prism goggles for the first three months of life (right eye, 20 prism diopter, base-in; left eye, 20 prism diopter, base-down), resulting in 15° esotropia, with a slight “V” pattern. Subject XT1 had exotropia (25° when fixating with the right eye and 35° to 40° when fixating with the left eye) and a strong “A” pattern, resulting from a bilateral medial rectus tenotomy performed during the first week of life.

Following eye muscle surgery or prism rearing, monkeys ET1 and XT1 were allowed to grow normally. After reaching maturity, they underwent surgeries to prepare for neurophysiologic experiments. All surgical procedures were performed in compliance with 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. Surgeries were performed in a dedicated facility under aseptic conditions using isoflurane anesthesia (1.25%–2.5%). Detailed descriptions have been reported previously.30,31

In brief, stereotaxic methods were used to implant a titanium head post (Crist Instruments Co., Inc., Hagerstown, MD) on the skull. In the same surgery, a search coil was implanted under the conjunctiva of one eye to allow the animal to fixate the target as it was stepped from one eye to the other. This was accomplished through the use of liquid crystal shutter goggles (Micron Technology, Inc., Boise, ID).

Data were collected with both eyes viewing and during monocular viewing with each eye. When using the goggles with the left eye occluded, subject XT1 appeared to have difficulty seeing targets more than ~10° to the left of fixation. Without the goggles, however, she always used the left eye to fixate targets to the left of straight ahead and the right eye for targets more than 10° to the right. Between those points, she tended to alternate. In this way we were able to obtain data with each eye fixating. Note that, due to this animal’s exotropia, the nonfixating eye always was directed to a point that was in darkness, 25° to 40° away from the target. For the target step task, the animal first was required to look at the target and maintain fixation for a variable interval (1.5–5 seconds). When this was accomplished successfully, the target then would step to a new location chosen at random. Possible target positions were: 2, 4, 6, 8, 10, 12, 15, or 20° from straight ahead in any of the eight cardinal directions. This task was used while the electrode was being advanced, to localize PPRF or abducens nucleus.

**Microstimulation Procedures and Localization of PPRF**

Extracellular neural recording and stimulation were performed using glass-coated tungsten microelectrodes (Alpha-Omega, Alpharetta, GA) with impedances ranging from 1 to 5 megohms (MΩ). For each monkey, the first few tracks were used to establish the location of PPRF with respect to well-known neurophysiologic landmarks, such as superior colliculus (SC), abducens nucleus, and the omnipause area. Cross different tracks were shifted systematically, in the mediolateral dimension until left and right burst neurons were encountered, with omnipause neurons isolated between the two. Next, the electrode location was shifted systematically caudally until abducens nucleus was found (verified by the characteristic “beehive” burst-tonic activity). Only after establishing the rostrocaudal and mediolateral borders of PPRF did we begin to collect stimulation data. To minimize the risk of current spread, all PPRF stimulation sites in this report were at least 0.5 mm rostral to previous tracks that had passed through abducens nucleus.

Once we encountered characteristic background bursting associated with ipsiversive saccades, we attempted to isolate individual LLBNs and/or MLBs. The electrode was advanced further until the characteristic saccade-related activity was no longer heard, then withdrawn to a point at least 300 μm away from either the dorsal or ventral edge of the structure, and stimulation delivered. Biphasic current pulses (0.25 ms, 30–50 μA, 100–400 Hz, 100–200 ms train duration) were delivered during fixation of static targets. For a given site, the stimulation parameters were adjusted to be as weak as possible, while still evoking robust, visually detectable movements.
**Figure 1.** Example data from stimulation sites in PPRF (A–F). Eye position traces are shown for three stimulation trains, with data aligned with respect to the first pulse. *Shaded areas* indicate the period of stimulation. (A, B) In the normal monkey, stimulation of this site in left PPRF caused a conjugate movement, with a short latency leftward component. The *upward component* also is conjugate, but it occurred at a much longer latency (>40 ms). (C, D) Stimulation of this site in left PPRF of monkey ET1 evoked a notably disconjugate movement, with a clearly higher velocity in the left eye. The *vertical component* was in opposite directions for the two eyes. (E, F) For this site in right PPRF of monkey XT1, the *horizontal component* was monocular, though an *upward component* was observed for both eyes.
As an additional control, stimulation was performed at 20 sites in abducens nucleus (six for monkey N1, five for XT1, and nine for ET1). Due to the high velocity of movements evoked by stimulation of motoneurons, the train durations were 100 ms. All other stimulation parameters were the same as those used for PPRF sites.

Data Analysis

Data were analyzed offline using Spike2 software and a custom program written in Matlab (Mathworks, Natick, MA). Data from a given stimulation train were analyzed only if the vectorial velocity of both eyes was less than $6'$/s at the time of the first pulse. The mean horizontal, vertical, and vectorial eye velocity was measured for each eye during a time window that began 10 ms after the first pulse (to allow for the normal delay between neural activity and eye movement), and ended with the offset of the train. The relationship between right and left eye velocity was assessed in two ways. First, the mean horizontal and vertical eye velocity was computed for each train. These values then were averaged across all accepted stimulation trains. The other approach was to plot the mean velocity for each train as a function of initial eye position. Linear equations were fit to these data separately for the two eyes, and separately for horizontal and vertical velocity. An $F$-test then was used to test the hypothesis that the two regression models had the same $y$-intercept.

Movement onset was defined as the point at which eye velocity exceeded $6'$/s and remained above that threshold for at least 3 ms. The latency of evoked movements was defined as the interval (in milliseconds) between the first stimulation pulse and movement onset. This was done separately for the horizontal and vertical components.

RESULTS

Stimulation was delivered to 22 sites in PPRF and 20 sites in abducens nucleus. To relate the results of stimulation to behavior, we first quantified the conjugacy of horizontal visually guided saccades in the strabismic animals. This analysis was based on a sample of 2267 saccades in monkey ET1 and 1745 in monkey XT1. For this data set, the saccade direction for the viewing eye had to be within $15'$ of horizontal. The range of amplitudes was approximately $0'$ to $30'$, left and right. Conjugacy was expressed as a gain value: left eye amplitude/right eye amplitude. The conjugacy of horizontal saccades was highly variable, but the gain was consistently higher for the left eye in monkey ET1 (mean left eye gain = 1.25). For monkey XT1, the gain was consistently higher for the right eye (mean left eye gain = 0.85).

Velocity of Evoked Movements

Figure 1 shows example data from one PPRF stimulation site in each of the three monkeys. Each panel shows eye position traces for three stimulation trains, aligned with respect to the first pulse. The top row shows horizontal (Fig. 1A) and vertical (Fig. 1B) eye position traces from monkey N1. Stimulation of this site in left PPRF evoked a leftward and upward ramp eye movement in both eyes. Note that the eyes remained closely aligned throughout each trial. Figures 1C and 1D show data from one site in monkey ET1. The evoked movements were
the velocities of evoked movements depended upon initial eye position, strabismic monkeys, the eyes started in different orbital positions. If this is the case, a given stimulation site in PPRF might simply reflect the fact that, for the strabismic monkeys, the eyes started in different orbital positions.

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**Figure 3.** Relationship between horizontal initial eye position and mean horizontal velocity. Linear regression analysis was performed separately for the left eye (blue) and right eye (red). Although the velocities of evoked movements depended upon initial eye position, the y-intercepts are quite different. Thus, the disconjugacy of evoked movements cannot be attributed solely to the fact that, for the strabismic monkeys, the eyes started in different orbital positions. Consistently disconjugate, with the left (ipsilateral) eye velocity clearly higher. Note that the vertical component in Figure 1D was in opposite directions for the two eyes. Figures 1E and 1F show data from a site in right PPRF of monkey XT1. Although there was a vertical movement in both eyes, the horizontal component was monocular.

Figure 2 compares the mean horizontal velocity of evoked movements for the left eye (vertical axis) and right eye (horizontal axis). Each dot represents data for a single site, with filled circles indicating significant differences between the two eyes (two-tailed t-tests, \( P < 0.05 \)). All five sites for monkey N1 fall on or near the unity line (black dots), though for one site in left PPRF the left eye velocity was slightly (and significantly) higher. This also was the case for several sites in the strabismic monkeys. However, the mean horizontal velocities were significantly different for 10/11 sites in monkey XT1 (blue) and 5/6 sites in monkey ET1 (red).

For the strabismic animals, the eye making the faster movement varied from site to site. For monkey XT1, stimulation caused the right eye to move faster for all four sites in right PPRF. For left PPRF, the left eye moved faster for 5/7 sites, compared to one site at which the right eye moved faster. Thus, stimulation of PPRF on either side of the brain tended to result in an increase in esotropia. For monkey ET1, the contralateral eye moved faster for 4/6 sites, resulting in an increase in exotropia. The ipsilateral eye moved faster for only one site. Across both strabismic animals, therefore, stimulation of PPRF increased the angle of strabismus for 13/17 sites. The reverse was true for only 2 sites.

A limitation of the above analysis is that, for the strabismic animals, the two eyes did not start in the same orbital position. If the velocities of evoked movements differ as a function of initial eye position, the disconjugacy in the strabismic animals might simply reflect the fact that the eyes do not start in the same place. If this is the case, a given stimulation site in PPRF might have the same potential to activate both eyes (if they could start in the same position). To address this, linear regression analysis was used to assess the relationship between initial eye position and evoked eye velocity. This was done separately for the right and left eyes. If the slopes or y-intercepts differ significantly, then the disconjugacy cannot be attributed solely to an initial eye position effect. Figure 3 illustrates this analysis for one site in monkey ET1. Although the velocities of the evoked movements clearly vary as a function of initial eye position, this relationship differs for the two eyes. As a result, the y-intercepts are quite different. Indeed, when the right eye was centered initially in the orbit, a robust leftward movement was evoked in the right eye. On other trials, when stimulation was applied with the left eye centered in the orbit, a slow rightward movement was evoked in the left eye. Thus, although the velocity of evoked movements varies with initial eye position, this alone cannot explain the disconjugacy.

Figure 4A compares the y-intercepts for the left eye (vertical axis) to those for the right eye (horizontal axis) for all sites in our sample. Filled symbols represent sites at which the y-intercepts were significantly different between the two eyes. For the normal monkey (black dots) all data points lie on, or very close to, the unity line. For one of these sites (filled black circle), however, the y-intercept for the left eye was slightly (and significantly) higher. For all 6 sites in monkey ET1 and 9/11 sites in monkey XT1, the y-intercepts differed significantly between the two eyes, indicating that the disconjugacy of evoked movements cannot be attributed solely to an initial eye position effect. If anything, the difference in the velocities of the two eyes was even more pronounced when initial eye position was taken into account.

**Vertical Movement**

Figure 1 suggests that PPRF stimulation in strabismic monkeys may evoke movements with an abnormal vertical component. To investigate this possibility quantitatively, the mean vertical velocity was analyzed for each site, using the same approach described above for the horizontal component. Figure 4B compares these data for the two eyes for each site. Although evoked movements were almost purely horizontal for some sites, for others there was a robust vertical component. For monkey N1, a significant difference was found between the two eyes for only one site. This was the same site at which the left horizontal velocity was slightly higher. Significant differences were found for 3/6 sites in monkey ET1 and 7/11 sites in monkey XT1. For four sites (marked with arrows, one in ET1 and three in XT1) the vertical component was in opposite directions for the two eyes.

To investigate the relationship between initial vertical eye position and vertical disconjugacy, we performed a linear regression analysis, as was done for the horizontal component. Figure 4C compares the resulting y-intercepts for the two eyes for all sites. Significant differences were found for 1/5 sites in monkey N1, 5/6 sites in monkey ET1, and 9/11 sites in monkey XT1. Thus, for the strabismic animals, the differences in mean vertical velocity between the two eyes cannot be attributed solely to vertical initial eye position.

A potential concern is that stimulation durations of 200 ms might be long enough to permit evoked movements to be modified by visual input. To address this possibility, we repeated the above analyses with one modification: the analysis window ended 40 ms after the first pulse. The results were highly similar to those reported above for the full 200 ms trains. For mean horizontal velocity, significant differences were found for 1/5 sites in monkey N1, 5/6 sites in monkey ET1, and 10/11 sites in monkey XT1. For all three animals, the same sites showed significant differences, regardless of
whether the analysis was based on the first 40 ms or the entire stimulation train. Furthermore, it always was the same eye that moved faster.

For the vertical component, significant differences were found for 3/5 sites for monkey N1, 5/6 for monkey ET1, and 9/11 for monkey XT1. For one site in monkey N1, 4 sites in monkey ET1, and 7 sites in monkey XT1 the same eye moved faster for the 200 ms train and within the first 40 ms. Mean vertical velocity never reached 4.8/s for either eye for any site in the normal animal. For the strabismic animals, however, the mean vertical velocity exceeded 5.8/s for at least one eye for 10/17 sites.

**Latencies of Evoked Movements**

Previous studies in normal monkeys have reported that PPRF stimulation evokes ipsiversive movements with latencies of approximately 14 ms.24 For the present study, the issue of latency is complicated by the fact that, for some sites, robust horizontal movements were evoked in only one eye. Since movement onset was based on a velocity threshold, and there often were large differences in the velocities of the two eyes, we were not confident that a robust quantitative comparison could be made. For the horizontal and vertical components, therefore, the mean latencies were computed based only on those sites at which...
mean velocity exceeded 10⁸/s. If this criterion was exceeded in both eyes, the average of the two was used. For all three animals, the mean latencies for the horizontal component were roughly comparable to the values reported in previous studies (19.0 ± 7.5 ms for monkey N1, 13.1 ± 8.7 ms for monkey ET1, and 14.6 ± 6.8 ms for monkey XT1). Across all sites in all animals the mean latency of the horizontal component was 15.1 ± 7.5 ms.

An important question is whether the vertical components observed for the strabismic animals might be due to antidromic activation of upstream structures. If so, one might expect the latency to the vertical component to be longer. For monkey N1, consistent short latency (<20 ms) vertical components (with mean velocity > 10⁸/s) were not observed for any site. For the strabismic animals, consistent vertical movements > 10⁸/s were observed for six sites. For these sites, the mean latency was 16.2 ± 5.9 ms (18.6 ± 9.1 ms for monkey ET1, 13.8 ± 0.8 ms for monkey XT1). Thus, robust vertical ramp movements sometimes were observed for the strabismic animals at latencies comparable to those for the horizontal component.

**Evoked Movement Direction**

The CircStat Matlab toolbox for circular statistics was used to compare the directions of evoked movements between the two eyes (one factor ANOVA). The results are shown in Figure 4D. For monkey N1 (black), a significant difference was found for 1/5 sites, though the mean directions even for this site differed by <5° (left eye, 158; right eye, 162; P < 0.01). In contrast, significant differences were found for 8/11 sites for monkey ET1 (red) and 5/6 sites in monkey ET1 (blue). For five sites in the strabismic animals the effect was quite dramatic, with the directions differing by more than 40° (Fig. 4D, arrows; see Figs. 1E, 1F for example traces from one such site). For two sites in monkey XT1, the directions differed by more than 90°.

**Effect of Fixating Eye**

We next considered whether or not the evoked movements for a given eye might vary, depending on whether or not that eye was fixating the target. To do this, we repeated the analysis shown in Figure 3 for the strabismic animals, this time separating the data according to viewing eye. This analysis was performed only if at least 10 trials were present in both conditions (fixating and nonfixating). For subject ET1, evoked movements were the same whenever the right eye fixated the target, regardless of whether the left eye was shuttered or open. Therefore, these data were pooled for purposes of this analysis. Figure 5 shows example data from two sites. Figure 5A shows data from one site that showed a particularly strong effect of viewing eye. For a given initial eye position the left eye velocity was much higher when the right eye was fixating. Figure 5B shows another site from the same animal. In this case, no significant difference was found for either eye.

Figures 6A and 6B show summary data for the horizontal and vertical components, respectively. For the horizontal component, a significant effect of viewing eye was found for a minority of sites in both strabismic monkeys (XT1, left eye = 3/7 sites, right eye = 1/7 sites; ET1, left eye = 2/5 sites, right eye = 0/5 sites). Similar results were obtained for the vertical component (XT1, left eye = 1/7 sites, right eye = 4/7 sites; ET1, left eye = 0/5 sites, right eye = 1/5 sites).

One might expect that the nonfixating eye would tend to move faster, but this was not always the case. For the horizontal component, there was one site, in right PPRF of monkey XT1, at which the fixating (right) eye moved faster. For the vertical component, there were two sites at which the right (fixating) eye moved faster (one in monkey XT1 and one in monkey ET1). For another site, the vertical component for the right eye was in opposite directions, depending on whether or not that eye was fixating the target.

**Stimulation of Abducens Nucleus**

It is possible that stimulation in the strabismic animals may have caused PPRF to "request" a conjugate movement that ended up being disconjugate due to abnormalities at the level of motoneurons, the plant, and/or eye muscles. To address this, we applied microstimulation to 20 sites in abducens nucleus.
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FIGURE 6. Summary data for the effect of fixation. For each site, linear fits were performed on the relationship between mean velocity and initial eye position. This was done separately for movements evoked when the left and right eyes were fixating. Each data point compares the y-intercepts for these fits for a given eye for a given site. Triangles represent data for monkey XT1, circles monkey ET1. Filled symbols indicate sites at which the regression lines relating velocity to initial eye position differed significantly, depending on which eye was fixating. Data for the left eye are shown in blue, the right eye in red. For a clear majority of sites there was no effect of fixation, though robust differences were found for some sites.

For the strabismic animals, note that the stimulation-evoked movements resulted in a decrease in the angle of strabismus for 12/14 sites. This result is the opposite of what would be expected if the eye misalignment were due solely to weakness of the muscles. For example, stimulation of right abducens nucleus in monkey ET1 always caused the right eye to move faster (lateral rectus) than the left (medial rectus). When linear fits were applied to the relationship between mean velocity and horizontal initial eye position, the y-intercepts were significantly different between the two eyes for 4/6 sites in monkey N1 and all sites in the strabismic animals (data not shown).

Figure 9 compares example sites for PPRF and abducens nucleus on the same side of the brain for monkeys XT1 (Figs. 9A, 9B) and ET1 (Figs. 9B, 9C). In Figure 9A, stimulation of right PPRF in monkey XT1 caused a consistent, robust rightward movement in the right eye, but no detectable horizontal movement in the left eye. Stimulation of abducens nucleus on the same side of the brain in the same animal caused the left eye to move faster (Fig. 9B). In Figure 9C, we see that stimulation of this site in left PPRF consistently caused the left eye to move faster. For all eight sites in right abducens nucleus of this animal, however, it was the right eye that moved faster (see example site in Fig. 9D). Thus, we see that PPRF stimulation did not simply mirror stimulation of abducens nucleus. For most sites, in fact, it was a different eye that moved faster.

DISCUSSION

The disconjugacy of movements evoked by PPRF stimulation strongly implies that premotor saccadic burst neurons are essentially monocular in strabismic monkeys. A similar idea has been proposed even for normal primates, though this has been highly controversial. A “pure” monocular model would involve individual MLBs targeting abducens motoneurons or internuclear neurons, but not both. However, it also is possible that individual MLBs target both, but not with the same connection weights. For example, in right PPRF of monkey XT1, perhaps the cells with stronger bursts activate abducens motoneurons more strongly than internuclear neurons, with the weaker bursting cells having the opposite tendency. In this way, a bias at the population level could lead to saccade disconjugacy even if single neurons send inputs to both eyes. Perhaps, at least early in postnatal development, the brain has the ability to alter these connection weights differentially to compensate for variations in the growth of orbital tissues and eye muscles between the two eyes. It also is necessary to consider whether or not our results could be accounted for by proposing that stimulation of PPRF in strabismic animals results in a conjugate command being sent to abnormal eye muscles and/or motoneuron pools. If this

six in monkey N1, nine in monkey ET1, and five in monkey XT1. Figure 7 shows example data from sites on both sides of the brain in all three animals. For the sites shown in monkeys N1 (Figs. 7A, 7B) and ET1 (Figs. 7C, 7D), the ipsilateral eye consistently moved faster. Note that, for the esotropic monkey, this had the effect of decreasing the angle of strabismus. A very different pattern was observed for the sites shown for monkey XT1. Regardless of whether the site was in left (Fig. 7E) or right (Fig. 7F) abducens nucleus, the left eye always moved faster.

Figure 8 compares mean velocity for the two eyes for all abducens stimulation sites. In the normal animal (black), evoked movements were conjugate for two sites, but for four others the ipsilateral eye moved much faster. The ipsilateral eye moved faster for all nine sites in the esotropic animal (red). For five sites in monkey XT1, the mean velocity for the left eye always was greater than that of the right (blue). This is striking for the three sites in right abducens nucleus in this animal, since this required indirect activation of the operated medial rectus muscle for the left eye, while movement of the right eye required only the direct activation of motoneurons for the lateral rectus (which was never operated on). Note that the contralateral eye never moved faster for any site in the other two animals (n = 15).

For the strabismic animals, note that the stimulation-evoked movements resulted in a decrease in the angle of strabismus for 4/6 sites in monkey N1 and all sites in the strabismic animals (data not shown). For most sites, in fact, it was a different eye that moved faster.
were the case, the direction of the disconjugacy should have been the same for the two structures. Instead, stimulation of PPRF and abducens nucleus usually produced opposite patterns of disconjugacy. It’s also worth noting that PPRF stimulation often evoked highly disconjugate movements in monkey ET1, even though we never operated on this animal’s eye muscles.

Taken together, these data supported the hypothesis that eye misalignment during a critical period of development (perhaps regardless of the cause) results in a cascade of abnormalities throughout the visual and oculomotor systems.

The present data also strongly implied that signals for the right and left eyes are at least partly separate in PPRF of strabismic monkeys, and that this structure outputs a disconjugate command.

A significant limitation of stimulation studies is the possibility of antidromic activation of upstream structures, activation of fibers of passage, and current spread to adjacent structures. Though we cannot exclude these possibilities entirely, they would not account for the markedly different results between normal and strabismic monkeys. We also have partially addressed these concerns by taking care to avoid

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**Figure 7.** Example data from six stimulation sites in abducens nucleus. *Left column:* sites in the left abducens nucleus. *Right column:* sites in right abducens nucleus. (A, B) For the two sites shown in monkey N1, the ipsilateral eye consistently moved faster. (C, D) For monkey ET1, the ipsilateral eye moved substantially faster. Note that the angle of strabismus always decreased during the course of stimulation. (E, F) For monkey XT1, the left eye always moved much faster than the right, regardless of which side of the brain was stimulated.
stimulating very ventral sites that may activate the abducens nerve, and by systematically varying the stimulation site along the rostrocaudal and mediolateral axes.

The relative numbers of abducens internuclear neurons and motoneurons may vary from site to site. For this reason, stimulation of a given site may cause the eyes to move at different velocities, even if physiologically realistic activation of the entire structure (if it were possible) would evoke conjugate movement. Although this kind of problem can never be avoided completely in any stimulation study, we have addressed this concern partially by comparing results between normal and strabismic monkeys, by taking care to avoid stimulating ventral sites that may activate the abducens nerve preferentially, and by systematically varying the stimulation site along the rostrocaudal and mediolateral axes. For monkey XT1, the contralateral eye moved much faster than the ipsilateral eye for all three abducens sites on the right side, a pattern that was never observed for any site in the other two animals. It is significant results were in subject XT1. This animal's exotropia depended on which eye was viewing the target. Most of the eye cells do not receive the same inputs for visually-guided movements. Adaptive processes may well strengthen the exotropia.

The present results do not exclude the possibility that neurons in supraoculomotor area (SOA) may modulate their activity during disconjugate, visually guided saccades in strabismus. In normal monkeys, some neurons in this area carry signals related to vergence velocity. Although to our knowledge there are no published quantitative analyses of SOA velocity neurons during saccades in strabismic animals, the tonic firing rates are correlated with the angle of strabismus. Nonetheless, the fact that stimulation of PPRF (which should have bypassed SOA) evoked highly disconjugate movements only in the strabismic monkeys points to the existence of abnormalities within brainstem circuits that control saccades.

We found several results to be surprising. First, while the disconjugacy of movements evoked by PPRF stimulation sometimes matched what was observed for visually-guided saccades (i.e., right PPRF in both strabismic animals), this was not always the case. The most notable inconsistency was observed for left PPRF in monkey XT1. In Figure 2, we see that this usually caused the left eye to move much faster than the right eye. For horizontal visually-guided saccades, however (see results), amplitudes were consistently larger in the right eye. However, it should be emphasized that PPRF stimulation evokes ramp eye movements rather than saccades. The velocity and amplitude of visually-guided saccades are governed by a local feedback loop that dynamically compares desired displacement with an estimate of current displacement. Thus, comparison of stimulation-evoked movements and visually-guided saccades is not straightforward. One possible explanation for our results is that separate pools of right and left eye cells do not receive the same inputs for visually-guided movements. Adaptive processes may well strengthen the command sent to one eye to compensate for abnormalities in PPRF, motoneurons, and the eye muscles. Stimulation, on the other hand, would send the same command to right and left eye cells. The present data, therefore, provided information about the movements that would occur if identical commands were sent to both eyes at the premotor level.

Second, the velocity of evoked movements sometimes depended on which eye was viewing the target. Most of the significant results were in subject XT1. This animal’s exotropia...
was consistently smaller when she viewed targets with the right eye. The pattern of results we observed might be explained if stimulation of some PPRF sites caused a relaxation of convergence. For sites in left PPRF, when the right eye is fixating, this would result in an enhancement of left eye velocity and a lower velocity of the right eye. It is not clear, however, why this would happen, or why the effect would be observed for some sites and not others.

Third, stimulation of abducens nucleus on either side of the brain caused the left eye to move faster in subject XT1. It is unclear why this should be the case, but it is possible that early surgical alteration of eye muscles resulted in unusual muscle growth patterns and/or unusual tuning of motoneurons. If it is the case that the left eye’s muscles are stronger, however, the fact that horizontal saccade amplitudes are consistently larger in the right eye indicated that saccade disconjugacy in strabismus cannot be solely a consequence of weak eye muscles.

Taken together, our data suggested a complex pattern of abnormalities within oculomotor circuitry in strabismus. Further work will be needed before a detailed picture emerges.

**Potential Explanations for Vertical Ramp Eye Movements**

Stimulation of PPRF might antidromically activate SC or descending branches from this structure on their way to vertical burst neurons in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). Activation of bifurcating axons might have occurred at a short enough latency to be consistent with our data. Even if this is the case, however, the fact remains that short latency, disconjugate vertical components were observed only in the strabismic monkeys. This still argues for abnormalities within saccade-specific pathways.

The PPRF contains at least two classes of saccade-related neuron, LLBNs and MLBs. Previous studies have shown that some LLBNs project to nucleus reticularis tegmenti pontis (N RTP), which projects to cerebellum. Activation of bifurcating axons might have occurred at a short enough latency to be consistent with our data. Even if this is the case, however, the fact remains that short latency, disconjugate vertical components were observed only in the strabismic monkeys. This still argues for abnormalities within saccade-specific pathways.

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**References**


