Published in final edited form as:
Strabismus. 2005 March ; 13(1): 33–41. doi:10.1080/09273970590910298.

Incomitance in Monkeys with Strabismus

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Abstract

Purpose—Rhesus monkeys reared with restricted visual environment during their first few months of life develop large ocular misalignment (strabismus). The purpose of this study was to describe 'A and V' patterns and DVD in these animals during fixation and eye movements and suggest that this form of rearing produces animals that are a suitable model to study mechanisms that might cause 'A/V' pattern incomitant strabismus and dissociated vertical deviation (DVD) in humans.

Methods—Eye movements were recorded during fixation, smooth-pursuit and saccades using binocular search coils in one monkey with esotropia, three monkeys with exotropia and one normal monkey.

Results—1) Monkeys reared with Alternating Monocular Occlusion or Binocular deprivation (tarsal plates intact) showed both horizontal and vertical misalignment during monocular and binocular viewing.

2) Large 'A' patterns were evident in 2 out of 3 exotropes while a 'V' pattern was observed in the esotrope.

3) Similar 'A/V' patterns were observed with either eye viewing and during fixation or eye movements.

4) The vertical misalignment, which consisted of the non-viewing eye being higher than the fixating eye, appeared to constitute a DVD.

Conclusion—Visual sensory deprivation methods that induce large strabismus also induce 'A/V' patterns and DVD similar to certain types of human strabismus. The source of the pattern strabismus could be central, i.e., altered innervation to extraocular muscles from motor nuclei, or peripheral, i.e., altered location of extraocular muscle pulleys.

Keywords

A/V patterns; dissociated vertical deviation; eye movement; monkey; incomitant strabismus; esotropia; exotropia

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INTRODUCTION

Incomitant strabismus is one in which the ocular misalignment varies with gaze position. One form of incomitant strabismus is 'A/V' pattern strabismus.[1,2] An increase in esotropia or decrease in exotropia in supraduction, as well as an increase in exotropia or decrease in esotropia in infraduction, is called an 'A' pattern. Similarly, an increase in exotropia or decrease in esotropia in supraduction, as well as an increase in esotropia or decrease in exotropia in infra-duction, is called a 'V' pattern.[3,4] As early as in 1951, it was suggested that more than 50% of patients with horizontal misalignment also show 'A/V' pattern incomitance.[2] Although the nomenclature primarily refers to variation of horizontal misalignment with vertical gaze, very often a vertical misalignment is present as well. Further, the vertical deviation usually varies with horizontal gaze, adding another dimension to 'A/V' pattern incomitant strabismus.[3,5,6] Depending on the type of misalignment and the variation with gaze angle, the source of the dysfunction causing A/V patterns has historically been attributed to underaction or overaction of extraocular muscles.[3] Overaction of the inferior oblique is most often associated with 'V' patterns while overaction of the superior oblique is associated with 'A' patterns.

More recently, the issue of overactivity/underactivity of oblique muscle has been the subject of controversy.[7,8] MRI evidence suggested that overaction of the inferior oblique was frequently absent in superior oblique palsy.[8] Another study showed that what was believed to be an inferior oblique palsy was actually a skew deviation in a set of patients with neurological disorders.[9] So it now appears that the concept of oblique muscle dysfunction is more a description of the state of eye alignment rather than a description of the mechanism that causes misalignment.[7]

Despite our advanced understanding of the anatomy and physiology underlying the oculomotor system, the physiological reason an extraocular muscle should appear to become over- or underactive is still unknown. Nothing is known about the central innervation that could result in appearance of overaction/underaction of individual muscles or yoke muscle pairs. Guyton and Weingarten[4] have proposed that loss of fusion leads to, among other things (for example horizontal misalignment), a torsional bias leading to torsional misalignment that effectively changes the plane of action of an extraocular muscle and produces the A/V patterns. More recent reports have pointed to a mechanical source for A/V pattern strabismus.[10–13] It has been suggested that static malpositioning or dynamic instability of extraocular muscle pulleys could result in 'A' and 'V' pattern strabismus. Studies examining MRI images of normal subjects and subjects with presumed oblique muscle dysfunction have shown that the placement of one or more rectus pulleys appears incorrect.[11,13–15] Further, using simulations of a mechanical plant (Orbit 1.8 Eidactics, San Francisco), Clark et al.[13] have shown that A/V pattern incomitancy can be simulated with inappropriately placed pulleys. In a recent imaging study, it was suggested that pulley and/or muscle instability could also contribute to the eye movements resulting in 'A/V' pattern strabismus.[11]

To gain a better understanding of the mechanism of incomitant (A/V pattern) strabismus in terms of physiologic mechanisms affected during development, it is useful to examine these patterns in an animal model. Here, we report that we are able to successfully produce 'A/V' patterns in a strabismic monkey model that involves visual sensory deprivation in the first few months of life. Some of the results have previously been presented in preliminary form.[16,28]

MATERIALS AND METHODS

Subjects and Rearing Paradigms

Behavioral data were collected from four strabismic (S1, S2, S3, S4) and one normal juvenile rhesus monkey (N1) (*Macaca mulatta*) weighing 3–7 kg. Monkeys with strabismus were reared at the Yerkes National Primate Research Center using visual sensory deprivation methods for the first 4–6 months of life designed to induce ocular misalignment but not affect visual acuity.[17] S2–S4 were reared using an alternating monocular occlusion (AMO) method, while S1 was reared using a binocular deprivation (tarsal plates intact) method (BDTP). Eye movement testing began when the animals were 1.5–2 years of age.

In the AMO rearing procedure, soon after birth (within the first 24 hrs), an occluding patch (either opaque goggles or dark contact lenses) is placed in front of one eye for a period of 24 hrs and thereafter switched to the fellow eye for the next 24 hrs. The patch is alternated daily for a period of 4–6 months. In this method, binocular vision is severely disrupted during the first few months of life, the critical period during which the monkeys normally develop proper eye alignment, stereovision and binocular sensitivity in the brain.[18–20] During rearing, the animals are checked every 2–3 hrs to verify that the occluding lens is in place. In our experience, the lens compliance is greater than 90%. The AMO method tends to induce large angles of esotropia or exotropia (>20 degrees in 2/3 animals) and ‘A’ or ‘V’ patterns. AMO monkeys do not develop amblyopia (personal communication, Dr. Ronald J. Boothe, visual acuity measured after the rearing period) and little latent or congenital nystagmus.[17,21]

Here we also report data from one animal that was reared with binocular deprivation with tarsal plates intact (BDTP). In this method, the animal’s eyelids were maintained in a closed state by tarsorraphy for the first three weeks of life. The tarsal plates contained inside the lids were left intact. Earlier we have reported that BDTP results in a large strabismus and small latent nystagmus.[17] When animals were reared with binocular deprivation but with tarsal plates removed, the latent nystagmus tended to be much larger, approaching saturation velocity.[17] Therefore, the binocular deprivation with tarsal plates removed preparation was not conducive to examining questions of misalignment during monocular viewing.

Surgical Procedures and Eye Movement Measurements

Following special rearing, the animals were allowed to grow normally (unimpeded vision) until they were 1.5–2 years of age when behavioral eye movement measurement experiments commenced. Sterile surgical procedures carried out under aseptic conditions using isoflurane anesthesia (1.25–2.5%) were used to implant a head stabilization post stereotaxically. In the same operation, a scleral search coil was implanted in one eye.[22] Later, in a second surgery, a second scleral search coil was implanted in the other eye. All procedures were performed in strict compliance with NIH guidelines and the protocols were reviewed and approved by the Institutional Animal Care and Use Committee at Emory University. Binocular eye position was measured using an electromagnetic search coil method (CNC Engineering, Seattle, WA).[23,24] Calibration of the eye coil signal was achieved by rewarding the monkey with 0.1 ml of juice when the animal looked at a small (0.25°) target spot that was rear projected on a tangent screen 57 cm away from the animal. Animals were trained for approximately 1–2 months before data collection. Calibration of each eye was performed independently during monocular viewing.

Experimental Paradigms, Data Acquisition and Analysis

The goal of the experiments was to describe the A/V patterns during fixation in the strabismic animals and also to examine alignment patterns during eye movements such as smooth-pursuit and saccades. In most experiments, the animals viewed monocularly. We also acquired some binocular viewing data to consider whether the animals had a DVD. The experimental paradigms used were: A) *Fixation*: Animals were required to fixate laser target spots located between ±20 degrees horizontally or vertically. B) *Smooth-Pursuit*: During smooth-pursuit, animals tracked sinusoidal horizontal or vertical motion of a laser target (0.2–0.3 Hz, ±10 degrees) during monocular viewing. C) *Saccades*:In saccadic experiments, the animals tracked step-like motion of a laser target that moved either horizontally or vertically to random locations between±20 degrees.

Binocular eye and target position feedback signals were processed with anti-aliasing filters at 200 Hz using 6-pole Bessel filters prior to digitization at 1 KHz with 16-bit precision. The data analysis using custom software built in MATLAB was aimed at quantifying the degree of horizontal and vertical misalignment during fixation and eye movements.

RESULTS

The animals used in this study have significant horizontal misalignment (Table 1), ranging from 10 to 30 degrees as measured during straight ahead gaze. In Table 1, we also summarize rearing conditions and some other factors relating to the state of the animals' strabismus that we have reported earlier.[17] Methodology relating to measurements of spatial acuity and stereo tracking has also been reported earlier.[17] The spatial acuity measured during binocular viewing was close to the range for normal infants.[25] Eye preference was considered absent because the animals tended to alternate the eye of fixation depending on target location.

A/V Patterns Observed During Fixation

All strabismic animals tested in this study showed incomitant strabismus that followed an 'A or V' pattern. Figure 1 shows a Hess screen chart illustration during monocular fixation for the four strabismic monkeys and the normal animal. In addition to the horizontal misalignment, all the strabismic animals also showed significant vertical misalignment. While the horizontal strabismus was either exotropia or esotropia, the vertical misalignment always consisted of the non-viewing or following eye being higher than the fixating eye (see panels of Fig. 1). The degree of horizontal or vertical strabismus was generally similar (though not equal) during either eye viewing, suggesting that paresis of a single muscle was not the cause of the strabismus. The change in horizontal and vertical misalignment with either vertical or horizontal gaze is apparent in all strabismic animals and absent in the normal animal. Thus, S1 and S2 showed a decrease in exotropia on up gaze and increase in exotropia on down gaze with either eye viewing ('A' pattern), and S3 showed an increase in esotropia on up-gaze and a decrease in esotropia during down gaze ('V' pattern). Subject S4, who had the smallest horizontal strabismus, showed a small 'V' pattern with the left eye viewing and a small 'A' pattern with the right eye viewing. In addition to the change in horizontal misalignment with vertical gaze, there was significant change in vertical misalignment with horizontal gaze. Even S4, who showed small change of horizontal misalignment with vertical gaze, showed a bigger change of vertical misalignment with horizontal gaze with the left eye viewing.

Our results suggested that the severity of the pattern strabismus induced using our rearing methods depends upon the amount of horizontal misalignment. Thus, from the Hess screen chart, we calculated an angle, θ, at the apex of the 'A' or 'V' pattern (see the legend to Fig. 1). This angular measurement was used to quantify the severity of the pattern strabismus. Thus, a larger angle measured at the apex of the 'A' or 'V' would indicate a more severe incomitancy, i.e., a greater change in horizontal misalignment with vertical gaze position. Figure 2 plots the pattern angle, θ, against the horizontal misalignment at primary gaze for all the animals. Data from the right eye viewing and the left eye viewing are pooled together after taking into account the sign (an exotropia was assumed positive and an esotropia was negative; also, an 'A' pattern resulted in a positive rotation angle while a 'V' pattern resulted in a negative rotation angle). The figure suggests that there is a correlation between the horizontal misalignment and the severity of the 'A/V' patterns in our animals. In other words, the A-pattern exotropia and the V-pattern esotropia observed in our animals raised with similar sensory deprivation methods could be due to a common central source.

A/V Patterns Observed During Eye Movements

While measurement of incomitancy during static fixation gives us information about neural circuits that control eye position (i.e., the step command), measurement of alignment during eye movements is necessary to provide information about central circuits that generate velocity commands (i.e., the pulse command) to move the eye. We therefore also examined variation of misalignment during horizontal and vertical eye movements. Figure 3 shows data collected during monocular (right eye viewing) horizontal and vertical smooth-pursuit or saccadic tracking in animal S2. Two points are to be noted in this figure. First, alignment patterns observed during smooth-pursuit or saccades are similar to those obtained during fixation (compare the horizontal and vertical misalignment in Figs. 1 and 3 for similar gaze angles). Figure 3 also shows that while the viewing eye (right eye) tracks the vertical or horizontal motion of the target laser spot with purely vertical or horizontal eye movements (smooth-pursuit or saccades), components of movement in the non-viewing left eye include both horizontal and vertical movement. Thus, eye movements in the non-viewing eye include an inappropriate vertical eye movement during horizontal tracking and an inappropriate horizontal eye movement during vertical tracking resulting in oblique eye movements and A/V patterns of strabismus. The inappropriate cross-axis component occurs simultaneously with the purposeful tracking eye movement, giving the appearance of simultaneous pulse and step components in both horizontal and vertical planes.

Alignment During Binocular Viewing

Our finding that the non-viewing eye was always higher than the viewing eye during monocular viewing suggested the presence of a DVD. We therefore also examined the misalignment during binocular viewing and compared it to monocular viewing. Figure 4, A and B shows fixation data at straight ahead for the esotropic animal S3 during OD, OS and OU viewing. Comparison of monocular and binocular viewing conditions show that during binocular viewing the animal adopted the same state as in the left eye viewing condition. Thus, when the target was straight ahead, the animal chose to fix the target with the left eye and the right eye is esotropic and hypertropic, similar to OS viewing.

Figure 4, C and D shows binocular viewing data from exotropic monkey S2 (left eye preference) during a saccadic tracking task. Panel C plots horizontal eye position and shows that the animal chose to fixate and track the step-like horizontal target motion with his left eye. The right eye is significantly exotropic. The vertical eye position traces (Panel D) show that significant vertical misalignment and cross-axis movements of the right eye are generated even during binocular viewing. Thus, this animal chose to fix the target with the left eye and replicated the behavior observed during monocular left eye viewing saccade tracking (i.e., right eye esotropic and hypertropic). We observed similar behavior in the other two animals where, during binocular viewing, they chose to adopt the state of one of the monocular viewing conditions. Thus, during binocular viewing of a straight ahead target, S1 adopted the OD viewing state and S4 also adopted the OD viewing state. In summary, during binocular viewing, the animal chose to fix with either one of the eyes, and the horizontal and vertical misalignment was similar to the corresponding monocular viewing condition. The eye of fixation usually depended on target location since the animals (except S2) did not show any eye preference.

DISCUSSION

One of the major goals of this report was to illustrate the efficacy of our rearing paradigms in inducing the incomitant ‘A/V’ pattern strabismus observed in many humans with strabismus. Thus, we have been able to show that a sensory deprivation method effective in inducing strabismus in rhesus monkeys is also effective in inducing an ‘A/V’ pattern. While the small number of test animals does not allow us to make claims on the reliability of the rearing paradigms in producing a specific pattern, it appears that ‘A’ pattern exotropia is the most common effect from our visual sensory deprivation rearing method. The observed ‘A’ pattern is very similar to ‘A’ pattern exotropia in humans as reviewed by Von Noorden and Campos.[3] The animal with ‘V’ pattern was similar to ‘V’ pattern esotropia in humans.[3] At this stage we are unable to determine why the same type of rearing sometimes gives rise to different forms of pattern strabismus (i.e., A or V pattern), although it appears from Fig. 2 that there is a relationship between the amount and type of horizontal misalignment and the pattern of the strabismus. The weakness in the correlation lies in the relatively small number of animals tested, particularly the number of esotropes. However, it would appear worthwhile to examine whether a similar correlation exists in the human data. We would predict that data-points from humans with ‘A’ pattern exotropia and ‘V’ pattern esotropia would lie on one linear regression line (as in Fig. 2 for our monkeys) while data-points from humans with ‘A’ pattern esotropia and ‘V’ pattern exotropia would lie on a second linear regression line that is orthogonal to the first one.

Our dynamic data from Figures 3 and 4 suggest that pulse and step components driving the tracking are also present in the inappropriate cross-axis component of the eye movement and that saccadic and smooth-pursuit eye movements are equally affected. One reason for this finding could be that the source of the cross-axis component is a miscalibration of central pre-motor circuits that separately control horizontal and vertical eye movements (e.g., cross-talk between horizontal and vertical neural integrators). Alternatively, the plane of action of the extraocular muscles in the non-viewing eye could be altered, due either to inappropriately placed pulleys or a torsional bias.

The question of whether the vertical misalignment observed during monocular and binocular viewing is a DVD is relevant. While a common characteristic of DVDis that the vertical misalignment is absent during binocular viewing, it has been shown to not always be true.[26] Sometimes, DVD is manifest while the patient is inattentive or conversely can appear during binocular viewing when the patient tries hard to fixate, as during reading. In our animals, the horizontal misalignment is very large. Also, the AMO rearing paradigm prevents development of any fusional capability. In this condition, therefore, we believe that the DVD is likely to remain manifest even during binocular viewing. We therefore propose that our rearing paradigm, in addition to horizontal misalignment and A/V patterns, also produces a manifest DVD. Further experiments that measure torsion would be necessary to test the hypothesis of Guyton et al.[26] that DVD is a result of a mechanism that suppresses cyclovertical latent nystagmus. Neuro-physiological experiments can now attempt to examine the locus of Bielschowsky’s idea of vertical vergence or alternatively the source of the vestibular imbalance that mediates the generation of DVD.[26,27]

So what could be the source of the ‘A/V’ patterns in our animals? Could the source be peripheral, i.e., could pulley heterotopy or muscle instability cause A/V patterns as suggested by MRI data in human patients? Alternatively, could it be central, i.e., due to innervational factors?[28] Finally, it could certainly be a hybrid problem involving both peripheral and neural factors. Imaging and neurophysiological experiments that address each of these factors would be necessary to make this determination. Guyton and Weingarten’s[4] idea of a torsional bias being the root cause for apparent oblique muscle dysfunction is plausible in some patients and neurophysiological experiments in our animals, examining structures that control torsion like the Interstitial Nucleus of Cajal, could be used to test their theory.[29] Only a few studies have examined the torsional eye movements in strabismus in detail.[30–33] There is some evidence for a problem in torsional control from reports suggesting that the primary position in relation to Listing’s law seems deviated in patients with trochlear nerve palsy compared to normals.[34] The etiology of the strabismus could possibly be helpful in determining the source of ‘A/V’ pattern incomitant strabismus. Thus, patients with strabismus due to orbital malformations or degenerative muscular disease could show ‘A/V’ strabismus due to mechanical problems such as pulley mislocalization.[11] Also, those patients who show no apparent anatomic evidence of oblique muscle overaction in a MRI could also fall into this category.[8] On the other hand, patients with strabismus due to congenital sensory problems, for example, could show ‘A/V’ patterns due to an innervational source that may or may not involve torsion.

SUMMARY

In summary, we have shown that monkeys reared with Alternating Monocular Occlusion or Binocular form-vision deprivation developed ‘A/V’ pattern incomitant strabismus. In all the strabismic monkeys, a vertical misalignment that resembled a DVD also accompanied the horizontal misalignment. The observed patterns were similar to clinical descriptions of overacting or underacting oblique muscles, more recently described as over-elevation/under-elevation or over-depression/under-depression in adduction. Alignment patterns during dynamic eye movements were similar to alignment patterns observed during static fixations, showing the presence of pulse and step components in the cross-axis movements. Imaging experiments examining pulley heterotopy and neurophysiological experiments examining motoneuron activity are necessary to distinguish between peripheral and central factors that might contribute to generation of A/V patterns of strabismus in our animals.

Acknowledgements

We would like to thank Tracey Brozygna for expert technical assistance and Alcides Fernandes for help with the surgery in animal S1. The work was supported by NIH grants EY015312 (VED), EY06069 (MJM), and RR00165 (Yerkes base grant).

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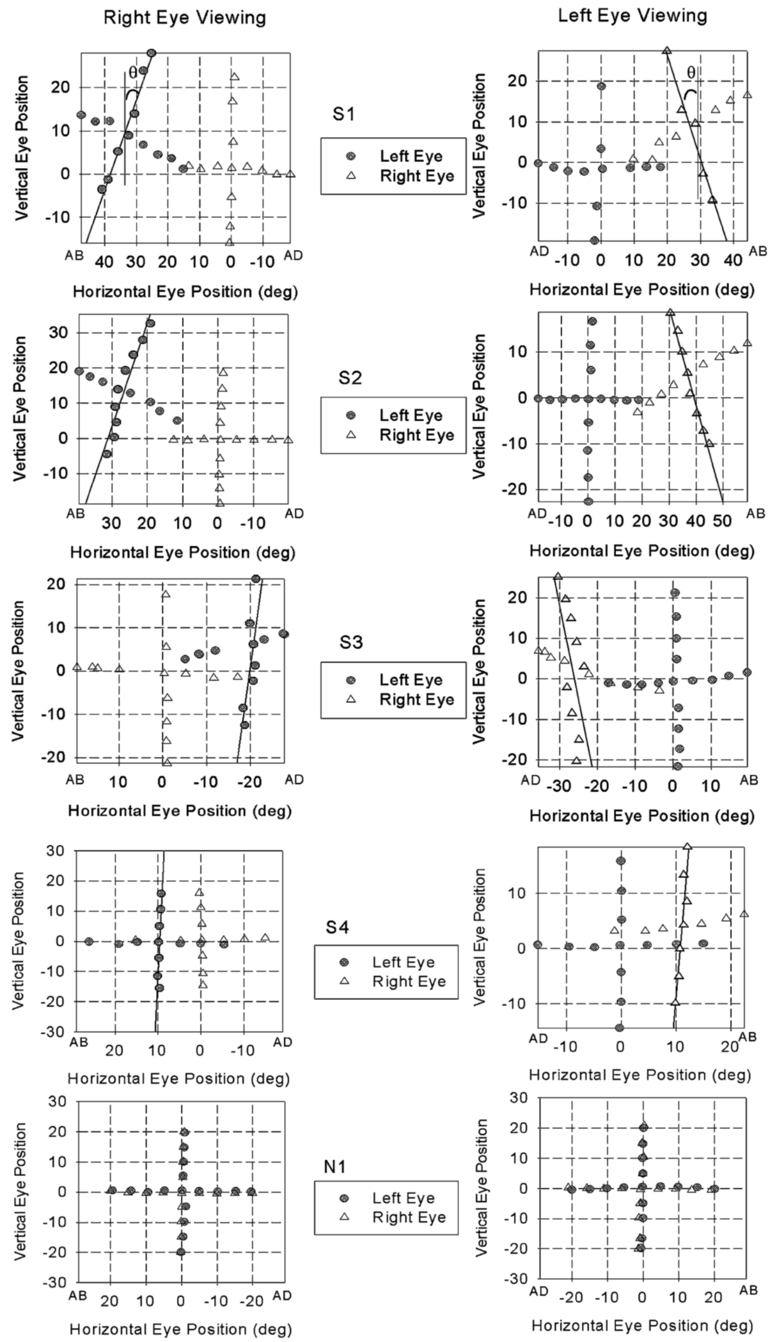

FIGURE 1.

Hess screen chart showing alignment patterns during monocular viewing in strabismic monkeys S1–S4 and in the normal monkey N1. The left column shows alignment data collected during right eye viewing and the right column shows alignment data collected during left eye viewing. Abduction is positive and Adduction is negative. Upward eye positions are positive and downward eye positions are negative. All the strabismic animals suffered from significant horizontal and vertical misalignment during either eye viewing. The horizontal misalignment was either an exotropia (S1, S2, S4) or an esotropia (S3). The following eye was always higher than the fixing eye suggesting the presence of DVD. In each case, there is a change in horizontal misalignment with vertical gaze position resulting in an ‘A’ or ‘V’ pattern. In addition, all the strabismic animals also showed a change of vertical misalignment with horizontal gaze position. The normal animal showed no misalignment and no evidence for 'A/V' patterns. The dark line shown in each plot is a linear regression of the vertical gaze positions of the non-viewing eye. The angle 'θ' as shown in the top panel of the figure was used to quantify the severity of the incomitance.

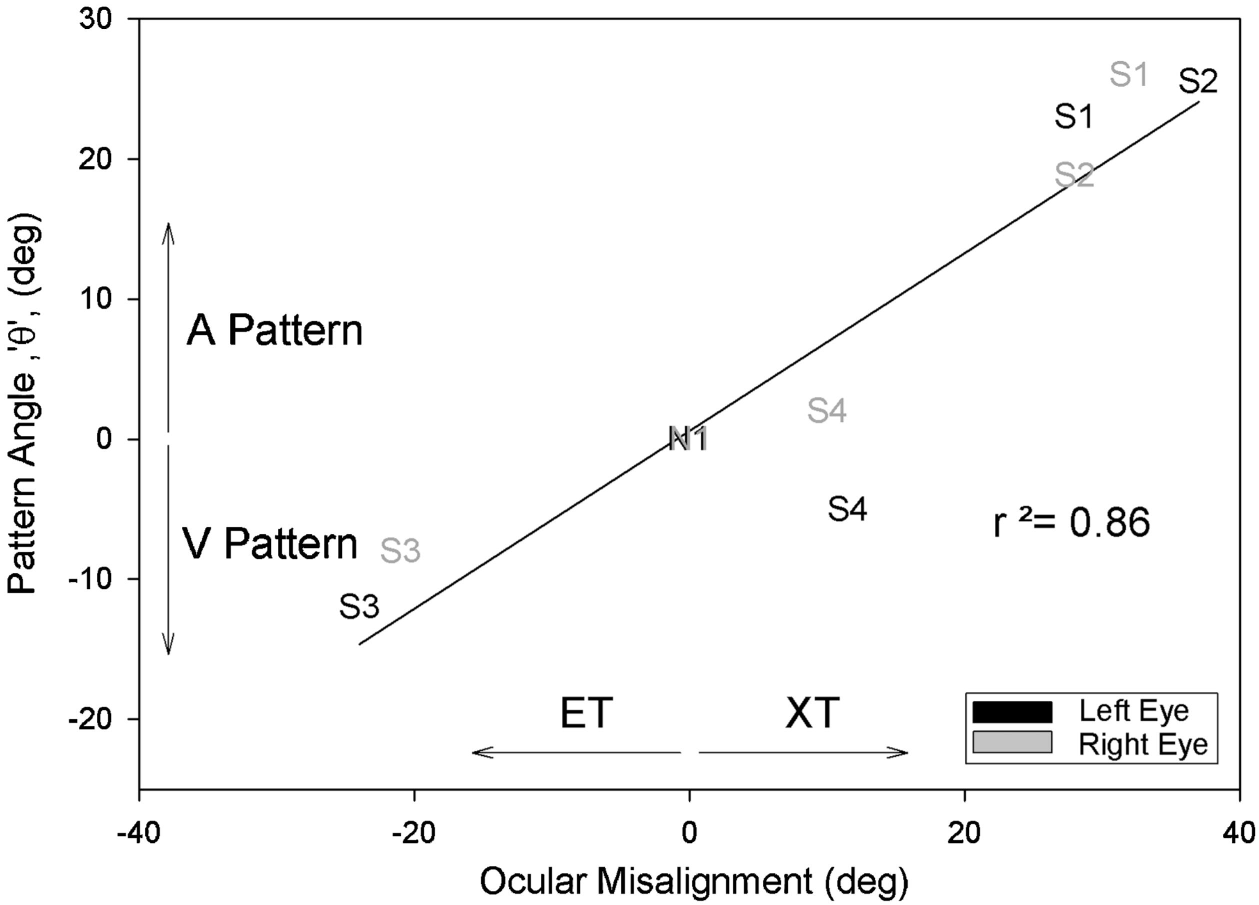

FIGURE 2.

Correlation of degree of A/V pattern incomitance with initial horizontal misalignment. The horizontal ocular mis-alignment during primary gaze is plotted vs. the degree of A/V pattern strabismus (measured as the angle at the apex of the ‘A’ or ‘V,’ = ‘θ’). On the X-axis, exotropia is plotted as positive and esotropia as negative. On the Y-axis, the ’A’-pattern results in positive angles, while a ‘V’ pattern results in negative angles. A significant correlation was discovered between the degree of horizontal misalignment (ranging from esotropia to exotropia) and the angular subtense (‘θ’) of the A/V pattern.

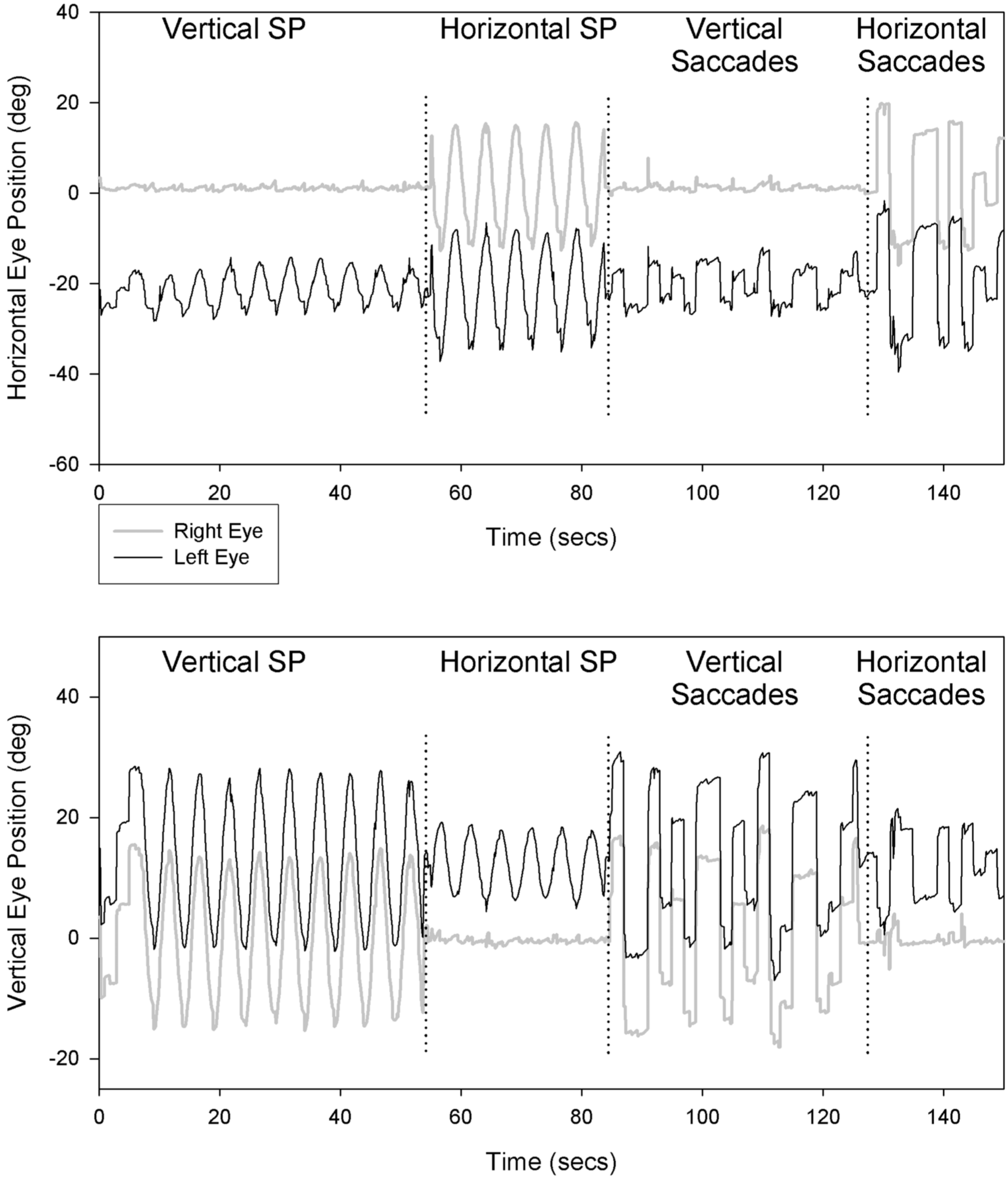

FIGURE 3.

A time series of data collected in exotropic animal S2 during horizontal and vertical saccades and smooth-pursuit (SP) while viewing with the right eye. The top panel shows horizontal position of the viewing (right) and non-viewing (left) eyes. The bottom panel shows vertical position of the viewing (right) and non-viewing (left) eyes. In each case, the viewing eye makes purely horizontal or vertical saccades or smooth-pursuit while the non-viewing left eye shows an inappropriate cross-axis component. Also, the magnitude of horizontal and vertical misalignment for specific gaze positions is similar to that obtained during static fixation as shown in Figure 1. The saccadic data shows that the cross-axis component includes both pulse and step components that occur simultaneously with the purposeful eye movement. Positive values indicate rightward or upward eye positions.

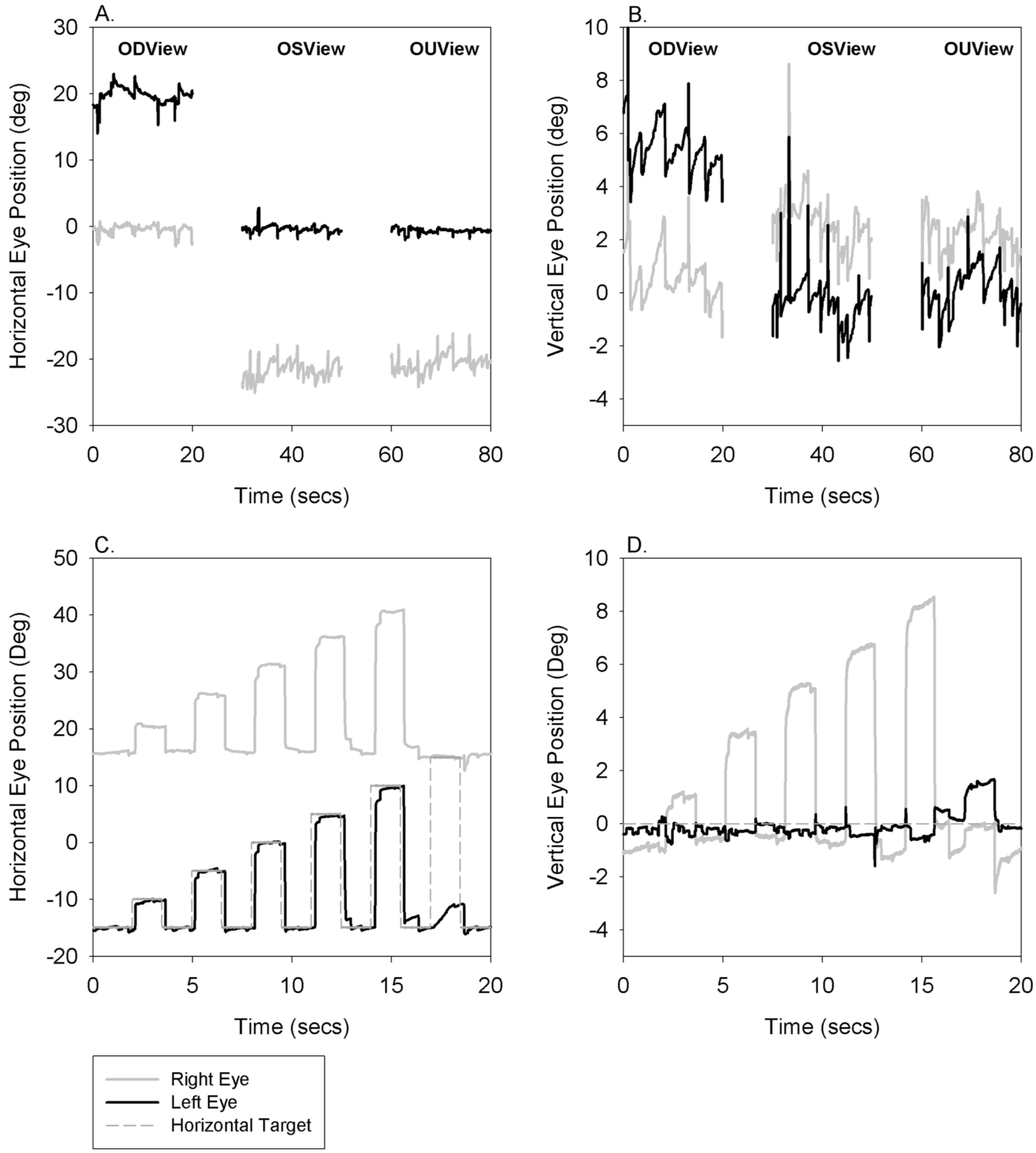

FIGURE 4.

(A + B). Panels A and B compare the horizontal and vertical misalignment observed during monocular and binocular viewing in animal S3. Horizontal and vertical misalignment in the OU condition is similar to the OS condition in monkey S3. (C + D). Panels C and D show horizontal and vertical eye position data during a saccade tracking sequence in monkey S2 as he viewed the target binocularly. This animal also chose to fixate and track the target with his left eye. The right eye shows horizontal and vertical misalignment and also cross-axis movements.

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TABLE 1

Summary of Rearing Paradigms and Psychophysical Measures

Name	Rearing condition	Duration of special rearing (months)	Alignment	Spatial acuity (OU viewing)	Eye preference	Binocular steroe tracking
S1	BDTP	21 days	30 deg XT	Data not available	None	Data not available
S2	AMO	6	29 deg XT	8.3 cpd at week 16	Left	Data not available
S3	AMO	4	21 deg ET	4.1 cpd at week 16	None	Data not available
S4	AMO	6	8 deg XT	5.1 cpd at week 14	None	Absent
Control	Normal	0	Orthotropia	Data not available	None	Present

BDTP = Binocular deprivation with tarsal plates intact; AMO = Alternate Monocular Occlusion; XT = exotropia; ET = esotropia; cpd = cycles/degree.