Comparison of naso-temporal asymmetry during monocular smooth pursuit, optokinetic nystagmus and ocular following in strabismic monkeys

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Abstract

Purpose: Under monocular viewing conditions, humans and monkeys with infantile strabismus exhibit asymmetric naso-temporal (N/T) responses to motion stimuli. The goal of this study was to compare and contrast these N/T asymmetries during three visually mediated eye tracking tasks – optokinetic nystagmus (OKN), smooth-pursuit (SP) and ocular following (OFR).

Methods: Two adult strabismic monkeys were tested under monocular viewing conditions during OKN, SP or OFR stimulation. OKN stimulus was unidirectional motion of a 30°X30° random dot pattern at 20, 40 or 80 °/s for 1 minute. OFR stimulus was brief (200ms) unidirectional motion of a 38°X28° whitenoise at 20, 40 or 80 °/s. SP stimulus consisted of foveal step-ramp target motion at 10, 20 or 40 °/s.

Results: Mean nasalward steady state gain (0.87 ± 0.16) was larger than temporalward gain (0.67 ± 0.19) during monocular OKN (p<0.001). In monocular OFR, the asymmetry is manifested as a difference in OFR velocity gain (nasalward: 0.33 ± 0.19, temporalward: 0.22 ± 0.12; p = 0.007). During monocular SP, mean nasal gain (0.97±0.2) was larger than temporal gain (0.66±0.14; p<0.001) as well as the mean nasalward acceleration during pursuit initiation (156 ± 61 °/s^2) was larger than temporalward acceleration (118 ± 77 °/s^2; p = 0.04). Comparison of N/T asymmetry ratio across the three conditions using ANOVA showed no significant difference.

Conclusions: Naso-temporal asymmetries are identified in all three visual tracking paradigms in both monkeys with either eye viewing. Our data are consistent with the current hypothesis for the mechanism for naso-temporal asymmetry that invokes an imbalance in cortical drive to brainstem circuits.

Introduction

A normally functioning visual-oculomotor system is able to maintain a relatively stable image of the object of interest on the fovea during self or object movement (Leigh and Zee 2006). Visual tracking and vestibular mechanisms are primarily responsible for gaze holding during target or self-motion (Miles 1998). Inability to accurately track a moving object produces motion blur, which may impair visual acuity (Westheimer and McKee 1975). Visual motion information originating in the left or right visual hemi-field is processed in contralateral visual cortical areas and thereafter brainstem structures and eventually results in a visually mediated tracking eye movement such as smooth-pursuit, ocular following or optokinetic nystagmus (Mustari, Ono et al. 2009) . The type of visually mediated tracking eye movement depends on characteristics of the visual stimulus such as stimulus size and stimulus duration.

Human and non-human primate infants show eye misalignment and disconjugate eye movements at birth (Boothe, Dobson et al. 1985). Binocular co-ordination and fixation is acquired during post-natal development as long as the visual and oculomotor experience is relatively undisturbed (von Noorden and Campos 2002). Disruption in sensory or motor fusion during the early critical period of development likely leads to a cascade of neural events eventually resulting in visual problems such as amblyopia and lack of binocular vision and oculomotor problems such as misaligned eyes or strabismus (Kiorpes 2015, Das 2016). In addition to eye misalignment, strabismus manifests with several associated features such as A/V patterns, dissociated deviations, alternating fixation, fixation instability and nystagmus (Das 2016). Another visual-oculomotor disruption associated with strabismus is with the processing of visual motion

information leading to disorders in visual tracking eye movements. Thus the classic description of naso-temporal asymmetry (N-T asymmetry) for humans and monkeys with strabismus or amblyopia, refers to the condition where under monocular viewing conditions they show robust visual and oculomotor responses for targets moving in the nasalward direction but weak to no response for targets moving in the temporalward direction (Tychsen and Lisberger 1986, Yildirim and Tychsen 2000, Foeller, Hasany et al. 2006, Ghasia and Tychsen 2014). When tested under monocular viewing conditions, horizontal optokinetic eye movements have been reported to be abnormal in adult strabismic subjects (Fu and Boothe 2001). Study in our lab on strabismic monkeys have also reported a naso-temporal asymmetry during OKN (Agaoglu, Agaoglu et al. 2015). In other reports on strabismic monkeys, naso-temporal asymmetry has been reported in smooth pursuit responses (Kiorpes, Walton et al. 1996, Tychsen 2007, Tychsen, Richards et al. 2008, Mustari and Ono 2011) as well as during ocular following, which is an open loop involuntary response to a short-duration full-field visual stimulus.

Although the concept of naso-temporal asymmetry is well described, it is not clear whether different visual tracking paradigms elicit the same or different amounts of asymmetry. Such a determination can only be performed in a study design wherein the same subjects are tested under all three conditions and to our knowledge such a study has not yet been undertaken. So, the objective of the current study was to quantify and compare the visual tracking responses of sensory induced strabismic juvenile monkeys during monocular smooth pursuit, ocular following response (OFR) and OKN. Results from this study have been reported before in abstract form (Joshi, Agaoglu et al. 2013).

Methods

Subjects and surgical procedures

      The study was performed on two strabismic juvenile rhesus monkeys (Macaca Mulatta). Strabismus was previously induced by disrupting binocular vision for four months starting the first day following birth using either daily alternating monocular occlusion with opaque contact lenses (monkey S1) or using 20 diopter Fresnel prisms oriented vertically in front of one eye and horizontally in front of the other eye (monkey S2)(Crawford and von Noorden 1980, Crawford, Harwerth et al. 1996). After 4 months of rearing with either technique the monkeys were allowed to grow normally with unrestricted vision till the age of 4 years before starting eye movement testing. At this time, the monkeys underwent separate surgical procedures to implant a head post for fixing the head during the experiments and scleral search coils in the two eyes for precisely recording eye movements (Judge, Richmond et al. 1980, Adams, Economides et al. 2007). Refer to our previous publications for further details on rearing and surgical procedures (Das, Fu et al. 2005, Joshi and Das 2011, Joshi and Das 2013). All surgical procedures were carried out in strict compliance of National Institute of Health (NIH) and the Association for Research in Vision and Ophthalmology (ARVO) guidelines for animal care and were reviewed by the Institutional Animal Care and Use Committee at the University of Houston.

Experimental paradigms and visual stimuli

      Three different visual tracking stimuli were presented to elicit optokinetic nystagmus (OKN), ocular following responses (OFR) and smooth-pursuit respectively.

The visual stimuli for smooth pursuit and OKN were projected on a large translucent tangent screen (32" x 32") placed at 60 cm distance in front of the monkey using a DLP projector running at 60Hz (Dell 3300mp). The OFR stimulus was presented on a 21" Viewsonic CRT monitor (G225f) place at distance of 60cm in front of the monkey. Visual stimuli were generated using custom-built programs in Matlab and a visual stimulus generator graphic card installed in a PC (VSG2/5 for Windows; Cambridge Research Systems, Kent, UK). During each visual tracking test, the animals viewed monocularly with either their right or left eye. Monocular viewing during OKN and OFR was enforced by occluding the fellow eye with an opaque occluder. During SP, the animals' wore a computer controlled LCD shutter goggle to enforce monocular viewing.

The stimulus for OKN experiments was a full field white noise pattern (30°x30°) which was moved horizontally (leftward or rightward) at 20, 40 or 80°/sec velocity for a duration of 60 sec and was thereafter followed by a blank period of 120sec.

During OFR testing, saccade targets were presented at random locations within ±30° horizontal and ±20° vertical range followed by a target jump to a straight ahead (center) location. As soon as the monkey made the centering saccade, a 38°X28° (full-field) noise pattern was moved horizontally (rightward or leftward) for a duration of 200msec at a velocity of 20, 40 or 80 °/sec. The strategy of triggering the full-field motion stimulus to immediately follow a centering saccade avoids saccadic intrusion during the OFR response and also induces a robust OFR eye movement (Kawano and Miles 1986, Miles, Kawano et al. 1986).

The smooth-pursuit task involved tracking step-ramp target motion (constant velocity target motion). In these experiments, the animals' visually tracked a 0.5° target

that moved either leftward or rightward at a velocity of 10, 20 or 40°/sec. In the step-ramp paradigm, at the beginning of each trial, the target briefly steps in a direction opposite to subsequent target motion and the amplitude of the step is adjusted so as to eliminate the initial catch-up saccade (Rashbass 1961).

Data analysis

Horizontal and vertical eye and target position signals were processed with analog anti-aliasing filters (Krohn-Hite; Krohn-Hite Corporation, Brockton, MA) at 400 Hz before digitization at 1 kHz with 12-bit precision (Alpha-Lab System; Alpha-Omega Engineering, Nazareth, Israel). Data analysis was performed using custom software routines (MATLAB; Mathworks Inc., Natick, MA). Eye velocity data were obtained from eye position data using central difference algorithm and position and velocity vectors were further filtered with a digital finite impulse response filter with a passband of 0-80Hz. Data analysis involved comparing parameters for nasalward and temporalward responses to target motion for each paradigm.

For OKN analysis, slow phase velocities were extracted from the slope of each slow-phase identified in the position data and thereafter OKN gain was calculated as the ratio of the steady state OKN velocity to the stimulus velocity. Mean OKN gain values were calculated for nasalward and temporalward stimuli at different speeds and viewing conditions (right eye or left eye). For OFR analysis, trials were sorted according to stimulus direction and velocity, and any trial contaminated with saccadic intrusion was discarded. OFR amplitude was calculated as the change in eye position over an 80msec time window commencing from the time of latency onset. OFR gain was

calculated as the ratio of mean eye velocity over 60-90msec period after stimulus onset to target velocity. For analysis of smooth-pursuit eye movements, trials were sorted according to target direction, target speed and viewing eye. Trials contaminated with saccades away from the target were eliminated from the analysis. For each trial, smooth pursuit latency was calculated as the time after stimulus onset when the eye velocity exceeded the baseline eye velocity (calculated over a 50ms time window prior to stimulus onset) by more than three standard deviations. We also calculated smooth pursuit gain, calculated as the ratio of steady state eye velocity to target velocity and peak acceleration that occurred during initiation of smooth-pursuit.

A two-way ANOVA, performed to determine the effect of velocity and direction factors on the dependent variable of gain, revealed no significance of velocity in all the three paradigms. Hence, the statistical analysis of data consisted of using paired t-test for comparison between mean nasal and temporal parameters for all three tracking responses, unless otherwise specified, with a significance value of $p<0.05$. One-way ANOVA at a significance level of 0.05 was used to compare the nasal-temporal gain ratio across the tracking paradigms.

Results

Monkey S1 showed an esotropic deviation of ~37° during left eye viewing and ~30° during right eye viewing. S2 showed an exotropic deviation of ~25° during left eye viewing and ~30° during right eye viewing. In addition, they both showed evidence of a Dissociated Vertical Deviation that measured ~2° (S1) and ~3° (S2) during straight ahead viewing. Both animals also showed a small fusion maldevelopment nystagmus of

~1 °/sec during fixation.

Optokinetic Nystagmus

Figure 1A shows a typical nasalward (top figure) and temporalward (bottom figure) position response for a 20 °/sec optokinetic stimulus in monkey S1 fixating with the left eye. In the top figure we see robust slow phases during nasalward (rightward) OKN and weaker responses for temporalward (leftward) OKN. Figure 1B shows the average slow phase velocity responses from monkey S2 for all stimulus speeds and both directions with the right eye viewing the target. For each speed, the nasalward responses (leftward) are larger than temporalward (rightward) responses. This asymmetry is also evident when we compare temporalward to nasalward OKN gains, for all speeds in both monkeys S1 and S2 (Fig 2). All the points in the scatter plot lie above the midline indicating larger nasalward gain than temporalward gain. Statistical comparison of the mean gain values (Nasalward: 0.87 ± 0.16; Temporalward: 0.67 ± 0.19) indicated a significant nasalward bias ($p < 0.001$).

-Figure 1 near here-

-Figure 2 near here-

Ocular Following Response

Ocular following responses are involuntary open loop responses to sudden motion of full field stimulus and are typically elicited with latencies less than 100msec. We observed similar response characteristics in strabismic monkeys for all stimulus speeds and in both directions. Figure 3 shows the average OFR velocity response for

different speeds in both nasalward and temporalward direction under monocular viewing conditions. The top row shows responses obtained from monkey S1 and bottom row shows response from monkey S2 under the left eye viewing condition (left column) and right eye viewing condition (right column). We did not find any difference in the OFR onset latency for both directions (mean nasalward OFR latency: 87 ± 1.0 msec; mean temporalward OFR latency: 86 ± 0.7; p =0.59). However nasalward and temporalward OFR gains (Figure 4) did indeed show significant differences in both monkeys. Nasalward response gains were significantly larger than temporalward gains (Mean OFR gain - nasalward: 0.33 ± 0.19, temporalward: 0.22 ± 0.12; p = 0.007).

-Figure 3 near here-

-Figure 4 near here-

Smooth Pursuit response

Smooth pursuit responses were elicited for step-ramp stimuli moving in either leftward or rightward direction thereby eliciting nasalward or temporalward response during monocular viewing. Figure 5 shows the left eye position traces from several trials in which monkey S1 tracked the 20°/sec stimulus moving temporalward (panel A) and nasalward (panel B). Several more catch-up saccades are interspersed while tracking the target moving in the temporalward direction compared to the nasalward direction, which is evidence of lower tracking gains. Figure 6 shows the average velocity responses from monkey S1 (top row) and S2 (bottom row) at stimulus speeds of 10, 20 and 40 °/sec under left eye viewing (left column) or right eye viewing conditions (right column). It can be readily appreciated that in both monkeys the nasalward responses

were robust compared to the temporalward responses with either eye viewing the target. Forced paired t-test (non-normal data) for SP onset latency showed no significant difference in the onset latencies between nasalward and temporalward tracking (mean nasalward SP latency: 107 ±9.7 msec; mean temporalward latency: 124±34.1 msec;; p = 0.09). Comparison of initial acceleration also showed significant nasalward bias in both monkeys (Figure 7; Mean initial acceleration - nasalward: 156 ± 61 °/s^2; temporalward: 118 ± 77 °/s^2; p = 0.04). Finally, significant differences were also identified in the steady-state tracking gain values for nasalward responses compared to the temporalward responses in both the monkeys at all speeds (Mean SP gain - nasalward: 0.97±0.2, temporalward: 0.66±0.14; p<0.001, Figure 7).

-Figure 5 near here-

-Figure 6 near here-

-Figure 7 near here-

Comparison between the three tracking paradigms

Qualitatively, our results showed naso-temporal asymmetry with bias towards stimulus moving in the nasal direction under all three visual tracking conditions of smooth pursuit, OKN and OFR. In order to develop a quantitative comparison, we calculated a nasal-temporal gain ratio for each condition tested. Figure 8 shows a box plot with median and 25th and 75th percentile of the naso-temporal ratio for the three paradigms. Statistical comparison of the ratios using a Kruskal-Wallis ANOVA on ranks showed no significant difference (p = 0.62).

-Figure 8 near here-

DISCUSSION

The main finding in this study was that naso-temporal asymmetry could be identified during all visual tracking eye movements (smooth-pursuit, OKN and ocular following). Further, comparison of degree of N/T asymmetry across the three visual tracking tasks using an index derived from ratio of nasalward gain to temporalward gain indicates no significant difference.

Comparison of N/T asymmetry during visual tracking tasks

Our results show that naso-temporal asymmetries in eye velocity responses are similarly manifested in strabismic monkeys across the three different visual tracking paradigms viz: OKN, OFR and smooth pursuit. However, each of these paradigms poses certain unique advantages and disadvantages. Unlike smooth-pursuit, OKN and OFR are both reflexive eye movements and therefore do not require cooperation of the subject. However they both require large field presentation of stimuli and OKN further requires some mechanism for continuous presentation of the stimulus. The advantage of SP testing is the ability to examine additional factors such as initial acceleration that are also sensitive to asymmetry.

No difference was observed in the onset latencies for the nasal or temporal responses in all three tracking condition. This suggests that the directional asymmetry is not influenced by afferent processing delays. Also no statistical difference was observed for N/T gain ratios between the three tracking conditions suggesting that the deficits arises in parts of the neural pathway common to all three tracking eye movements;

perhaps early visual motion processing areas in the brain such as in the striate (V1) and extra-striate visual cortex (MT and MSTd) which play a central role in foveal or parafoveal motion detection.

Implications on mechanisms for N/T asymmetry

N/T asymmetry is not restricted to strabismus and amblyopia. A similar naso-temporal asymmetry is observed in normal infants during monocular OKN testing (Fuchs and Mustari 1993) (Boothe, Dobson et al. 1985). The directional bias for nasalward response tends to resolve with the development of the cortical visual pathways by around 6 months of age (Atkinson 1979, Lewis, Maurer et al. 2000). In another study, Boothe and colleagues have used monocular visual evoked potential (MVEP) responses to vertically oriented gratings moving horizontally in either nasal or temporal direction to show the presence of naso-temporal asymmetry in infant monkeys and the progressive decrement in the asymmetry with normal development by the end of ~6 weeks (equivalent to ~6 months in human) (Brown, Wilson et al. 1998). In infancy, the monocular OKN response is governed by a subcortical direct projection from the retina to the contralateral NOT (nucleus of the optic tract), a structure that responds preferentially to ipsiversive motion (Distler, Vital-Durand et al. 1999). During the course of normal binocular development, a cortical motion sensitive pathway (MT/MST) projecting to subcortical areas (NOT) assumes importance over the direct subcortical circuit. So one hypothesis could be that the naso-temporal asymmetry seen in adult strabismus is due to lack of development of the cortical pathway and the preservation of the direct subcortical pathway (for nasalward responses). Tychsen has suggested an

alternative model for N/T asymmetry wherein rather than preservation of the direct subcortical pathway, loss of binocular connections from cortical areas (MT/MST) to brainstem areas (NOT and DLPN-dorsolateral pontine nucleus) results in asymmetric responses to monocular stimuli (Tychsen 2007, Tychsen, Richards et al. 2008, Tychsen, Richards et al. 2010). Our finding that the naso-temporal asymmetry is similar during OKN, OFR and SP supports this later hypothesis, as it is known that volitional smooth-pursuit is subserved by a cortico-ponto-cerebellar pathway involving MT/MST in cortex, DLPN/NRTP (nucleus reticularis tegmenti pontis) in the pons and flocculus in the cerebellum. Therefore disruption of binocularity in MT/MST and disruption of signaling from MT/MST to brainstem areas important for visual tracking such as NOT and DLPN can lead to similar N/T asymmetry during OKN, OFR and SP.

Study Limitations

Although our stated goal was to compare N/T asymmetry across the three visual tracking eye movements, we cannot be certain that the stimuli that we provided to the optokinetic, ocular following and smooth-pursuit systems are equivalent. We chose to use 10, 20 and 40 °/sec stimulus velocities for pursuit and 20, 40 and 80 °/sec stimulus velocities for OKN and OFR since these velocities produce robust responses in the normal system and the expectation is that the response gains are linear within this range of stimulus velocities. Also comparison of N/T gain ratios helps to minimize differences across speeds. A technical issue with the OKN stimulus was that it did not encompass the entire visual field. However previous studies have shown that the OKN response is dominated by motion in the central 10° of the visual stimulus and our

stimulus was significantly larger than this value. Another technical issue with the OFR

stimulus was we were unable to obtain robust responses (nasalward or temporalward)

when we used the projector/tangent screen combination that we used for SP or OKN.

Therefore we proceeded to use a CRT monitor for delivering the OFR stimulus. Despite

these apparent technical differences in visual stimulation, we indeed found that the N/T

gain ratios were fairly similar across the different paradigms.

Acknowledgements:

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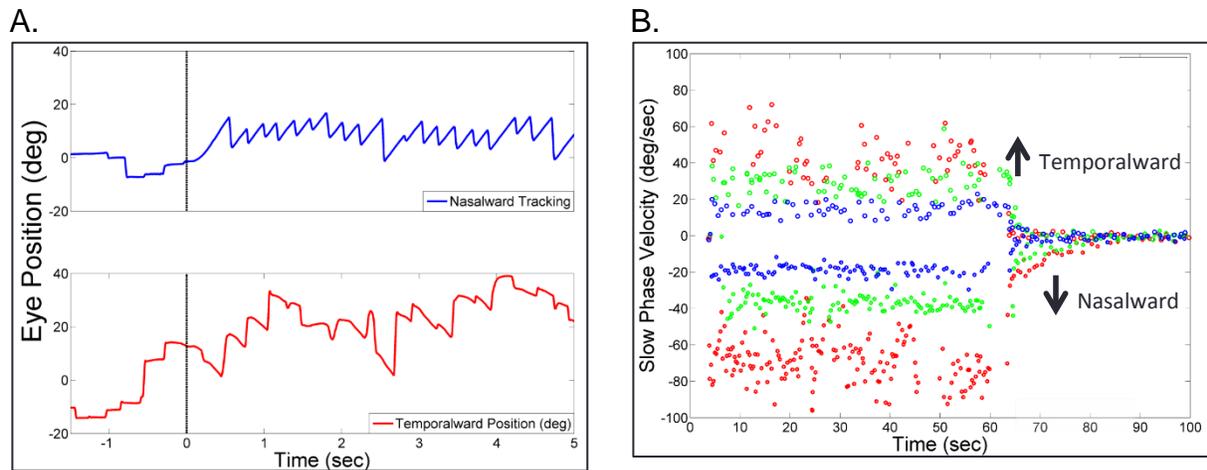
Figure 1. Panel A shows eye position response for nasalward and temporalward directed OKN stimuli in monkey S1. Nasalward OKN responses is robust compared to temporalward OKN response. B. Comparison of OKN slow phase velocity response for nasalward and temporalward directions at 20 (blue), 40 (green) and 80 (red) °/sec stimulus velocities in monkey S2. Slow phase velocities are reduced for temporal OKN compared to nasalward OKN. Positive values indicate rightward eye positions and negative values indicate leftward eye positions.
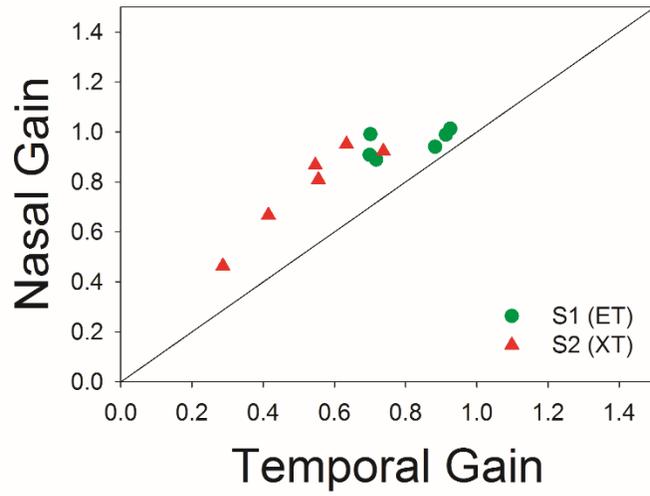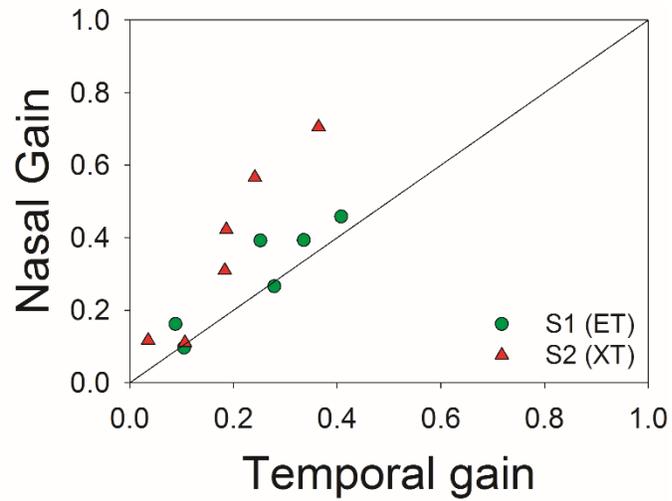
Figure 2: Nasal vs Temporal gain comparison in OKN shows a significant increase in nasalward gain at all speeds in both the monkeys during both right and left eye viewing conditions.
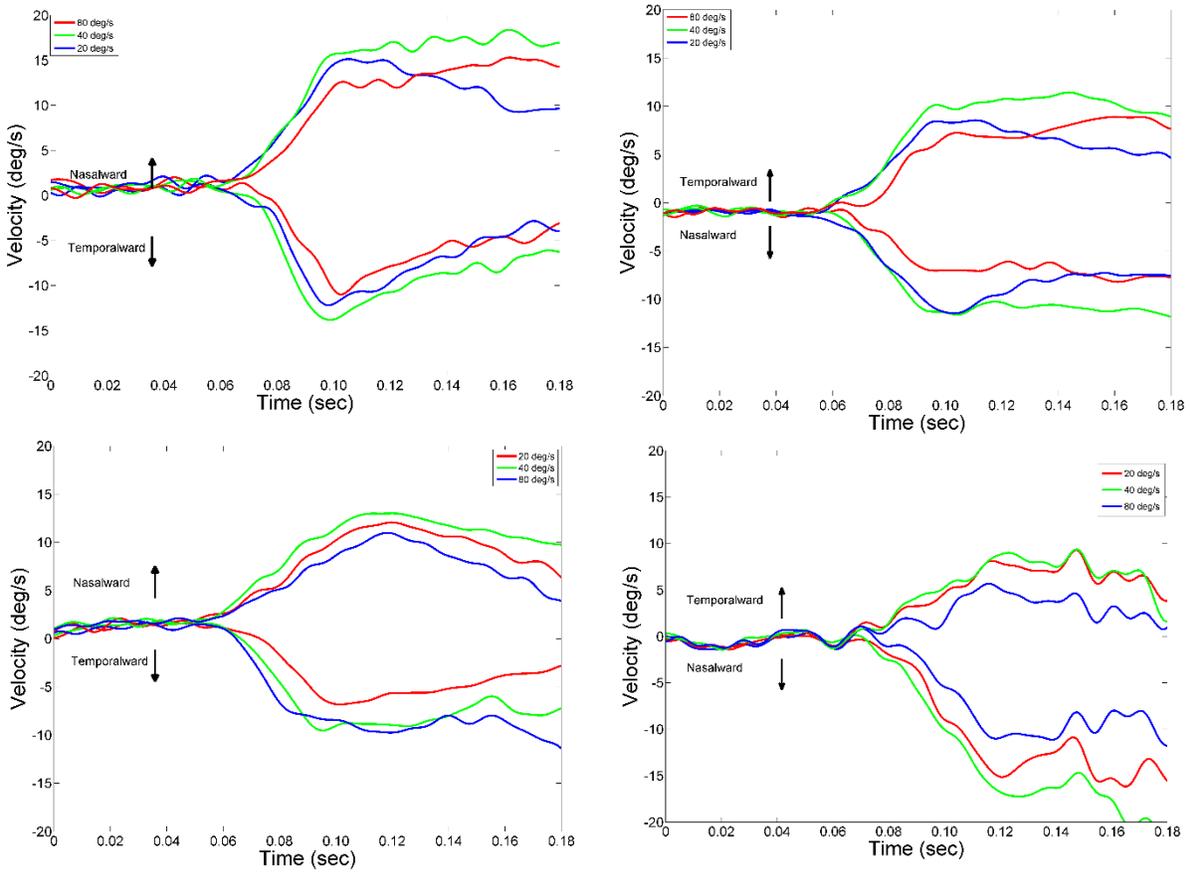
Figure 3: Ocular following responses from S1 (top row) and S2 (bottom row) for stimulus velocities of 20, 40 and 80 °/s in nasalward or temporalward directions. The plots in the left column show data for left eye viewing while right eye viewing data is shown in the right column. Positive values indicate rightward eye velocities and negative values indicate leftward eye velocities.

Figure 4: Nasal vs Temporal gain comparison during ocular following showed a significant increase in nasalward gain in both the monkeys during both right and left eye viewing conditions.
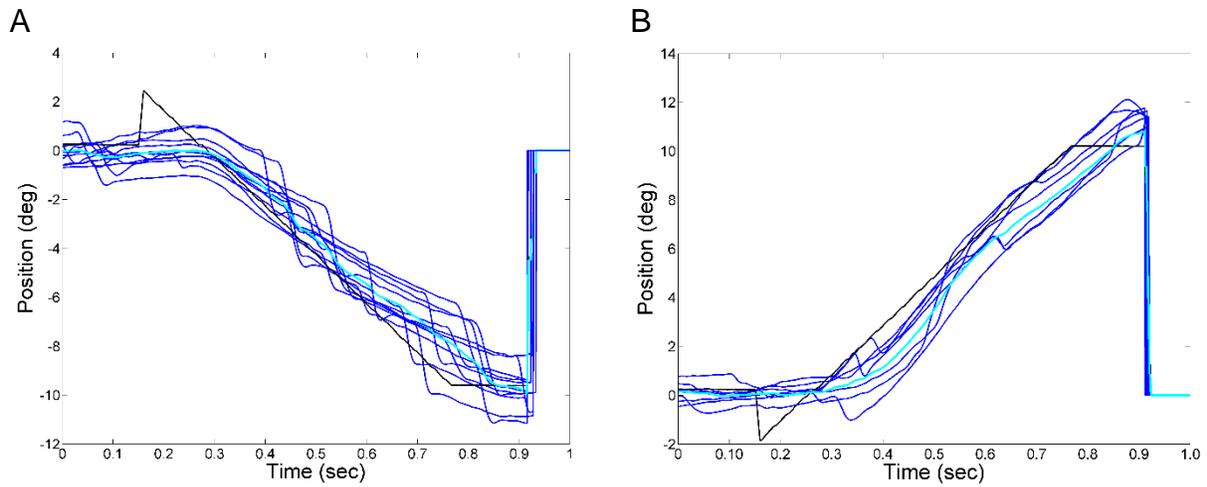
Fig 5: Plots showing left eye position data from several trials for the esotropic monkey's (S1) tracking a step-ramp stimuli in the leftward (temporal, panel A) and rightward (nasal, panel B). Notice the large number of catch up saccades made during temporalward tracking compared to the nasalward tracking
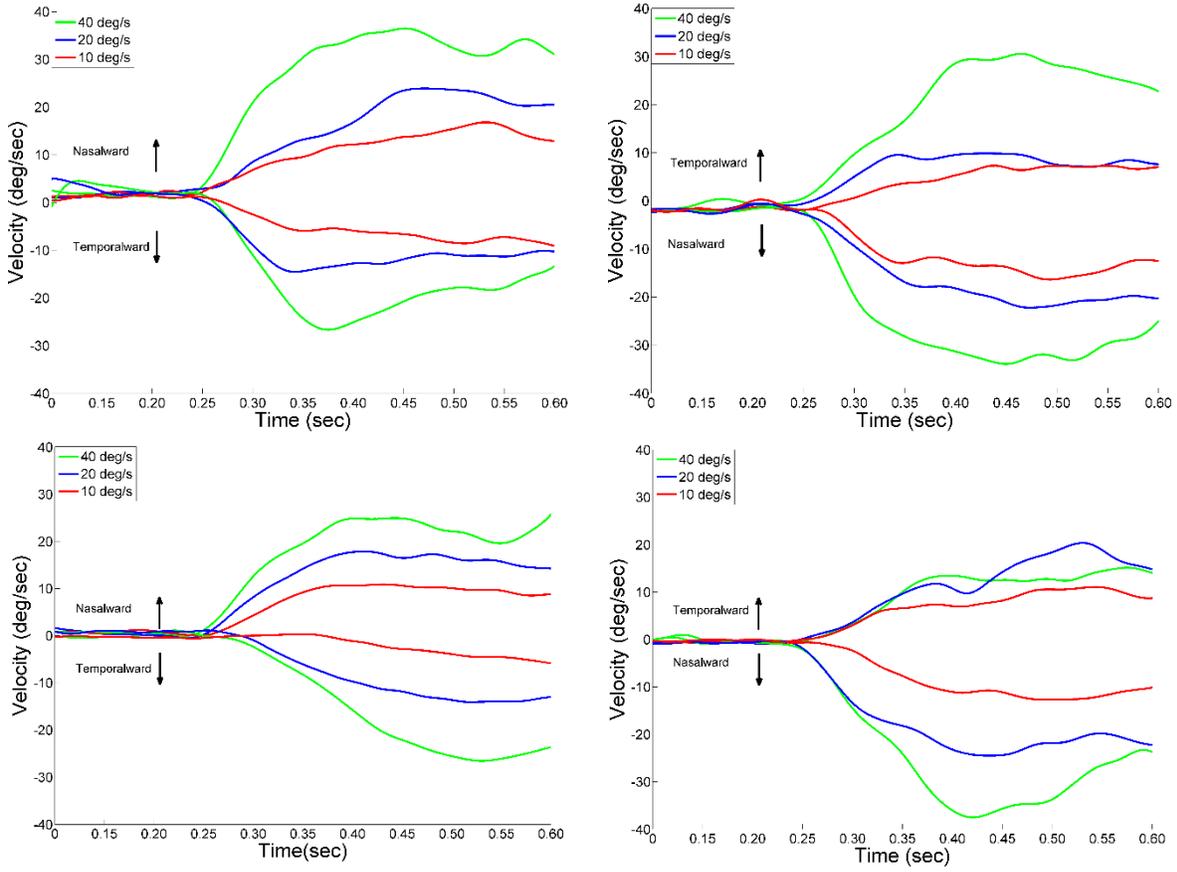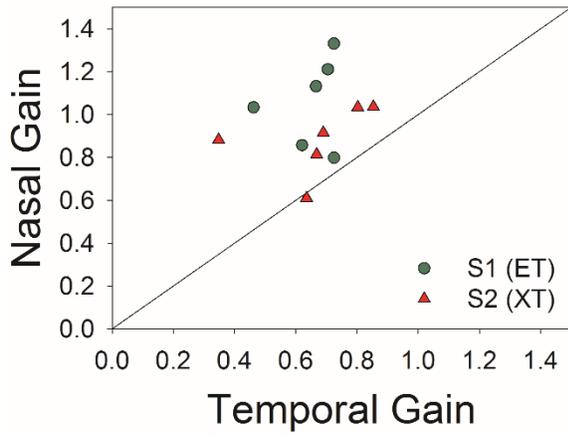
Figure 6: Smooth pursuit response from S1 and S2 under left eye (left column) and right eye (right column) viewing condition at 3 different stimulus velocities. Temporalward smooth-pursuit is less robust (slower initiation and lower steady state gain) compared to nasalward smooth-pursuit. Target motion onset is at the 0.15sec mark.
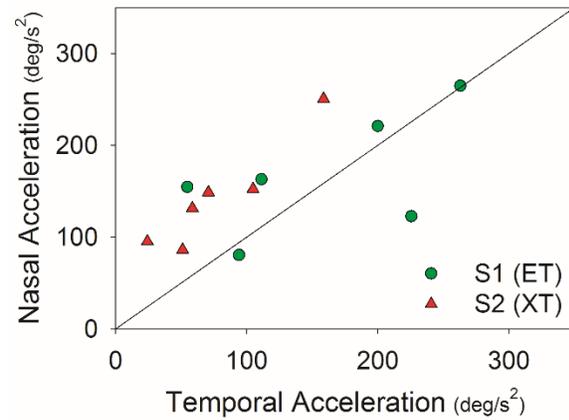
A.

B.

Fig 7: Panel A shows a comparison of nasal vs temporal gain and Panel B shows a comparison of nasal vs temporal acceleration for the three step-ramp stimulus velocities.
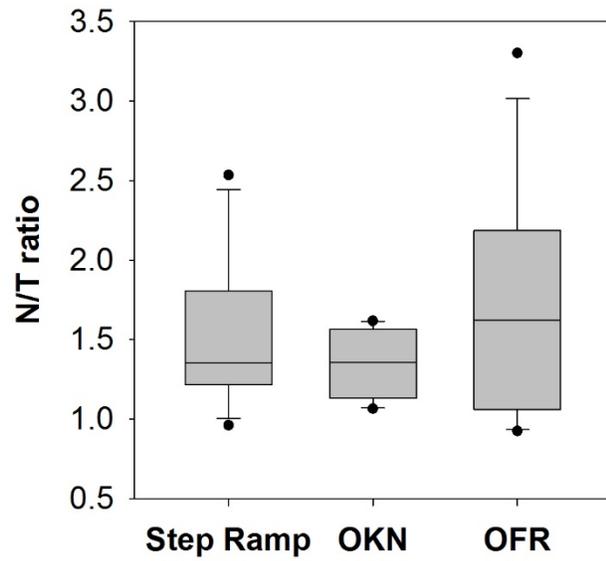
Fig 8: Box plots comparing naso-temporal gain ratio across the three visual tracking paradigms. Boundaries of the box are 25th percentile and 75th percentile points. 5th and 95th percentile values are the error bars.