Modification of Visually Guided Saccades by a Nonvisual Afferent Feedback Signal

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Purpose. To investigate the role of extraocular muscle afferent signals in the control of saccadic eye movements.

Methods. A suction scleral contact lens was used to impede the movements of the right eye while subjects executed visually guided saccades to briefly presented targets. Movements of the left eye were measured using infrared oculography. Saccade amplitude, peak velocity, and duration were analyzed trial by trial and compared before, during, and after the right eye was impeded.

Results. When the right eye was impeded, the amplitudes of saccades executed by the left eye were reduced. There was no alteration in the main sequence relationships. The amplitude effect had a rapid onset and offset. There was no evidence that the effects built up over a number of trials, nor was there evidence that individual saccades were modified on-line.

Conclusions. These results are consistent with the hypothesis that extraocular muscle afferent signals provide a feedback signal of the movements of the eyes that is used to produce rapid adjustments of oculomotor output when required. (*Invest Ophthalmol Vis Sci.* 2000;41: 2561–2565)

Precise control of eye movement is important, not just for its own sake but also for effective vision and interaction with objects in the visual world. It might be thought that all possible sources of information would be used to monitor and control the position or movements of the eyes. However, although the muscles that move the eyes in the orbits, the extraocular muscles (EOMs), are well endowed with intramuscular receptors, it is generally believed that afferent signals from these receptors are not involved in the control of eye movement at least in the short term.[1,2]

Single-unit recording studies in various species have demonstrated that afferent signals arising from the EOMs reach a wide range of oculomotor and visual structures in the central nervous system, including brainstem oculomotor centers (vestibular nuclei, nucleus praepositius hypoglossi, and oculomotor nuclei[3–6]), the cerebellum,[6] the lateral geniculate nucleus,[7,8] midbrain oculomotor and visual processing centers (the superior colliculus in the cat[9] and optic tectum in the pigeon[10,11]), and the visual cortex.[12,13] Furthermore, EOM afferent signals carry information related to the parameters of eye movement rather than simply a gross signal indicating the occurrence of eye movement to many of these centers[4,11] and there modify the processing of information (for example, visual or vestibular information) in a functionally specific manner.[11,14,15] Evidence from human studies also indicates that EOM afferent signals are involved in longer term adaptive control of eye movement.[16,17] Recent human studies using single EOM vibration to induce afferent signals have shown that EOM afferent signals from one eye modify the position of the other eye[18] and influence the programming of memory-guided saccades.[19] Although in the monkey the removal of EOM afferent signals does not disable accurate saccades,[20] this does not rule out the possibility that, when available, EOM afferent signals contribute to oculomotor control.

One reason a role for a peripheral feedback signal is usually discounted in the oculomotor system is that it is argued that the EOMs operate under conditions of fixed load. Thus, a given efferent signal always has a reliable and predictable effect on the position of the eyes. We have altered this condition by impeding the movement of one eye to cause an acute increase in EOM load. We measured the movement of the other eye during a visually guided saccade task to assess the response of the oculomotor system to this perturbation.

Materials and Methods

All procedures conformed to the Declaration of Helsinki for research involving human subjects and had local ethics board approval. All subjects gave informed consent. Three adult male subjects with normal or corrected-to-normal visual acuity and normal eye movements were tested (PK, 36 years of age, one of the authors; RH, 31; and KB, 27). A suction scleral contact lens[21] was used to impede the movement of the right eye while subjects performed a visually guided saccade task with the left eye. The lens had a short stalk that was placed in an adjustable holder clamped to the experimental table. Attachment of the lens to the eye by light suction did not cause the eye to move posteriorly but simply impeded its rotation. Thus, with the lens in place, when subjects were asked to make voluntary horizontal saccades, we observed that the right eye continued to move under the lens, but not by as far as the (free-to-move) left eye. The movements of the left eye were measured using an infrared corneal reflection device (Iris; Skalar Medical, Delft, The Netherlands). Eye position signals were digitized at 1 kHz

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with 12-bit precision using an intelligent interface (model μ1401; Cambridge Electronic Design, Cambridge, UK). The eye position and a time marker of the appearance of the visual target were displayed on the computer screen; data from 100 msec before to 500 msec after the appearance of the target were stored on disc for analysis off-line.

Saccade targets, generated by a visual stimulus generator (Cambridge Research Systems, Rochester, UK), were presented on a monitor, which subjects viewed from 57 cm with the left eye. Head movement was prevented by a chin rest and cheek pads. A fixation target appeared in the center of the screen for a random period of 0.5 to 1.5 sec. This was extinguished and replaced by a saccade target (0.3° black square on a light background) which was displayed for 200 msec and appeared randomly at one of four locations: 5° or 10° to either the left or right of fixation. Targets were presented in three runs of 52 trials. In the first and third runs, the right eye was occluded, and in the second run the right eye was impeded with the suction scleral lens. Before lens placement, several drops of local anesthetic (Proxymetacaine Minims; Chauvin, Romford, UK) were instilled in the right eye. The lens was then placed in the eye and gentle suction applied. The lens remained in place for approximately 5 minutes, and once the experiment had been completed, intraocular pressure was measured, and the corneal surface was examined.

Data were analyzed off-line, using an analysis program that displayed the recorded eye position, the calculated eye velocity, and the time at which the target appeared. For each record in which target appearance was preceded by steady fixation, the amplitude, duration, peak velocity and latency of the primary saccade were measured. Data from anticipatory saccades (i.e., latency <80 msec) were not included in the analysis. A calibration factor was calculated from the first run by plotting the maximum gaze amplitude (i.e., primary plus subsequent corrective saccades when these occurred) of each individual trial in digital-to-analogue converter units against the target amplitude in degrees and using linear regression analysis to obtain the slope of the relationship.

Results

Subjects executed monocular saccades to the briefly presented (200 msec) targets with reasonable accuracy. When the right eye was impeded, subjects reported no discomfort and no perceived difficulty in either seeing the target with the left eye or executing saccades in response to the targets.

When movements of the right eye were impeded, the mean saccade amplitudes of the left eye were reduced in each of the three subjects in all experimental sessions (Fig. 1). For saccades executed in response to targets appearing 5° and 10° to the right of fixation, mean pooled saccade amplitude was reduced by 23% compared with the original level when the right eye was free to move. This reduction was statistically significant (Students t-test, $P < 0.001$, $t = 8.88$ for R5, $t = 11.57$ for R10). For targets appearing 5° and 10° to the left of fixation, the reductions in mean saccade amplitude were 15% ($t = 5.39$; $P < 0.001$) and 17% ($t = 6.33$; $P < 0.001$), respectively. After the lens had been removed, the mean saccadic amplitudes of the left eye increased toward the normal (prelens) control values (Fig. 1B). In response to targets appearing 5° and 10° to the right, mean saccade amplitudes increased by 22% ($t = 6.86$; $P < 0.001$) and 25% ($t = 8.55$; $P < 0.001$), respectively. In response to targets appearing 5° and 10° to the left, mean saccade amplitudes increased by 7% ($t = 2.26$; $P < 0.05$) and 11% ($t = 3.52$; $P < 0.001$), respectively.

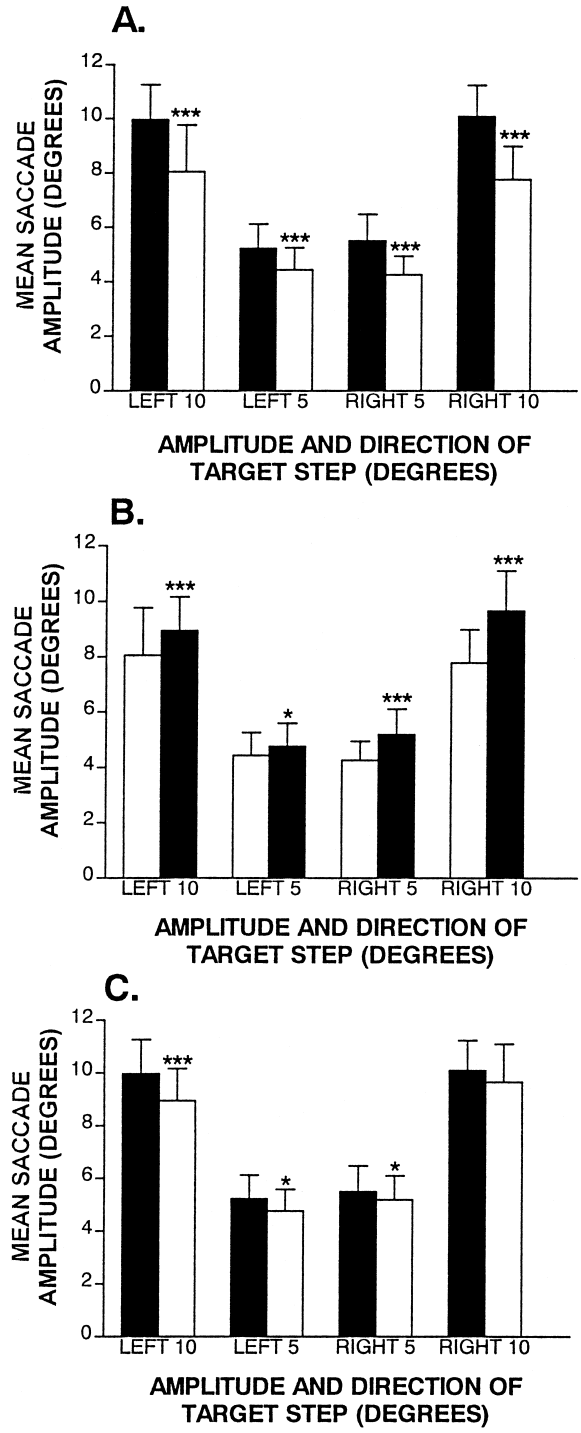

Figure 1. Plots of pooled mean (±SD) left eye saccade amplitude for each of four target positions. (**A**) Comparison of mean amplitudes before (*filled bars*) and while (*open bars*), (**B**) while (*open bars*) and after (*filled bars*), and (**C**) before (*filled bars*) and after (*open bars*) the right eye was impeded. Statistically significant differences (Student's *t*-test) between column pairs (***$P < 0.001$; *$P < 0.05$).

We noted that the left eye saccade amplitudes after the suction contact lens had been removed sometimes remained slightly lower than the original amplitudes recorded before the

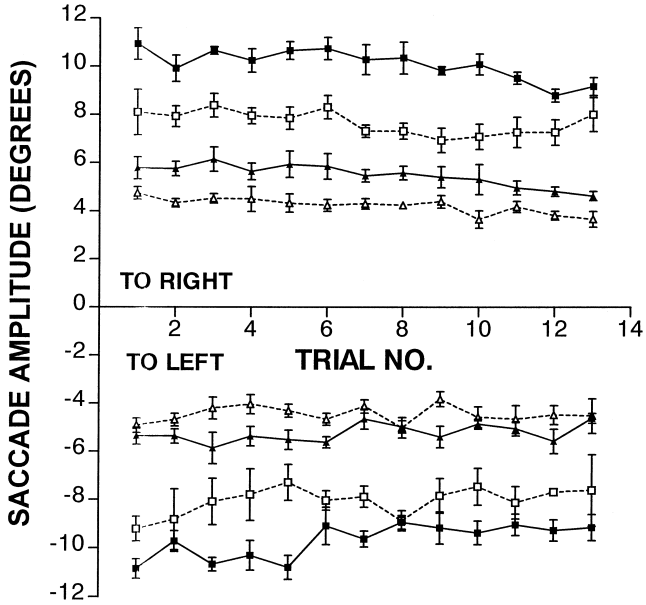

Figure 2. Trial-by-trial pooled mean (±SEM) left eye saccade amplitude before (*filled symbols*) and while (*open symbols*) right eye was impeded. *Squares*: right and left 10° data; *triangles*: right and left 5° data. Amplitude was reduced from the first trial and there is little indication that the reduction built up during the run.

suction contact lens was inserted (Fig. 1C). For the pooled data rightward saccade amplitudes for 5° and 10° remained 6% (t = 2.01; $P < 0.05$) and 4% (t = 1.88; not significant) lower than the prelens control values. Leftward saccade amplitude for 5° and 10° were 9% (t = 3.26; $P < 0.05$) and 8% (t = 3.54; $P < 0.001$) lower, respectively.

Recording began within approximately 90 seconds of lens insertion in most runs, and on one occasion within less than 60 seconds. Figure 2 shows trial-by-trial mean (±SEM) amplitudes (data pooled across subjects and sessions). The pooled data are very similar to the individual data. Note that saccade amplitude was reduced in the first trial. Linear regressions of amplitude on trial number for both the pooled and individual data showed either no significant deviation in the slope from zero or no significant difference in the slope of the line between the eye-free and eye-impeded conditions. Thus, there was no evidence of a build up in the effect.

We found no evidence of any alterations in the amplitude–velocity relationship. Typical data from one subject in a single experiment are plotted in Figure 3A. When the right eye was impeded, the peak velocity of left eye saccades was no lower than would be predicted, given the reduction in amplitude. There was no evidence from this analysis that saccade duration was modified inappropriately (Fig. 3B). Thus, although the amplitudes were reduced when the right was impeded, the velocity and duration scaled by an appropriate amount. There was little evidence that impeding the movement of the right eye affected the latencies of left eye saccades.

We examined the velocity profiles of saccades with and without the right eye impeded. All profiles were aligned using the latency measurements; for two experiments in two subjects we calculated mean profiles (Fig. 4). Peak velocity when the right eye was impeded was lower, as expected. The duration of these mean profiles was only slightly reduced. There was little evidence of the profiles' being distorted in any way. The impeded profile diverged from the free profile at or near the beginning of the saccade. Examination of velocity profiles trial by trial confirmed that from the first trial, there was a large reduction in peak velocity, with little evidence of further clear reductions.

In two subjects, a control experiment was run in which the procedures were identical with those described, including the instillation of local anesthetic into the right eye. However, the lens was not placed in the right eye, it was occluded. In these runs we observed no consistent alteration in any of the saccade parameters. In particular, there was no alteration in saccade amplitude.

Discussion

The assumption that the EOMs operate in conditions of unchanging load, coupled with the absence of a monosynaptic stretch reflex in the macaque monkey[22] and the ability of monkeys to make accurate saccades when the EOMs have been deafferentated[20] have been taken to justify the view that EOM afferent signals play little or no role, at least in the short term,

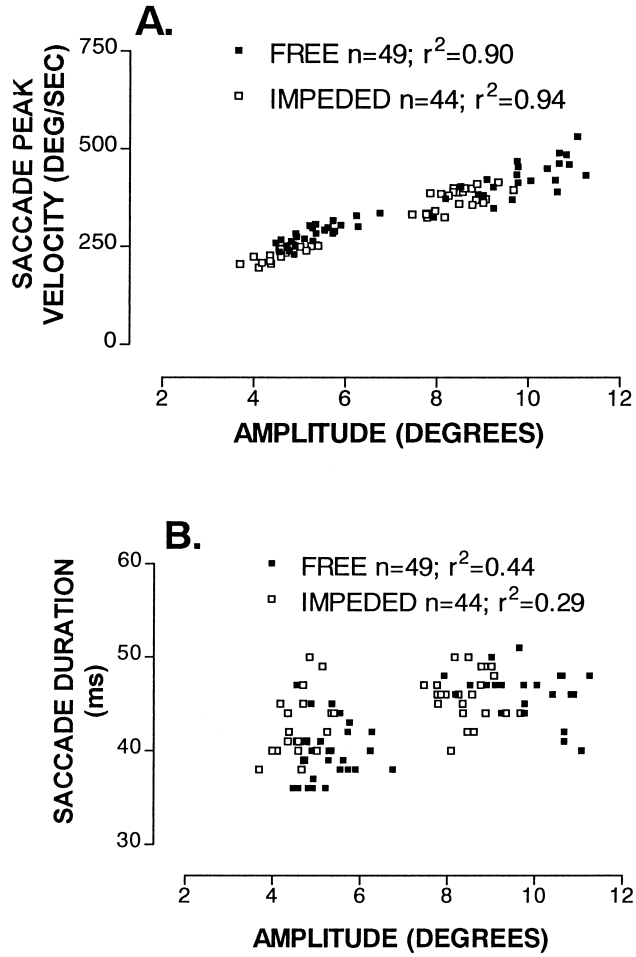

Figure 3. Typical individual subject data showing relationship between saccade amplitude and velocity (**A**) and amplitude and duration (**B**). *Filled symbols*: right eye free (prelens run); *open symbols*: right eye impeded. All correlation coefficients were statistically significant ($P < 0.001$). Linear regressions of peak velocity on amplitude and duration on amplitude demonstrated no statistically significant difference between free and impeded data.

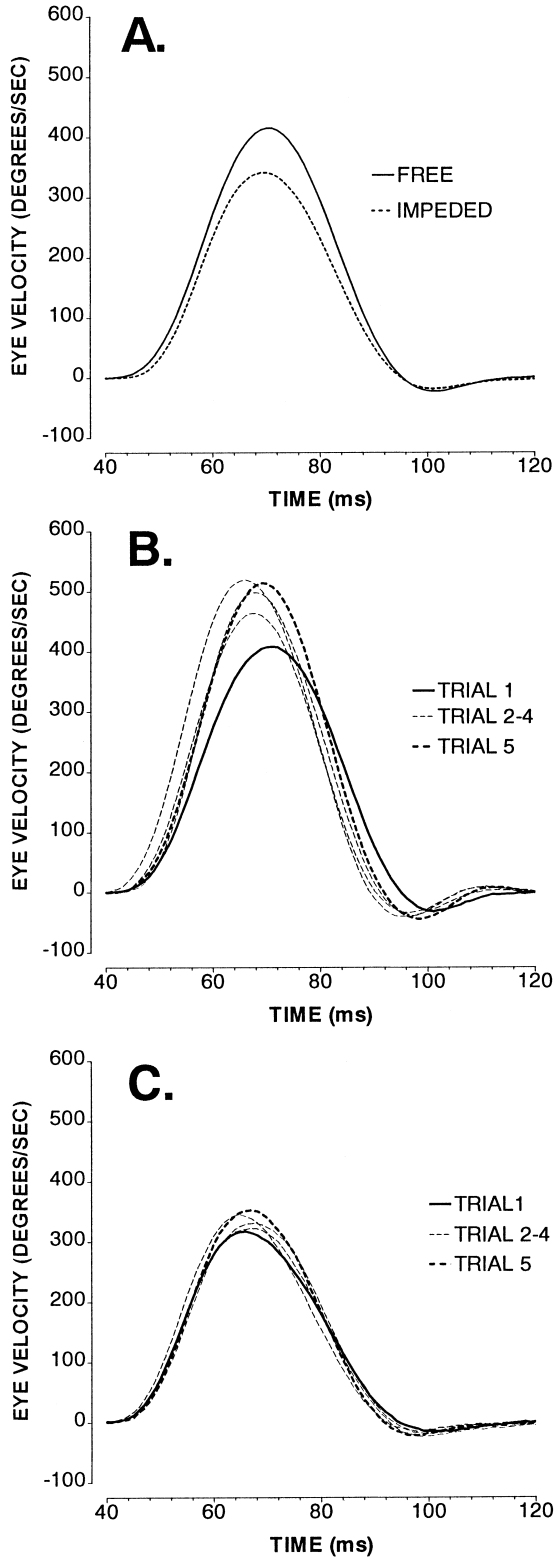

FIGURE 4. Typical velocity profiles from a single subject. (**A**) Mean velocity profiles for eye-free (*solid line*) and eye-impeded (*broken line*) conditions in response to a target appearing 10° right. (**B**) First five individual saccades for eye-free condition, the mean of which is plotted in (**A**). *Solid line*: first trial; *broken line*: fifth trial. (**C**) First five individual saccades for eye-impeded condition, the mean velocity of which is plotted in (**A**). *Solid line*: first trial; *broken line*: fifth trial. Note trial 1 peak velocity was reduced, and no further reduction was observed.

in the control of eye movement. By impeding one eye, we have acutely altered the load under which the EOM operate. We do not know, of course, the extent to which load was increased. Observation demonstrated that the impeded eye did not move as far as the unimpeded eye, although the extent of this was variable.

We have shown that in these circumstances the oculomotor system made rapid adjustments. From the first trial in which the right eye was impeded, that is within a maximum of a few tens of seconds of lens placement, saccade amplitude in the other eye was reduced. Note that this response is quite different from other types of adaptive response observed in the oculomotor system. These involve internal comparison of retinal information indicating a difference between desired and actual eye position[23] or retinal slippage information.[24] In our experiments there was no retinal error. The nonseeing eye was impeded, and the brief target presentation time ensured that when, in the impeded condition, the seeing eye landed short of the target position, no retinal error was generated.

The clearest evidence of the oculomotor response to impeding one eye was the effect on saccade amplitude. There was no evidence of this built up over even a short period of a few seconds, or a small number of trials, although there was some evidence that when the lens was removed some residual amplitude reduction remained. Most examples of adaptation of oculomotor parameters build up over a larger number of trials, or over a period during which adapting stimuli are presented. There was, however, little evidence that each saccade was modified on-line. Had this been the case, we would have expected the velocity profiles of saccades in the impeded condition to diverge from the control profiles some short period after the beginning of the saccade. As Figure 4 shows, there was little evidence of this.

Finding a reduction in saccade amplitude was unexpected. However, this could be interpreted as evidence that the saccade system seeks, at least in the circumstances used in these experiments, to preserve conjugacy. Thus, because the right eye is not moving as far as intended, the drive to the left eye is reduced. It remains to be seen whether the controller responds in this manner in different circumstances or when different types of eye movement (e.g., smooth pursuit) are manipulated. Although saccade amplitude was clearly modified, the amplitude–velocity relationship was apparently unaffected. The peak velocity of saccades in the impeded condition was reduced to the extent that might be predicted from the amplitude reduction. Although we found no statistically significant alteration of the amplitude–duration relationship, the examination of the velocity profiles suggested that the duration of saccades in the impeded condition was not as short as might be predicted.

We have shown that there is a feedback signal, which in the absence of a retinal error signal induces alterations in visually guided saccades. In our experiments there was always a period between the placing of the lens and the beginning of the experimental run. However, this was kept a short as possible and was usually no longer than 90 seconds. During this time, little specific visual information was available to aid any adaptive process. Any saccades executed were not responses to specific saccade targets but were voluntary saccades made on request to check the lens position. In the experimental run the amplitude effect was always present from the very first trial and did not subsequently build up (see Fig. 2). It seems highly unlikely that an adaptive process begun during the 90 second

prerun period would be completed by the end of the prerun period. Rather, the results are suggestive of the operation of an afferent signal that indicates that the eye is impeded and induces rapid modifications of the oculomotor system.

The impeded eye was anesthetized, and although this does not rule out entirely the possibility of a mechanoreceptive source for these signals, it seems unlikely. The more likely candidate source for the effects we have observed is EOM intramuscular proprioceptors. The human EOMs are well known to have relatively high numbers of muscle spindles and also palisade endings, which may be unique to the EOM.[2] Single-unit recording studies in various animal species have shown that afferent signals arising from EOM intramuscular receptors are able to modify the processing of information in the brainstem "on-line"—that is, as soon as the afferent signals are induced, information processing is modified. It does not build up over a number of trials or cycles of stimulation.[3,5,14] However, if a feedback signal were acting on the brainstem gaze centers directly, we would have anticipated alterations in the some of the main sequence parameters or their relationships. Furthermore, if afferent signals were being distributed separately and directly to subareas of the horizontal gaze center (e.g., to the burst-generating circuitry in the paramedian pontine reticular formation and the integrator circuitry in the nucleus praepositus hypoglossi), we might have observed mismatches between the saccade pulse and the saccade step. There was no evidence of any of these. We speculate therefore that EOM afferent signals act at a higher level in the saccade control circuitry to exert their effects. Two candidate sites would be the cerebellum or superior colliculus, both of which are known to receive EOM afferent signals.[6,9,11]

An implication of these results is that alteration of, or damage to, EOM intramuscular receptors or their afferent pathway in one eye alters, in the course of a few minutes, the movements of the other eye. Presumably in the presence of the resultant retinal error signals, recalibration quickly follows. Thus, in experimental circumstances in which the available visual information is not carefully controlled, it could be concluded that removal of afferent feedback has no effect, whereas what is observed is the result of an effective recalibration of the oculomotor system.

Our results also suggest further experiments that would test the hypothesis that EOM afferent signals are involved in oculomotor control. Surgery involving the tendinous insertion of the EOM disrupts the intramuscular receptors found in this region of the muscles.[25] If our experiments were repeated in subjects with altered EOM proprioception—for example, in patients in whom the horizontal recti in one eye had been operated on to realign the eyes, we would predict that when the surgically treated eye is impeded, a different pattern of effect to that reported herein would be observed. Specifically, when the surgically treated eye is impeded, we would expect that the saccade amplitude reduction effect in the nontreated eye would be absent or reduced. We further predict that when the impeded eye is the nontreated eye, the saccade amplitude effect would be similar to that reported herein.

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