

# Saccadic System Plasticity in Humans

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A subject with a medial rectus paresis secondary to a partial third nerve palsy was forced to use the affected eye for six days while the good eye was constantly patched. Saccadic eye movements were carefully measured each day; the gain increased, with a time constant of 0.85 day. The patch was then switched to the paretic eye and the gain decreased, with a time constant of 1.54 days. This demonstrated central nervous system plasticity of the pulse and step of neural activity responsible for the generation of saccades in the adult human. In addition to gain changes, postsaccadic drift velocity and saccadic velocity/amplitude relationship alterations during the patching are reported. A major conclusion that can be drawn from analysis of these data is that the gain changing is accomplished by pulse width changes rather than pulse height (firing frequency), which was not markedly altered.

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Gonshor and Melvill Jones [2, 3] and Robinson [7] have demonstrated that the vestibuloocular reflex can be extensively modified by the use of reversing prisms. They showed that within several days, vestibularly induced eye movements reversed and went in the same direction as the head instead of in the normally occurring counter movement that constitutes the reflex. Analogous to this plasticity of the vestibuloocular reflex, adaptation of the central mechanisms subserving saccadic eye movement generation has been demonstrated in both humans and animals in response to extraocular muscle paresis.

Kommerell et al [4] reported on 1 of 3 patients, each of whom developed a unilateral abducens nerve palsy in the visually superior eye that had always been used for fixation. With the paretic eye patched in this unique patient, the nonparetic eye made hypermetric (overshooting) saccades, reflecting the central nervous system's attempt to increase neural activity to the habitually fixating paretic eye. The hypermetria disappeared after three days of patching.

Optican and Robinson [5] detached the horizontal rectus muscles of one eye in monkeys. With the normal eye viewing, the weak eye made hypometric saccades that undershot by about 50% and then drifted toward the target position with initial velocities up to 50 degrees per second. When the patch was switched to the good eye, the hypometric saccades of the weak eye gradually increased in amplitude until they became almost orthometric. When the patch was returned to the weakened eye, so that

the normal eye was again viewing, the gain (output/input, in which output is the actual size of saccades and input is the desired size of saccades) of the paretic eye decreased to its original value in three to five days (i.e., the hypometria returned).

We report here our extensive investigation of the plastic changes of the saccadic mechanism in a patient with a third nerve paresis. We have demonstrated for the first time in a human various aspects of saccadic plasticity such as: the time constants of both the gain change and the initial drift velocities; the directionality of gain changes; the differences between centering and lateral saccades during gain changing; and the effects on the saccadic velocity/amplitude relationship.

## Case Description

Two weeks prior to our investigation, a 58-year-old man suddenly developed a right third nerve palsy with ptosis and limitation of adduction and of upward and downward movement. Before that time this commercial airline pilot had had normal binocular vision (20/20 OU). The right eye could be adducted approximately 17 degrees; abduction was full. The paresis remained unchanged until the seventh day after our initial examination, when adduction amplitude began to increase. Both pupils were approximately 4 mm in dim lighting, and each reacted briskly to light and near stimuli.

Intravenous edrophonium chloride (Tensilon) testing on three separate occasions did not alter the lid position or ocular motility by either clinical observation or eye movement recording. CAT scans and tomograms of the superior

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orbital fissures and cavernous sinus were normal, as were laboratory studies except for an abnormal glucose tolerance test (fasting, 100 mg/dl; 1 hour, 210; 2 hours, 75; 3 hours, 45; 4 hours, 81).

## Methods

Eye movement recordings were made using infrared oculography. Instantaneous velocity was obtained by electronic differentiation of the position signal. The entire system bandwidth was DC–100 Hz (Biometrics Model 200 and a rectilinear Beckman Type R dynograph). The patient was seated in a modified dental chair with head brace and chin rest. Targets viewed were red light-emitting diodes mounted on an arc 1.14 m from the patient. Recordings were carried out in subdued light. The initial recording was made when the patient was first referred to our laboratory two weeks after the onset of the paresis. The extent of the paresis was measured. After calibration, several series of refixations were recorded between 0 and 10 degrees left, first with the right, then with the left eye viewing. Binocular refixations were then recorded between 0 and  $\pm 10$  degrees.

After this first session (day 0), a patch was taped over the patient's good left eye, forcing him to use the paretic right eye at all times. For days 1 through 6 an identical procedure was followed. Recordings were obtained at the same time every day. The patch was removed and the paresis measured as a check for spontaneous recovery. The apparatus was then calibrated for each eye individually. The same sequence of refixations was carried out as on day 0; at their conclusion, the patch was replaced. The eye undergoing patching was able to view for only about ten minutes a day during the recording session, and this in very dim light. The patient was a knowledgeable, cooperative man, intensely interested in the experiment, who followed all instructions faithfully. At the end of recording on day 6, the patch was switched to the paretic eye, where it remained on days 7 through 9. At the end of day 9, patching was terminated, and a final recording was made on day 10 after 24 hours of binocular vision.

Records were analyzed for saccadic gain (the ratio of

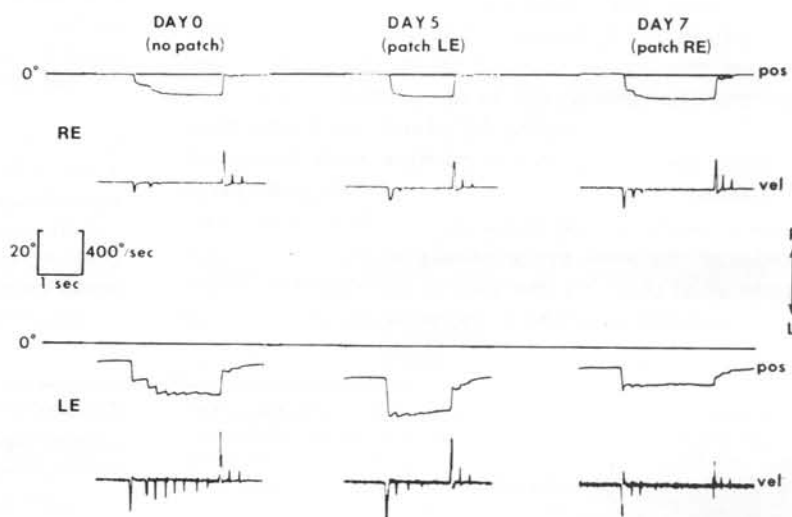
saccadic amplitude to target distance), saccadic peak velocity, and drift velocity (defined as the initial postsaccadic velocity measured by the velocity channel) in both the fixating and the nonfixating eye. His tropia necessitated monocular viewing for unambiguous gain determinations. We made daily measurements of the ocular deviation during binocular and monocular viewing.

## Results

Examples of the actual eye movement recordings on days 0, 5, and 7 are presented in Figure 1. All three recordings were with the right eye viewing and the left eye under cover (accounting for the exophoria). The eye movements were into the field of action of the paretic rectus (to the left), followed by a saccade to the right (back to the midline). On day 0, an initial undershooting saccade of the paretic eye was followed by a slow drift to the left, whereas the left initially overshoot, followed by a slight rightward drift. A curious phenomenon, which appears to be uniocular gaze-evoked nystagmus, then occurred in the left eye. In fact, the low right eye gain and extremely low amplitude of the required saccades in the right eye had masked their presence. This figure shows the increase of amplitude in both eyes for leftward movements from days 0 to 5 (during which time the normal left eye was patched), which is in sharp contrast to the lack of amplitude change in either eye for rightward movements. On day 7, two days after reversal of the patch, the amplitude of the right eye with leftward movements diminished.

Figure 2A illustrates the changes in gain for leftward gaze in the paretic right eye during the course of the experiment. The points shown are the means

Fig 1. Eye movement position (pos) and velocity (vel) records of both eyes taken on days 0, 5, and 7 under the patch conditions indicated.



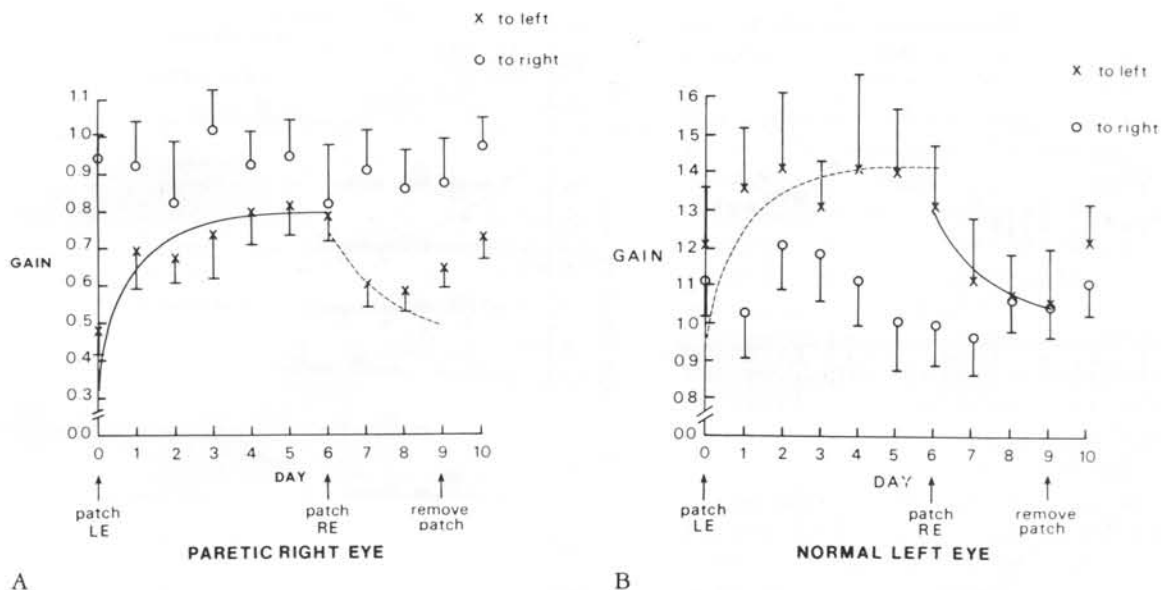


Fig 2. (A) Saccadic gain ( $G$ ) variations of the right eye during right fixation for movements in both the paretic (leftward) and the nonparetic (rightward) direction. The solid curve is the best mean-squares fit exponential:  $G = 0.79 (1 - 0.59 e^{-t/0.85})$  ( $r^2 = 0.84$ ). Dashed curve is from B and is fitted by eye to the right eye data. In this and succeeding figures, vertical bars indicate 1 standard deviation. (B) Saccadic gain variations of the left eye during left eye fixation. Solid curve is the best mean-squares fit exponential:  $G = 1 + 0.28 e^{-t/1.54}$  ( $r^2 = 0.89$ ). Dashed curve is from A and is fitted by eye to the left eye data.

of 50 saccades in the direction of the paresis and are plotted for the eye while it was fixating. No differences existed between centering and eccentric saccades, so they were combined for analysis. Also shown is the gain variation for the right eye in the rightward (nonparetic) direction. Figure 2B is a similar illustration of the gains of the left eye in both directions over the ten-day course of the experiment. Because the onset of the paresis occurred fourteen days prior to the beginning of the experiment, some adaptation in the paretic direction was apparent even on day 0; the gain for the nonparetic left eye was already greater than 1.0. The curve for the unpatched right eye showed a large increase in gain by day 1 (from 0.4 to 0.7), followed by a slower increase to a plateau of approximately 0.8 by day 4. A best mean-squares exponential fit ( $r^2 = 0.84$ ) to these points is shown by the solid curve in Figure 2A, which has a time constant of 0.85 day. The gain in the left eye also increased during this initial period when it was patched. In Figure 2B, the curve for the right eye in Figure 2A is shown shifted up in value and superimposed (dashed curve) on the more variable left eye data.

After reversal of the patching on day 6, the gain in the paretic direction immediately began to fall. The left eye gain would have been expected to drop to 1.0, but the spontaneous recovery from the paresis, which began on day 7, acted against this. Because of the recovery, we terminated the patching on day 9. The decreasing left eye gain was fitted with an exponential curve ( $r^2 = 0.89$ ), as shown by the solid curve in Figure 2B, which has a time constant of 1.54 days. When this curve was superimposed on the right eye data (dashed curve in Fig 2A), poor agreement was found after day 7 due to the recovery of medial rectus function.

As is apparent from Figure 2, although there was appreciable day-to-day variation in the gains for the two eyes when movements were in the nonparetic direction, no definite trend was present, and patching had no effect on these movements.

Given the marked changes in gain in the paretic direction during the course of the experiment, we were curious whether the peak saccadic velocity in the paretic eye was also affected by patching. Since saccadic amplitude (gain) increased with time, it was necessary to normalize the velocity/amplitude relationship so that saccades of different amplitudes could be compared. This was accomplished with the use of a velocity/amplitude curve fitted to the averaged saccadic response data of 6 normal subjects. The velocities of our patient's saccades were then expressed as percentages of the normal velocities given by this curve. Thus, any improvement in peak saccadic velocity could be separated from an increase in gain. Figure 3 illustrates normalized velocity/amplitude curves for leftward movements made by

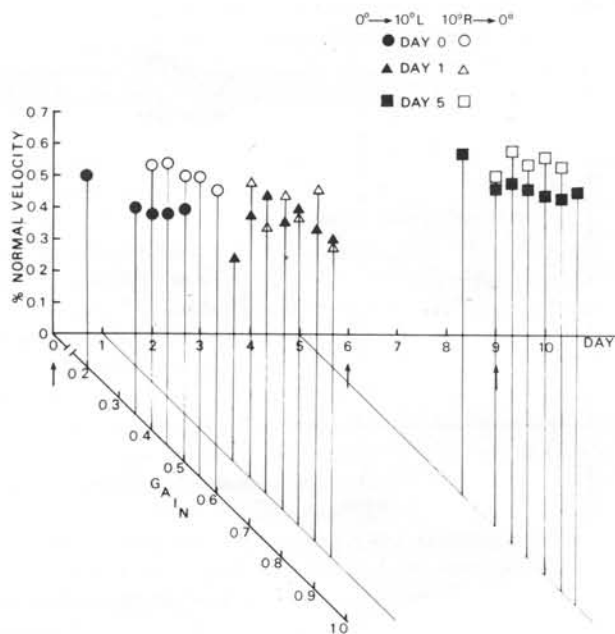


Fig 3. Saccadic peak velocity as a percentage of normal versus gain and day (right eye, right eye fixing) shown for three days. Movements are in the paretic (leftward) direction, both centering and lateral saccades. Arrows in this and succeeding figures indicate patching changes as given in Figure 2.

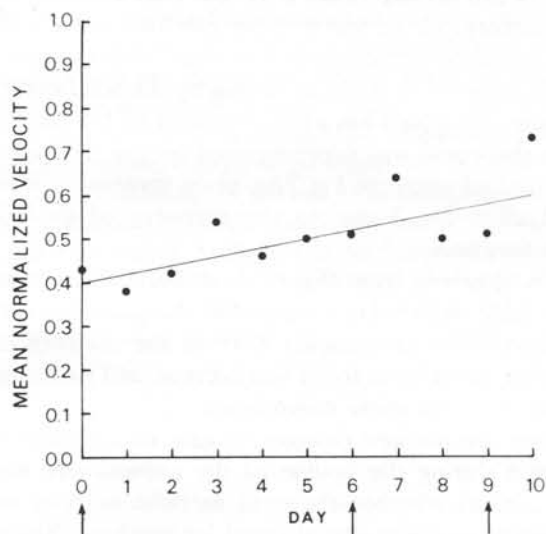


Fig 4. Mean normalized saccadic peak velocities ( $\bar{V}_N$ ) versus day, right eye with right eye fixing. Best mean-squares fit regression line equation is:  $\bar{V}_N = 0.4 + 0.02 t$  ( $r^2 = 0.57$ ).

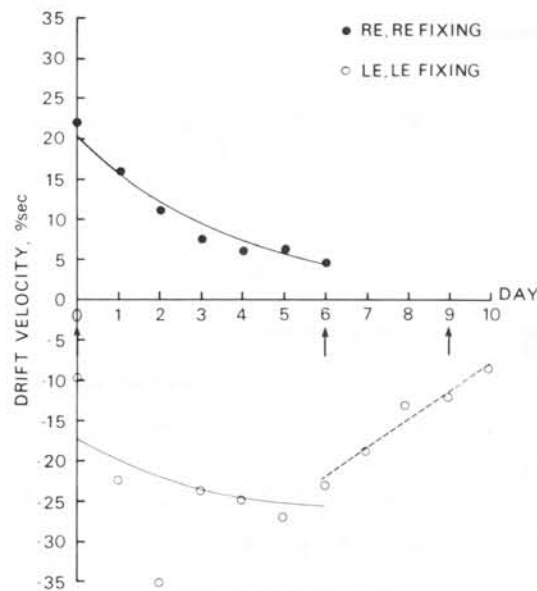


Fig 5. Initial drift velocities ( $V_d$ ) for leftward saccades. Upper points: right eye with right eye fixing. Best mean-squares exponential fit:  $V_d = 1.94 e^{-t/3.85}$  ( $r^2 = 0.95$ ). Lower points: left eye with left eye fixing. Best mean-squares exponential fit for days 0 to 6, excluding day 2:  $V_d = 10.2 e^{-t/3.13}$  ( $r^2 = 0.79$ ). Best straight-line fit for days 6 to 10:  $V_d = 43.5 + 3.5 t$  ( $r^2 = 0.96$ ).

the paretic eye in the direction of the paresis. Each point is the average of at least eight movements. Although the mean gain increased during the time the good eye was patched, the normalized velocity did not change appreciably. This was reflected by the increased duration of these saccades. The velocity change is examined further in Figure 4, which shows the normalized velocities of the range of gains obtained during each day's testing averaged together. The straight line fitted to the data ( $r^2 = 0.57$ ) shows a slight upward trend that was present throughout the ten days of the experiment (slope = 0.02); it appeared to be independent of patching conditions. The normalized velocities of leftward saccades of the good eye were: 1.13 (day 0), 1.04 (day 2), and 1.08 (day 5), also reflecting no gain-related change.

When a saccade failed to bring the eye accurately on target, it drifted slowly to the target's position. Figure 5 illustrates the drift velocities in the two eyes after rightward movements; the measured eye was always fixating. The drift velocity of the right eye steadily declined and that of the left eye increased during the time in which the left eye was patched. When the patch was switched, the left eye drift became slower; sufficient data for the paretic right eye were not available during this period since the exotropia placed the eye beyond the range of accurate recording. The right and left eye drift velocity points

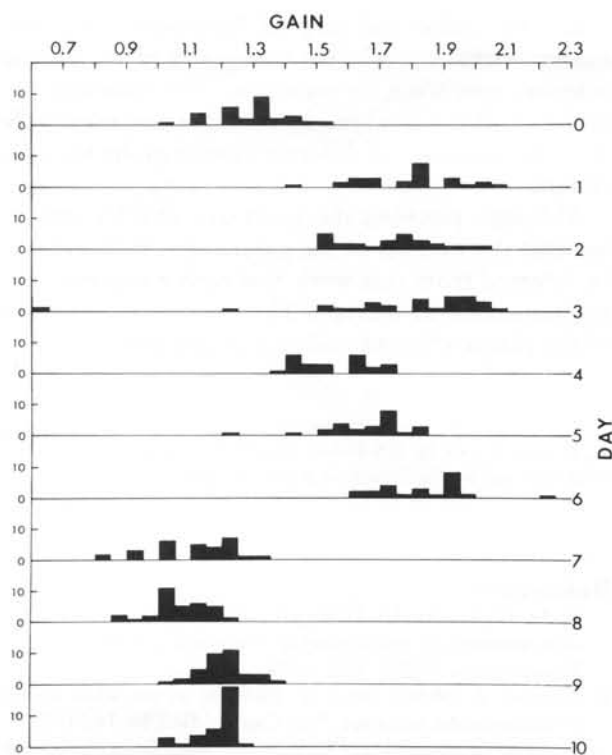


Fig 6. Histogram of saccadic gain distributions for the left eye during right eye fixation shown on each of the ten days of the experiment. These gains were measured for leftward movements from 10 degrees right to 0 degrees.

were both fitted with exponential curves ( $r^2 = 0.95$  and  $0.79$ , respectively), that had time constants of  $3.84$  and  $3.12$  days, respectively. In the left eye curve, the outlying point on day 2 was not used for fitting. The left eye data, obtained during right eye patching, were well fit by a straight line ( $r^2 = 0.96$ ).

Exophorias in each eye fluctuated between  $4$  and  $14$  degrees, with no apparent trend. The same was true for the small exotropia present during binocular viewing; it varied between  $0$  and  $4$  degrees. The patching had no effect on either.

The wide variations in gain of the nonfixating eye and the changing shapes of the gain distributions during the course of the experiment are illustrated in Figure 6. The distributions seemed to broaden following the initial system perturbations that occurred on days following a change in patching conditions (i.e., days 0 and 6). As recovery advanced, the distributions became tighter (e.g., days 9 and 10).

## Discussion

Changes in saccadic gain during the course of the experiment reflected plastic alterations in the neural mechanism responsible for saccadic eye movements. The right medial rectus paresis caused leftward saccades of the right eye to be both hypometric and

slower than normal saccades of similar amplitude. Forcing the paretic eye to be used at all times exerted a strong influence on the ocular motor system to effect a gain increase that maximized the motility of this eye. We demonstrated for the first time the temporal course of plastic adaptation in the human saccadic mechanism. The time constants of  $0.85$  and  $1.54$  days for increase and decrease of gain, respectively, are within the range found in studies of animal saccadic plasticity [5] and human vestibuloocular system adaptation [2, 3]. The stability of the paresis, as measured by the maximum adduction of the affected eye, assured that the saccadic gain increase in the initial portion of the experiment reflected adaptive changes in the central nervous system as distinct from simple clinical improvement. Our attempt to drive the gain back down to unity in the good eye was interrupted, however, by the beginning of recovery in the paretic eye. Fortunately, the adaptive process and recovery in that eye acted in opposition to each other, thereby posing no risk of confounding their effects. The reason for the increase in gain of the good left eye from day 9 to 10 (see Fig 2B) is not entirely clear unless the patient chose to fixate with his improving paretic eye during the 24 hours without patching that preceded the recording.

The contrast between the pronounced change in saccadic gain for movements into the paretic field and the simultaneously unaffected saccades in the opposite direction (see Fig 2) demonstrated that plastic adaptation can be directionally selective in humans. Optican and Robinson [5] found similar directional independence of gain change in monkeys.

Saccadic peak velocity, unlike gain, remained relatively unimproved by the patchings; thus, although the ocular motor system was capable of partially overcoming the amplitude errors caused by the peripheral neuropathy, it could not bring the resulting saccades much closer to normal velocities. The corrective adaptive process acted selectively on the input to the saccadic mechanism (i.e., affecting only overall gain), rather than altering the form of the innervation itself. Since, in the paretic eye, the saccadic gain and duration increased and the normalized velocity did not, only the pulse width was effectively changed. Either the pulse height (firing frequency) did not increase, or it did and was not reflected by the paretic nerve. However, if we add to this the normalized velocity data of leftward saccades of the good left eye, which also showed no change, we must conclude that the gain change was accomplished by pulse width changes and that the pulse height (firing frequency) was maintained at normal levels for the various saccadic amplitudes. The slight upward trend of the normalized peak velocities over the whole ten days (see Fig 4) may indicate an otherwise impercep-

tible recovery of function in the nerve; this was independent of the patching.

Single cell recordings from abducens and oculomotor neurons [1, 6, 8] indicate that a pulse increase in neuronal firing frequency initiates saccades, and a step change (to the new steady-state firing frequency) is responsible for stopping and maintaining the eyes at the new eye position. Thus, the pulse-step is the neural activity sequence underlying saccadic eye movements.

Figure 5 illustrates that changes in the relationship between the pulse and step of neural activity occurred during the patching process. A drift following a saccade indicated a pulse-step mismatch. The eye passively drifted from the position initially given by an inadequate pulse to the gaze angle specified by the step. On day 0 the paretic eye showed a considerable drift toward the target. At the same time, the yoked left eye drifted back from an initial overshoot. After the good eye was patched, drift was reduced in the right eye and increased in the left, indicating adaptation serving to reduce the mismatch between pulse and step responses in the paretic eye. Because of Hering's law, this correction of undershooting in the paretic eye caused a simultaneous increase of overshooting in the normal eye. These changes indicate that the ocular motor system was able to alter and reduce the pulse-step mismatch despite its apparent inability to increase the firing rate of the pulse (which would produce a velocity increase) to overcome the slowed response of the right eye. Like the plastic adaptation of saccadic gain, this was a position rather than a velocity correction.

In summary, through alternate patching of the paretic and normal eyes of a patient with a third nerve palsy, we were able to induce plastic adaptive changes in saccadic gain and in the relationship be-

tween the pulse and step of brainstem firing frequency without producing changes in saccadic peak velocity, exophoria, or exotropia. This indicates the presence of a central mechanism that can selectively alter the operation of different aspects of the saccadic system.

Although patching the good eye enables one to increase the motility of the paretic eye, it should not be inferred from this work that such a procedure is recommended as therapy. The obvious reversibility of the plastic changes makes it impractical.

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