Slow Target–Directed Eye Movements in Ataxia-Telangiectasia

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PURPOSE. To analyze the slow eye movements that shift the direction of gaze in patients with ataxia-telangiectasia (A-T).

METHODS. Eye and head movements were recorded with search coils in three patients with A-T during attempted gaze shifts, both with the head immobilized and free to move.

RESULTS. Gaze shifts frequently included both saccadic and slow components. The slow movements were recorded after 42% of saccades and had an average peak velocity of 6.1 deg/sec and a mean amplitude of 2.0°. They occurred with the head stationary and moving, could be directed centripetally or centrifugally, had velocity waveforms that were relatively linear or exponential, and always moved the eyes toward the visual target.

CONCLUSIONS. The slow movements appear to differ from pursuit and vestibular eye movements and are not fully explained by the various types of abnormal eye movements that can follow saccades, such as gaze-evoked nystagmus or postsaccadic drift. Their origin is uncertain, but they could represent very slow saccades, due to aberrant inhibition of burst cell activity during the saccade. (Invest Ophthalmol Vis Sci. 2002; 43:686–691)

Minimal eye motion typically occurs before or after saccades.1 When the head is stationary, post-saccadic eye movement is usually attributed to a mismatch between the phasic (pulse) and tonic (step) components of the saccade command.2 When the head is moving, slow gaze shifts are generally ascribed to partial cancellation of the vestibulo-ocular reflex (VOR).3 In the head-fixed cat, however, slow post-saccadic eye movements have been described that shift the direction of gaze toward the visual target.4,5 These movements are not characteristic of either a pulse-step mismatch or cancellation of the VOR, and their basis is uncertain.

We have observed that some patients with the genetic disorder ataxia-telangiectasia (A-T) shift gaze with a combination of saccadic and slow eye movements, both of which direct the eyes toward the visual target.6 These slow eye movements have not been described in other human subjects, but appear qualitatively similar to those recorded in the cat. To characterize these movements and to determine their interaction with head motion, we recorded eye and head movements in several patients with A-T during head-fixed and head-free gaze shifts.

METHODS

Eye and head movements were recorded with the magnetic search coil technique, with coils placed in one eye and in the center of the forehead. The head coil was calibrated by passively orienting the head to the horizontal 0° and right 10° positions, and the eye coil was calibrated by having subjects fixate targets at 0° and right 10° with the head centered. Data were filtered at 90 Hz, sampled at 500 Hz, and stored in a computer for off-line analysis.

Coil recordings were made in three patients (age range, 15–23 years) in whom A-T was diagnosed according to standard criteria.7 The consent of the patients and their parents was obtained according to the Declaration of Helsinki, and all experimental procedures were approved by the Johns Hopkins Committee on Clinical Investigation.

Gaze shifts were tested with the head immobilized on a bite bar and with the head free to move. Patients viewed an array of light-emitting diodes 125 cm in front of the head and made gaze shifts along the horizontal axis for target jumps from 0° to right 10°, right 10° to 0°, 0° to left 10°, and left 10° to 0°. Pursuit movements were also recorded with the head immobilized. The pursuit target was back projected onto a translucent screen and moved to the right and left at a constant velocity of 20 deg/sec.

Data were analyzed off-line with an interactive computer program. The position of the eye and head coils was determined with a linear calibration. The coils gave direct measurements of gaze position (defined as eye position in space = eye coil) and head position (head coil). Eye position in the orbit was calculated as gaze minus head position. Gaze, eye, and head velocity signals were obtained by digitally differentiating the position signals and by filtering them at 30 Hz with a seven-point Gaussian filter. The beginning of the rapid gaze movement (gaze saccade) was defined as the point where gaze velocity first exceeded 20 deg/sec, and the end of the movement was defined as the point where gaze velocity declined to less than 45 deg/sec. The amplitude and peak velocity were determined for the initial gaze saccade in each gaze shift.

For head-fixed gaze shifts, the amplitude, duration, and peak velocity of the slow post-saccadic movements were quantified for centrifugal saccades. Similar measurements were not made for centripetal saccades, because all three patients had impaired gaze holding that resulted in centripetal slow phases. The onset of the slow movement was defined as coincident with the end of the saccade and the end of the slow movement as the point at which gaze velocity returned to a steady value of zero. Although slow movements could also precede the initial saccade, such presaccadic movements were infrequent and therefore were not analyzed quantitatively. Head-free gaze shifts were analyzed by separating the slow post-saccadic movements into components that were due to VOR cancellation and components that were independent of head motion, as described in the Results section.

RESULTS

Gaze saccades were markedly hypometric in the three subjects, but their peak velocities were appropriate for the amplitude of the gaze shift (Fig. 1). In the head-fixed condition, many
gaze shifts consisted of a combination of saccades and slow movements (Fig. 2). The slow movements typically followed saccades without a detectable latency, but could also precede the initial saccade. These movements were always corrective, because they moved the eyes toward the visual target. They were recorded for both centrifugal and centripetal gaze shifts and had velocity profiles that were either relatively linear or velocity-decreasing. The characteristics of the slow eye movements that followed centrifugal, head-fixed saccades are summarized in Table 1. These movements occurred after 42% of initial saccades in the three subjects, and had an average amplitude of 2.0° and an average peak velocity of 6.1 deg/sec. A small fraction of the head-fixed eye movements had dynamic characteristics that fell between saccades and the typical postsaccadic slow movements. For example, the second eye movement in Figure 3 had an amplitude of 5° but its peak velocity was relatively low (approximately 70 deg/sec).

The head movements recorded during head-free gaze shifts were generally smaller than the size of the target displacement (Fig. 4) and averaged 2.3° to 5.8° in the three subjects. The temporal relationship between head motion and the gaze shift was variable, because the head movement could precede (Fig. 4A) or follow (Fig. 4B) the primary gaze shift, or both could occur concurrently. When the head movement and gaze shift did not coincide, the VOR appeared to function normally with a gain near unity. For example, in Figure 5A the head movement was completed before the initial gaze saccade, and a comparison of head and gaze velocity (Fig. 5B) demonstrates

![Figure 1](image1.png)

**Figure 1.** Amplitude and peak velocity of the initial gaze saccades in head-fixed (○) and head-free (●) conditions. All target displacements were 10°. **Solid lines:** mean values measured in a population of normal subjects in the same laboratory.**

![Figure 2](image2.png)

**Figure 2.** Gaze position and velocity profiles for two head-fixed gaze shifts. Saccade velocities are clipped at the upper and lower extremes of the figures.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Frequency (%)</th>
<th>Amplitude (deg)</th>
<th>Duration (sec)</th>
<th>Peak velocity (deg/sec)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>2.4 ± 1.9</td>
<td>0.58 ± 0.4</td>
<td>5.5 ± 2.5</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>2.5 ± 1.9</td>
<td>0.41 ± 0.2</td>
<td>7.2 ± 4.4</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>1.5 ± 0.5</td>
<td>0.31 ± 0.1</td>
<td>6.5 ± 3.1</td>
<td>11</td>
</tr>
<tr>
<td>1–3</td>
<td>42</td>
<td>2.0 ± 1.5</td>
<td>0.44 ± 0.3</td>
<td>6.1 ± 3.2</td>
<td>28</td>
</tr>
</tbody>
</table>

Data are limited to head-fixed, centrifugal gaze shifts (0° to right 10°, 0° to left 10°). Frequency indicates the percentage of initial gaze saccades that were followed by slow movements. The mean ± SD and number of observations are indicated.
that after the saccade, gaze shifted slowly to the left while the head velocity oscillated around zero. This uncoupling between head and gaze velocity indicates that the VOR had a gain near unity after the saccade and that cancellation of the VOR was not responsible for the prolonged slow gaze shift. In contrast, when the head movement and gaze shift occurred concurrently (Fig. 6A), head and gaze velocity were clearly linked (Fig. 6B), indicating that the VOR was partially canceled.

To quantify the dependence of the postsaccadic gaze shifts on VOR cancellation, instantaneous (desaccaded) gaze velocity was plotted against head velocity, and the slope and \( y \)-intercept of a linear regression of the data were calculated (Fig. 7). If VOR cancellation was complete during the slow postsaccadic movement (i.e., VOR gain was zero), then head and gaze velocity should be linked, and the regression slope of the data should have a value of unity (Fig. 7, dashed line). If the VOR functioned normally during the gaze shift (i.e., its gain was unity), then head and gaze velocity should be independent and the regression slope should have a value of zero. With this approach, the VOR gain during the nonsaccadic portions of the gaze shift can be estimated as \( 1 - \) regression slope. Gaze movements that were not dependent on VOR cancellation (and hence were unaffected by head motion) should shift the data points away from zero along the \( y \) (gaze velocity) axis. The average velocity of this VOR-independent component was therefore estimated by calculating the \( y \)-intercept of the regression plot.
Figure 7 illustrates this analysis for the gaze shifts shown in Figures 5 and 6. When the head movement and gaze shift did not coincide (Fig. 5), the regression line had a slope of $-0.03$ and a $y$-intercept of $-2.5$ (Fig. 7A), indicating that the VOR gain was approximately 1.03 and that gaze shifted leftward independently of head motion with a mean velocity of 2.5 deg/sec. This analysis was applied to 20 gaze shifts in which the head movement and gaze shift did not coincide and yielded an average VOR gain of 1.04 $\pm$ 0.08 (SD) and an average VOR-independent component of 3.1 $\pm$ 1.3 deg/sec (SD). In contrast, when the head movement and gaze shift coincided (Fig. 6), the regression slope was 0.66 (indicating a VOR gain of 0.33) and the $y$-intercept was $-2.6$ deg/sec (Fig. 7B). Analysis of 20 similar gaze shifts yielded an average VOR gain of 0.42 $\pm$ 0.21 and an average VOR-independent component of 2.8 $\pm$ 1.5 deg/sec.

Eye movements were also recorded in the three patients with A-T while they attempted to track a pursuit target moving horizontally at a constant velocity of 20 deg/sec. These visually guided movements, recorded with the head immobilized, were markedly impaired in all subjects, and were characterized by smooth movements of low velocity (gain ranged from 0.12 to 0.37) interrupted by frequent corrective saccades (Fig. 8).

**DISCUSSION**

The principal finding in this study is that patients with A-T shift the direction of gaze with a combination of saccades and slow movements. The slow movements could precede the initial saccade, but more typically followed both the initial and corrective saccades. Similar slow movements were observed in a prior study of A-T, but were not analyzed in detail and were attributed to vestibular slow phases. In our subjects, however, these movements clearly occurred in the absence of vestibular nystagmus, could be centrifugal or centripetal, occurred with the head stationary or moving, and always directed the eyes toward the visual target. The dynamics of these movements are similar to the slow eye movements that have been described in the head-fixed cat.

The mechanism underlying the slow gaze movements in A-T is uncertain. Because these movements were frequently recorded when head motion was minimal, VOR cancellation clearly cannot be their sole underlying mechanism. Unlike normal subjects or patients with congenital defects in saccade initiation, however, the patients with A-T canceled the VOR to a variable degree during small-amplitude gaze shifts when the gaze shift and head movement coincided. It is interesting to note that the three subjects had markedly impaired pursuit and could not significantly reduce their VOR gain during passive, whole-body, sinusoidal rotation. This suggests that the VOR cancellation evident during active, head-free gaze shifts may depend on a mechanism that uses the efferent command sent to the neck or proprioceptive afference and may be largely independent of the pursuit system.

Postsaccadic drift can shift the direction of gaze and occurs if the step command is not accurately matched to the pulse. Because patients with A-T have several eye-movement deficits...
that are associated with dysfunction in the cerebellar flocculus, the brain region responsible for minimizing post-saccadic drift, it is likely that a pulse-step mismatch contributes to the slow, post-saccadic movements. The dynamic characteristics of these movements, however, are not typical of post-saccadic drift, because they often had a prolonged duration and a relatively linear velocity profile. Post-saccadic drift, in contrast, has an exponential velocity profile with a time constant close to that of the oculomotor plant (approximately 200 ms).

Normal subjects can generate slow eye movements to step displacements in target position, which is considered a form of anticipatory pursuit. The patients with A-T had abnormal visually guided pursuit, however, and anticipatory pursuit has not been observed in patients with cerebellar disease who have a similar degree of pursuit impairment. Neural integration is abnormal in A-T and produces centripetal drift of the eyes during attempted eccentric gaze. Although these movements would augment centripetal slow movements, they served to attenuate the centrifugal movements that were frequently recorded. Finally, although the recordings presented herein were monocular, physical examination of these subjects demonstrates that the slow eye movements were approximately conjugate and hence were not due tovergence.

In sum, the slow gaze shifts in A-T probably have components that are the result of VOR cancellation (when the head is moving), post-saccadic drift, and impaired neural integration (for centripetal movements). An additional undefined mechanism also appears to contribute to these movements. It has been suggested that a slow eye movement pathway projects directly to the motor neurons, bypassing the saccadic pause cell-burst cell system, and there is limited evidence of such a pathway in the cat. In the patients with A-T, if the burst cell activity responsible for the rapid portion of the saccade were prematurely terminated, the remainder of the gaze shift could in theory be generated by this slow pathway. Furthermore, the saccade abnormalities evident in A-T (increased latency, hypometric amplitude) suggest aberrant suppression of burst cell activity during attempted gaze shifts. If the burst cells were partially inhibited during the saccade or at its onset, pre- or post-saccadic eye movements of markedly reduced velocity could result, driven by the subset of burst neurons that remain active. This mechanism, which suggests that the slow movements are actually low-velocity saccades, is supported by the observation that burst cell activity continues in the cat during slow, post-saccadic gaze shifts. Because the velocity of some gaze shifts in the patients with A-T were between normal saccades and the typical slow movements (Fig. 3, for example), it is plausible that the fast and slow components of the gaze shifts may represent different ends of a spectrum of movements generated by the same saccade mechanism.

Although slow saccades historically were thought to be pathognomonic for disease in the burst cells, there is considerable experimental and clinical evidence that dysfunction at higher levels, such as the basal ganglia and superior colliculus, can result in slowing of saccades. As does Huntington disease, A-T may slow saccades by disturbing the saccade generating mechanism at a level above the burst cells. Patients with A-T may also generate a spectrum of saccade velocities, however, ranging from those with essentially normal dynamics to extremely slow movements that cannot be readily identified as saccadic.

Acknowledgments

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