

Chapter 65

Coordination of Head and Eyes during the Performance of Natural (and Unnatural) Visual Tasks

Eileen Kowler, Zygmunt Pizlo, Guo-Liang Zhu, Casper J. Erkelens, Robert M. Steinman, and Han Collewyn

A classical problem in understanding the control of movement in natural environments is the question of how different motor activities—movements of the eyes, head, and arms, for example—are linked in space and in time to create effective and well-coordinated patterns of action. Perhaps the most compelling modern statement of this problem was made by Lashley (1951), who was seeking what he called “a syntax of movement,” which he defined as “an habitual order or mode of relating the expressive elements ... which may be imposed upon a wide range and a wide variety of specific acts.” (p. 122). Lashley rejected the idea that individual movements were triggered by isolated sensory signals because this, he believed, could not account for the elegant and apparently effortless patterns of action found in such activities as the coordinated leg movements of insects or the trotting and pacing of a horse. Lashley argued that the key to the achievement of coordinated patterns of action was to program diverse motor responses with reference to a single, central spatial map and a single internal clock. This chapter, inspired by Lashley’s ideas, examines the coordinated movements of the head and the eyes during the performance of natural, and some unusual, visual tasks.

Lashley’s ideas have led many researchers in human movement control to try to describe and to model the spatial and temporal coordination of action sequences. Consider a few relatively recent examples:

1. Viviani and Terzuolo (1980) described consistent spatial and temporal relationships in human handwriting that remained constant despite changes in the size of the written characters or the speed of writing.

2. Sternberg et al. (1978a, 1978b) found that the latency to begin a sequence of spoken syllables or typed keystrokes, and the time between successive responses in the sequence, depended on the number of elements in the sequence. They accounted for their results by a memory-search model, in which programs for all the movements of the sequence are created in advance, and individual programs are retrieved before the execution of each response element.

3. Rosenbaum et al. (1983, 1984) concluded that the motor programs are stored in a hierarchically structured memory based on the rhythmic patterns of movement sequences they observed in a finger-tapping task.

Saccadic eye movements, like sequences of finger movements or spoken syllables, are also programmed as structured sequences of movements. Zingale and Kowler (1987) found results quite similar to those of Sternberg et al. when they asked subjects to scan an array of one to five target points arranged in a simple two-dimensional pattern. The latency of the first saccade of the sequence, and the time between successive saccades, increased with the number of targets to be scanned. Also, intersaccadic intervals depended on the ordinal position of the saccade within the sequence, resulting in idiosyncratic, rhythmic patterns of scanning. These results show that properties of saccades depend on the sequence in which they occur. The results are consistent with the idea that saccadic programs are prepared and stored in advance of the execution of the sequence, and retrieved when

needed during the execution of the sequence, just as Sternberg et al. had suggested for typing and speech.

Zingale and Kowler (1987) suggested that preprogrammed saccadic sequences are useful because they facilitate the coordination of saccadic eye movements with other concurrent voluntary movements, an idea in keeping with Lashley’s notion of a shared internal clock used to ensure the proper temporal correspondence of concurrent motor activities. An incidental observation supported this view. Zingale and Kowler asked one of their subjects to try to look from one target point to the next as rapidly as possible. The experiment, like the rest of their experiments, was done with the head stabilized by a bite board because of limitations of the eye movement recording instrument (Double Purkinje Image Tracker). Under the instruction to scan as quickly as possible, intersaccadic intervals were reduced and saccadic accuracy was poorer, as would be expected. What was not expected was the strong discomfort in the neck muscles the subject felt, as if she was straining to continue to do the task while keeping her head from flying off the bite board. It was as if the internal instruction to “make a saccade to each target point” was, in fact, inseparable from the internal instruction to orient to each target point by turning the head and eye at the same time.

Several studies have attempted to demonstrate links between the programming of concurrent head and eye movements (for a review, see Jeannerod, 1988). These studies predominantly have been restricted to single movements rather than movement sequences. Evidence for the concurrent programming of movements of the head and eyes comes mainly from observations that (1) a saccadic eye movement can occur at about the same time as the onset of electromyographic (EMG) activity in the neck muscles (e.g., Bizzi et al., 1971), and (2) neck EMG activity can be observed when saccades are programmed while the head is held in place (Berthoz and Grantyn, 1986).

The research described in the preceding paragraphs has provided several interesting demonstrations of the concurrent programming of head and eye movements and of the programming of structured sequences of movements. These demonstrations, however, have been restricted to a few, relatively simple and artificial laboratory tasks, not necessarily representative of the way the head and eye are used together in more natural situations. This is a serious limitation. We know little about the kinds of coordinated head and eye movement patterns in the natural behavioral repertoire. Moreover, we know little about the factors that make some patterns more valuable for the acquisition of visual information than others. Finally, and most importantly, we know little about the inherent constraints that make certain patterns of concurrent head and eye movements relatively easy, and others difficult or impossible, to program. Acquiring information on this last topic is critical for the development of models of the internal mechanisms, such as Lashley’s shared internal clock and shared spatial map, that are responsible for the coordinated movements of the head and eyes.

In order to begin to understand the kinds of head and eye movement patterns human beings choose during natural tasks, we measured movements of the head and eyes during reading

We chose to study reading because the eye movement pattern is fairly stereotypical and has been subjected to extensive empirical and theoretical investigation (for review, see O'Regan, 1990). Therefore, we were able to begin with a clear idea of what sort of saccadic patterns to expect. Nevertheless, most of the research on reading (and certainly any research using highly sensitive eye monitors) has been done with subjects whose heads were stabilized by bite boards or chin rests, or subjects who were constrained by having to peer through the eyepieces of oculographic recorders. As a result, little or nothing is known about the patterns of eye and head movements that characterize reading when the head is free to move.

To emphasize the naturalistic character of the task, we had subjects read actual pages of text (rather than electronic displays) with both eyes at a typical reading distance. The distance we used was small enough (29.5 cm) so that we had to measure head translations, in addition to eye and head rotations, in order to obtain an accurate measure of the position of the line of sight along the page of text.

Two other tasks were studied. First, we looked at the eye and head movement pattern when the subject was asked to scan individual letters separated by distances about equal to the length of words in the text we tested. This letter-scanning condition was tested to find out whether characteristics of the head and eye movement pattern were unique to reading, or would be shared with a task making about the same demands on the spatial properties of saccades but making different demands on the cognitive apparatus of the subject. Second, inspired to a large degree by the characteristics of eye and head movements we observed during reading, we asked a subject to execute a variety of unusual head and eye movement patterns. In this experiment, we tried to deliberately decouple the expected spatial relationships between concurrent movements of the head and the eyes. This last experiment introduces a new and potentially promising paradigm that can be used to explore the limits of the capacity of the human being to link concurrent head and eye movements.

Methods

Eye and head movement recording

Two-dimensional rotations of the right and left eyes and of the head relative to earth-fixed coordinates were recorded by the revolving magnetic field monitor at the University of Maryland. Horizontal and vertical angles were measured with an accuracy of 1 minute of arc and were sampled and stored at 488 Hz. These angles were insensitive to translational movements of the head over the range of motions employed in the experiments. [For a more detailed description of this instrument, see Collewyn et al. (1981, 1988a) and Chapter 64, this volume.]

The position of the head in space was measured with an acoustic ranging system (a very highly in-house modified SAC Associates 3-D Grafpen). A sparking device (henceforth, "sparker"), attached to the top of the head, emitted 60-kHz ultrasonic pulses whose acoustic wavefronts were picked up by three microphones at a sampling frequency of 61/s. The instrument determined the distance of the sparker from each of the microphones based on the propagation times of the sound pulses. These distances were converted to a three-dimensional Cartesian coordinate system. The overall accuracy of the measurement, including all the various sources of imprecision, was about 1 mm.

Subjects

Two of the authors (E. K. and H. C.) served as subjects for the reading experiment. Both are highly experienced eye movement subjects. E. K. is myopic and read with her usual contact lenses. H. C. read without spectacle correction. Another author (R. S.) served as a subject for the second experiment in which head and

eye movements were measured during the inspection of a square array of targets. R. S. does not require spectacle correction for distance vision.

Stimuli

Figure 65-1 illustrates the subject and the stimulus used in the reading trials. The stimulus consisted of pages of text from the novel *Maxwell's Train* (Hyde, 1984). The page of text to be tested for the trial was attached to a wooden board that was mounted on a tabletop at an angle of 75° with the horizontal. The horizontal distance between the midpoint of the center of rotation of the two eyes and the text was 29.5 cm. At this distance a line of text, which measured 10.7 cm across and contained on average 61 characters, subtended 20.4°.

Stimuli for the letter-scanning condition were pages of text from the same book in which only single letters, spaced at intervals approximately equal to the length of words, were visible.

In a second experiment, the subject tried to execute a variety of usual and unusual patterns of head and eye movements. Details of this experiment are described later, along with the results.

Procedure for reading and letter-scanning tasks

Each subject was tested in one recording session consisting of 16 trials lasting 30 seconds each. The head was on the bite board (head-fixed condition) for the first and last four trials, and off the bite board (head-free condition) for the middle eight trials of the session. The last trial in each group of bite board trials and the

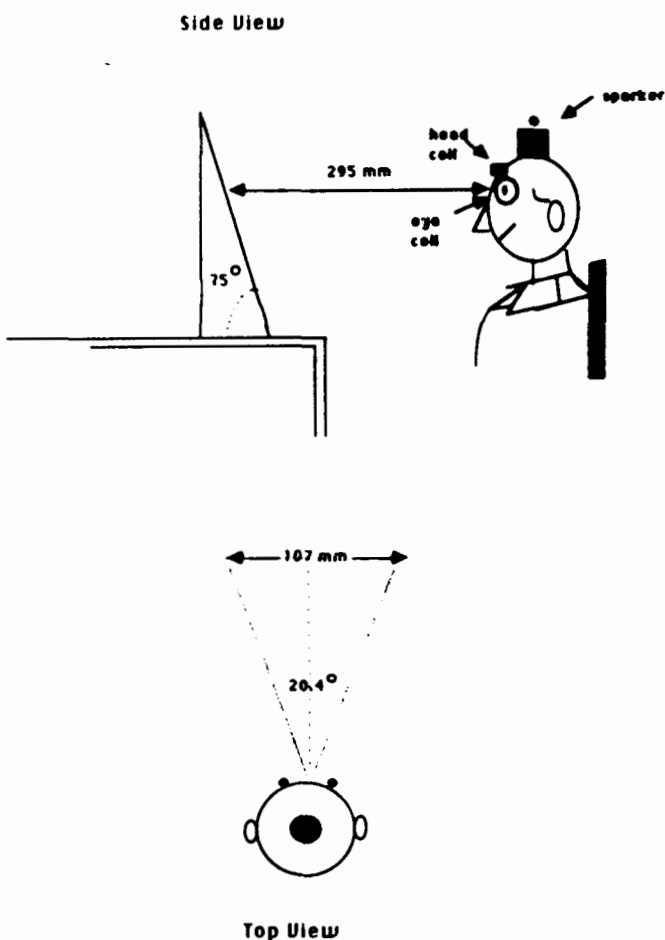


Fig. 65-1. Sketch of a subject viewing the stimulus. The page of text was mounted on the inclined board located 29.5 mm from the midpoint of the center of rotation of the subject's eyes.

last two trials in the group of head-free trials were letter-scanning trials. The rest were reading trials.

Subjects were instructed to read at what they considered to be their normal pace for the material presented. They were told to start reading at the portion of the text corresponding roughly to eye level when the experimenter gave the signal to begin. A few seconds later the experimenter pushed a button that initiated the collection of data. Subjects read with the expectation that their comprehension of the material would be tested at the end of the recording session.

Calibration session

The experiments were preceded by a brief calibration session in which we measured:

1. The output of the head and eye sensor coils when the head was on the bite board and each eye was fixating directly ahead.
2. The output of the sparker when positioned (1) at the origin of the three-dimensional coordinate system, and (2) on top of the subject's head while the subject was aligned on the bite board. In this standard bite board position, the midpoint of the center of rotation of the two eyes coincided with the origin of the three-dimensional coordinate system. These two measurements made it possible to determine the location of the center of rotation of each eye during the experimental trials when the sparker was worn on top of the head.
3. The output of the sparker and the head and eye sensor coils when the subject fixated, in turn, the letters at the upper left, upper right, lower left, and lower right corners of the page of text.

Data analysis

In the first stage of data analysis the output of the sparker and the measured head rotation were used to determine the position of the center of rotation of each eye in three-dimensional space (see Chapter 64, this volume, for details). Next, this measurement of the center of rotation of each eye was combined with the measured eye rotation to determine the position of each line of sight on the page of text. Finally, the movements of each line of sight along the page were analyzed to detect saccades, and measure the sizes of these saccades and of the intersaccadic intervals. Saccades were detected by an acceleration criterion whose accuracy was confirmed by inspection of analog records. We ignored saccades, and intersaccadic intervals containing saccades, smaller than 2 mm on the page, which was about the distance between the centers of adjacent characters. Such small saccades are exceedingly rare during normal reading (Cunitz and Steinman, 1969).

Results

Coordination of head and eye during reading

Head rotations during reading were larger when the head was free than when the head was on the bite board. The average trial standard deviation (S.D.) of head rotations with the head on the bite board was 5.4 minutes of arc for H. C. and 4.1 minutes of arc for E. K. Average S.D.s with the head free were 42.3 minutes of arc for H. C. and 24.7 minutes of arc for E. K. The S.D.s with the head free are about twice what is observed when subjects try to hold the head as still as possible without artificial support during maintained fixation (Skavenski et al., 1979; Steinman et al., 1982).

Figure 65-2 (top) shows an example of the head and eye movements made by H. C. during reading. The top trace shows head rotations and the bottom trace shows rotations of the left eye (rotations of the right eye did not differ appreciably). The pattern of head rotations varied during the trial. During the third and

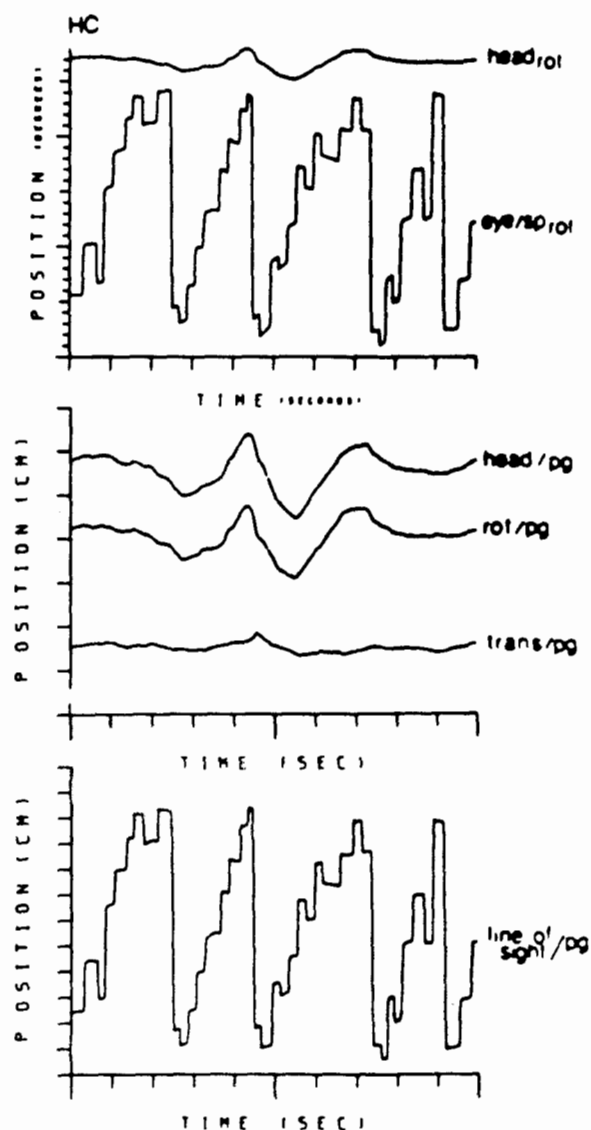


Fig. 65-2. Results of a sample reading trial for subject H. C. (Top) Horizontal rotation of the left eye and the head as a function of time during reading. Upward deflection of the traces indicates rightward eye or head motion. (Middle) Total movement of the head (head/pg), the rotational component (rot/pg), and the translational component (trans/pg) on the page of text. These traces represent the positions of an imaginary line connecting the midpoint of the center of rotation of the left eye with the plane of the page. (Bottom) Horizontal position of the line of sight of the left eye on the page of text.

fourth seconds, H. C. made a fairly large (about 2°) rightward head rotation as his eyes moved rightward across the line of text. The saccade returning the eyes to the next line of text was, of course, rapid, but the return sweep of the head took more than 1 second to complete. This means that for nearly 0.5 seconds H. C. was making saccades to the right, as he began to read a new line, while his head continued to move to the left. Figure 65-2 (top) also shows some fairly fast intersaccadic drifts opposite to the direction of head rotation.

The middle graph in Figure 65-2 shows the total movement of the head (top trace), along with the rotational (middle trace) and translational (bottom trace) components. In all three traces head position is expressed in centimeters along the page of text. These traces represent the position of an imaginary line projected from the center of rotation of the left eye onto the page. The rotational

component of head motion clearly dominated, but translations were evident, particularly during the large head movement in the fourth and fifth seconds.

The bottom graph in Figure 65-2 shows the position of the line of sight in centimeters on the page of text. The movements of the line of sight resulted from both the movement of the center of rotation of the eye in three-dimensional space and the rotation of the eye in space about its center. The intersaccadic drifts were somewhat smaller than the intersaccadic drifts seen in the pure eye rotational component (top graph). (The scales on the top and bottom graph are approximately equivalent, allowing this comparison to be made.) This reduction in intersaccadic drift means that some of the intersaccadic eye rotation, seen in the top graph, was actually compensation for the small translational movements of the eye in space produced by the translations of the head.

Figure 65-3 illustrates the same phenomena for another of H. C.'s trials. The head movements and the saccades were in opposite directions during the second and the final seconds of the

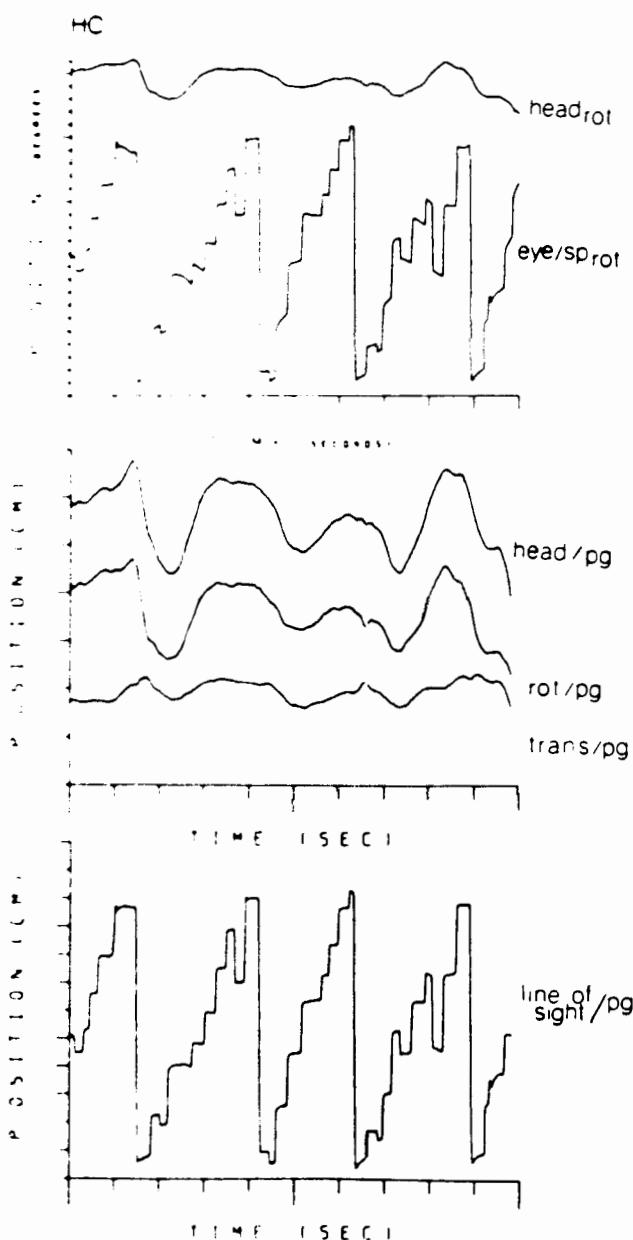


Fig. 65-3. Results of another sample reading trial for subject H. C. Top, middle, and bottom graphs as detailed for Figure 65-2.

record. The reduction in intersaccadic drift is again seen in the bottom graph, showing the position of the line of sight on the page, and showing, once again, that eye rotations are used to compensate for translations. Similar results were obtained for subject E. K. She, like H. C., used eye rotations to compensate for translational movements of the eye in space. Unlike H. C., however, the direction of her head movements was rarely opposite to the direction of her saccades.

In summary, the head moves during reading, but not in a stereotypical pattern. We found clear differences in the amplitude of the head movements over the course of the trial. Also, in some instances the head moved in the same direction as the reading saccades; in other instances it moved in the opposite direction. Eye rotations compensated well for head movements, producing a fairly stable line of sight during intersaccadic intervals.

Saccades during reading and scanning with the head fixed and free

Figure 65-4 (top) shows the average duration of the intersaccadic intervals and the average size (in millimeters on the page) of the rightward saccades during reading when the head was on the bite board and when it was free to move. The only reliable differences between the head-fixed and head-free performances were for subject H. C., who had slightly shorter intersaccadic intervals and slightly longer saccades when his head was free to move.

There were no differences between the saccadic patterns with the head fixed and with the head free when single letters were scanned (Figure 65-4, bottom). Intersaccadic intervals were, however, 40 to 100 ms longer during scanning than during reading. Saccades were also a bit shorter during scanning, but the slightly reduced size of the saccades was not sufficient to account for the increase in intersaccadic interval (see Wyman and Steinman, 1973; Kowler and Anton, 1987). The shorter intersaccadic intervals observed during reading than during the presumably easier scanning task is a puzzling phenomenon, observed first by Huey (1900) in one of the earliest studies of eye movements during reading. The puzzle is why the processing of cognitive material speeds up, rather than slows down, the concurrent motor pattern.

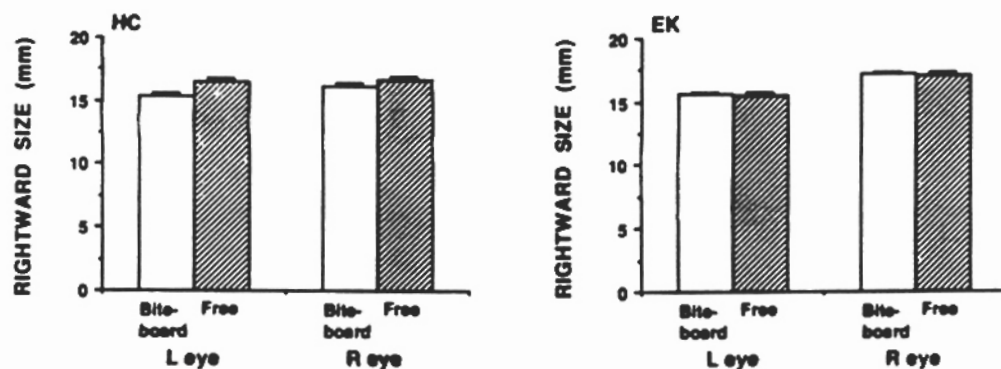
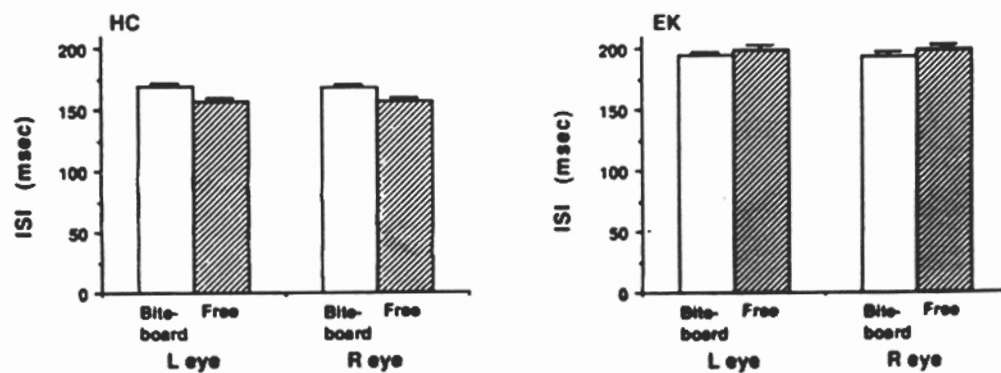
Intersaccadic speeds

The analysis of intersaccadic speeds confirmed that eye rotations compensated well for head movements. Average intersaccadic speeds, shown in Figure 65-5, were slightly faster with the head free than with the head on the bite board during the scanning task, but were either the same or slightly faster with the head on the bite board during reading. The intersaccadic speeds were small relative to the size of the characters. The largest drift (H. C.'s left eye while he was on the bite board during reading) carried the line of sight only 0.9 mm (about the width of one character) during his brief (169-ms) intersaccadic interval. This drift, however, was about 1°/sec. This is about five to ten times as fast as the drift speed observed during maintained fixation with the head on a bite board (Steinman et al., 1973) but quite similar to the drift speed observed during maintained fixation when head movements are permitted (Skavenski et al., 1979; Steinman and Collewyn, 1980; Steinman et al., 1982).

Limits of spatial and temporal coordination of the eye and head

Our results thus far show a clear, but flexible, relationship between movements of the eye and head. This would seem to suggest that human beings have the capacity to program different sorts of spatial and temporal patterns of head and eye movements depending on strategy and choice. We sought to understand the limits of this flexibility by asking a subject (R. S.) to attempt a

READ



SCAN

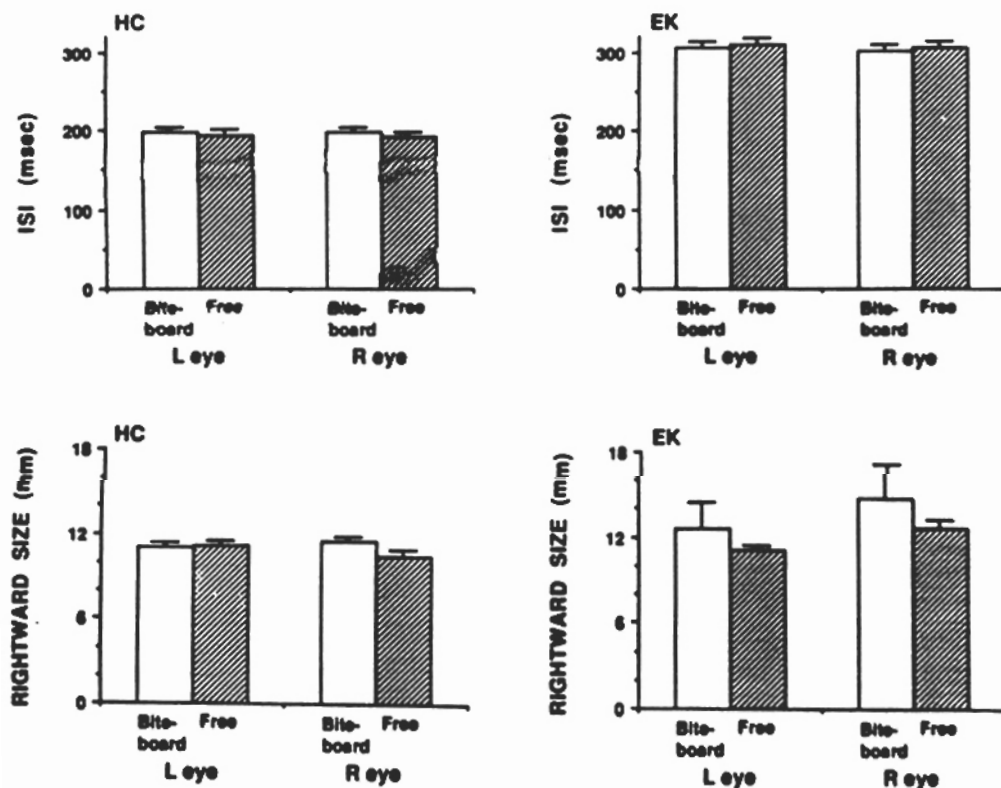


Fig. 65-4. (READ) Mean intersaccadic interval (top) and mean size of rightward saccades on the page of text (bottom) during reading. (SCAN) Mean intersaccadic interval (top) and mean size of right-

ward saccades on the page of text (bottom) during scanning individual letters. Vertical bars indicate 1 S.E. Means are based on 600 to 700 saccades for reading and on 150 to 200 saccades for scanning.

INTERSACCADIC SPEED

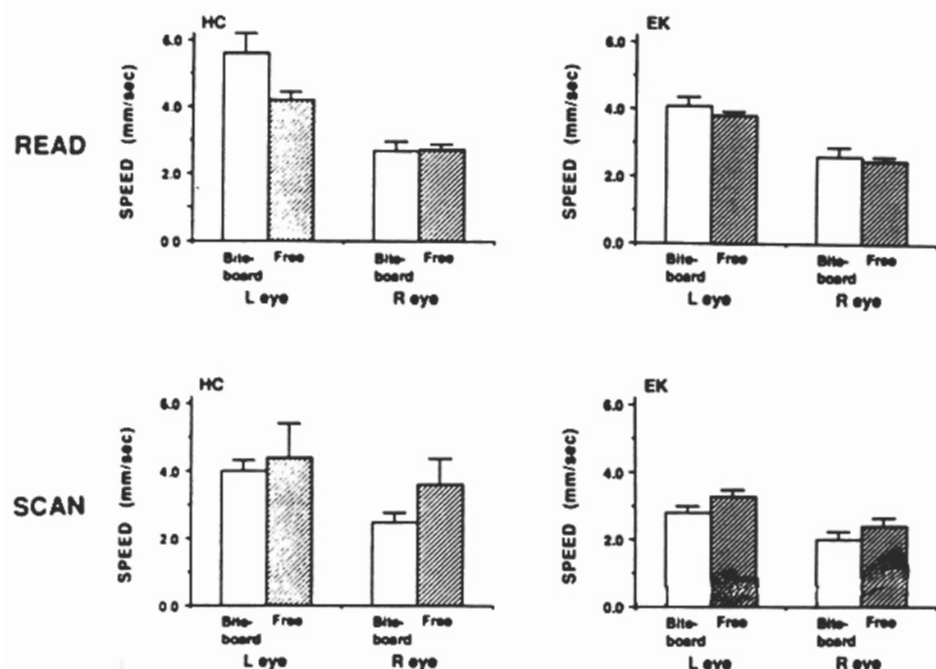


Fig. 65-5. Mean intersaccadic speed during reading (top) and during scanning of individual letters (bottom) in mm on the page per second. Vertical bars indicate 1 S.E. Means are based on 600 to 700 saccades for reading and 150 to 200 saccades for scanning.

variety of natural, and some unusual, head and eye movement patterns.

He looked at an array of eight small, brightly colored square targets, arranged in a square pattern on a distant wall (7.9 m). Adjacent targets were separated by 5.5°. The room lights were left on so that the subject saw the stimuli in the typical cluttered laboratory environment. We measured rotations of the head and the right eye. The use of distant targets made it possible to dispense with the recording of head translations (Steinman et al., 1982).

Figure 65-6 (top) shows head and eye movements when R. S. was scanning the perimeter of the rectangle, looking from one target to the next, while trying to keep his head as still as possible. Head movements were quite modest, comparable to those measured while attempting to keep the head as still as possible during maintained fixation (Skavenski et al., 1979; Steinman et al., 1982). The graph in the middle of Figure 65-6 shows head and eye movements when R. S. was asked to adopt what he considered to be his natural scanning pattern, and not to worry about producing any particular pattern of head or eye movements. Under this instruction head movements became larger and the saccade rate increased as well. The bottom graph shows head and eye movements when the subject was asked to scan as fast as possible. Both the saccade rate and the amplitude of the head movements increased. Apparently, freedom to move the head in concert with the eye increases the speed of scanning.

We next asked the subject to look in the center of the array of targets and to try to move the eyes in one direction and the head in the opposite direction. He managed only one instance (see the top graph of Fig. 65-7, the 13th second of the trial) in which the head moved to the left and the eyes moved to the right. He had more success at first when he deliberately slowed the head movements (bottom graphs), but even here the head and eyes eventually fell back into synchrony. The subject could move his head up while moving the eyes to the right (Fig. 65-7, middle) but he made frequent, inappropriate horizontal head movements (one was opposite to the direction of the saccade!) along with the required horizontal saccades.

In Figure 65-8 the subject scanned the array of targets while shaking his head either horizontally (top graph) or vertically (bot-

tom graph). Scanning was more erratic than in the earlier performance (Fig. 65-6), but far more interesting were the large spontaneous head movements, almost equal to the angular separation of the targets on the orthogonal meridian. The spatiotemporal pattern of these emergent head movements corresponded to the spatiotemporal pattern of the saccades on the same meridian.

These scanning tasks show a natural tendency for a spatial and temporal link between the movements of head and eyes. The link is not compulsory—it may be broken with effort—but in the absence of the concerted effort to execute independent patterns of head and eye movement, the natural tendency is to produce a common spatial and temporal pattern. It is extremely difficult and quite unnatural to move against this tendency.

Discussion

Our investigations of head and eye movements during reading and during scanning, and our attempts to encourage the performance of unusual head-eye movement combinations, have revealed three characteristics about the normal coordination of head and eye movements.

First, moving the head can increase the rate of saccades. This was most apparent in two circumstances: the reading trials of H. C. and the scanning of the array of targets by R. S. Allowing the head to move has also been found to shorten saccadic latency during certain target-tracking tasks (see Chapter 71, this volume). We found that moving the head did not always increase saccade rates, however. For example, saccade rates were the same for head-fixed and head-free reading for E. K. and for scanning of the individual letters for both H. C. and E. K. We suspect that the discrepancy is due to the relative difficulty of the different tasks, with head movements being most helpful when tasks were more demanding. Scanning the array of targets may have benefited from head movements because the saccades were large (about 5° to 6°) relative to the saccades during reading (about 3°). The saccades made by H. C. during reading may have benefited from head movements because his intersaccadic intervals during reading were shorter than those of E. K. and shorter than either of their intersaccadic intervals during letter scanning.

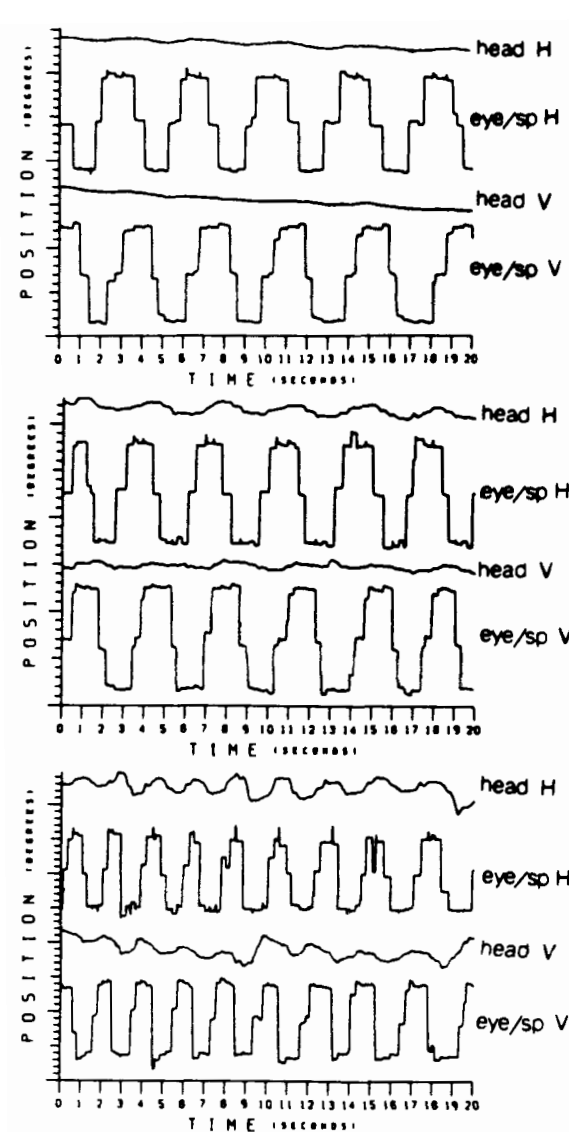


Fig. 65-6. Horizontal (H) and vertical (V) rotations of the head and right eye in space for subject R. S. as he scanned the square array of targets while trying to keep his head as still as possible (top), scanned the array in a natural manner (middle), and scanned the array as fast as possible (bottom).

This pattern of results suggests that head movements, rather than having a uniform and compulsory effect on saccade rates, are instead most valuable when saccadic performance is pushed toward its limits. The problem now is to understand why head movements should be able to expand saccadic capacity. Does freeing the head to move help the eyes, or does holding the head interfere with oculomotor performance? We prefer the second alternative. If telling oneself to look at a target leads naturally to inseparable instructions to move both the head and the eyes (Zingale and Kowler, 1987), then perhaps the effort to keep the head still, either on or off the bite board, impairs the ability to move the eyes.

The second characteristic we observed is that the ability to execute unusual patterns of head and eye movements is different during a task with clear cognitive components (reading) than during less natural tasks in which the observer is simply trying to direct the eye to an eccentric target devoid of any cognitive significance (something we probably rarely do in natural viewing outside the laboratory). For example, we found instances in

which the head and eyes moved in opposite directions during reading, a pattern that could be created only with great effort during scanning of targets. We also replicated the classical observation that intersaccadic intervals are substantially shorter during reading than during scanning (Huey, 1900). These observations point to the importance of high-level control in the programming of movement. By high-level control, we are referring not to unspecified cognitive involvement but, more specifically, to the way in which the initial representation of the commands to orient the head and eyes are intimately linked to the ongoing cognitive processes involved in the spatial analysis of the visual scene. This link has been proposed for the programming of smooth and saccadic eye movements, but its extent and nature are certainly not well understood at present (see Kowler 1990, for review).

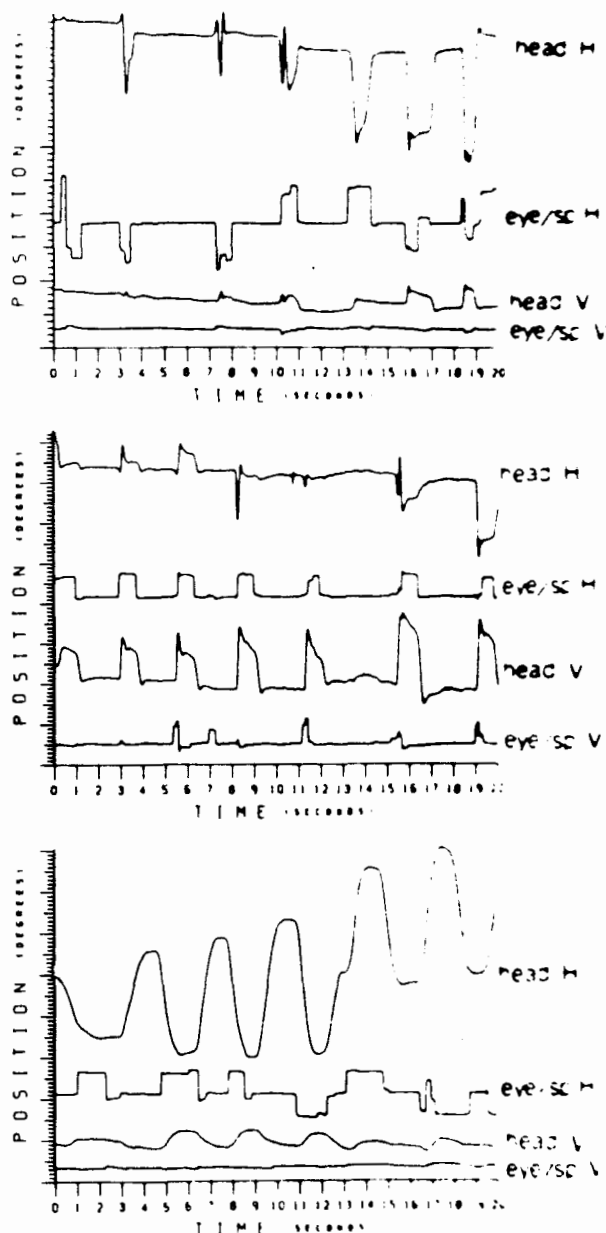


Fig. 65-7. Horizontal (H) and vertical (V) rotations of the head and right eye in space for subject R. S. as he tried to move his head and eyes in opposite horizontal directions (top), in orthogonal directions (middle), and in opposite horizontal directions with slow head movements (bottom).

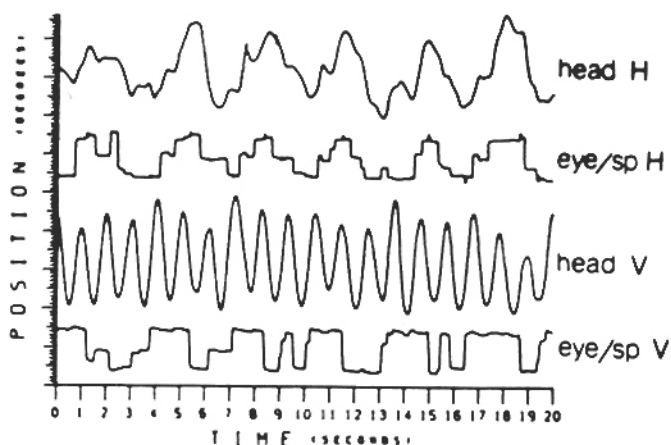
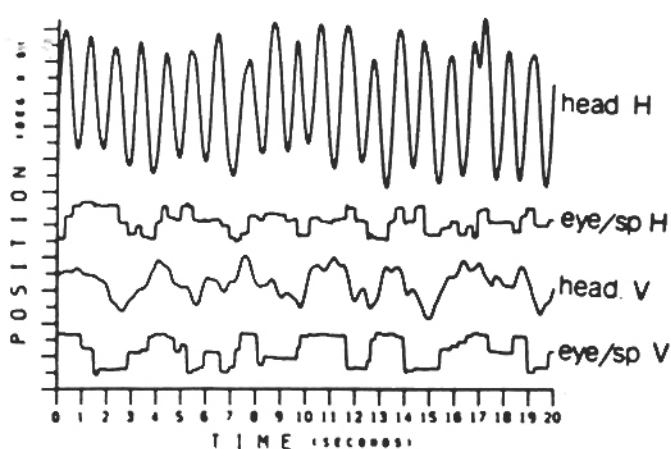


Fig. 65-8. Horizontal (H) and vertical (V) rotations of the head and right eye in space for subject R. S. as he scanned the square array of targets while shaking his head horizontally (top) or vertically (bottom).

Finally, our results revealed a natural tendency to program head and eye movements concurrently in similar spatial and temporal patterns. We saw this in the general agreement of the pattern of eye and head motions during reading, and more vividly in the tendency of R. S. to move his head in the same direction and at the same time as he made saccades during scanning, unless he made explicit efforts to avoid doing this. Distraction by another task (e.g., shaking the head along the horizontal or vertical meridian) was sufficient to evoke large head movements entrained with the pattern of saccades. These observations are consistent with the suggestion made earlier in the discussion that there is a natural tendency to formulate a single, high-level motor program to orient both head and eyes, rather than to issue head and eye movement commands separately. We found that separate commands to the head and eyes are possible, but only with special effort and, perhaps, with some sacrifice in the precision of the visual or oculomotor performance.

Future Directions

The nature of the central program to orient head and eyes to selected visual targets is, as of now, poorly understood, although several of the basic phenomena and problems have been identified. Perhaps progress can be made by continuing the approach described here—the exploration of scanning during natural tasks and the use of special tasks to tax the capacity of the system by requiring unusual patterns of head and eye movements. The latter approach seems particularly promising: failures of perceptual discrimination have told us much about the operation of sensory systems. Perhaps the failure to be able to execute “unnatural” patterns of coordinated head and eye movements will provide a technique for understanding the nature and organization of the underlying motor programs.

Acknowledgments. This research was supported by grant 88-0171 from the U.S. Air Force Office of Scientific Research, Life Sciences Directorate, to E. K.; grant EY-04647 from the National Institutes of Health—NEI to R. M. S.; and grant 900-550-092 from the Netherlands’ Foundation for Medical Research (MEDIGON) to H. C.