Chapter 3

The Saccadic System

THE PURPOSE OF SACCADES

Saccades are rapid eye movements that shift the line of sight between successive points of fixation (Fig. 3–1). The term saccade is French in origin, referring to the jerking of a horse's head by a tug on the reins or to the flicking of a sail in a gust of wind. Javal[334] and Landolt[378] first used the word saccade to describe the rapid eye movements associated with reading or voluntary changes of gaze. Saccades include a range of behaviors that encompass voluntary and involuntary shifts of fixation, quick phases of vestibular and optokinetic nystagmus, and the rapid eye movements that occur during REM sleep.[782] Abnormalities of saccades are often distinctive and point to disorders of specific mechanisms. Thus, saccades have become an important research tool to study a wide range of issues in the neurosciences.[392]

Dodge,[157] working with J.J. Cogan, the father of David G. Cogan, in the early 20th century, was the first to distinguish saccades clearly from other types of eye movements. He explicitly stated their function: "to move the eyes so that the point of interest will be seen with the visual center of the retina". Yarbus[769] emphasized the importance of saccades in visual search. The function of voluntary saccades in primates is directly linked to the pres-

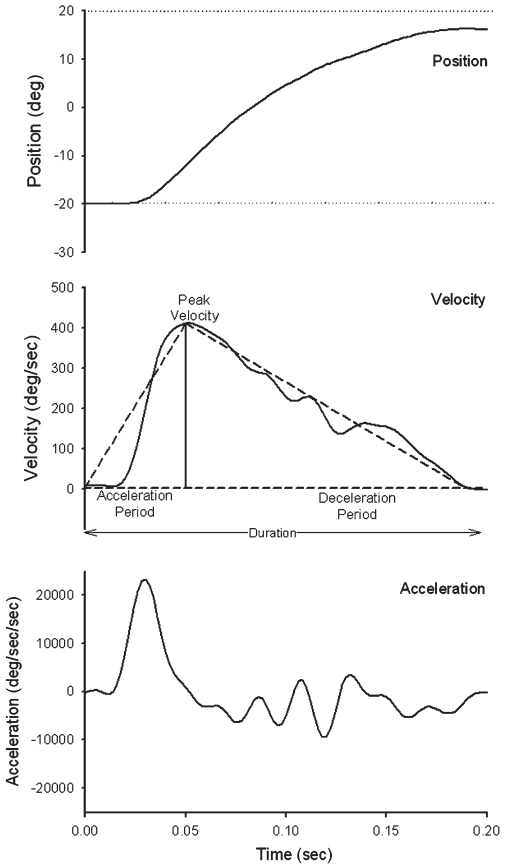


Figure 3–1. Representative record of a 36-degree horizontal saccade made by a normal subject in response to a 40-degree target jump (dotted lines in top panel). Corresponding position, velocity, and acceleration records for this saccade are shown. In the middle panel, components of the velocity waveform are shown, including the acceleration period and total duration, the ratio of which gives a measure of the skewing of the velocity waveform. Positive values correspond to rightward movements.

ence of a fovea, because images are best seen if located there. Animals without a fovea, such as the rabbit, only make voluntary saccades in association with head movements.[121,122] Afoveate animals also produce quick phases of nystagmus during passive head movements so that the slow phases of vestibular and optokinetic nystagmus do not drive the eyes into an extreme orbital position and the oncoming visual scene can be perused.

Saccadic eye movements consist of a hierarchy of behavior, from the most rudimentary of all saccades—quick phases of vestibular nystagmus during passive rotation in darkness—through reflexive saccades made in response to the sudden appearance of a novel visual stimulus, to higher-level volitional behavior such as saccades directed toward the remembered location of a visual target (Table 3–1). This organization can be applied in the clinical neuro-ophthalmologic examination. For example, if voluntary saccades cannot be generated, then it is useful to test progressively more reflexive types of saccades down to the quick phases of nystagmus. A comparable approach is used in the neurologic localization of motor disorders of all types.

BEHAVIOR OF THE SACCADIC SYSTEM

We will discuss in turn the main characteristics of saccades: velocity and duration, waveform and trajectory, reaction time or latency, and accuracy. A number of ingenious paradigms have been developed to test aspects of saccadic responses to visual stimuli (Fig. 3–2).

Table 3–1. **Classification of Saccades**

Classification	Definition
Volitional Saccades	Elective saccades made as part of purposeful behavior
Predictive, anticipatory	Saccades generated in anticipation of or in search of the appearance of a target at a particular location.
Memory-guided	Saccades generated to a location in which a target has been previously present (Fig. 3–2C).
Antisaccades	Saccades generated in the opposite direction to the sudden appearance of a target (after being instructed to do so; Fig. 3–2D).
To command	Saccades generated on cue.

(Continued on following page)

Table 3–1. *(continued)*

Classification	Definition
REFLEXIVE SACCADES	Saccades generated to novel stimuli (visual, auditory or tactile) that unexpectedly occur within the environment.
EXPRESS SACCADES	Very short latency saccades that can be elicited when the novel stimulus is presented after the fixation stimulus has disappeared (gap stimulus; Fig. 3–2B)
SPONTANEOUS SACCADES	Seemingly random saccades that occur when the subject is not required to perform any particular behavioral task.
QUICK PHASES	Quick phases of nystagmus generated during vestibular or optokinetic stimulation or as automatic resetting movements in the presence of spontaneous drift of the eyes.

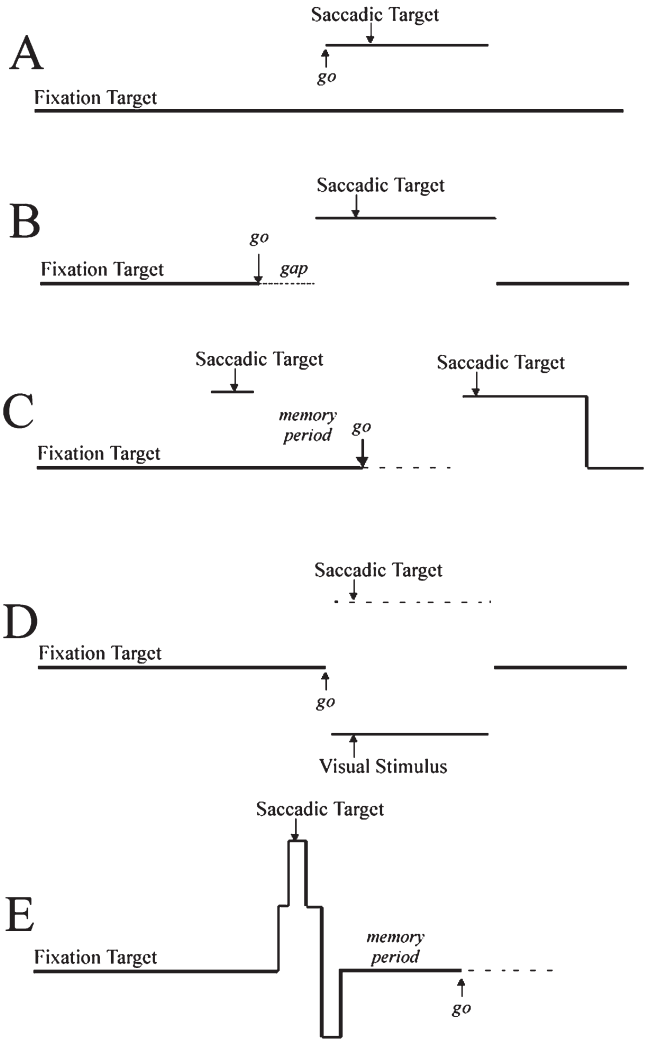


Figure 3–2. Schematic of laboratory stimulus paradigms commonly used to test saccades. In each case "go" indicates the signal for the subject to look toward the "saccadic target." (A) Overlap paradigm, in which the central fixation target stays on throughout. (B) Gap paradigm, in which fixation target is switched off before visual target is switched on. (C) Memory target task. The subject views the fixation target during the time that the visual target is flashed and after several seconds (the memory period), the fixation light is switched off and the subject looks towards the remembered location of the target. (D) The antisaccade task. The subject is required to look in the opposite direction when the visual stimulus is presented. (E) Sequence of saccades task. A series of targets at several locations are turned on in turn. After a memory period, the fixation light goes out as a signal for the subject to make a series of saccades towards the remembered series of target locations.

Saccadic Velocity and Duration

Saccades show consistent relationships among their size, speed, and duration. Thus, the larger the saccade, the greater its top speed and the longer its duration. However, even large saccades (Fig. 3–1) do not last much longer than 100 ms, which is the response time of the visual system. This means that visual feedback cannot be used to change the size of a saccade once started. Rather, the brain must monitor accuracy at the end of each saccade and make an appropriate adjustment to ensure long-term accuracy. Representative plots of peak velocity or duration as a function of amplitude are shown in Figure 3–3, and are often referred to as *main sequence relationships*,[38,80] a term borrowed from the classification of stars by astronomers. These relationships are consistent enough that they can be used to define ranges for normal saccades; deviations of measured eye movements from these intervals indicate either abnormal saccades or non-saccadic eye movements. For saccades that are smaller than about 20 degrees, there is a linear relationship between amplitude and *peak velocity*; above 20 degrees, peak velocity shows a progressive "soft" saturation with asymptotic values of about 500 degrees per second. Main-sequence relationships also apply to the smallest saccades (microsaccades);[417] these relationships are discussed under Visual Fixation in Chapter 4. A commonly used equation to describe the main sequence relationship is:

$$\text{Peak velocity} = \text{Vmax} \times (1 - e^{-\text{Amplitude}/C})$$

where Vmax is the asymptotic peak velocity and C is a constant. Other equations, such as power functions, have been used to describe the relationship between amplitude and peak velocity for smaller saccades.[225,385] The application of this and other equations describing the main sequence relationships during the laboratory evaluation of saccades is discussed below (Measurement of Saccadic Eye Movements).

The *duration* of saccades are approximately linearly related to their amplitudes for movements from 1 to 50 degrees. Power functions can be used to describe the relationship between amplitude and duration for saccades of all sizes (Fig. 3–3B).[223,225,385,769] Acceleration and its derivative, jerk, are greater than for other types of eye movement and can be used to identify saccades.[764] Saccadic speed and duration cannot be voluntarily controlled. However, a number of factors may cause variability in the peak velocity and duration of saccades of similar size, even for the same individual, from day to day.[81] For example, saccades are slower when made in darkness, to the remembered locations of visual stimuli, in anticipation of target jumps,[724] and when made in the opposite direction to a visual stimulus

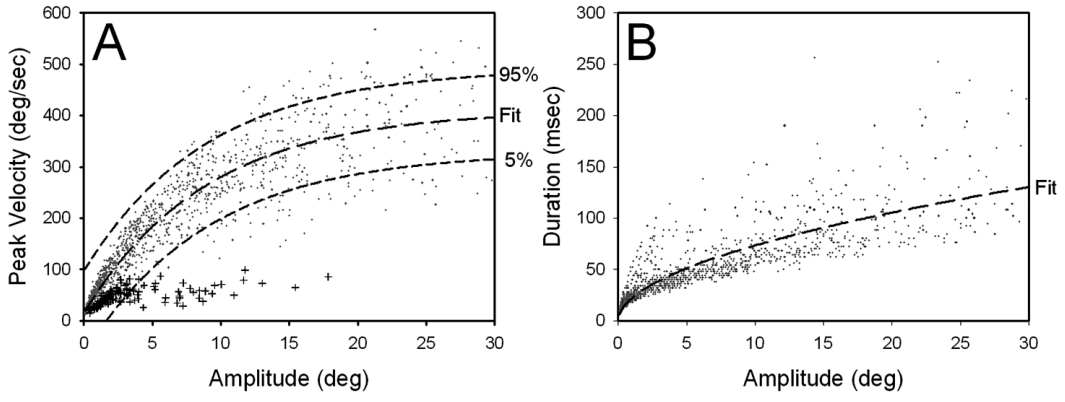


Figure 3–3. Dynamic properties of saccades. (A) Plot of peak velocity versus amplitude of vertical saccades. Data points (dots) are saccades from 10 normal subjects. These normal data are fit with an exponential equation of the form Peak Velocity = Vmax × (1 - $e^{-\text{Amplitude}/C}$), where Vmax is the asymptotic peak velocity, and C is a constant defining the exponential rise is shown. Also plotted are the 5% and 95% prediction intervals. The crossed points indicate vertical saccades from a patient with Niemann-Pick type C disease (see Fig. 5B), which lie outside the prediction intervals for normals. (B) Plot of duration versus amplitude. The data from 10 normal subjects are fit with a power equation of the form: Duration = D_1*Amplitude^n, where D_1 is the duration of a 1 degree saccade, and n is the parameter to be determined.

(the antisaccade task; Fig. 3–2D).[55,87,657,658] Saccades made between visual targets alternating position at a higher frequency (e.g., >1 Hz) are faster than to targets alternating at a lower frequency (e.g., <0.2 Hz).[405] Saccades are also faster when made in association with manual tasks,[184] or if the fixation target is turned off before the stimulus for the saccade appears ("gap" stimulus; Fig. 3–2B).[547] Saccade velocity also depends upon the direction of the movement and the initial and final orbital position.[4,121,122,523] Centripetal saccades (directed toward the center) tend to be faster than centrifugal saccades. Upward saccades made in the upper portion of the ocular motor range are slower than upward saccades made in the lower portion of the ocular motor range.[121] It is not settled whether saccadic velocity declines with age.[317,539,640,642,668,317] Saccades of normal velocity can be made by young infants if they are suitably aroused.[653] Thus, all of these factors, as well as the measurement technique, must be considered when comparing saccadic behavior in different subjects or in patients with neurological disease (see Measurement of Saccadic Eye Movements).

Saccadic Waveform

The shape of the temporal waveform of the saccade, especially its velocity profile, is another useful way to characterize saccades (Fig. 3–1). The *skewness*, or asymmetry, of the waveform can be estimated simply from the ratio of the time to reach maximum velocity (the acceleration phase) to the total duration of the saccade (middle panel of Fig. 3–1); other mathematic functions have also been used to measure skewness.[731] The skewness ratio is about 0.5 for small saccades (acceleration and deceleration phases are equal in duration) and falls to values of about 0.2 for the largest saccades (peak velocity is reached earlier relative to the end of the saccade). Skewness also increases for antisaccades, saccades made to remembered targets, and saccades made under fatigue or decreased vigilance.[658]

Another measurement of saccades, which is related to the velocity waveform, can be calculated from the ratio: *peak velocity/mean velocity (Q)*.[45,276,277,323,374] In humans, Q is about 1.6 and holds even for slow saccades made by fatigued subjects and some disorders of saccades. The value of Q is related to the velocity waveform (Fig. 3–1). A triangular velocity waveform gives a value of 2.0, whereas a rectangular waveform yields a value of 1.0; saccadic velocity profiles yield an intermediate value.[374,731] Saccades with Q values exceeding 2.0 usually have a velocity waveform interrupted by a transient, discrete deceleration (see Disorders of Saccadic Waveform).[374]

Another useful approach for analyzing saccades is by examining *phase-plane plots* of eye position versus eye velocity or acceleration (Fig. 3–11B); such plots have proven useful in investigation of abnormal saccades, saccades made with vergence movements, and corrective saccades in patients with vestibular hypofunction.[526]

During saccades, the eyes do not move perfectly together.[121,122] For horizontal refixations, saccades of the abducting eye tend to be larger, faster, and more skewed than concomitant saccades of the adducting eye. This disconjugacy between the two eyes leads to a transient intrasaccadic divergence. For vertical refixations, the eyes are better yoked, although idiosyncratic horizontal vergence movements may occur (often transient divergence with upward saccades, and convergence with downward saccades).[179,728,774] The interaction of saccades and vergence is discussed further in Chapter 8.

Following a horizontal saccade there is usually a brief drift of the eyes that has both disjunctive (vergence) and conjugate (version) components. The disjunctive component of this post-saccadic drift is convergent and may compensate for divergence during saccades. The conjugate component is in the direction of the prior movement, and may compensate for the tendency for most saccades to slightly undershoot the target. Such *post-saccadic drift* has been called a *glissade*,[753] and has been attributed to a mismatch between the sizes of the phasic (pulse) and tonic (step) components of the innervation generating saccades (see Fig. 1–3, Chapter 1). The eye drifts in a glissade because orbital elastic forces pull the eye to a position in the orbit corresponding to the new step level of innervation. Glissades occur more frequently in fatigued subjects.[40]

At the end of a saccade, an oppositely directed, post-saccadic movement occasionally occurs and appears to be as fast as a small saccade (1/4 to 1/2 degree). Such small saccades have been called *dynamic overshoots*.

Dynamic overshoots can occur after saccades of all sizes, but are more conspicuous after small saccades, including square-wave jerks (saccadic intrusions).[2] They may be conjugate or more prominent in the abducting eye;[82,343,725] they also occur with large saccades or if subjects blink with the eye movement. The origin of dynamic overshoots is debated. On the one hand, they might arise from the mechanical properties of orbital tissues rather than a central reversal of innervation;[573] measurements of the forces generated by extraocular muscles support this interpretation.[443] On the other hand, dynamic overshoots have been attributed to brief reversals of the central saccadic command.[37] Such a reversal of saccadic innervation would normally bring the eye to an abrupt stop but, if too large, would lead to a dynamic overshoot. Large dynamic overshoots occur in patients who show saccadic oscillations such as ocular flutter (Fig. 3–4).

Saccadic Trajectory

When humans make saccades in oblique directions, the horizontal and vertical components show minor slowing compared with purely vertical or purely horizontal saccades of similar size.[57,590] For diagonal saccades (45-degree inclination), the horizontal and the vertical components are similar and the trajectory is nearly straight (Fig. 3–5A). For oblique saccades made at angles other than 45-degree inclination, a smaller component that stays on the main sequence for velocity and duration does not last as long as the larger component,[39,57,258] and the trajectory of the saccade, at least in humans, tends to be curved. When the brainstem mechanism generating either the horizontal or vertical components of oblique saccades is impaired, oblique saccades have strongly curved trajectories that are evident at the bedside (see Fig. 3–5B and Video Display: Disorders of Saccades). The significance of the trajectories of oblique saccades is discussed further under Models for Saccade Generation, Pathophysiology of Saccadic Abnormalities, and Three-Dimensional Aspects of Eye Rotations (Chapter 9).

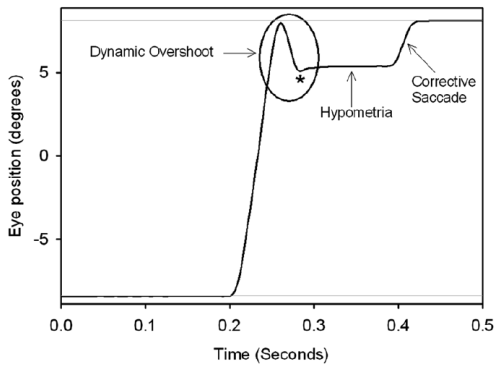


Figure 3–4. Example of a large "dynamic overshoot" in a patient recovering from brainstem encephalitis causing ocular flutter. A small oppositely directed dynamic overshoot (indicated by an asterisk) also occurs. The patient is making horizontal saccades between a stationary target (gray lines). Note that after the initial movement is over, the eye is not on target (it is hypometric) and a subsequent corrective saccade is made. Positive values correspond to rightward movements.

Saccadic Reaction Time (Latency)

The interval between target presentation and when the eye starts to move in a saccade (conventionally identified by when eye speed exceeds some threshold, such as 30 degrees per second) has received intensive study because it reflects various aspects of visual processing, target selection, and motor programming. Saccadic reaction time depends upon the nature of the stimulus—both its modality and the temporal properties of target presentation. Factors such as the amount of information available and the urgency to make a decision influence saccade latency.[107a,562]

SACCADES MADE TO DISPLACEMENTS OF A VISIBLE TARGET

When a visual target jumps from one point to another, normal subjects generate a saccade within about 200 ms. Individual latency values for a number of such trials are not distributed normally (in the statistical sense), but are skewed, with more values having higher latencies. If, however, the reciprocal of latency is plotted, as a measure of "promptness," the distribution of values is closer to a normal one.[108] It has been suggested that the variability in saccadic initiation time shown by any subject reflects the time needed to decide whether a target is in fact present.[108] Studies using a larger number of potential stimuli have shown

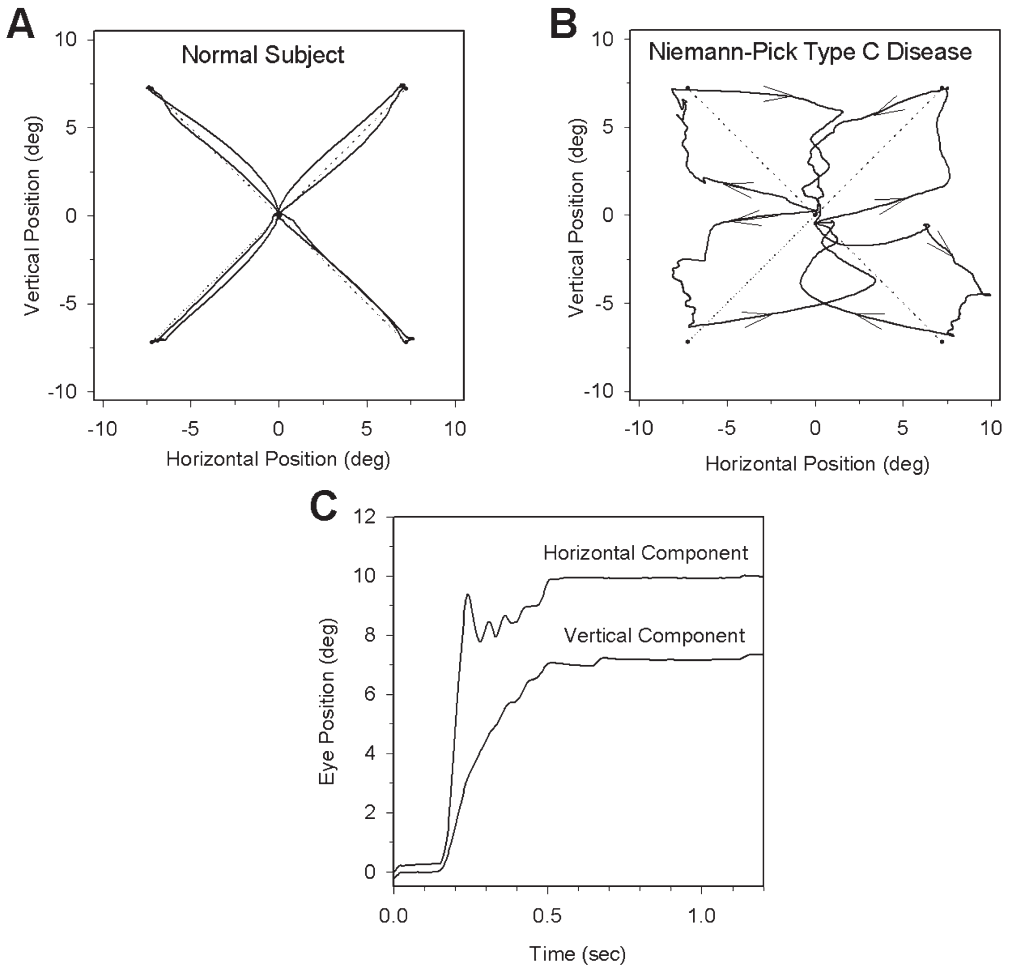


Figure 3–5. Trajectories of oblique saccades. (A) Comparison of trajectories of oblique saccades made to and from four target positions starting at primary position in a normal subject and (B) in a patient with Niemann-Pick type C disease,[590] who showed a selective slowing of vertical saccades. Arrowheads in (B) indicate the direction of eye movement. The trajectory of the target jump is shown as a dotted line. The trajectories of the patient's saccades are strongly curved, reflecting the initial, faster, horizontal component and the later, slower, vertical component. (C) Time plot comparing horizontal and vertical components of an oblique saccade made by the patient with Niemann-Pick type C disease. Horizontal oscillations occurred after the horizontal component had ended, but while the vertical component was still going on. Amplitude-peak velocity plots of vertical saccades made by this patient are shown in Fig. 3–3A.

that saccadic programming obeys Hick's law—a logarithmic relationship exists between response time and the number of alternative choices.[388]

Aside from the motivational and attentive state of the subject,[254] a number of properties of the stimulus influence saccadic initiation time. These include luminance, size, contrast, and complexity;[20,146,159,160,254,514,747,786] the nature of the visual task;[450a] whether the target is visual or auditory;[772] the size of the intended eye movement and the orbital position from which it starts;[216] the predictability of the target's motion;[588,617,646] the specific instructions given to the subject (i.e., cognitive set);[326] the presence of distracting stimuli;[133a,308a,746] the laterality of the target;[308] and the patient's age.[96,109,317,465,539,593a,642,653]

GAP AND OVERLAP STIMULI

Often, the stimulus for a saccade is the appearance of a novel object in the visual scene. In the laboratory, this type of stimulus is conve-

niently created by turning on a peripherally located, small "target light" in a darkened room, and turning off the "fixation light," which the subject is currently viewing with the fovea. The temporal relationship between when the fixation light is extinguished and the target light is illuminated also influences saccade latency. Reaction time is smaller when the fixation light is turned off 100 to 400 ms before the peripheral target appears ("gap" stimulus) and greater when the fixation light remains illuminated after the peripheral target appears (the "overlap" stimulus; Fig. 3–2A).[338,564,565] In the gap paradigm (Fig. 3–2B), human subjects generate some saccades with short reaction times—*express saccades*; latencies are as low as 100 ms.[197,201,202,424] Children make express saccades more easily than adults.[358] The facility improves with practice,[203] and is performed best for the target positions (saccadic vectors) used during training,[517,603a] suggesting that express saccades reflect a predictive mechanism. However, express saccades are still generated even if gap and overlap stimuli are randomly presented in a block of trials.[751] A cautionary note is that a factor contributing to the generation of express saccades concerns the direction of the recentering saccade from the prior trial; a short latency response is more likely if this recentering saccade is in the same direction as the upcoming target jump.[107] Express saccades are probably a laboratory phenomenon, being unlikely to occur in natural viewing conditions, in which a number of visual stimuli are simultaneously present.[603]

Express saccades can be generated equally well if the gap stimulus is used during fixation or smooth pursuit;[372] this implies that, in the case of the gap stimulus, "fixation" may be defined more in terms of keeping the fovea pointed towards a visual object than suppression of an eye movement. However, the shortened latency achieved with the gap stimulus applies much more to saccades than to pursuit or vergence.[371,694] Thus, it appears that the gap stimulus mainly releases an attentional fixation mechanism for saccadic gaze shifts. No equivalent change in latency can be achieved in response to auditory stimuli.[638]

Evidence reviewed below suggests that the rostral pole of the superior colliculus plays an important role in such release of fixation.[164,165,483] In monkeys, express saccades are completely eliminated with lesions of the superior colliculus but not with lesions of the frontal lobes.[271,605] Thus, express saccades provide a way of testing collicular function in humans. So-called spasm of fixation, in which a patient cannot change gaze until the fixation target is removed, may be an extreme case of the retarding influence of a persistent fixation target (overlap paradigm) upon saccade latency. Caution is required, however, in interpreting increased saccadic latency as being purely collicular in origin, since it may also be due to defects in the ability to disengage, shift, and reengage visual attention.[254,478,552] Overall, the ability to generate express saccades is probably related to an ability to turn off the fixation mechanism, a process that is influenced by directed visual attention.[752]

ANTISACCADES

To investigate the control of voluntary (as opposed to reflexive) saccades, a special test paradigm called the antisaccade task has been developed (Fig. 3–2D and Fig. 12–14, Chapter 12).[265,467] In this task, the subject is required to suppress a saccade (the "prosaccade") toward a stimulus that appears in the periphery of vision and generate instead a voluntary saccade of equal size towards the opposite side—the mirror location (the "antisaccade"). These two separate components depend on independent mechanisms,[199] which appear to compete with each other.[373] After time for the antisaccade to be made, a target light is turned on at the correct location, to check the accuracy of the movement. The simplest measure of errors of the response to this test concerns the direction of the initial saccade, expressed as the ratio of prosaccades to antisaccades; this can be tested at the bedside.[135] Normal subjects initially make frequent errors on this task, but with a brief period of practice, error rates are typically about 25%, being greater in subjects with shorted prosaccade latencies, with less eccentric target positions, and with shorter fixation periods.[187,660] Antisaccades may be less accurate, slower,[173a] and made at longer latency than prosaccades.

When the fixation point is turned off before the peripheral target is presented (gap stimulus), antisaccades are generated at a latency of about 175 ms and with errors on about 15% of trials; error rates increase if targets are more

eccentric.[198] Children develop the ability to make antisaccades by adolescence.[215] In adults, the latency of antisaccades increases with age.[96,504] Patients with a variety of cerebral lesions, especially those involving the frontal lobes, show abnormalities on the antisaccade task. They are unable to suppress a reflexive saccade towards the visual target and have difficulty generating a voluntary saccade towards an imagined location. In addition, individuals who make unusually frequent express saccades, such as those with developmental dyslexia, tend to make greater numbers of prosaccade errors on the antisaccade task.[72] Such a deficit could be due to an impaired ability by the rostral pole of the superior colliculus to suppress reflexive saccades. Study of the properties of antisaccades and prosaccades made in response to more complex stimuli may provide further insights into the mechanisms of normal and abnormal saccadic programming, and they are being used to probe a range of disorders including schizophrenia (see Chapter 12).[50,659]

A related behavior is the countermanding task, in which subjects are required to make visually guided saccades on most trials but, on some, to withhold a saccade if a stop signal (such as reappearance of the fixation cue) is presented.[269,270,270] The reaction time to the stop signal is about 135 ms and is not influenced by its luminance. The stop signal may be located in the central or peripheral part of the visual field,[30] and auditory cues may also be used to stop the planned saccade.[102,124] The behavior of subjects on the countermanding task has been successfully predicted by a model in which the target initiates a response preparation signal that races against the signal initiated by the cue to inhibit the saccade.[269] The countermanding task has proven useful in understanding the contributions of frontal cortical areas to the voluntary control of saccades,[600] and has also motivated related studies of patients with frontal lobe lesions.[319]

Saccadic Accuracy

ACCURACY OF VISUALLY GUIDED SACCADES

The ideal ocular motor response to the sudden appearance of a target of interest in the visual periphery is an eye movement that rapidly reaches, and abruptly stops at, the target. Such saccades must be accurate whether the target is stationary or moving.[176,586] Saccades may be inaccurate or dysmetric in two general ways: according to whether or not the size of the rapid, pulse portion of the saccade is inappropriate (called saccadic pulse dysmetria); and whether or not the eyes drift at the end of the saccade (called post-saccadic drift or a glissade). Postsaccadic drift is often attributed to a mismatch between the two major components of saccadic innervation—the pulse and the step—producing pulse-step mismatch dysmetria. Eye movement records are usually necessary to determine whether the postsaccadic drift is conjugate or disjunctive. However, disjunctive drifts are often evident in internuclear ophthalmoplegia, when the slow adducting saccade results from the inability of the demyelinated medial longitudinal fasciculus to conduct the high-frequency discharge of the pulse; thus it is the step that mainly carries the eye, in a glissade, towards the target (see Video Display: Pontine Syndromes). In this section, we will mainly deal with features of pulse dysmetria. Saccadic step dysmetria will be discussed in the section on Adaptive Control of Saccadic Accuracy.

Normal individuals frequently show small degrees of *saccadic pulse dysmetria*—most commonly undershooting (hypometria) of the target (Fig. 3–6). The degree of dysmetria is usually relatively small, typically 10% of the amplitude of the saccade for non-predictable visual targets,[55,715] and is even less for small saccades.[370] For oblique saccades, the net trajectory of the movement is more accurate than the initial direction.[185] Hypometria is usually more prominent for centrifugally directed saccades (that is, those directed toward the periphery) and for saccades of larger amplitude. Normal individuals occasionally make hypermetric (overshooting) saccades when the saccade is small or directed centripetally (toward the center) and especially downward.[121] Fatigue and age may also influence saccade accuracy. Tired subjects may make two small, closely spaced saccades rather than a single saccade, and elderly subjects tend to make more hypometric saccades.[6,317] Infants frequently make several small saccades, instead of one large saccade, to an eccentric target.[653]

The amount of saccadic pulse dysmetria is also influenced by the particular task. Saccades to targets already present are considerably

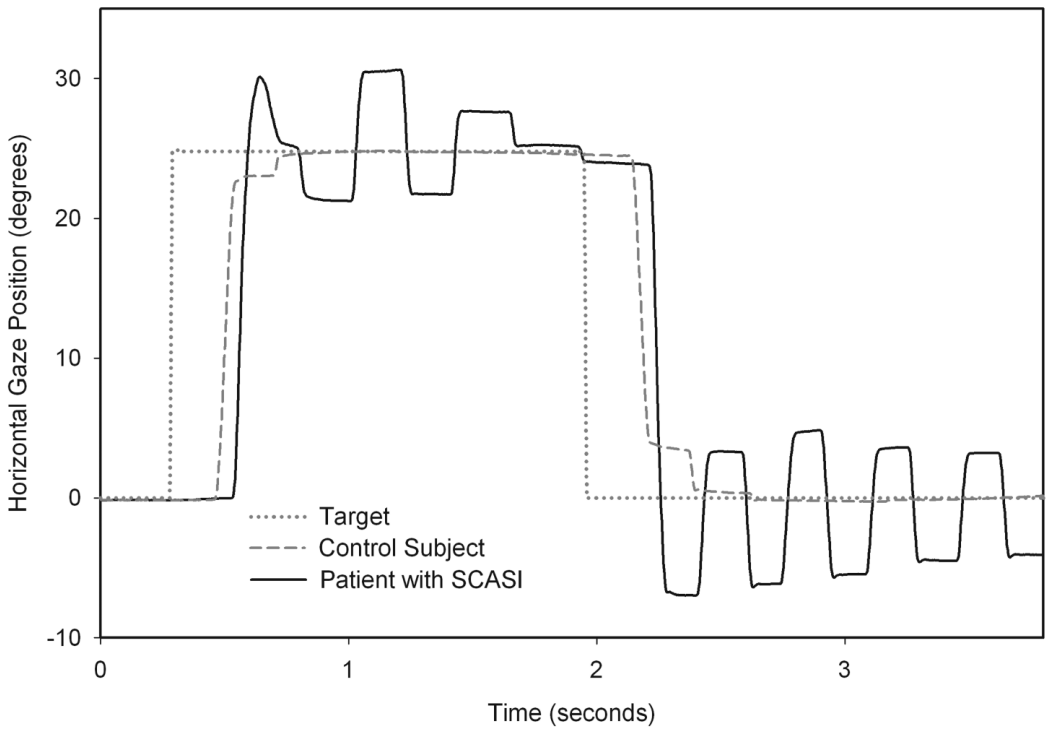


Figure 3–6. Examples of horizontal saccades made by a normal subject (gray, dashed line) and a patient with a spinocerebellar degeneration (solid line) in response to a 25-degree target jump (dotted line) from center position to right 25 degrees. After a reaction time, the normal subject makes an initial saccade that is hypometric, followed by a subsequent correction. A similar pattern occurs after the target returns to center. The patient shows hypermetria, overshooting the target when it jumps to the right, and especially when it jumps back to center, following which there are macrosaccadic oscillations about the point of fixation.[691] Positive values correspond to rightward movements.

more accurate than saccades to suddenly appearing targets.[394] Dysmetria at the end of the primary saccade is greater along the axis between the two targets (so-called amplitude dysmetria) than away from the axis between the two targets (direction dysmetria).[732] If targets appear in a set of positions, saccades overshoot the near positions and undershoot the far; this is referred to as the range effect, and it is established after only a few trials.[340,342] It may be one example of a general strategy that the brain uses to predict which motor movement will be required to achieve its goal.

Saccadic accuracy is also influenced by the background on which the target sits (the "global" effect). Moreover, if two targets are presented simultaneously and not too far apart, the saccade will often take the eye to a position between them—*averaging saccades*.[177,196,466,514] Such saccades often show variable, curved trajectories.[27,168,404] As the distance between the targets increases, the proportion of averaging saccades decreases and the eye more commonly lands on one of the two targets. If the target consists of a word, the eye usually lands close to its center;[54] (see Saccades during Visual Search and Reading, below). Changing the size or luminance of one of two targets will cause the saccade to bring the eye closer to the larger or brighter target.[146]

ACCURACY OF MEMORY-GUIDED SACCADES

When normal subjects attempt to make saccades to the remembered location of a target that they viewed a few seconds before, they do so with a little more variability than if the target were visible.[42,55,757,787] The accuracy of memory-guided saccades is generally similar whether normal subjects maintain steady fixation or shift gaze using smooth pursuit or an eye-head or body movement during the memory period (i.e., from the time of target presen-

tation until they are required to make the memory-guided saccade, in darkness).[78,327,360a,369,399a,501,613,787] This implies that the brain takes into account the gaze shift that has occurred during the memory period. Although the brain might monitor such gaze shifts by monitoring neural signals of eye movements—efference copy or corollary discharge,[236,667,700b] visual estimates of the direction of gaze assume greater importance, when they are available.[787] The accuracy of memory-guided saccades is affected by lesions at a variety of sites, but especially with those located in the dorsolateral prefrontal cortex (see Box 12–21, Chapter 12).

CORRECTIVE SACCADES

When normal individuals undershoot the target, they usually make a corrective saccade with a latency of 100 ms to 130 ms (Fig. 3–6).[55] Such corrective movements can occur even when the target is extinguished before the initial saccade is completed. Therefore, a nonvisual or "extraretinal" signal can provide information about whether the first movement is accurate, so that a corrective saccade can be triggered if necessary. Such nonvisual information is most likely based upon monitoring of efferent ocular motor commands or efference copy ("effort of will"; see Chapter 1). Nonvisual mechanisms for generating corrective saccades are also apparent when subjects make saccades in complete darkness to remembered locations of targets.[787] If a saccade made in darkness brings the eye to a position more than about 5 degrees away from the location of the previously seen target, an accurate corrective saccade is usually made.[503] Vision, however, is still important for getting the eye on target. The probability of occurrence of a corrective saccade and its accuracy increase, and the latency to the corrective saccade decreases, if a visual signal is available at the end of the initial saccade.[151,546] Furthermore, visual information may be used during the deceleration phase of a saccade to trigger a corrective movement.[175]

Quantitative Aspects of Quick Phases of Nystagmus

The quick phases of vestibular and optokinetic nystagmus can also be characterized by their velocity, amplitude, and timing.[641] Over 95% of quick phases are less than 10 degrees in amplitude; they tend to be slightly slower than similar-sized voluntary saccades.[223] The amplitude-peak velocity relationships and amplitude-duration relationships of upward and downward quick phases are similar, but tend to be slower than horizontal quick phases.[223,224] The size and frequency of quick phases are such that they tend to bring the eye into the anticompensatory direction (i.e., the direction opposite to that of the slow phase).[438] An exception occurs when a subject, sitting inside a revolving, striped, optokinetic drum, is specifically instructed to follow a stripe, as it moves from one side to the other, and then to make a saccade in the other direction to acquire another stripe (look nystagmus). On the other hand, if the subject is asked to stare straight ahead as the stripes pass by, quick phases are smaller and more frequent (stare nystagmus). Quick phases of nystagmus have a randomness to them,[643] and probably defy the use of common statistical models to summarize their behavior.[714] Saccades that "catch-up" during smooth pursuit are also somewhat stochastic; both position and velocity information concerning the tracking error are used to trigger these movements in normals.[138,621a] During vestibular nystagmus generated by active head movements quick phase landing is programmed using information provided by the vestibular system.[554] Braking saccades, which are encountered in individuals with congenital nystagmus, also show similar dynamic properties to other types of saccade.[333]

In patients with saccadic palsies, quick phases may be absent, and gaze is a tonically deviated in the direction of the stimulus (see Video Display: Disorders of Saccades).[226] In some patients, the timing and amplitude of quick phases may be abnormal, just as the latency and amplitude of voluntary saccades may be abnormal. Thus, in patients with Wallenberg's syndrome, the amplitude of quick phases towards the side of the lesion is greater than in the other direction, a similar pattern to their ipsipulsion of voluntary saccades (see Video Display: Medullary Syndromes). Patients with congenital ocular motor apraxia may show a defect in the initiation of quick phases during passive head rotation; the eyes intermittently deviate tonically in the compensatory (slow phase) direction (see Video Display: Congenital Ocular Motor Apraxia).[780]

Ballistic Nature of Saccadic Movements

The duration of most saccades is less than 100 ms, so visual information does not have time to influence these movements once they begin. Saccades are not truly ballistic, however, because they can be modified in mid-flight by factors presented just before the eye starts to move. The first ideas on how the central nervous system processes visual information for saccades were developed by Westheimer,[754] who showed that if a target jumped to a new location and then promptly (less than 100 ms) returned to the origin—a double-step stimulus motion—the subject would still make a saccade away from the current location of the target (Fig. 3–7). Then, after a fairly constant interval (150 ms– 200 ms), the subject would make another saccade back to the original position of the target. The interval between saccades was relatively independent of the interval between the target jumps away from and back to the initial position. These findings suggested that the saccadic system can react to only one stimulus at a time, and there is a refractory period, during which a second saccade cannot be initiated after the first.

Young and Stark[771] recognized that the type of behavior shown in Westheimer's experiments was compatible with what control systems engineers call a sampled data system. They hypothesized that a "snapshot" of the visual information, at a given instant, is "sampled" by the saccadic system. If an object of interest is observed in the periphery of this "snapshot," a decision is made to generate a saccade that will bring the image of the target onto the fovea. Based on the retinal error (the distance between the retinal location of an image and the fovea), the size, direction, and duration of the upcoming saccade are calculated and an irrevocable decision to generate the saccade is made. A preprogrammed saccadic command is then generated, based upon the visual information that was acquired during the initial "snapshot." Once the saccade is completed, the visual world is again "sampled" to determine if another saccade is still needed to bring the target of interest onto the fovea. Westheimer's results could then be interpreted by assuming that the return of the target to its initial position was not actually "seen" by the saccadic system until after the first saccade was made. Therefore, a normal saccadic latency, determined by the interval between "snapshots," was required before making a second saccade to bring the eyes back to the target.

Although the sampled-data model accounts for many aspects of saccadic eye tracking, such a scheme does not explain all of the responses that normal individuals make. If Westheimer's experimental paradigm is expanded to include target jumps of different sizes and directions,

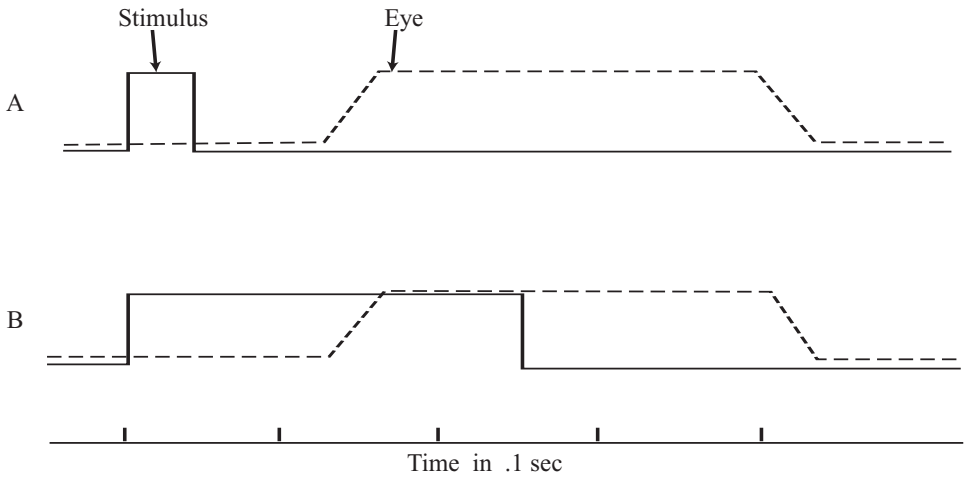


Figure 3–7. Saccadic eye movement responses to double-step target jumps. Horizontal position is on the ordinate scale. Note that the intersaccadic interval remains constant in spite of the different durations (compare A and B) between the two target jumps. (Reproduced, with permission, from Westheimer G. Eye movement responses to a horizontally moving visual stimulus. Arch Ophthalmol 52, 932-941, 1954. Copyright 1954, American Medical Associatation.)

and if a large number of responses are analyzed, it can be shown that visual information can be continuously acquired and used to modify the initial saccadic response until about 70 ms before the movement begins.[29,41] This is approximately the time it takes visual information to traverse the retina and central visual pathways and reach the brain stem ocular motor mechanisms.

Furthermore, the saccadic system does not have an obligatory refractory period; two saccades may occur with virtually no intersaccadic interval in response to the appropriate sequence of double-step motion of the stimulus.[56,249,432] Slow saccades (see Video Display: Disorders of Saccades), which occur in certain neurological diseases, can be interrupted in mid-flight when the target position is changed, even after the eye has already begun to move.[411,777] When presented with two-dimensional, double-step stimuli, normal subjects may make a single curved saccade, rather than two successive straight saccades, indicating that the saccade trajectory has been modified in-flight.[726] The earliest responses to such two-dimensional, double-step stimuli suggest that direction and amplitude may be programmed separately.[238,557a] If both targets are visible (double-cue paradigm) differences of saccadic responses from the classic double-step paradigm can be mainly attributed to the visual stimuli rather than any change in motor programming of eye movements.[648] When voluntary prosaccades or antisaccades are pitted against quick phases of vestibular nystagmus induced by rotational stimulation, an interaction between these two different types of rapid eye movement occurs that suggests parallel programming of each followed by convergence of components.[721,722] In sum, the central nervous system appears able to change saccades throughout their programming. Normal saccades only appear to be ballistic because of their high velocities and brief durations.

Saccades during Visual Search and Reading

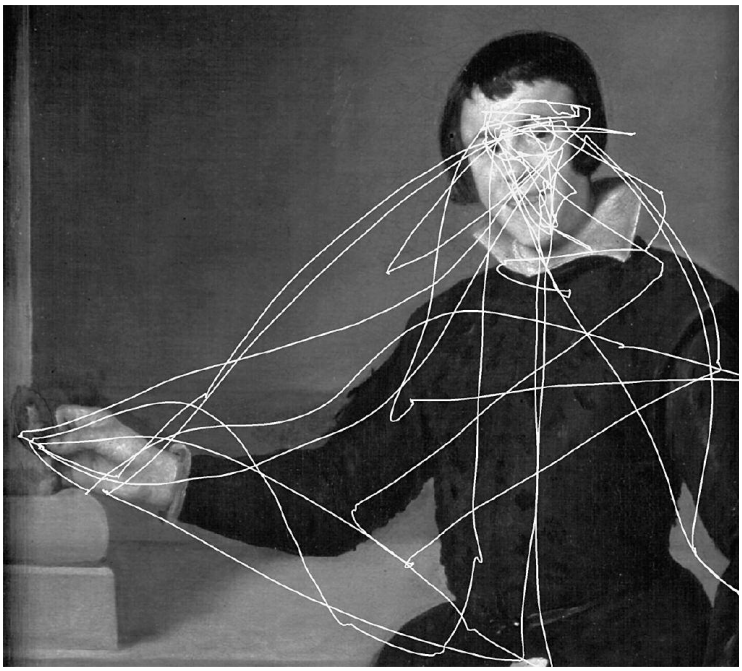
One important function of saccades is for visual search of the environment. Since best vision corresponds to the fovea of the retina, it behooves us to point the fovea at features of interest. Yarbus[769] first systematically studied visual search by recording subjects' eye movements as they scanned pictures of faces and scenes. The idiosyncratic pattern of eye movements made when viewing a pictorial display is called a scan path (Fig. 3–8A).[196a,196b,353,401,492]

Saccades made during visual search for targets embedded in an array of stimuli are not random and such behavior can be quantified and used to study visual attention.[416,462] It is suggested that during visual search, the scan path minimizes the cognitive and attentional load.[28] During manual tasks such as copying a design, frequent eye movements are used to scan the display for information, rather than committing that information to working memory.[44,183] A factor influencing scan paths is the phenomenon referred to as *inhibition of return*, whereby search for novel features will take precedence over those recently inspected. Thus, saccades to features recently inspected show longer reaction times.[570] Electrophysiological and clinical studies have suggested that the cerebral cortex, possibly the orbitofrontal lobes, contribute to this behavior.[163,306]

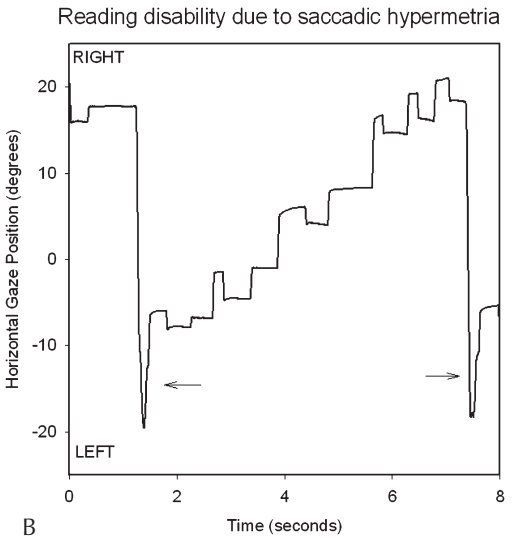
Patients suffering from *hemispatial neglect* show an inability to attend to the contralateral half of space, which biases their attention towards the ipsilesional side, and so impairs their ability to search contralesional space. Furthermore, search behavior in patients with hemispatial neglect combines a spatial bias with loss of working memory for locations previously searched.[318,407,569,650]

Interpretation of ocular motor behavior during *reading* remains controversial and is difficult to interpret in the context of the known control of saccades.[427a,679] For example, there is disagreement as to whether the spaces between words, or the words themselves, serve to guide saccades.[180–182,559,738] In this regard, different languages presents different visual challenges.[337] However, it seems probable that cognitive processes are more important for driving the eyes through the text than the visual features of the text itself.[561] Similarly, it has been suggested that when subjects read music, the pattern of saccades reflects not the visual stimulus or the manual response, but the flow of information from the musical score to performances.[357]

Eye movements have been widely used as an experimental tool to investigate mechanisms underlying *developmental dyslexia*. There has even been a research effort to determine



A



B

Figure 3–8. (A) Example of normal saccadic scan path during visual search of a painting. (Portrait of the jester Calabazas by Diego Velázquez is reproduced with permission of the Cleveland Museum of Art.) Each line represents a saccade as the subject moves his fixation point from one feature of interest to the next. (B) Reading in a patient with a form of spinocerebellar degeneration.[691] He moves his fixation point along the line from left to right is a series of small saccades, which often overshoot the target (word), requiring a corrective saccade. When he makes a saccade to the left to begin the next line, he overshoots the target (arrows) and often loses his place; these abnormal saccades made reading difficult and tiring.

whether developmental dyslexia is actually caused by abnormal control of saccadic eye movements;[91a] lack of consensus may, in part, reflect the heterogeneity of patients with dyslexia.[140] Thus, for example, in some patients, the underlying cause of the reading disability may be auditory-linguistic defects,[139] whereas in others, it is due to defects of dynamic visual perception.[200] Specifically, it has been suggested that some individuals with developmental dyslexia have motion-processing disorders leading to a less stable visual percept.[680] Two defects have been identified on psychophysical testing: a deficit in detecting coherent motion and a deficit in discriminating velocities.[759] Further studies may clarify whether such indi-

viduals have impaired ocular-tracking responses to first and second-order motion stimuli, a subject discussed in Chapter 4.

One reproducible finding is that dyslexic children often show impairment of steady fixation,[71,72,174] with excessive numbers of square-wave jerks.[134] The presence of this fixation abnormality in dyslexics during non-reading tasks suggests that the underlying abnormality may not be caused by language problems alone.[174] Similarly, children with attention deficit hyperactivity disorder show difficulty suppressing saccades and deficits on spatial working memory tasks when they are unmedicated.[104,359,461,464] When presented with two targets at different eccentricities, normal readers make an averaging saccade to an intermediate location ("center of gravity"), but dyslexics generate saccades that land closer to the less eccentric target, suggesting a deficit in processing of global spatial information for eye movements.[133] Dyslexic subjects show a greater reaction time for saccade made back to words just read—a variant of inhibition of return.[560]

Although the relationship between eye movement abnormalities and childhood dyslexia is not clear, patients with certain types of *acquired saccadic abnormalities* do have difficulty reading.[116] This effect is seen in patients with slow saccades or saccadic palsy due to brainstem lesions; with acquired ocular motor apraxia due to bihemispheric disease; with large saccadic intrusions or oscillations (Fig. 3–8B), and various forms of nystagmus.[274] Homonymous hemianopia may disrupt reading eye movements, especially when it is due to damage of the occipital white matter.[784] Patients with Alzheimer's disease show longer fixation periods and more saccades per line that may correspond with difficulties in reading.[406]

Visual Consequences of Saccades

An important perceptual problem is how the brain can correctly interpret motion of images on the retina as being due to movement of the eyes rather than of the visual scene. It is possible to identify two components of this problem: the perception of motion during the eye movement, and correct localization of an object in space following a gaze shift.

VISUAL STABLITY DURING SACCADES

We appear not to see during saccadic eye movements. Even though the seen world is rapidly sweeping across the retina, there is no sense of motion or a blurred image. One proposed explanation for this is that the clear perceptions before and after a saccade would mask the "gray-out" due to image motion on the retina at speeds up to 500 degrees per second.[105] Another hypothesis is that, since it is still possible to see lower spatial frequencies in an image when it moves across the retina at speeds of up to 800 degrees per second, there must be selective suppression of vision for lower spatial frequencies during saccades.[94,153] Current evidence indicates that both mechanisms—visual masking and saccadic suppression—contribute to an uninterrupted view of the world despite making several saccades per second.

Thus, on the one hand, some visual stimuli, such as fast-drifting gratings, can only be seen during saccades,[227] arguing against saccadic suppression of vision. Furthermore, magnocellular neurons in the lateral geniculate nucleus show only a weak suppression followed by strong enhancement of visual activity during saccades.[557,563] When stationary gratings of low spatial frequency (0.18 cycles per degree) are presented briefly during saccades, they may appear to move opposite to the direction of the eye movement.[110] This perception of motion is strongest if the gratings are presented during the first part of saccades, and is absent if they are visible at the end of the saccade. Thus, visual masking seems to account, at least partly, for not seeing during saccades.

On the other hand, it is still possible that an efference copy of saccades affects the magnocellular pathway and cortical visual areas concerned with motion vision, inducing a form of saccadic suppression.[705] Thus, functional imaging studies have demonstrated decreased regional cerebral blood flow in the lateral geniculate nucleus, and striate cortex during repetitive saccades made in darkness,[522,693] and evoked potentials induced by visual stimuli presented during saccades are reduced.[21] Moreover, phosphenes—small illusory visual perceptions—due to retinal simulation are suppressed during saccades, but phosphenes induced by transcranial magnetic stimulation

(TMS) to the occiput remain visible, suggesting that a suppressive process takes place between retina and visual cortex.[709]

Another line of evidence comes from patients who make pathologically slow saccades.[777] One such individual was able to modify saccades in mid-flight in response to target jumps, but was unable to detect the target's motion, suggesting that saccadic programming occurred without conscious awareness of the visual stimulus.[411] Similarly, normal subjects appear to adjust their saccades in response to targets presented at the onset of the movement, when they are not consciously perceived.[229] Only rarely do pathologically increased numbers of saccades, either intrusions or oscillations, disrupt vision and this probably occurs when the intersaccadic interval falls below 50 ms.[153] Thus, more studies are required to clarify a classic problem for visual physiology—why we do not see during saccades.

SPATIAL CONSTANCY FOLLOWING SACCADIC GAZE SHIFTS

While every saccadic eye movement causes the entire visual world to be shifted upon the retina, we are still able to maintain an appropriate sense of straight ahead with a 3-D spatial component.[756] How do we ensure such spatial constancy? The classic explanation is that our central nervous system monitors the "effort of will" and then sends this motor information, referred to as efference copy or corollary discharge, to sensory systems.[284] In this way, our perceptual sense knows and adjusts for the shift of images upon the retina using an egocentric frame of reference. It is also possible that extraocular proprioception could serve this function, but the current view is that such inputs are more important for long-term adaptive changes in the ocular motor systems,[228,263,396,397] or perhaps during mechanical hindrance of eye movements.[361]

Other evidence suggests that the brain estimates the location of objects in space with reference to other objects in the visual scene —exocentric cues.[137,524,524] For example, if visual targets are flashed just before, or during, a saccade, they are incorrectly localized as judged by subsequent saccades or finger pointing.[103,137,307,442,520,543,663] If efference copy were the mechanism by which spatial constancy was maintained, then there should be no difference in spatial localization of targets presented just before or after a saccade. The changes in visual responses to targets flashed just before a saccade may reflect changes in apparent visual direction and an apparent compression of visual space and time that is dependent on the post-saccadic visual references.[380,420,452a,587] This visual compression tends to occur at the intended target of a saccade and may last for hundreds of milliseconds.[34]

If subjects are trained on a saccadic adaptation task, they perceive separated targets, flashed before and after the saccade, as being in the same place.[35] This finding has been interpreted as showing that perception uses a signal based upon the intended saccade before adaptation, and that such a signal is used to prompt comparisons of percepts before and after saccades. Thus, efference copy could be used by the brain, not as a precise record of gaze commands, but rather as a cue to re-evaluate the visual consequences of eye movements, as suggested by MacKay.[415]

The situation may differ, however, if visual cues are lacking. Thus, a classic line of evidence to support the role of efference copy in spatial localization is that, in darkness, normal subjects perceive a small after-image, induced by a photoflash, as moving with the eye.[419] The afterimage is stationary on the retina, and its movement in space is probably due to efference copy signaling movement of the eye. However, if a large after-image of a complex scene is induced, it does not seem to move as the eye drifts in darkness.[524] Thus, a large visual after-image appears to override non-visual cues about eye movements.

Other experiments have shown that visual estimates of the direction of gaze are given preference over efference copy, even if the visual information is corrupted by illusory stimuli. For example, if a target is flashed on a moving background, a memory-guided saccade made a few seconds later is consistently inaccurate in manner determined by movement of the background. [664,787] This finding suggests that, during saccades, visual inputs become less reliable, but the brain still puts more reliance on visual than on extraretinal information. Thus, if a visual target is displaced during a saccadic eye movement, its movement may go unnoticed,[149] even if the saccade was pathologically slow.[411] If, however, the target is only shown in its new position 100 ms after the sac-

cade ends, then its displacement to a new position is detected,[150] as if the lack of an immediate post-saccadic visual cue breaks the assumption of a stationary world. It seems that the brain weighs visual and extraretinal estimates of the direction of gaze,[344] putting more reliance on the visual estimates except when visual factors are not available. Although the visual system provides flawed information during each saccade, theoretical explanations have been offered to account for how the brain is able to piece together the puzzle.[486]

NEUROPHYSIOLOGY OF SACCADIC EYE MOVEMENTS

In this section we review the neural machinery by which saccades shift the line of sight so that an image detected in the retinal periphery is brought to the fovea, where it can be seen best. In primary visual cortex (V1, Brodmann area 17), the location of a visual stimulus is represented by the distribution of activity on the surface of the cortex: different parts of this cortical map correspond to different locations on the retina. The neural representation of the motor command for the saccadic response by brainstem neurons is quite different. The ocular motoneurons encode the characteristics of the saccade in terms of their temporal discharge; the size of the saccade is proportional to the total number of discharge spikes. The ocular motoneurons lie in the third, fourth, and sixth cranial nerves and cause the extraocular muscles to move the eyes with respect to the head (that is, in craniotopic coordinates). This means that the brain must transform the stimulus, which is encoded in terms of the location of active neurons within visual cortex (i.e., "place-coded"), into the saccadic command on ocular motoneurons, which is encoded in terms of discharge frequency and duration (i.e., "temporally coded"). Furthermore, a transformation from retinal coordinates into craniotopic coordinates is necessary. The retinal coordinates are two-dimensional, whereas the eye rotates about three axes.[132] We will return to these issues as we discuss the Brainstem Pathways for Saccades, and the cortical and subcortical structures that project to them. After reviewing the electrophysiological findings, a synthesis in the form of models for saccade generation will be presented.

Brainstem Pathways for Saccades

FINAL SACCADIC COMMAND FROM OCULAR MOTONEURONS

Electrophysiological studies of the behavior of ocular motoneurons in monkeys have delineated the changes in innervation that accompany saccades (see Fig. 1–3, Chapter 1 and Video Display: Disorders of Saccades). During a saccade, a high-frequency burst of phasic activity can be recorded from the agonist ocular muscle and, as shown in experimental animals, from the corresponding ocular motoneurons. This burst of activity, the saccadic pulse of innervation, starts about 8 ms before the eye starts to move,[725] and generates the forces necessary to overcome orbital viscous drag so that the eye will quickly move from one position to another. Following a saccade, the agonist eye muscle and its ocular motoneurons assume a new, higher level of tonic innervation, the saccadic step of innervation, which holds the eye in its new position against orbital elastic restoring forces. The transition between the end of the pulse of innervation and the beginning of the step of innervation is not abrupt but gradual, taking up to several hundred milliseconds. This is the slide of innervation. Hence the change in innervation accounting for saccades is actually a pulse-slide-step (Fig. 5–3B).[510,573]

If one records from the antagonist muscle or its motoneurons, one finds reciprocal innervational changes.[656] The antagonist muscle is silenced during the saccade by an inhibitory, off-pulse of innervation; at the end of the saccade, the antagonist assumes a new, lower level of tonic innervation, the off-step. Measurement of muscle forces generated by extraocular muscles indicates that the eye comes to rest at the end of a saccade owing to the viscous forces of the orbital tissues rather to than any "active braking" by the antagonist muscle.[443]

BRAINSTEM SACCADIC PULSE GENERATOR

Two types of neurons are critical components of the brainstem network that generates premotor commands for saccades: burst neurons and omnipause neurons, which are schematized in Figure 3–9 and Table 3–2.[98] Following the saccade, the eye is held in position by a

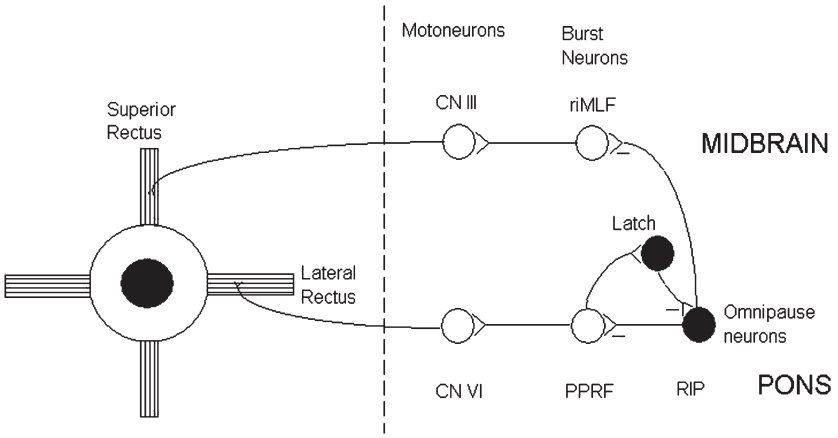


Figure 3–9. Schematic of brainstem network for saccade generation. Motoneurons innervating horizontally acting extraocular muscles receive saccadic commands from burst neurons in the paramedian pontine reticular formation (PPRF). Motoneurons innervating vertically acting motoneurons receive saccadic commands from burst neurons in the midbrain rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). Both sets of burst neurons are inhibited by omnipause neurons that lie in the pontine nucleus raphe interpositus (RIP). A saccade is initiated by a trigger signal that inhibits omnipause neurons; subsequently, hypothetical latch neurons, which receive input from burst neurons, inhibit omnipause neurons until the saccade is complete.

tonic, step-command that is generated by the neural integrator (see Chapter 5 and Fig. 1–3, Chapter 1). Classic basic and clinical studies have demonstrated that the caudal pons is important for horizontal saccades and the rostral mesencephalon for vertical saccades.[206,675] For horizontal saccades, burst neurons within the paramedian pontine reticular formation (PPRF) are essential (see Box 6–3, Fig. 6–1, and Fig. 6–2).[311] For vertical and torsional sac-

Table 3–2. **Brainstem Neurons Contributing to Saccade Generation**

Name	Properties
Premotor (medium-lead) burst neurons	Discharge ~ 12 ms prior to saccade onset
	Project monosynaptically to ocular motoneurons
Excitatory (EBN)	Horizontal EBN: Paramedian pontine reticular formation (PPRF)
	Vertical EBN: Rostral interstitial nucleus of medial longitudinal fasciculus (riMLF)
Inhibitory (IBN)	Horizontal IBN: Medullary reticular formation (MedRF)
	Vertical IBN: Interstitial nucleus of Cajal and riMLF
Long-lead burst neurons (LLBN)	Discharge > 40 ms prior to saccade onset
	Project to premotor burst neurons
	Located throughout brainstem reticular formation including nucleus reticularis tegmenti pontis (NRTP)
Collicular burst neurons	Discharge > 50 ms prior to saccade onset; location on superior colliculus related to size and direction
Omnipause neurons (OPN)	Tonic discharge that ceases ~ 16 ms before saccade onset
	Project to premotor burst neurons
	Located in nucleus raphe interpositus (rip)
Latch-circuit neurons	Reticular formation neurons that carry saccadic and smooth-pursuit signals
	Presumed to receive input from EBN and project to OPN

cades, burst neurons within the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) play the equivalent role (see Box 6–5, Fig. 6–3, and Fig. 6–4). Omnipause neurons lie in the nucleus raphe interpositus, in the midline of the pons (see Box 6–3 and Fig. 6–2).

PREMOTOR BURST NEURONS

Pontomedullary Burst Cells

In humans, *excitatory burst neurons* (EBN) lie in the PPRF, rostral to the abducens nucleus, corresponding to the medial part of the nucleus reticularis pontis caudalis.[316,681] The EBN begin discharging at a high frequency, about 12 ms prior to, and time-locked with, the horizontal component of all types of saccades and quick phases.[286,725] Electrophysiological evidence suggests that some individual EBN in the PPRF encode saccades monocularly (i.e., for movements of one eye or the other).[783] EBN discharge preferentially for ipsilateral saccades and they appear to create the immediate premotor command that generates the pulse of activity for horizontal saccades. Three pieces of evidence support this hypothesis. First, during saccades, the instantaneous burst cell firing rate of EBN is closely correlated with instantaneous eye velocity,[288,725] and the total number of spikes in the burst of activity (the integral of the discharge rate) is proportional to the amplitude of the ipsilateral, horizontal component of the saccades. Second, stimulation of the PPRF elicits ipsilateral saccades.[118] Third, a unilateral lesion within the PPRF abolishes the ability to generate ipsilateral saccades.[287] Note, however, that EBN in the PPRF also discharge during vertical and oblique saccades,[725] and bilateral PPRF lesions not only abolish horizontal saccades but also cause slowing of vertical saccades.[273,287]

The EBN project directly to the ipsilateral abducens nucleus, where they contact both abducens motoneurons and internuclear neurons. Abducens internuclear neurons project up the contralateral MLF, to contact the medial rectus subgroup of the contralateral oculomotor nucleus (Fig. 6–1, Chapter 6). Thus, for example, during rightward horizontal saccades, the excitatory pulse reaches the ocular motoneurons from EBN in the right PPRF. The EBN also project to the perihypoglossal and vestibular nuclei, which are important for integrating the saccadic pulse into a step, to hold the eye steady at the end of the saccade. In addition, EBN also project to cell groups of the paramedian tracts (see Box 6–4, Chapter 6), which relay a copy of all ocular motor commands to the cerebellum. Finally, EBN project to ipsilateral inhibitory burst neurons, which we discuss next.

Inhibitory burst neurons (IBN) for horizontal saccades have been identified just caudal to the abducens nucleus in the nucleus paragigantocellularis dorsalis of the dorsomedial portion of the rostral medulla.[315,682] The IBN receive inhibitory inputs from omnipause neurons and contralateral IBN; they receive contralateral excitatory inputs from the superior colliculus.[689] The IBN send their axons across the midline to the contralateral abducens nucleus to inhibit contralateral abducens motoneurons and interneurons during ipsilateral saccades. Like EBN, IBN also project to the vestibular nuclei, nucleus prepositus (neural integrator), and to cell groups of the paramedian tracts.[682] One role of IBN is to silence activity in the antagonist muscle during horizontal saccades, which is an example of Sherrington's law of reciprocal innervation. A second role may be to help end the saccade when the eye is on target.[549] The synaptic connections between EBN and IBN in the pons and medulla is postulated to form a neuronal network (Fig. 3–10), in which IBN inhibits IBN, thereby forming positive feedback loops that are potentially unstable, leading to high-frequency saccadic oscillations, such as ocular flutter (discussed further under Pathophysiology of Saccadic Abnormalities).[553]

Midbrain Burst Cells

The EBN in the riMLF encode the vertical and the torsional components of saccades, just as EBN in the PPRF encode the horizontal component.[97,314,356,736] Excitatory EBN for upward and for downward saccades appear to be intermingled in the riMLF, although their projection pathways show some differences.[459,460] Thus, it appears that upward EBN in the riMLF project bilaterally to motoneurons, but downward EBN project only ipsilaterally (Fig. 6–5, Chapter 6). Electrophysiological studies have shown that EBN discharge most vigorously for rapid eye movements that rotate the eyeball in a plane parallel to that of a pair of reciprocally acting vertical semicircular canals

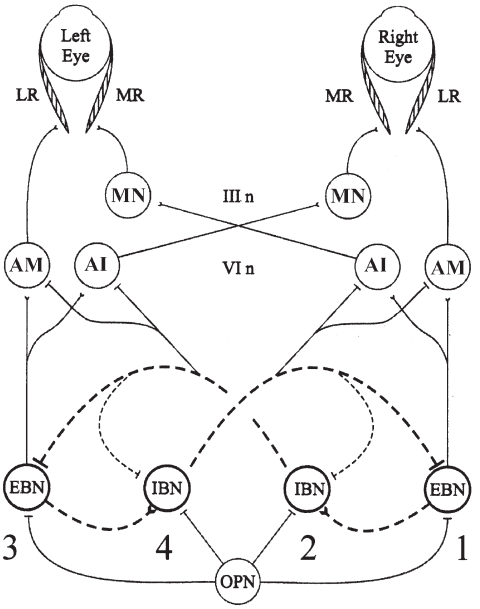


Figure 3–10. A brainstem neural network model for generation of horizontal saccades. Projections with flat ending are inhibitory, the others excitatory. Saccades require reciprocal innervation to the medial rectus (MR) and lateral rectus (LR) of both eyes. The LR is driven by the ipsilateral abducens nucleus (VI n) motoneurons (AM). The VI n also contains abducens internuclear neurons (AI) that send their axons to the contralateral oculomotor nucleus (III n), which drive the MR of the other eye. Excitatory burst neurons (EBN) provide the saccadic drive to ipsilateral AM and AI. EBN also project to inhibitory burst neurons (IBN). IBN provide inhibition to the contralateral AM and AI. Thus, an EBN/IBN pair provides reciprocal innervation. IBN also provide inhibition to the contralateral EBN and IBN. A consequence of this cross-coupling is that the EBN/IBN pairs form a short-latency, positive feedback loop. When omnipause neurons (OPN) are active, they prevent this loop from oscillating. At the beginning of a saccade, OPN neurons cease discharge allowing one set of EBN (1) to start firing and activate ipsilateral IBN (2). During IBN (2) firing, contralateral EBN (3) receive a hyperpolarizing input that keeps them silent. At the end of the saccade, when the IBN (2) cease firing, the EBN (3) start to discharge because of rebound depolarization, which stimulates ipsilateral IBN (4), which, in turn, inhibit the original EBN (1) that fired. Thus, the EBN-IBN pairs tend to spontaneously oscillate whenever the omnipause neurons are inhibited and there is no specified saccadic command. (Adapted from Ramat S, Leigh RJ, Zee DS, Opticon LM. Ocular oscillations generated by coupling of brainstem excitatory and inhibitory saccadic burst neurons. Exp Brain Res 160, 89–106, 2005, with kind permission of Spinger Science and Business Media.)

(e.g., right anterior and left posterior canals).[736] For example, EBN in the right riMLF increase their discharge when the right eye extorts and the left eye intorts. While the direction of torsion is fixed for EBN on each side, the direction of vertical rotation is upward in some and downward in others. Therefore, unilateral lesions have only mild effects on vertical saccades, but abolish ipsilateral torsional saccades. For example, with a lesion of the right riMLF, torsional quick phases, clockwise from the point of view of the subject (extorsion of the right eye and intorsion of the left eye) are lost.[690] Bilateral lesions in riMLF abolish all vertical and torsional saccades.[690]

Recent studies suggest that in monkey, the riMLF does not contain inhibitory burst neurons. Instead, the adjacent interstitial nucleus of Cajal, and surrounding reticular formation, contains neurons that send GABAergic projections to contralateral ocular motoneurons in CN III and IV and could turn out to be the vertical IBN.[311] Reciprocal connections between vertical EBN and IBN seem possible, so that a neural network similar to that postulated for horizontal saccades could account for vertical saccadic oscillations (discussed further below in Pathophysiology of Saccadic Abnormalities).

In addition to their projections to ocular motoneurons in the CN III and CN IV nuclei, vertical EBN also send axon collaterals to the interstitial nucleus of Cajal (see Fig. 6–4, and Box 6–6).[459,460] The latter structure appears to contain not only vertical IBN, but also burst-tonic neurons, thus contributing to the velocity-to-position integrator for vertical and torsional eye movements. This scheme is supported by the results of pharmacologically inactivating the interstitial nucleus of Cajal; vertical and torsional saccades can still be made, but there is centripetal post-saccadic drift, indicating impaired vertical gaze-holding.[131]

OMNIPAUSE NEURONS

Omnipause cells lie in the nucleus raphe interpositus, which is located in the midline between the rootlets of the abducens nerves (see Fig. 6–2, Chapter 6).[99,379] Omnipause neurons are medium-sized with prominent dendrites that extend horizontally across the midline. These neurons utilize glycine as their neurotransmitter,[313] consistent with their inhibitory function. An important crossed projection to the omnipause cell region arises from the rostral pole ("fixation zone") of the superior colliculus.[101,220,221] Additional projections to the omnipause neurons are from the frontal eye fields,[677] the supplementary eye fields,[651] the central mesencephalic reticular formation, the

long-lead burst neurons in the rostral pons and midbrain,[627] and the fastigial nucleus.[490] Omnipause cells send inhibitory projections, which are mainly crossed, to EBN in the pons, to IBN in the medulla, and to the riMLF.[481,500]

Omnipause neurons discharge continuously except immediately before and during saccades, when they pause. Omnipause cells cease discharging during saccades in any direction, hence their name. Omnipause cells also cease discharging during blinks,[289] and their discharge rate is modulated by static vergence angle.[95] When omnipause cells are experimentally stimulated in the monkey, the animal is unable to make saccades or quick phases in any direction, although other types of movements, such as vestibular slow phases, can still be elicited.[755] If omnipause cells are stimulated during a saccade, the eye decelerates abruptly in mid-flight (Fig. 3–11).[349,350] Based on these findings, it appears that omnipause cells tonically inhibit all burst cells, and when a saccade

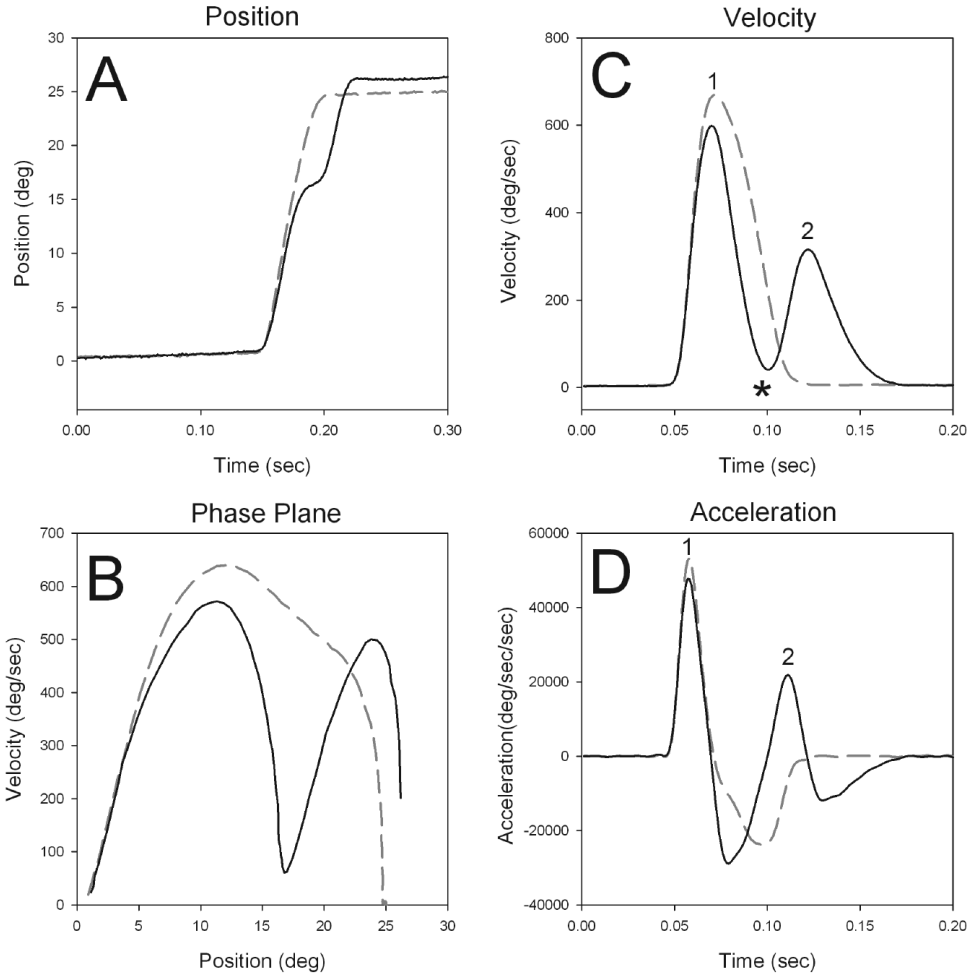


Figure 3–11. Experimental interruption of saccades in monkey. To interrupt saccades in mid-flight, omnipause neurons were stimulated at 400 Hz, with a 20-ms train of bipolar pulses, applied 4 ms–5 ms after saccade onset. Control saccades are shown in gray dashed lines and interrupted saccades in solid black line. (A) Comparison of position records of individual control and interrupted saccade trials. Note how the final position of interrupted saccade is greater than the control. (B) Phase plane plots of the same two saccades shown in A, demonstrating the abrupt fall in velocity with stimulation. (C) Average eye velocity traces are shown from 12 normal control trials and 16 trials in which saccades were interrupted by stimulation of omnipause neurons. During interrupted saccade trials, after the first velocity peak (1) eye velocity drops to 41.3 degrees per second (*) before increasing again to a second peak (2). (D) Acceleration responses corresponding to velocity records in C. (Data provided by courtesy of E. L. Keller.)

is called for, the omnipause cells themselves must be inhibited to permit the burst cells to discharge. By acting as an inhibitory switch, omnipause cells help maintain the necessary synchronization of the activity of premotor saccadic burst neurons to drive the eyes rapidly during the saccade and to keep the eyes still when the saccade is over. Recent studies in monkeys have shown that omnipause neurons may be inhibited by about 30% during smooth-pursuit movements,[444] suggesting that they have a more general function of gating visually mediated eye movements, as part of a visual fixation system.

Experimental lesions with excitotoxins or muscimol in the omnipause region cause slow horizontal and vertical saccades.[339,662] This effect is perhaps surprising, given the "high gain" properties of burst neurons, and one prediction of lesioning the "saccadic switch" would be uncontrollable saccadic oscillations, such as opsoclonus. An explanation for slow saccades may be that omnipause neurons exert a paradoxical influence on burst neurons. Since they are glycinergic, omnipause neurons normal inhibit burst neurons. However, it has been shown that glycine can actually facilitate N-methyl-D-aspartate (NMDA) receptor currents.[11] It has been postulated that when burst neurons synchronously receive a trigger signal from long-lead burst neurons (discussed next) and cessation of omnipause discharge, the result is a post-inhibitory rebound that produces the high acceleration typical of saccades.[447,448,448a] Thus, if omnipause neurons are lesioned, there will be no glycine to enhance the NMDA receptor currents (i.e., no post-inhibitory rebound), and saccades will be slower, depending solely on inputs from long-lead burst neurons.

What inhibits the omnipause neurons until the saccade is complete and the eye is on target? Intracellular electrophysiological studies indicate that omnipause neurons receive a powerful inhibitory input that completely turns them off just before a saccade is initiated;[770] this has been attributed to a "trigger signal," perhaps driven by inputs from the rostral pole of the superior colliculus. After this initial inhibition, the level of membrane hyperpolarization of omnipause neurons is temporally linked with current eye velocity, and this sustained hyperpolarization keeps omnipause neurons "off" for the remainder of the saccade. Since the discharge of excitatory burst neurons is also correlated with eye velocity during the saccade, they may be the source of sustained hyperpolarization of omnipause neurons via local inhibitory neurons called latch neurons (Fig. 3–9). Certain PPRF neurons have been identified that might serve as latch neurons.[444] Theoretically, should the latch circuit malfunction, then the eye would not get on target, but would prematurely decelerate; such behavior is encountered in certain disorders (see Prematurely Terminated Saccades).[332,591]

LONG-LEAD BURST NEURONS AND THE CENTRAL MESENCEPHALIC RETICULAR FORMATION

Neurons that start to discharge 40 ms or more before saccades are found throughout the brainstem. Some long-lead burst neurons (LLBN) lie in the pons and midbrain,[339a] and receive projections from the superior colliculus.[627] They project to pontine EBN, medullary IBN, and omnipause neurons; they also project to the nucleus reticularis tegmenti pontis (NRTP). These mesencephalic LLBN discharge before and during saccades to their "movement field." The portion of the mesencephalic reticular formation that lies just lateral to the CN III nucleus (central mesencephalic reticular formation, cMRF) [119] contains neurons that have reciprocal connections with the superior colliculus,[113,458] and it has been postulated that they may serve in a feedback loop.[742] These neurons also receive projections from the supplementary eye fields and fastigial nucleus; they project heavily to omnipause neurons and NRTP, and start to discharge more than 40 ms before saccades.[266] Within the population of cMRF neurons are some units with low background activity that could provide a "trigger signal" to the omnipause neurons; other units with high background activity could provide tonic inputs to omnipause neurons and specify saccade size via projections to NRTP.[288] Experimental lesions of the cMRF cause hypermetria of contralateral and upward saccades and hypometria of ipsilateral and downward saccades; fixation may be disrupted by large saccadic intrusions.[743] More rostral inactivation of the MRF impairs vertical saccades.[744]

Other LLBN lie in NRTP and project mainly to the cerebellum via the middle

peduncle; some LLBN project to the PPRF.[627] Thus, it seems that LLBN may serve more than one function. Those LLBN that receive input from the superior colliculus may synchronize the onset and end of saccades, by virtue of their projections to omnipause and premotor burst neurons.[288,627]

Higher-Level Control of the Saccadic Pulse Generator

It is now clear that several distinct cortical areas are involved in the voluntary control of saccades. The anatomical connections of these areas and the way that they project to the brainstem saccadic pulse generator are summarized in the text and Boxes of Chapter 6, and in Figure 3–12. The two main brainstem targets of the cortical eye fields are the superior colliculus and the pontine nuclei, especially NRTP, which project, in turn, to the cerebellum. In comparison, direct projections from the cortical eye fields to the PPRF and riMLF are meager, although projections to omnipause neurons have been demonstrated.[678]

The superior colliculus, which receives inputs from all the cortical eye fields, may coordinate the discharge of burst and omnipause neurons. The importance of the superior colliculus is demonstrated by the finding that inactivation of collicular burst neurons blocks the effects of frontal eye field stimulation.[272] However, destructive lesions here do not

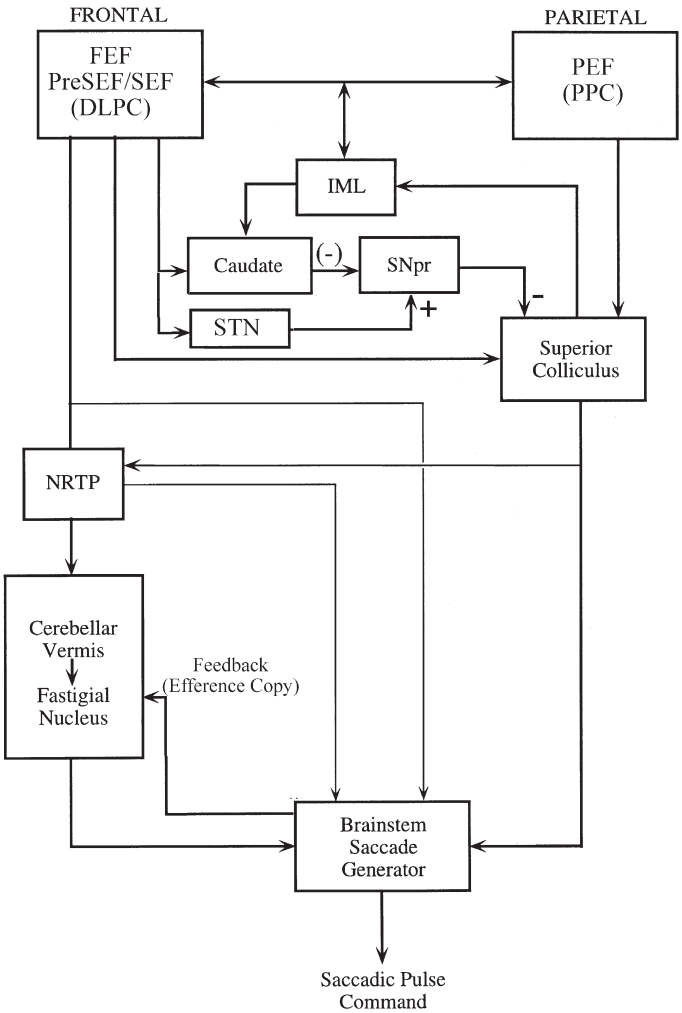


Figure 3–12. Block diagram of the major structures that project to the brainstem saccade generator (premotor burst neurons in PPRF and riMLF). Also shown are projections from cortical eye fields to superior colliculus. DLPC, dorsolateral prefrontal cortex; FEF, frontal eye fields; IML, intramedullary lamina of thalamus; NRTP, nucleus reticularis tegmenti pontis; PEF, parietal eye fields; PPC, posterior parietal cortex; SEF, supplementary eye fields; SNpr, substantia nigra, pars reticulata; STN, subthalamic nucleus. Not shown are the pulvinar, which has connections with the superior colliculus and both the frontal and parietal lobes, projections from the caudate nucleus to the subthalamic nucleus via globus pallidus, and the pathway that conveys efference copy from brainstem and cerebellum, via thalamus, to cerebral cortex. −, inhibition, +, excitation.

permanently abolish voluntary saccades,[17,271] and so the cortical projection to NRTP and the cerebellum also seems important. Conversely, saccades can still be made after destructive frontal eye field lesions. A crucial finding is that bilateral lesions of the frontal eye fields and the superior colliculus cause an enduring, severe deficit of voluntary saccades.[607] A similar defect occurs with combined bilateral lesions of the frontal and parietal eye fields.[409] Thus, parallel descending pathways are involved in generating voluntary saccades, and it appears that each is capable of performing spatial-to-temporal and retinotopic-to-craniotopic transformations of neural signals.

Superior Colliculus

VISUAL AND MOTOR LAYERS OF THE SUPERIOR COLLICULUS

The superior colliculus consists of seven layers.[669,761422,458,576] Early studies established that the dorsal layers of the superior colliculus are "visual" in terms of their properties and that the more ventral intermediate and deep layers are "motor."[10,24] The dorsal layers receive an orderly retinal projection, such that the visual field (which is compressed logarithmically relative to amplitude) is mapped onto its surface (Fig. 3–13A).[136] These layers receive visual inputs directly from the retina and from the striate cortex and send efferents to the pretectal nuclei, lateral geniculate body, and pulvinar.

The ventral layers contain a "motor map" (Fig. 3–13B) defined by the eye movements that are produced by electrical stimulation.[571,606] Although there are connections between the dorsal and the ventral layers,[456,457] in primates, cerebral cortical projections to the ventral superior colliculus are dominant. Furthermore, there is some independence between visually induced activity in the dorsal layers and movement activity in ventral layers, and there is a 40-ms delay between visual activity in the dorsal and ventral layers.[425,761] Thus, in primates, the superficial layers do not seem critical for generating eye movements, and the rest of this section will deal with only the connections and properties of the ventral layers of the superior colliculus.[410] To preview our discussion, the role of the superior colliculus depends on its retinotopic map, and the relative timing and level of neuronal activity across that map. The rostral pole is concerned with fixation and small saccades, and more caudal portions of the superior colliculus are important for target selection and initiation of eye and eye-head gaze shifts.

ANATOMICAL CONNECTIONS OF THE VENTRAL LAYERS OF THE SUPERIOR COLLICULUS

Afferents

Important projections to the ventral layers arise from striate, extrastriate and parietal cortex, and from the frontal lobes (Fig. 3–12).[576] Thus, the frontal eye field, supplementary eye field, and dorsolateral prefrontal cortex all project to the superior colliculus; some of these pathways are direct and some are via the basal ganglia, including the caudate nucleus and the pars reticulata of the substantia nigra (SNpr). In addition, the pedunculopontine tegmental nucleus (PPTN), which appears to promote saccade generation as part of a general effect on attention, sends nicotinic projections to the superior colliculus.[363–365]

The superior colliculus has reciprocal connections with the central mesencephalic reticular formation,[458] and receives inputs from the nucleus prepositus hypoglossi.[275] The rostral pole receives an input from the cerebellar fastigial nucleus.[423] Serotonin, acetylcholine, and gamma-amino butyric acid (GABA) have all been identified as transmitters in the ventral layers.

Efferents

The ventral layers project to critical structures in the brainstem that generate the premotor commands for saccades. These include the PPRF and riMLF, the nucleus prepositus hypoglossi, the nucleus reticularis tegmenti pontis (NRTP), the central mesencephalic reticular formation, and the vestibular nuclei. The ventral layers also send ascending projections to the FEF via the central and medial dorsal thalamus.[616,666] Descending outputs from the ventral layers of the superior colliculus are carried via an ipsilateral tectopontine pathway and a contralateral tectoreticular pathway. The latter crosses in the dorsal

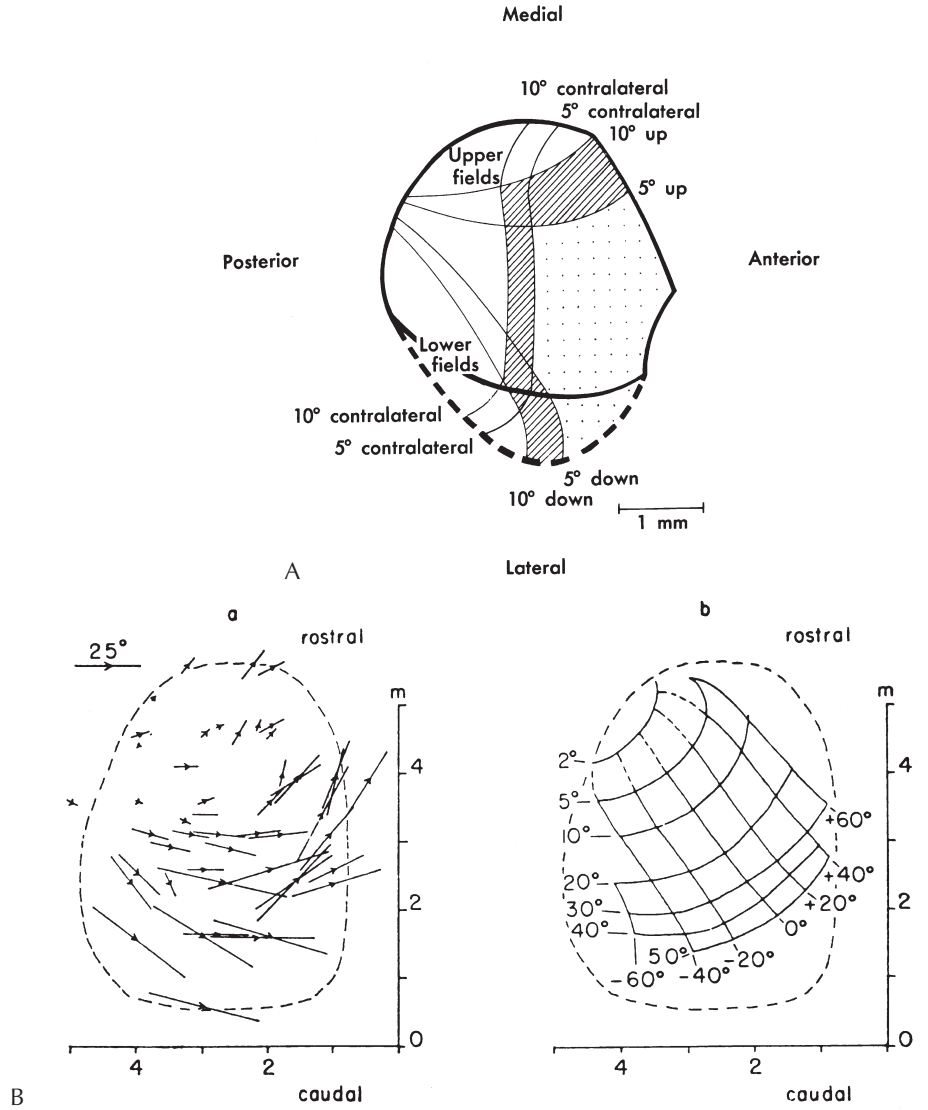


Figure 3–13. The topography of maps in the superior colliculus. (A) Representation of the visual field on the surface of the right colliculus. The stippled area represents the part of the contralateral visual field within 5 degrees of the fovea. Stippled and striped areas combined represent the part of the contralateral visual field within 10 degrees of the fovea. (Reproduced from Cynader M, Berman N. Receptive field organization of monkey superior colliculus. Neurophysiol 35, 187-201, 1972, with permission of the American Physiological Society.) (B) The motor map of the ventral layers of the left superior colliculus, based on stimulation studies. On the left, arrows indicate the direction and amplitude of saccades produced by stimulation. On the right are smoothed contours of the motor map. Isoamplitude lines (2 to 50 degrees) run from medial to lateral, and isodirection lines (–60 to +60 degrees) run from anterior to posterior. (Reprinted from Robinson DA. Eye movements evoked by collicular stimulation in the alert monkey. Vision Res 12, 1795-1808, 1972, with permission from Elsevier.)

tegmental decussation of Meynert and, as the predorsal bundle, lying ventral to the MLF, carries descending branches destined for the pontine and medullary reticular formation and ascending branches destined for the rostral midbrain.[252,457,458,458]

FUNCTIONAL ANATOMY OF THE SUPERIOR COLLICULUS REVEALED BY STIMULATION

Microstimulation of the ventral layers of the superior colliculus has provided many insights

into the organization of this structure.[571,606] Stimulation of the rostral pole of the motor map suppresses saccades.[222] This "fixation zone" of the superior colliculus sends a monosynaptic excitatory projection to omnipause neurons,[101] which inhibit premotor burst neurons.

Stimulation more caudally induces saccades at latencies that imply disynaptic connections with premotor burst neurons;[351] it is suggested that long-lead burst neurons are interposed.[449] In general, the direction and size of the saccade are functions of the site of stimulation (above a certain threshold), rather than the strength of the stimulus. However, the current position of the eye also influences saccade size, with the amplitude of contralateral saccades increasing as the eye starts from progressively more ipsilateral positions. Furthermore, threshold required to stimulate a saccade is raised if the subjects actively fixates the target.[672] Nonetheless, once threshold has been reached, saccades occur in an 'all or none" fashion. The smallest saccades are elicited rostrally, the largest caudally. Saccades with upward components occur with more medial stimulation, those with downward components, with more lateral stimulation. Purely vertical saccades only occur with bilateral simultaneous stimulation of corresponding points.

This "motor map" is in polar coordinates (Fig. 3–13B), but lacks the 3-D (i.e., torsional) information required to implement Listing's law, which must be computed elsewhere.[729] Saccades of similar size (isoamplitude) correspond to lines running medial-to-lateral (largest with stimulation caudally), and saccades of similar direction (isodirection) correspond to lines running anterior to posterior (0 degree corresponding to a pure, horizontal, contralateral saccade). Stimulation in the caudal third of the ventral motor map produces combined eye-head gaze-shifts; both eye and head movements are directed contralateral to the side stimulated;[129] eye-head movements are discussed further in Chapter 7.

NEURAL ACTIVITY OF THE VENTRAL SUPERIOR COLLICULUS DURING SACCADES

The first studies of the activity of single neurons in the ventral layers of the superior colliculus in monkeys trained to make saccades to visual targets revealed a variety of cell types that showed responses related to either the visual stimulus, or to the saccadic movement, or to both.[171,671,760,762] Many subsequent studies have identified neurons with a range of properties. Thus, some neurons that respond to visual stimuli do so in anticipation of a saccade that will bring a target into their receptive field,[745] or show activity related to the likelihood that a target will be the goal of a saccade.[52,241] Quasivisual neurons hold in spatial register the amplitude and the direction of the upcoming required saccade (i.e., they encode the motor error signal necessary to acquire the target).[674] Neurons may even be active during covert shifts of visual attention, during which there is no eye movement.[321] Neurons also respond to auditory stimuli, either alone or in combination with visual stimuli, when the two are spatially aligned.[58] Such units may also have somatosensory receptive fields.[253,748] Thus, the superior colliculus neurons have multisensory properties, which are generally encoded in retinotopically coded movement fields.[253,335,748]

Two main populations of *saccade-related cells* have been defined in the ventral layers: build-up neurons, which have a prelude of activity before their saccade-related burst, and collicular-burst neurons, which are intermixed and slightly more dorsal.[410,471,761] Both build-up and saccadic-burst neurons project out of the superior colliculus, and may be extremes of a continuum rather than two separate types of cells.[471] The *rostral pole* of the motor map, corresponding to small saccades, projects to omnipause neurons, and may be important for sustaining fixation.[101,220,469,470]

Build-up neurons start to discharge when a visual stimulus becomes the target for a saccade.[472] Like collicular burst neurons, the location of build-up cell activity initially occurs at a site on the motor map related to the amplitude and direction of the upcoming saccade. However, unlike the location of discharging collicular burst cells, which remains constant throughout the eye movement, there appears to be a rostral spread of prelude activity of build-up neurons (a moving wave or hill) towards the rostral pole.[261,472] It had been postulated that this spread of activity amongst the build-up neurons population could achieve the spatial-temporal transformation of signals that is needed to provide the reticular burst neurons with the saccadic command. Thus, it was

postulated that when the spreading wave of activity reached the fixation neurons at the rostral pole, the saccade would end.[472] However, electrophysiological studies have provided evidence against this hypothesis; the superior colliculus seems important in triggering, but not in steering or stopping, saccades.[13,624,661] The prelude of activity on build-up neurons is much smaller than the saccade-related burst, and its role in movement control is uncertain.

The site of maximum activity on the collicular motor map is related to the desired displacement, or change in eye orientation. During the course of a saccade, the site of maximum activity of the saccade-related burst neurons does not change, but their discharge rates decline as the eye approaches the target. Although it was found that the temporal discharge of collicular neurons decays in proportion to instantaneous motor error (the difference between current and desired eye position),[741] subsequent evidence found that their discharge is not calculating a dynamic motor error signal.[13,173,389,468]

Build-up and burst neurons located in the caudal part of the superior colliculus appear to encode the overall intended gaze displacement,[65] and their discharge properties are consistent with the notion that they indirectly drive premotor burst neurons in the brainstem reticular formation. Thus, when large target jumps elicit multiple small saccades to reach the goal, the locus of activity on the superior colliculus restarts after each small saccade at the locus corresponding to the remaining distance to the goal.[65] Thus, although the superior colliculus does not compute a dynamic motor error (e.g., to control saccade trajectory) during a saccade, it does represent the static motor error between saccades.

During more complex tasks, such as saccades to two sequentially flashed targets,[545] or visual search,[430,431] saccadic trajectories can become strongly curved if the brain starts going toward one target and then, in midflight, turns toward another target. Neurons in the ventral layers clearly encode the retinotopic location of each target, and the site with the highest activity switches during the saccade to indicate which target is the instantaneous goal. In these studies, it was found that the locus of activity on the superior colliculus corresponded to the locations of the target, but not to the direction and amplitude of subsequent saccades. These studies reveal that whenever the retinotopic location of the target does not match the ensuing saccade, the collicular activity always reflects the location of the target, and does not encode the saccade. In the context of early collicular studies that showed that monkeys can make saccades after superior colliculus lesions,[607] this dissociation leads to an important conclusion. The ventral superior colliculus does not encode saccadic eye movements, rather it encodes the current retinotopic goal; the movement needed to reach that goal is controlled from somewhere else, presumably the cerebellum.[508] The application of multi-electrode arrays,[544] and functional imaging,[455] may provide further insights into how ensembles of superior colliculus neurons contribute to a range of ocular motor behaviors.

EFFECTS OF PHARMACOLOGICAL INACTIVATION AND LESIONS OF THE SUPERIOR COLLICULUS

Insight into the role of the ventral layers of the superior colliculus in saccade generation has been gained by local injection of two agents: the GABA-A agonist muscimol, which increases normal GABA inhibition and thereby decreases neuronal activity, and the nonspecific GABA antagonist bicuculline, which increases neuron activity by decreasing normal GABA inhibition. Injection of muscimol into the rostral pole of the superior colliculus reduces latencies to those of express saccades; furthermore, steady fixation is disrupted by saccadic intrusions. Conversely, injection of bicuculline into the rostral pole increases saccadic latency, and sometimes no saccade is generated. Injection of muscimol or bicuculline into more caudal regions of the superior colliculus reverses their effects. Thus, inactivation with muscimol (or lidocaine) causes impaired initiation of saccades, which are hypometric and slow.[302,304,387] Caudal bicuculline injections cause fixation instability, with saccadic intrusions. Injection of nicotine into the superior colliculus produces express saccades for movements corresponding to the site of the injection.[12] These findings support the suggestion that the fixation neurons at the rostral pole of the superior colliculus suppress saccades both through excitation of omnipause neurons,[101] and by inhibiting collicular burst

neurons.[760] However, inputs from structures other than the superior colliculus, such as cMRF, also influence omnipause neurons and the timing of saccadic onset.[188] If muscimol is injected locally into the superior colliculus at a point corresponding to small saccades (Fig. 3–13), and the monkey makes a large saccade, the saccade has a curved trajectory and the error depends on how far the goal is from the site of the lesion. This finding supports the hypothesis that the initial direction of a saccade is determined by a population average (such as the center of gravity of the distribution of activity),[387] which is displaced away from the area that has been pharmacologically inactivated.[548]

Conventional lesion studies have been less revealing than acute pharmacological inactivation, in part because of the effects of recovery and adaptation. Discrete electrolytic lesions of the superior colliculus cause an enduring increase in reaction time as well as some slowing of saccades,[271] but the accuracy of saccades recovers. Following larger surgical lesions, the frequency of spontaneous saccades is diminished during scanning of a visual scene, but not in complete darkness.[17] During fixation of a stationary target, the monkey without a superior colliculus is less easily distracted by peripheral stimuli and makes fewer saccades away from the fixation target. Saccadic accuracy is mildly impaired. Most important, short-latency express saccades are permanently abolished.[605] When lesions of the superior colliculus are combined with lesions of the caudal medial thalamus, [18] or with the frontal eye field (see Frontal Eye Field, in the following section), more long-lasting and severe ocular motor abnormalities are produced.[607]

Lesions restricted to the superior colliculi are rare in humans. One patient had undergone removal of an angioma from the right superior colliculus, and but also had evidence of dorsal midbrain syndrome.[291] Spontaneous horizontal saccades to the left occurred less frequently and were more commonly followed by corrective saccades; saccadic latency was normal. Another patient with a hematoma largely restricted to the right superior colliculus showed defects in latency and accuracy for contralateral saccades, and increased numbers of errors in the antisaccade task.[537] Recent functional imaging has demonstrated activation of the superior colliculus in humans engaged in visual search,[240,620] and showed increased inactivation for saccades made at decreased latency in response to testing with the gap paradigm.[483]

A SYNTHESIS OF THE INFLUENCE OF THE SUPERIOR COLLICULUS ON THE CONTROL OF SACCADES

In summary, based upon an intense research effort over the past 30 years, it appears that the superior colliculus plays an important role in target selection, and initiating saccades, and contributing to their speed. The superior colliculus may initiate saccades by providing a "trigger signal" to omnipause neurons, burst neurons, and possibly the cerebellum. However, another part of the brain, perhaps the frontal eye fields, must be able to adapt and provide a substitute for that trigger signal after superior colliculus lesions. Furthermore, cerebellar lesions lead to enduring saccadic dysmetria, implying that the superior colliculus alone cannot control saccades. Recent research has emphasized that whenever the target location and required eye movement differ, the superior colliculus always encodes the target location in retinal coordinates, but not the required eye movement.[508] Thus, it appears that the details of generating the saccade and getting it on target depend much more on the brainstem reticular formation and cerebellum, respectively. Clinicians seldom think about the superior colliculus when they interpret abnormal eye movements, partly because of the rarity of selective lesions in humans. It is also possible that the effects of superior colliculus lesions have been missed, since special testing for changes of saccade latency is usually needed. The new hypothesis that links collicular function to saccade latency and the initiation and speed of the saccade, but not to saccade accuracy, suggests future clinical tests that could more easily detect the consequences of superior colliculus lesions. Functional imaging studies are beginning to confirm a similar role for the superior colliculus in humans as in macaque.[240,483,620]

The Role of the Frontal Lobe

Since Ferrier stimulated the premotor cortical area 8 of monkeys and elicited contralateral

eye movements,[195] several distinct areas of prefrontal cortex have been identified that contribute to the voluntary control of saccades. The best known is the *frontal eye field*, which was first identified in humans by electrical stimulation.[75,243,525] The location of the homologue of the frontal eye field in humans has been recently defined by functional imaging studies, and lies in the anterior wall of the precentral sulcus, close to the intersection with the superior frontal sulcus.[402] Three other areas, the *supplementary eye field*, *dorsolateral prefrontal cortex*, and *anterior cingulate cortex* have also been shown to influence voluntary saccades. In addition, other areas of cortex, such as in the dorsomedial frontal lobes, likely contribute to saccades made as a component of more complex behaviors.[455,499] As we discuss each cortical area, we will summarize studies in monkey that have defined its role, and supplement this with information from humans, based upon functional imaging, magnetic or intra-operative stimulation, and behavioral changes caused by lesions. The anatomical location and connections of these three areas are described in Chapter 6 and summarized in Figure 6–8, and Boxes 6–19, 6–20, and 6–21.

THE ROLE OF THE FRONTAL EYE FIELD

Effects of Microstimulation of Frontal Eye Field

In rhesus monkey, microstimulation studies have been crucial in defining the extent of the FEF (along the posterior portion of the arcuate sulcus—part of Brodmann area 8),[91] and have also provided insights into FEF function. Stimulation at any site on the FEF elicits a saccade of a specific direction and amplitude. A "motor map" is present with larger saccades evoked from stimulation of the dorsomedial portion of the FEF, and smaller saccades from stimulation of the ventrolateral part.[91] Usually, the movement is oblique, with a contralateral horizontal component; bilateral stimulation is required to elicit a purely vertical saccade. The latency from frontal eye field stimulation to the onset of a saccade is about 30 ms–45 ms, similar to that for stimulation in the superior colliculus. Stimulation in FEF at currents that are below the threshold needed to produce saccades may change properties of neurons in secondary visual areas; this finding presumably reflects a mechanism by which visual areas are normally advised of upcoming eye movements.[451,452] Intra-operative FEF stimulation in humans undergoing surgery for intractable epilepsy, at the posterior end of the middle frontal gyrus, produces eye movements that are directed contralaterally, often with an upward component; the direction sometimes depends on starting eye position.[75]

Microstimulation of the FEF can also *suppress* saccades under certain experimental conditions.[331] Thus, stimulation of a wide area of the FEF suppresses ipsiversive visually guided and memory-guided saccades at stimulus intensities lower than those for eliciting electrically evoked saccades. However, stimulation near the spur of the arcuate sulcus, which corresponds to the smooth-pursuit portion of FEF, suppresses both types of saccades in any direction. This part of the FEF projects to the "fixation region" at the rostral pole of the superior colliculus and also to omnipause neurons in the pons.[92,92,678] Stimulation is most effective in suppressing saccades when applied 40 ms–50 ms before saccade onset, probably having its effects at the level of the superior colliculus or PPRF. Stimulation of one FEF affects the activity of cells in the other FEF, in a manner conducive to coordination between the two eye fields.[608] In a patient with a frontal lobe tumor, per-operative stimulation over parts of the FEF arrested self-paced saccades.[441]

Physiological Properties of Frontal Eye Field Neurons

Only occasional FEF neurons discharge before spontaneous saccades made in complete darkness, though many neurons discharge after such movements. The most useful information about activity of single neurons in the FEF has been gained from experiments in which monkeys were trained to perform a variety of saccadic tasks for reward.[90,246] Different subpopulations of FEF neurons encode the visual stimulus,[69,70,596] the planned saccadic movement,[597] or both. Like the superior colliculus and parietal eye fields, some FEF cells show movement of their receptive fields that anticipate the visual consequences of planned saccades.[718] Although the discharge of FEF neurons is related to the amplitude and direc-

tion of voluntary saccades, their discharge during saccades does not dynamically encode signals such as motor error (the difference between current and desired eye position, which is required to guide the eyes to their target).[629]

Frontal eye field neurons also discharge for visual and motor aspects of *memory-guided saccades*.[208,719] FEF lesions in humans cause systematic errors of memory-guided saccades.[542] However, other cortical areas contribute,[43] notably dorsolateral prefrontal cortex (discussed below). When monkeys perform a double-step task, in which two target lights are flashed in succession before the eye has time to move, most units discharge not in relation to the retinal location of the second target but according to the saccade needed to acquire it.[246] Such cells behave similarly to quasivisual cells of the superior colliculus, since their activity encodes the desired change in eye position. Pharmacological inactivation of the mediodorsal thalamus, which relays corollary discharge from the superior colliculus to FEF, causes the second saccade in response to a double-step stimulus to become inaccurate,[667] implying that the FEF rely on efference copy information to correctly program the second saccade.

Neurons that appear to be concerned with *disengaging fixation* before a saccade increase their discharge when the fixation light is turned out, even before the new target becomes visible.[154] Some FEF neurons show properties indicating that they contribute to selection of the target to which a saccade will be made,[601] the decision whether to look at it or not,[270] and the process of visual scanning of a complex visual scene.[93,279]

The FEF appear to contribute to programming of the *antisaccade response* (Fig. 12–14). Thus, functional imaging studies indicate that FEF are activated bilaterally during both prosaccades and antisaccades, but more so for the latter. [126] Patients with FEF lesions show a normal percentage of errors on the antisaccade task, but their correct antisaccades are made at increased latency.[532,567] Thus, it has been suggested that, during the antisaccade task, triggering of the intentional, correct antisaccade depends upon FEF, whereas inhibition of reflexive misdirected saccades is due to dorsolateral prefrontal cortex, which is discussed below.[532]

The FEF are also activated during covert visual search, during which eye movements are suppressed.[161] Furthermore, magnetic stimulation over human FEF interferes with visual search tasks in which eye movements are not required.[463] Additional insights into the mechanism that suppresses saccade initiation can be gained from a *countermanding task*, in which monkeys are required to make visually guided saccades on most trials but, on a fraction of trials, to withhold a saccade on the basis of reappearance of the fixation cue.[600] Electrophysiological properties of FEF during this task have identified neurons that reflect behavioral responses, and indicate that these units are concerned with generation or suppression of saccades.

Effects of Frontal Eye Field Lesions on Saccade Generation

Acute pharmacological inactivation with muscimol causes a contralateral "ocular motor scotoma" with abolition of all reflex, visual, and voluntary saccades with sizes and directions corresponding to the injection site.[155] With unilateral muscimol inactivation of FEF, during attempted fixation there is a gaze shift towards the side of the lesion, and inappropriate saccades directed ipsilaterally may disrupt fixation. Thus, these results are similar to the effects of injecting these agents into the superior colliculus; inactivation of either structure causes substantial defects in reflex visual and voluntary saccades. Acute destructive lesions of the FEF in monkeys produce an increase of latency for contralateral saccades and a decrease of latency for ipsilateral movements; in other words, an increase of express saccades ipsilateral to the side of the lesion.[602]

More subtle changes in the generation of visually guided saccades are present with chronic experimental lesions of the FEF, including decreased frequency and size of movements,[607] and defects of saccades made to paired or multiple targets that are presented asynchronously.[602] In humans also, chronic lesions of the FEF cause relatively minor deficits. There is increased latency of visually guided saccades to contralateral targets, especially when tested using the overlap paradigm (fixation light remains on during testing, Fig. 3–2A).[85,414,567] Although abnormalities on the antisaccade task have been reported,[413] this

may reflect additional involvement of dorsolateral prefrontal cortex, an issue discussed below.[532] Visual and memory-guided saccades are also inaccurate (see Box 12–21, Chapter 12).[233] In summary, the FEF in humans appears more concerned with voluntary than reflexive saccades, a view supported by functional imaging studies.[454]

ROLE OF THE SUPPLEMENTARY EYE FIELD

The supplementary eye field (SEF) lie just anterior to the supplementary motor cortex, in the dorsal medial portion of the frontal lobe;[612] in humans this corresponds to the upper part of the paracentral sulcus.[256] *Stimulation* in the SEF elicits saccades at low thresholds though at slightly longer latency than in the frontal eye fields.[612] Initial studies, using microstimulation, seemed to indicate that the eye was driven to a specific orbital position.[611] This was unlike the results of stimulation of the FEF, which produced an eye movement of specific size and direction, determined by the site stimulated. More recent evidence indicates that rostral SEF encodes saccades in an eye-centered frame whereas caudal SEF encodes saccades in a head-centered frame.[418,521,614]

Like the FEF, SEF contain neurons that discharge prior to voluntary saccades,[592] but also discharge during a range of more complex behaviors. Thus, SEF neurons also respond during *conditional learning*[114] and *antisaccades*.[614] Some SEF units fire before eye movements to the right or left end of a horizontal bar, irrespective of the location of the bar in the visual field; such neuronal activity is referred to as object-centered.[506] During a *countermanding task*, in which subjects make visually guided saccades on most trials but, on some, are required to withhold a saccade on the basis of reappearance of the fixation cue, SEF neurons are variously active after errors, after successful withholding, or in association with reinforcement.[688] Thus, SEF units show interesting differences from FEF neurons on the countermanding task,[600] and while some FEF neurons appear concerned with generation or suppression of saccades, neurons in the SEF (and the anterior cingulate cortex) respond on trials in which a saccade is erroneously not canceled and reward will not be given.[688] In comparison with other cortical eye fields, SEF appears most concerned with internally guided target selection based upon reward during prior trials.[19,106,117]

Neurons in SEF are active when monkeys are trained to make a *learned sequence of saccades*.[325,325,403] This finding is consistent with clinical studies that suggested that the SEF lesion, especially on the left side, disrupt the ability to carry out a learned sequence of saccades.[232,235] Inactivation of SEF in monkeys impairs the ability to respond to a double-step task,[665] and TMS over SEF in humans disrupts the order of responses to a double-step stimulus.[712] During testing of sequences of saccades (Fig. 3–2E), TMS studies have shown that the SEF could be crucial at two distinct times: during the learning phase (presentation of the visual targets), and just after the go signal, when the subject must initiate the sequence of saccades.[475] Further support for the notion that the SEF is concerned with eye movements that are programmed as part of learned, complex behaviors is supported by functional imaging studies in humans, which have demonstrated increased activation during a series of memory-guided saccades.[280,528] However, other cortical areas also contribute to longer-term memory of sequences of saccades, including the right medial temporo-occipital area, which was activated in the vicinity of the boundary between the parahippocampal and lingual gyri, as well as the parieto-occipital fissure.[255,538]

The role of the supplementary motor area (SMA) in general, and SEF in particular, has recently been linked to pre-supplementary motor cortex (pre-SMA), which is active during learning new sequences of movements,[292] including eye movements when they are contextually relevant to a task.[324,403] Microstimulation of pre-supplementary motor cortex in monkey reduces the reaction time of upcoming saccades.[324] One patient with a discrete lesion affecting one SEF had difficulty in changing the direction of his eye movements, especially when he had to reverse the direction of a previously established pattern of response.[319] Functional activation in parts of human pre-SMA in humans appear to corresponding to volition and conflict (Fig. 1–7, Chapter 1), whereas registration of success or failure activates the supplementary eye fields.[477] Therefore, SEF, SMA, and pre-SMA may work together to coordinate complex and

sequential movements.[703] The cerebellum is also important for learning motor sequences, but cerebellar lesions do not impair visuomotor memory or spatial working memory.[488]

ROLE OF DORSOLATERAL PREFRONTAL CORTEX

Although not a conventional "eye field" (as defined by low threshold for stimulation of saccades), neurons in the dorsolateral prefrontal cortex (DLPC) of monkey, in the posterior third of the principal sulcus (see Fig. 6–8, Chapter 6), corresponding to Walker's area 46, contribute to the voluntary control of saccades (Box 6–21).[217,278] DLPC is reciprocally connected with posterior parietal cortex, and inactivation of either area similar reduces activity of the other's neurons during memory-guided saccades.[111] Networks of neurons in DLPC of monkey show an ability to hold specific visuospatial coordinates in a topographical memory map; thus, they are important for generating *saccades to remembered target locations*,[127,128,697] including visual search.[320] Some units in DLPC that respond to spatial signals show increased activity during a response for which reward is expected.[362] Both D1-dopamine and 5 hydroxytryptamine 2-A receptors appear to play an important facilitating role in this spatial working memory, and injection of antagonist for either transmitter impairs performance on memory-guided saccade takes.[598,599,758]

In humans, DLPC is activated when subjects make memory-guided saccades.[395,495,593,692] Patients with lesions affecting this area show defects of memory-guided saccades, with increased variability.[538,542] Functional imaging studies suggest that DLPC contributes to spatial memories for up to about 20 seconds;[593] thereafter other mechanisms assume importance for "medium-term" memory. Furthermore, single-pulse or repetitive transcranial magnetic stimulation over DLPC in normal subjects impairs the accuracy of memory-guided saccades, but only if delivered within a few seconds of target presentation.[84,473,493,494] Evidence for a substrate for medium-term spatial memory comes from studies of patients with lesions involving the parahippocampal cortex, who show inaccuracy of saccades made to target locations that were committed to memory up to 30 seconds previously.[541] Parahippocampal cortex may operate both serially with DLPC and in parallel through connections with posterior parietal cortex.[538] For spatial memory ranging up to minutes, the hippocampal formation may be important.[538] Patients with lesions affecting DLPC also show impaired ability to make "predictive saccades" that anticipate regularly occurring target jumps.[532]

Both the FEF and DLPC appear to contribute to programming of the *antisaccade response*, but in different ways. Thus, on the one hand, the right hemisphere DLPC is activated during antisaccades,[144,205] and patients with lesions affecting the DLPC have an increased percentage of errors in the antisaccade test.[532] On the other hand, patients with FEF lesions have a normal percentage of errors on the antisaccade task, but make their correct antisaccades at increased latency. Taken together, it appears that during the antisaccade task, inhibition of reflexive misdirected saccades is due to DLPC, whereas triggering of the correct antisaccade depends upon FEF.[538] Evidence from patients with subcortical lesions has indicated that increased errors on the antisaccade task can be ascribed to interruption of a pathway running from DLPC to the superior colliculus in the anterior limb, genu, or anterior part of posterior limb of the internal capsule.[125,230]

THE ROLE OF CINGULATE CORTEX

Cingulate cortex includes Brodmann areas 24 (anterior cingulate) and 23 (posterior cingulate). The anterior cingulate makes oligosynaptic connections with brainstem ocular motor structures.[455] Some, but not all, electrophysiological studies have suggested that the anterior cingulate cortex is important for monitoring the consequences of saccades, such as learning new motor sequences, particularly if they are rewarded.[328,480] Less is known about posterior cingulate cortex, where neurons discharge after saccades, in proportion to reward size, and expected saccade value.[427,505]

In humans, functional imaging demonstrates activation in the anterior cingulate cortex during self-paced saccades, memory-guided saccades, memorized triple saccades, and antisaccades.[23,162,205,280,529] Thus, it has been proposed that, in humans, there is a cingulate eye field, located in the posterior part of

the anterior cingulate cortex, at the junction of Brodmann areas 23 and 24.[234]

Studies of two patients with small infarcts in the cingulate eye field on the right hemisphere caused increased saccadic reaction time and decreased gain for saccades made during the overlap task (Fig. 3–2A), and bilateral errors on the antisaccade task (Fig. 3–2D).[234] In a more recent study, surgical resections of tumors involving the anterior cingulate cortex also caused errors on the antisaccade task.[440] More electrophysiological and clinical studies are needed to clarify the role of cingulate cortex in the control of saccades.

The Role of the Parietal Lobe

The parietal lobe appears to influence the control of saccades in two principal ways. First, the posterior parietal cortex is important for shifts of visual attention, which may be accompanied by saccades. Second, the parietal eye fields (PEF) are directly involved in programming saccades to visual targets.

ROLE OF POSTERIOR PARIETAL CORTEX

Electrophysiological studies have shown that in monkey, area 7a of the inferior parietal lobule contains populations of neurons that respond to visual stimuli and discharge mainly after saccades have been made (Fig. 6–8).[46] It appears that the activity of some of these neurons is influenced not just by visual stimuli but also by eye and head position.[22,88,88] This finding has led to the hypothesis that a neural network of such cells could encode a visual target in spatial or craniotopic coordinates.[22,767] Furthermore, neurons in the posterior parietal lobe may be involved in representing visual locations during visual search, and maintaining a memory for the location of saccadic targets.[386]

Functional imaging studies in humans have demonstrated preferential activation in the right angular gyrus, during visually induced, but not internally generated, saccades,[454] and an analogous role has also been attributed to the supramarginal gyrus.[527]

In normal human subjects, a defect of memory-guided saccades is produced if transcranial magnetic stimulation is applied to the posterior parietal area early during the memory period.[476,515] If TMS is applied while subjects respond to double-step target jumps, and the stimulus is timed just after the first saccade, then the second saccade becomes inaccurate because of disruption of the craniotopic coding.[723] Antisaccades are also delayed by transcranial magnetic stimulation over parietal cortex; a similar effect is possible over frontal cortex if the stimulus is delivered later, suggesting flow of information from posterior to anterior during presaccadic processing.[704]

Acute human unilateral posterior parietal lesions, especially right-sided, cause contralateral *hemispatial neglect* and may confine saccades to the ipsilateral hemifield of gaze (Box 12–20, in Chapter 12).[453] Such patients show increased latency of visually guided saccades, and this is especially the case with right-sided lesions.[534] Because of hemineglect, patients have impaired ability to search contralateral space with saccades. In addition, such patients are unable to retain in working memory which targets they have seen before during visual search.[318] Thus, the defect of visual search in patients with parietal hemineglect combines a hemispatial attentive bias with an impaired memory for targets previously seen, which are reported as new.[676]

Bilateral posterior parietal lesions cause Balint's syndrome,[531] which includes difficulty initiating voluntary saccades to visual targets, and impaired visual scanning.[408] These deficits, which are described further in Chapter 12, may reflect disruption of the normal mechanisms by which posterior parietal cortex transforms visual signals into head or body-centered coordinates.

ROLE OF THE PARIETAL EYE FIELD

Animal Studies

In rhesus monkey, the PEF lies adjacent to area 7a, in the caudal third of the lateral bank of the intraparietal sulcus, an area called LIP (Fig. 6–8). *Electrical stimulation* on the lateral wall of the intraparietal sulcus produces saccades of similar direction irrespective of the starting position of the eye.[706] However, if the floor of the intraparietal sulcus and its underly-

ing white matter are stimulated, the direction of the resulting eye movements appears to depend upon starting eye position. Thus, the summed output of the population of neurons in PEF may be concerned with saccades to targets coded in head-centered coordinates.[706]

Unlike area 7a, LIP neurons *discharge prior to* saccades;[46,47] some neurons also discharge during fixation (suppression of saccades).[60] Like cells in area 7a, the response of LIP neurons is influenced by eye position,[22] as well as other sensory modalities such as sounds.[400] These cells in LIP also show a shift of their visual response field that anticipates the consequence of the upcoming gaze-shift;[169,376] the phenomenon is also reported in other visual areas,[479] and corresponding changes have been seen in humans using functional imaging.[433,439] Thus, the ensemble activity of LIP neurons encodes the spatial and temporal dynamics of the monkey's attention across the visual field.[73]

Another important property of LIP neurons is their ability to remain active while the monkey is required to withhold eye movements and *remember the desired target location*.[47,518] Some neurons also encode a memory of motor error, similar to quasivisual cells found in the superior colliculus and frontal lobe.[83,120,426,540,575] During antisaccades, LIP neurons respond to the visual stimulus,[781] but show little saccade-related behavior.[250] Thus, LIP neurons appear to encode not so much the intended saccade, but rather the current locus of attention.[245,540]

Experimental *inactivation of LIP* causes increased latency for both visually and memory-guided saccades into contralateral hemispace.[399] Saccade dynamics are spared. Contralesional memory-guided saccades also become hypometric whereas ipsilesional saccades may be hypermetric. The accuracy of the second saccade in a contralateral double-step response is also impaired.[398] In addition, inactivation of LIP increases search time for a contralateral target during serial visual search, suggesting that one important contribution of LIP to oculomotor behavior is the selection of targets for saccades in the context of competing visual stimuli.[749] These results are consistent with the hypothesis of an attentional network contributing to fixation engagement and disengagement in a subregion of LIP.[61]

The PEF projects to the superior colliculus, and is important in the triggering of visually guided saccades.[194] Electrophysiological studies have revealed that, from parietal cortex to colliculus, there is a continuous evolution of signal processing, representing activity at nearly every stage of visuomotor transformation.[519,763] Moreover, the time course of the neural response suggests that monkey PEF accumulates sensory signals pertinent to the selection of targets for saccades.[635] Evidence from monkeys and humans indicates that the parietal-superior colliculus pathway runs in the most posterior region of the posterior limb of the internal capsule; lesions of this pathway impaired reflexive but not memory-guided saccades.[231]

Human Studies

In humans, functional imaging has located the PEF in the medial wall of the posterior half of the intraparietal sulcus, adjacent laterally to the anterior part of the angular gyrus and medially to the posterior part of the superior parietal lobule.[89,474] A similar area shows retinotopic activation during saccades to remembered targets.[634]

Lesions involving the PEF in humans cause prolonged latency of visually guided saccades during gap or overlap stimuli (Fig. 3–2).[476 534] Increased latency of visually guided saccades is more pronounced with right-sided parietal lesions, and is more prominent than with FEF or SEF lesions.[85,534] A similar effect results in normal subjects if transcranial magnetic stimulation is applied to the PEF region.[178,717a] It has been suggested that the greater latency that results when the fixation light is left on indicates that the PEF is important for disengagement of fixation before generating a saccade.[535]

Parietal lesions also impair the ability to make two saccades to two targets flashed in quick succession. In response to this double-step stimulus, the brain must take into account not only the retinal location of both targets, but also the effect of the eye movements.[170,281,281] Patients with right parietal lesions show errors when the first target appears in the left hemifield and the second in the right; the first saccade may be accurate, but the second is not. This deficit may be present even though there is no inattention or difficulty responding to the

reverse order of presentation, or of making single saccades to left-sided targets. It appears that there has been disruption of the ability to monitor the size of the first saccade using efference copy.[170,281,281]

SUMMARY OF FRONTO-PARIETAL INFLUENCES ON THE CONTROL OF SACCADES

To summarize, the influence of frontal and parietal cortex on the control of saccades appears to be via two parallel descending pathways (Fig. 3–12). One pathway is via the frontal eye field to the superior colliculus (directly, and indirectly, via the basal ganglia).[285] The supplementary eye fields and dorsolateral prefrontal cortex also project to brainstem regions. Pathways from these prefrontal areas appear more concerned with preparation for self-generated changes in gaze as part of remembered, anticipated, or learned behavior.[297] The other pathway is directly from posterior parietal cortex to the superior colliculus. This pathway is more concerned with reorienting gaze to novel visual stimuli and in particular with shifting visual attention to the location of new targets appearing in extrapersonal space. However, the strong interconnections between parietal and frontal lobes and their common projection sites preclude a strict separation of function between the two pathways.[630] Thus, for example, lesions of both posterior parietal cortex and DLPC may impair memory-guided saccades.[533] Also important are connections between each cerebral hemisphere, since split-brain monkeys show impaired responses to double-step tasks when each stimulus is presented into a different visual hemifield.[66] Subsequent recovery implies that subcortical pathways, at least in monkey, are able to compensate for loss of interhemispheric connections. Finally, neurons in each of these cortical areas may modulate their activity when the correct behavior is to be rewarded.[117]

The Role of the Thalamus

Several different parts of the thalamus contribute to the programming of saccades, including the central nuclei of the internal medullary lamina, the mediodorsal nuclei, the ventrolateral nuclei, and the pulvinar. In humans, functional imaging has shown activation of the thalamus during voluntary saccades.[529]

THE ROLE OF THE INTERNAL MEDULLARY LAMINA

Neurons scattered throughout the internal medullary lamina (IML), which is the fiber pathway separating the medial from the lateral thalamic mass, show saccade-related properties.[610,610,615,702] IML neurons receive inputs from cortical and brainstem structures concerned with eye movements, including the superior colliculus, but project only to the cortex and basal ganglia. These connections suggest that IML might be important for relaying an efference copy of eye movement commands from the brainstem to the cortical eye fields.[616,666]

Electrical stimulation in the region of the IML elicits contralaterally directed saccades that may either be of fixed size and direction or directed to an orbital position. Neurons in IML discharge in relationship to spontaneous and visually guided, contralateral saccades.[615] During a visually guided delayed saccade task, neurons encode the visual stimulus, the delay, presaccadic and motor signals; some units appear to carry an efference copy of eye movements.[765] Consistent with the effects of stimulation, some units appear to encoded saccades in craniotopic rather than retinotopic coordinates. Other types of neurons in IML stop discharging during saccades but show a strong postsaccadic increase in activity, or discharge during steady fixation.[610,615]

Another important region is the mediodorsal nucleus, which serves as a thalamic gateway to prefrontal cortex,[701] and relays, amongst a range of other modalities, signals from the superior colliculus.[59,666] Thus, after inactivation of the mediodorsal thalamic nucleus with muscimol, on a double-step task, monkeys consistently show inaccuracy of the second saccade.[667] Consistent with this concept, tasks requiring a sequence of saccades (such as the double-step paradigm) are impaired when the central thalamus is affected by disease.[236] In Chapter 12, a patient with a thalamic metastasis is described, who made normal visually guided and memory-guided saccades, except when he made a smooth pursuit movement during the memory period. Thus, it appeared

that he was unable to register a change of eye movement during the memory period, perhaps because of interruption of an efference copy of his pursuit movements.

A third region is the ventrolateral thalamus, which relays cerebellar signals to cerebral cortex concerned with self-triggered saccades.[700a] When disease affects the cerebellar thalamus, patients show impaired ability to adapt their saccades to novel visual demands as well as to responding correctly to double-step target displacements.[59,237]

THE ROLE OF THE PULVINAR

Two separate parts of the pulvinar, which has reciprocal connections with posterior parietal cortex,[390] are related to saccades. Each appears to make distinctive contributions to saccades. Neurons in the *inferior-lateral pulvinar* respond to retinal image motion when it is produced by a moving stimulus, but much less so if it is due to a saccade.[577] Thus, this region might contribute to the process of saccadic suppression, although this suggestion needs confirmation.

In the *dorsomedial pulvinar*, visually responsive neurons are not retinotopically organized and seem more important for shifts of attention towards salient features in the environment.[63,504,574] Injection of GABA antagonists and agonists into the dorsal medial portion of the lateral pulvinar facilitates or retards, respectively, the ability of an animal to shift its attention toward the contralateral visual field.[578] In humans, functional imaging supports that idea that the pulvinar is important for directing visual attention.[345,377]

Electrolytic lesions in the pulvinar of monkeys cause a paucity of saccades towards blank portions of the visual field, and gaze appears to be "captured" by visual stimuli.[720] Other studies, however, have revealed relatively normal patterns of visual search after pulvinar lesions.[62] As previously noted in the Behavior of the Saccadic System, normal subjects show a decrease in saccadic reaction time if the fixation point is turned off synchronously with the appearance of the visual target compared with leaving the fixation target on (overlap paradigm). However, patients with posterior thalamic lesions, but without hemineglect, show no such decrease in reaction time for visually triggered saccades.[551] This result confirmed older studies of the effects of pulvinar lesions in humans, which reported difficulties in disengaging visual fixation when a shift of attention is to be made.[498,785] Taken together, these experimental and clinical results suggest that the pulvinar in humans contributes to the mechanisms for shifting visual attention, but more research is needed.

The Role of the Basal Ganglia

Although the frontal and parietal eye fields project directly to the superior colliculus (Fig. 3–12), a second pathway running through the basal ganglia plays an important role, especially in selecting targets that will be rewarded.[297] In essence, the substantia nigra pars reticulata (SNpr) maintains a tonic inhibition of collicular-burst neurons. Thus, for a saccade to be initiated by this pathway, the caudate nucleus must disinhibit the SNpr. In turn, the caudate depends on cortical inputs to signal the need to suppress the tonic inhibition of the superior colliculus by SNpr. In considering what role this pathway could play in the control of saccades, we examine the properties of the caudate nucleus, SNpr, and the subthalamic nucleus. We then provide a synthesis of the possible overall function of the basal ganglia in the control of saccades, and consider the effects of human lesions.

THE ROLE OF THE CAUDATE NUCLEUS

The caudate (and parts of the putamen) receive inputs concerning the programming of saccades from the FEF, SEF, DLPC, and the intramedullary lamina (IML) region of the thalamus.[297] A second important input is a dopaminergic projection from the substantia nigra, pars compacta, which may convey reward-related signals. The caudate projects directly to the SNpr and, via the external segment of the globus pallidus, to the subthalamic nucleus.[482] Saccade-related neurons in the caudate lie at the junction of the head and body of this structure (the central longitudinal zone).

Projection neurons have a low rate of discharge that increases prior to saccades.[294,295,649] This presaccadic activity is related more to the behavioral context of the saccade than its size

and direction.[296] Specifically, the activity of these caudate neurons shows a strong dependency on memory, expectation, attention, and reward.[296,329,348,750] Thus, some neurons change their discharge rate systematically, even before the appearance of the visual target, and usually fire more when the contralateral position is associated with reward.[383,384] Putative interneurons show less reward-related modulation of their activity.[649] Functional imaging studies in humans have demonstrated activation of the putamen and substantia nigra during memory-guided saccades.[496]

Experimental, unilateral dopamine depletion of the caudate and adjacent putamen causes impairment of contralaterally directed saccades.[346] The major deficit is for memory-guided saccades, which become hypometric, slow, and delayed.[368] In addition, there is contralateral hemineglect.[450] Dopamine also likely plays an important role in reward-contingent saccadic behavior, since studies of learning in patients with Parkinson's disease have shown that they become more sensitive to positive outcomes (carrot) than negative ones (stick) after they are administered dopamine medication.[207]

In a patient with bilateral lesions affecting the body of the caudate nucleus, memory-guided saccades were impaired whereas memory-guided finger-pointing was intact.[733] Patients with chronic lesions involving the putamen show deficits in saccades made to remembered locations and in anticipation of predictable target motion; visually guided saccades are intact.[734]

THE ROLE OF SUBSTANTIA NIGRA PARS RETICULATA

The saccade-related cells in SNpr lie in its lateral portion (near the cerebral peduncle) and project to the intermediate layers of the superior colliculus. Neurons in SNpr have high tonic discharge rates that decrease prior to voluntary saccades that are either visually guided or made to remembered target locations.[267,298,299–301] These neurons probably contribute to both target selection and saccade initiation.[53] Those SNpr neurons that decrease their discharge, and thereby disinhibit superior colliculus neurons, may show greater modulation of responses that are rewarded.[268,595]

The direct projections from the caudate nucleus to SNpr are mainly inhibitory. In addition, the SNpr receives excitatory projections from the subthalamic nucleus (Fig. 3–12). Stimulation of caudate neurons produces suppression or facilitation of SNpr neurons, the latter possibly due to a multisynaptic pathway.[293] However, neurons in the SNpr that seemed important for memory-guided saccades are usually inhibited by stimulation of the caudate.

The SNpr sends inhibitory projections to the superior colliculus, which are probably GABAergic. Injection of muscimol (a GABA agonist) into SNpr has a similar effect to injection of bicuculline (a GABA antagonist) into the superior colliculus: repetitive, irrepressible saccades occur, which are directed contralaterally to the side of the injection.[303] These saccadic intrusions appear to occur due to loss of the normal suppressive effect of SNpr on collicular-burst neurons rather than any effect on the fixation neurons at the rostral pole of the superior colliculus.[469]

THE ROLE OF THE SUBTHALAMIC NUCLEUS

Another basal ganglion, the subthalamic nucleus, contains neurons that discharge in relation to saccades.[421] The subthalamic nucleus appears to provide a second basal ganglionic pathway by which the cortical eye fields may influence the control of saccades via the basal ganglia (Fig. 3–12). The caudate nucleus projects, via the external segment of the globus pallidus, to the subthalamic nucleus.[482] This pathway appears to be double inhibitory, so that the overall effect of caudate inputs is excitation of the subthalamic nucleus. The subthalamic nucleus sends excitatory projections to the SNpr. Thus, it seems that the caudate has both a direct pathway to SNpr that is inhibitory, and an indirect pathway via the subthalamic nucleus that may be facilitatory. Consistent with this, stimulation of caudate neurons may produce either suppression or facilitation of SNpr neurons, the latter possibly due to the indirect pathway.[293]

In human patients undergoing placement of stimulating electrodes for treatment of Parkinson's disease, it has been possible to record single units in the ventral part of the subthalamic nucleus, where units discharge in relation to, but usually following, eye movements.[193] Discharge of some human subthalamic neurons is cued to self-paced saccades.

SYNTHESIS OF THE CONTRIBUTION OF BASAL GANGLIA TO THE CONTROL OF SACCADES IN THE CONTEXT OF CLINICAL DISORDERS

A simplified view of this basal ganglia pathway is that there are two serial, inhibitory links: a caudo-nigral inhibition that is only phasically active and a nigro-collicular inhibition that is tonically active. In addition, the subthalamic-nigral pathway is excitatory. Through these pathways, the basal ganglia appear to facilitate the initiation of more voluntary, self-generated types of saccades made in the context of learned behaviors, prediction, memory, and reward. Conversely, the basal ganglia could aid steady fixation by preventing unwanted reflexive saccades to stimuli that, at that particular moment, would be disruptive. As is discussed in Chapter 12, the means by which the frontal eye fields influence the superior colliculus is complex and might produce either difficulties in initiating or suppressing saccades. Both deficits have been described in patients with disorders affecting the basal ganglia, such as Huntington's disease.[382] However, the system is almost certainly more complex; for example, the direct and indirect caudate projections to SNpr may be serving different functions during complex behaviors.

Studies of the effects of human diseases affecting basal ganglia have focused on behavior such as memory-guided or predictive saccades. For example, memory-guided saccades are impaired after pallidotomy for Parkinson's disease,[76] but improved with subthalamic nucleus stimulation.[568] Pallidotomy increases saccadic intrusions on steady fixation— "square wave jerks."[33,497] In the future studies of patients with basal ganglionic disease, there is need for development of experimental strategies that involve reward for carrying out memory-guided and other saccade tasks.

The Cerebellar Contribution to Saccades

A major projection from the cortical eye fields is to the cerebellum, via the pontine nuclei (Fig. 3–12).[739] In addition, several important saccade-related structures in the brainstem project to the cerebellum. A role for the cerebellum in the control of saccades has been suspected since Hitzig[305] and Ferrier[195]elicited eye movements by electrical stimulation. Although more than one cerebellar area contributes to the programming of saccades, the dorsal vermis and caudal fastigial nucleus play key roles. The cerebellar hemispheres may also contribute to the control of saccades (Fig. 3–14),[279a,487] but their role has yet to be defined; the same is true of the basal interstitial nucleus.[699] Before reviewing these areas, we will first examine the role of a pontine nucleus that is a major relay for saccadic commands to the cerebellum.

NUCLEUS RETICULARIS TEGMENTI PONTIS

The nucleus reticularis tegmenti pontis (NRTP), which lies ventral to the rostral PPRF (see Fig. 6–3),[708] contains neurons that discharge in relation to a variety of eye movements, including saccades.[130] Its medial portion receives inputs from the frontal and supplementary eye fields.[652,677] The caudal part of NRTP receives inputs from the superior colliculus.[239] Portions of the NRTP project to the dorsal vermis and caudal fastigial nucleus.[490,768] The NRTP contains long-lead burst neurons, which project to the cerebellum and PPRF.[626]

Neurons in the caudal NRTP show similarities to collicular burst neurons, encoding the size and direction of saccades. However, unlike collicular neurons, they encode the 3-D eye displacement vectors.[730] Neurons in NRTP differ from those in riMLF by encoding both directions of torsional movement on each side of the brainstem. Microstimulation in NRTP elicits movements with an ipsilateral component that has a fixed torsional component. Inactivation of NRTP with muscimol caused torsional "errors" implying that NRTP normally ensures that saccadic eye movements obey Listing's law.[730] The influence of NRTP on the 3-D control of eye movements may depend upon its cerebellar projections.[655] The NRTP also contains neurons with activity related to pursuit and vergence, making it a possible site for coordination of these different classes of eye movements. The dorsolateral pontine nucleus (DLPN) also contains neurons that show saccade-related activity,[156] but generally seems more concerned with smooth pursuit. Pursuit and vergence aspects of the

pontine nuclei are discussed in Chapters 4 and 8, respectively.

THE ROLE OF THE DORSAL VERMIS

The "ocular motor vermis" consists of lobules VI and VII (parts of the declive, folium, tuber, and pyramis); its anatomical connections are summarized in Box 6–12.[768] Purkinje cells in the dorsal vermis discharge about 15 ms before saccades in a preferred direction.[502] Stimulation of the vermis produces saccades with an ipsilateral component;[585] with currents near to threshold, a topographic organization is evident.[489] Stimulation of vermal lobule V evokes saccades that range from upward to horizontal, while stimulation of lobules VI and VII evokes saccades that range from horizontal to downward. The vertical component of the elicited saccade is larger when stimulation is more medial. Saccadic direction is largely dictated by the anatomic location of stimulation in the cerebellum just as it is in the frontal eye fields and in the superior colliculus. In contrast to the latter structures, though, saccades evoked by cerebellar stimulation are graded in amplitude and, to a minor extent, direction, as a function of stimulus intensity. Furthermore, the amplitude of the elicited saccade, and the amount of postsaccadic drift, depend upon the initial position of the eye in the orbit.

If the vermis is stimulated while the monkey is making a naturally occurring saccade, the saccade trajectory is modified more than if stimulation is applied during fixation.[352] This implies that the cerebellum may be directly involved in feedback control of the amplitude of individual saccades. Furthermore, if an animal's eyes are perturbed by cerebellar stimulation just prior to the generation of a voluntary saccade to a visual target, the ensuing saccade does not land on target.[242] This is unlike the accurate corrective movements that occur when the frontal eye field,[604] or the superior colliculus,[672] are stimulated just prior to a saccade.

Unilateral pharmacological decortication of the dorsal vermis causes marked ipsilateral hypometria and mild contralateral hypermetria, with a gaze deviation away from the side of the inactivation (see Box 12–4).[594] Ablative lesions of the dorsal vermis also cause saccadic dysmetria that is mainly hypometria.[696] The dysmetria concerns the saccadic pulse, and there is no post-saccadic drift as is seen after ablation of the cerebellar flocculus and paraflocculus,[779] or total cerebellectomy.[512] Symmetrical lesions cause bilateral hypometria of horizontal saccades, with a slight increase in saccadic latency. Asymmetrical lesions cause hypometria and increased latency of ipsilateral saccades, so that express and anticipatory saccades are abolished.[696] Centrifugal movements tend to be smaller and made at longer latency than centripetal movements. The dynamic characteristics of saccades are also affected, with abnormal waveforms, and decreased speed during both the acceleration and deceleration phases; these changes are not dependent of the starting position of the eye in the orbit. Finally, the ability to adapt saccades to visual demands is impaired by lesions of the dorsal vermis.[696]

How do the dorsal vermis (lobule VII) and the caudal part of the fastigial nucleus, to which it projects, play such key roles in governing the accuracy of saccades? Although Purkinje cells in the dorsal vermis show variability in the timing of their discharge with respect to each saccade, the populations of these neurons encode the time when a saccade must stop to land on target.[707] Consistent with

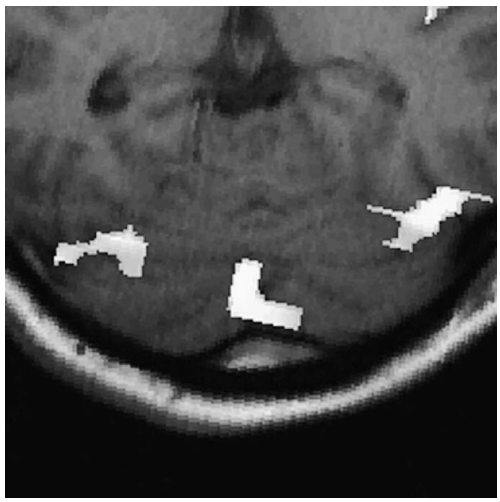


Figure 3–14. Activity of the cerebellum during a saccadic task as revealed by functional magnetic resonance imaging (fMRI). The subject was making voluntary, self-paced saccades between two visible targets. There is increased metabolic activity in the midline cerebellum (dorsal vermis and underlying fastigial nuclei) and also in the cerebellar hemispheres. Similar activation occurred if saccades were made in darkness between remembered target locations. (Courtesy Dr. Manabu Honda of Kyoto, Japan.) (From Honda M, Zee DS, Hallett M. Cerebellar control of voluntary saccadic eye movements in humans. Soc Neurosci Abstr 15, 1189, 1997.)

this scheme, after dorsal vermis lesions, the amplitude of saccades become more variable.[696]

THE ROLE OF THE FASTIGIAL NUCLEUS

Besides receiving inputs from Purkinje cells of the dorsal vermis, the caudal part of the fastigial nucleus, the fastigial oculomotor region (FOR), also receives a copy of the saccadic commands, which are relayed by NRTP from the frontal eye fields and superior colliculus.[490] The main projection from the fastigial nucleus crosses within the fellow fastigial nucleus, and enters the uncinate fasciculus, which runs in the dorsolateral border of the superior cerebellar peduncle, to reach the brainstem. Important projections of the caudal fastigial nucleus are to omnipause neurons, inhibitory burst neurons in the rostral medulla, excitatory burst neurons in the PPRF and riMLF, the mesencephalic reticular formation, thalamus, and the rostral pole of the superior colliculus.[423] Some of these connections are summarized in Box 6–13, and in Figure 3–12.

Neurons in the caudal fastigial nucleus discharge about 8 ms before onset of saccades with contralateral components, but generally towards the end of saccades with ipsilateral components.[213,283,501] These neurons also modulate their discharge according to saccade size and eye velocity, but not eye position.[360] Under normal circumstances, the fastigial nucleus might influence saccades by providing an early drive to premotor burst neurons during contralateral saccades and a late brake during ipsilateral ones.[213] These ideas are summarized in Figure 3–15.

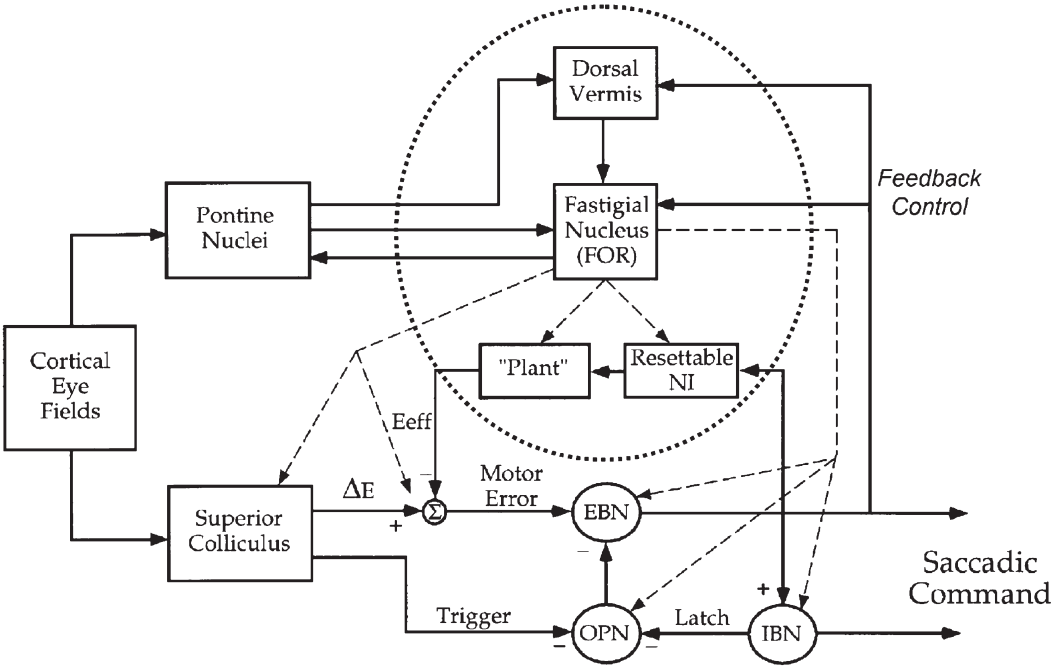


Figure 3–15. Hypothetical scheme for the role of the cerebellum in the generation of saccades. The superior colliculus, and probably the frontal eye field, provide a neural signal representing desired change in eye position (ΔE), which is compared with an efference copy of current eye position (Eeff), to give motor error, the signal that drives the premotor burst neurons (EBN). The superior colliculus rostral pole also provides the trigger signal to initiate the saccade, which inhibits omnipause neurons (OPN), which then stop inhibiting EBN, and (projection not shown) inhibitory burst neurons (IBN). The EBN project to IBN, which act as a latch circuit to stop OPN from discharging until the end of the saccade (when motor error is zero). The output of EBN and IBN constitute the saccadic command, which projects to ocular motoneurons. To generate Eeff, the output of EBN (and IBN, not shown) must be integrated (Resettable NI) and adjusted to account for non-linearities due to the orbital contents ("Plant"). This local feedback circuit may be partly located in the cerebellum. The dorsal vermis and fastigial ocular motor region (FOR) receive inputs from the pontine nuclei, such as NRTP, and climbing fiber inputs from the inferior olive (not shown). The dorsal vermis inhibits FOR, which projects to several elements of the brainstem saccade generator (broken lines), including EBN, IBN, and OPN. The dorsal vermis and FOR could lie within the internal saccadic feedback loop (dotted ellipsoid). −, inhibition, +, excitation.

Fastigial nucleus lesions produce marked hypermetria of saccades.[631,632] Destructive lesions are effectively bilateral because axons destined for the brainstem cross within the fastigial nucleus itself. A more effective way of demonstrating the contribution of the fastigial nucleus to saccade generation has been to use muscimol to pharmacologically inactivate the caudal fastigial nucleus on one side (see Box 12–4, Chapter 12).[581,584] A unilateral injection causes hypermetria of ipsilateral saccades (typical gain 1.3) and hypometria of contralateral saccades (typical gain of 0.7),[584] which affects saccades of all sizes.[330] The acceleration of ipsilateral saccades is increased and that of contralateral saccades is decreased. Hypermetria is slightly greater for centripetal (centering) saccades than centrifugal saccades. Vertical saccades show ipsipulsion (diagonal trajectory towards the side of inactivation) with unilateral fastigial nucleus lesions. With bilateral injections, all saccades, both horizontal and vertical, become hypermetric.[584] Microstimulation of the fastigial nucleus also inhibits its activity and has a similar effect to muscimol. Such stimulation only biases the trajectory of saccades if it is applied during the course of the movement.[244]

Complete cerebellectomy in trained monkeys creates an enduring saccadic pulse dysmetria.[512] In this case, all saccades overshoot, though the degree of overshoot is greatest for centripetally directed movements. The degree of saccadic hypermetria may be so great that the animal shows repetitive hypermetric saccades about the position of the target, a form of macrosaccadic oscillations (see Video Display: Disorders of Saccades). Monkeys with a complete removal of the cerebellum also show postsaccadic drift, implying pulse-step mismatch dysmetria. At the end of the rapid, pulse portion of the saccade, the eyes drift on, as a glissade, for a few hundred milliseconds, toward the final eye position. As noted above, saccadic pulse dysmetria can be attributed to involvement of the dorsal vermis and fastigial, whereas post-saccadic drift reflects involvement of the vestibulocerebellum (flocculus and paraflocculus).[779] Thus, the dorsal cerebellar vermis and underlying fastigial nuclei appear to function in controlling the size of the saccadic pulse, while the flocculus and paraflocculus seem to be responsible for appropriately matching the saccadic step to the pulse.

Scheme for the Control of Saccadic Metrics by the Dorsal Vermis and Fastigial Nucleus

Based on electrophysiology and the pharmacological inactivation studies summarized above, it is possible to offer a hypothetical scheme for way that the dorsal vermis and fastigial nucleus govern saccades to get the eye on target. Thus, early activity in one fastigial nucleus could be important for accelerating the eye at the beginning of a saccade, and the later activity in the other fastigial nucleus could be critical for stopping the eye on target. Thus, delay or abolition of the later, decelerating fastigial activity will cause hypermetria (Fig. 3–6) because the eye will not decelerate and stop on target. Central to this scheme is the concept that the brain monitors its own motor commands, referred to as corollary discharge or efference copy. Since saccades are brief, vision cannot be used to guide the eye to the target. However, the cerebellum could monitor a corollary discharge of the saccadic command and terminate the eye movement when it is calculated to be on target. How could this be achieved? Corollary discharge of all ocular motor signals are encoded on cell groups of the paramedian tracts (PMT), a group of neurons distributed throughout the brainstem to which all premotor ocular motor structures project.[100] The PMT cell groups project to the cerebellum and could, along with other mossy fiber projections from pontine nuclei, provide the cerebellum with the corollary discharge that it needs to stop the saccade on target. For vertical saccades, a different circuit including the posterior interpositus nucleus, which receives inputs from the ventral paraflocculus, could provide a similar role.[580] Such feedback of motor signals through the cerebellum requires that eye velocity signals be converted to a representation of current eye position by a resettable integrator.[508,511]

Thus, in patients with saccadic hypermetria (Fig. 3–6B) (see Video Display: Disorders of Saccades), feedback signals to the fastigial nucleus—which are required to stop the eye on target—could arrive late, or not at all.[691] Clinically, fastigial nucleus lesions are effectively bilateral, because the axons cross in the opposite nucleus; affected patients show bilateral hypermetria (Fig. 12–4). However, inter-

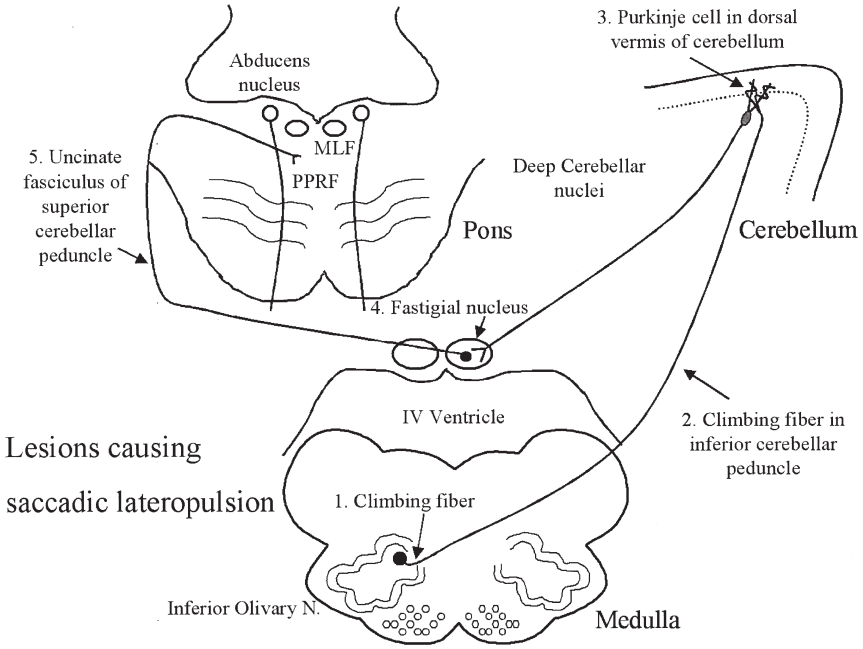


Figure 3–16. Hypothetical scheme to account for lateropulsion of saccades.[584,711,740] Interruption of climbing fibers originating from the inferior olivary nucleus may occur prior to their crossing in the medulla (1) or as they enter the inferior cerebellar peduncle (in Wallenberg's syndrome. (2). Loss of climbing fiber inputs to Purkinje cells in the dorsal vermis causes the latter to inhibit the fastigial nucleus (4), which causes ipsipulsion of saccades. Pharmacological inactivation of the dorsal vermis (3) causes contrapulsion (although clinical lesions produce bilateral hypometria). Interruption of crossed fastigial nucleus outputs in the superior cerebellar peduncle (uncinate fasciculus, 5) causes contrapulsion. Thus, contrapulsion arises at sites 1, 3 and 5, and ipsipulsion at sites 2–4.

ruption of inputs to the cerebellum in the inferior peduncle—as occurs in Wallenberg's syndrome—causes ipsipulsion (Fig. 3–16); it is postulated that increased activity of Purkinje cells causes a unilateral fastigial nucleus "lesion".[740] Interruption of the crossed output of the fastigial nucleus in the superior cerebellar peduncle causes contrapulsion of saccades (overshooting contralaterally, undershooting ipsilaterally).[683,740] Rarely, climbing fibers from the inferior olivary nucleus are lesioned before crossing the midline and passing into the inferior cerebellar peduncle;[711] this causes contrapulsion of saccades. Experimental studies indicate that lesions of the posterior interpositus nucleus may affect the accuracy of vertical saccades,[580] but this has not yet been documented clinically.

In sum, the cerebellum appears to be important for the control of saccadic accuracy, including both amplitude and direction, and possibly in correcting for position-dependent changes in the mechanical properties of the eye muscles and orbital tissues. This capability appears to function both in an "on-line" fashion, since cerebellar dysmetria is apparent immediately after inactivating the fastigial nuclei, as well as in the long term, as part of the process of adaptive control of saccade accuracy. This pivotal role of the cerebellum in the control of saccades is supported by finding that neither frontal eye field or superior colliculus lesions alone causes enduring changes in saccadic metrics; in each case, another area must be computing the size and dynamics of saccades, and the cerebellum seems the likely candidate. The role of the cerebellum is taken further in the next section, which attempts to identify its place in models for saccade generation.

MODELS FOR SACCADE GENERATION

With advances in knowledge of the saccadic system, quantitative hypotheses (models) to

account for generation of these movements have grown in scale and complexity. Initial attempts used a classic control systems approach (see David A. Robinson's notes on the accompanying compact disc) whereas, more recently, neural-network models, which attempt to describe the contributions by distinct populations of neurons, are cast from a neuromimetic point of view. Here we briefly present a history of how saccadic models have developed, to provide the reader with a notion of the way that concepts about the generation of saccades have grown over the past half-century.[239a] Most of our account will be concerned with models of brainstem and cerebellar contributions to saccade generation, since the effects of cerebral cortex and basal ganglia on saccade dynamics are less well worked out. However, attempts have been made to model more complex aspects of saccadic behavior such as responses to remembered targets by neurons in LIP,[445,766] visual search by FEF,[446] and the role of the superior colliculus in a range of behaviors, including antisaccades.[713]

MODELS FOR HORIZONTAL SACCADES

Early notions of the generation of saccades proposed that the duration of the pulse of activity that creates saccades was predetermined or preprogrammed according to desired saccadic amplitude.[754] Studies of patients with slow saccades, however, led to an alternative hypothesis that suggested saccades are generated by a mechanism that drives the eyes to a particular orbital position rather than moves the eyes a specified distance.[777] By continuously comparing desired eye position and actual eye position (the latter is probably based on monitoring an internal, efference copy of the eye position command) the neurons that generate the saccadic pulse would be driven until the eye reaches the target, when they would automatically cease discharging. This is the original local-feedback model for saccades proposed by D.A. Robinson[572] (Fig. 3–17A). It has the advantage that it automatically generates the main sequence relationships between amplitude and peak velocity or duration for saccades (Fig. 3–2).[725] The model also accounts for slow but accurate saccades made both by some patients with neurological disease and by normal subjects taking various sedative or hypnotic medications.[336] It can also produce saccadic oscillations such as flutter if the omnipause neurons malfunction or are inhibited.[778] Although the notion of local feedback has sometimes been called into question,[339] the evidence to support it remains substantial. Thus, if a saccade is arrested in mid-flight by briefly stimulating the omnipause neurons, a new saccade is generated to get the eye on target within 70 ms (Fig. 3–11), which is shorter than could have been achieved by responding to the visual consequences of the arrested movement.[349,350] Furthermore, patients with slow saccades often get their eye on target,[411,777] and slow saccades induced by experimental inactivation of the rostral PPRF may be accurate.[49] Thus, it appears that a signal is used to ensure that the burst neurons discharge until the planned movement is achieved.

Subsequent physiological studies have called for modifications of the original Robinson model, while retaining the notion of local feedback control of saccade generation. One important revision is that the command signal is a desired change in eye position (Fig. 3–17B).[336] This signal would be compared continuously with an efference copy of the actual change in eye position, to determine when to terminate the saccade. Inherent in this modification of the local-feedback model is the idea of separate integrators, one common neural integrator for conversion of eye velocity to eye position commands (for all types of conjugate eye movements, discussed in Chapter 5) and a separate resettable neural integrator that operates specifically on saccadic velocity commands in the feedback loop that controls the duration of the saccadic pulse.[3,49,336,375,485,670,673]

At present, the anatomical basis for local feedback control of burst neurons and the resettable integrator for saccades is not understood.[249,609] One proposal is that the feedback involves long-lead burst neurons rather than premotor burst neurons.[622] In this model (Fig. 3–17C), long-lead burst neurons are also the proposed site for the second, saccade-specific integration. However, this model is not consistent with some anatomical projections of the superior colliculus,[101] cannot simulate the staircase of saccades that occurs with sustained stimulation of the superior colliculus, [86] and cannot account for saccadic oscillations such as flutter and opsoclonus.

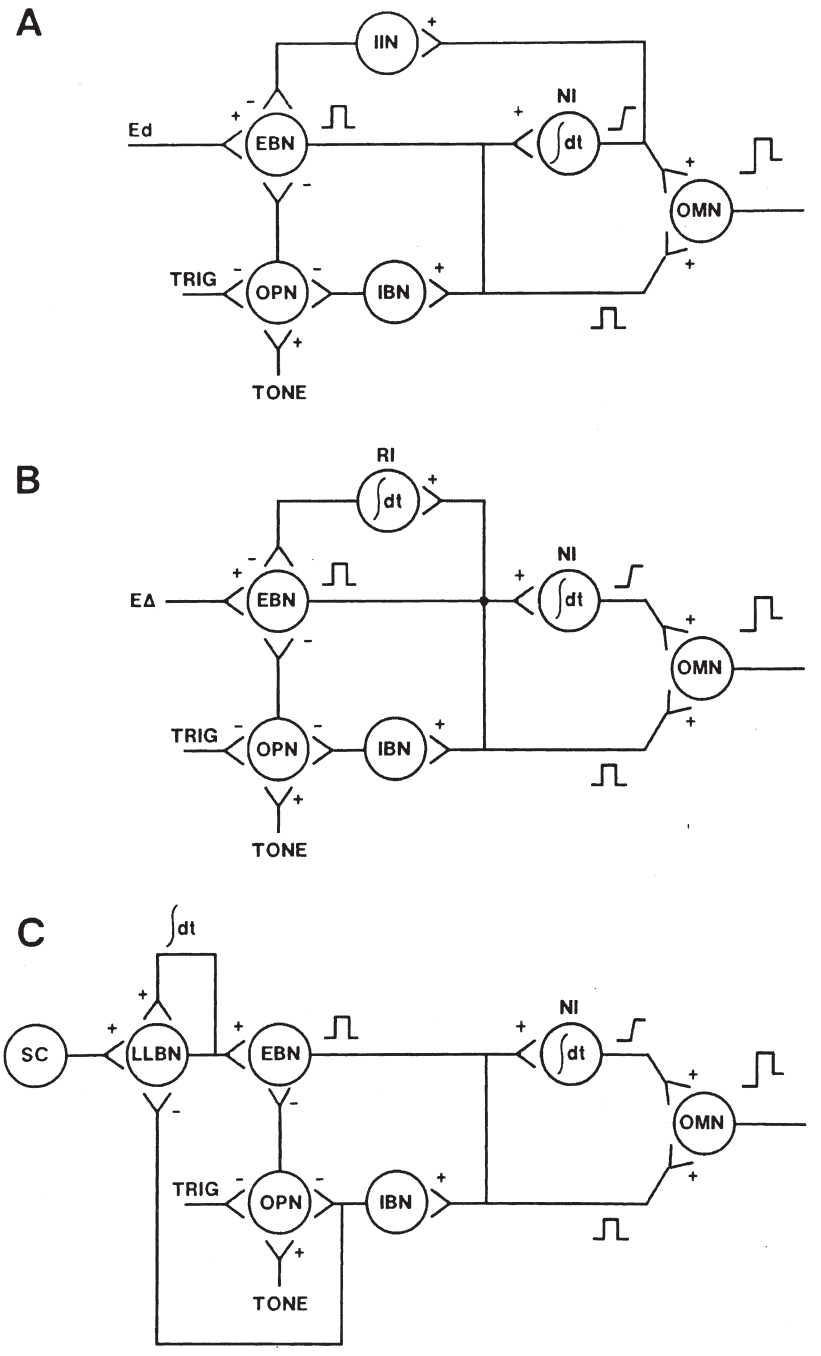


Figure 3–17. Models of the saccadic pulse generator. (A) Model after Robinson.[572] A desired eye position signal (Ed) excites burst neurons (EBN), which in turn project to the ocular motoneurons (OMN), to the neural integrator (NI) and to the inhibitory burst neurons (IBN). Omnipause neurons (OPN) have a tonic level of discharge (TONE) but are inhibited by a trigger signal (TRIG) when a saccade is desired. During the saccade, OPN are kept silent by IBN. The output of the NI is fed back as an efference copy of eye position to EBN via an inhibitory interneuron (IIN). When this signal becomes equal to Ed, the burst neurons cease discharging and the saccade is over. (B) Model after Jürgens and colleagues.[336] The input to the burst neurons is now a *desired change in eye position* (EΔ). This signal is compared with an efference copy of eye position, which is now derived from a separate, resettable neural integrator (RI) specific to the saccadic system. (C) Model modified from Scudder.[622] Long-lead burst neurons (LLBN) receive excitatory signals from the superior colliculus (SC) and are the site for the saccade-specific integration of velocity to position signals. The saccade is terminated by comparing the integral of an efference copy of saccade velocity (via IBN) and the integral of the input from the superior colliculus.

A second suggestion is that feedback control of saccades and the saccadic integrator involves the superior colliculus.[741] However, pharmacological inactivation of the superior colliculus does not produce effects consistent with predictions of this model,[13] as is discussed in the section on the superior colliculus.[508]

Third, it has been proposed that local feedback occurs via a cerebellar loop (Fig. 3–15).[389,511,549] This proposal is consistent with the anatomical connections between the premotor burst neurons, dorsal vermis and fastigial nucleus, and with experimental evidence that the cerebellum is important for getting saccades on target.[389,511,549] However, high-frequency oscillations, thought to be saccadic in origin,[555] occur in patients with lesions involving the fastigial nucleus that cause hypermetria (see Video Display: Disorders of Saccades). This and other observations have led to an alternative model to account for saccadic oscillations,[553] which depend on the synaptic connections between burst neurons (Fig. 3–10). Specifically, it has been shown that there are connections by which IBN inhibit IBN;[682] these form positive feedback loops that are potentially unstable. For example, during a saccade to the right, left-sided EBN will be inhibited by IBN. However, when the saccade is over, if EBN show post-inhibitory rebound,[447,448] they will start discharging again. It has been postulated that this is the mechanism underlying high-frequency saccadic oscillations, such as ocular flutter.[553]

MODELS FOR OBLIQUE SACCADES

The ocular motoneurons innervate extraocular muscles that rotate the eyes approximately in Cartesian coordinates (e.g., the medial and lateral rectus rotate the globe a specified distance horizontally). However, the saccade-related neurons in the superior colliculus and premotor burst neurons in the brainstem discharge for oblique movements, and so one aspect of modeling saccades is whether these structures encode the saccadic command in polar or Cartesian coordinates. In other words, do the two populations in the PPRF and riMLF become strongly coupled or do they remain independent? In one view of the way that oblique saccades are programmed, the "common source" saccade model, the command from the superior colliculus to burst neurons is specified in polar coordinates: an oblique (radial) velocity at angle θ.[727] Neural circuitry then converts this into a signal multiplied by cosine θ for the horizontal PPRF burst neurons and a signal multiplied by sine θ for the vertical riMLF burst neurons. This model predicts: (1) the horizontal and vertical components of oblique saccades may have different durations and peak velocities than when similar-sized movements are made as purely horizontal or vertical saccades; (2) the horizontal and vertical components will have synchronous onset and offset; (3) the peak velocities of the horizontal and vertical components of the saccade are scaled by cosine θ and sine θ, respectively; (4) the trajectory of the oblique saccade will be straight. An alternative hypothesis, the Cartesian coordinate model, proposes that the central command for the oblique saccade is broken down into horizontal and vertical eye displacement components before being sent to the horizontal and vertical burst neurons.[57,258] The critical predictions of this so-called independent model are: (1) the horizontal and vertical saccadic components of oblique saccades will have the same duration and peak velocity as when made as purely horizontal or vertical saccades; (2) although the horizontal and vertical components of oblique saccades will have a synchronous onset, they may end at different times; (3) the trajectory of oblique saccades could be curved.

Normal human saccades are so brief that it is often difficult to distinguish between the predictions of these two models. However, oblique saccades that have dissimilar horizontal and vertical components often appear curved,[39] and could have different times of offset of the two components.[258] Nonetheless, peak velocities of horizontal and vertical components are reported to be scaled as predicted by the common source model.[727]

Studies of patients with selective slowing of the vertical or horizontal components provide interesting results. Thus, patients with selective slowing of vertical saccades due to Niemann-Pick type C disease show markedly curved oblique saccades (Fig. 3–5B).[590] The initial movement is mainly horizontal and most of the vertical component occurs after the horizontal component has ended (i.e., the two components end at quite different times). After completion of the horizontal component of an oblique saccade, the eyes oscillate hori-

zontally "in place" at 10 Hz–20 Hz until the vertical component ends (Fig. 3–5C). These horizontal oscillations probably occur because omnipause neurons are silent until the vertical component is complete, and after the horizontal component is over, the normal horizontal burst neurons lack a motor error signal to drive them and so oscillate until the whole saccade is completed. Similar oscillations are encountered during some oblique saccades made by normal subjects.[57] Curved oblique saccades are also encountered in patients with spinocerebellar ataxia who show selective slowing of horizontal saccades (see Video Display: Disorders of Saccades). Partial inactivation of the PPRF in monkey with lidocaine also produces oblique saccades with curved trajectories.[49]

Nonetheless, monkeys and some healthy humans make straight saccades during oblique movements. To account for straight trajectories of oblique saccades, a third model was suggested in which there was cross-coupling between the output of horizontal and vertical pulse generators.[258] However, other studies have shown that changes of peak velocity predicted by this model with coupled outputs do not occur, and suggested that it is more likely that it is the inputs that are coupled (common source).[49,57] A fourth model to account for the variable curving of oblique saccades encountered in humans and monkeys consists of a distributed network of neurons, which is able to simulate several characteristics of oblique saccades, with no cross-coupling between the two pulse generators.[550] Thus, the data are still somewhat conflicting and further studies of normal subjects and patients with selective slowing of horizontal or vertical saccades should provide the opportunity to test these several models.

NEUROMIMETIC MODELS FOR SACCADES IN TWO AND THREE DIMENSIONS

More recently, models have been developed that seek to account more realistically for the way that the brainstem and cerebellum control saccade generation. Thus, some models attempt to account for saccades interrupted by electrical stimulation of omnipause neurons,[25,219] as well as the curved trajectories encountered when more than one visual stimulus is presented in terms of activity of multiple populations of superior colliculus neurons.[26] Other efforts have modeled the resettable integrator for saccades as a population of neurons in the fastigial nucleus.[549]

The development of reliable methods to measure 3-D eye rotations has led to development of models to account for rotations of the eye in three planes during saccades. In fact, the position of saccadic eye rotations are essentially restricted to rotation about axes that lie in the frontal plane (Listing's plane—see Fig. 9–3 in Chapter 9), and so three degrees of freedom are reduced to two degrees. What remains to be settled is the mechanism that imposes Listing's law, and the relative contributions made by the mechanical and suspensory properties of the orbital tissues on the one hand,[142,510,558,619] and by neural factors on the other.[550,717] Specifically, rotations are noncommutative, which means that the brain must specify the order of rotations to get the eye to the correct tertiary position. The discovery of pulleys that guide the extraocular muscles (discussed in Chapter 9) may provide a means by which the brain can delegate at least some aspects of the complexities of 3-D rotations to a mechanical "analog computer" in the orbit.[141] This topic is discussed further in Chapter 9.

ADAPTIVE CONTROL OF SACCADIC ACCURACY

The first reports of adaptation in the saccadic system were in patients with partial abducens nerve palsies who preferred to view with their paretic eye, because it had better vision.[367] With the affected eye viewing, saccades made by the paretic eye were accurate even in the direction of the muscle weakness. The saccades of the nonparetic eye, on the other hand, were much larger and had post-saccadic drift. With the paretic eye covered and the "normal" eye viewing, the saccades of the nonparetic eye both overshot the target and showed post-saccadic drift. In other words, saccadic innervation had been readjusted (to both eyes, consistent with Hering's law of equal innervation) in an attempt to improve the performance of the habitually fixating but paretic eye. Both the pulse amplitude and the pulse-step match dysmetria created by the palsy had been repaired. Kommerell and colleagues[367] then patched the paretic eye of their patients continuously,

requiring them to use their nonparetic eye. When examined after three days, the patients had readjusted the amplitude of the saccadic pulse and the pulse-step match so that saccades made by the nonparetic eye became accurate. In other words, the central nervous system changed saccadic innervation to meet best the visual needs of the habitually viewing eye.

It was subsequently shown that the change in saccadic amplitude was accomplished by prolonging the duration of the saccadic pulse alone, without an increase in its height.[5,323] If pulse height had increased, the peak velocity of saccades made by the normal eye would have increased; it did not. Moreover, the adaptive changes were specifically tailored to the mechanical needs dictated by the particular orbital positions from and to which the saccade was to be made.[513] Another clinical example of this adaptive capability concerns patients with internuclear ophthalmoplegia, who often show saccadic overshoot and backward postsaccadic drift in the abducting eye. This "abduction nystagmus" may be accounted for, in some patients, by the same mechanism that adjusts innervation conjugately in response to a peripheral muscle palsy.[167,775] Further discussion on saccadic changes in paralytic strabismus is provided in Chapter 9.

Experimentally Induced Saccadic Adaptation

In normal subjects, saccadic pulse dysmetria can be simulated by changing the position of the target just before the eye reaches it, forcing the subject to make a corrective saccade after every target jump.[310,429] After as few as 150 such trials, subjects automatically make saccades that are bigger or smaller, depending upon the particular nature of the induced dysmetria.[16,152,633,684] Saccadic adaptation also produces a recalibration of shifts of attention that accompany saccades.[428] The presence and timing of the post-saccadic visual error are important determinants of the amount (gain) of adaptation.[583,628,636]

A *pulse-step match dysmetria* can be simulated by making a large, projected visual stimulus drift briefly after every saccade. Both humans and monkeys soon learn to preprogram a postsaccadic drift of the eyes, by creating a pulse-step mismatch that nearly matches the artificial motion of the visual scene.[341,509]

Saccadic adaptation may be specific to the context of the stimulus conditions;[647] for example, adaptation for movements in one direction does not automatically lead to adaptation in another.[145] Adaptation may depend on orbital eye position and the vector of the movement; this is important for everyday life, when we make saccades from constantly changing starting positions in a range of directions.[15] Thus, adaptation with increased gain can be induced with the eyes in right gaze and with decreased gain in left gaze.[644] When adaptation is required for just one size of saccade, movements of other sizes or directions are less adapted.[491,687] When adaptation is required for two movements, averaging saccades (which fall between the two visual targets) also show some adaptation.[14] During adaptation in a context-based manner (such as a gain increase on right gaze and a gain decrease on left gaze), subjects adapt better if they are given rest period between each training state.[9] This is the phenomenon by which consolidation of motor learning is facilitated and has potential implications for rehabilitation of ocular motor and vestibular disorders by programs of eye movement training. Once induced, saccadic adaptation may last for days.[15a]

The visual features of the stimulus, such as color or visual background,[579] as well as otolithic signals,[645] have relatively small effects on the learning process compared with the nature of the saccadic response.[148] Thus, on the one hand, saccadic gain adaptation induced by step movements of a single target does not transfer to saccades made during scanning of an array of targets, or to remembered locations of single targets.[147] On the other hand, adaptation achieved during scanning an array of targets transfers to memory-guided saccades, but not to step movements of a single target.[147] Furthermore, adaptation of memory-guided saccades does not transfer to saccades during scanning or to single target jumps.[148]

Saccades induced by electrical stimulation of the superior colliculus in monkeys can be adapted if a visual stimulus is presented at a location different from where the eye movement ended.[437] This adaptation shows incomplete transfer to normal visually guided saccades, suggesting need for involvement of cortical areas in normal adaptation of saccades to single target jumps. However, adaptation of normal visually guided saccades does transfer

to express saccades, suggesting the importance of cortical and cerebellar contributions.[309] Furthermore, adaptation to visually guided saccades transfers to express saccades. Briefly delaying the presentation of the post-saccadic target impedes adaptation, and has led to the suggestion that the brain compares the post-saccadic image with the one that would be predicted for the planned saccade.[36] All these findings emphasize the important role of context in motor learning, and suggest that multiple areas of the brain may be involved in facilitating motor learning, so that saccadic metrics are tailored to a specific environmental circumstance (see below).

Hypotheses to Account for Saccadic Adaptation

How can these diverse properties of saccadic adaptation be explained? Although results from adaptation experiments in monkeys may differ,[212,623] the transfer of adaptation from one type of saccade in human is specific and has suggested a hypothesis based on current notions of the control of saccades.[148] Thus, memory-guided saccade adaptation may depend on dorsolateral prefrontal cortex; scanning saccades adaptation on the frontal eye field; and adaptation of saccades to target jumps on the parietal eye field and superior colliculus. Such a hypothesis could be tested by studying saccadic adaptation in patients with discrete cortical lesions, and provides a tool to clinicians to investigate the cerebral control of saccades.[147] A model to account for the way that the superior colliculus could contribute to saccadic adaptation, by changes in the nature of the spreading of activation, has also been proposed.[257] Other aspects of saccadic adaptation such as occur following abducens nerve palsy are discussed under Adaptive Changes of Eye-Head Saccades in Chapter 7, Disconjugate Adaptation in Chapter 8, and Saccades in Paralytic Strabismus in Chapter 9.

Neural Substrate for Saccadic Adaptation: The Role of the Cerebellum

Which structures in the central nervous system participate in the adaptive control of saccadic accuracy? The most compelling evidence supports a role for the cerebellum. Thus, functional imaging of human subjects while they are carrying out a saccadic adaptation task shows selective activation in the cerebellar dorsal vermis, but not in the FEF or superior colliculus.[143] Furthermore, experimental cerebellectomy completely abolishes the adaptive capability—for both the pulse size and the pulse-step match.[512] Monkeys with lesions restricted to the *dorsal cerebellar vermis* cannot adapt the size of the saccadic pulse—they have pulse-size dysmetria.[48,696] *Fastigial nucleus* neurons show changes in their discharge properties after saccadic adapation,[625] and inactivation of the fastigial nucleus impairs saccadic adaptation.[322,582] Monkeys with *floccular lesions* show a different disturbance of saccadic adaptation: they cannot match the saccadic step to the pulse to eliminate pulse-step mismatch dysmetria.[513] Patients with cerebellar disease, especially cerebellar degeneration, show impaired saccadic adaptation.[685] Finally, neuronal activity in nucleus reticularis tegmenti pontis (NRTP), which projects to the cerebellum, shows changes during saccadic adaptation.[698]

Taken together, this evidence suggests that the repair of conjugate saccadic dysmetria is mediated by two different cerebellar structures. The dorsal cerebellar vermis and the fastigial nuclei control pulse size; the flocculus and paraflocculus control the pulse-step match. Does the cerebellar contribution to saccadic adaptation extend to all types of saccades? One patient with a midline cerebellar hemangioblastoma showed greater hypermetria for saccades made to single-target presentations than during saccadic scanning of a display of targets.[686] This finding implies that the cerebellum is also involved in context-specific motor learning. In fact, the cerebellum is ideally poised to implement context-specific motor learning as it has access to all the necessary afferent and corollary discharge signals to determine the context in which the next saccade is to occur.

The dorsal vermis and fastigial nucleus may also participate in the repair of disconjugate saccadic dysmetria, since patients with cerebellar disease show disconjugacy of saccades,[735] experimental vermal lesions cause saccadic disconjugacy,[695] and experimental inactivation by cooling of the fastigial nucleus causes disconjugate dysmetria.[737] Although visual signals are probably most important in providing the error signal that drives disconju-

gate saccadic adaptation, extraocular proprioception also contributes. Thus, monkeys deprived of proprioceptive information by section of the ophthalmic branch of the trigeminal nerve show abnormalities in disconjugate adaptation after surgically induced CN IV palsy, although it does not interfere with visually mediated adaptation.[396,397]

Other Areas Contributing to Saccadic Adaptation

Although the cerebellum projects to presaccadic circuits, there is evidence that it may not have the final word on saccadic behavior. For example, in normal monkeys that have undergone saccadic adaptation training, tasks requiring a sequence of saccades (such as the double-step paradigm) are performed appropriately, because even if the initial response is adapted (and inaccurate), the subsequent saccade gets the eye on target.[700] One possible explanation for this behavior relates to projections of cerebellar regions concerned with saccadic accuracy to cerebral cortex via the thalamus. Thus, inactivation or lesions of the dorsal vermis,[696] the fastigial nucleus,[582] or the ventrolateral thalamus to which the cerebellum projects,[237] all impair the ability to adapt saccades to new visual demands.

Inactivation of another pathway from the superior colliculus via the medial dorsal thalamus to the frontal eye field impairs the second saccade in the response to double-step stimuli in non-adapted monkeys, suggesting that this pathway is important so that the brain can keep a record of prior movements using corollary discharge signals to the cortex.[667] However, this pathway seems not to play a role in responses to saccadic adaptation since electrophysiological evidence indicates that the superior colliculus does not contribute to saccadic adaptation, although more rostral sites such as the frontal lobes and basal ganglia might.[172] In this regard, an interesting finding is that patients with Parkinson's disease have difficulties with adaptation of memory-guided, but not visually guided, saccades.[412]

SACCADES AND MOVEMENTS OF THE EYELIDS

Saccades are often accompanied by blinks, but only recently have their interactions been systematically studied.[189] At a cortical level, the FEF, SEF, and PEF are all activated during both saccades and blinks,[79] although there is perhaps more activation of the inferior precentral sulcus with blinks.[347] Here we focus on two aspects: the coordination of vertical saccades and eyelid movements, and the effects of blinks on saccades. The interaction of four separate forces determines the position of the eyelids. Upward forces are mainly due to the levator palpebrae superioris (LPS),[186] with Müller's smooth muscle, which bridges the LPS and its tendon, making a minor contribution. Downward forces are due to stretching of tendons and ligaments connected to LPS, and the orbicularis oculi muscle.[186]

The eyelids closely follow vertical gaze shifts, including saccades. Thus, eye and lid saccades show similar dynamic properties.[192, 262] Upward lid saccades are due to a burst of activity in the LPS muscle and its motoneurons,[211] which lie in the unpaired, central caudal nucleus of the oculomotor nuclear complex (see Fig. 9–9 , Chapter 9). Downward lid saccades are due entirely to elastic forces, which close the eye when the LPS relaxes. The orbicularis oculi muscle is electrically silent except during blinks or voluntary lid closure. Thus, neural coordination of vertical gaze and lid position is due to a synkinesis between the vertically acting extraocular muscles and the LPS. How is this achieved?

The main elevator of the eye, the superior rectus, has a common embryology to LPS and these two muscles are connected by a common sheath of intermuscular fascia. However, the muscles are structurally different, and their motoneurons lie in distinct subnuclei of the oculomotor nucleus. It appears that a key structure in the coordination of vertical saccades is the M-group of neurons, which lie adjacent and medial to the caudal third of the riMLF, and project strongly to the LPS motoneurons, but also to subnuclei supplying the superior rectus and inferior oblique, and frontalis muscles.[312] The M-group appears to receive inputs from upward burst neurons in the riMLF, and may have connections with the nucleus of the posterior commissure. Thus, whereas lid retraction is a classic sign of posterior commissure lesions,[31] patients who have slow vertical saccades accompanied by lid lag but without lid retraction could have involvement of the M-group.[218,312]

Blinks typically occur 20 times per minute. During a blink, a burst of activity occurs in the normally quiescent orbicularis oculi muscle, while at the same time, tonic activity in the levator palpebrae ceases.[190] How do they affect eye movements? If blinks are made during fixation of a stationary target, the eyes transiently move down and toward the nose;[123] such movements are slower than saccades and are due to a co-contraction of all extraocular muscles except the superior oblique muscle.[191] Blinks are often made with saccades; the probability of a blink occurring increases with the size of the gaze shift.[191,192] Blinks caused substantial changes in the dynamic properties of horizontal saccades, decreasing peak velocity and increasing duration.[247,589] These changes are unlikely to be due to a summation of the down-and-inward movement produced by blinking and the saccade, since there is no direction preponderance in the slowing of saccades. Furthermore, saccades made with blinks show an increased incidence of dynamic overshoots (Fig. 3–18).[589]

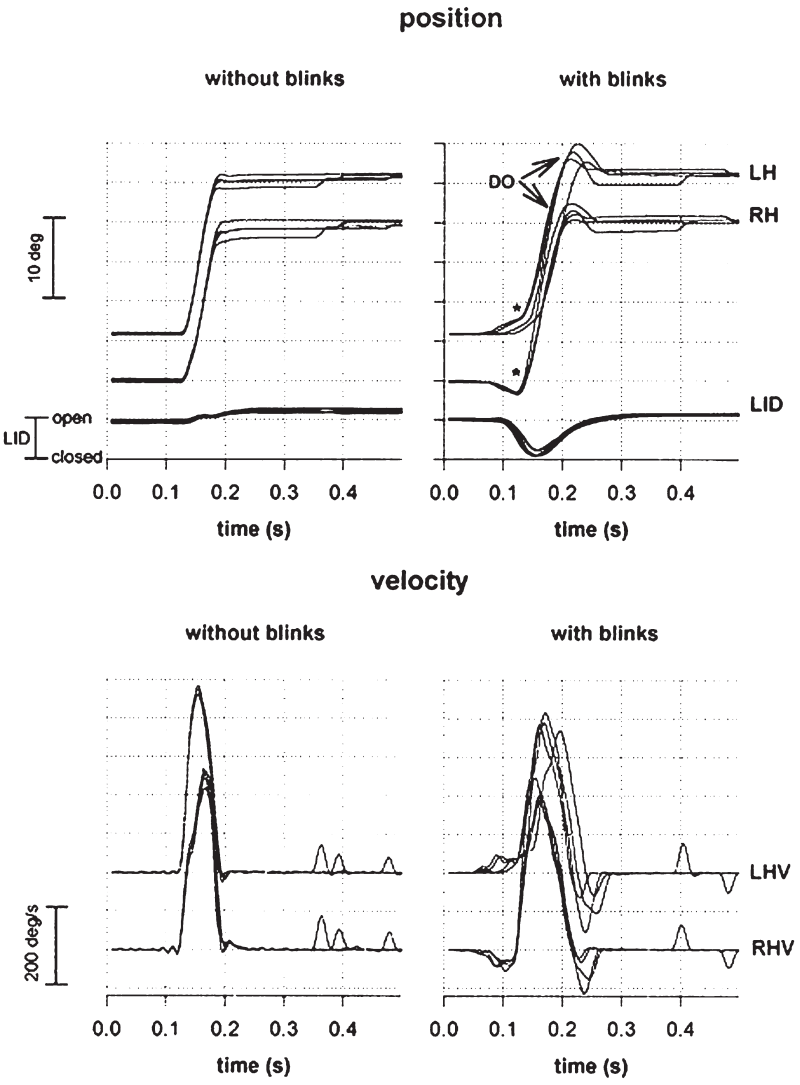


Figure 3–18. Effect of blinks on saccades from a normal subject. Position records are shown above and corresponding velocity traces below. Note that peak velocities are smaller, for similar-sized saccades, when the subject blinks with the saccade. Also note that dynamic overshoots (DO)—oppositely directed postsaccadic movements—occur more frequently with blinks. LH, left horizontal position; LHV, left horizontal velocity; RH, right horizontal position; RHV, right horizontal velocity. (Courtesy of Klaus G. Rottach.)

Electrophysiological studies have demonstrated suppression of discharge in superior colliculus burst neurons during blinks; after the blink, activity resumes and persists until the perturbed saccade is completed.[248] Since blink-perturbed saccades generally get on target, it seems likely that there is a mechanism, downstream from the superior colliculus, to compensate for the blink-induced saccade perturbation. It may even relate to the cerebellum, since vermal lesions lead not only to saccadic dysmetria but also a decrease in the blinks associated with saccades. It also seems likely that omnipause neurons are silent during both blinks and saccades and, if the blink outlasts the saccade, the eyes might briefly oscillate around the new eye position as a dynamic overshoot. Normal subjects and patients with opsoclonus or ocular flutter may show oscillations during blinks,[264, 290] or during eyelid closure.

Although blinks tend to slow down saccades, a paradoxical finding is that blinks may actually speed up abnormally slow saccades in patients with degenerative or other diseases.[773] In this case, the blink may cause a more synchronized and complete inhibition of the omnipause neurons, allowing the burst neurons a better chance to discharge. This may also be the mechanism that patients with ocular motor apraxia employ (along with a head movement) to initiate a saccade (see Video Display: Acquired Ocular Motor Apraxia). Whatever the mechanism, it is clear that studies of saccades must take into account the occurrence of blinks, which may substantially affect these eye movements. Furthermore, methods of eye movement recording that depend upon measuring a biological signal such as the corneal-retinal potential, may be confounded by lid movements (see Appendix B).

EXAMINATION OF SACCADES

Clinical Examination of Saccades

Saccadic eye movements are best examined at the bedside by instructing the patient to fixate alternately upon two targets—such as the tip of a pen and the examiner's nose. Saccades in each direction can be examined in each field of gaze in both the horizontal and vertical planes. The examiner should determine: Are saccades of normal velocity? Are they promptly initiated? Are they accurate? Do the eyes move together? (See Appendix A for a summary.)

Saccadic slowing, such as the lag of the adducting eye in internuclear ophthalmoplegia (INO), can be best appreciated when the patient is instructed to rapidly refixate between two widely spaced targets (see Video Display: Pontine Syndromes); identification of mild INO often requires measurement of eye movements.[210] Another useful technique to detect slow adduction is with a hand-held "optokinetic" drum or tape. Quick phases made by the affected eye are smaller and slower. If slowing of saccades occurs in only one plane of movement, it can be easily appreciated when the patient makes saccades between diagonally placed targets. The rapid, normal component is completed before the slower, orthogonally directed component, so that the saccade trajectory is strongly curved (see Fig. 3–5B and Video Display: Disorders of Saccades).

Saccade latencies can be appreciated by noting the time it takes the patient to initiate the saccade. Saccadic dysmetria can be inferred by the direction and size of corrective saccades made to acquire the fixation target (see Video Display: Disorders of Saccades). Since small saccades (as little as 1/2 degree) can be detected by careful observation, saccadic dysmetria can be easily observed clinically at the bedside. Normal individuals may undershoot the target by a few degrees when refixations are large, and saccadic overshoot may occur normally for centripetal and especially downward saccades. This tendency toward downward overshoot in normals may also appear when making horizontal refixations, when a slight downward component necessitates an upward corrective saccade. The dysmetria should disappear with repetitive refixations between the same targets.

If a saccade abnormality is detected, the strategy is to localize the disturbance within the hierarchical organization of the saccadic eye movement system (Table 3–1). First, establish whether or not the disease process affects reflexive types of saccades. Quick phases can be examined by spinning the patient in a swivel chair to elicit vestibular nystagmus or by using an optokinetic drum to elicit optokinetic nystagmus. Loss of quick phases usually points to a brainstem process affecting premotor burst neurons. Next, exam-

ine the ability of the patient to make a saccade to a suddenly appearing visual target. Determine if saccades can be made without a visual target or in response to auditory targets, or ask the patient to refixate under closed lids or behind Frenzel goggles. Loss of voluntary saccades with preservation of reflexive saccades and quick phases is characteristic of acquired ocular motor apraxia. One can also test the ability to make more volitional types of saccades by asking the patient to make saccades, rapidly, back and forth, between two stationary targets, first to command and then spontaneously. In Parkinson's disease, for example, the ability to make predictive saccades can be assessed by asking the patient to change fixation while the examiner holds up the index finger of each hand, positioned to elicit horizontal saccades across the patient's midline. Initially the patient is instructed to "look at the finger on your right, on your left," and so on until the patient falls into a predictable sequence set by the examiner's instructions. Then the examiner asks the patient to continue making such saccades on his or her own (i.e., without verbal cues). Certain patients, typically those with Parkinson's disease, make accurate saccades during verbal instructions but hypometric saccades when they are self-paced (see Video Display: Parkinsonian Disorders).

It is also possible to elicit antisaccades at the bedside. The examiner holds both hands up and asks the patient to look to the finger that does not move.[135] Errors on the antisaccade task, with saccades towards the visual stimulus are encountered with disease affecting the prefrontal cortex.

If saccade initiation seems impaired, observe gaze changes when the patient makes a combined eye-head movement to see if an accompanying head movement can facilitate the production of a saccade. Some patients with ocular motor apraxia employ this strategy (see Video Display: Acquired Ocular Motor Apraxia). The effect of blinks should also be noted since they may facilitate the ability to initiate saccades,[393] speed-up slow saccades,[773] or induce saccadic oscillations.[264] Finally, the effects of fatigue upon saccadic eye movements, for example in myasthenia gravis, may be tested by asking the patient to repetitively refixate between two targets.

During attempted steady fixation, extraneous saccadic eye movements (saccadic intrusions—which imply impaired ability to suppress saccades) should be noted. Subtle degrees of abnormal fixation behavior can be best appreciated during ophthalmoscopy. The motion of the optic nerve head of one eye is observed as the patient attempts to fixate a target with the other. In some patients, saccadic oscillations such as flutter and opsoclonus can be induced by blinks or by asking the patient to make a combined saccade-vergence movement.[68]

Measurement of Saccadic Eye Movements

While many abnormalities of saccadic velocity, initiation, and accuracy can be easily appreciated at the bedside, more subtle changes can be detected only by analysis of eye movement recordings. To obtain reliable recordings of saccade trajectories, one must have a measuring system with a high bandwidth (preferably greater than 150 Hz, which requires a digitization rate of at least 300 Hz), and which reproduces faithfully the saccade trajectory. These methodological issues are reviewed in Appendix B. The search coil and corneal reflection techniques usually meet these requirements as well as offering adequate sensitivity ($<$0.1 deg), and linear range ($\pm$ 20 deg). Electrooculography (EOG), however, induces a number of artifacts in the eye movement trace due to movement of the lid, movement of the opposite eye, and a muscle action potential spike at the onset of the saccade.[158] With EOG, the speed of abducting saccades appears to be lower than that of adducting saccades though recordings with the search-coil and infrared reflection techniques indicate that the opposite is actually the case. EOG is unreliable for measurement of vertical saccades.

Saccadic gain (saccade amplitude/target amplitude) is the usual measure of saccadic accuracy. Saccadic amplitude is usually defined by the position of the eye at the start of the saccade and the position of the eye when the saccadic pulse is finished. (Conventionally, saccade onset is defined by the rise of eye velocity to some arbitrary value, such as 30 degrees per second, and saccade pulse offset is defined by the dropping of eye velocity below that value.) Saccadic gain can be tested using both stationary and moving targets; both target position and velocity are used in programming of mov-

ing targets,[259] and lesions in the posterior cerebral hemisphere may produce a specific deficit in saccade accuracy for moving targets.[77,484]

The most common measurements of saccadic dynamics are peak velocity and duration; both are conventionally plotted as a function of amplitude (Fig. 3–2). In addition, the shape of the velocity waveform and its skewness (the ratio of time-to-peak velocity to total saccadic duration, see Fig. 3–1) may be helpful. Postsaccadic drift, the unusual waveforms observed in myasthenia gravis, and some types of ocular oscillations are examples of saccadic abnormalities that are best detected with eye movement recordings. Recordings of eye movements are essential if one wants to analyze carefully quick phases of vestibular nystagmus induced in darkness, saccades made to auditory targets, and saccades made in combination with head movements. Comparison of latencies of saccades made in different behavioral contexts (e.g., gap-overlap tasks, antisaccades, predictive saccades, saccades on command) also requires quantitative measurements of eye movements. Measurement of saccades is also helpful to confirm the diagnosis of internuclear ophthalmoparesis. After measuring a range of horizontal saccades, the ratio of abducting/adducting peak velocity or peak acceleration is calculated for the patient and compared to a normative database.[209]

Even though certain properties of saccades—such as peak velocity—are relatively "machine-like," such measures are influenced by a number of factors, such as target luminance and attention, and possibly by the age of the patient. It is therefore essential to compare measurements in any patient with 95% confidence limits defined by an age-matched control group during similar testing in that laboratory.

PATHOPHYSIOLOGY OF SACCADIC ABNORMALITIES

The clinical disorders that cause saccadic abnormalities are described in Chapters 10 and 12, and some abnormalities are summarized in Table 3–3. Here our review aims to apply current knowledge about the normal generation of saccades to present a scheme for thinking about saccadic abnormalities (see also Video Display: Disorders of Saccades). From

Table 3–3. **Summary of Enduring Effects of Lesions on Saccades***

Site of Lesion	General Effects of Lesions
Motoneurons and ocular motor nerves	Slowed saccades; limited range of movement
Premotor burst neurons	Slow saccades
PPRF	Horizontally
RiMLF	Vertically and torsionally
Omnipause neurons	Saccadic oscillations (opsoclonus and flutter); Slow horizontal *and* vertical saccades
Cerebellar dorsal vermis (bilateral)	Saccadic hypometria
Cerebellar fastigial nucleus (bilateral)	Saccadic hypermetria
Superior colliculus	Loss of short-latency (express) saccades
Thalamus	Inaccurate responses to double-step stimuli
Parietal eye field	Increased latency of visually guided saccades Inaccurate responses to double-step stimuli Impaired visual search
Frontal eye field	Bilaterally increased latency to overlap stimuli, remembered targets, and in antisaccade task Contralateral hypometria to visual or remembered targets
Supplementary eye field (SEF) and pre-SEF	Impaired ability to make a remembered sequence of saccades, and to reverse the direction of a previously established pattern of response

Table 3–3. *(continued)*

Site of Lesion	General Effects of Lesions
Dorsolateral prefrontal cortex	Impaired ability to make saccades to remembered target locations and errors on the antisaccade task. Impaired visual search
Basal ganglia	Difficulties in initiating voluntary saccades in tasks that require learned or predictive behavior, and working memory (such as visual search)

*More than one behavioral disturbance has been attributed to certain lesions.

a pathophysiological point of view, abnormalities of saccades can be classified into disorders of the saccadic pulse, disorders of the saccadic step, or saccadic pulse-step mismatch (Fig. 3–19). For example, a change in the amplitude (size) (approximately width × height) of the saccadic pulse creates overshoot or undershoot (saccadic dysmetria). A decrease in the height of the saccadic pulse, which reflects discharge frequency, causes slow saccades. A mismatch between the saccadic pulse and step creates post-saccadic drift or glissades. If the saccadic step cannot be sustained, the eye drifts toward the central position after each eccentric saccade, creating gaze-evoked nystagmus. In addition, there may be disturbance of the voluntary initiation or suppression of saccades.

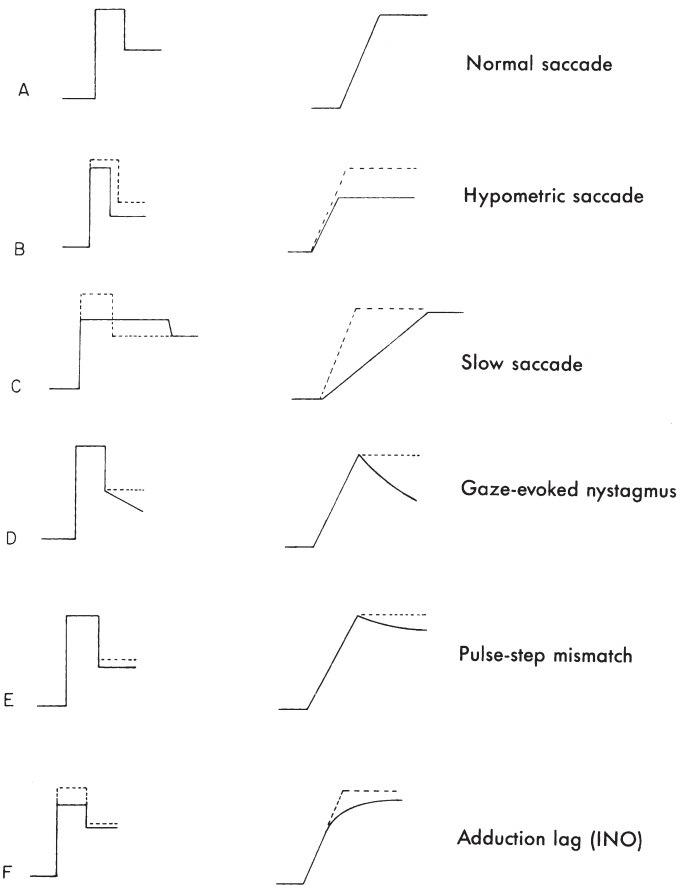


Figure 3–19. Disorders of the saccadic pulse and step. Innervation patterns are shown on the left, eye movements on the right. Dashed lines indicate the normal response. (A) Normal saccade. (B) Hypometric saccade: pulse amplitude (width × height) is too small but pulse and step are matched appropriately. (C) Slow saccade: decreased pulse height with normal pulse amplitude and normal pulse-step match. (D) Gaze-evoked nystagmus: normal pulse, poorly sustained step. (E) Pulse-step mismatch (glissade): step is relatively smaller than pulse. (F) Pulse-step mismatch due to internuclear ophthalmoplegia (INO): the step is larger than the pulse, and so the eye drifts onward after the initial rapid movement.

Disorders of Saccadic Velocity

Saccades are usually defined as being too slow or too fast if their peak velocities fall outside the normal peak velocity-amplitude relationship (main sequence, Fig. 3–3). Small-amplitude saccades that appear to be too fast usually occur when a saccade is interrupted in mid-flight, such that its final intended position is not reached. They are characteristic of myasthenia gravis (see Video Display: Diplopia and Strabismus).[51,507] Thus the saccade, rather than being too fast, is actually too small; this, in effect, increases its peak velocity-amplitude relationship. Abnormalities in the orbit, such as tumors, which restrict the motion of the globe in certain orbital positions can also lead to these seemingly fast saccades. Saccades that actually are faster than normal occur in some patients with saccadic oscillations such as flutter and opsoclonus (see Figs. 3–4 and 10–15)[64,778] (see Video Display: Disorders of Saccades), or macrosaccadic oscillations,[691] in patients with prematurely terminated saccades (Fig. 3–20),[591] and in some individuals who stutter.[166]

Slow saccades of restricted amplitude usually reflect abnormalities in the ocular motor periphery, such as an extraocular muscle or ocular motor nerve paresis, or in the medial longitudinal fasciculus (MLF), such as the slow adduction of internuclear ophthalmoplegia (see Video Display: Pontine Syndromes). Slow saccades occurring with a full ocular motor range are usually caused by central neurological disorders, summarized in Table 10–15 (see Video Display: Disorders of Saccades). Possibilities include direct disruption in the brainstem neural networks generating the saccadic pulse, either because of intrinsic disturbances of burst neurons, or because of failure to recruit a portion of burst cells. This latter problem could arise from a loss of higher-level excitatory inputs to burst cells or an abnormality in inhibition of omnipause cells. If the omnipause cells are at fault, slow saccades can be explained by desynchronization of the discharge of burst neurons or by failure to recruit a certain proportion of burst neurons during the saccade. Alternatively, slow saccade may occur because omnipause neurons no longer provide glycine, which can facilitate N-methyl-D-aspartate (NMDA) receptor currents;[11] thus, burst neurons may lack the post-inhibitory rebound that is postulated to produce the high acceleration typical of saccades.[447,448,448a]

Thus, while it was originally believed that slow saccades due to central disorders were pathognomonic of burst cell dysfunction, it has become apparent that disturbances of higher level structures including the cerebral hemispheres,[716] and superior colliculus,[302] can lead to saccade slowing. Nonetheless, selective

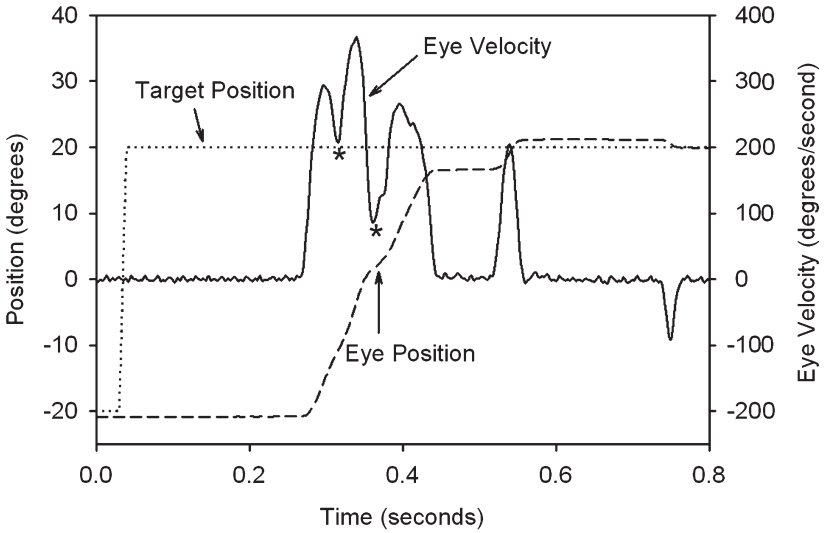


Figure 3–20. Representative records of horizontal saccades made by a patient with late-onset Tay-Sachs disease. The velocity record shows saccades with transient decelerations during which eye velocity declines, but not to zero, and then increases again (indicated by*). Thus these saccades appear to stall in mid-flight, a behavior similar to that induced by experimentally stimulating omnipause neurons during a saccade (Fig. 3–11).

slowing of horizontal saccades indicates pontine disease (PPRF), whereas selective slowing of vertical saccades suggests upper midbrain dysfunction (riMLF) (see Video Display: Midbrain Syndromes).[67] In patients with selective slowing of horizontal or vertical saccades, diagonal saccades often show a characteristically curved trajectory (Fig. 3–5B). Some patients with slow vertical saccades show curved trajectories even during vertical refixations; this might be an adaptive strategy that employs a normal horizontal component to completely inhibit omnipause neurons and so maximize the vertical component. In Gaucher's disease, a similar curved trajectory looping upwards is seen in association with slow horizontal saccades. Finally, saccadic velocities may be lower in drowsy, inattentive, or drug-intoxicated patients.[336,618,710]

Disorders of Saccadic Accuracy

Saccadic pulse dysmetria, especially hypermetria, is the hallmark of cerebellar disease. It is often asymmetric—*lateropulsion*, so that there is hypermetria of saccades in one direction and hypometria of saccades in the other. It is possible to offer a hypothesis that accounts for the direction of lateropulsion encountered in such patients (see Fig. 3–16 and Video Display: Disorders of Saccades). An important experimental finding, on which this hypothesis rests, is that pharmacological inactivation of the fastigial nucleus causes ipsipulsion (Fig. 3–16, site 4).[584] Thus, interruption of olivocerebellar climbing fibers within the medulla before they cross (Fig. 3–16, site 1), cause contrapulsion.[711] More commonly climbing fibers are interrupted within the inferior cerebellar peduncle (Fig. 3–16, site 2) in Wallenberg's syndrome, causing ipsipulsion. In both cases, interruption of climbing fibers may lead to increased simple-spike activity of Purkinje cells in the ipsilateral dorsal vermis, which, in turn, inhibits the underlying fastigial nucleus.[740] Conversely, removal of inhibition on fastigial nucleus neurons by pharmacological inactivation of the dorsal vermis (Fig. 3–16, site 3) causes contrapulsion,[594] although clinical lesions of the vermis are usually bilateral and so cause bilateral hypometria. Since the output of the fastigial nucleus is crossed, then lesions of the superior cerebellar peduncle (Fig. 3–16, site 5) cause contrapulsion—hypermetria of contralateral saccades and hypometria of ipsilateral saccades.

Patients with extreme degrees of saccadic hypermetria may show macrosaccadic oscillations: a series of hypermetric saccades made about the position of the target (see Video Display: Disorders of Saccades).[32,632] Occasionally, saccadic hypermetria reflects an adaptive response to a peripheral ocular motor deficit[367] or occurs after edrophonium is given to a myasthenic patient (see Video Display: Diplopia and Strabismus).[366]

Saccadic hypometria occurs with a variety of cerebellar and brain stem disorders. Postsaccadic drift, reflecting pulse-step match dysmetria, has been reported in patients with both central and peripheral ocular motor disorders. Visual defects may also lead to saccadic dysmetria. For example, patients with hemianopia may make hypermetric and hypometric saccades (depending on direction) to keep the target within the intact part of the visual field.[434,436,516] Patients with lesions in posterior parietal-temporal cortex may show saccadic dysmetria that is specific for moving, but not stationary, targets (Fig. 4–9).[391] Large unilateral lesions of the cerebral hemispheres may cause ipsilateral hypermetria and contralateral hypometria (see Video Display: Disorders of Smooth Pursuit), especially if there is neglect.[435] Unilateral hemispheric lesions may also lead to a biasing of vertical saccades toward the side of the lesion.[435,716]

Prematurely Terminated Saccades

In certain disorders saccades are very hypometric and the eye gets on target through a "staircase of small saccades." In Parkinson's disease, this occurs when patients make either memory-guided saccades,[355] or self-generated saccades (see Video Display: Parkinsonian Disorders). However, in such patients, the intersaccadic interval between each saccade in the series is no different from control subjects, about 200 ms.

Distinct from this phenomenon are transient decelerations, evident on the velocity records especially of larger saccades. Although normal subjects occasionally show this behavior for large saccades,[7] it is encountered during most gaze shifts in patients with some disorders affecting the brainstem and cerebellum, such as late-onset Tay-Sachs disease and

Wernicke's encephalopathy (Fig. 3–20).[332,591] Since the intersaccadic interval is shortened, and peak deceleration is increased for any saccadic pulse size (measured from peak velocity), it has been postulated that these disorders constitute a specific disorder of the "latch" circuit (Fig. 3–9) that normally inhibits omnipause neurons until the planned saccade is completed.[591] Support for this hypothesis is provided by similar findings when saccades are interrupted by experimental stimulation of the omnipause neurons (compare Fig. 3–11 and Fig. 3–20).[350] Note that transient decelerations also cause an abnormal velocity waveform with peak velocity/average velocity (Q) values that exceed 2.0 (see Saccadic Waveform).[374]

Disorders of Saccadic Initiation

Disorders of saccade initiation range from slight increases in saccadic reaction time, not perceptible at the bedside, to latencies greater than several seconds. The variability of reaction time may also be increased. Allowances must be made for the patient's age, state of consciousness, and level of attention. Saccadic latencies are increased in the presence of visual abnormalities such as amblyopia.[115] Patients with focal hemispheric lesions, especially those affecting the cortical "eye fields" may show increased latencies. Bilateral frontoparietal lesions produce a severe defect of saccade initiation called ocular motor apraxia (see Video Display: Acquired Ocular Motor Apraxia).[530] Such patients may be alert and cooperative but have impaired or delayed initiation of voluntary saccades, whereas random saccades and quick phases of nystagmus are normal.

Patients with disease of the basal ganglia such as Huntington's disease show a characteristic abnormality of saccadic initiation (see Box 12–17, in Chapter 12). Single saccades made in response to the sudden appearance of a visual target—reflexive saccades—are performed relatively normally with appropriate latencies and amplitudes. More volitional saccades, however, are impaired. Patients with Huntington's disease show a greater increase in latency for initiating saccades on command and during predictive tracking than for more reflexive saccades to novel visual stimuli.[381] Patients with Parkinson's disease show difficulties in making self-paced saccades between two visible targets (see Video Display: Parkinsonian Disorders).

Diffuse hemispheric disease may cause impaired ability to anticipate the location of a target moving in a predictable fashion.[354] Patients with Alzheimer's disease make express saccades in response to a gap stimulus, similar to normals, but also show greater variability of saccadic reaction times, probably due to difficulties with sustaining attention and suppressing reflexive movements.[8] Finally, in certain circumstances, saccadic latencies may actually be decreased, for example in some patients with progressive supranuclear palsy (PSP), in which the superior colliculus and its connections with the brainstem reticular formation may be involved.[536]

Inappropriate Saccades: Saccadic Intrusions and Oscillations

Saccades are inappropriate if they interfere with foveal fixation of an object of interest. Normally, subjects can suppress saccades during steady fixation. Saccadic intrusions are inappropriate movements that take the eye away from the target during attempted fixation (see Box 10–14 and Fig. 10–15, in Chapter 10). They occur spontaneously, without the appearance of a novel visual stimulus. They should be differentiated from excessive distractibility, wherein novel visual targets that are behaviorally irrelevant evoke inappropriate saccades. Excessive distractibility can be demonstrated in the antisaccade task (Fig. 3–2D).[776] When instructed to make a saccade in the direction opposite to that of a visual stimulus, patients with Huntington's disease, Alzheimer's disease, schizophrenia, and frontal lobe lesions make an inappropriate saccade to the visual target (see Fig. 12–14 in Chapter 12).[204,214,260,382,535,639] Patients with Parkinson's disease also make more errors on the antisaccade task.[112]

Several types of saccadic intrusions are recognized (Box 10–14, Chapter 10). At one end of the spectrum are *square-wave jerks*, which are small (typically 0.5 degrees), horizontal, involuntary saccades that take the eyes off the target and are followed, after an intersaccadic interval of about 250 ms, by a corrective saccade that brings the eyes back to the target (see Video Display: Parkinsonian Disorders). They may occur in normal individuals at frequencies of 20 per minute or greater;[1] they are

reduced in frequency when subjects attempt to fix upon the remembered location of a target.[637] Normal subjects who have frequent square-wave jerks have no accompanying disorders of saccadic control.[251] Square-wave jerks are prominent in certain cerebellar disorders (especially Friedreich's ataxia) and PSP. These disorders may be due to dysfunction of saccade control by the superior colliculus or its inputs. Thus, microinjection of nicotine into the caudal superior colliculus in monkeys causes express saccades,[12] and nicotine is reported to increase square-wave jerk frequency in humans.[654] The superior colliculus has reciprocal connections with the central mesencephalic reticular formation, which is involved in PSP, and receives inhibitory projections from the substantia nigra, pars reticulata. Pallidotomy as therapy for Parkinson's disease is reported to increase the frequency of square-wave jerks,[33,497] perhaps by disrupting projections from the basal ganglia to the superior colliculus.

Another disorder that disrupts steady fixation is *macrosaccadic oscillations* (see Video Display: Disorders of Saccades). These may be an extreme form of saccadic hypermetria (Fig. 3–6), and are encountered in cerebellar disease that involves the fastigial nucleus or its output,[632] but are also reported with discrete pontine lesions that involved the region of the omnipause neurons.[32]

At the other end of the spectrum of saccadic abnormalities are back-to-back horizontal saccades without an intersaccadic interval. If such oscillations occur only in the horizontal plane, they are termed *ocular flutter*; if they occur in all directions, the oscillation is called *opsoclonus* (see Video Display: Disorders of Saccades). Some normal individuals can generate brief bursts of horizontal saccadic oscillations (voluntary flutter or "voluntary nystagmus") (see Video Display: Disorders of Saccades). Diseases associated with flutter and opsoclonus often also cause brainstem and cerebellar findings. Such oscillations probably reflect an inappropriate, repetitive, alternating discharge pattern of different groups of burst neurons. It was originally proposed that three factors contributed to saccadic oscillations without an intersaccadic interval: (1) the inherently high discharge rates (gain) of saccadic burst neurons, even for very small saccades; (2) the existence of central processing delays that make a system susceptible to oscillations; and (3) abnormalities of the brain stem omnipause cells (or their inputs), which normally inhibit burst neurons during fixation.[778] In support of this hypothesis, some patients manifest transient saccadic oscillations in association with blinks,[264] or vergence movements,[68] both of which inhibit omnipause neurons. Against the hypothesis that omnipause cell dysfunction is the primary cause of opsoclonus or flutter are two findings: (1) at autopsy some patients who had had opsoclonus showed no abnormalities in the region in which omnipause cells are located [566] and (2) pharmacological inactivation of the omnipause cell region in monkeys produces slow saccades,[339,662] not oscillations. Nonetheless, ocular flutter has been reported due to a pontine demyelinative lesion, with subsequent resolution of the oscillations as the patient recovered from the exacerbation of multiple sclerosis.[621]

An alternative hypothesis for flutter and opsoclonus is that saccadic oscillations arise because of the synaptic organization of premotor burst neurons (Fig. 3–10), in which positive feedback loops and post-inhibitory rebound properties of burst neurons predispose to saccadic oscillations.[447,448,553] Changes in the synaptic weighting of such circuits could produce oscillations whenever the omnipause neurons are inhibited.[556] In addition, cerebellar disease might, through projections of the fastigial nucleus to the premotor burst neurons, indirectly increase the likelihood of saccadic oscillations. Experimental lesions of the cerebellum in monkey have never led to flutter or opsoclonus, but this might be due to species differences. Patients with saccadic oscillations show activation of the fastigial nucleus on functional imaging,[282] but this might simply reflect increased frequency of saccades. New models for saccades that incorporate the membrane properties of burst neurons, or cerebellar neurons,[74] may provide suggestions for new treatments for opsoclonus. This is discussed further in Chapter 10.

SUMMARY

1. Saccades are rapid eye movements that change foveal fixation. They comprise both voluntary refixations and the quick phases of vestibular and optokinetic nystagmus. Saccades are characterized by a relatively invariant relationship between their amplitude and peak velocity (Fig.

3–3). The velocity of large saccades may exceed 500 degrees per second and their duration is generally less than 100 ms, which is less than the visual reaction time.

2. Saccades have many characteristics that suggest that they are under open loop or ballistic control. However, the saccadic system can acquire and use visual information continuously up to the initiation of the saccade to modify the amplitude and the direction of the impending saccade.
3. The main innervational change underlying saccadic eye movements is a pulse-step: the pulse is a saccadic eye velocity command that overcomes orbital viscous drag; the step is an eye position command that holds the eye in position against orbital elasticity (Fig. 1–3).
4. Excitatory burst neurons, within the pontine and mesencephalic reticular formation, generate the premotor commands for the horizontal and vertical components of saccades, respectively. Inhibitory burst neurons, located in the rostral medulla for horizontal saccades, assure reciprocal innervation by suppressing activity in motoneurons of antagonist muscles. Burst neurons are tonically inhibited by omnipause neurons except when a saccade is required. The duration of burst cell discharge appears to be under internal feedback control by neural pathways, since vision is too slow to guide saccades to their target.
5. The cerebral hemispheres can trigger saccades via parallel descending pathways (Fig. 3–12) to the superior colliculus and thence to the brainstem reticular formation. More volitional saccades (Table 3–1), made in the context of learned or remembered behavior, depend upon the frontal eye fields, which project both directly and indirectly (via the basal ganglia) to the superior colliculus. More reflexive saccades, to the locations of novel targets suddenly appearing in the external world, depend more upon direct projections from the parietal cortex to the superior colliculus. When the superior colliculus is damaged, recovery is probably mediated by direct projections from the frontal eye fields to the brain stem.
6. The basal ganglia, via serial, inhibitory projections, from the caudate nucleus to the substantia nigra pars reticulata and from the substantia nigra pars reticulata to the rostral pole of the superior colliculus, serve to inhibit extraneous reflexive saccades during attempted fixation and to facilitate volitional saccades in the context of remembered and learned behavior and reward.
7. The cerebellum (Fig. 3–15) calibrates saccadic amplitude (dorsal vermis and fastigial nucleus) and the saccadic pulse-step match (flocculus) for optimal visuoocular motor behavior. The cerebellum also influences the dynamics and the initiation (latency) of saccades.
8. Disorders of saccades consist of abnormalities of velocity, accuracy, initiation, prematurely terminated saccades, and the presence of saccadic intrusions and oscillations. Saccadic disorders can be classified according to whether the saccadic pulse, the saccadic step, or the pulse-step match is inappropriate (Fig. 3–19). Dysfunction of specific cell types within the brain stem reticular formation may account for various types of saccadic disorders.

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