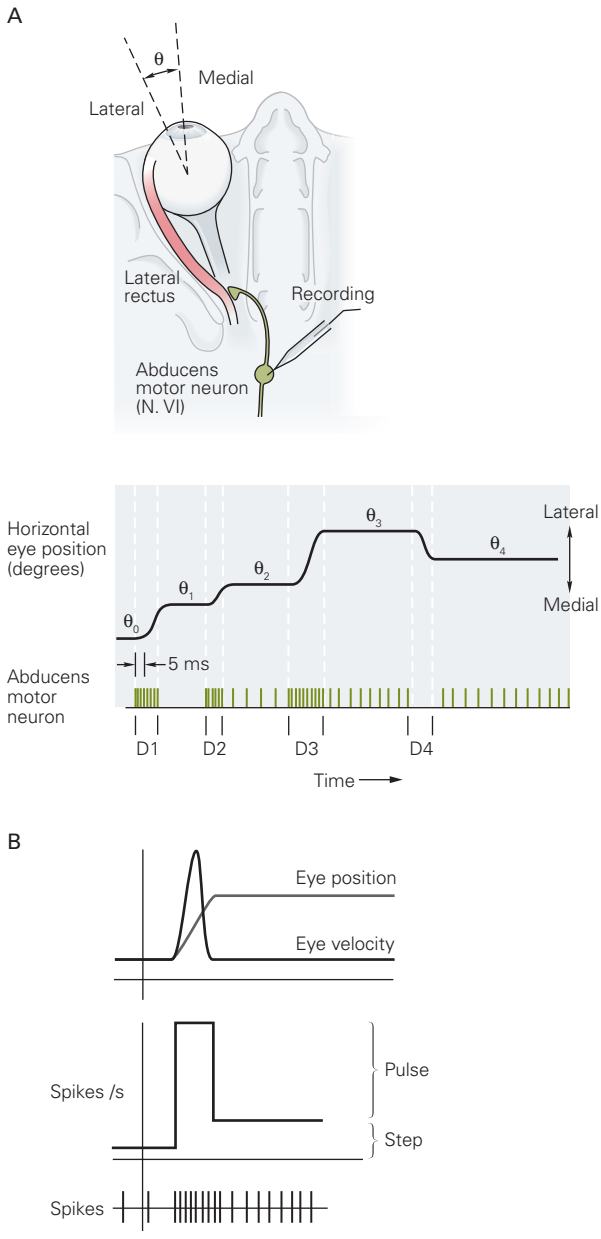


Figure 35–7 Oculomotor neurons signal eye position and velocity.

A. The record is from an abducens neuron of a monkey. When the eye is positioned in the medial side of the orbit, the cell is silent (**position** θ_0). As the monkey makes a lateral saccade, there is a burst of firing (**D1**), but in the new position (θ_1), the eye is still too far medial for the cell to discharge continually. During the next saccade, there is a burst (**D2**), and at the new position (θ_2), there is a tonic position-related discharge. Before and during the next saccade (**D3**), there is again a pulse of activity and a higher tonic discharge when the eye is at the new position (θ_3). When the eye makes a medial movement, there is a period of silence during the saccade (**D4**) even though the eye ends up at a position (θ_4) associated with a tonic discharge. (Adapted from Fuchs and Luschei 1970.)

B. Saccades are associated with a step of activity, which signals the change in eye position, and a pulse of activity, which signals eye velocity. The neural activity corresponding to eye position and velocity is illustrated both as a train of individual spikes and as an estimate of the instantaneous firing rate (spikes per second).

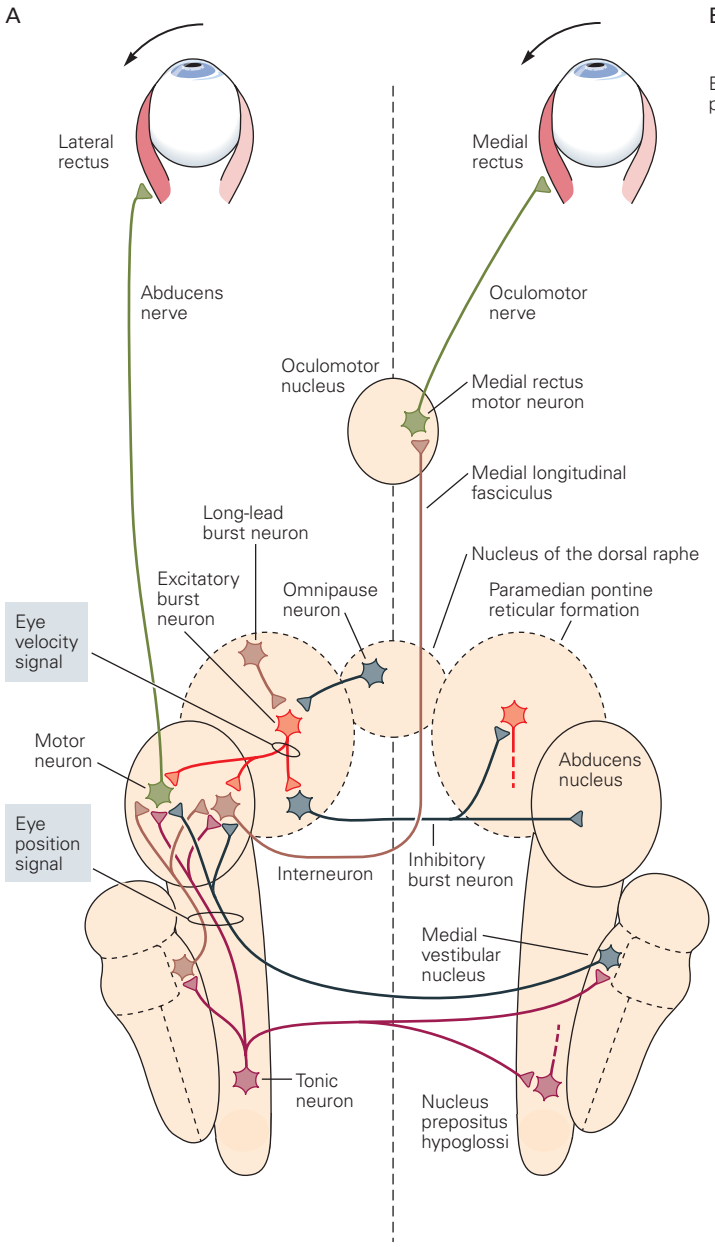
the pulse, then the eye drifts away from the target after the saccade. As described later, the pulse and step are generated by different brain stem structures.

The Motor Circuits for Saccades Lie in the Brain Stem

Horizontal Saccades Are Generated in the Pontine Reticular Formation

The neuronal signal for horizontal saccades originates in the paramedian pontine reticular formation, adjacent to the abducens nucleus to which it projects (Figure 35–8A). The paramedian pontine reticular formation contains a family of *burst neurons* that gives rise to the saccadic pulse. These cells fire at a high frequency just before and during ipsiversive saccades (toward the same side as the discharging neurons), and their activity resembles the pulse component of oculomotor neuron discharge (Figure 35–7B).

There are several types of burst neurons (Figure 35–8B). Medium-lead excitatory burst neurons make direct excitatory connections to motor neurons and interneurons in the ipsilateral abducens nucleus.



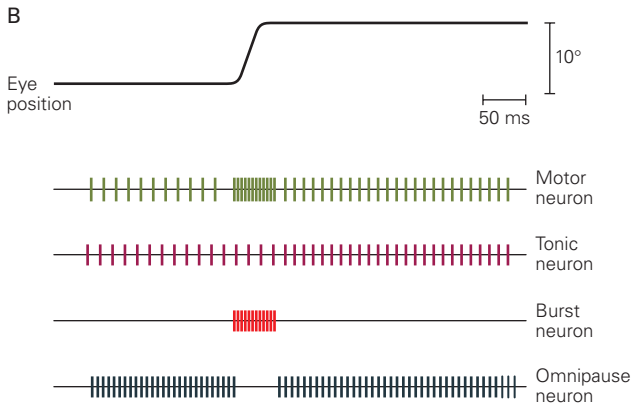


Figure 35–8 The brain stem motor circuit for horizontal saccades.

A. *Eye velocity component.* Long-lead burst neurons relay signals from higher centers to the excitatory burst neurons. The eye velocity component arises from excitatory burst neurons in the paramedian pontine reticular formation that synapse on motor neurons and interneurons in the abducens nucleus. The abducens motor neurons project to the ipsilateral lateral rectus muscles, while the interneurons project to the contralateral medial rectus motor neurons by axons that cross the midline and ascend in the medial longitudinal fasciculus. Excitatory burst neurons also drive ipsilateral inhibitory burst neurons that inhibit contralateral abducens motor neurons and excitatory burst neurons.

Eye position component. This component arises from a neural integrator comprising neurons distributed throughout the medial vestibular nuclei and nucleus prepositus hypoglossi on both sides of the brain stem. These neurons receive velocity signals from excitatory burst neurons and integrate this velocity signal to a position signal. The position signal excites the ipsilateral abducens neurons and inhibits the contralateral abducens neurons. (**Gray** neurons are inhibitory; all other neurons are excitatory. The vertical **dashed line** indicates the midline of the brain stem.)

B. Different neurons provide different information for a horizontal saccade. The motor neuron provides both position and velocity signals. The tonic neuron (nucleus prepositus hypoglossi) signals only eye position. The excitatory burst neuron (paramedian pontine reticular formation) signals only eye velocity. The omnipause neuron discharges at a high rate except immediately before, during, and just after the saccade.

Long-lead burst neurons drive the medium-lead burst cells and receive excitatory input from higher centers. Inhibitory burst neurons suppress the activity of contralateral abducens neurons and contralateral excitatory burst neurons and are themselves excited by medium-lead burst neurons.

A second class of pontine cells, *omnipause neurons*, fires continuously except around the time of a saccade; firing ceases shortly before and during all saccades (Figure 35–8B). Omnipause neurons are located in the nucleus of the dorsal raphe in the midline (Figure 35–8A). They are GABAergic (γ-aminobutyric acid) inhibitory neurons that project to contralateral pontine and mesencephalic burst neurons. Electrical stimulation of omnipause neurons arrests a saccade, which resumes when the stimulation stops. Making a saccade requires simultaneous excitation of burst neurons and inhibition of omnipause cells; this provides the system

with additional stability, such that unwanted saccades are infrequent.

If the motor neurons received signals from only the burst cells, the eyes would drift back to the starting position after a saccade, because there would be no new position signal to hold the eyes against elastic restorative forces. The appropriate tonic innervation is required to keep the eye at the new orbital position. This tonic position signal, the saccadic step, can be generated from the velocity burst signal by the neural equivalent of the mathematical process of integration. Velocity can be computed by differentiating position with respect to time; conversely, position can be computed by integrating velocity with respect to time.

For horizontal eye movements, neural integration of the velocity signal is performed by the medial vestibular nucleus and nucleus prepositus hypoglossi (Figure 35–8A) in conjunction with the flocculus of the cerebellum. As expected, animals with lesions of these areas make normal horizontal saccades, but the eyes drift back to a middle position after a saccade. Moreover, integration of the horizontal saccadic burst requires coordination of the bilateral nuclei prepositi hypoglossi and medial vestibular nuclei through commissural connections. Thus, a midline lesion of these connections also causes failure of the neural integrator.

Medium-lead burst neurons in the paramedian pontine reticular formation and neurons of the medial vestibular nucleus and nucleus prepositus hypoglossi project to the ipsilateral abducens nucleus and deliver respectively the pulse and step components of the motor signal. Two populations of neurons in the abducens nucleus receive this signal. One is a group of motor neurons that innervate the ipsilateral lateral rectus muscle. The second group consists of interneurons whose axons cross the midline and ascend in the medial longitudinal fasciculus to the motor neurons for the contralateral medial rectus, which lie in the oculomotor nucleus (Figure 35–8A).

Thus, medial rectus motor neurons do not receive the pulse and step signals directly. This arrangement allows for precise coordination of corresponding movements of both eyes during horizontal saccades and other conjugate eye movements. The susceptibility of the medial longitudinal fasciculus to strokes and multiple sclerosis make it clinically important.

Several cerebellar structures play an important role in the calibration of the saccade motor signal. First, the oculomotor portion of the dorsal vermis, acting through the caudal fastigial nucleus, controls the duration of the pulse and thus the accuracy of the saccade. The fastigial nucleus increases saccade velocity at the beginning of contraversive saccades and contributes to braking ipsiversive saccades to end the saccade. Second, the flocculus and paraflocculus of the vestibulocerebellum calibrate the neural integrator to ensure that the step is properly matched to the pulse, in order to hold the eyes at the new position after each saccade.

Vertical Saccades Are Generated in the Mesencephalic Reticular Formation

The burst neurons responsible for vertical saccades are found in the rostral interstitial nucleus of the medial longitudinal fasciculus in the mesencephalic reticular formation (Figure 35–3). Vertical and torsional neural integration are performed in the nearby interstitial nucleus of Cajal. The pontine and mesencephalic systems participate together in the generation of oblique saccades, which have both horizontal and vertical components.

Purely vertical saccades require activity on both sides of the mesencephalic reticular formation, and communication between the two sides occurs via the posterior commissure. There are not separate omnipause neurons for horizontal and vertical saccades; pontine omnipause cells inhibit both pontine and mesencephalic burst neurons.

Brain Stem Lesions Result in Characteristic Deficits in Eye Movements

We can now understand how different brain stem lesions cause characteristic syndromes. Lesions that include the paramedian pontine reticular formation result in paralysis of ipsiversive horizontal gaze of both eyes but spare contraversive and vertical saccades. A lesion of the abducens nucleus has a similar effect, as both abducens motor neurons and interneurons are affected. Lesions that include the midbrain gaze centers cause paralysis of vertical gaze. Certain neurological disorders cause degeneration of burst neurons and impair their function, leading to a progressive slowing of saccades.

Lesions of the medial longitudinal fasciculus disconnect the medial rectus motor neurons from the abducens interneurons (Figure 35–8A). Thus, during conjugate horizontal eye movements, such as saccades and pursuit, the abducting eye moves normally but adduction of the other eye is impeded. Despite this paralysis in version movements, the medial rectus typically acts normally in vergence movements because the motor neurons for vergence lie in the midbrain, as will be discussed later. This syndrome, called an *internuclear ophthalmoplegia*, is a consequence of a brain stem stroke or demyelinating diseases such as multiple sclerosis.

A lesion of the cerebellar fastigial nucleus causes ipsiversive saccades to overshoot their targets (*hypermetric* saccades), due to failure of normal termination of the saccadic burst. Contraversive saccades undershoot their targets (*hypometric* saccades). Correspondingly, damage to the oculomotor vermis disinhibits the fastigial nucleus and causes hypometric ipsiversive saccades. This may be due to an additional failure to compensate for the position-dependent passive forces of the orbital tissues.

Saccades Are Controlled by the Cerebral Cortex Through the Superior Colliculus

The pontine and mesencephalic burst circuits provide the motor signals necessary to drive the extraocular muscles for saccades. However, among higher mammals, eye movements are ultimately driven by cognitive behavior. The decision of when and where to make a saccade that is behaviorally important is usually made in the cerebral cortex. A network of cortical and subcortical areas controls the saccadic system through the superior colliculus (Figure 35–9).

The Superior Colliculus Integrates Visual and Motor Information into Oculomotor Signals for the Brain Stem

The superior colliculus in the midbrain is a major visuomotor integration region, the mammalian homolog of the optic tectum in nonmammalian vertebrates. It can be divided into two functional regions: the superficial layers and the intermediate and deep layers.

The three superficial layers receive both direct input from the retina and a projection from the striate

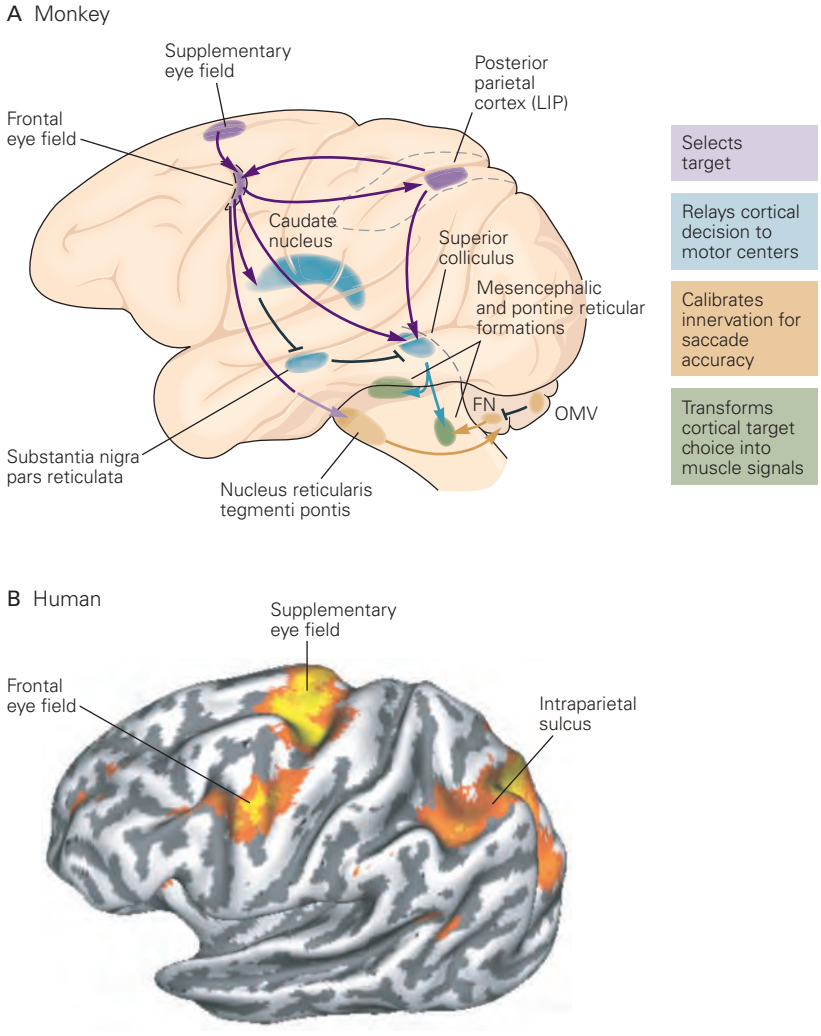


Figure 35–9 Cortical pathways for saccades.

A. In the monkey, the saccade generator in the brain stem receives a command from the superior colliculus. That command is relayed through the pontine and mesencephalic burst circuits, providing the motor signals that drive the extraocular muscles for saccades. The colliculus receives direct excitatory projections from the frontal eye fields and the lateral intraparietal area (**LIP**) and an inhibitory projection from the substantia nigra. The substantia nigra is suppressed by the caudate nucleus, which in turn is excited by the frontal eye fields. Thus, the frontal eye fields directly excite the colliculus and indirectly release it from suppression by the substantia nigra by exciting the caudate nucleus, which inhibits the substantia nigra. The oculomotor vermis (**OMV**) of the cerebellum, acting through the fastigial nucleus (**FN**), calibrates the burst to keep saccades accurate.

B. This lateral scan of a human brain shows areas of cortex activated during saccades. (Adapted from Curtis and Connolly 2008.)

cortex representing the entire contralateral visual hemifield. Neurons in the superficial layers respond to visual stimuli. In monkeys, the responses of half of these vision-related neurons are quantitatively enhanced when an animal prepares to make a saccade to a stimulus in the cell's receptive field. This enhancement is specific for saccades. If the monkey attends to the stimulus without making a saccade to it—for example, by making a hand movement in response to a brightness change—the neuron's response is not augmented. Neurons in the superficial layers of the superior colliculus are functionally arranged in a retinotopic map of the visual field in which representation of the visual field closest to the fovea occupies the largest area (Figure 35–10).

Neuronal activity in the two intermediate and deep layers is primarily related to oculomotor actions. The movement-related neurons in these layers receive visual information from the prestriate, middle temporal, and parietal cortices and motor information from the frontal eye field. The intermediate and deep layers also contain somatotopic, tonotopic, and retinotopic maps of sensory inputs, all in register with one another. For example, the image of a bird will excite a vision-related neuron, whereas the bird's chirp will excite an adjacent audition-related neuron, and both will excite a bimodal neuron. Polymodal spatial maps enable us to shift our eyes toward auditory or somatosensory stimuli as well as visual ones.

Much of the early research describing the sensory responsiveness of neurons in the intermediate layer was done in anesthetized animals. To understand how the brain generates movement, however, the activity of neurons needs to be studied in alert, active animals. Edward Evarts pioneered this approach in studies of the skeletomotor system, after which it was extended to the oculomotor system.

One of the earliest cellular studies in active animals revealed that individual movement-related neurons in the superior colliculus selectively discharge before saccades of specific amplitudes and directions, just as individual vision-related neurons in the superior colliculus respond to stimuli at specific distances and directions from the fovea (Figure 35–11A). The movement-related neurons form a map of potential eye movements that is in register with the visuotopic and tonotopic arrays of sensory inputs, so that the neurons that control eye movements to a particular target are found in the same region as the cells excited by the sounds and image of that target. Each movement-related neuron in the superior colliculus has a *movement field*, a region of the visual field that is the target for saccades controlled by that neuron. There is a map of movement fields in the intermediate layers that is in register with the map of visual receptive fields in the overlying superficial layers. Each movement neuron discharges before a saccade to the center of the overlying visual receptive field. A map of saccades evoked by electrical stimulation of the intermediate layers resembles the visual map.

Movement fields are large, so each superior colliculus cell fires before a wide range of saccades, although each cell fires most intensely before saccades of a specific direction and amplitude. A large population of cells is thus active before each saccade, and eye movement is encoded by the entire ensemble of these broadly tuned cells. Because each cell makes only a small contribution to the direction and amplitude of the movement, any variability or noise in the discharge of a given cell is minimized. Similar population coding is found in many sensory systems (Chapter 17) and the skeletal motor system (Chapter 34).

Activity in the superficial and intermediate layers of the superior colliculus can occur independently: Sensory activity in the superficial layers does not always lead to motor output, and motor output can occur without sensory activity in the superficial layers. In fact, the neurons in the superficial layers do not provide a large projection directly to the intermediate

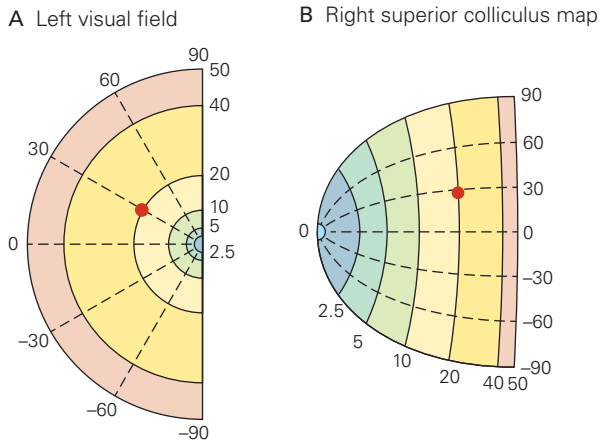


Figure 35–10 Neurons in the superior colliculus are organized in a retinotopic map.

A. Map of the left visual field in polar coordinates. **Dashed lines** represent the angle and **solid lines** the eccentricity.

B. Spatial map of neurons in the superior colliculus represented in polar coordinates of the visual field. In the nucleus, more neurons represent the part of the visual field close to the fovea and fewer neurons represent the periphery. For example, a stimulus appearing at 20° eccentricity and 30° elevation in the visual field (**red dot**) will excite neurons at the location of the red dot on the collicular map. (Reproduced, with permission, from Quaia et al. 1998.)

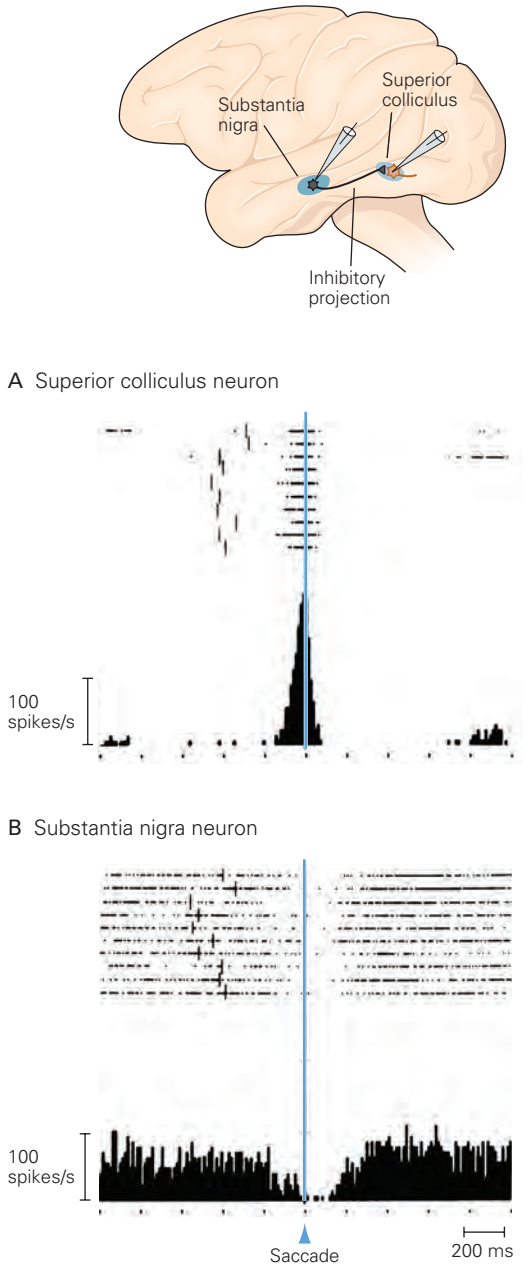


Figure 35–11 Neurons in the superior colliculus and substantia nigra are active around the time of a saccade. (Reproduced, with permission, from Hikosaka and Wurtz 1989.)

A. A neuron recorded from the region in the superior colliculus from which the neuron in B could be excited antidromically fires in a burst immediately before the saccade. Raster plots of activity in successive trials of the same task are summed to form the histogram below. The small vertical lines in the raster indicate target appearance. The trials are aligned at the beginning of the saccade (**blue line**).

B. A neuron in the substantia nigra pars reticulata is tonically active, becomes quiet just before the saccade, and resumes activity after the saccade. This type of neuron inhibits neurons in the intermediate layers of the superior colliculus.

layers. Instead, their axons terminate on neurons in the pulvinar and lateral posterior nuclei of the thalamus, which relay the signals from the superficial layers of the superior colliculus to cortical regions that project back to the intermediate layers.

Lesions of a small part of the colliculus affect the latency, accuracy, and velocity of saccades. Destruction of the entire colliculus renders a monkey unable to make any contraversive saccades, although with time, this ability is recovered.

The Rostral Superior Colliculus Facilitates Visual Fixation

The most rostral portion of the superior colliculus receives inputs from the fovea and the foveal representation in primary visual cortex (V1). Neurons in the intermediate layers in this region discharge strongly during active visual fixation and before small saccades to the contralateral visual field. Because the neurons are active during visual fixation, this area of the superior colliculus is often called the fixation zone.

Neurons here inhibit the movement-related neurons in the more caudal parts of the colliculus and also project directly to the nucleus of the dorsal raphe, where they inhibit saccade generation by exciting the omnipause neurons. With lesions in the fixation zone, an animal is more likely to make saccades to distracting stimuli.

The Basal Ganglia and Two Regions of Cerebral Cortex Control the Superior Colliculus

The superior colliculus receives a powerful GABAergic inhibitory projection from neurons in the substantia nigra, which fire spontaneously with high frequency. This discharge is suppressed at the time of voluntary eye movements to the contralateral visual field (Figure 35–11B) by inhibitory input from neurons in the caudate nucleus, which fire before saccades to the contralateral visual field.

The superior colliculus is controlled by two regions of the cerebral cortex that have overlapping but distinct functions: the lateral intraparietal area of the posterior parietal cortex (part of Brodmann's area 7) and the frontal eye field (part of Brodmann's area 8). Each of these areas contributes to the generation of saccades and the control of visual attention.

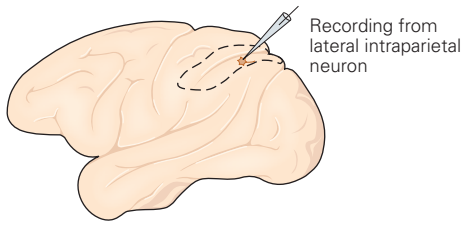
Perception of attended objects in the visual field is better than perception of unattended objects, as measured either by a subject's reaction time to an object suddenly appearing in the visual field or by the subject's ability to perceive a stimulus that is just barely

noticeable. Saccadic eye movements and visual attention are closely intertwined (Figure 35–5).

The lateral intraparietal area in the monkey is important in the generation of both visual attention and saccades. The role of this area in the processing of eye movements is best illustrated by a memory-guided saccade. To demonstrate this saccade, a monkey first fixates a spot of light. An object (the stimulus) appears in the receptive field of a neuron and then disappears; then the spot of light is extinguished. After a delay, the monkey must make a saccade to the former location of the vanished object. Neurons in the lateral intraparietal area respond from the moment the object appears and continue firing after the object has vanished and throughout the delay until the saccade begins (Figure 35–12A), but their activity can be also dissociated from saccade planning. If the monkey is planning a saccade to a target outside the receptive field of a neuron and a distractor appears in the field during the delay period, the neuron responds as vigorously to the distractor as it does to the target of a saccade (Figure 35–12B).

Lesioning of a monkey's posterior parietal cortex, which includes the lateral intraparietal area, increases the latency of saccades and reduces their accuracy. Such a lesion also produces selective neglect: A monkey with a unilateral parietal lesion preferentially attends to stimuli in the ipsilateral visual hemifield. In humans as well, parietal lesions—especially right parietal lesions—initially cause dramatic attentional deficits. Patients act as if the objects in the neglected field do not exist, and they have difficulty making eye movements into that field (Chapter 59).

Patients with Balint syndrome, which is usually the result of bilateral lesions of the posterior parietal



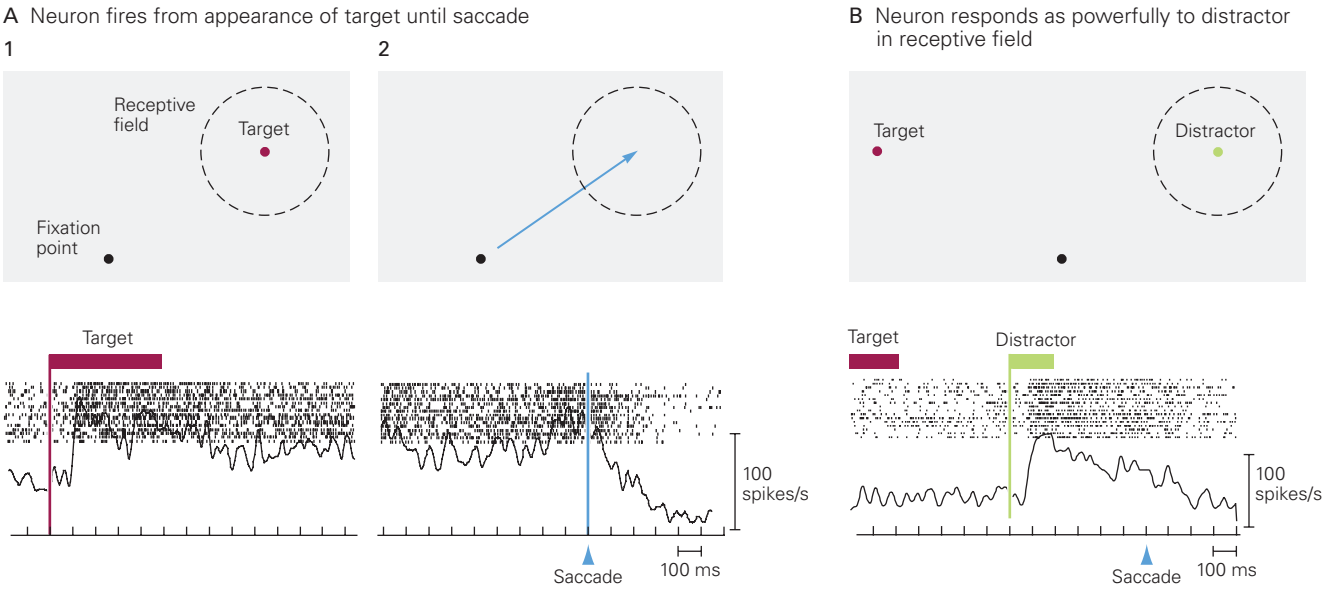


Figure 35–12 A parietal neuron is active before memory-guided saccades. Traces are aligned at events indicated by vertical lines. (Adapted, with permission, from Powell and Goldberg 2000.)

A. The monkey plans a saccade from a fixation point to a target in the receptive field of a neuron in the lateral intraparietal cortex. The neuron responds to the appearance of the target (**1**). It continues to fire after the target has disappeared but before the signal to make the saccade and stops firing after the onset of the saccade (**2**).

B. The monkey plans a saccade to a target outside the receptive field. The neuron responds initially to a distractor in the receptive field as strongly as it did to the target of a saccade.

and prestriate cortex, tend to see and describe only one object at a time in their visual environment. These patients make few saccades, as if they are unable to shift the focus of their attention from the fovea, and can therefore describe only a foveal target. Even after these patients have recovered from most of their deficits, their saccades are delayed and inaccurate.

Compared to the neurons in the parietal cortex, neurons in the frontal eye field are more closely associated with saccades. Three different types of neurons in the frontal eye field discharge before saccades.

Visual neurons respond to visual stimuli, and half of these neurons respond more vigorously to stimuli that are the targets of saccades (Figure 35–13A). Activity in these cells is not enhanced when an animal responds to the stimulus without making a saccade to it. Likewise, these cells are not activated before saccades that are made without visual targets; monkeys can be trained to make saccades of a specific direction and amplitude in total darkness.

Movement-related neurons fire before and during saccades to their movement fields. Unlike the movement-related cells in the superior colliculus, which fire before all saccades, movement-related neurons of the frontal eye field fire only before saccades that are relevant to the monkey's behavior (Figure 35–13B). These neurons, especially those whose receptive fields lie in the visual periphery, project more strongly to the superior colliculus than do the visual neurons.

Visuomovement neurons have both visual and movement-related activity and discharge most strongly before visually guided saccades. Electrical stimulation of the frontal eye field evokes saccades to the movement fields of the stimulated cells. Bilateral stimulation of the frontal eye field evokes vertical saccades.

Movement-related neurons in frontal eye field control the superior colliculus through two pathways. They excite the superior colliculus directly and they release it from the inhibitory influence of the substantia nigra by exciting the caudate nucleus, which in turn inhibits the nigra (Figure 35–9A). The frontal eye field also projects to the pontine and mesencephalic reticular formations, although not directly to the burst cells.

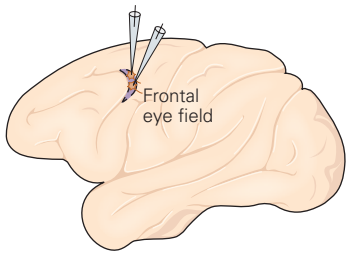
Two other cortical regions besides LIP that have inputs to the frontal eye field are thought to be important in the cognitive aspects of saccades. The supplementary eye field at the most rostral part of the supplementary motor area contains neurons that encode spatial information other than the direction of the desired eye movement. For example, a neuron in the left supplementary eye field that ordinarily fires before rightward eye movements will fire before a leftward saccade if that saccade is to the right side of the target. The dorsolateral prefrontal cortex has neurons that discharge when a monkey makes a saccade to a remembered target. The activity commences with the appearance of the stimulus and continues throughout the interval during which the monkey must remember the location of the target.

We can now understand the effects of lesions of these regions on the generation of saccades. Lesions of the superior colliculus in monkeys produce only transient damage to the saccade system because the projection from the frontal eye field to the brain stem remains intact. Animals can likewise recover from cortical lesions if the superior colliculus is intact. However, when both the frontal eye field and the colliculus are damaged, the ability to make saccades is permanently compromised. The predominant effect of a parietal lesion is an attentional deficit. After recovery, however, the system can function normally because the frontal eye field signals are sufficient to suppress the substantia nigra and stimulate the colliculus.

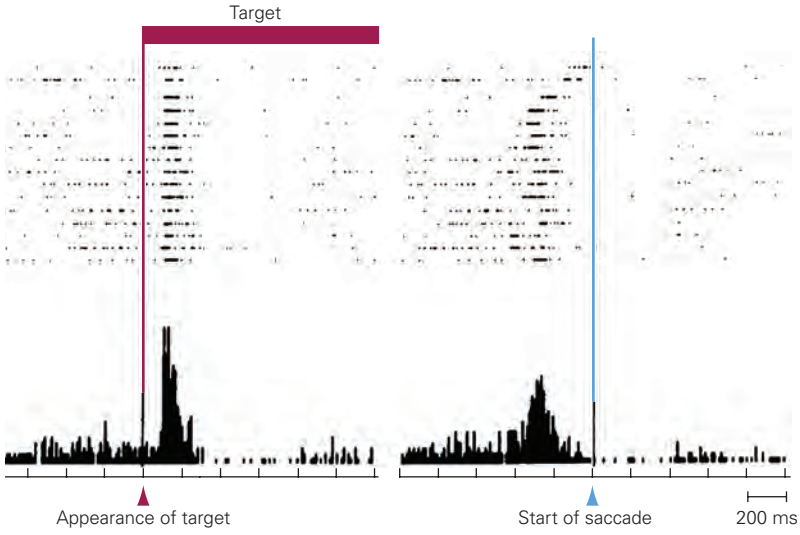
Damage to the frontal eye field alone causes more subtle deficits. Lesions of the frontal eye field in monkeys cause transient contralateral neglect and paresis of contraversive gaze, which recover rapidly. The latter deficit may reflect the loss of frontal eye field control of the substantia nigra; this loss of control means that the constant inhibitory input from the substantia nigra to the colliculus does not get suppressed, and the colliculus is unable to generate any saccades. Eventually the system adapts, and the colliculus responds to the remaining parietal signal. After recovery, the animals have no trouble producing saccades to targets in the visual field but have great difficulty with memory-guided saccades. Bilateral lesions of both the frontal eye fields and the superior colliculus render monkeys unable to make saccades at all.

Humans with lesions of the frontal cortex have difficulty suppressing unwanted saccades to attended stimuli. This is easily shown by asking subjects to make an eye movement away from a stimulus, the "anti-saccades task." For example, if a stimulus appears on the left, the subject should make a saccade of the same size to the right. To do this, the subject must attend to the stimulus, without turning the eyes toward it, and use its location to calculate the desired saccade to the opposite direction. Patients with frontal lesions have great difficulty suppressing the unwanted saccade to the stimulus.

As we have seen, neurons in the lateral intraparietal area of monkeys are active when the animal attends to a visual stimulus whether or not the animal makes a saccade to the stimulus. In the absence of frontal eye field signals, this undifferentiated signal is the only one to reach the superior colliculus. In humans, the failure to suppress a saccade is therefore to be expected



A Visual neuron responds to the stimulus and not to movement



B Movement-related neuron responds before movement but not to stimulus

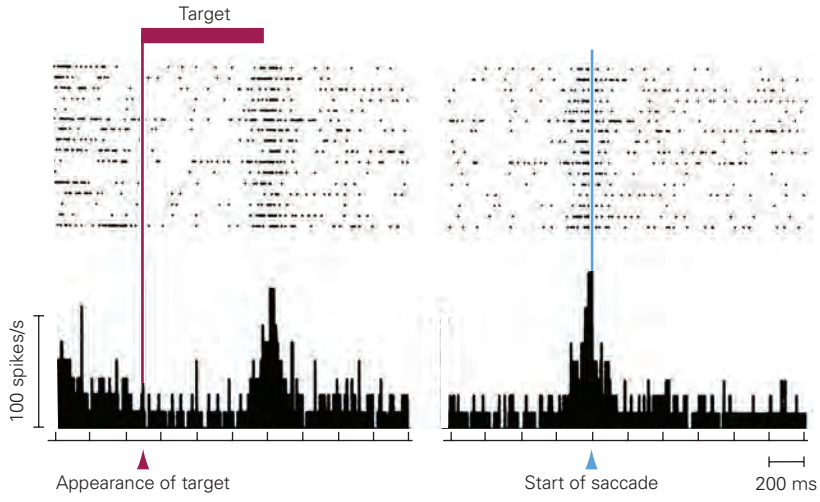


Figure 35–13 Visual and movement-related neurons in the frontal eye field. (Reproduced, with permission, from Bruce and Goldberg 1985.)

A. Activity of a visual neuron in the frontal eye field as a monkey makes a saccade to a target in its visual field. Raster plots of activity in successive trials of the same task are summed to form the histogram below. In the record on the left, the individual trials are aligned at the appearance of the stimulus. A burst of firing is closely time-locked to the stimulus. In the record on the right, the trials are aligned at the beginning of the saccade. Activity is not well aligned with the beginning of the saccade and stops before the saccade itself commences.

B. Activity of a movement-related neuron in the frontal eye field. The records of each trial are aligned as in part **A**. The cell does not respond to appearance of the saccade target (*left*) but is active at the time of the saccade (*right*).