Visuomotor Integration

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Abstract

The term "Visuomotor Integration" refers to the computations preformed by the brain that underlie the visual control of movements. Over the past 50 years, neurophysiological studies performed in alert animals have provided considerable insight into the actual mechanisms responsible for Visuomotor Integration. In particular, to date, we have a particularly refined understanding of the neural control and pathways that govern eye movements. Notably, pioneering studies have provided key insights regarding how the activities of small clusters of neurons effectively shape the motor commands required to produce accurate

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eye movement. As a result, our understanding of the brainstem mechanisms that underlie the premotor and motor control of eye movements is now remarkably precise. In turn, this strong foundation has proven to an advantage for neuroscientists in search of improving our understanding of the neural encoding of higher-level processes that link sensation and action, such as attention, perception, and decision-making. As a result, investigators have most recently taken on fundamental questions such as: (1) How does the brain accumulate information to arrive at the decision to make an eye movement? (2) How does the brain strikes a balance between optimizing behavioral accuracy and currently available rewards when making eye movements? (3) What is the linkage between the specific deficits observed in patients and deficits in the underlying neural circuits that control eye movements?

Keywords

Attention · Behavior · Binocular · Brainstem · Calibration · Cerebellum · Circuit · Cognitive · Compensation · Conjugate · Decision · Disconjugate · Disparity · Extraocular · Extra-retinal · Extrastriate · Eye · Fovea · Frontal cortex · Gaze · Learning · Midbrain · Motoneuron · Motor · Movement · Multimodal · Multisensory · Muscle · Neuron · Oculomotor · OKN · Optokinetic · Orbital · Parietal cortex · Perception · Plasticity · Premotor · Pursuit · Reflex · Retina · Saccade · Salience · Sensory · Subcortical · Superior colliculus · Transformation · Vergence · Vestibular · Vestibulo-ocular · Visual · Visuomotor · VOR

Introduction

The oculomotor system is unique among motor control systems in that we know many details of the circuitry underlying the generation of eye movements and can measure them with a high degree of accuracy. One key advantage relates to the oculomotor plant itself – specifically, the eye, the extraocular muscles, and the surrounding orbital tissue. In particular, the eye differs from the limbs and body in that there are no joints in the system, there is no stretch reflex involving the eye muscles, and the eyeball has little inertia. In addition, during eye movements, the activity in antagonistic muscles is correlated in a reciprocal manner. For instance, to make a horizontal eye movement to look to the right, the lateral rectus muscle of the right eye contracts, while the medial rectus muscle of the same eye relaxes.

As a result of the combination of these simplifying features, the relationship between motoneuron discharge and eye movements is relatively simple. This fact has, in turn, facilitated the analysis of the central premotor circuitry involved in generating the relatively small number of stereotyped oculomotor behaviors. This chapter will first consider the findings of this original ground-laying work in relation to the specific pathways that have been identified to control the six classes of eye movements. The extensive body of knowledge available regarding the premotor and motor neural control of eye movements has, in turn, contributed to our understanding

of the neural control of higher order processes. Notably, the visuomotor integration required to produce eye movements has provided essential insight into the neural computations underlying higher brain functions such as attention, perception, and decision-making. Accordingly, we will next consider recent progress in these areas of active research. Finally, the oculomotor system continues to serve as an important model system for testing new concepts and techniques related to sensorimotor control. New approaches combining behavioral, imaging, cellular, molecular, and genetic techniques are now being used in conjunction with anatomical, theoretical, and electrophysiological approaches to better understand the workings of this system. Thus, the chapter will end with a discussion of several salient topics including: the integration and coordination of oculomotor subsystems during everyday life, the function and mechanical constraints produced by extraocular muscle pulleys on eye movements, and the neurobiology of ocular motility disorders.

What Does the Brain Need to Tell the Muscles to Make Accurate Eye Movements?

Overview and Classification of Eye Movement Types

A principal function of eye movements is to move the fovea, or visual axis of gaze, so that it is placed on and subsequently kept aligned with an object of interest in the visual field. The fovea is the small central portion of the retina where an especially high receptor density provides the fine resolution that is responsible for sharp central vision. Among mammals, it is found only in simian primates and humans, corresponding to approximately 1° of the visual field in the latter.

In the early 1900s, Raymond Dodge first described the five different classes of eye movements that are used to redirect or stabilize the visual axis of gaze (Dodge 1903). Of these, three classes, (i) saccades, (ii) smooth pursuit, and (iii) vergence eye movements, are voluntary eye movements, which are made to direct the visual axis of gaze to a particular object in the visual field. First, saccades are rapid and discontinuous eye movements that we generate constantly during our daily life. We make saccades whenever we are reading, scanning our visual environment, or even viewing a static visual image. For example, when viewing the image illustrated in Fig. 1, saccades are mainly directed toward the salient features of the face such as the eyes and mouth. Smooth eye movements are made to track a small moving target so that its image falls on the fovea and can be viewed with the greatest accuracy. It is not possible to initiate smooth pursuit eye movements in the absence of a moving target (i.e., with the eyes closed, in the dark, or when viewing a stationary visual scene). Even though a moving target is needed to start a pursuit eye movement, the act is voluntary, since the subject can choose whether or not to track the target. Vergence eye movements function to move the two eyes through different angles so that they can converge on near or far targets. Any time we rapidly reorient our eyes between targets located at different eccentricities and depths, vergence and saccadic subsystems work together to accurately control binocular viewing.

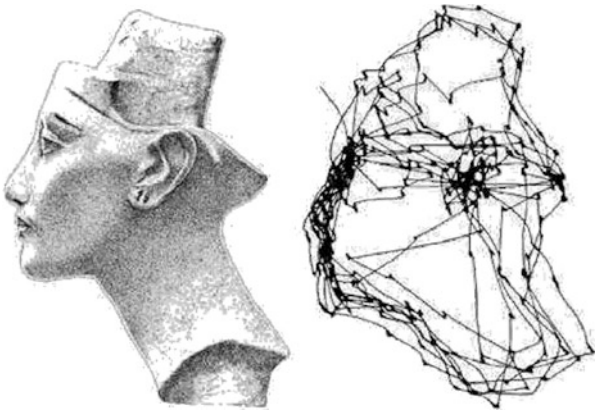

Fig. 1 Over 50 years ago, Alfred Yarbus showed that the pattern of an observer's eye movements depend on the saliency of the features in the visual scene. Here, the eye movements of the observer are traced (dark lines) while viewing a bust of Nefertiti. Eye movements are directed to particularly salient features, such as the nose, mouth, and eyes. The rapid eye movements between the various fixation points are known as saccades

The remaining two classes of eye movements, the (iv) vestibulo-ocular (VOR) and (v) optokinetic (OKR) reflexes function to hold images stationary on the retina. These reflexive eye movements work in concert to move the eye in the opposite direction of head motion during our daily activities. They are of critical importance, since image movement across the retina can seriously impair visual acuity. The optokinetic system is driven by the relative motion of the visual world across the retina (retinal slip) that occurs when the head moves. It complements the VOR in order to stabilize vision, for example, when very low frequency head movements are used to scan a visual scene.

Ocular Structure and Its Functional Implications

The Extraocular Eye Muscles and Motoneurons In everyday life, it is essential that the brain precisely moves our eyes so that each fovea is aimed at the same point in space. The movement of each eye is controlled by six extraocular muscles, which together generate the net force required to rotate the eye to a new position. Accordingly, eye position is conventionally described in terms of the angle (in degrees) that the eye has rotated, and eye velocity is described in terms of the angle (in degrees) that the eye has rotated per second (deg/s).

As shown in Fig. 2a, the six extraocular muscles that control the rotation of each eye are arranged in three antagonistic pairs. First, the lateral and medial recti muscles control horizontal movements (i.e., the temporal-nasal rotation of each eye, respectively). Second, the superior and inferior recti muscles predominantly control

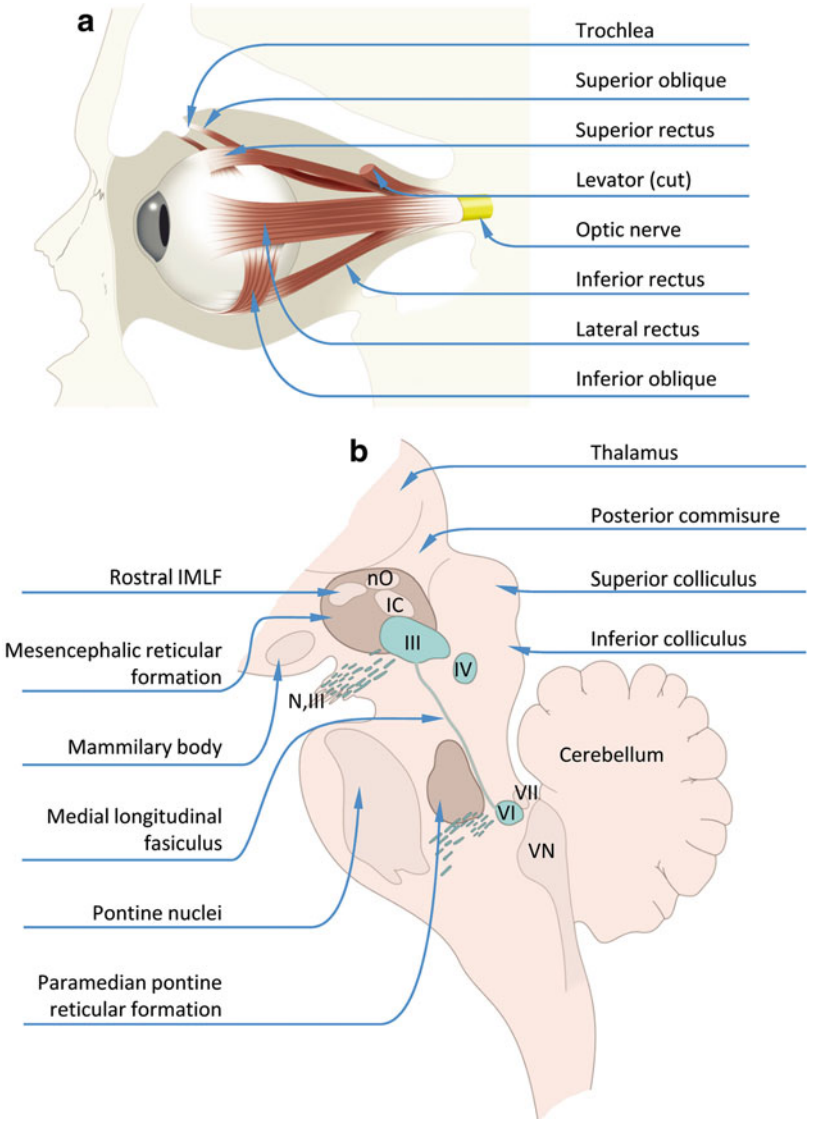

Fig. 2 (**a**) A lateral view of the left eye showing the global insertions of the extraocular motoneurons. Note that the orbital wall has been removed. Each of the four recti muscles (left, right, superior, and inferior) insert anterior to the equator of the globe. Contraction of these muscles rotates the cornea in the direction of the activated muscle. In contrast, the two oblique muscles (superior and inferior) insert posterior to the equator. Contraction of these muscles rotates the cornea clockwise and counterclockwise (as viewed from the subject) as well as vertically. Also shown is the trochlea through which the superior oblique runs through before inserting into the globe. (**b**) The motor and premotor oculomotor nuclei are shown in a parasagittal slice through the cerebellum, midbrain, pons, and thalamus of a rhesus monkey brain. The abducens nucleus (VI) and its nerve are located in the pons directly caudal to the paramedian pontine reticular formation.

vertical movements (i.e., the up-down rotation of each eye, respectively). Third, the superior and inferior oblique muscles control the torsional rotation of the eye, as well as its elevation. Thus, together, our three pairs of extraocular muscles allow the eye to rotate with three degrees of freedom (Fig. 3). A particularly unique feature of extraocular muscle is that it is comprised of two distinct layers, a global layer and an orbital layer. These two layers contain fibers with different response properties (e.g., fatigability, fusion frequency, and contraction times). In comparison to the muscles of the skeletal system, extraocular muscles in both the global and orbital layers have relatively fast contraction times.

Each of the six extraocular muscles is driven by motoneurons in one of three cranial nerve nuclei (Fig. 2b), namely, the oculomotor (III) nucleus, abducens (VI) nucleus, and trochlear (IV) nucleus. Specifically, motoneurons in the oculomotor (III) nuclei drive the medial, superior, and inferior recti. Motoneurons in the trochlear (IV) nuclei drive the inferior and superior oblique muscles. And finally, motoneurons in the abducens (VI) nuclei drive the lateral recti. Importantly, both the oculomotor (III) and trochlear (IV) nuclei can be subdivided into specific anatomical regions each of which controls a distinct muscle. Thus, a given motoneuron within each of these three cranial nerve nuclei projects to only a single muscle. Additionally, some neurons within these three cranial nerve nuclei are not motoneurons but are internuclear neurons – neurons that send projections to control the antagonist muscle of the opposite eye. For example, motoneurons in the left abducens project to lateral rectus, while internuclear neurons in the left abducens project contralaterally to the motoneurons in the right oculomotor (III) nucleus. This arrangement provides a neural substrate to generate conjugate eye movements; movements in which both eyes move in the same direction.

Mechanics of the Oculomotor Plant When moving the eye to a new position, the extraocular muscles must generate an active force to overcome the passive restraining forces of the eye and its surrounding tissues. In 1964, David Robinson – a researcher at Johns Hopkins University in Baltimore – established the nature of the passive forces that the extraocular muscle must overcome. First, he showed that the mechanical properties of the eyeball and its orbital tissues are dominated by viscoelastic properties. Second, he made the surprising discovery that the inertia of the eyeball is negligible. Together, these two discoveries have proven to be central to our understanding of the neuronal control of eye movements.

To develop an intuition of the viscoelastic properties of the eye, consider first a pure elasticity – for example, the force produced by a spring (Fig. 4a). According to

Fig. 2 (continued) The oculomotor nucleus (III) and its nerve (N.III) are in the midbrain, adjacent to the mesencephalic reticular formation. Caudal to the oculomotor nucleus is the trochlear nucleus (IV). VN, vestibular nuclei; IC, interstitial nucleus of Cajal; nD, nucleus of Darkschewitz; rostral iMLF, rostral interstitial nucleus of the medial longitudinal fasciculus

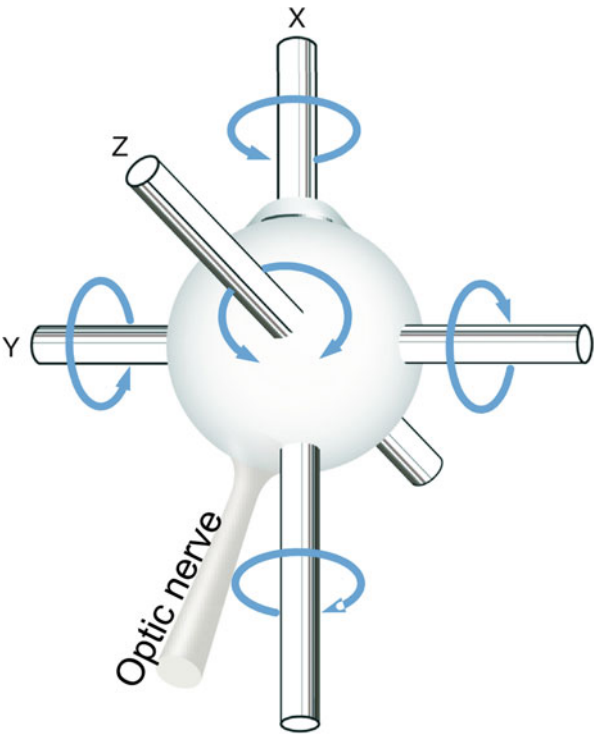

Fig. 3 A postero-superior view of the right eye shows the three axes of eye rotation. Rotation about the vertical "Z" axis, controlled by the lateral and medial recti muscles, results in eye movements to left or right. Rotation about the transverse "Y" axis, controlled by the superior and inferior recti muscles, elevates and depresses the eye. Finally, rotations about the anteroposterior "X" axis result in counterclockwise as well as upward and downward eye motion

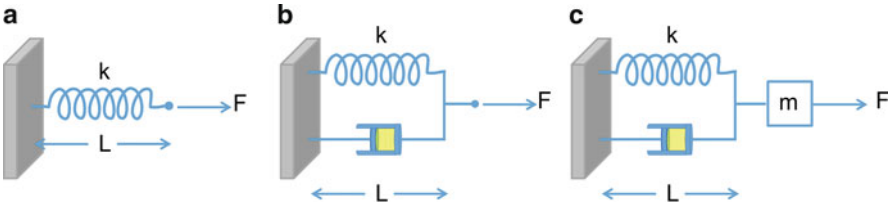

Fig. 4 Building blocks of a mechanical system representing the eye and its associated connective tissues. (**a**) A mechanical system with pure elasticity (Hooke's Law: F = kL). (**b**) Representation of a mechanical system with an elasticity and viscosity arranged in parallel. The net effect is a viscoelastic system that is described by the relationship: F = kL + r(dL/dt). (**c**) Representation of the same system when a mass (m) is added. Because the inertia of the eye does not significantly affect the system, the simple circuit in (**b**) provides an excellent description of the dynamics of the oculomotor plant

Hook's law, the force (F) required in order to stretch a spring of a stiffness k to a length L is described by the simple equation:

$$F = k * L$$

Next, to understand the meaning of "viscosity," consider the example of the standard hypodermic syringe. To make an injection, a doctor or nurse pushes on the piston of the syringe. In turn, the fluid within the syringe moves forward. Notably, if a constant force (F) is applied to the piston, it will move forward with a constant velocity which depends on the viscosity, r, of the fluid within the syringe. Specifically, the force (F) required to push the piston forward is described by the simple equation:

$$F = r * dL/dt$$

where the viscosity (r) represents the thickness of the fluid, and dL/dt the velocity of the piston/fluid motion. For instance, it would take more force to move honey through the syringe than water since honey has a considerably thicker consistency.

Because the mechanical properties of the eyeball and its orbital tissues are dominated by viscoelastic properties, this system can be described using a simple representation that incorporates both elasticity and viscosity (Fig. 4b). Accordingly, the force required to move the eye is described by the simple first-order differential equation:

$$F = kL + r(dL/dt) \quad (1)$$

As a result of its *elastic properties*, the eye's natural tendency is to "spring" back to its center position when moved right/left or up/down. Second, as a result of its *viscous properties*, more and more force is required in order to move the eye at faster and faster velocities.

As mentioned above, David Robinson made the second discovery that the inertia of the eyeball is negligible. This important fact greatly simplifies the force required to move the eye. If the inertia of the eye is significant, then the force produced by the extraocular muscles would also need to offset this force to move the eye. Specifically, according to Newton's Second Law, the net force $F - kL - r(dL/dt)$ acting on the mass equals the product of the mass times the acceleration, or m (dL2/dt2). Thus, the complete system (Fig. 4c) would be described by the second-order differential equation

$$F = kL + r(dL/dt) + m(d2L/dt2)$$

However, David Robison demonstrated that the addition of small weights to the eye had little influence on eye movement dynamics, indicating that the inertia of the eye does not significantly affect the system. Accordingly, the simple formulation in Eq. (1) provides an excellent description of the dynamics of the oculomotor plant.

How does mathematical formulation in Eq. (1) actually relate to the real eye and its surrounding tissues? The single values of k (spring stiffness) and r (viscosity) effectively represent the combined contributions of multiple physical elements, including the eye's suspensory ligaments, the conjunctiva, as well as the passive and active elements of the oculomotor muscles. Given the potential complexity of

the plant, it is remarkable how much of its mechanics are captured by a simple equation.

The Motor Control of Eye Movements

Relationship Between Motoneuron Activity and Eye Movement The relatively simple relationship between force and eye movement represented by Eq. (1) has proven to be advantageous for understanding the neural control of eye movements. This is because muscle force is strongly related to motoneuron discharge. Thus, in turn, the relationship between motoneuron discharge and eye movements is also relatively simple. This fact can be easily appreciated by comparing oculomotor motoneuron discharge with the eye movements it generates.

In the 1970s, neuroscientists began to make recordings from single motoneurons in the oculomotor nucleus of alert monkeys during steady fixation, smooth pursuit, VOR, and saccadic eye movements. The analysis of the firing rate of individual motoneurons demonstrated that the response of a given neuron was closely related to eye position and velocity across all classes of eye movements. The ability of motoneurons to encode position can be easily appreciated in Fig. 5, which shows the activity of a typical inferior rectus motoneuron. First, when the eye is centered in the orbit (i.e., position = 0), the neuron discharges at a constant firing rate (Fig. 5a). Next, consistent with the pulling direction of the inferior rectus, the neuron's firing rate increases to move the eye downward. On the other hand, its activity is inhibited when the eye looks upward. The sustained firing rate which is observed after the saccade once the eye has reached its target is proportional to eye position (in this case vertical). Accordingly, a given neuron's discharge can be described by the relationship

$$R = kE + R_0 \text{ (when } E' = 0) \tag{2a}$$

where R is the steady-state firing rate, E is eye position, and R_0 is the resting rate when the eyes are pointing straight ahead (E = 0). The specific relationship between discharge rate and eye position during fixation is shown in Fig. 5b. The actual values of eye position sensitivities (slope, k) and thresholds (the x-intercept, ET, when R = 0) vary across individual motoneurons.

The response of the same neuron is also modulated in response to eye velocity. This can be appreciated by recording the neuron's activity during vertical smooth pursuit eye movements (Fig. 6a), then comparing the neuronal responses as the eye moves at different velocities past the same orbital position (arrows). Although eye position is constant, neuronal firing rate is not. In fact, neuronal firing rate is proportional to eye velocity (Fig. 6b).

$$R = rE' + R_0 \text{ (when } E = 0) \tag{2b}$$

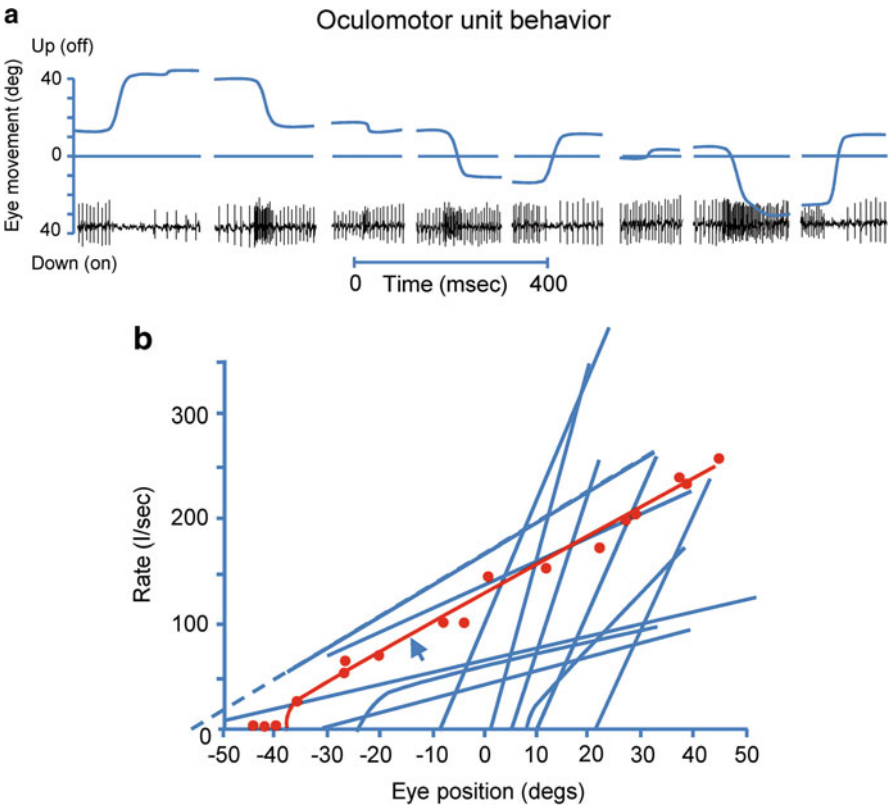

Fig. 5 (**a**) A typical inferior rectus extraocular motoneuron produces a burst of action potentials to drive downward saccadic eye movements. The neuron then fires at a steady tonic rate proportional to eye position after the saccade, producing the muscle tension required to offset the elasticity of the extraocular tissues and hold the eye steady in the orbit. Saccades in the opposite (upward) direction are accompanied by a silencing of discharge. Neuronal firing (lower traces) during vertical saccadic eye movements (upper traces) is shown. (**b**) During fixation, the firing rate of an individual motoneuron varies linearly as a function of eye position. Each blue line represents data from a different neuron

where r is the eye velocity sensitivity (slope of Fig. 6b) and E′ is the eye velocity. Thus, by combining Eqs. 2a and 2b, it becomes clear that a single first-order differential equation describes the relationship between motoneuron responses and eye movement:

$$R = kE + rE' + R_0, \tag{3}$$

Equation 3 describes the relationship between neuronal firing and eye movement across many conditions. For example, it can be used to describe eye movements during VOR and OKN as well as during fixation and pursuit. In this formulation, the

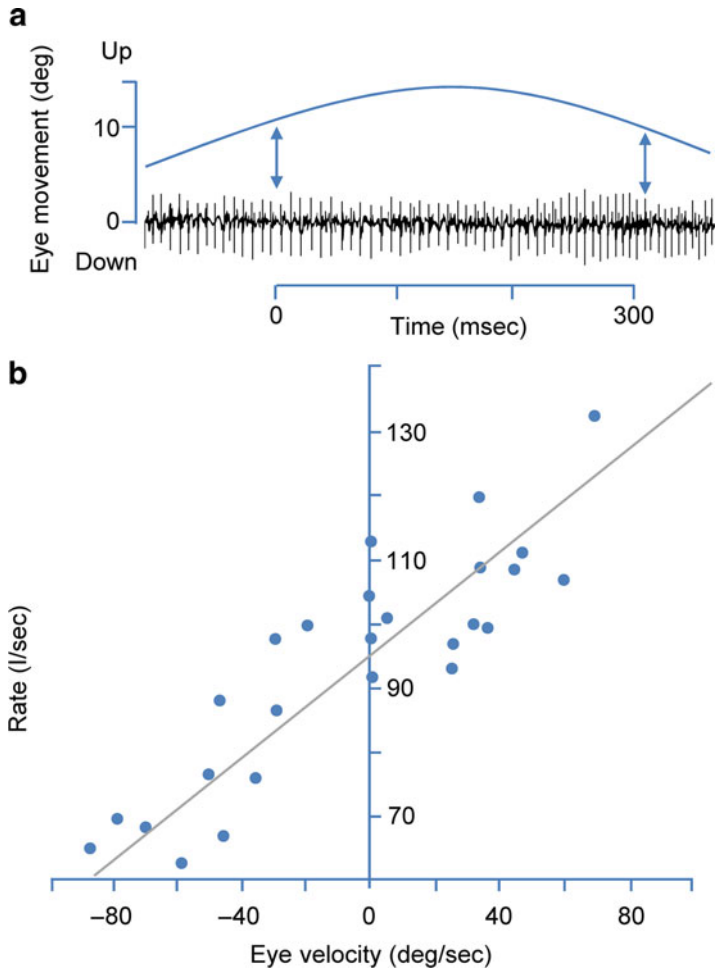

Fig. 6 (**a**) During smooth pursuit, motoneuron firing rate encodes eye velocity. Times at which the eye passed through the same orbital position at different velocities (in this case in opposite directions) are indicated by the two vertical arrows. (**b**) Motoneuronal firing rates as a function of eye velocity. The figure illustrates measurements made for the neuron in (**a**) as the eye crossed through the same position while moving at different velocities. (Modified from Robinson 1970)

resting rate R_0 can take on negative values. This occurs when E_T, the eye-position threshold (the value of E at zero discharge), is positive. To account explicitly for E_T, the relationship can be rewritten as

$$R = k(E - E_T) + rE'$$

The ratio r/k represents the time constant of the system. To see this, we can solve Eq. 3 for a step change in firing rate, ?R. The resulting eye position is

$$\Delta R = kE + rE' \tag{4}$$

Recall that the force required to move the eye is represented by Eq. (1) and is thus also described by a simple first-order differential equation. Accordingly, for a step change in force F, the solutions of Eqs. 1 and 4 will have the same form. The time constant of Eq. 1 can be directly measured by applying precise forces to the eye and measuring the resultant rotation. In particular, the simple first-order model in Eq. (1) predicts that, when an external force is removed, the eye's drift back to $E = 0$ should be a simple exponential that decays with a time constant r/k. This is illustrated in Fig. 7, where the slow exponential return has a time constant of ~250 ms.

Thus, the mechanical properties of the eyeball and its orbital tissues (i.e., Eq. 1) are dominated by a time constant near 250 ms, a value which is determined by its viscoelastic properties. Given that muscular force is proportional to motoneuron discharge rate, the dynamics of the plant and motoneuron discharge will be matched when their time constants are equal. Indeed, on average, the ratio (r/k) characterizing motoneuron discharges (i.e., in Eq. 4) well approximates the 250 ms time constant of the extraocular plant.

A Pulse-Step Command Drives Saccadic Eye Movements How do the motoneurons drive saccadic eye movements? Is a step change in firing rate sufficient to command a saccadic movement? The answer is no. While a step change in motoneuron discharge will produce a step change in force, the eye would still remain ~37% from its final position after ~250 ms as a result of the mechanical properties of the eyeball and its orbital tissues (i.e., Eq. 1). Put another way, the time constant of the eye movement would correspond to that illustrated in Fig. 7. In reality, however, accurate saccades can be made so that the eye is in its final position in less than

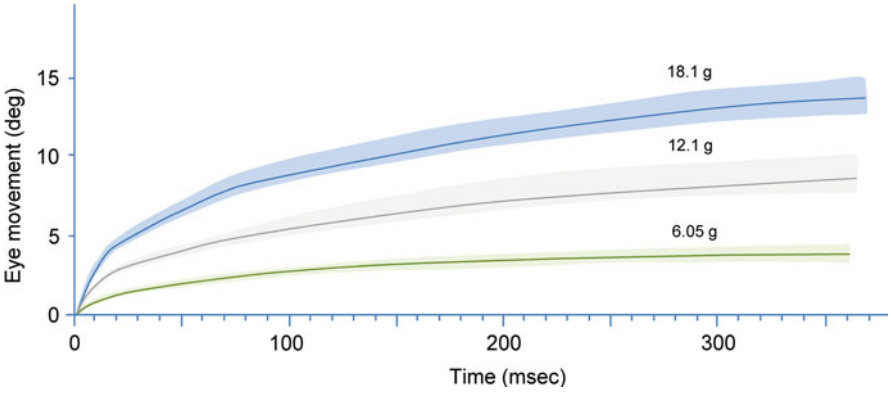

Fig. 7 To understand the mechanics of the oculomotor plant, weights were applied to the eye causing it to move to an eccentric position. The weights were then released, causing the eye to exponentially rotate back to center position with a time constant of 250 ms as predicted by the viscoelastic properties of the muscles and surrounding orbital tissues. Shaded areas denote the observed variability in movement trajectories. (Modified from Robinson 1964)

100 ms. This then implies that motoneurons do not generate a simple step command to produce saccades.

In order to generate saccades in this shorter time frame, motoneurons must generate a burst (or "pulse") of action potentials. This strategy is essential for overcoming the viscous drag of the eye in the orbit. These saccade-related bursts of firing can reach rates as high as 500 spikes/s. The neural circuitry responsible for generating this phasic activity pattern is well understood and is further discussed below. Once the eye then reaches its final position at the end of a saccade, it is then held stable by the tonic firing of the extraocular motoneuron which in turn produces a sustained contraction of the extraocular muscle. This tonic activity is represented by the position-dependent term in Eq. (4). The difference between a neuron's tonic discharge rate at the initial and new eye positions is referred to as the "step." Thus, to compensate for the dynamics of the eye and surrounding tissues, motoneurons send a pulse-step command signal to extraocular muscles to drive saccades (Fig. 8a). Notably, the dynamics of the plant and motoneuron discharges are well matched to ensure optimal control; their time constants are both ~250 ms.

Evidence for the extraocular motoneuronal step-pulse command can be found by recording extraocular muscle tension during saccades. Following initiation of the saccade, muscle tension rises to a peak and then decays to a steady-state level within 350 ms, with the peak tension proportional to the magnitude of the rotation of the eye relative to center position (Fig. 8b). In addition, the evidence for the step-pulse command can be found more directly by recording the activity of single motoneurons (Sylvestre and Cullen 1999). For example, note that the example inferior rectus motoneuron shown above in Fig. 5 produces a burst of spikes during downward saccades, and that it produces a tonic discharge so that the eye remains gazing downward and does not drift back to center. In contrast, the responses of motoneurons which project to the antagonist superior rectus muscle are inhibited during downward saccades in a manner comparable to that of the inferior rectus motoneuron during upward saccades.

Ocular Dynamics and the Premotor Control of Saccadic Eye Movements

Two distinct inputs to the extraocular motoneurons produce saccadic "pulse" and "step" commands that are required to compensate for the dynamics of the eye and surrounding tissues. First, neurons in the paramedian pontine reticular formation (PPRF) and mesencephalic reticular formation (MRF) provide the pulse command that is required to rapidly drive the eye to the new position (see also Fig. 2b). The PPRF receives upstream inputs from the contralateral superior colliculus and frontal eye fields. Neurons in this area of the reticular formation, saccadic burst neurons (BNs), discharge at a high frequency during horizontally directed saccades. BNs send direct projections to the motoneurons (MNs) of the oculomotor and abducens nuclei which drive the horizontal eye movements. Consistent with its role in

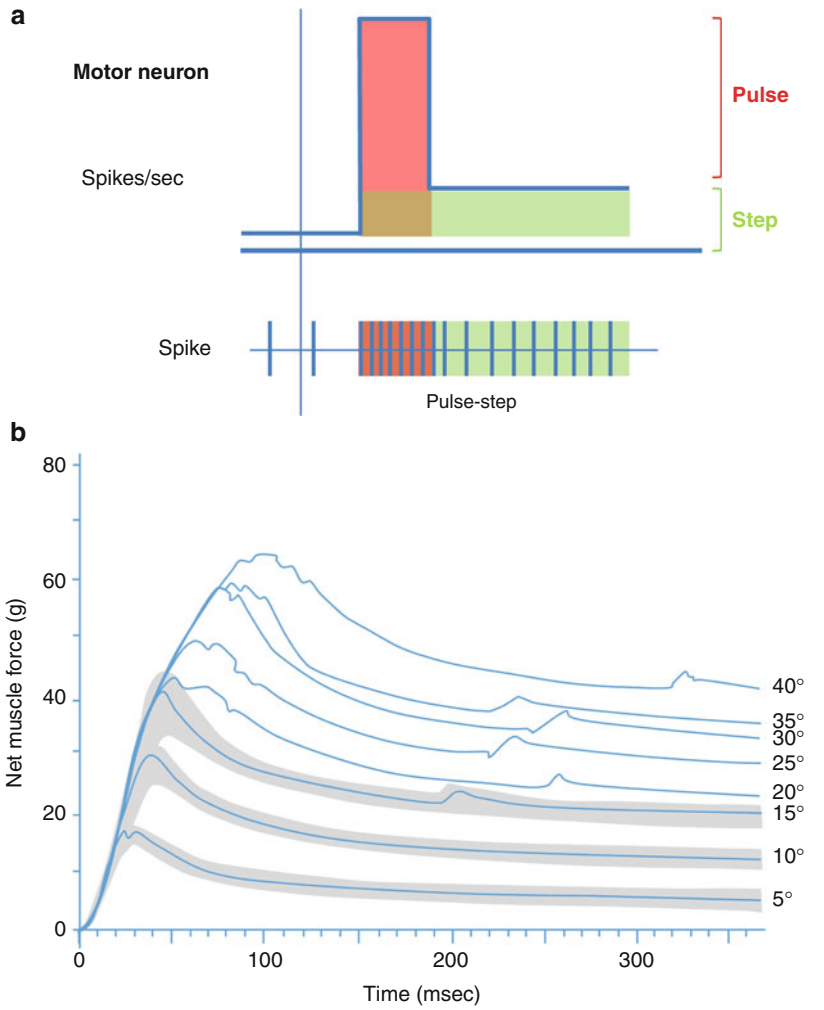

Fig. 8 (**a**) Schematic of the pulse step command generated by extraocular motoneurons to drive saccades. (**b**) Isometric muscle force measured when applying force to an occluded eye that was restrained using a suction contact lens. Motor commands were issued to the restrained eye by having the subject fixate different positions with the other, viewing eye. Muscle tension rapidly reaches a peak during the saccade and then declines more slowly to a steady level during fixation. The motoneuron burst discharge (i.e., the "pulse") underlies the transient increase in muscular tension that produces the high velocity achieved during a saccade. Following the saccade, sustained activity in the motoneurons (i.e., the "step") produces a tonic elevation in muscle force which, in turn, holds the eye steady at its new position. (Modified from Robinson 1964)

controlling horizontal saccades, lesions to the PPRF result in an inability to produce ipsilateral saccadic eye movements. The MRF is functionally analogous to the PPRF, with the notable exception of the premotor neurons of the MRF that send direct inputs to the motoneurons in the oculomotor and trochlear nuclei which control

vertical eye movements. Thus, together, premotor commands originating in the PPRF and MRF send direct projections to the extraocular motoneurons to provide the required "pulse" input for saccades in all directions.

Second, neurons in the nucleus prepositus (NPH) and medial vestibular nuclei (MVN) and in the interstitial nucleus of Cajal (INC) provide the step command that is required to hold the eye steady at its new position (see Fig. 2b). Premotor neurons in the nucleus prepositus (NPH) and medial vestibular nuclei (MVN) encode horizontal eye position information during fixation to produce the step command required after horizontal saccades. On the other hand, premotor neurons in the interstitial nucleus of Cajal (INC) provide the vertical eye position input required following vertical saccades. Notably, the eye position (i.e., step) signals encoded in the NPH/MVN and INC are computed by integrating (in the mathematical sense) the pulse signals produced by the PPRF and MRF (see Fig. 9). Because the "pulse" signal is largely proportional to the velocity of the eye, its integration produces the necessary eye position (or equivalently "step") command. It should be noted that the neuronal integration of the pulse command by neurons in the NPH/MVN and INC is imperfect. As a result, following saccades the eyes gradually drift back to center position with a time constant of ~25 s. Moreover, consistent with the role of NPH/MVN or INC in producing the step command, lesions to these areas produce more rapid post-saccadic drift back to center position in the expected directions. Figure 10 shows the effect of a kainate acid lesion in the NPH/MVN on horizontal versus vertical eye movements. Note the inability to sustain horizontal gaze position following a saccade.

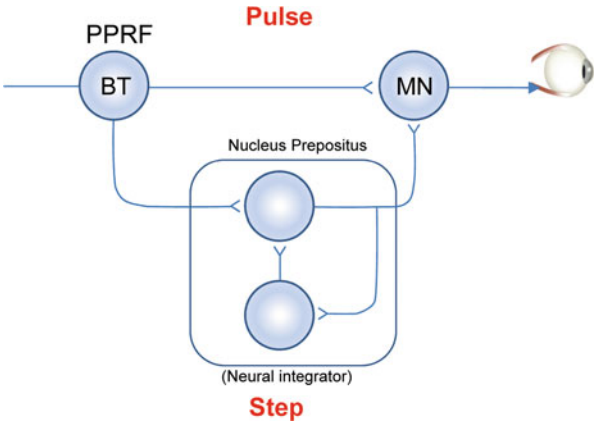

Fig. 9 A circuit model of horizontal saccade generation. The discharges of burst neurons in the paramedian pontine reticular formation (PPRF) directly drive the extraocular motoneurons (MN) to produce the "pulse" component of the saccadic command. In addition, burst neurons project to the neural integrator (NI) of the nucleus prepositus thus providing the "step" component of the saccadic command. The sustained firing of neurons in the NI is achieved through positive feedback of recurrent connections between neurons within the same nucleus (shaded box labeled "Neural Integrator")

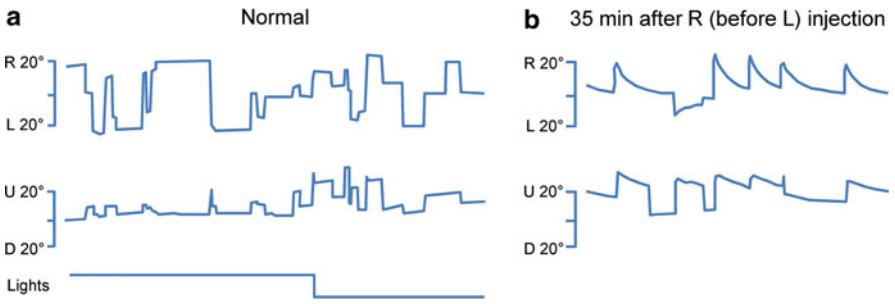

Fig. 10 (**a**) Target-directed and spontaneous saccades recorded from a normal monkey. In the first half of the recording, the monkey fixated a target located either 20° to the right or left. In the second half of the recording, the lights were turned off and spontaneous eye movements were recorded. Note that horizontal gaze holding was steady even in total darkness. (**b**) Spontaneous saccades recorded in total darkness from the same monkey as in (**a**) at various times following a lesion of the medial vestibular and prepositus hypoglossi nuclei, an area hypothesized to be the locus of the neural integrator for horizontal eye movement commands. (Modified from Cannon and Robinson 1987)

All models of the oculomotor neural integrator employ a system of reverberating collaterals in order to perform the neural integration of the pulse input from the BNs of the PPRF and INC (Fig. 9: note feedback within the nucleus prepositus). Single-unit recordings performed from neurons in the integrators (i.e., NPH/MVN and MRF) demonstrate that the integration takes place gradually. In particular, the eye movement sensitivities of single neurons vary from encoding pure velocity commands, to various combinations of velocity and position commands, to pure position commands. Further, recent experiments that recorded from multiple single units simultaneously found synchrony between pairs of NHP neurons, which varies as a function of eye position during ocular fixations and as a function of distance between neurons (Dale and Cullen 2015). Importantly, neighboring neurons exhibit unexpected levels of positive synchrony, which is maximal during contralateral fixations and weakest when neurons are located far apart from one another (>300 μm). Consequently, to accommodate neuronal data, current models of the neural integrator now incorporate a network comprised of several layers of cells.

The Motor Control of Conjugate Versus Disconjugate (i.e.,Vergence) Eye Movements

Eye movements are often conjugate, meaning that both eyes move together in the same direction and at the same speed. In fact, vertical eye movements are always conjugate. Horizontal eye movements can be disconjugate when vergence eye movements are made in order to focus on a near object. There is an important pathway from the abducens nucleus to the oculomotor nucleus which mediates horizontal conjugate eye movements (Fig. 11). Internuclear neurons (interneurons) in the abducens nucleus carry a copy of the signals which are generated by the

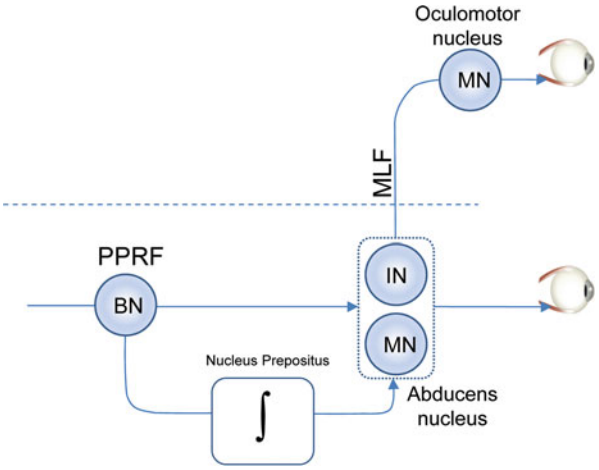

Fig. 11 The premotor pathway for controlling conjugate eye movements. There are two types of neurons in the abducens nucleus: (1) motoneurons which project to the lateral rectus and (2) internuclear neurons which carry the same pulse-step command but project to medial rectus motoneurons (within the oculomotor nucleus) that project to the contralateral eye. Accordingly, the internuclear pathway allows the activity in the medial rectus muscle of one eye to be identical to that of the lateral rectus muscle in the other. A reciprocal pathway in which internuclear neurons within the oculomotor nucleus project to the abducens motoneurons of the contralateral eye also exists but is not shown for simplicity

abducens motoneurons (except vergence signals) to contralateral medial rectus neurons. This pathway allows the activity in the medial rectus muscle of one eye to be identical to that of the lateral rectus muscle in the other. This way, the two eyes move together in the horizontal plane, except during vergence eye movements. The axons of internuclear neurons course rostrally via a fiber bundle called the medial longitudinal fasciculus to the oculomotor nucleus. Bilateral lesions to this pathway result in a clinical syndrome called anterior internuclear ophthalmoplegia. Persons with these lesions are incapable of moving either eye medially, except during convergent eye movements.

When both eyes move the same amount (i.e., during conjugate eye movements), the relationship between the activity of extraocular motoneuron and the motion of the eye it controls is not determined by the specific type of eye movement that is produced. Instead, neuronal responses are related to the position and velocity of the eye. For this reason, the extraocular motoneurons constitute a final common path for conjugate eye movements. For each class of eye movement, different premotor inputs to the motoneurons shape the commands to compensate for the mechanics of the eye plant. For example, the semicircular canals of the vestibular system are stimulated by head acceleration (i.e., the second derivative of head position). Accordingly, a main function of the angular VOR premotor pathway is to produce the eye position drive required to keep gaze stable. As a result, this transformation requires integrating head acceleration twice. The first integration is immediately

performed as a result of the mechanical properties of the semicircular canals; the discharge rates of vestibular afferents and vestibular nuclei neurons are proportional to head velocity. At higher frequencies of rotation, the dynamics of the eye and surrounding tissue perform the second integration. However, orbital mechanics are not capable of performing the second integration at frequencies below ½ Hz. Thus, in this frequency range, the second integration is performed by neurons in the nucleus prepositus, medial vestibular nuclei, and nucleus of Cajal; the same neurons which function also function as a "neural integrator" for saccadic eye movements.

Finally, it is important to note that the relationship between the activity of a given extraocular motoneuron and the eye motion can differ for vergence versus conjugate eye movements. As a result, extraocular motoneurons do not serve as the final common path when considering vergence eye movements. This is because extraocular motoneurons which project to the singularly versus multiply innervated eye muscle fibers receive a different weighting of premotor inputs. Notably, motoneurons that project to multiply innervated fibers receive relatively larger upstream inputs from regions that have been implicated in vergence eye movements. As a result, a differential motoneuron input to specific classes of muscle fibers specifically shapes the final motor command to control vergence eye movements.

How Does the Brain Control the Five Classes of Eye Movements?

Gaze Redirection: Saccades and Gaze Shifts

The term "saccade" is derived from the French word for twitch; saccades last for only a fraction of a second and can reach speeds of up to 900 deg/s (left panel; Fig. 12a). Saccades are under voluntary control and can be made in the dark or with the eyes closed. During our everyday life, we make saccades constantly to rapidly direct gaze to a specific target of interest in our visual space, and these movements are among the most accurate movements that we can produce. Visually-directed saccades have finite latencies such that the commanded eye movement lags behind the presentation of the visual target by $>$150 ms.

The Superior Colliculus Controls Both the Amplitude and Direction of Saccades and Gaze Shifts It has long been appreciated that the superior colliculus (SC), a bilateral structure located on the roof of the midbrain, plays an especially important role in visuo-oculomotor integration required for controlling saccades. The SC effectively serves as a hub that integrates input from multiple cortical areas. In particular, the deep and intermediate layers of the superior colliculus receive inputs from the frontal eye fields and posterior parietal cortex, and from the basal ganglia. Cells in these deeper SC layers are arranged in a functional "motor map," organized with reference to the amplitude and direction of the eye movement that must be made to bring an object of interest onto the fovea (discussed in more detail in the next section). These cells send direct contralateral projections to three main areas of the brainstem that form the circuit responsible for the premotor control of saccades and

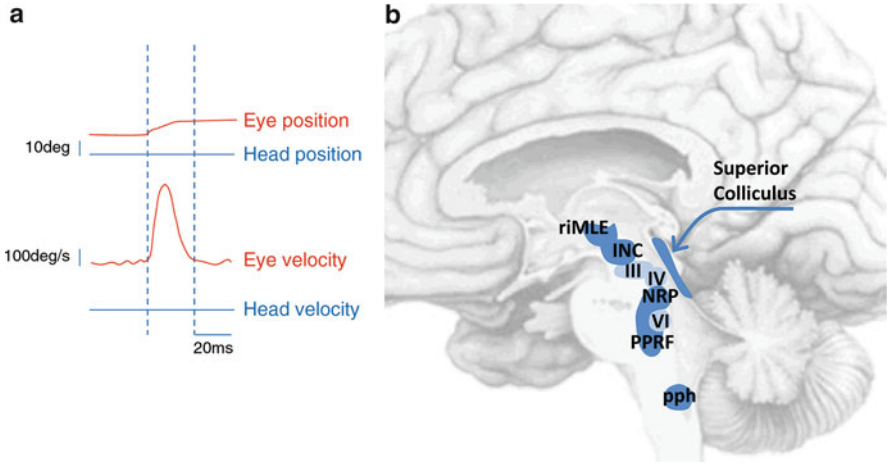

Fig. 12 (**a**) Saccadic eye movements are produced voluntarily and can reach speeds of up to 900 deg/s (left). (**b**) The premotor pathway for producing saccades. Command signals, issued in the deep layers of the superior colliculus, are delivered to burst neurons (BNs) in the paramedian pontine reticular formation (PPRF). The cortical inputs to the superior colliculus are not shown

are collectively called the brainstem saccadic burst generator (Fig. 12b), namely: (1) The paramedian pontine reticular formation (PPRF) which contains the burst neurons (BNs) that drive horizontally directed saccadic eye motion via their direct projections to the motoneurons (MNs) to control horizontal eye movements (lesions of the SC and PPRF produce paralysis of contralateral and ipsilateral saccadic eye movements, respectively); (2) The mesencephalic reticular formation which is functionally similar to the paramedian pontine reticular formation, except that the premotor BNs in the riMLF drive saccadic eye motion via their direct projections to the motoneurons to control vertical and torsional motion; (3) The nucleus raphe pontis which contains omnipause neurons (OPNs) that pause for saccades made in all directions. Projections from neurons in this nucleus prevent saccadic eye movements by inhibiting the saccadic burst neurons in the PPRF and in the mesencephalic reticular formation. The connections between these neurons in the premotor saccadic circuitry as well as examples of their discharges are shown in Fig. 13.

The Superior Colliculus Is Organized as a Motor Map Stimulation studies have shown that the superior colliculus is organized as a motor map (Fig. 14). The main features of this motor map are: (1) It can be described by a series of iso-amplitude lines which run medial-laterally (Fig. 14a), and a series of iso-direction lines that run rostral-caudally (Fig. 14b). For example, stimulation of increasingly caudal sites will produce larger and larger saccades, (2) SC stimulation produces eye movements for which the horizontal component is in the contralateral direction, and (3) The amplitude and direction of the resulting saccade does not depend on initial eye position (Fig. 14 inset). In addition, single-unit recording experiments have indicated that the tuning of a given neuron to saccade direction and amplitude (i.e., the neuron's

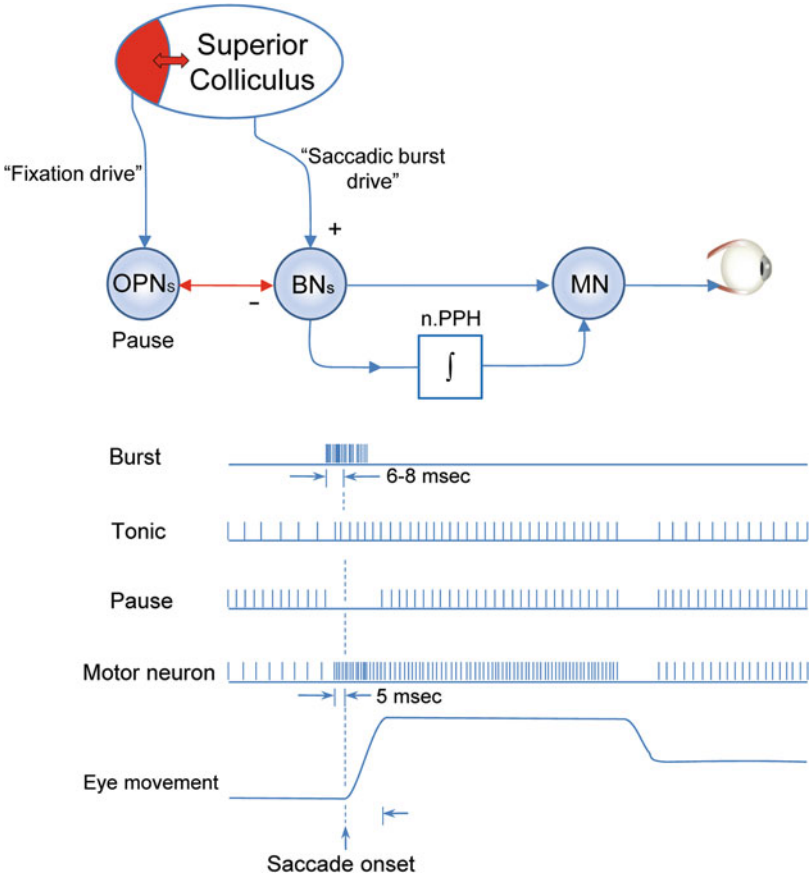

Fig. 13 To initiate a saccade, an excitatory input signal from the caudal superior colliculus drives burst neurons (BNs) in the paramedian pontine reticular formation (PPRF). BNs then drive motoneurons (MNs) directly and via the prepositus (n.PPH). The caudal superior colliculus and BNs also send inhibitory projections to the rostral superior colliculus and omnipause neurons (OPN), respectively, to inhibit fixation. Burst neuron activity shuts off when eye is on target (i.e., when target position – eye position = 0) and the saccade ends

"movement field") corresponds well to its location on the motor map that was initially determined via stimulation studies.

The discovery of the SC motor map led to the question: What are the motor coordinates of this map? When the SC is stimulated with the subject's head restrained, it appears to provide an organized mapping of saccade amplitude and direction. However, stimulation of the more caudal regions of the SC in many species (monkey, cat and especially barn owl) produces rapid head as well as eye movements. Two example eye-head movements produced by stimulating the caudal superior colliculus are shown in Fig. 15. These results led to the discovery that the

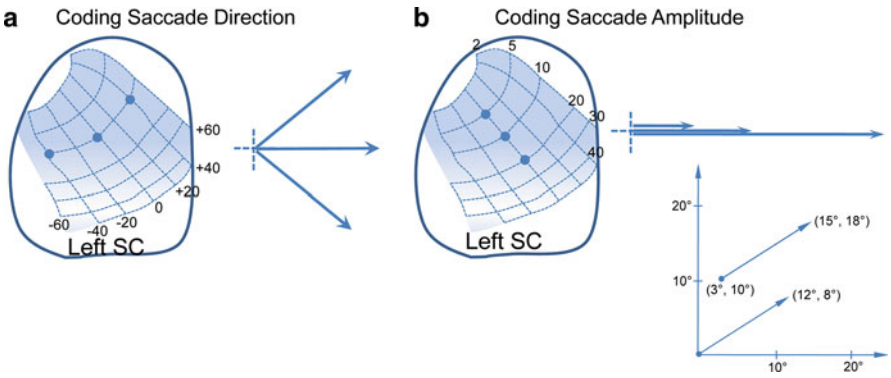

Fig. 14 The superior colliculus arranged topographically as a motor map on which the vector (direction (**a**) and amplitude (**b**)) of the coded movement varies systematically and continuously with location

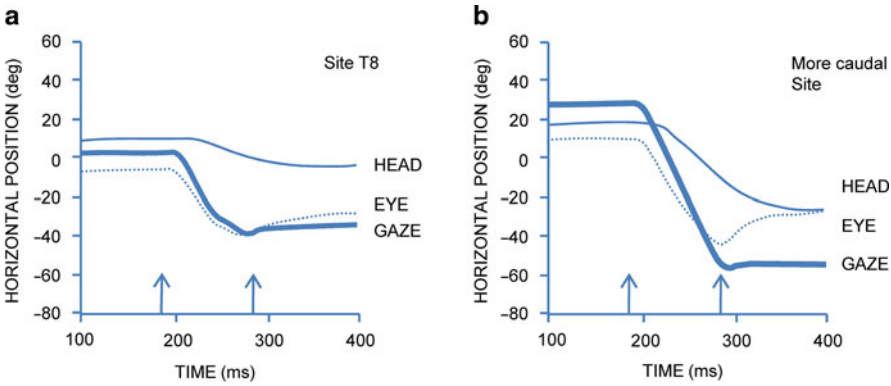

Fig. 15 Stimulation-induced movements evoked at two different collicular sites. A more caudal site was stimulated in **(b)** compared to **(a)**. Horizontal gaze, head, and eye positions are shown. Left vertical arrow indicates stimulation onset; right vertical arrow indicates stimulation offset. In all panels, gaze traces are shown in bold. (Modified from Freedman et al. 1996)

map of the superior colliculus is a motor map that actually controls total *gaze displacement* (where gaze-in-space = eye-in-head and head-in-space). Indeed, in addition to its projections to areas involved in the premotor control of saccadic eye movements, the SC sends projections to neurons in the medullary reticular formation that project to the cervical spinal cord. This shared control of eye and head movement pathways facilitates the accurate realignment of the axis of visual gaze via rapid, coordinated eye-head gaze shifts.

Single-Unit Recording Experiments Have Also Been Used to Understand What Information Is Encoded by the Neurons in the Superior Colliculus Do the neurons discharge as a result of (1) the appearance of a target at a particular location

on the retinal map or, alternatively, (2) the generation of a saccadic eye movement of a particular amplitude? The answer to this question was addressed in a pioneering study performed by David Sparks and his co-workers who used an ingenious behavioral paradigm called the "double-step saccade paradigm" to differentiate between a neuron's sensory and motor responses (Mays and Sparks 1980). The logic of the paradigm (shown in Fig. 16) is as follows: In all trials, the animal initially fixates a target (O). In "single-saccade trials," a saccade is then made from target O to target B, or a saccade is made from target O to target A. In single-saccade trials, the neuron's firing does not change for O-B saccades (Fig. 16b) but does burst before

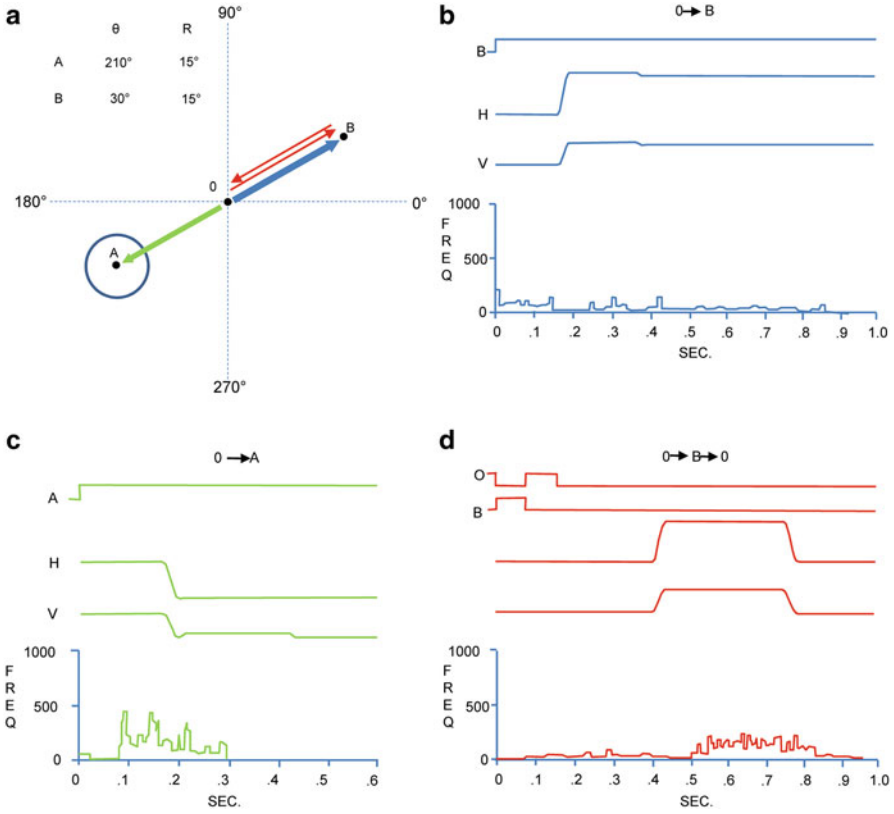

Fig. 16 Typical response of a superior colliculus cell on single- and double-saccade trials. (**a**) The example neuron's receptive field was centered about location A. (**b**, **c**) Target onset, horizontal and vertical eye position, and instantaneous spike frequency during single saccades made to targets B and A, respectively. Rightward eye movements are shown as upward deflections of the horizontal trace; upward movements, as upward deflections of the vertical trace. (**d**) Double-step trial in which a saccade was made from 0 to B, and then back to 0. Importantly, targets B and 0 were presented for durations that were so brief (80 ms) that all were off before the eye left the fixation point at 0. Note that the neuron fired a burst in panel D as well as C, because the direction and distance of the second saccade of the double-step task (**d**) and the saccade from the fixation target 0 to target A (**c**) were the same. (Modified from Sparks and Mays 1980)

O-A saccades (Fig. 16c). Then, to establish whether the presaccadic burst is a sensory or motor response, the same neuron is recorded during a "double-saccade trial" from target O to target B – and then back to target O (Fig. 16d). An important aspect of this experiment is that both targets disappear before the first saccade is made. Thus, a target never appeared on the retina at the point that would have corresponded to the location of target A in the single O-A saccade trial. Yet, for the double-step trial, the neuron discharges for the B-O saccade (which is of the same amplitude as the O-A saccade). Thus, the neuron's response is linked to the generation of a saccadic eye movement of a particular amplitude and not the appearance of a target at a particular location on the retinal map.

The Direction and Amplitude of a Saccadic Movement Is Read Out from a Population of Neurons If one only had access to the information encoded by a single SC neuron, there would be ambiguity in coding of both saccade amplitude and direction. For example, consider the neuron shown in Fig. 17. This neuron produces the same discharge for a 9° rightward saccade (i.e., vector F) as it does for a 22° oblique saccade (i.e., vector 6).

This result is typical of neurons in the intermediate and deep layers of the SC. Since each neuron is broadly tuned, the control of saccades cannot be understood by viewing only a single neuron. In reality, saccade trajectory is based on a "population average" of the firing of the entire active population of neurons. In the same way, arm movement direction is coded by the response of a population of neurons in the arm region of motor cortex. For this reason, simultaneous electrical stimulation at two different locations on the SC motor map produces a saccade with a vector which is the average of the saccade vectors that would have been produced by stimulation of each site independently. Similarly, inactivation of a specific region of the SC produces systematic errors in saccade direction and amplitude that corresponds to that expected from the population average. Recent studies have addressed the question: How does the brain calculate the population average of SC neuronal activity? The saccade vector choice made from a population of neurons is consistent with a probabilistic coding strategy underlying movement choice rather than a winner-takes-all (WTA) or population vector average.

Feedback Control Ensures the Accuracy of Saccades and Gaze Shifts Saccadic eye movements are among the most accurate voluntary eye movements that we make. How does the brain produce such fast yet accurate movements? A first guess might be that the location of the target relative to the eye could be used to provide feedback to tell the brain when the eye has reached its target; however, the latencies of the visual pathways are simply too long to be used to ensure accuracy. A minimum of 100 ms processing time occurs between the appearance of a visual stimulus and an eye movement response. In contrast, a saccade typically begins and ends within 100 ms. Accordingly, an internal estimate of current eye position (rather than target location) is employed to ensure saccade accuracy.

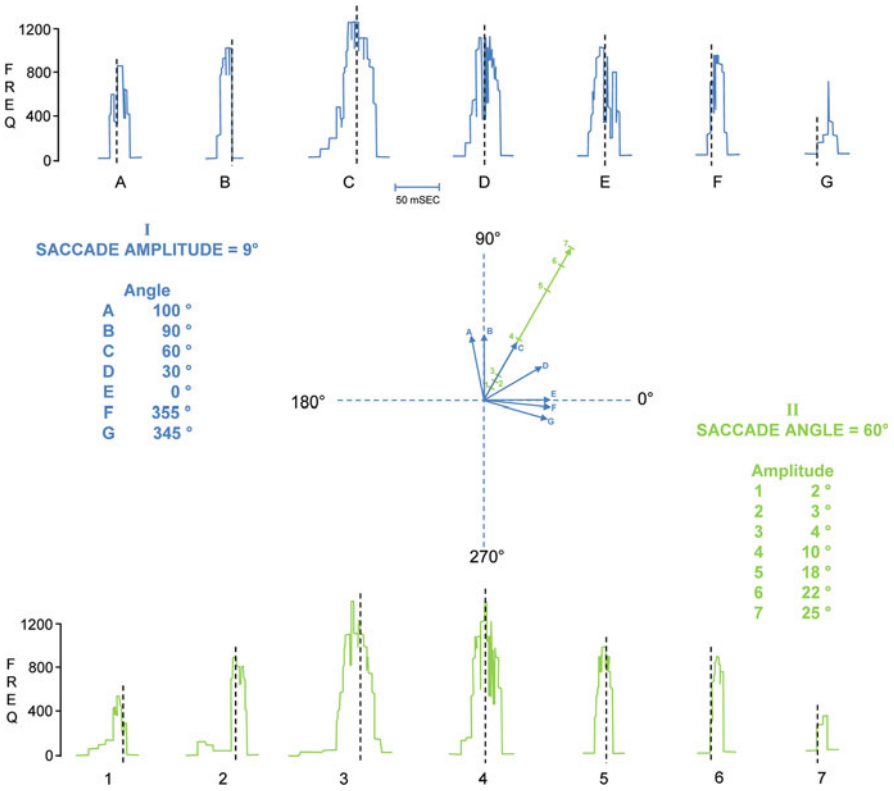

Fig. 17 Responses of superior collicular neurons can be identical for saccades of different directions and amplitudes. The firing rate of an example neuron is shown in I and II. **I.** Neuronal discharges for seven saccades of optimal amplitude (9°) but of different directions. **II.** Neuronal discharges for seven saccades all made in the optimal direction (0 = 60°) but of different amplitudes. Note, in particular, the similarity of the burst profile for saccades B, F, 2, and 6, although these saccades differ greatly in direction and amplitude. The dashed lines represent saccade onset. (Modified from Sparks and Mays 1980)

Figure 18 illustrates the main features of a simple feedback circuit which could ensure movement accuracy. There are several key features of this circuit. First, a burst of activity (i.e., the pulse command) from the premotor burst neurons (BNs) drives the saccade. As mentioned in section "What Does the Brain Need to Tell the Muscles to Make Accurate Eye Movements?," BNs also project to the NPH/MVN or INC – nuclei which integrate this burst to produce the step command required for holding the eye steady at its new position. Next, an internal representation of the commanded eye position command (E*) is fed back to the SC for comparison with desired eye position Ed. As a result, the difference between Ed and E* produces an error signal (em): Ed – E* = em. It is this error signal that continues to drive the BNs. Finally, when em = 0 (i.e., actual = desired eye position (Ed = E*)), the saccade

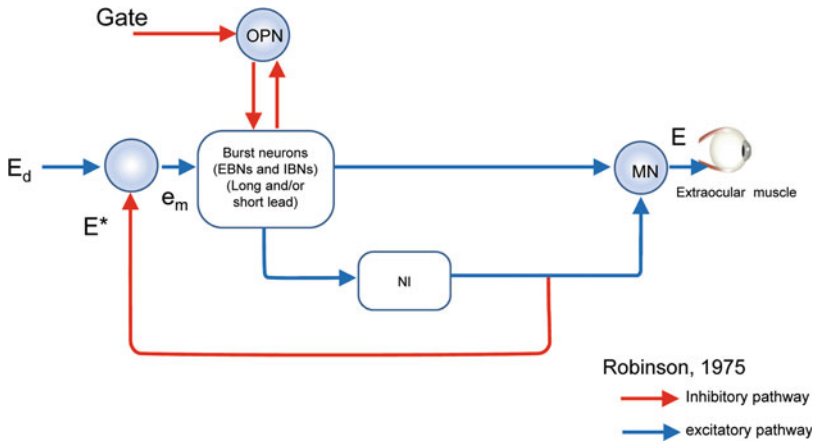

Fig. 18 Schematic of the Robinson model of the brainstem saccade generator. A neural representation of eye position is subtracted from target position in space, and to generate motor error

ends because there is no drive to the BNs. In this way, negative feedback of the commanded eye position can be used to produce an accurate eye movement.

How does this model correspond to what we know about the brain, and in particular the SC? As discussed above, the SC motor map is in eye movement (retinocentric) coordinates and not head-centered coordinates. Stated another way, saccade cells in the SC discharge the same burst for a given amplitude and direction of saccade, regardless of where the eyes are at the start of a saccade (recall Fig. 14, inset above). A small modification to this simple model shown in Fig. 19 accounts for this property of SC neurons, namely, that the SC compares the *change* in desired versus current eye position (Ed), rather than the *absolute* desired versus current eye position. Accordingly, a second integrator is added to the model so that the feedback consists of an internal feedback of the change in eye position (i.e., ΔE*) rather than absolute eye position (E*). ΔE* is then compared with the desired change in eye position (ΔEd) and it is this difference (which remains "em") that drives the burst neurons.

The SC is comprised of two main classes of neurons: (1) Saccadic **Burst neurons** whose responses have been described above in relation to Figs. 16 and 17. These neurons do not discharge during fixation, but produce high frequency bursts before the onset of saccades with vectors corresponding to their location on the motor map, and (2) **Buildup neurons**, which were more recently discovered. Buildup neurons have a low resting discharge during fixation and then produce a very long anticipatory buildup of low frequency activity prior to a saccade. Figure 20 shows the activity of 10 burst cells and 10 buildup cells at locations across the SC motor map during a 50° horizontal saccade. Panel A shows the location of the neurons relative to the motor map of the SC; panel B shows the time varying activity of each of the 10 burst and buildup neurons before, during, and after the 50° saccade (beginning with the firing of the most rostral neurons as the first trace).

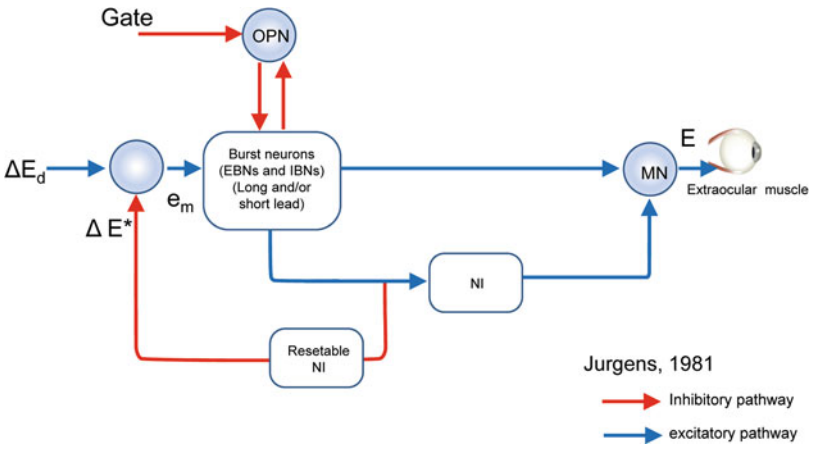

Fig. 19 Schematic of the Jurgens model of the brainstem saccade generator. This model accounts for the finding that cells in the superior colliculus discharge the same burst for a saccade of a specific amplitude and direction, regardless of where the eyes are at the start of a saccade. Note that in comparison to the original Robinson model (Fig. 18), the Jurgens model includes a second integrator which computes the change in eye position (i.e., ΔE*) rather than absolute eye position (E*)

Neurons termed "fixation cells" are found the most rostral regions of the SC. In contrast to SC burst and buildup neurons, fixation cells are tonically active during fixation and pause for all but the smallest of saccades. Notably, these neurons strongly resemble the omnipause neurons of the nucleus raphe pontis that are an integral part of the premotor saccade circuit (see Fig. 13). Accordingly, activation of this area results in fixational, rather than saccadic eye movements. This phenomenon is illustrated in Fig. 21, where bilateral electrical stimulation of the rostral pole suppresses the saccades while a monkey performs the visually guided saccade paradigm.

The sequence of events that takes place within the SC to generate a saccade is shown in the schematic cartoons of Fig. 22. Initially, the fixation cells of the SC rostral pole are active ("Fixation"). The activity of these cells ensures fixation by directly suppressing saccades because fixation cells (1) send inhibitory projections to the saccade-related cells in the caudal SC and (2) project to activate the omnipause neurons of the raphe nucleus.

Next, before the initiation of a saccade, attention is disengaged from the current point of fixation and shifted to a new target ("Saccade Preparation"). This shift in attention is reflected a decrease in fixation cell activity and a corresponding increase in the long lead anticipatory activity of buildup cells. Excitatory inputs to the SC motor map from cortical areas such as the frontal eye fields, supplementary eye fields, and posterior parietal cortex as well as disinhibition from the substantia nigra are likely to

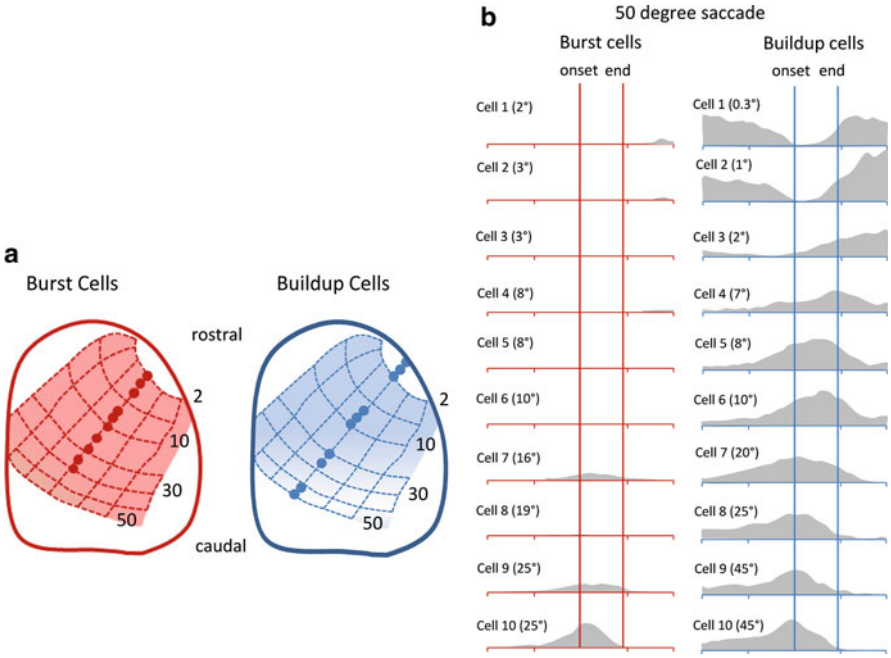

Fig. 20 (**a**) Locations of 10 burst neurons and 10 buildup cells chosen to span most of the rostro-caudal length of the superior colliculus (SC). (**b**) Firing rates are shown for each cell during a 50° saccade. Left and right vertical lines indicate saccade onset and saccade end, respectively. Only the most caudal burst cells discharge for the generation of a 50° saccade. (Note, the low activity of some rostral burst cells after the end of the saccade is related to the generation of small corrective saccades.) In contrast, all buildup cells were active during the saccade. The small numbers to the left of each neuron's response indicates its location on the SC motor map. The two most rostral buildup cells are fixation cells. (Modified from Munoz and Wurtz 1995)

trigger this spatial shift in activity across the SC. In addition, reciprocal inhibitory connections between the fixation and buildup cells help to facilitate the shift.

Finally, once the new target has been selected, the activity of the fixation neurons has been fully suppressed, while that of the buildup neurons has increased even further. At this stage, as a result of the accumulating buildup cell activity, SC burst neurons are triggered to fire ("Saccade Onset"). Their burst then drives the premotor saccadic pathway and a saccade is produced. During saccades, the SC's output is not predetermined, or "ballistic." Instead, the saccadic command to brainstem eye and head-motor premotor circuits is updated as a result of changes in the current eye trajectory (or equivalently gaze trajectory, when both eye and head movements are made). In this way, SC is part of a feedback circuit that, during saccades and rapid eye-head gaze shifts, encodes the distance between eye and target (i.e., error), irrespective of gaze trajectory characteristics. The saccade ends when error is zero ("Saccade End").

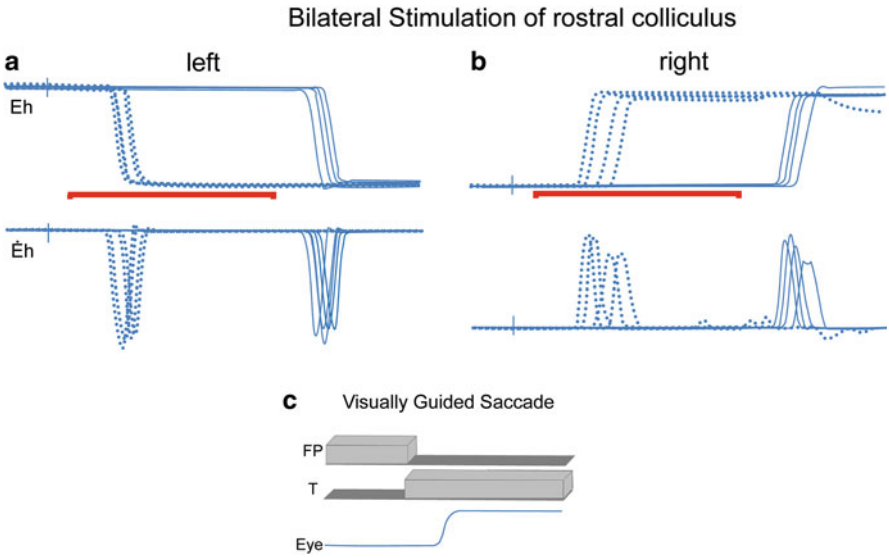

Fig. 21 Simultaneous bilateral stimulation of both rostral poles suppresses saccades in all directions. This is shown for leftward and rightward saccades in panels **a** and **b**, respectively, where five control trials (dotted traces) and five stimulation trials (solid traces) are superimposed in each panel. The vertical tick on the eye position traces indicates the time of target onset, and the red horizontal bar under the eye position traces indicates the time of stimulation. (Modified from Munoz and Wurtz 1993)

Gaze Redirection: Smooth Pursuit

Smooth pursuit eye movements are made by simian primates and humans to maintain the image of a moving target stable on the fovea. These smooth eye movements are typically elicited within 100 ms of target motion onset. When target velocity is constant, the smooth tracking movement will accurately track targets moving as fast as 50 deg/s (Fig. 23a). However, the smooth pursuit system is challenged by motion trajectories for which velocity changes dynamically as a function of time. As a result, pursuit tracking becomes increasingly inaccurate for sinusoidal frequencies in excess of 1 Hz. To account for these properties of eye movements, the smooth pursuit system is generally modeled as a negative feedback controller in which a retinal velocity error signal (i.e., the difference between target velocity and eye velocity) drives eye movement with a delay of approximately 100 ms delay. While retinal position and acceleration errors can modulate pursuit eye movements, their influence is less marked. In addition, non-visual mechanisms such as anticipation and target predictability can improve pursuit performance.

A number of parallel and interconnected pathways are involved in initiating and maintaining these eye movements. Of particular importance is a corticopontocerebellar pathway arising in areas of the extrastriate cortex that are selectively responsive to visual motion (Fig. 23b). Notably, when tracking a moving target, neurons in middle temporal

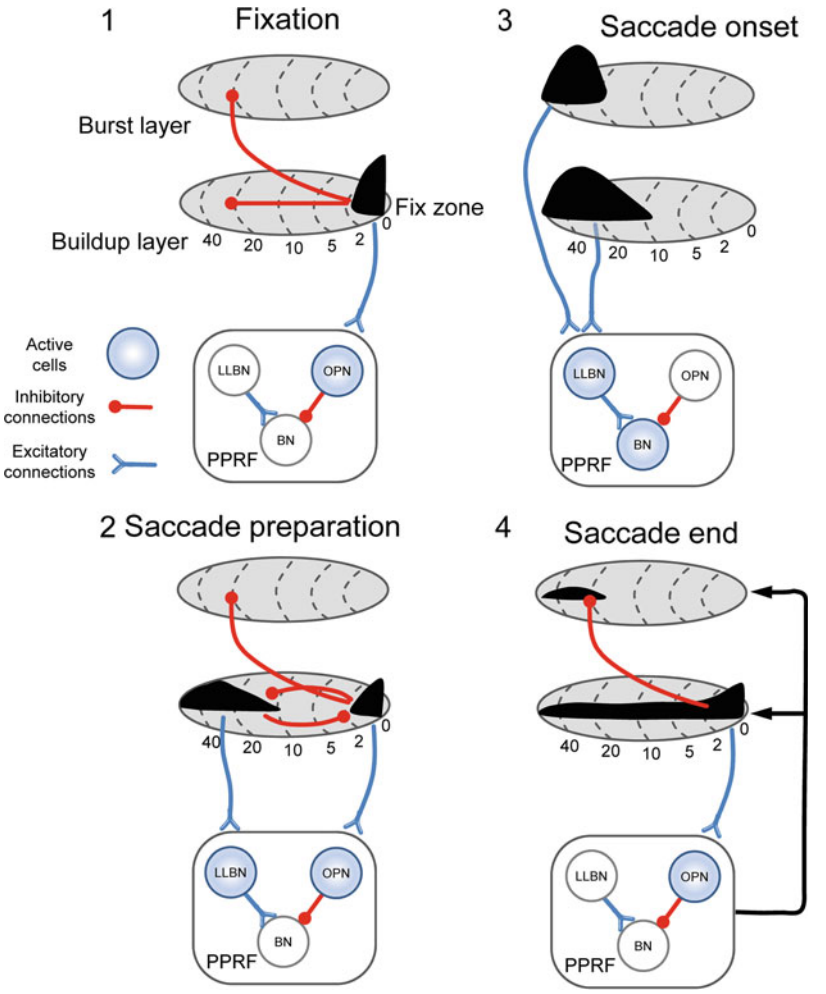

Fig. 22 Schematic representation of sequence of activity in the SC during generation of a saccadic eye movement. Blue lines ending in open angles are excitatory connections. Red lines ending in filled circles are inhibitory connections. *Abbreviations*: PPRF, paramedian pontine reticular formation; BN, PPRF burst neurons; LLBN, PPRF long-lead burst neurons; OPN, omnipause neurons. See text for details. (Modified from Munoz and Wurtz 1995)

cortex (area MT) encode the direction and velocity of visual target motion. In turn, these motion signals are transmitted to medial superior temporal cortex (area MST) as well as the smooth eye movement region of the frontal eye fields (FEF_{SEM}) – areas in which the transformation from visual sensory signals to motor commands begins. Neurons in these cortical areas are transmitted to the oculomotor cerebellum through brainstem regions, including the dorsolateral pontine nucleus (DLPN), nucleus reticularis tegmenti pontis (NRTP), and pretectal nucleus of the optic tract (NOT). Finally, the cerebellar pursuit

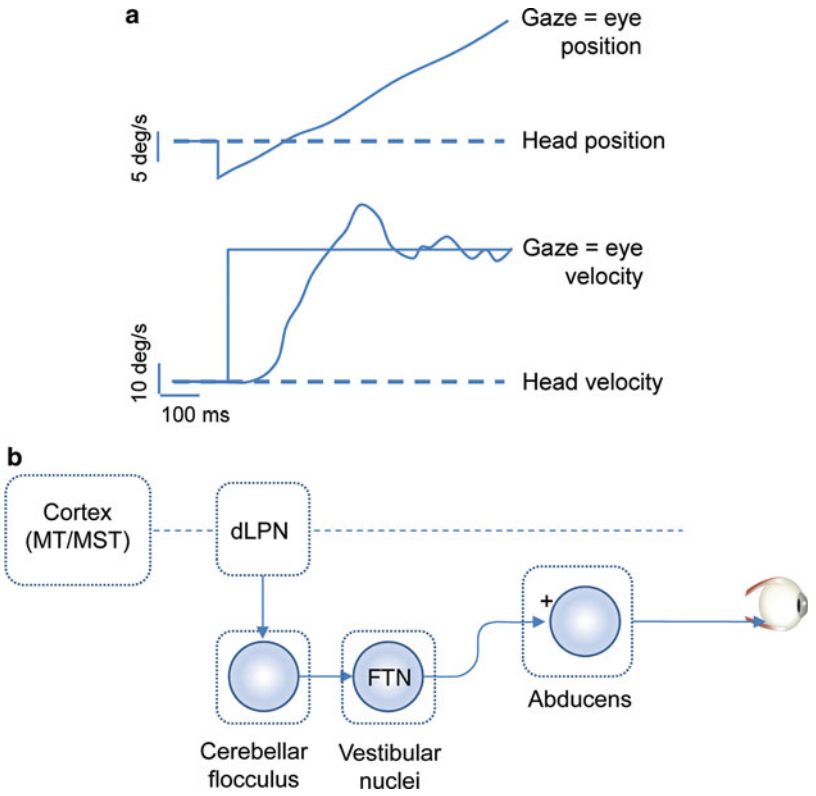

Fig. 23 (**a**) Pursuit eye movements, which are used to follow moving objects, lag target motion by ~90 ms (left). (**b**) The cortical and brainstem circuit for the generation of smooth pursuit movements. *Abbreviations:* dLPN, dorsolateral pontine nuclei; MT/MST, medial temporal neocortical areas

regions – specifically the floccular lobe and vermis – access the brainstem circuitry via projections to cerebellar target neurons located in within the vestibular nuclei. These cerebellar target neurons, in turn, project to the extraocular motoneurons located in the III, IV, and VI cranial nuclei to drive pursuit eye movements.

The visuomotor transformation required for the execution of smooth pursuit can be tracked by the characteristics of the neuronal responses at each stage of the corticopontocerebellar pathway described in Fig. 23b. First, neurons in area MT encode visual motion relative to the retina, while neurons in areas MST and FEF_{SEM} combine retinal as well as extra-retinal signals, including: eye movement signals and predictive/anticipatory information. The integration of retinal as well as extra-retinal information is required to provide an accurate estimate of the necessary pursuit command by the brainstem and cerebellum. At the final stage of processing, the modulation of premotor neurons in the vestibular nuclei and their cerebellar inputs are similar, with the exception that the former exhibit no residual modulation related to retinal slip. This indicates that any preceding sensory influences are completely

transformed into the required pursuit motor command at the premotor level. It is important to note that the cerebellum is not only an important stage of the visuomotor transformation required for the generation of pursuit eye movements, but that it is also a site of pursuit motor learning. The cerebellum ensures that the pursuit system remain accurate by calibrating its amplitude and dynamics continuously throughout life.

Gaze Redirection: Vergence

Vergence eye movements are made to optimize visual perception when looking between targets located in our dimensional environment. Specifically, to redirect the axis of visual gaze between near and far targets, the two eyes must rotate by different amounts. The difference between the two angles through which each of the two eyes rotate is called the vergence eye movement. The generation of vergence eye movements allows foveated animals to precisely align the visual axes of their two eyes on targets of interest.

The visual axis of gaze can be redirected from a near to a far target (or vice-versa) by making either fast or slow vergence eye movements. When gaze redirection is accomplished without a saccade, it is referred to as slow vergence (Fig. 24a). The dynamics of saccade-free vergence are relatively sluggish compared to those of

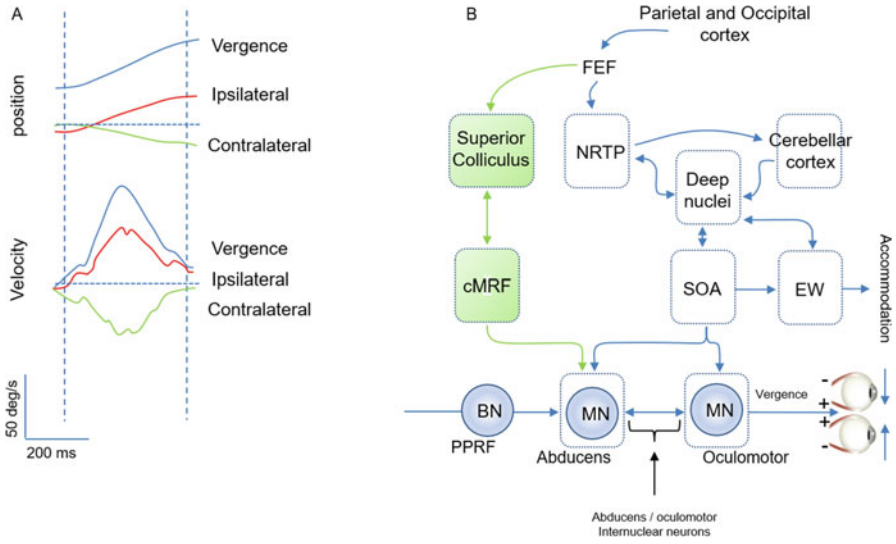

Fig. 24 (**a**) Vergence eye movement commands, which move the eyes in opposite directions so that their gaze angles can converge at varying depths, are characteristically much slower than saccades (left). (**b**) The circuitry involved in producing slow vergence eye movements. *Abbreviations:* BN, pontine saccadic burst neurons; cMRF, central mesencephalic reticular formation; EW, Edinger-Westphal nucleus; FEF, frontal eye field; LRMN and MRMN, lateral and medial rectus motoneurons; NRTP, nucleus reticularis tegmenti pontis; SOA, supraoculomotor area

saccades and even pursuit. For example, the velocity of pure vergence is typically <20 deg/s, while that of saccades is typically >200 deg/s. However, in everyday life, we usually combine both saccadic and slow vergence eye movements in order to quickly and accurately redirect gaze between near and far targets. During the fast saccadic component of these movements, termed disconjugate saccades, the eyes rapidly rotate by different amounts and with different trajectories. As a result, the visual axis of gaze is redirected by fast vergence eye movements. Recent studies have provided insight into how the brain generates slow versus fast vergence eye movements.

Information about target depth is derived by combining visual information from both eyes early in visual processing. Specifically, disparity-sensitive (i.e., depth-sensitive) neurons are found in primary visual cortex (i.e., area V1). Areas of extrastriate occipital and parietal cortex differentially combine this disparity information with other visual signals. For example, areas of the dorsal visual pathway, such as area MT, combine disparity signals with motion signals to estimate structure from motion or self-motion. Regions of the ventral visual pathway, such as V2, V4, and IT, use disparity information to achieve perception of three-dimensional object shape. Notably, neurons within the frontal eye fields (FEFs) and lateral intraparietal area (LIP) contribute to the processing required to transform visual disparity information into the binocular control commands required to move each eye so that it is aligned with the target of interest. In addition, neurons encoding either near or far targets can be found within the nucleus reticularis tegmenti pontis (NRTP) and deep cerebellar nuclei. In turn, these cortical and cerebellar areas transmit vergence-related signals to the premotor circuitry (the supraoculomotor area [SOA] and adjacent reticular formation around SOA) that controls vergence eye movements, as well as to areas (i.e., the Edinger-Westphal [EW] nucleus) that control accommodation.

At the brainstem level, slow and fast vergence eye movements are largely controlled by two distinct premotor pathways. First, a group of midbrain cells in the supraoculomotor area (SOA), termed near response neurons, project to the oculomotor motoneurons to control slow vergence eye movements (Fig. 24b). Specifically, near response neurons encode the required slow vergence velocity and position motor commands to produce saccade-free vergence. In addition, recent microstimulation and single-neuron results further suggest that the rostral superior colliculus also plays a key role in the generation of slow vergence velocity via projections to the cMRF (central mesencephalic reticular formation), which in turn drives the oculomotor motoneurons in Abduces (Fig. 24b). Second, neurons within the premotor pathway controlling conjugate saccadic eye movements (i.e., the pathway described in section "Gaze Redirection: Saccades and Gaze Shifts") also carry substantial vergence-related information to drive disconjugate saccades (Fig. 13). In particular, saccadic burst neurons (BNs), which receive input from the caudal superior colliculus, send a vergence-related drive command to the oculomotor motoneurons required to produce fast vergence eye movements (Van Horn et al. 2010, 2012). In everyday life, these two parallel premotor pathways work together to

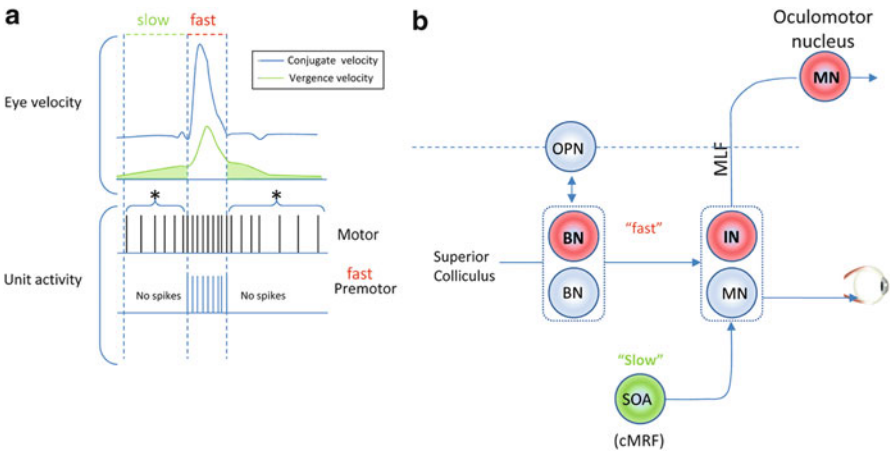

Fig. 25 (**a**) The two top traces illustrate a typical disconjugate saccadic eye movement. Note, the movement is characterized by a period of fast vergence to quickly redirect the eyes (i.e., dashed box labeled "fast") as well as initial and late periods of slow vergence which binocularly position the eyes and ensure accurate visual perception (i.e., early and late components of movement shaded in green). The typical unit activity of motoneurons (motor; gray units) and SBNs (premotor; blue units) associated with this movement are shown below. Note that while motoneurons fire during both periods of slow (see asterisks) and fast vergence, SBNs fire only during the fast component of the movement. (**b**) The circuitry that controls disconjugate saccadic eye movements. The saccadic burst generator drives the fast component of the movement, and the pathway shown in Fig. 24 controls the early and late periods of slow vergence which binocularly align the eyes. *Abbreviations*: MN, motoneuron; cMRF, central mesencephalic reticular formation. (Modified from Cullen and Van Horn 2011)

control binocular movements. The saccadic premotor circuitry drives the fast vergence eye movement to the new target, while the slow pathway serves to precisely align the fovea of each eye on a target after the saccade, thereby ensuring optimal binocular perception. Current research is now aimed at understanding how the coordinated inputs to the distinct fast and slow premotor pathways work together to ensure accurate binocular gaze positioning (Fig. 25).

Gaze Stabilization: The Vestibulo-ocular and Optokinetic Reflexes

As discussed in Jay Goldberg's Chapter on the "Vestibular System," the vestibulo-ocular reflex (VOR) transforms vestibular information into a compensatory eye movement command in order to keep visual images stable on the retina during everyday activities such as walking and running. For example, as the head turns to the left, the vestibular pathways that mediate the VOR command an eye movement to the right. The magnitude of the VOR eye movement is comparable (but opposite in direction) to the head movement. As a result, the axis of visual gaze remains pointed at the same point in visual space. During sustained, applied movements, the

compensatory eye movements can bring the eye to its limit of excursion well before the head movement is completed. Consequently, an additional feature is added to the VOR: when the eye reaches an eccentric position, it is quickly commanded back to a new starting position. The pattern of alternating slow compensatory and rapid resetting eye movements (termed slow phases and quick phases, respectively) is referred to as vestibular nystagmus. The quick phase uses some of the same neural machinery involved in the generation of voluntary saccades (see Fig. 13).

The VOR uses information from both the semicircular canals and otolith organs to compensate for rotations and translations of the head in space. The pathways mediating the VOR are also described in detail in the "Vestibular System" chapter. Briefly, the most direct pathway mediating the VOR is a three neuron arc, which ensures its remarkably fast (~5 ms) response time (Fig. 26a). While the VOR functions to rapidly and effectively stabilize gaze over the broad range of head movements generated during walking or running, it does not effectively stabilize gaze at lower frequencies of head rotation. This is because the mechanical properties of the semicircular canals that

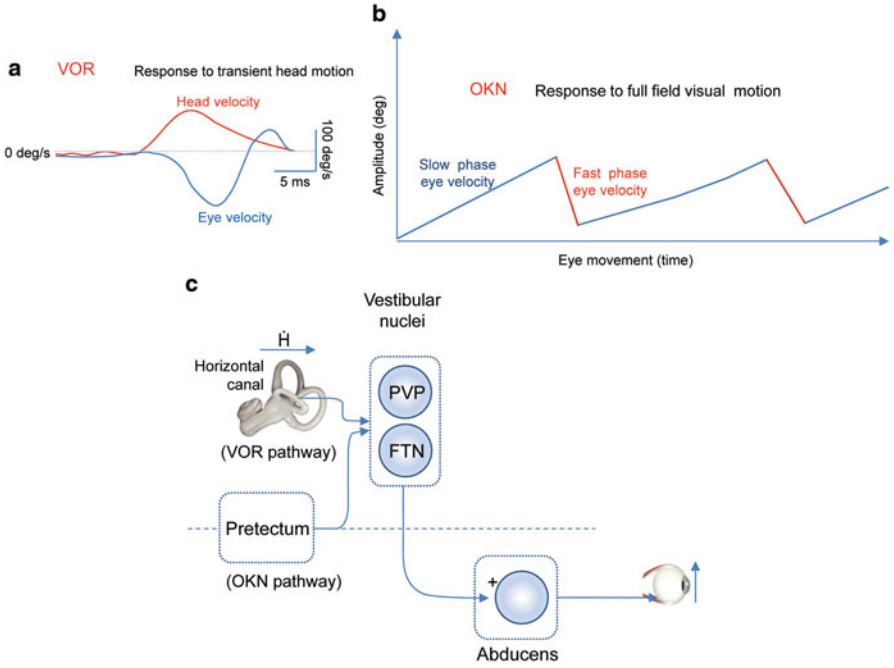

Fig. 26 (**a**) In response to head motion, the VOR produces an eye movement with a latency of 5 ms. This fast response is consistent with the minimal delays of the three neuron pathway that control the reflex. (**b**) The optokinetic eye movement response (OKR) produced in response to full field visual motion stabilizes the visual world. In response to constant velocity motion, these movements are comprised of two components: a slow compensatory movement as well as a fast resetting quick phase. (**c**) The cortical and brainstem circuit for the generation of optokinetic eye movements. The pretectum targets the same premotor cells groups in the vestibular nuclei that control the VOR. (Modified from Huterer and Cullen 2002)

sense head rotation are not well tuned to code low frequency motion. Thus, for frequencies below 0.1 Hz, a second reflex eye movement, termed the optokinetic reflex (OKR), complements the VOR to ensure stable gaze.

The optokinetic system uses visual rather than vestibular inputs to stabilize the visual axis of gaze in space. In everyday life, it is typically driven by the motion of the visual world across the retina (retinal slip) that occurs when the head moves relative to space. This produces an eye movement response called the optokinetic reflex. Notably, in response to sustained visual motion, the reflex produces optokinetic nystagmus (OKN), which consists of alternating slow compensatory and quick resetting eye movements in the opposite direction (Fig. 26b). The resultant slow phase is characterized by an initial rapid rise in eye velocity that begins within 100–200 ms of the start of visual motion and is followed 1–2 s later by a slower buildup of eye velocity.

Physiological studies have shown that the fast component of optokinetic eye movements is largely generated by the same cortico-pontine-floccular circuit that generates smooth pursuit eye movements (Fig. 23), whereas the slow component is mediated by subcortical pathways (Fig. 26c). Specifically, the cortico-pontine-floccular pathway, makes a major contribution to driving the initial phase of OKN. This pathway has already been described in relation to the control of pursuit eye movements (see Fig. 23). Accordingly, the initial rise in OKN eye velocity is reduced following flocculectomy. In contrast, a second subcortical pathway that includes the nucleus of the optic tract (NOT) is responsible for the slower buildup of optokinetic eye movement (reviewed in Leigh and Zee 2015). Specifically, visual information is transformed by NOT neurons and sent to neurons in the vestibular nuclei and nucleus prepositus to drive the extraocular motoneurons. In addition, regions of the vestibulo-cerebellum continuously calibrate the amplitude and dynamics of both the OKR and VOR to ensure stable gaze throughout life.

The accessory optic system (AOS) also makes a significant contribution to the control of optokinetic eye movements. This region is interconnected with the NOT, but also receives cortical input from areas MT, MST, and striate cortex. The relative importance of different visual inputs (subcortical versus cortical) to the visual-motor transformation underlying the OKR pathways is species dependent. In primates, visual cortex lesions produce a substantial asymmetry in temporal and nasally directed OKN responses. Interestingly, similar asymmetries have been reported for the OKN responses of human infants, in whom the pathways to cortical visual areas are less well developed. Additionally, lateral-eyed species (i.e., species with no depth perception) such as rabbits also show significant temporal-nasal asymmetries in their OKN responses. Thus, the cortical inputs to NOT function ensure stable binocular vision in primates by producing symmetric OKN responses of both eyes.

Interactions Between Eye Movement Pathways

The traditional method of studying the pathways that produce saccades, smooth pursuit, vergence, and the VOR/OKR has led to an excellent understanding of the visual-motor transformations underlying each of these types of eye movements.

However, it is important to keep in mind that during most natural voluntary orienting and tracking behaviors, two or more subsystems work together to control gaze. For example, anytime we rapidly reorient our eyes between targets located at different eccentricities and depths, the vergence and saccadic "pathways" are not separate. Instead, the same neurons provide the integrated binocular command that is required to drive both conjugate and disconjugate saccades (see Fig. 25 above). Similarly, when the head is not restrained, coordinated eye and head movements are commonly used to rapidly redirect the gaze axis to a new target in space. During such movements (called "gaze shifts"), an intact VOR would command an eye movement in the direction opposite to that of the intended shift in gaze and would thus be counterproductive. In actuality, the VOR is not intact. Instead, it is suppressed via interactions between the saccade and VOR pathways such that head motion contributes to the redirection of gaze (recall, gaze = eye-in-head + head-in-space). Specifically, the saccadic pathway sends strong inhibitory projections to the VOR pathway (Fig. 27). Thus, the VOR and saccadic "pathways" also work together to ensure the rapid and accurate redirection of gaze during combined eye-head gaze shifts (reviewed in Cullen 2019). Ongoing research is currently directed at establishing how the brain coordinates interactions between different eye movement subsystems to accurately control gaze in everyday life.

Eye movements provide a window into the neural computations underlying higher brain functions, such as attention, perception, and decision-making.

The last 40 years of oculomotor research has provided considerable insight into the visuomotor transformations that govern the control of eye movements.

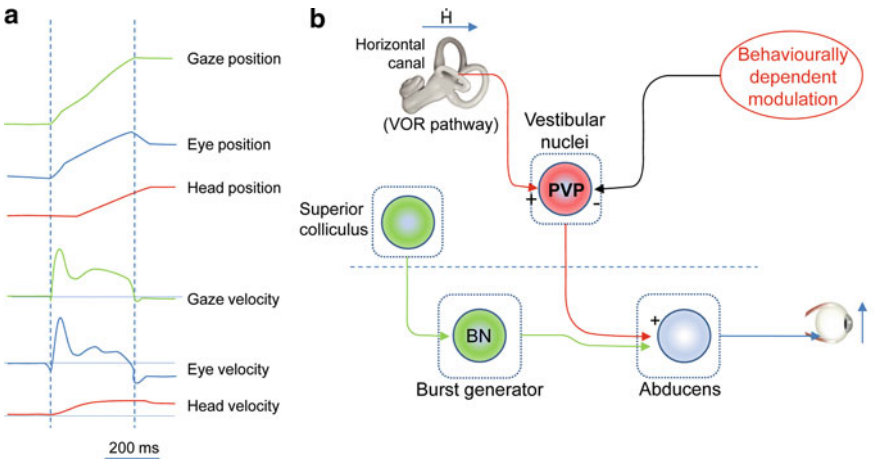

Fig. 27 In everyday life, we use coordinated eye and head movements to redirect our axis of gaze (gaze = eye-in-head + head-in-space). (**a**) A typical example of a gaze shift produced by coordinated eye-head movement. (**b**) A schematic of the interactions that occur between the VOR (red) and saccadic (green) premotor pathways during gaze shifts. The efficacy of the VOR pathways is suppressed via behaviorally dependent inputs, which allow the head movement to contribute to the shifting the axis of visual gaze relative to space

In particular, single-unit recording, anatomical tracing, and lesion studies have demonstrated how information is processed by brainstem premotor circuits to control voluntary and reflex eye movements. Because of its relative simplicity, namely the straightforward relationship between extraocular motoneuron activity and eye movement, we now have an excellent understanding of how small clusters of brainstem neurons are sequentially activated, and their output is decoded to produce eye movements.

More recent work has focused on a higher-level question, namely: How does the brain ultimately make the decision of where to look? Again, to answer this question, neurophysiologists have recorded from clusters of neurons, in this case located in cortical areas, as well as in the brainstem. Consider the saccadic eye movements made while scanning the image shown in Fig. 1. During viewing, saccades are preferentially made to areas that are the most interesting or salient, namely the eyes and mouth of the face. These areas are of critical importance to us since they provide the most insight into the individual's emotional state. But how does the brain decide to search an image using a specific series of saccades? There is accumulating evidence that the brain's strategy of selecting the next saccade target during visual search is guided by a "priority" or alternatively visual "salience map," namely a two-dimensional map in which a single scalar quantity (priority/salience) is represented at each point. A conceptualized view of the priority map hypothesis is shown in Fig. 28. The inputs to the map include stimulus-driven (i.e., bottom-up) signals as well as information related to the specific goals of the ongoing task or behavior (i.e., top-down signals). Bottom-up signals are available from neurons in extrastriate cortex (e.g., areas V4 and inferotemporal cortex; for more details, see ▶ Chap. 38, "Cortical Processing of Visual Signals" by David Fitzpatrick) which respond to specific features of visual targets. Top-down information can be provided by neurons in areas such as prefrontal cortex and the basal ganglia – areas thought to encode signals related to task goals and predictions of reward. Ultimately, the brain selects the point of highest priority/salience to convert visual input into an orienting saccade.

Neurophysiological studies of visual search indicate that neurons within the intermediate layers of the superior colliculus, as well as in cortical areas that project directly to the superior colliculus, including the frontal eye fields (FEFs) and lateral intraparietal area (LIP), form a distributed salience map. Each of these areas receives bottom-up and top-down inputs from numerous subcortical and cortical structures, including the substantia nigra pars reticulata and extrastriate cortex (Fig. 29). To better understand the neurophysiological evidence for a salience map, consider the superior colliculus buildup neurons such as those shown in the schematic in Fig. 22. As a decision is made to make a saccade, the neuron's saccade-related motor response will reflect the probability of selecting a specific stimulus as the target of the impending saccade. Figure 30 shows a neuron that was recorded while a monkey was randomly presented with one to eight potential targets. When the odds were 100% that the target in the cells receptive field would be the ultimate target of a commanded saccade, there was a fast buildup of activity. In contrast when the odds were only 1/8, the buildup of activity was markedly less. Cortical neurons in areas FEF

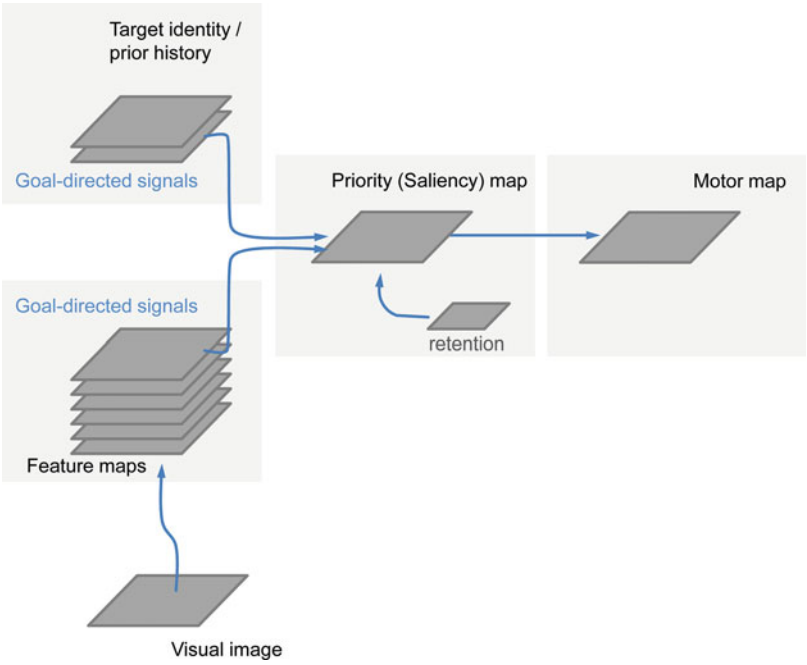

Fig. 28 A schematic representation of a priority map which is an important feature of many current models of visual attention and visual search. The inputs to the map include stimulus-driven (called "bottom-up") signals as well as goal-directed (called "top-down") signals. Most implementations of the map include a process to prevent the selection of the previously examined target (i.e., inhibition of return). Competition between targets on the priority map is resolved by winner-take-all mechanism, such that ultimately the saliency map sends a single output to a separate motor map. (Modified from Hamker 2006)

and LIP can show a comparable buildup of activity that correlates with target certainty. Moreover, findings using other saccade tasks such as paired presentations of a "target & distracter" or a "pop-out" tasks support the idea that the presaccadic activity of superior colliculus and FEF and LIP cortical areas encode target salience. Importantly, of these structures, the superior colliculus is effectively the point of no return with respect to saccade generation. This is because once its burst neurons have issued a saccade command, a saccade will be generated by the brainstem premotor pathway.

A related concept that has received considerable attention in the field of cognitive neuroscience is the phenomenon of "inhibition of return" – which also plays a critical role in visual search. The overall idea is that an "inhibitory tag" is placed on objects that have been recently been inspected. This tag then serves to ensure that the search strategy does not end up caught in a loop, where saccades are continually redirected back to a single highly salient feature in the visual scene. There is behavioral evidence for this idea, namely the observation that saccadic reaction times to a stimuli presented in a previously cued location are longer than they were for the first saccade to the same location. A neural correlate of this effect can

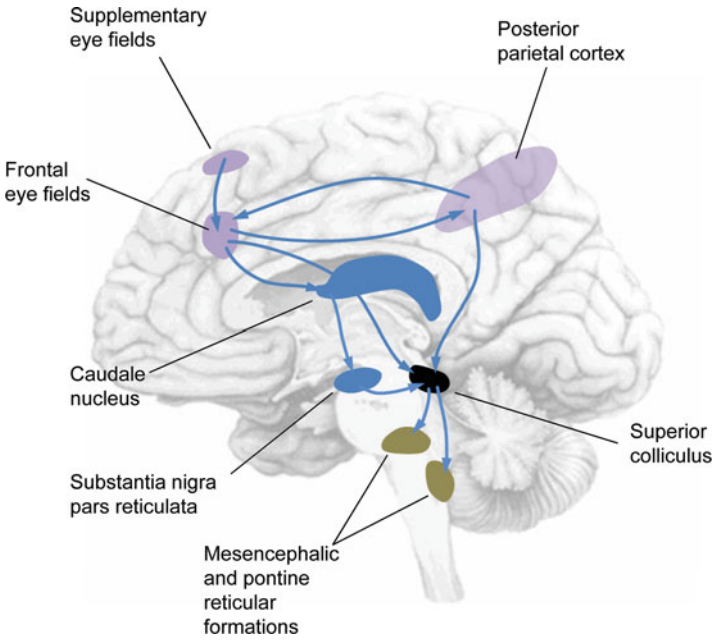

Fig. 29 Inputs from cortex (purple shading) and basal ganglia (blue shading) to the superior colliculus (black shading) command the premotor circuitry to produce saccades

also be found in the superior colliculus. Notably, stimulus-related responses to previously cued targets are attenuated and the magnitude of this response is correlated with subsequent saccadic reaction times.

Current research is now directed toward understanding the specific computations that the brain uses to accumulate information to arrive at simple decisions. Notably, nearly all studies of the neurobiological substrates of visuospatial attention incorporate eye movement behaviors as a behavioral measure. In addition, the control of action – such as saccades – entails not only signals that can initiate and execute movements but also signals that can cancel previously commanded movements. To understand the mechanisms that underlie the decision to make or restrain a saccade, experimenters have used two key tasks: (1) the antisaccade task and (2) the countermanding saccade task.

Over the past decade, the antisaccade task has become an indispensable tool for investigating how well different patient groups can suppress "automatic" sensorymotor responses such as a saccade to a visual target. During the antisaccade task, the subject is required to make a saccadic eye movement away from a visual target, rather than toward it (Fig. 31). Patients with specific neurological deficits, for example, patients diagnosed with frontal lobe disorders, find it difficult to suppress saccades to visual targets when presented. Moreover, the ability to perform the antisaccade task improves during human maturation (i.e., from childhood, to adolescence, to adulthood), most likely reflecting the time course required for full

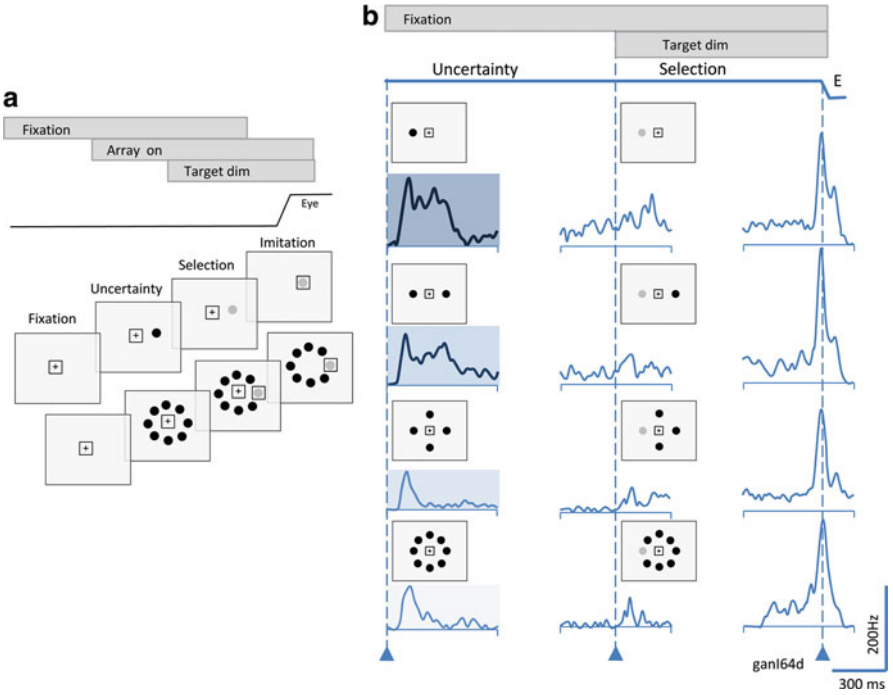

Fig. 30 (**a**) Schematic of the spatial arrangement of visual targets during an experiment designed to test the effect of uncertainly on neuronal responses. As examples, the one possible target and eight possible target experiments are shown. The cross represents the fixation point, and target stimuli are shown as black filled circles. The gray filled circle represents the target that is selected by the experimenter. (**b**) The activity of a superior colliculus buildup neuron during the task shown in (**a**). Note that as the number of possible targets increases, the activity in the uncertainty (selection) period decreases. (Modified from Basso and Wurtz 1997)

maturation of the connectivity between the frontal lobes and other brain areas. When monkeys are engaged in an antisaccade task, the responses of neurons that drive saccades in the superior colliculus (SC) and frontal eye fields (FEF) are inhibited even before the target appears so that automatic (i.e., sensory driven) saccades are voluntarily suppressed (Johnston and Everling 2008). Thus, we now have profound insight into how the brain suppresses the automatic responses of neurons that drive saccades when a visual target is behaviorally irrelevant (i.e., not salient).

The ability to countermand actions can be substantially impaired in brain disorders such as schizophrenia and Parkinson's disease. In the countermanding saccade task, the presentation of a saccade target is intermittently followed by the appearance of a stop cue that indicates that the subject should cancel the planned movement. The process of making the decision to suppress the saccade effectively becomes a race between neural motor preparation and neural cancellation processes, such that the signal that reaches its activation threshold first will determine whether a saccade is generated or cancelled (Fig. 32). This race is evident in the responses of neurons in the distributed "salience map" for saccade generation (i.e., superior colliculus, FEFs, LIP).

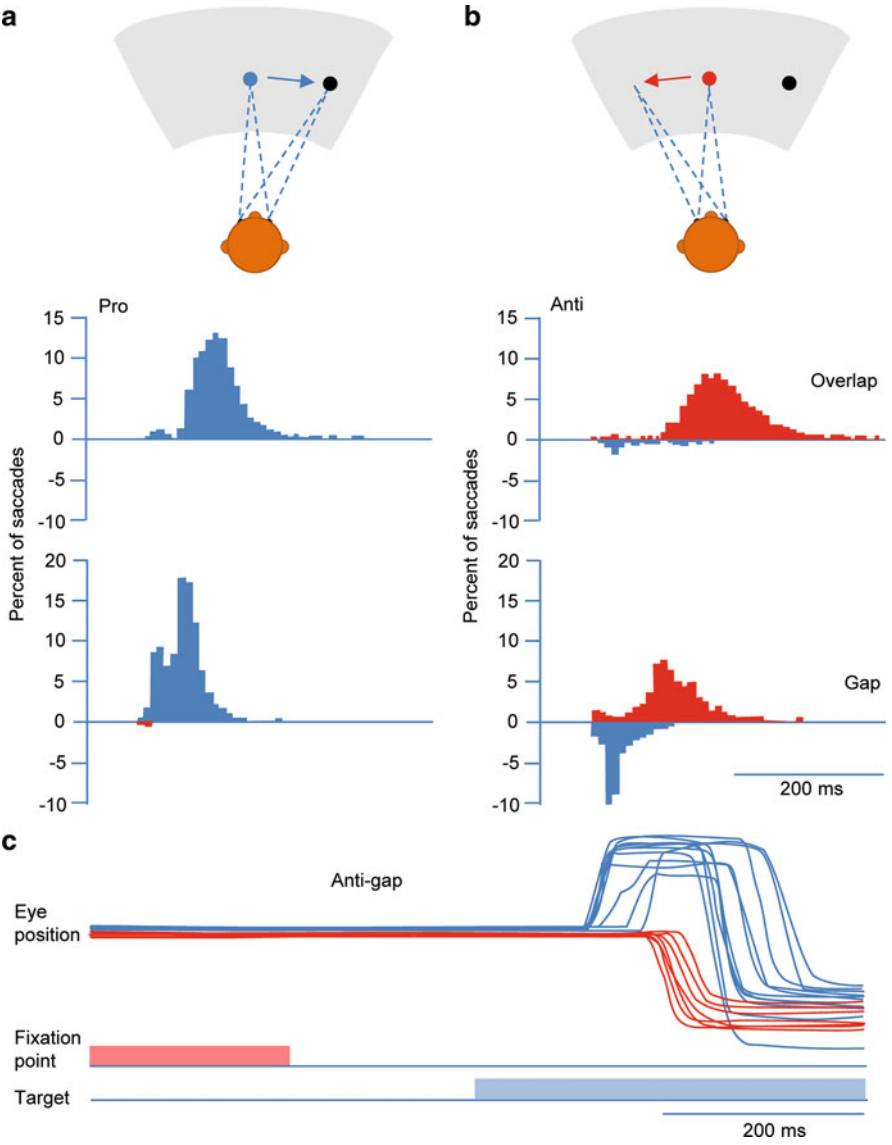

Fig. 31 (**a**, **b**) Schematic illustrating the antisaccade task. The color of the fixation target is used to signal the subject to generate either a pro-saccade (**a**) or an antisaccade (**b**). The panels below the task schematic show the distribution of reaction times for correct (above abscissa) and error (below abscissa) responses in each task. (**c**) Example eye position traces were recorded while a monkey performing the antisaccade task with correct responses shown in red, and error responses shown in blue. (Modified from Munoz and Everling 2004)

Current research is now directed at understanding implications of dysfunctional processes underlying inhibitory control of action in humans. Differences in the performance of healthy and schizophrenic subjects during a countermanding saccade

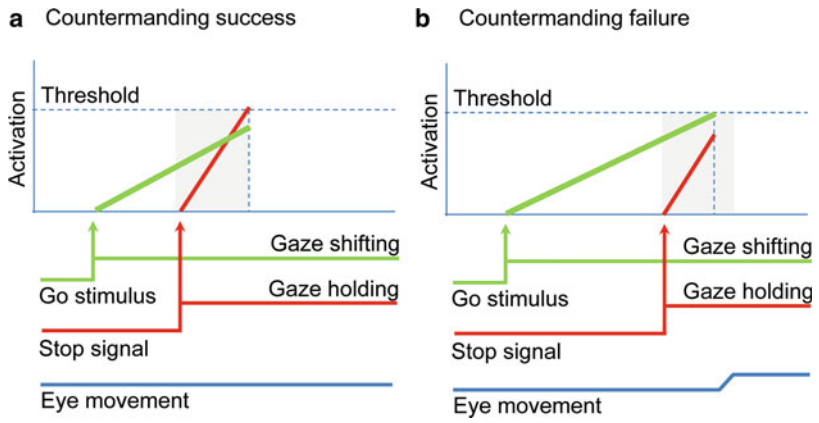

Fig. 32 Schematic of the model of the countermanding task, in which the behavioral outcome is represented as a race between GO (green) and STOP (red) processes. (**a**) If the gaze-holding process reaches a critical threshold before the gaze-shifting process, successful saccade cancellation occurs. (**b**) In contrast, if the gaze-shifting process reaches threshold first, then a saccade will be triggered. (Modified from Curtis et al. 2005)

task have begun to provide insight into why the inhibitory control in action of these patients is impaired.

Motor Learning, Calibration, Plasticity, and Reward in the Oculomotor System

Motor learning is essential for the acquisition and calibration of new skills as well as the reacquisition of skills that have been compromised as a result of brain lesions or disease. Notably, recent studies of eye movements including saccades, smooth pursuit, and the vestibulo-ocular reflex (VOR) have provided important new insights into the connections between neurons, neural circuits, and motor performance that drive learning. These new insights are possible because of the well-characterized circuits that underlie eye movements. Major advances in the field form two main themes. First, several lines of research have clarified the cerebellum's causal role in motor learning. Specifically, recording studies have established how changes in the activity of Purkinje cells and their inputs drive motor learning during saccade adaptation and pursuit adaptation, as well as VOR motor learning.

The "Vestibular System" chapter describes in detail our understanding of the circuitry and mechanisms that underlie motor learning in the vestibulo-ocular reflex. This learning is required to calibrate the VOR to ensure stable gaze in everyday life. For example, after wearing magnifying or minimizing spectacles, the gain of the VOR will increase (gain-up) or decrease (gain-down), respectively, to produce stabile gaze during head turns. Peter Thier's ▶ Chap. 54, "Cerebellum: Eye Movements," considers the cerebellum's role in motor learning during saccade and pursuit

movements in detail. In addition, innovative studies using transgenic approaches to probe oculomotor learning have recently revealed that the cerebellum can influence motor outputs via distinct, complementary premotor pathways, and that feedforward inhibition from interneurons back to their target principal cells (i.e., the Purkinje cells of the cerebellum) helps to regulate this plasticity. Also, ongoing research is also now providing important new insights into how reinforcement and motor error cues guide learning. In particular, trial-by-trial analyses have shed new light on how the brain decides among multiple motor strategies to maximize the reinforced motor performance. Notably, advances in both areas are likely to challenge many fundamental assumptions of motor learning models.

Although our understanding of eye movement control and learning in the dynamic environment of life continues to expand, the question of how the brain strikes a balance between optimizing currently available rewards and calibrating behavioral outcomes remains open. Accordingly, progress in this area will require that the different saccadic tasks used in these fields be brought together. In particular, the responses of descending cerebellar pathways during eye movement adaptation need to be considered in relation to the cortical and basal ganglia processes that occur during learning to gain further insight regarding the importance of reinforcement on guiding saccade adaptation.

Finally, it is important to emphasize that feedback also plays a critical role in producing the on-line visuomotor transformations that underlie eye movements. For example, as detailed above, the prefrontal cortex instructs the brainstem to make a specific eye movement, and in turn, the brainstem drives the eye movement. However, it is important to note that the brainstem also reports back to the cortex on how well the behavior was performed. For example, the eye movement command that is ultimately produced by the superior colliculus is sent back to the frontal eye fields such that premotor cortex is updated regarding the fact that an eye movement has been produced. This motor feedback is referred to as corollary discharge and allows the cortical neurons to predict the dynamic changes in the encoding of the visual scene that should occur as a result of the commanded eye movement. It is essential that the brain keeps track of the movements it makes so as to accurately process sensory input and coordinate complex movements.

Outlook

To date, we have made great progress in our understanding of the basic neurobiology of the oculomotor system. However, our knowledge is not complete, and new findings must continue to be incorporated into concepts on the intermediary high-level processes linking sensation and action. In particular, new ideas regarding the encoding of saccadic eye movements within the superior colliculus are emerging in parallel with studies relating collicular activity to high-level processes. Recent work on the lateral intraparietal area has emphasized its contribution to higher-level processes via a salience map, yet understanding the reference frame in which this area encodes oculomotor commands has proven to be far from trivial.

Neuroanatomical information about the feedforward and feedback projections of frontal eye field neurons must also inform theories of saccade production and cognitive control. By directing new research into understanding the generation and cognitive control of eye movements, we aim to better understand the precise neurobiological mechanisms by which high-level processes are integrated into the transformation from sensation to action.

Additionally, while the oculomotor system has provided one of the most productive platforms for understanding motor control, the core methodologies for investigating this system have remained surprisingly static. The techniques underlying extracellular recording and electrical microstimulation in awake, behaving primates have remained essentially unchanged since 1960s. While these techniques continue to be tremendously productive, particularly when applied across multiple recording sites, there are limits to the statements that can be made about the contribution of a particular neuron or area to oculomotor function. Moreover, while an array of anatomical techniques is available to describe the inputs, outputs, and microcircuitry of a given area, such techniques are still only rarely combined with physiological approaches. Methodological advances within cellular and molecular biology are now being applied within systems neuroscience. When combined with new techniques allowing for simultaneous high density recording of hundreds of individual neurons, these new approaches hold the promise of breaking new ground in our understanding of the brain mechanisms of motor behavior. For example, optogenetic techniques enable the transfection of selected cell types with a light-sensitive protein, rendering them responsive to certain wavelengths of lights. This technique has recently been applied in awake non-human primates and provides the ability to selectively silence target sub-populations of neurons. In addition, ongoing in vitro experiments within cortical and subcortical areas such as the superior colliculus continue to describe, in increasing detail, the microcircuitry neural structures, in turn linking microcircuit function to oculomotor behavior. These studies are likely to provide vital insights into the linkage between the specific eye movement deficits observed in patients (such as the inhibition difficulties that autistic patients have when performing an antisaccade task) and deficits in synaptic transmission in the underlying neural circuits.

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