THE BRAINSTEM CONTROL OF SACCADIC EYE MOVEMENTS

David L. Sparks

The modern era of oculomotor research began with the advent of the chronic single-unit recording method in the late 1960s. Research carried out in the intervening years has made it possible to provide a detailed description of the saccadic command signals that are generated by motor neurons and the formation of these signals in premotor brainstem regions. These findings have been assimilated in control-systems models that simulate important behavioural features of saccades. Despite these great advances, key issues, such as the nature of the feedback signal and the location of the comparator, are unresolved and some of the factors that have impeded progress can be identified.

Movements of the eye have several advantages as a model system for studying the neural control of coordinated, goal-directed movements. Eye movements can be measured accurately, only six muscles control the position of each eye, and the circuits that control eye movements do not need to compensate for variable loads. The neurons that control eye movements are readily accessible to microelectrodes, and oculomotorists think that they understand the types of computation that must be performed to control such movements. The saccadic system is the most intensely studied oculomotor subsystem (BOX 1 and TABLE 1). Information about the distance and direction of a target image from the current direction of gaze is used to produce a rapid movement (a saccade) that brings the image of the target onto or near to the fovea. In this review, I present a brief, general overview of what is known about the brainstem control of saccade execution and evaluate advances in a few key areas.

Horizontal, vertical and oblique saccades

Describing the saccadic command signals that are issued by motor neurons[1–5] and understanding how these commands are constructed in premotor brainstem regions[6–10] were important goals of early chronic single-unit studies. Another goal was to explain the neural bases of stereotyped features of saccades. The relationship between saccade amplitude and duration is linear over a wide range of amplitudes. A single exponential function fits logarithmic plots of peak velocity against amplitude for saccades ranging from the smallest microsaccades up to the largest movements[11].

Motor neuron command signals. The eyes are rotated by the synergistic action of three pairs of extraocular muscles (FIG. 1a). Horizontal eye rotations are produced, primarily, by the medial and lateral rectus muscles. Vertical rotations are accomplished by cooperative contractions of combinations of the superior/inferior rectus and superior/inferior oblique muscle pairs (FIG. 1a). The motor neurons that innervate the extraocular muscles are found in the III (oculomotor), IV (trochlear) and VI (abducens) cranial nerve nuclei (FIG. 2a).

FIGURE 1b illustrates the activity of an abducens motor neuron that innervates muscle fibres in the lateral rectus muscle. Similar activity is recorded from motor neurons that innervate the other extraocular muscles. Abducens motor neurons generate a vigorous burst of spikes (a pulse) before lateral saccades, in which the lateral rectus is the agonist muscle (FIG. 1b, top). The duration of the burst of spike activity is approximately equal to the duration of the saccade. During saccades in the opposite direction, when contraction of the lateral rectus opposes the movement, the discharge ceases completely (FIG. 1b, bottom). During the fixation intervals between saccades, motor neurons discharge at a constant rate that is linearly related to eye position (FIG. 1c). The firing rate increases

Division of Neuroscience, Baylor College of Medicine, Houston, Texas 77030, USA.
e-mail: sparks@cns.bcm.tmc.edu
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PLANT
A term used in control theory to refer to that which is controlled. In the case of eye movements, the oculomotor plant refers to the globe, extraocular muscles, orbital suspensory tissues and any other passive orbital tissues that influence rotation of the eye.

Box 1 | Eye-movement systems

Eye movements are controlled by several subsystems (TABLE 1), each processing different aspects of sensory stimuli, and producing movements with different temporal profiles and reaction times. In primates, visual acuity is high for images that fall on the fovea, where the density of photoreceptors is greatest, but poor for images that fall on peripheral regions of the retina. 'Gaze-shifting' systems allow high-spatial-frequency samples of the visual environment by controlling the direction of the foveal projections of the two eyes. The saccadic system processes information about the distance and direction of a target image from the current position of gaze, and generates high-velocity movements (saccades) of both eyes that bring the image of the target onto or near the fovea. The pursuit system uses information about the speed of a moving object to produce eye movements of comparable speed, thereby keeping the image of the object on or near the fovea. Using information about the location of a target in depth, the vergence system controls the movements of the eyes that will bring the image of the target onto the foveal regions of both eyes.

Visual acuity also depends on the speed of image motion across the retina: 'image slip' must be low for acuity to be high. The oculomotor 'gaze-holding' subsystems compensate for head and body movements that would otherwise produce large shifts of the images of stationary objects across the retina. Vestibular signals related to rotation or translation of the head or body mediate the compensatory eye movements of the vestibulo-ocular reflexes (VOR). Visual signals about the speed and direction of full-field image motion across the retina initiate optokinetic reflexes that supplement the VOR in the low-frequency range.

from zero, when eye position is below threshold (the angle at which the cell is first recruited into action), to about 300 spikes s^{-1} for extreme lateral positions (FIG. 1c). Some abducens motor neurons are recruited into action when the eye is directed 30–40° medially, with the lateral rectus muscle as the antagonist.

When the eye moves, images sweep across the retina and interfere with visual processing. This interference can be minimized by producing short-duration movements. However, the movement that occurs when motor neuron commands are issued depends on the physical properties of the PLANT. Models of the plant that were developed before the first recordings of motor neuron activity had been obtained[12] predicted the motor neuron commands that are needed to generate a saccade. First, a pulse of innervation is required to overcome the viscous drag of the orbital tissue and move the eye at a high speed. The pulse must gradually decline to a final step of innervation that produces a sustained change in muscle tension that compensates for the elastic properties of the plant. Individual motor neurons produce a pulse (the burst), slide (the pulse gradually decays) and step (the position-related change in tonic activity) pattern of activity that is remarkably similar to the innervation signal required by Robinson's early model[12] of the oculomotor plant.

Table 1 | Oculomotor subsystems

Subsystem	Computation	Reaction time (ms)	Velocity (deg. s^{-1})
Gaze shifting			
Saccadic	Distance of target image from fovea	200	400–800
Pursuit	Target velocity	125	0–30*
Vergence	Location of target in depth	160	30–150‡
Gaze holding			
Vestibular	Rotation or translation of head or body	15	Follows head up to 800 deg. s^{-1}
Optokinetic	Speed and direction of full-field image motion	60	Supplements VOR in low-frequency range

*If target motion is unpredictable. ‡Faster if it occurs in conjunction with a saccade.
VOR, vestibulo-ocular reflex.

Brainstem sources of pulse and step commands. Commands for the horizontal and vertical components of saccades originate in different regions of the brainstem[13–15]. Commands for horizontal movements are produced by premotor neurons in the pons and medulla, whereas premotor neurons in the rostral midbrain control vertical movements[16–22].

Several types of neuron that show horizontal saccade-related activity are found in the paramedian zone of the paramedian pontine reticular formation (PPRF) and in the medulla (FIG. 2). Omnipause neurons (OPNs) discharge at a relatively constant rate during fixation, but stop firing during saccades in all directions. The pause begins before the discharge of burst neurons and ends before the end of the saccade. Long-lead burst neurons (LLBNs) and excitatory burst neurons (EBNs) generate high-frequency bursts of activity before ipsilateral saccades (FIG. 3a). The burst of LLBNs is not as tightly coupled to saccade onset as the burst of EBNs. EBNs make excitatory, monosynaptic connections[23,24] with neurons in the ipsilateral abducens (VI) and provide the main source of excitatory drive for the saccade-related pulse of motor neuron activity. The amplitude, duration and velocity of saccades are coupled to the number of spikes generated, burst duration and peak firing rate of the burst of activity, respectively. The tonic activity of many neurons in the nucleus prepositus hypoglossi (NPH) and the medial vestibular nucleus (MVN) is proportional to horizontal eye position, and these cells provide the excitation that is required for the step of motor neuron activity.

Activity in the PPRF is specifically related to the control of horizontal saccades and the horizontal component of oblique saccades (FIG. 3b). Microstimulation of neurons in the PPRF produces horizontal movements[25]. The velocity of saccades to horizontal targets is reduced after reversible inactivation of neurons in the rostral PPRF (FIG. 3c), whereas the speed of saccades to vertical targets remains unaffected[26].

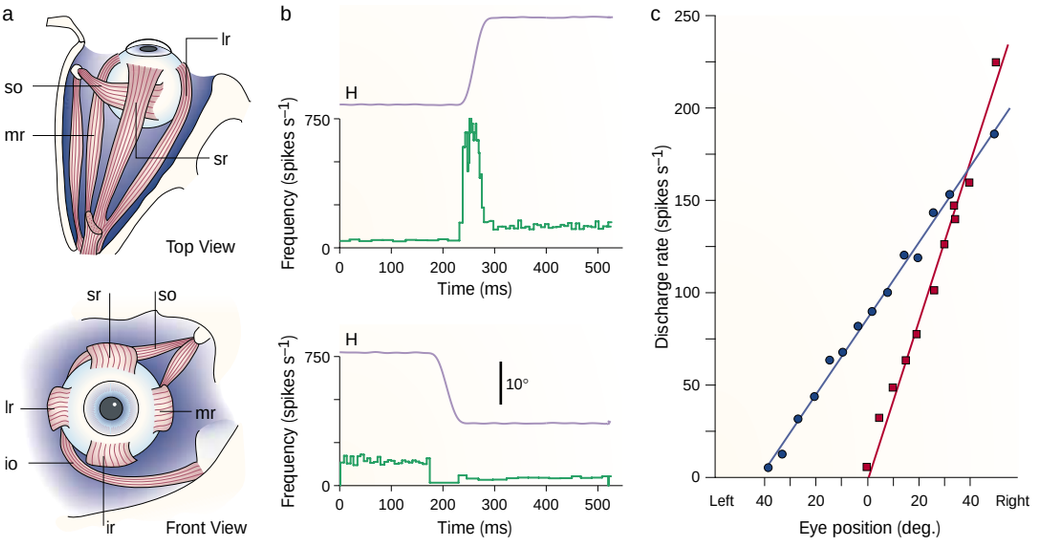

Figure 1 | **Extraocular muscles and typical activity of motor neurons. a** | Drawings of the extraocular muscles showing top and front views of the right eye. The horizontal components of eye rotations are generated by the medial rectus (mr) and lateral rectus (lr) muscles. Vertical and torsional movements are accomplished by the activation of combinations of the superior/inferior rectus (sr/ir) and superior/inferior oblique (so/io) pairs. **b** | The top panel shows horizontal eye position (H; up = right) and a plot of instantaneous spike frequency (the reciprocal of interspike interval) of an abducens motor neuron during a rightward saccade. The bottom panel shows the activity of the same cell during and after a leftward saccade. The motor neuron discharges at a constant rate during fixation, generates a burst before and during the rightward saccade, and stabilizes at a higher, tonic rate during the postsaccadic fixation. **c** | Plot of the rate of discharge during fixation intervals as a function of horizontal eye position for two abducens neurons. There is a linear relationship between the discharge rate and eye position.

Premotor neurons in the rostral midbrain produce the vertical pulse and step commands. Neurons in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) generate a high-frequency burst before vertical saccades and convey this signal monosynaptically to the motor neurons[16–22]. Vertical EBNs that discharge before upward saccades are intermingled with those that discharge before downward saccades in the riMLF. The duration, amplitude and speed of vertical saccades are functions of the burst duration, number of spikes generated and frequency of discharge of vertical burst neurons respectively[19]. Neurons in the interstitial nucleus of Cajal (NIC) and the vestibular nucleus discharge tonically at rates that are linearly related to vertical eye position, and provide the excitatory inputs that produce the step change in motor neuron activity.

Coordination of horizontal and vertical commands. Many saccades have both horizontal and vertical components. Although the commands for the two components are generated in different regions of the brainstem, pontine OPNs inhibit both horizontal and vertical EBNs[27], and tend to synchronize the onsets of the two components. If these commands were otherwise completely independent, movements with horizontal and vertical components of different amplitudes would be curved, because of the associated differences in duration. In fact, oblique saccades are not markedly curved. When the amplitudes of the two components are unequal, the duration of the smaller component is greater than the duration of a pure horizontal or a pure vertical saccade of the same amplitude, and its velocity is reduced[28–31]. The increased duration of the minor component is neurally mediated; abducens neurons[29] and midbrain burst neurons[19] show a decrease in average firing rate and an increase in burst duration under these conditions.

Control of torsional rotations

Donders' and Listing's laws. Saccadic eye movements are stereotyped and obey certain 'laws'. In terms of understanding the three-dimensional control of saccades, the most important of these are Donders' and Listing's laws. Ignoring the small translations that occur during ocular rotations, the eye can be modelled as a ball-and-socket joint with a fixed centre of rotation and three rotational degrees of freedom. The combined actions of the six extraocular muscles allow the control of eye position in all rotational directions. So, theoretically, the line of sight could be directed to a particular location in the visual world with an infinite number of eye positions that are produced by an infinite number of combinations of innervation signals to the six muscles (imagine aiming a laser pointer at a particular object and then rotating it around its long axis). Measurements of the actual rotations of the eye indicate that the eye does not usually use all three degrees of rotational freedom. According to Donders' law, if the head is upright and stationary, and the visual environment is stable, the torsion, or twist of the eye about the line of sight, is invariant for any one direction of the line of sight. For each direction of gaze,

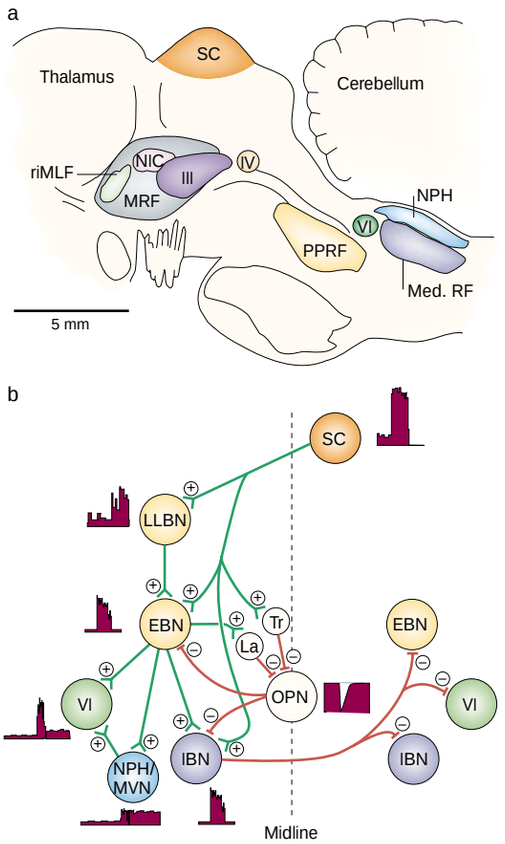

Figure 2 | **Location and connections of brainstem saccade-related neurons. a** | Drawing of the brainstem of a monkey, showing the locations of areas discussed in the main text. III, oculomotor nucleus; IV, trochlear nucleus; VI, abducens nucleus; Med. RF, medullary reticular formation; MRF, midbrain reticular formation; NIC, interstitial nucleus of Cajal; NPH, nucleus prepositus hypoglossi; PPRF, paramedian pontine reticular formation; riMLF, rostral interstitial nucleus of the medial longitudinal fasciculus; SC, superior colliculus. Modified, with permission, from REF. 13 © 1982 Springer-Verlag. **b** | A diagram of the connections of the cell types that are crucial components of models of the horizontal burst generator. VI, abducens motor neuron; EBN, excitatory burst neuron; IBN, inhibitory burst neuron; LLBN, long-lead burst neuron; NPH/MVN, cells in nucleus prepositus hypoglossi or medial vestibular nucleus; OPN, omnipause neuron; SC, superior colliculus. Note the crucial role of the OPNs. These cells inhibit the EBNs, which innervate the motor neurons, and the IBNs, which inhibit motor neurons that innervate antagonistic muscles. Saccades are initiated by a trigger signal (Tr) that inhibits the OPNs. The OPNs are prevented from resuming their tonic discharge during the generation of the saccade command by the activity of 'latch' neurons (La), inhibitory interneurons that relay an inverted output of the EBN burst. Modified, with permission, from REF. 14 © 1996 Elsevier Science.

the eye assumes one, and only one, orientation in the head, and this orientation is independent of the route the eye takes to reach that position. Stated differently, the amount of torsion is uniquely determined by the degree of horizontal and vertical rotation.

Listing's law specifies the particular orientation, or CYCLOROTATION, of the globe for each gaze position. Given an eye position called the primary position, and a head-fixed plane known as Listing's plane (orthogonal to the gaze line in the primary position), Listing's law states that the eye adopts only those positions that can be reached from the primary position by a single rotation about an axis in Listing's plane. Listing's law has been shown to hold during fixations, saccades and smooth pursuit movements. A full description of the brainstem control of saccades must account for the implementation of Donders' and Listing's laws.

Motor neuron commands. Torsional rotations are produced by contractions of combinations of superior/inferior rectus and superior/inferior oblique muscle pairs. Consider the activity of motor neurons that innervate one of these muscles, the superior oblique. On the basis of its pulling direction (FIG. 4a), the superior oblique muscle produces a downward movement with an inward (anticlockwise from the perspective of the subject) torsional component. So, increases in the firing rates of superior oblique motor neurons would be expected to produce rotations around the torsional and vertical axes. However, in accordance with Listing's law[32], during saccadic and pursuit movements made when the head is upright and stationary, the range of torsional eye positions is small. Bursts of activity are associated with downward saccades and, during fixation intervals, steady rates of discharge are linearly related to the vertical position of the eye (FIG. 4b). Listing's law does not hold for rotations of the eye that are generated during vestibular stimulation, and the range of torsional eye positions can be extended by placing subjects in different static roll positions. Under these conditions, the ON-DIRECTION of superior oblique motor neurons has a significant anticlockwise torsional component[32] (FIG. 4c).

The torsional pulse and step commands. As noted above, burst neurons in the riMLF provide monosynaptic excitatory input to the motor neurons that are involved in vertical and torsional rotations of the eye. There are four subpopulations of burst neurons. The right riMLF contains burst neurons with up and down on-directions, but both also discharge during movements with a clockwise (from the subject's point of view) torsional component[33]. Burst neurons in the left riMLF are maximally active during movements that have anticlockwise torsional components combined with either upward or downward directions (FIG. 4d). Reversible inactivation of the right riMLF impairs the generation of quick phases with clockwise components; inactivation of the left riMLF impairs movements with anticlockwise torsional components.

FIGURE 4e shows the pattern of activity of burst cells in the PPRF and riMLF that must occur to produce clockwise torsional movements, or saccades with upward or downward directions[34]. During pure vertical movements, cells in the right riMLF issue commands for a vertical movement and for a clockwise torsional rotation. The torsional command is not obeyed, because cells in the left riMLF are simultaneously sending a competing command for an anticlockwise torsional rotation.

CYCLOROTATION
Rotations around the anteroposterior axis of the globe are known as cycloductions or cyclorotations.

ON-DIRECTION
The direction of movement associated with the maximal discharge of a neuron.

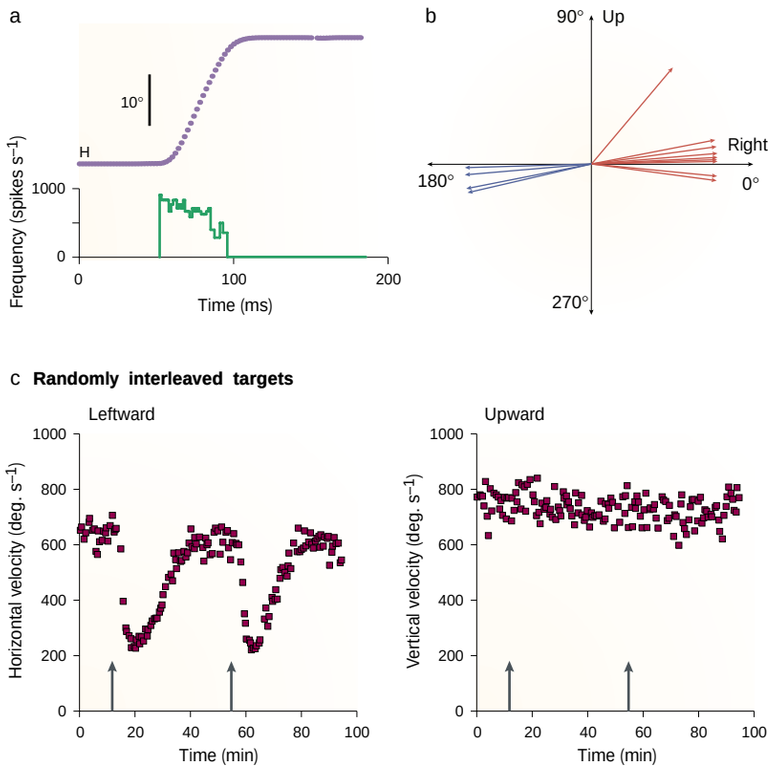

Figure 3 | **The PPRF controls the horizontal component of saccades. a** | Plots of horizontal eye position (H; up = right) during a rightward saccade and frequency of the instantaneous discharge of an excitatory burst neuron (EBN) in the right paramedian pontine reticular formation (PPRF) in association with the movement. **b** | Plots of the 'best-direction' for 14 putative EBNs in the PPRF. Almost all of the neurons are clearly specific for horizontal movements[26]. **c** | The effect of consecutive injections of lidocaine into the PPRF on the peak velocity of saccades to horizontal (left) and vertical (right) target displacements as a function of time. Each point represents a measurement from a single trial; the arrows indicate the times of injections. The measurements shown in the two panels are synchronous because the targets were randomly interleaved. Amount of lidocaine: injection 1, 150 nl; injection 2, 200 nl. After the injection, peak horizontal velocity dropped from about 600° s^{-1} to about 200° s^{-1}. Velocity gradually recovered during the next 30 min, before the second injection occurred. The right panel shows the peak velocity of vertical movements to a target presented 20° above the fixation position. These trials were randomly interleaved with the horizontal movements shown in the left plot. Injections had a large effect on horizontal velocity, but no significant effect on vertical movements. Modified, with permission, from REF. 26 © 2002 New York Academy of Sciences.

Motor neurons in the oculomotor and trochlear nuclei receive excitatory inputs, proportional to vertical and torsional eye position, from neurons in the NIC and the superior vestibular nuclei. NIC neurons show burst–tonic firing patterns during vertical saccades, and lesions or pharmacological inactivation of the NIC impair the ability to maintain vertical and torsional eye positions[35,36].

Command signals in the superior colliculus

The superior colliculus (SC) is the brainstem region that provides the main input to the pontine and midbrain pulse–step generator circuits. The SC receives signals from many cortical and subcortical areas, and sends outputs, at least indirectly, to all of the premotor areas that are involved in the control of eye and head movements[37]. Neurons in the intermediate layers of the SC respond to visual, auditory and somatosensory stimuli, and some are multimodal. The same layers contain other neurons that generate commands for orienting movements of the eyes and head.

Experiments in which the effects of combined cortical and collicular lesions have been tested indicate that, of the SC, the cortical frontal eye fields (FEFs) and the striate visual cortex, none is necessary for the generation of saccades to visual targets[37,38]. If the FEFs are intact, permanent unilateral collicular lesions produce a decrease in the frequency and a small increase in the latency of contralateral saccades[39]. FEF lesions do not prevent saccade generation[40], but monkeys with combined lesions of the SC and FEFs cannot initiate saccades to visual targets[40]. Reversible-inactivation experiments provide a better indication of the role of the FEFs and SC in the control of saccades in normal animals. Large deficits in saccade accuracy and latency are observed after reversible inactivation of the SC[41–44]. Changes in the direction and amplitude of eye movements, evoked by stimulation of the FEFs after inactivation of the SC, support the hypothesis that, in normal animals, much of the control of saccades by the FEFs is mediated through the SC[45].

Early studies of the role of the SC in motor control were conducted in head-restrained animals, in which microstimulation in the intermediate and deeper layers produces contralateral saccadic movements of both eyes with a latency of 20–30 ms (REFS 46,47). The direction and maximal amplitude of stimulation-evoked saccades depend on the location of the stimulating electrode in the SC, but smaller movements will be produced by stimulation of the same site if the stimulation train is not sustained until the site-specific maximal amplitude is obtained[48,49]. Cells that increase their discharge rate before saccades and project to other premotor areas mediate these stimulation-evoked movements. One type of cell generates a high-frequency burst of spikes 18–20 ms before saccade onset (FIG. 2b). The activity of these neurons is tightly coupled to saccade onset, but each cell discharges before a range of saccades that have particular directions and amplitudes, the 'movement field' of the cell. The burst precedes movements of the same direction and amplitude, regardless of the initial position of the eye in the orbit; the discharge is related to changes in eye position, not to movements to a particular position.

Cells that generate saccade-related bursts (and which, when stimulated, produce saccades) are arranged topographically in the SC (FIG. 5a). Neurons in the rostral SC discharge before movements with small amplitudes, whereas those in the caudal SC discharge before larger movements. Upward saccades are represented medially; downward saccades, laterally (FIG. 5b). The location of the active population of collicular neurons in the topographical map of movement fields, rather than their spike frequency or other attributes of firing, codes information about saccade direction and amplitude. Unlike pontine and midbrain EBNs, individual collicular neurons do not encode saccade amplitude or velocity by the number or frequency of spikes generated (FIG. 5c,d).

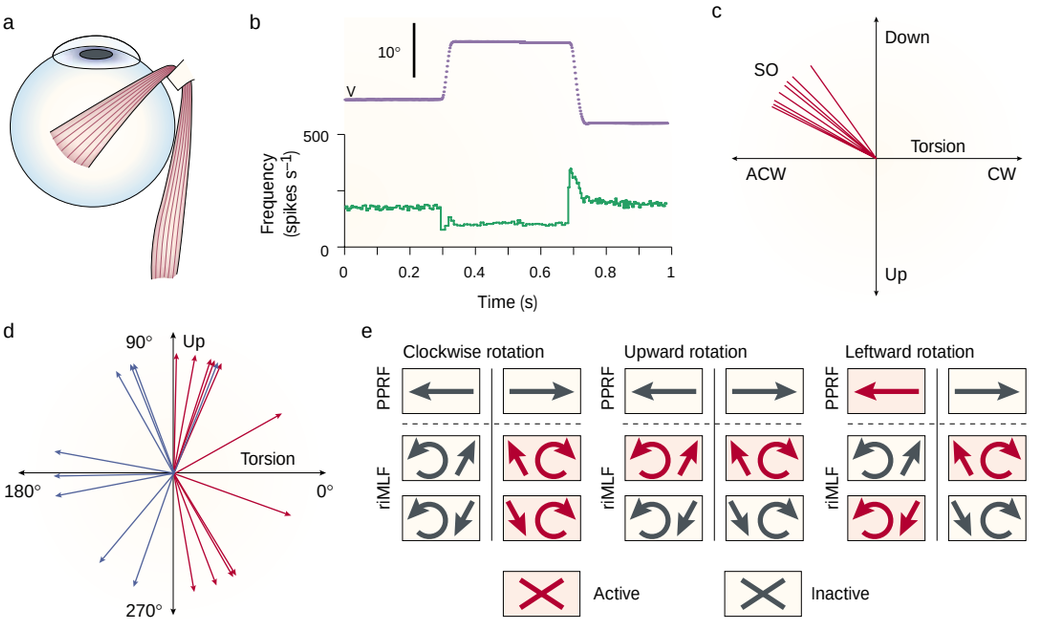

Figure 4 | **Control of torsional rotations. a** | Drawing of the superior oblique muscle of the left eye. **b** | Plot of vertical eye position (*V*) and instantaneous spike frequency of a motor neuron that innervates the superior oblique muscle, before, during and after upward and then downward saccades. **c** | On-directions in Listing's reference frame of superior oblique motor neurons projected onto the *x* (torsional) and *y* (vertical) planes. ACW, anticlockwise; CW, clockwise. Modified, with permission, from REF. 32 © 1999 Springer-Verlag. **d** | Best-directions of excitatory burst neurons (EBNs) in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). Cells in one riMLF (red) have either up or down on-directions and a positive torsional component to the best-direction. Cells in the opposite riMLF (blue) have up or down best-directions with a negative torsional component. Modified, with permission, from REF. 33 © 1989 Springer-Verlag. **e** | Scheme describing how cells in the riMLF must be recruited to produce different types of movement. To produce clockwise rotation (during vestibular stimulation, for example) up and down cells in right riMLF must be recruited. The up and down (and small left and right) components cancel , but clockwise torsion summates. To produce an upward saccade, up cells in the left riMLF and up cells in the right riMLF must be recruited. The up components add, whereas left and right components, and clockwise and anticlockwise torsion, cancel. To produce a leftward saccade, cells in the left paramedian pontine reticular formation (PPRF), up cells in the right riMLF and down cells in the left riMLF are recruited. The torsional and vertical components of riMLF activity cancel, but leftward components add. Modified, with permission, from REF. 34 © 1992 The American Physiological Society.

The movement fields of SC neurons are large and coarsely tuned[50,51]. As a consequence, many neurons are active before and during each saccade. The results of reversible-inactivation experiments are consistent with the predictions of vector-averaging models that assume that each member of the active population contributes to the direction and amplitude of the ensuing movement[42,52,53].

Microstimulation of the deeper layers in the caudal SC produces coordinated movements of the eyes and head (FIG. 5e). As for natural orienting movements, the ratio of the eye and head contributions to the gaze shift depends on the initial position of the eye in the orbit[54] (FIG. 5f). The three-dimensional (horizontal, vertical and torsional) characteristics of stimulation-evoked movements of the eyes and head[55] are almost identical to those of visually guided movements. The collicular map is two-dimensional. Collicular commands specify the horizontal and vertical components of eye and head movements, but not the torsional component[56,57]. Donders' and Listing's laws for the head and eye are implemented by downstream modifications of the collicular command.

How are coordinated movements of the eyes and head represented at the level of individual collicular neurons? It is surprisingly difficult to determine whether the activity of collicular cells represents a command to move the eyes or the head, or a command for a change in gaze that can be accomplished by different combinations of eye and head movements[58]. More experiments are needed, but studies of the activity of collicular neurons in head-unrestrained cats[59] and monkeys[60] indicate that the activity of movement-related cells represents a general command for a change in the direction of gaze, not a specific command for moving either the eyes or the head.

At one level of analysis, the task of programming a particular saccade or a particular gaze shift that involves coordinated movements of the eyes and head merely involves activating the appropriate region of the collicular map. Once collicular neurons are driven into a high-frequency burst mode[61], an accurate movement of the desired direction and amplitude will occur. For small changes in gaze that can be accomplished by eye movements, the speed and amplitude of the movement will be related in a lawful manner, and the horizontal and vertical

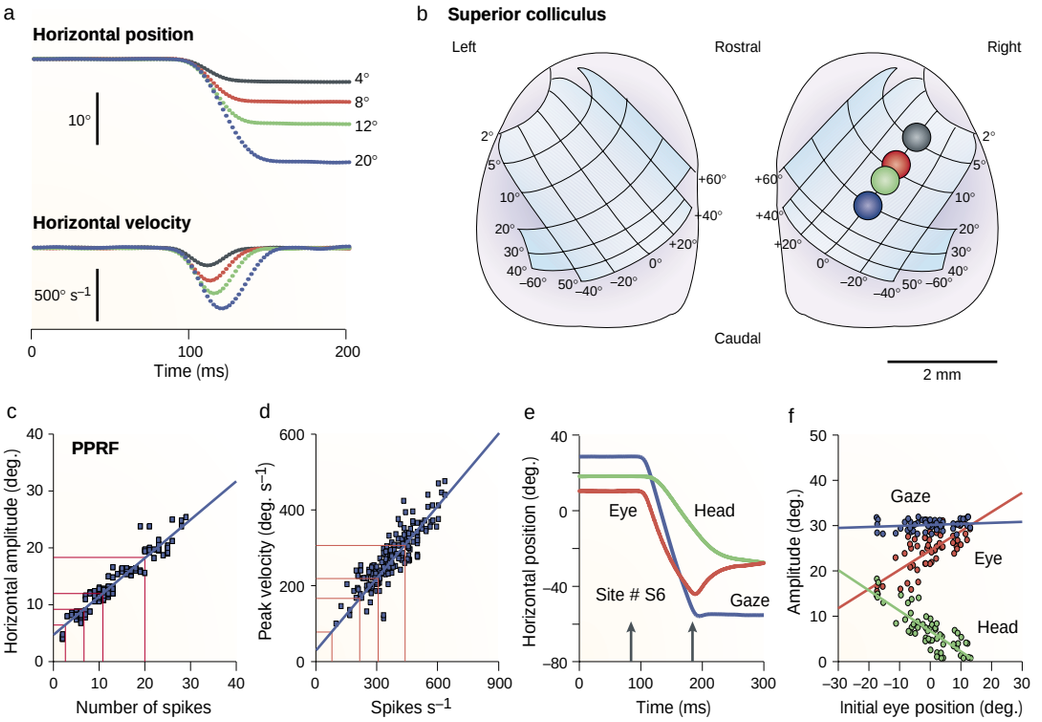

Figure 5 | **Comparison of PPRF and collicular control of saccades. a** | Horizontal position and velocity traces representing four leftward saccades of different amplitudes. **b** | The cells that are maximally active before each movement reside in different regions of the collicular motor map. Information about saccade direction and amplitude is represented as a place code. It is the location of the cells in the map, not their discharge characteristics, that determines saccade direction and amplitude. Isoamplitude lines (2°, 5°…40°) and isodirectional lines (0°, ±20°…±60°) are shown. **c** | Plot of horizontal amplitude as a function of the number of spikes in the burst of a paramedian pontine reticular formation (PPRF) neuron. **d** | Plot of average horizontal velocity as a function of peak frequency in the saccade-related burst of a cell in the PPRF. **e** | A coordinated movement of the eye and head produced by microstimulation of neurons in the deeper layers of the caudal superior colliculus. The positions of the eye, the head and the gaze, and the sum of eye and head, are plotted as a function of time. The arrows indicate the onset and offset of the stimulation train. The stimulation train consisted of brief 0.2 ms pulses of stimulation delivered at 500 Hz with a current of 50 μA. Shortly after the onset of the stimulation train, the eye began to move to the left, and after a short delay, the head began to move in the same direction. When gaze reached a particular amplitude, the head continued to move for about 100 ms, but the eye counter-rotated and the direction of gaze remained stable. This stimulation-evoked gaze shift is remarkably similar to visually guided gaze shifts of this amplitude. **f** | This plot shows 57 gaze shifts evoked by stimulation of the same collicular site with the same stimulation parameters. The position of the eyes in the orbits at the time of stimulation onset varied from 20° left to 14° right, but a gaze shift of about 30° was always evoked. This 30° gaze shift was sometimes accomplished with a 15° head movement and a 15° eye movement; at other times, it was seen with a 5° head movement and a 25° eye movement. Stimulation of a particular collicular site using constant stimulation parameters produces gaze shifts that have relatively constant amplitudes and directions, but does not produce a particular eye movement coupled with a particular head movement. Panels **e** and **f** modified, with permission, from REF. 54 © 1996 The American Physiological Society.

components will be coordinated so that the trajectory is relatively straight. Premotor cells in the PPRF and riMLF will generate the patterns of excitation that are required for a pulse and step of motor neuron innervation, and the movement will automatically obey Listing's law. For larger changes in gaze that are accomplished by a combination of eye and head movements, the ratio in which the eyes and head are recruited into action will be automatic, depending on the initial positions of the eyes in the orbit and the amplitude of the requested movement. The horizontal, vertical and torsional positions reached by both the eyes and the head will obey Donders' and Listing's laws. The commands to accomplish this are generated by neurons with broadly tuned receptive fields and coarsely tuned movement fields. The intrinsic and extrinsic anatomical connections are such that even crude, non-physiological stimulation is sculpted into spatial and temporal patterns of activity that generate movements that are indistinguishable from those produced by normal physiological inputs.

From this perspective, understanding the neural basis of the execution of orienting gaze shifts is reduced to solving four problems: first, determining how the appropriate region of the collicular map is addressed by other brain areas; second, describing the spatial and temporal pattern of collicular output associated with the initiation and execution of the gaze shift; third, understanding the intrinsic and extrinsic connections that mould the collicular output during the course of the movement; and fourth, describing the transformations of collicular signals that occur before the command signals reach the motor neuron pools.

Descriptions of the progress that has been made in solving some of these problems and the factors that impede more rapid advances are given below. Progress in understanding how the (primarily) place-coded command signals in the SC are translated into temporally coded signals in the motor neurons has been slow[62], perhaps because there is little agreement on the transformations that are required or where they occur, and because of limitations of available methods.

Models of the saccadic system

Horizontal, vertical and oblique saccades. Although early models of saccade generation were ballistic, with the number of spikes in the motor neuron burst being determined before the movement began, current models assume that saccades are under feedback control. Two observations triggered this change. The first was the finding that patients with neurological lesions produce slow saccades, some of which seem to be modified mid-flight[63], which stimulated the development of a feedback model[64]. The second was that saccades to briefly visible targets can be interrupted mid-flight by microstimulation of the pontine OPNs that inhibit the EBNs. If the interruption is brief, the saccade is resumed after the interruption and directs the line of sight to the location of the (no longer visible) target[17,65–67]. In addition, reversible inactivation of neurons in a small region of the PPRF produces large reductions in saccadic velocity, but the duration of the movements increases to compensate for the changes in speed, as would be expected if the activity of EBNs were under feedback control[26].

What is the source of the feedback? It is not visual: a saccade ends before signals from the retina reach central visual areas that could provide the necessary feedback. Nor is it derived from sensory receptors in extraocular muscles: saccadic accuracy is not affected significantly by the elimination of proprioceptive feedback[68]. Zee and colleagues[63] proposed that a copy of a motor command (corollary discharge) is used as a feedback signal for controlling saccade amplitude, a suggestion that has been incorporated into almost all contemporary models of the saccadic system.

Robinson used some of the neural elements shown in FIG. 2 in a local-feedback model that was designed to simulate horizontal saccades[64]. The model has two inputs: a signal of the desired horizontal position of the eyes (DHP) and a trigger signal. Saccades are initiated by a trigger signal that briefly inhibits the pause cells, permitting the EBNs to discharge at a rate that is proportional to the horizontal motor error (the difference between the DHP and an internal estimate of current horizontal eye position, CHP). The pulse of activity that is generated by EBNs is transmitted directly to motor neurons and to a neural integrator[69,70]. The neural integrator converts the pulse into a step of activity (observed in the activity of tonic cells) that is sent to motor neurons and used as the estimate of CHP. Once activated, this circuit drives the eye at a high velocity until the representation of CHP matches the DHP signal. At this point, the eye stops on target and the pause cells are allowed to resume firing, thereby inactivating the saccadic generator until a new trigger signal arrives.

Most current models of the saccadic system have modified Robinson's original model[64] (position model) so that the input to the burst generator circuits is the desired change in eye position (displacement models). The main inputs to the saccade burst-generator circuits are signals related to changes in eye position, not signals of the desired orbital position of the eye.

Both position and displacement models can generate saccades with normal velocity profiles and produce saccades of all sizes that have correct amplitude–duration and amplitude–velocity relationships. However, position or displacement models that merely include independent pulse–step controllers for the horizontal and vertical components of saccades do not produce oblique saccades with straight trajectories. Even if the onsets of the pulses generated by the horizontal and vertical controllers are synchronized by OPNs, their offsets can be asynchronous and result in curved saccades. To prevent this, the velocity of the minor component must be reduced by lowering the discharge frequency of its EBNs so that the durations of the two components are equal[19]. Several modifications of Robinson's model have been proposed[71–74] to account for the coordination of the horizontal and vertical components of oblique saccades. The models assume that the increase in duration of the smaller component occurs because of coupling between the vertical and horizontal burst generators. Existing data are more consistent with the predictions of models in which the cross-coupling occurs at the input stage[74] rather than at the output stage[73].

Three-dimensional models. The position and displacement models described above use a neural integrator to construct an eye-position signal (the step command) from the output of saccade-related burst neurons in the pons and midbrain (the pulse command). Tweed and Vilis[75] argued that because of the NON-COMMUTATIVITY of spherical rotations, eye position is not the integral of eye velocity, and that models using a Robinsonian neural integrator cannot be easily extended to handle three-dimensional rotations. They outlined a model of the saccadic system[76] in which a signal of the desired gaze displacement was coded in head coordinates upstream of the SC. The gaze-vector signal passed through a LISTING'S LAW OPERATOR and the output was combined with a signal of current eye position to determine the site of collicular activation. The site of activation in the SC controlled the rotation of the eye in three dimensions rather than, as is usually assumed, in two. The Listing's law operator, a constraint on craniotopic eye position, was placed upstream of the SC so that the operation occurred at a level where saccades are still coded in craniotopic coordinates. Experiments motivated by this model[56,57] failed to find evidence for torsional-eye-movement signals in the SC.

Nonetheless, this model stimulated interest in devising schemes by which Listing's law can be obeyed. Some saccade models emphasize the importance of the mechanical properties of the oculomotor plant in the

NON-COMMUTATIVITY
Having the property that the results of a mathematical operation on elements might produce different results depending on the order in which the elements are used.

LISTING'S LAW OPERATOR
A hypothetical neural circuit that performs the computations required to implement Listing's law.

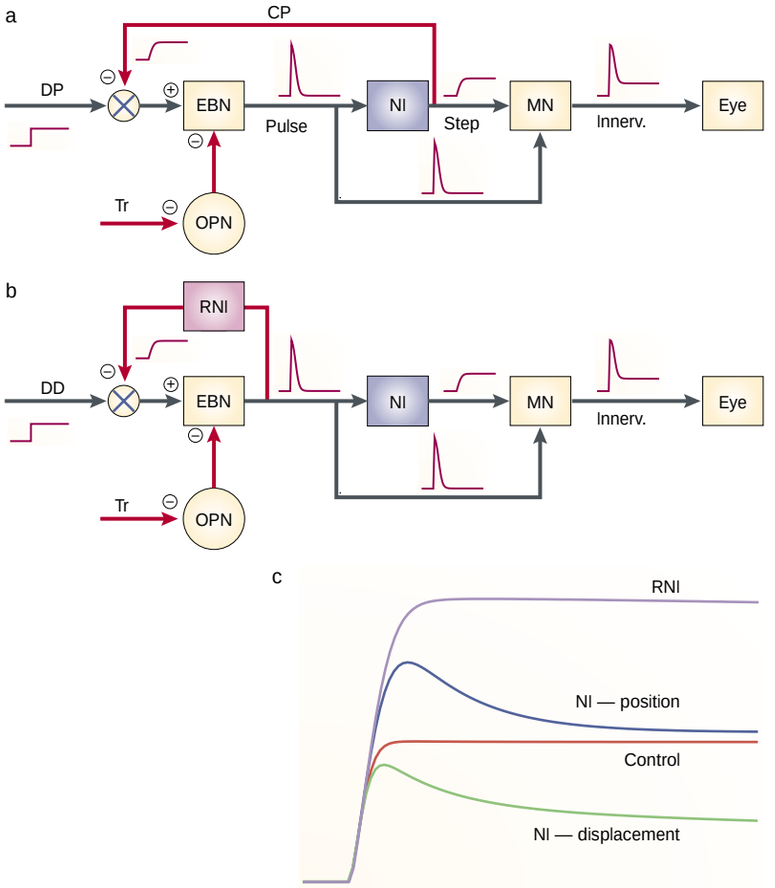

Figure 6 | **Position and displacement models of saccade generation. a** | Schematic drawing of a position model. CP, current position; DP, desired position; EBN, excitatory burst neuron; MN, motor neuron; NI, neural integrator; OPN, omnipause neuron; Innerv., innervation signal; Tr, trigger signal. **b** | Schematic drawing of a displacement model. DD, desired displacement; RNI, resettable neural integrator. **c** | Predicted consequences of lesions of the NI and RNI. Red trace, control saccade; blue trace, effect of lesion of NI in position model; green trace, effect of lesion of NI in displacement model; purple trace, effect of lesion of RNI.

implementation of Listing's law, and an explicit torsion signal is not used. These models are based on profound changes in our understanding of the functional structure of extraocular muscles. Historically, the muscles could be represented as 'strings' that run straight from their origin in the posterior orbita to their insertion into the globe. But it has been discovered that the paths and pulling directions of extraocular muscles are dominated by fibromuscular pulley structures that restrict the paths of the muscles[77]. The implications of muscle pulleys for the neural control of eye movements are still being explored[78,79]. Some researchers[80–82] are convinced that independent control of the torsional component of eye position is required to explain observed violations of Listing's law (vestibulo-ocular reflexes or combined eye–head movements). Whether pulleys allow the oculomotor system to operate without non-commutative computations is still under debate[83]. The hypothesis that the brain has a Listing's operator — a network that converts two-dimensional information about target direction into three-dimensional commands for eye movements — is also controversial.

Unresolved issues

Several key issues concerning the neural control of saccades are unresolved. Two of these are the type of feedback signal that is used in the control of saccades, and the location of the neurons that are involved in comparing the input and feedback signals. Some of the factors that have impeded progress in these areas are described in this section.

Three types of corollary discharge feedback are used in current models of the saccadic system. Position models use a copy of the command for the step change in eye position. Displacement models use a signal derived from the pulse command that represents how far the eye has moved during the current saccade. Other models assume that it is gaze (the direction of the line of sight) that is under feedback control[84,85], and these models also require a feedback signal about head movement. The anatomical location of comparator circuits also remains unresolved. Proposed sites for the comparator include the SC, cerebellum, PPRF (for the horizontal component) and riMLF (for the vertical and torsional components). Why have these fundamental questions about the type of feedback used and the location of the comparator not been answered?

Intermingling of signals in the brain. The first potential problem is that signals that are segregated in the models are often intermingled in the brain. Schematic diagrams of position and displacement models are shown in FIG. 6. FIGURE 6c shows a control saccade (red trace) and movements produced after simulated lesions. Immediately after a lesion of the neural integrator (NI in FIG. 6a–c), position models predict that saccades will be hypermetric (FIG. 6c, blue trace), whereas displacement models predict a small hypometria (FIG. 6c, green trace). Because the step command will be too small, both models predict that the eye will not maintain the postsaccadic position.

These differential predictions of alternative models are difficult to test, because the activation or inactivation of neurons that carry one signal also influences the activity of neurons that convey different signals in adjacent brain regions. Consider horizontal saccades. Neurons in the MVN and NPH convey the output of the neural integrator to motor neurons, but because of the proximity of these nuclei to the abducens nucleus, and the spread of pharmacological agents used to produce reversible inactivation, experimental results are difficult to interpret. Hypometria or the absence of hypermetria could be due to the inactivation of nearby motor neurons. Perhaps because of these problems of interpretation, inactivation experiments[86–88] have focused on the failure to maintain the postsaccadic position rather than on saccadic accuracy. The accuracy of saccades to visual targets was not impaired significantly after permanent lesions of the NPH and MVN[89], but accuracy was not

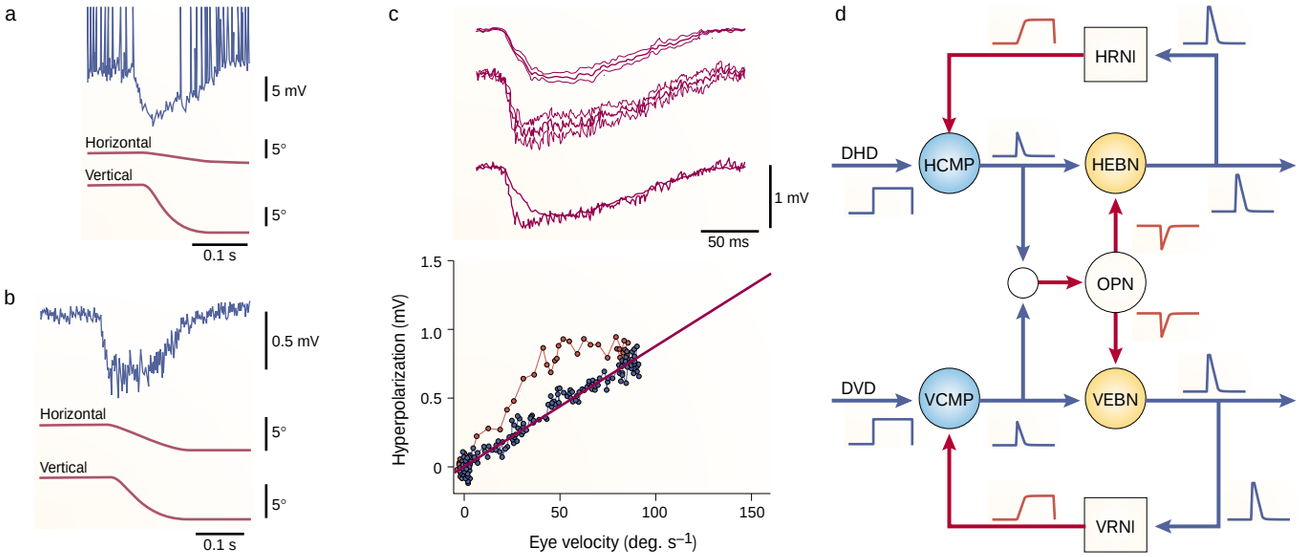

Figure 7 | **Saccade-related hyperpolarization in OPNs. a** | Intracellular recording of the membrane hyperpolarization and pause of firing that are associated with a saccade. **b** | Saccade-related hyperpolarization after inactivation of the spike-generation mechanism. **c** | The top panel shows the relationship between the saccade-related hyperpolarization of omnipause neurons (OPNs) and instantaneous eye velocity. Average eye velocity for four saccades with similar velocity profiles is plotted in the top traces (thick and thin lines indicate the mean ± s.e.m.); average membrane potential is presented in the middle traces. Average velocity and average membrane potentials are superimposed in the third set of traces. The bottom panel shows the relationship between the instantaneous amplitude of the hyperpolarization and the instantaneous eye velocity. The red circles represent the increasing phase of eye velocity; the blue circles represent the declining phase of eye velocity. During the declining phase, the OPN hyperpolarization and eye velocity are almost perfectly aligned (r = 0.98). Modified, with permission, from REF. 93 © 1999 The American Physiological Society. **d** | The hyperpolarization observed in OPNs is the mirror image of the combined outputs of horizontal (HCMP) and vertical (VCMP) comparators. DHD, desired horizontal displacement; DVD, desired vertical displacement; HEBN, horizontal excitatory burst neuron; HRNI, horizontal resettable neural integrator; OPN, omnipause neuron; VEBN, vertical excitatory burst neuron; VRNI, vertical resettable neural integrator. Red lines and arrows represent inhibitory signals; blue lines and arrows indicate excitatory signals.

measured immediately after the lesions, and compensatory mechanisms could have masked an initial deficit. For vertical saccades, cells with activity that represents the output of the neural integrator reside in the NIC, and the activation or inactivation of neurons in this nucleus is also likely to affect the pulse output because of the proximity of the NIC to the riMLF.

Displacement models predict that lesions of the resettable neural integrator (RNI in FIG. 6b,c) will produce hypermetric movements with normal pulse–step innervation ratios (FIG. 6c, purple trace). This prediction is also difficult to test. For example, in two models[90,91] of horizontal saccades, the comparison occurs at the level of LLBNs in the PPRF. Although cells with the discharge properties required by these models have been observed[14,15] and the anatomical connections required by the models are known to exist, it is difficult to test these models by the inactivation of neurons, because the output neurons (EBNs) and the cells that carry the feedback signal reside in the same area.

Signals that are separate in the models might be carried by different neurons in the same nucleus; alternatively, a single neuron might carry more than one signal. In the vertical pulse-generator circuit, the burst cells in riMLF project to the NIC, where the vertical step signal is generated. Some cells in the NIC generate a saccade-related burst that is transmitted back to riMLF and could provide a feedback signal of vertical displacement[35]. If this is the feedback pathway, the results of inactivation of NIC will be equivocal. Both the feedback pathway and the output of burst–tonic cells in NIC (providing excitation that contributes to the motor neuron burst) will be affected.

Relative timing of signals. The relative timing of saccade-related signals cannot be used as the sole criterion for identifying the location of the comparator circuit. If visual or proprioceptive signals were the source of the feedback signals, then neural events that precede the onset of a movement could be excluded from consideration as a feedback signal. But movement-related signals that occur before saccade onset or during the execution of the movement could be the source of corollary-discharge feedback. In theory, the comparison between signals that represent the desired movement and the corollary-discharge feedback could occur in any neural structure receiving inputs from cells with activity that specifies the desired movement and from cells with activity that relates to the pulse or step command. Given the extensive reciprocal connections between the brainstem areas involved in generating the pulse–step command, few brainstem regions can be excluded from consideration as the locus of the comparator using timing as the criterion.

Different models produce similar signals. Electrophysiological findings that are consistent with the predictions of feedback models of the saccadic system might not distinguish between models that use different types of feedback signal. For example, the firing rate of pontine burst neurons is highly correlated with motor error, the difference between instantaneous eye position and desired eye position[92]. The finding that the relationship between firing rate and motor error follows a common trajectory for saccades of all sizes provides strong support for the hypothesis that saccades are under feedback control, but the motor error signals produced by position and displacement models are identical.

Yoshida and colleagues[93] found that the membrane potential of OPNs showed a large hyperpolarization before each saccade and that the hyperpolarization was sustained for the duration of the movement (FIG. 7a,b). The hyperpolarization has two components. The initial, steep segment has a sudden onset and is not highly correlated with eye velocity. Later, the hyperpolarization gradually declines as the velocity of the saccade is reduced; the decay of the hyperpolarization has a time course similar to that of the decay of eye velocity. Attenuation of the hyperpolarization is due to the temporal summation of inhibitory postsynaptic potentials; accordingly, the hyperpolarization can be reversed to depolarization by the intracellular injection of Cl^- ions.

The relationship between the instantaneous amplitude of the hyperpolarization and the instantaneous eye velocity is shown in FIG. 7c. During the declining phase of the eye velocity, the OPN hyperpolarization and eye velocity are almost perfectly aligned for horizontal, vertical and oblique saccades. As models indicate, the OPNs receive a strong inhibitory input before saccade onset, presumably from the 'trigger' signal. The OPN-mediated inhibition of horizontal and vertical EBNs is removed, and the EBNs generate a burst of activity. During the saccade, OPNs continue to receive inhibitory inputs that reflect the integrated output of horizontal and vertical EBNs, exactly the signal that is required by feedback models, as indicated schematically in FIG. 7d. So, intracellular recordings from OPN neurons in alert cats provide strong evidence for the existence of a feedback signal, but because of the similarity of signals in position and displacement models, the data are consistent with predictions of both types of model.

Single-cell activity versus population output. Many models of the saccadic system are 'lumped' models, in which the signal generated by a population of neurons is represented by a single element in the model. The activity of individual cells in the population might differ significantly from the total population output. From the perspective of understanding saccade generation, it is crucial to obtain good estimates of the population output. But this is problematic, as illustrated in the following example.

The total innervation needed to hold the eyes in a fixed position depends on the eye position[94,95]; the innervation required to produce a saccade of a given amplitude depends on both initial position and saccade direction[95,96]. It is important to learn how the position-dependent

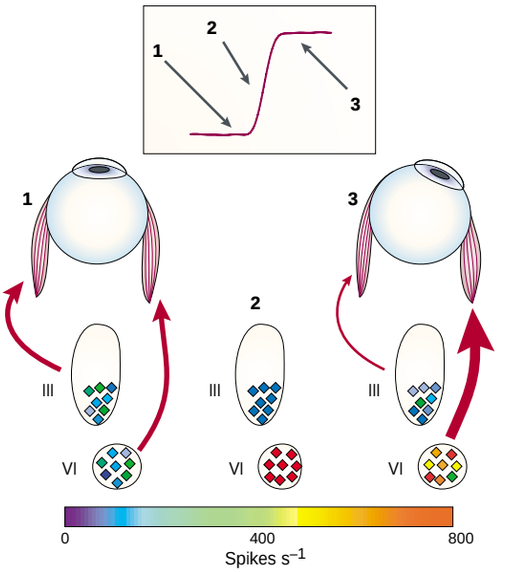

Figure 8 | **Activity of motor neurons innervating agonist and antagonist muscles before and during a saccade.** When the eye is in a stable position near the centre of the orbit, a subset of motor neurons in the abducens nucleus (VI) discharge steadily at low rates. A subset of motor neurons in the oculomotor nucleus (III) that innervate the medial rectus will also be active. The eye is centred in the orbit horizontally because the output (represented by the width of the arrows) of the two motor neuron pools is approximately equal (time **1**). During a lateral saccade, all abducens motor neurons are recruited into action and discharge at high rates while, for a brief period, the medial rectus motor neurons are silent (time **2**). After the saccade (time **3**), more abducens motor neurons are active at higher rates (compared with the presaccadic fixation interval) and fewer medial rectus motor neurons are active. This change in the ratio of tonic output of the two motor neuron pools produces the step in innervation that is required to hold the eye in the new postsaccadic position.

signals are generated, but the innervation signals that are delivered to the extraocular muscles (FIG. 6) cannot be determined from single-cell recordings. FIGURE 8 illustrates, schematically, the pattern of recruitment of motor neurons that innervate the medial and lateral rectus muscles during a horizontal saccade. It is obvious that eye motion and postsaccadic eye position depend on the pattern of activity in both agonist and antagonist motor neuron pools[97,98]. Extraocular muscles contain at least six muscle fibre types with unique histochemical and ultrastructural features[99]. Some are twitch fibres that are typical of mammalian skeletal muscle, but slow muscle fibres, more characteristic of avian and amphibian muscles, are also found in extraocular muscle. The contractile strength of the muscle fibres varies over a large range[100–102]. Ideally, we would like to reconstruct the spatial and temporal pattern of motor neuron activity and weight the activity of each motor neuron by a factor reflecting the contractile properties of the muscle fibres that are innervated. However, the outputs of the motor neuron pools are not well characterized. Sample sizes of motor neuron activity are much too small to provide veridical estimates. Furthermore, during chronic single-unit studies, the

muscle fibre type that is innervated by the motor neuron being studied is not known.

A similar problem exists at each previous stage of signal processing. For example, motor neurons burst for saccades in the pulling direction of the muscle and pause for saccades against the pulling direction. In detailed versions of position and displacement models, motor neurons are continuously driven in push–pull by ipsilateral and contralateral burst cells[92]. So, an accurate description of the EBN input to motor neuron pools (pulse in FIG. 6) requires a reconstruction of the outputs of the populations of ipsilateral and contralateral burst cells that project to the motor neurons. Moreover, the signal of each cell must be weighted by a measure of the synaptic strength of the cell's connection with motor neurons. Current estimates of the EBN input to motor neurons are obtained by averaging the outputs of putative EBNs (cells with functional properties similar to those of identified EBNs). It is assumed that all the cells in the sample actually send projections to motor neurons, and that the synaptic weightings for the cells are equal.

Summary

Overall, there have been important advances in our understanding of the brainstem mechanisms involved in saccade execution — the foundation on which studies of higher-level processing (for example, target and response selection, attention and plasticity) are based. Anatomical studies have provided a detailed outline of the connectivity of the brainstem structures involved in the control of saccades[103]. Descriptions of the morphological features and connectivity of functional classes of cells (which must be defined in studies of behaving animals) have emerged from heroic anatomical and electrophysiological studies[14]. Chronic single-unit recording experiments have provided a broad picture of the types of saccade-related activities that are generated by brainstem neurons and the temporal flow of these signals. These findings have been incorporated into detailed models of the saccadic system. As methods for measuring eye movements were refined and new psychophysical data became available, the goals of neuroanatomical and neurophysiological experiments were modified to search for neural and peripheral mechanisms that account for the newly discovered behavioural relationships. Progress in understanding the low-level control of saccades has been impeded by the physical intermingling of different signals and the associated inability to study the functional consequences of removing or modifying particular signals. The difficulty of accurately reconstructing the signals produced by populations of distributed neurons, and the weighting with which signals are transmitted to muscle or other brain regions, are factors that must be overcome. These are problems that are encountered in all areas of systems neuroscience.

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Acknowledgements

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