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Why move the eyes if we can move the head?

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ABSTRACT: To see while moving is a very basic and integrative sensorimotor function in vertebrates. To maintain visual acuity, the oculomotor system provides efficient compensatory eye movements for head and visual field displacements. Other types of eye movement allow the selection of new visual targets and binocular vision and stereopsis. Motor and premotor neuronal circuits involved in the genesis and control of eye movements are briefly described. The peculiar properties and robust biomechanics of the oculomotor system have allowed it to survive almost unchanged through vertebrate evolution. © 2000 Elsevier Science Inc.

KEY WORDS: Eye movements, Extraocular motoneurons, Oculomotor system, Optokinetic reflex, Prepositus hypoglossi, Saccades, Vestibulo-ocular reflex.

INTRODUCTION

To read these lines, your eyes have to move from left to right in short, fast, angular displacements called *saccades*. Each saccade is followed by a period of ocular immobility called *fixation*. Since stable images on our retina are necessary for accurate visual perception, acquisition of visual information only takes place during eye fixations. So, for reading, the eyes do not move smoothly along the printed line. Once the semantic content of a group of words (2–3) is grasped, the eyes will repeat the saccade, in the direction of the printed line, to the next group of words. During reading, saccade amplitude is about 2–3° (i.e., the amplitude of 6–10 typographic characters), but with a high angular velocity (up to 500°/s), and a duration 30–50 ms. Each fixation usually lasts for 200–300 ms. As the mean latency to elaborate a saccadic movement is 150–200 ms, saccade programming has to be carried out at the same time as the acquisition of information from the text during eye fixation. The number of eye saccades and the duration of each intermediate fixation depend on the conceptual difficulty of the read text [18]. When your eyes arrive at the right end of the printed line they have to perform a larger saccade (10–20° depending on the page width) to the beginning of the next line down, and so on to the end of the article (Fig. 1A).

Obviously, human eyes are not designed exclusively for reading from left to right, as in other cultures, people are able to read at the same speed from right to left (Arabic writing) or vertically (Chinese ideographic systems). Although we are not conscious of eye movements during reading, you might notice them by softly applying a finger to the upper eyelid. But then, the attention focus will concentrate on eye motorics and not on the text content. Finally, if you get tired with what you are reading, your saccades will decrease in velocity and precision, and eye fixation will become less stable, with a decrease in visual acuity. If your attention is completely disconnected from the text, your eyes will probably stay motionless at the center of the orbits, your lids will close, the tone of your neck muscles will decrease, and you will have a restorative nap on the journal.

TYPES OF EYE MOVEMENT

Two Motor Reflexes Designed for Eye Stability

Primates (but not horses) have lost independent mobility of their ears for sound location, probably in parallel with higher neck mobility. But different motor systems have different motor constraints. For example, if the eyes were stuck to the head (like a stamp), the head would need to be as motionless as the printed page, and at a fixed distance from it, for us to be able to see the letters. Since in reality our head is always moving, its movements would make reading impossible, unless we managed to have motionless eyes fixed on the motionless text. You will be aware of part of the problem if you attempt to read at the same time as eating a bag of crunchy potato chips. In fact, primates (including humans) are able to respond to objects that do not move, but we still need a stable image on our fovea for visual acuity.

Try the following simple experiment. Fix your eyes on a word on this page and shake your head (as in the gesture of "no"). You will notice that the head movement (usually carried out at 0.5–1 Hz) does not impede your ability to go on reading. In this situation, reading is possible because the head movement is compensate by the *vestibulo-ocular reflex* (VOR), which evokes a movement of the eyes in a direction opposite to that of the head. Thus, the fovea remains focused on the text despite the head rotation (Fig. 1B).

You will also notice that the contrary is not symmetrical. That is, if, keeping your head still, you move this journal in a sinusoidal fashion at a speed similar to the one you used to move your head, you will be unable to see the written words. However, if you try again, this time moving the journal very slowly in your visual field, you will be able to read it, as when moving the head (Fig. 1C). This second automatic response allowing a global visual motion to be followed with the eyes is called the *optokinetic reflex* (OKR). Two important conclusions can be drawn from this experiment. The first is that each of these reflexes covers a different range in the speed of visual objects travelling over the retina. The second is that they have a different origin: the VOR is generated by activation of the vestibular apparatus located within the bony labyrinth, while the

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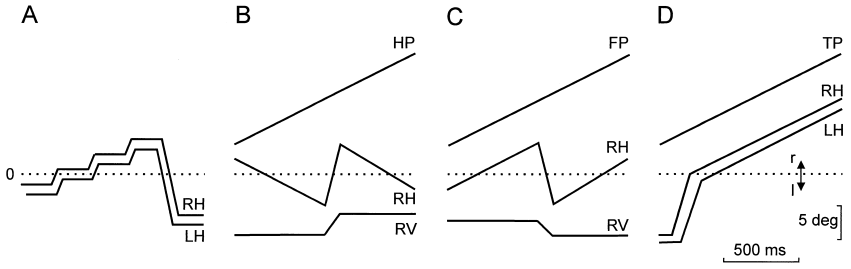

FIG. 1. Different types of eye movement. (A) Eye movements during reading. Eye movements during head (B) and global visual field (C) displacement at constant angular velocity. (D) Smooth pursuit of a visual target. Abbreviations: RH, LH, horizontal position of right and left eyes; RV, vertical position of the right eye; HP, FP, TP, head, global visual field and visual target position. Dotted lines indicate eye central (zero) position in the orbit. The slope of the represented lines indicate eye, head, global visual field, and target velocity (in deg/s), respectively. Vertical arrows indicate movement direction: l, left; r, right.

OKR depends on retinal information about the angular (or linear) displacement of the visual field. The VOR is preferentially operative at head rotations between 0.1–7 Hz. For slow head rotation ($<$0.1 Hz) the VOR decreases in *gain* (i.e., the quotient of eye velocity and head velocity), but visual acuity is still maintained because of the contribution of the OKR [19]. In fact, the two reflexes cooperate to keep visual targets on the fovea; that is, to maintain the gain of the VOR close to 1, indicating complete compensation of head movements. Thus, VOR is still present in darkness, but decreases in gain in a few tens of second.

Since movement of the eye in the orbit is limited, compensation of a continuous rotation of the head in the same direction is impossible. Thus, compensatory eye movements (in the direction opposite to that of the head) are interrupted from time to time by fast anticompensatory eye movements (in the same direction as that of the head). The sum of compensatory and anticompensatory eye movements is called *nystagmus* (Greek for "a nod"). The nystagmus is always named after the direction of the fast component. A continuous optokinetic stimulus (whole visual field rotating in the same direction) will also induce nystagmus, with the fast phase in the direction opposite to that of the movement of the visual field.

A further example to illustrate that visual inputs cooperate to maintain a stable visual world, and the corresponding subjective sensation, is the following description by Ernest Hemingway (from his novel *Fiesta*): "I was very drunk and I did not want to shut my eyes because the room would go round and round. If I kept on reading that feeling would pass". Alcohol induces a pathologic nystagmus that can be canceled out by fixating the eyes on the letters during reading. In fact, the VOR can be canceled (with more or less extensive training) so as, for example, to be able to read during walking, or during voluntary gaze shifts.

When one moves sideways on a train, the linear acceleration also evokes a translational VOR. In this situation it is interesting to note that visual contribution to eye compensation is dependent on the proximity of the object of interest, because movement is faster for closer objects than for distant ones.

Other Types of Eye Movement

The VOR and OKR responses are both present in all of the vertebrates in which they have been studied [1,7]. Indeed, it is possible for some species to move the eyes without moving the head (eye saccades), but not the opposite, i.e., moving the head without a compensatory eye response. Most vertebrates are keen movers, and it seems obvious that to move in the world, it is necessary to see, and that to see, it is necessary to maintain a stable visual field on the retina. This is the result of the action of the two aforementioned eye reflexes. However, there are three further types of eye movement that are peculiar to specific classes of vertebrates [19,20].

For those species with afoveate, homogeneous retinae, the visual gaze stabilization carried out by the VOR and the OKR is apparently sufficient for appropriate visual perception. However, species with a specialized retinal area for precise vision (fovea, area centralis) need to focus the desired targets on it. Accordingly, only foveate animals make saccadic movements independent of the head. A saccade is a rapid movement of the eyes, which changes the line of sight and translates the image of the target from an eccentric retinal location to the fovea. Although saccades usually move the eyes toward objects of interest, saccades can also be made in the dark or toward memorized targets. Saccades are ballistic movements, as they can not be easily modified during their performance, and are among the fastest and most precise movements made by vertebrates, humans included. During alertness, we make 2–3 saccades/s. Since vision is blurred during saccades, the motor system has evolved to make them very rapidly. In humans, saccades last for 20–150 ms and reach speeds of 800°/s. The amplitude and duration of saccades can be modified voluntarily, but not their velocity, which depends on the angular distance of the target.

From a functional point of view, VOR, OKR and saccades complement to each other. The first two help to keep the fovea on targets, while saccades bring new targets onto the fovea. Saccade kinetics are similar to those of VOR and OKR fast phases and, in part, are carried out by the same brain stem premotor circuits. Functionally, however, they appear as opposites, as fast phases bring the eyes to the center of the orbit while saccades direct it to the periphery in a search for new attractive targets. In this sense, saccades are more related to primitive optokinetic responses in afoveate animals, since, in both cases, the aim is to keep the eye on target. Saccades are voluntary in humans, but their spontaneous character in other species (such as the goldfish) depends on the length of the observation period. In a quiet environment, goldfish have a tendency to repeat the same sequence of saccadic movements, scanning their surroundings 4–5 times/min. On the other hand, to explore a face or a picture, or to select a few lines from a written text demand complex cognitive decisions. In this case,

saccades have a long latency and are probably computed in parallel to the fixation periods in which visual information is acquired [18].

It seems that only primates are able to follow the displacement of a single target moving in a fixed visual field. In humans, visual stimuli moving as slowly as 2.5°/s are seen as moving across the retina. The only way to observe a moving object in detail (size, shape, color) is to keep it stable on the fovea. The smooth pursuit system allows the eyes to rotate at the same angular velocity as that of the target, to avoid the drift of its image on the retina (which would compromise visual acuity). Thus, if global visual motion is the optimal stimulus for the OKR, a single target moving over a stationary background is necessary for activation of the smooth pursuit system. Although smooth pursuit is a voluntary movement and requires a high degree of attention to be carried out properly, its performance is automatic, and depends on target speed (Fig. 1D).

Frontal-eyed animals need to move their eyes in a conjugate way in order to keep binocular vision. So, angular displacements of one eye have to be followed by those of the other at exactly the same speed and amplitude, or diplopia will occur. For us, the retinal images seen by each eye at distances >30 m are practically identical. However, disjunctive (i.e., convergent or divergent) eye movements or *vergences* are also needed in frontal-eyed animals to keep a target in focus on both foveae when the distance of the target is <30 m. Vergences are slow angular displacements of the eyes. Lateral-eyed animals (e.g., pigeon, chameleon) also perform vergences, for example, to peck a wheat seed or to catch a fly with the tongue. The position of the eyes in the head determines how much binocular vision each species has. For example, for humans it is about 180°, but for the pigeon it is only 10°. Obviously, overlaps in the monocular field of each eye reduce the total space covered, but increase the area with binocular vision and stereopsis.

To summarize, for depth perception and stereopsis, the same points of both foveae must focus on the same object. This is accomplished by coordinated (conjugate or disjunctive) movements of the eyes, assisted by accommodation and pupillary constriction (meiosis). If the object moves it must be followed by the smooth pursuit system to maintain visual acuity. Fast and slow displacements of the head are compensated with the help of the VOR and the OKR, respectively. Finally, if some appealing object appears at the periphery of our visual field, a saccade will place it on the fovea, and small microsaccades then will proceed with the fine exploration of the target [20].

Although it cannot be considered as a movement proper, eye *fixation* is also a result of the activity of the oculomotor system. For foveate animals, eye fixation is the way to explore a motionless target visually by scanning it without eye movements.

MUSCLES AND MOTONEURONS INVOLVED IN EYE MOVEMENTS

Muscles Versus Movements

For the oculomotor system, the eye represents a fixed load, with constant viscoelastic properties that need a negligible antigravitational action. All extant vertebrates with mobile eyes have six extraocular muscles attached to the rotating eyeball: superior, inferior, medial and lateral recti, and superior and inferior obliques. These muscles are arranged (by pairs of agonist/antagonist actions) in a precise way such that the eye can be rotated about any axis in three dimensions. Thus, abduction and adduction of the eye are accomplished by the lateral and medial recti muscles. Elevation and depression of the eye, as well as eye intorsion and extorsion, are the result of the activity of the other four muscles, their respective roles depending upon the initial position of the eye in the orbit. Those species provided with a nictitating membrane also have a retractor bulbi muscle involved in translational, rather than rotational, eye movement [17].

Extraocular eye muscles are highly specialized with regard to mitochondrial content, innervation and contractile patterns, presence of contractile protein isoforms, etc. In fact, while limb muscle fibers can currently be classified in four basic types, up to six different fiber types have been reported for extraocular muscles, according to their innervation pattern (single, multiple), fatigue resistance (high, intermediate, low), contracting pattern (twitch, slow), and recruitment order. On the whole, the extraocular musculature can perform complex tonic and phasic activities and presents a high resistance to motor fatigue.

All types of eye movement share the same muscles as well as the same population of motor neurons, but each is generated by a different brain circuit [5,15,17,19]. An interesting evolutionary question is why, having the same set of extraocular muscles, are all vertebrate species not able to make the same set of five eye motor responses (VOR, OKR, saccades, smooth pursuit and vergence). Since the limitation is not a matter of orbital biomechanics, or of the number of available muscles, it must be due to the absence of neural circuits needed to generate a given sort of eye movement. The different types of eye movement are acquired through vertebrate evolution, mainly in relation to the appearance of specific brain stem (and higher) neural centers peculiar to each motor function. This is not a process susceptible to motor learning, as no individual will ever be able to learn an eye movement if the species to which it belongs was not provided with the necessary neural circuits (i.e., smooth pursuit in a frog or a rabbit). Accordingly, it appears that, for eye movements, learning is restricted to modifications in the physiological range of each type of eye response.

Extraocular Motoneurons

Extraocular muscles are innervated by motoneurons located in three brain stem motor nuclei: oculomotor, trochlear and abducens. Oculomotor motoneurons innervate (in mammals) the ipsilateral medial and inferior recti and the inferior oblique muscles, and the contralateral superior rectus. Trochlear motoneurons innervate the contralateral superior oblique muscle. Finally, abducens motoneurons innervate the ipsilateral lateral rectus muscle. The firing rate of extraocular motoneurons is on average about 10 times higher than that of spinal motoneurons, and encodes both eye velocity and eye position. A phasic motoneuronal firing will produce a fast, strong, muscular contraction, necessary to overcome the viscous drag of the orbit, and evoke a fast eye displacement (i.e., a saccade or a fast phase component of the VOR or the OKR). Extraocular motoneurons are also capable of a sustained tonic firing, necessary to counteract the restoring elastic components of orbital tissues when eye position is maintained [6,19].

The highly conservative pattern of the extraocular motor system regarding muscle organization and motoneuronal innervation is remarkable. However, there is a major difference regarding the location of oculomotor motoneurons innervating the medial rectus muscle. Medial rectus motoneurons are located contralaterally in elasmobranchs, but are ipsilateral to the innervated muscle in bony fish and tetrapods [1,7]. Since the innervation pattern of vestibular inputs to ocular motoneurons follows a contralateral excitatory, ipsilateral inhibitory rule, the shift in medial rectus motoneuron location introduced a need for a midline-crossing pathway carrying vestibular signals to medial rectus motoneurons synergistic with ipsilateral abducens motoneurons. In fact, the neural connection subserving this role, the abducens internuclear neuron pathway, is present in bony fishes and tetrapods, but apparently absent in elasmobranchs. Although initially abducens internuclear neurons played a role in coordinating the VOR of the two eyes of lateral-

eyed animals, they were later given the additional task of subserving eye conjugacy [3].

Besides its constant load, additional peculiarities of the extraocular motor system are the absence of a stretch reflex and the lack (with some exceptions) of recurrent inhibition by axon collaterals of ocular motoneurons [6,19].

Extraocular motoneurons are not specialized in function, that is, all of them participate in all types of eye movement, but each one has a recruitment threshold that depends on eye position in the orbit. In the alert behaving state, most of them (the exact percentage depends on the species) are firing at primary eye position. The discharge rate of extraocular motoneurons is linearly related to the evoked eye position and velocity. In fact, the firing properties of ocular motoneurons can be accurately captured by a first-order linear model of the oculomotor apparatus [19]. In cats, their firing rate (mean values) increases by 7 spikes/s per degree of eye position, and by 1 spike/s per deg/s of eye velocity, in the pulling direction of the innervated muscle. Motor unit size is about 1:10–20, but no information is available regarding the innervation pattern of the different types of muscle fibers, which comprise the extraocular muscles [17].

NEURAL CONTROL OF EYE MOVEMENTS

Premotor Neural Circuits

Extraocular motoneurons represent the final common pathway interposed between oculomotor-related brain centers and extraocular muscles; that is, motoneurons have to be able to translate to extraocular muscles the precise neural commands that characterize each type of eye movement [6]. As illustrated in Fig. 2, the set of brain stem premotor nuclei projecting monosynaptically to the oculomotor system is very well-known, particularly for the abducens nucleus. This is composed of a fourfold system of reciprocal (excitatory and inhibitory) direct projections originating in the pontomedulary reticular, vestibular, prepositus hypoglossi and mesencephalic perioculomotor nuclear areas and which terminate in the abducens nucleus with a distinctly graded efficacy. This fourfold system is involved in the generation of fast (saccades, fast phases) eye movements, slow compensatory movements of vestibular and visual origins, eye fixation and vergences, respectively [6,8,15,19]. Moreover, this monosynaptic premotor system is shared in some ways, either by convergence of different types of movement-related signals onto the same set of monosynaptic premotor neurons (i.e., VOR and OKR on vestibular neurons) or by similar oculomotor commands arising from different high-level centers (i.e., cortical and superior colliculus saccadic commands on pontomedullary reticular neurons).

Head-movement signals arriving at the vestibular nucleus by primary labyrinthine and otolith afferents are carried out to ocular motoneurons by second-order vestibular neurons. These neurons convey a neural signal proportional to head velocity. Most of the second-order vestibular neurons projecting monosynaptically on abducens motoneurons are of the position-velocity-pause type; that is, they carry a (weak) eye-position signal together with the signal corresponding to head velocity and they make a pause during saccades in all directions. Second-order vestibular neurons related to signals arriving from the horizontal canal are located mainly in the medial vestibular nucleus. Their projections are excitatory on contralateral abducens motoneurons and internuclear neurons, and inhibitory on the same two abducens neuronal populations on the ipsilateral side. As explained above, VOR signals reach medial rectus motoneurons located in the oculomotor nucleus mainly by the interposed abducens internuclear neuron pathway. In this way, canal inputs excite synergistic and disfacilitate antagonistic muscles, simultaneously. As gravitational action is always present, the smallest imbalance in this bilateral system will be able to evoke an unwanted nystagmus. The vertical system follows a similar design, with vestibular neurons sending contralateral excitation to ocular motoneurons and inhibitory terminals to ipsilateral vertical motoneurons. These pathways represent the three-neuron arc characteristic of the VOR: primary vestibular afferents contacting receptor cells at the vestibular apparatus and projecting to second-order neurons in the vestibular nucleus, second-order neurons projecting to ocular motoneurons, and the motoneurons projecting to extraocular muscles. However, it should be kept in mind that vestibular signals also reach higher integrative centers, including the parietal cortex.

Optokinetic signals from the retina arrive at the nucleus of the optic tract located in the pretectum and at the accessory optic terminal nuclei of the mesencephalon [2]. These nuclei project to medial vestibular neurons from where OKR signals are carried out to ocular motoneurons. In primates, there is a long-loop pathway also involved in the OKR. In this case, visual signals travel from the retina to the magnocellular layers of the lateral geniculate nucleus, and further to the striate cortex (area 17), middle temporal (MT) area and medial superior temporal (MST) area. The MST area projects to the dorsal and ventral paraflocculus and to the posterior vermis through the dorsolateral pontine nuclei.

The medial vestibular nucleus is not the only neural structure where visual and vestibular information converges. Vestibular signals reach the flocculus carried by mossy fibers, which are collaterals of first-order and second-order vestibular neurons. Further, both the nucleus of the optic tract and the MST area project to the cerebellum through the pontine nuclei. Finally, visual signals from the nucleus of the optic tract also reach the flocculus as climbing fibers by a projection through the inferior olive. The role of the flocculus seems related to the interaction between VOR and OKR, mainly that of enhancing (or reducing) eye velocity to adjust it to the velocity of the visual target.

Adaptability of the VOR to the experimental manipulation of visual and/or vestibular signals (i.e., using reversing glasses, and magnifying or minifying lenses) is frequently used as an experimental model for motor learning. Since natural interaction between the VOR and the OKR systems is assumed to have been present during the last 500 million years [1], it is surprising how this simple, well-evolved way of neural plasticity is so resistant to convincing accounts regarding the place and the neural mechanisms involved. Both cerebellar cortex and vestibular nuclei have been proposed as the site for this motor learning to occur [10,12].

Motor commands for saccadic movements can originate in the superior colliculus and in the cerebral cortex, mainly in frontal eye field and posterior parietal areas [2,8,15]. In particular, the superior colliculus computes the size and direction of required saccades and projects (via tectal long-lead burst neurons) to the nucleus reticularis pontis oralis where the so-called long-lead burst neurons (LLBN) seem to be located. Frontal eye field neurons project both to the superior colliculus and to the LLBNs. These latter neurons project to the paramedian pontine reticular formation, where horizontal saccades motor commands are generated. Specifically, LLBNs project to short-lead excitatory burst neurons (EBN) located in the nucleus reticularis pontis caudalis, rostral to the abducens nucleus, and to inhibitory burst neurons (IBN) located caudally to the abducens nucleus in the nucleus paragigantocellularis dorsalis. The EBNs project monosynaptically to ipsilateral abducens motoneurons and encode saccade duration, amplitude and velocity, while the IBNs project monosynaptically on contralateral abducens motoneurons, suppressing firing of the latter during ipsilateral saccades. In the EBN area, reticulo-spinal burst neurons related to gaze displacements which involve both eye and head movement are also encountered. The LLBNs also project to

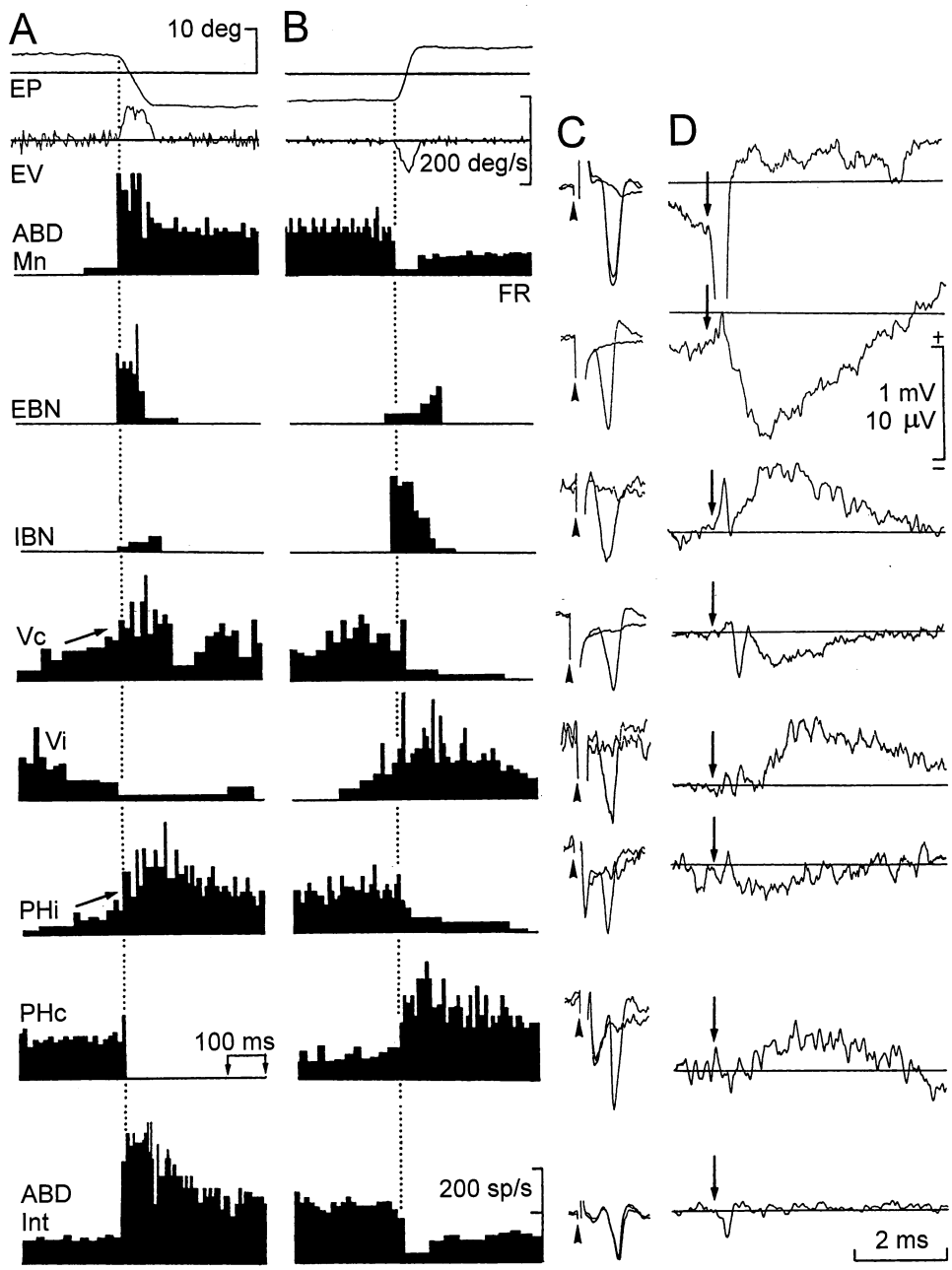

FIG. 2. Firing rate (A,B), antidromic activation (C), and averaged field potentials (D) induced by short-lead excitatory (EBN) and inhibitory (IBN) burst neurons, and by ipsi- and contralateral vestibular (Vi, Vc) and prepositus (Phi, PHc) neurons projecting to the abducens (ABD) nucleus. Recordings were carried out in alert cats. (A,B) Neuronal activity during spontaneous saccades in the on- and off-direction, respectively. (C) Antidromic all-or-nothing activation of recorded neurons by microstimulation from ABD nucleus. Arrow-heads indicate the beginning of the stimulus. (D) Average of field potentials recorded in the ABD nucleus triggered (arrow) by these identified neurons. Abbreviations: EP and EV, horizontal eye position and velocity; FR, firing rate. The discharge rate, antidromic identification from their projecting sites, and field potential induced by ABD motoneurons (Mns) and internuclear neurons (Int) are also shown. From Escudero and Delgado-García [6]. Reproduced with permission of Springer-Verlag GmbH & Co. KG.

the nucleus raphe interpositus, where omnipause neurons are located. Omnipause neurons carry out a continuous inhibition of EBNs and IBNs, but are inhibited by LLBNs and collicular inputs when EBN and IBN are excited (Fig. 3). Finally, the vertical saccade system seems to be located in the rostral interstitial nucleus of the medial longitudinal fasciculus and the interstitial nucleus of Cajal and influences vertical ocular motoneurons.

Neuronal information regarding saccades reaches the cerebellar cortex via the nucleus reticularis tegmenti pontis. Both the superior colliculus and the LLBNs project to that nucleus. The cerebellum

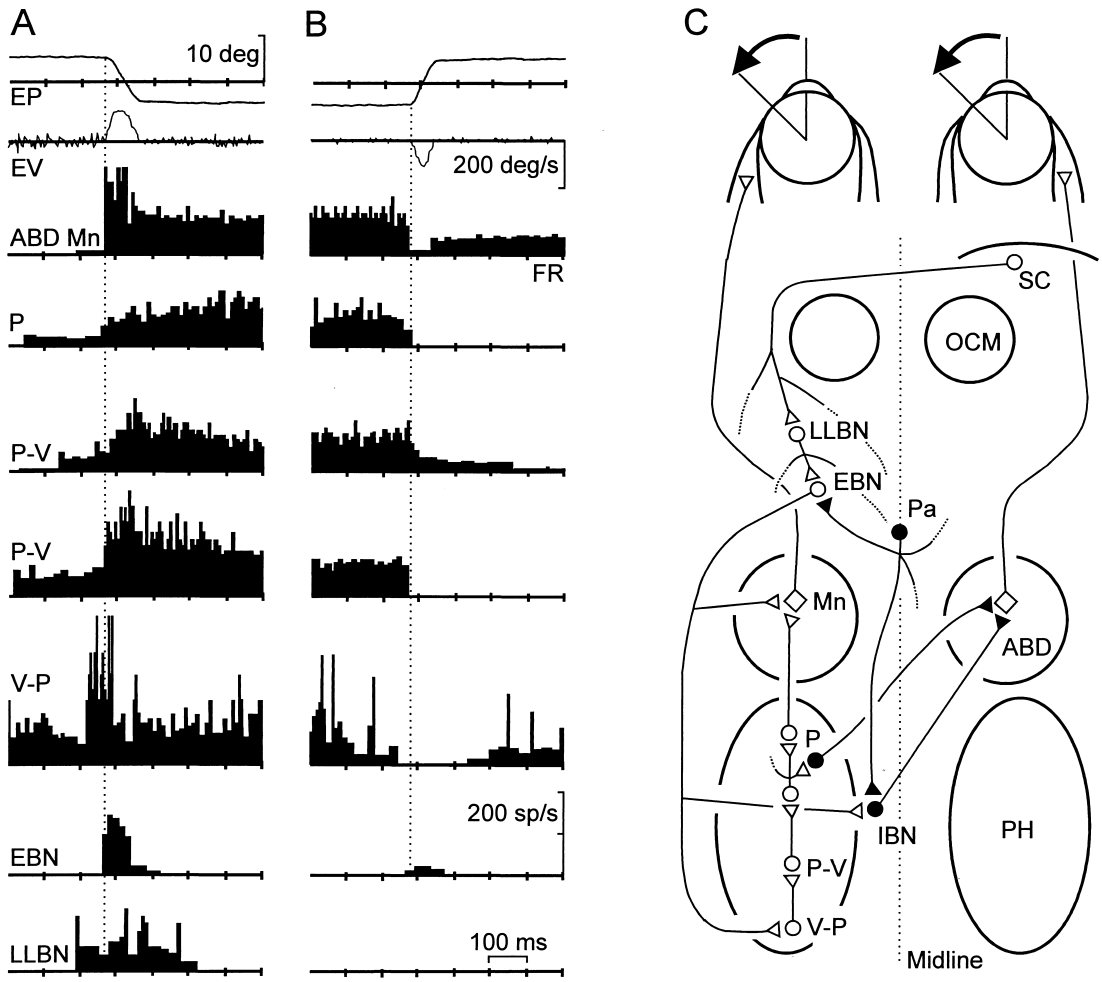

FIG. 3. Generation of the eye-position signal in the prepositus hypoglossi (PH) nucleus. (A,B) Firing rate of seven different types of neuron during eye fixations before and after on- and off-directed saccades. From bottom to top: firing rates (FR) of a long-lead burst neuron (LLBN), an excitatory burst neuron (EBN), four PH neurons showing *velocity-position* (V-P), *position-velocity* (P-V) or *position* (P) signals, and an abducens motoneuron (ABD Mn). The corresponding horizontal eye position (EP) and velocity (EV) for these neural activities are also illustrated. (C) Diagram showing the possible pathways generating eye-position signals following a saccade triggered form the superior colliculus (SC). Abbreviations: OCM, oculomotor nucleus; IBN, inhibitory burst neuron; Pa, omnipause cells. Modified from Escudero et al. [5]. Reproduced with permission of The Physiological Society.

also seems to participate in saccade control, as lesions of the posterior vermis or of the fastigial nucleus produce several types of saccadic dysmetria [9]. Many other brain stem, thalamic (intralaminar nuclei), basal ganglia and cortical structures are involved in the control of saccades [15]. The overwhelming complexity of ocular motor pathways indicates that the gaze control system, because of its evident involvement in cognitive processes, is probably more complex than expected from purely motoric considerations.

Smooth pursuit eye movements depend on a cortico-pontino-cerebellar circuit [2]. Visual signals corresponding to the local motion of the target arrive at the striate cortex (V1) from the retina and the lateral geniculate nucleus. From here, they are transferred to other visual areas of the occipital and posterior parietal cortex (mainly areas MT, MST, and 7a). Specifically, speed and direction of target movement are processed in the MT area. Motion signals of the visual target are sent to the cerebellum via the cortico-pontine pathway, arriving at the cerebellar cortex as mossy fibers. The cerebellar flocculus projects to vestibular nuclei and from these to ocular motoneurons. Other circuits, including the frontal eye field and descending projections that reach the nucleus prepositus hypoglossi, are also involved in the genesis and control of smooth pursuit motor commands.

Horizontal conjugate eye movements are generated in the abducens nucleus [3]. Abducens internuclear neurons convey a signal similar to that present in abducens motoneurons to medial rectus motoneurons located in the contralateral oculomotor nucleus. The efficacy of eye conjugacy in different species (goldfish, pigeon, rat, cat, rabbit and monkey) runs parallel to the progressive intermingling of motoneurons and internuclear neurons within the abducens nucleus. Eye accommodation and vergence signals are produced in the midbrain, in regions close to the oculomotor nucleus. In particular, a band of oculomotor internuclear neurons surrounding this motor nucleus as a dorsal cap projects to the abducens nucleus, carrying vergence signals. While abducens internuclear neurons are excitatory and project exclusively to contralateral

medial rectus motoneurons, descending oculomotor internuclear neurons are both GABAergic and non-GABAergic and project bilaterally to abducens neurons.

In Search of the Integrator(s)

Each eye-movement subsystem (i.e., vestibular, saccadic) generates a signal that is proportional to the needed eye velocity. But to obtain a complete compensation of head position or to maintain eye position on target following a voluntary saccade, motoneurons also need an eye-position signal [4,5,8,15]. Although a common eye-position signal neural integrator subserving all of the eye-movement subsystems was proposed initially [19], available experimental data indicate that there are several integrators, depending on the origin of the eye-movement commands and on the eye movement plane. Thus, horizontal and vertical eye-position signals are integrated separately in the nucleus prepositus hypoglossi and in the interstitial nucleus of Cajal. Integration is assumed to take place in these nuclei and/or in the functional interactions they established by their reciprocal connections with both the vestibular nuclei and the cerebellum (flocculus, mainly). Other brain stem and cerebellar structures also carry eye-position signals, such as the medial vestibular nucleus and a few neuronal groups scattered in the brain stem, and the cerebellar fastigial nucleus [5,8,9].

An interesting question is: how are eye-position signals generated by neuronal circuits? A proposed hypothesis is that these neuronal integrators could generate position signals from successive synaptic steps in cascade, lateral or retrograde chain systems. These chains would be superimposed upon the shorter, direct pathways carrying eye-velocity signals. This cascade organization for neural integration is illustrated in Fig. 3 for the nucleus prepositus hypoglossi. The presence of cascade-like, polysynaptic connections could explain the presence in this nucleus of neuronal types with intermediate eye motor signals (velocity, velocity-position, position-velocity, position, etc.), and the high susceptibility of eye-position neuronal systems to drugs, anesthetics, mental state, and attention level (Fig. 3). Pure position neurons and other neuronal types carrying eye-position and eye-velocity signals seem to project monosynaptically from the prepositus hypoglossi and the interstitial nucleus of Cajal to the oculomotor nuclei [5,8]. The stabilizing role of the intrinsic membrane properties of ocular motoneurons in the generation of eye-position motor commands to extraocular muscles should also be considered. The algebraic addition of these different sources of eye-position signals upon the distal dendrites of ocular motoneurons could be further elaborated by the intrinsic active properties of motoneuron membrane to produce the stable firing rate they display during eye fixation [4].

Recent experiments in goldfish [16] and cats [13,15] suggest the presence of separate integrator mechanisms to store eye-velocity signals and to generate pure eye-positions ones. Recently, we have used pharmacological tools to dissociate the two integrating mechanisms. Thus, nitric oxide synthase inhibitors applied directly to the nucleus prepositus hypoglossi of alert cats produce alterations of eye velocity, but not of eye position. Moreover, a group of prepositus neurons located laterally, in a marginal zone close to the medial vestibular nucleus (characterized by having a nitric oxide-sensitive guanylyl cyclase) seems to be involved in the generation of eye-position signals, as demonstrated by the application of nitric oxide-donors [13]. Thus, the unilateral administration of the nitric oxide synthase inhibitor L-nitro-arginine methyl ester (L-NAME, in Fig. 4) in the nucleus prepositus hypoglossi produced ramp-like eye movements in a direction contralateral to the injected side, interrupted by fast phases directed ipsilaterally. In contrast, the administration of the nitric oxide donor S-nitroso-N-acetylpenicillamine (SNAP, in Fig. 4) in the same nucleus

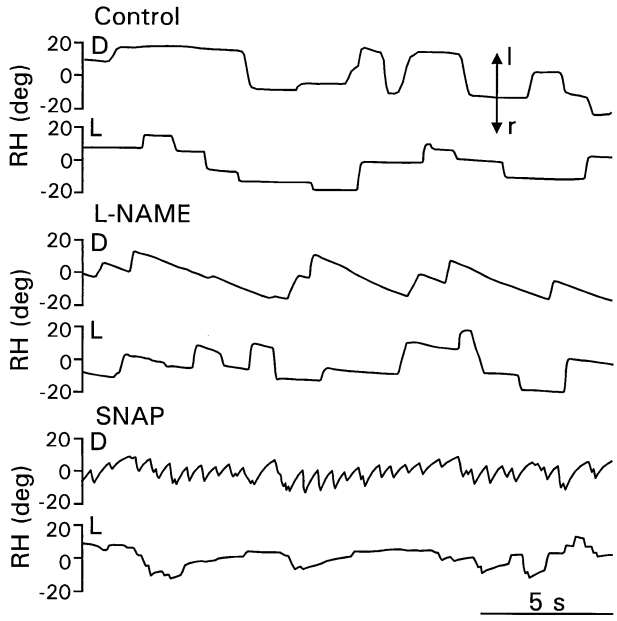

FIG. 4. Recordings of right eye position in the horizontal plane (RH) obtained in the alert cat under control conditions and following injection of the indicated drugs in the left prepositus hypoglossi nucleus. Recordings were carried out in darkness (D) and light (L) conditions. Doses and time of the illustrated records after the injection were as follows: L-nitro-arginine methyl ester (L-NAME), 28 nmol, 4 (D) and 5 (L) min; S-nitroso-N-acetylpenicillamine (SNAP), 20 nmol, 3 (D) and 5 (L). Eye position is plotted as degrees of rotation in the horizontal plane. Vertical arrows indicate movement direction: l, left; r, right. From Moreno-López et al. [13]. Reproduced with permission of Cell Press.

produced an exponential drift of eye position directed ipsilaterally. Accordingly, the nucleus prepositus hypoglossi seems to contain more than one neuronal integrator. In this regard and based upon lesion and pharmacological experiments carried out in cats [14] and monkeys [11] it can be further suggested that prepositus hypoglossi neurons are involved in the processing of eye velocity signals, while eye position signals are generated in the marginal zone located between prepositus and medial vestibular nuclei.

Concluding Remarks

Going back to the title of this short review, and from a phylogenetic point of view, eye movements were originally necessary to make vision possible during head movement. Across evolution, other types of eye-movement responses appeared together with the development of the necessary and sufficient neuronal circuits and/or centers involved in their genesis and control. Motor and premotor brain stem circuits and centers generating eye movement signals that terminate monosynaptically upon extraocular motoneuron pools are reasonably well known, while available information on higher-level brain centers is increasing rapidly. Present knowledge regarding the neural control of eye movements represents a beautiful example of how brain structures produce overt behaviors. Finally, recent experimentation is advancing our knowledge with regard to neuronal sites and processes involved in the generation of eye-velocity and eye-position signals.

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