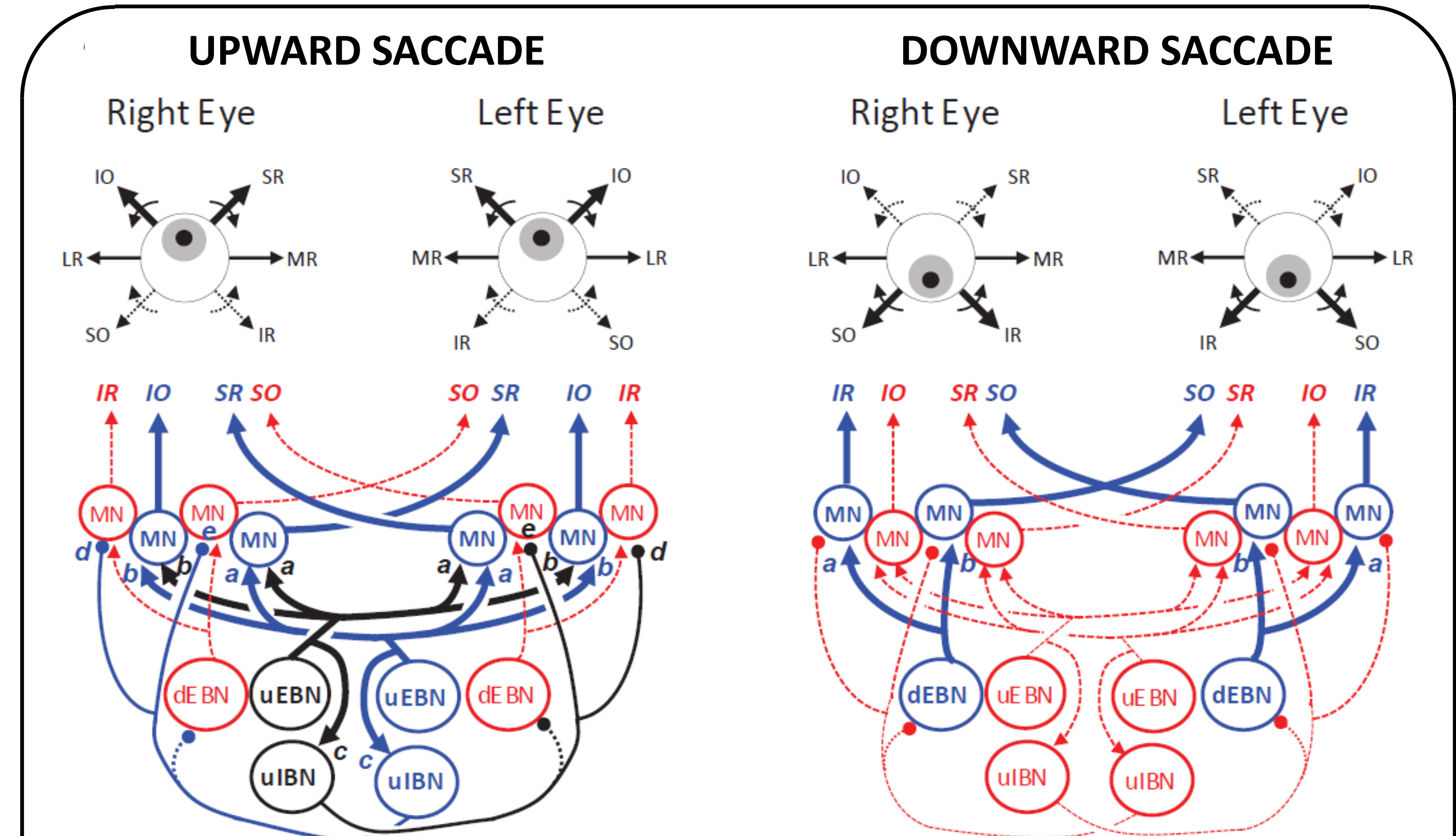
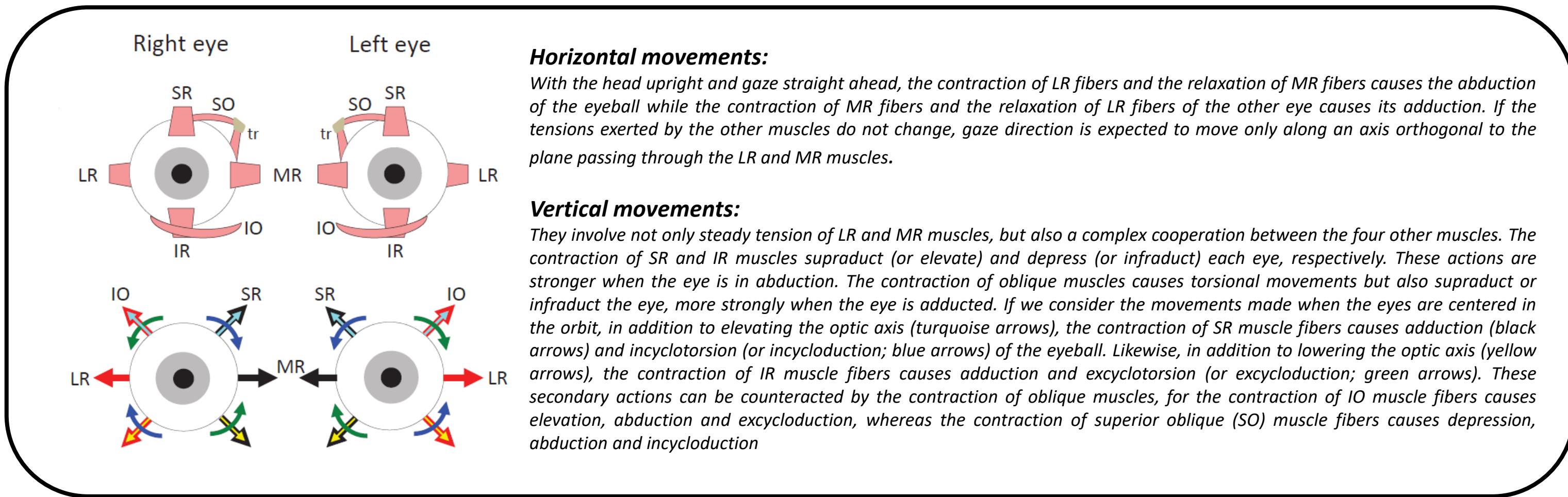




The appearance of an object in the visual field triggers a rapid gaze shift toward its location. This orienting response consists of a rapid rotation of the eyes, the saccade, which can be accompanied by a rotation of the head. If the target moves, the saccade is followed by a slow movement of the eyes and a catch-up saccade. Instead of describing the path leading from the target-evoked retinal activity to the changes in muscle tension, we shall take the reverse path. Starting from the muscle contractions, we shall proceed upstream and describe the organization that, in the brainstem and cerebellum, enables us to rapidly and accurately orient the foveae towards visual targets located at different eccentricities. Thus, we shall discover the considerable knowledge that neurophysiologists and neuroanatomists gathered during the last six decades with non-human species (mostly monkey and cat).

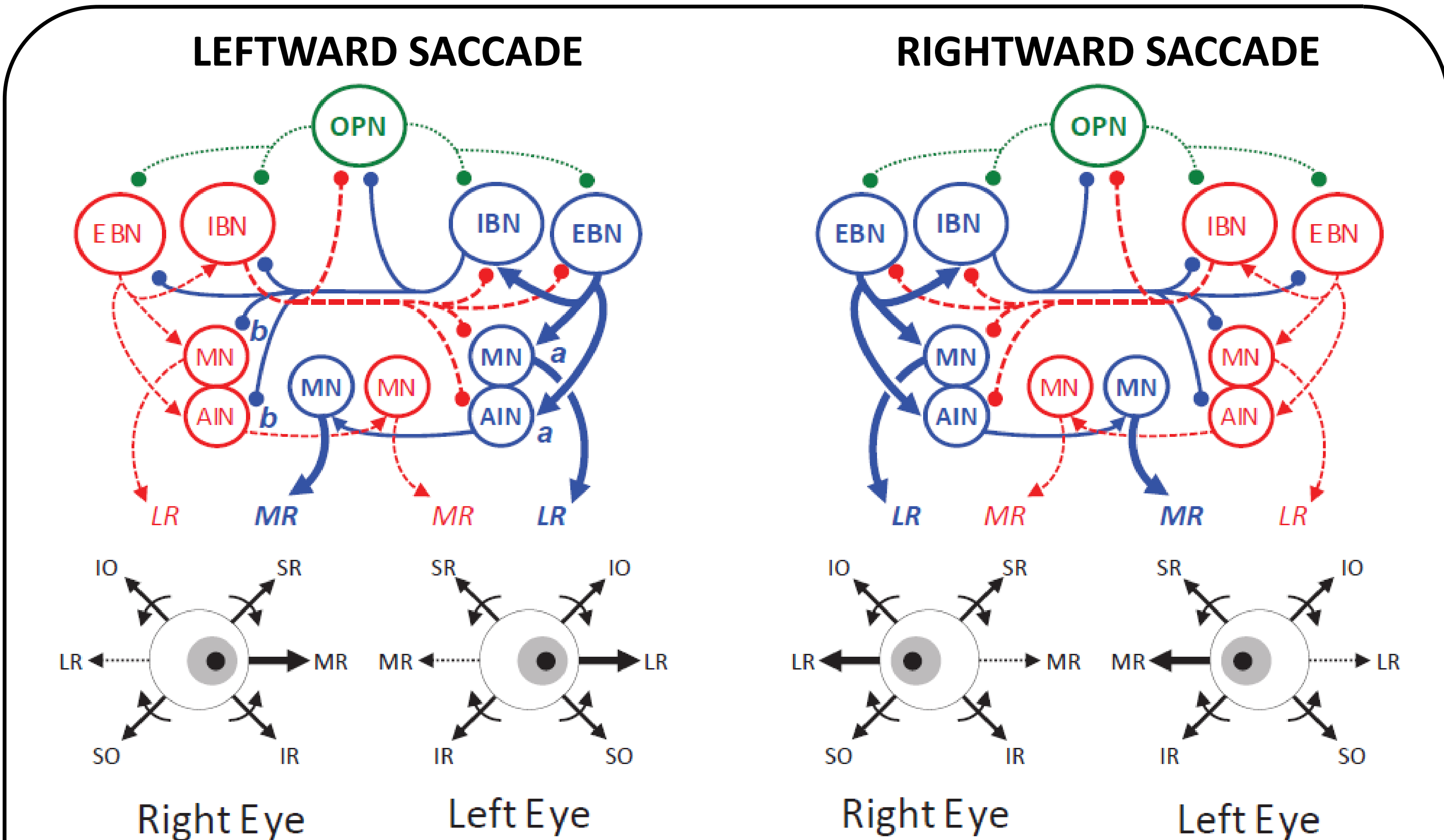
Technical developments offered the possibility to measure precisely the time course of eye and head movements and to study correlations between the firing rate of neurons and kinematic parameters (amplitude, velocity, acceleration and various differences called errors). These correlation studies should not lead us to believe that a one-to-one correspondence exists between the multiple neuronal networks within which activities propagate and the homogeneous mathematical medium with which the movements are quantified. Contrary to the physical space, the medium of neuronal activity is neither homogeneous nor passive. Moreover, reducing the neuronal chains to units encoding geometric or kinematic relations between gaze target directions conceals the antagonisms between muscles but also the antagonisms between the multiple channels that drive each movement.



For upward saccades, the agonist muscles are the IO and the SR and the antagonist muscles the IR and the SO. In addition to elevating the eye, the contraction of SR fibers causes incycloduction, whereas contraction of IO fibers causes excycloduction. Thus, the incycloduction caused by the motor commands to the SR combines with the excycloduction caused by the commands to the IO. The observation of negligible torsional component during upward saccades suggests that the two torsions cancel each other out. Such a balance of force likely involves bilateral activity in the midbrain because for each eye, the motor neurons innervating the SR muscle are located in the contralateral OMN whereas the motor neurons innervating the IO muscle are located in the ipsilateral OMN. The two sets of commands during upward saccades must be adjusted in a timely manner, and an asymmetry in the bilateral motor drive would engender a torsional component. The excitatory commands responsible for generating upward saccades are issued by burst neurons located in the left and right rostral interstitial nucleus of the medial longitudinal fasciculus (RIMLF). These commands are doubly bilateral: on the one hand, the burst emitted by premotor neurons (uEBN) in the left RIMLF excite the motoneurons innervating the SR of both eyes (black synapses a) and motor neurons innervating the IO of both eyes as well (black synapses b); on the other hand, the burst emitted by uEBNs in the opposite RIMLF excite the same motoneuronal group (blue synapses a and b). In addition to recruiting the motor neurons, the uEBN also excite neurons that inhibit the motor neurons that innervate the antagonist muscles (IR and SO, synapses c). Located in the interstitial nucleus of Cajal, these cells (uIBN) inhibit the motor neurons in the contralateral oculomotor nucleus, i.e., cells responsible for the contraction of the IR of the contralateral eye (synapses d) and motor neurons responsible for the contraction of the SO of the ipsilateral eye (synapses e). However, contrary to uEBN, uIBN do not send bilateral projections to the motor neurons innervating the SO fibers. Their projections make synaptic contacts only with motor neurons on the contralateral side. As for the upward saccades, the discharge of neurons located in each side of the brain is capable of causing downward saccades of both eyes. The premotor excitatory burst neurons leading to downward saccades (dEBN) are also located in the RIMLF. However, unlike the uEBN, the dEBN do not send bilateral projections to the motoneurons; their projection is ipsilateral only. During downward saccades, the SO and IR fibers of both eyes contract because the dEBN excite 1) the motor neurons in the ipsilateral OMN, which cause the contraction of IR muscle fibers of the ipsilateral eye (synapses a), and 2) the motor neurons which, in the ipsilateral trochlear nucleus, cause the contraction of SO muscle fibers of the contralateral eye (synapses b). In addition to lowering the eyes, the contraction of SO fibers causes an incyclotorsion of the eye while the contraction of IR muscle fibers causes its excyclotorsion. The commands from the ipsilateral OMN for excyclotorsion combine with commands from the contralateral trochlear nucleus for incyclotorsion. Precisely how these opposite torsional components cancel each other out during downward saccades remains unexplained. A bilateral adjustment at the level of premotor burst neurons seems inevitable. Moreover, the neural processes in charge of the relaxation of antagonist muscles during downward saccades remain to be characterized.

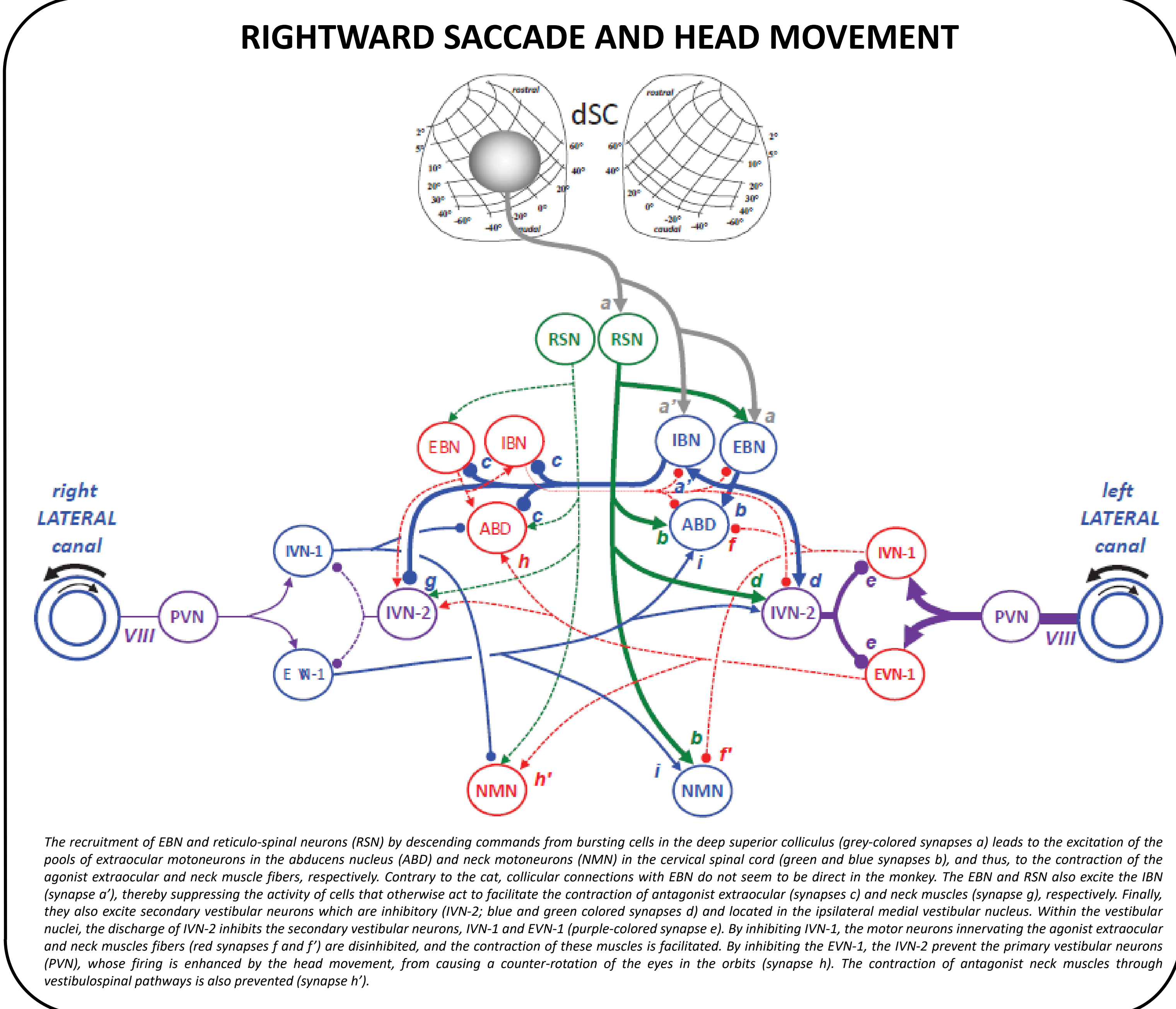
During vertical saccades, the EBN involved in the generation of horizontal saccades do not fire. Some IBN in the dPGRF emit action potentials whose number increases with saccade size. As MN and AIN in the ABD do not fire during vertical saccades, the contralateral exertion by IBN in the left and right dPGRF cancel each other out. If no perfect symmetry exists between the set of active neural elements (number of neurons and of synaptic boutons) located on each part of the reticular formation, then the observation of strictly vertical saccades indicates that a process adjusts the bilateral activity of IBN during vertical saccades. This adjustment likely involves the bilateral fastigial activity.

The bilateral control is not restricted to the group of IBNs, which are primarily involved in the horizontal saccades. In addition to elevating both eyes, the discharge of motor neurons in the right OMN causes, as a secondary action and via the contraction of the right eye's IO and the left eye's SR, a rightward deflection of both eyes during vertical saccades while the discharge of motor neurons in the opposite side causes a leftward deflection. Likewise, in addition to lowering both eyes, the dEBN in the right RIMLF lead to the contraction of the left eye's SO and the right eye's IR, causing a leftward deflection of their trajectory while dEBN in the left RIMLF cause a rightward deflection during vertical saccades. The straightness of vertical saccades (no horizontal deviation) implies then that the horizontal deflection caused by the leftward action of the muscles elevating or depressing the eyes are also canceled in the motor drives. In summary, the generation of straight vertical saccades rests upon a balance of bilateral motor activation, which itself depends upon an adjustment of premotor commands that takes into account the structural (neurons and their connectivity) and functional (firing properties, secondary and tertiary consequence of muscle contractions) asymmetries between the oculomotor territories that are distributed on either side of the brain stem. The saccade-related neurons in the left and right fastigial nuclei and in the oculomotor vermis regulate this bilateral balance. Indeed, most of them burst during vertical saccades and their asymmetric perturbation deflects horizontally the trajectory of vertical saccades. Bilateral activity in the two deep superior colliculi is also involved with their medial halves for driving upward saccades and their lateral halves driving downward ones. The contribution of the deep superior colliculi and caudal fastigial nuclei differs insofar as horizontal saccades involve bursting activity of cells in one superior colliculus (contralateral) whereas saccade-related neurons burst in both caudal fastigial nuclei.

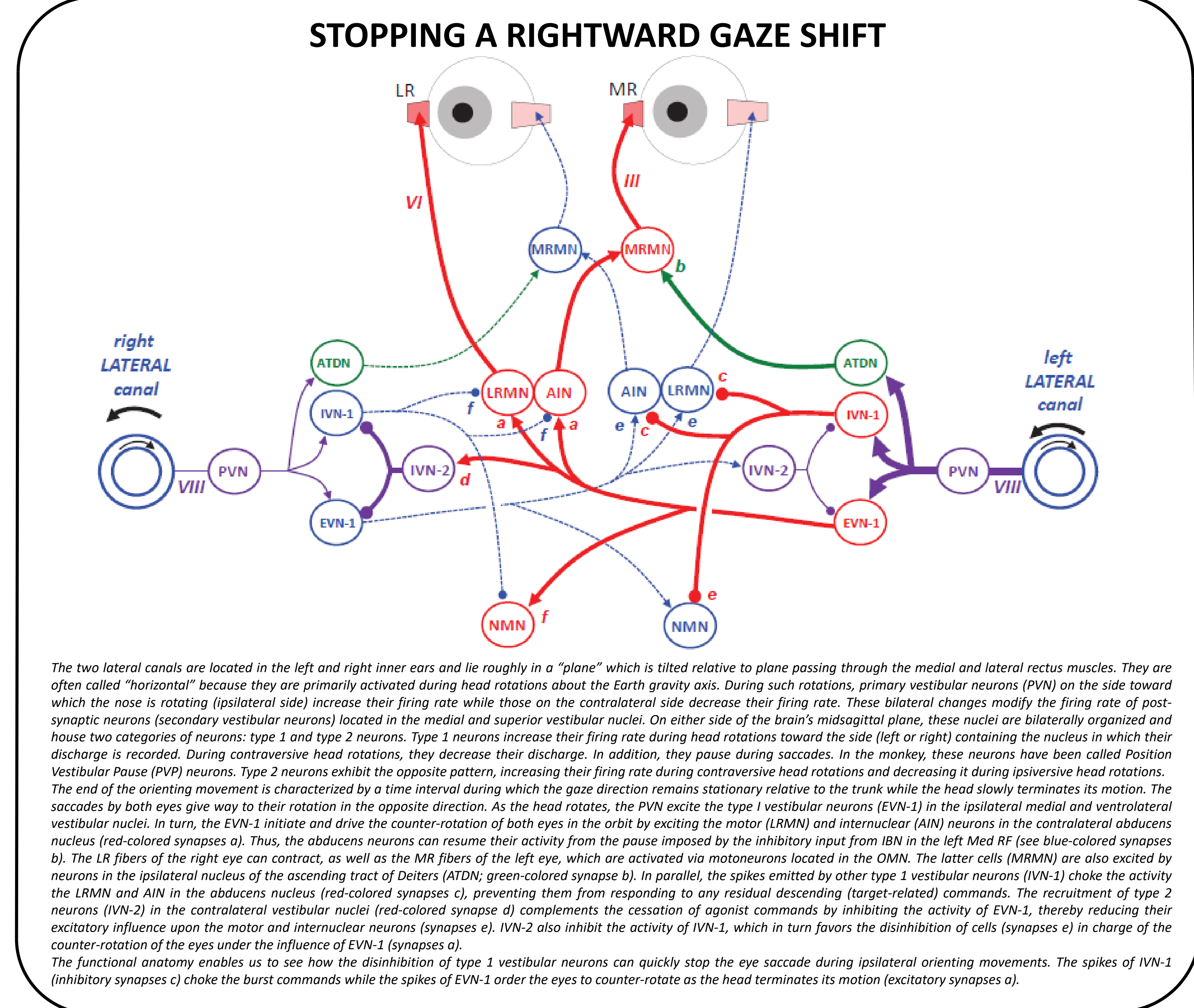


Motor neurons in the abducens nucleus (ABD) and in the oculomotor nucleus emit bursts of action potentials that cause the phasic contraction of muscle fibers. The burst discharge of cells in the OMN is triggered and supported by spikes emitted by internuclear neurons (AIN) located in the contralateral ABD. The bursts of abducens motor (MN) and internuclear (AIN) neurons are driven by afferent input from excitatory burst neurons (EBN) located in the ipsilateral paramedian pontine reticular formation (synapses a). The abducens neurons also receive excitatory input from internuclear burst-tonic neurons in the contralateral oculomotor nucleus (not shown). Discharging during saccades and increasing their firing rate during convergence, these cells are possibly involved in the motor drive for conjugate saccades. Otherwise silent, the EBN fire trains of action potentials whose interspike interval is smaller for larger saccades. Contrary to statements made in numerous articles, the instantaneous firing rate of EBN is not a replica of instantaneous eye velocity.

The relaxation of antagonist muscles results from a pause in the firing of motor neurons innervating them. This pause is itself caused by inhibitory input from burst neurons (IBN) located in the contralateral dorsal paragoniatocellular reticular formation (synapses b). In addition to bursting during ipsiversive horizontal saccades ("on-direction" response), approximately half of these inhibitory burst neurons also emit spikes during contralateral horizontal saccades (off-direction response). Thus, the agonist motor drive is a combination of excitatory and inhibitory presynaptic input from the ipsilateral EBN and contralateral IBN, respectively. The relative strength of these antagonist premotor inputs is under the descending influence of saccade-related burst neurons located in regions involved in other functions, such as the left and right caudal fastigial nuclei (located in the deep medial cerebellum) and the contralateral deep superior colliculus (in the midbrain tectum). The bilateral fastigial input seems to exert an influence that is more modulatory than the collicular influence because, contrary to lesions in the superior colliculus, fastigial lesions do not suppress or delay the generation of saccades. During rightward saccades, the active circuit is mirror reversed. However, contrary to what the schema suggests, it is likely that the circuits producing rightward and leftward saccades are not completely symmetric, insofar as symmetry means equal number of active neurons, equal number of synapses and neuromuscular junctions.



The recruitment of EBN and reticulo-spinal neurons (RSN) by descending commands from bursting cells in the deep superior colliculus (grey-colored synapses a) leads to the excitation of the pools of extraocular motoneurons in the abducens nucleus (ABD) and neck motoneurons (NMN) in the cervical spinal cord (green and blue synapses b), and thus, to the contraction of the agonist extraocular and neck muscle fibers, respectively. Contrary to the cat, collicular connections with EBN do not seem to be direct in the monkey. The EBN and RSN also excite the IBN (synapse a'), thereby suppressing the activity of cells that otherwise act to facilitate the contraction of antagonist extraocular (synapses c) and neck muscles (synapse c'), respectively. Finally, they also excite secondary vestibular neurons which are inhibitory (IVN-2; blue and green colored synapses d) and located in the ipsilateral medial vestibular nucleus. Within the vestibular nuclei, the discharge of IVN-2 inhibits the secondary vestibular neurons, IVN-1 and EVN-1 (purple-colored synapse e). By inhibiting IVN-1, the motor neurons innervating the agonist extraocular and neck muscles fibers (red synapses f and f') are disinhibited, and the contraction of these muscles is facilitated. By inhibiting the EVN-1, the IVN-2 prevent the primary vestibular neurons (PVN), whose firing is enhanced by the head movement, from causing a counter-rotation of the eyes in the orbits (synapse h). The contraction of antagonist neck muscles through vestibulospinal pathways is also prevented (synapse h').



The two lateral canals are located in the left and right inner ears and lie roughly in a "plane" which is tilted relative to plane passing through the medial and lateral rectus muscles. They are often called "horizontal" because they are primarily activated during head rotations about the Earth gravity axis. During such rotations, primary vestibular neurons (PVN) on the side toward which the nose is rotating (ipsilateral side) increase their firing rate while those on the contralateral side decrease their firing rate. These bilateral changes modify the firing rate of post-synaptic neurons (secondary vestibular neurons) located in the medial and superior vestibular nuclei. On either side of the brain's midsagittal plane, these nuclei are bilaterally organized and house two categories of neurons: type 1 and type 2 neurons. Type 1 neurons increase their firing rate during head rotations toward the side (left or right) including the nucleus in which their discharge is recorded. During contraversive head rotations, they decrease their discharge. In addition, they pause during saccades. In the monkey, these neurons have been called Position Vestibular Pause (PVP) neurons. Type 2 neurons exhibit the opposite pattern, increasing their firing rate during contraversive head rotations and decreasing it during ipsiversive head rotations. The end of the orienting movement is characterized by a time interval during which the gaze direction remains stationary relative to the trunk while the head slowly terminates its motion. The saccades by both eyes give way to their rotation in the opposite direction. As the head rotates, the PVN excite the type 1 vestibular neurons (EVN-1) in the ipsilateral medial and ventrolateral vestibular nuclei. In turn, the EVN-1 initiate and drive the counter-rotation of both eyes in the orbit by exciting the motor (LRMN) and internuclear (AIN) neurons in the contralateral abducens nucleus (red-colored synapses a). Thus, the abducens neurons can resume their activity from the pause imposed by the inhibitory input from IBN in the left Med RF (see blue-colored synapses b). The LR fibers of the right eye can contract, as well as the MR fibers of the left eye, which are activated via motoneurons located in the OMN. The latter cells (MRMN) are also excited by neurons in the ipsilateral nucleus of the ascending tract of Donders (ATDN; green-colored synapse b). In parallel, the spikes emitted by other type 1 vestibular neurons (IVN-1) choke the activity the LRMN and AIN in the abducens nucleus (red-colored synapses c), preventing them from responding to any residual descending (target-related) commands. The recruitment of type 2 neurons (IVN-2) in the contralateral vestibular nuclei (red-colored synapses d) complements the cessation of agonist commands by inhibiting the activity of EVN-1, thereby reducing their excitatory influence upon the motor and internuclear neurons (synapses e). IVN-2 also inhibit the activity of IVN-1, which in turn favors the disinhibition of cells (synapses e) in charge of the counter-rotation of the eyes under the influence of EVN-1 (synapses a).

The functional anatomy enables us to see how the disinhibition of type 1 vestibular neurons can quickly stop the eye saccade during ipsilateral orienting movements. The spikes of IVN-1 (inhibitory synapses c) choke the burst commands while the spikes of EVN-1 order the eyes to counter-rotate as the head terminates its motion (excitatory synapses a).

In the majority of models proposed during the last decades, the movements were considered as driven by error signals encoding displacement vectors in physical space. These models were definitely useful to communicate concepts and to bring a comprehensive picture of the complexity underlying the generation of movements. However, embedding geometric and kinematic notions within the inner functioning of the brain (i.e., mapping intrinsic neuronal signals with extrinsic behavioral measurements) may be misleading because different constraints characterize the neurophysiological and kinematic descriptions. Rather than outcomes of processes reducing geometric or kinematic errors, the eye movements merely consist of transitions between multiple equilibria opposing populations of neurons whose activity leads to mutually antagonist movement tendencies.

Further empirical investigation is still required to determine and explain several other issues: i.e., whether and how the networks underlying orienting movements of the eyes and head interact with those generating other types of goal-directed action such as reaching movements of the hand or locomotion; whether and how they interact with the networks involved in the navigation and the memory of locations; and whether and how they support the learning of new skills and possibly the acquisition of more abstract knowledge such as geometry or counting. With the recent multiplication of cognitive studies that use eye-tracking techniques to explore the so-called "inner space" with quantitative methods, more effort is required to characterize what exactly are those covert processes that eye movements would express.