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# 5 Neurophysiology of gaze orientation: 6 Core neuronal networks

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13

## 14 Abstract

15 The appearance of an object triggers a shift of gaze toward its location. This orienting response  
16 consists of a rapid rotation of the eyes, the saccade, sometimes accompanied by a head  
17 rotation. In this chapter, instead of describing the path leading from the target-evoked retinal  
18 activity to the changes in muscle tension, we shall take the reverse path. Starting from the  
19 muscle contractions, we shall proceed upstream and describe the core neuronal networks  
20 that, in the brainstem and cerebellum, enables us to rapidly and accurately orient the foveae  
21 towards visual targets located at different eccentricities and depths.

22  
23



24

25 **Keywords**

26 Brain stem

27 Cerebellum

28 Eye movement

29 Fixation

30 Gaze

31 Head movement

32 Monkey

33 Neurophysiology

34 Non-human primate

35 Orienting

36 Pursuit

37 Reticular formation

38 Saccade

39 Tracking

40 Vergence

41

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44

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46

## 47 Key points/objectives

48 Complementing several past reviews, this chapter brings a synthesis of the considerable  
49 knowledge that neurophysiologists and neuroanatomists gathered in the monkey during the  
50 last six decades, with the aim to explain the neuronal underpinnings of one of the most basic  
51 spatial abilities, i.e., directing gaze toward the location where something just happened.

52

53



84 compartmentalization of extraocular muscles may lead to revise this view (Demer, 2015).  
85 Moreover, precise measurements made in human subjects revealed a transient torsion during  
86 horizontal saccades (Straumann et al. 1995), suggesting brief changes in the activation of the  
87 other extraocular muscles.

88         The neural control is more complicated when gaze moves vertically. Vertical  
89 movements involve not only steady tension of LR and MR muscles, but also a complex  
90 cooperation between the four other muscles. The contraction of superior and inferior rectus  
91 muscles supraduct (or elevate) and depress (or infraduct) each eye, respectively. These actions  
92 are stronger when the eye is in abduction. The contraction of oblique muscles causes torsional  
93 movements but also supraduct or infraduct the eye, more strongly when the eye is adducted.  
94 If we consider the movements made when the eyes are centered in the orbit, in addition to  
95 elevating the optic axis (turquoise arrows in Fig. 1B), the contraction of the superior rectus  
96 (SR) muscle fibers causes adduction (black arrows) and incyclotorsion (or incycloduction; blue  
97 arrows) of the eyeball. Likewise, in addition to lowering the optic axis (yellow arrows in Fig.  
98 1B), the contraction of the inferior rectus (IR) muscle fibers causes adduction and  
99 excyclotorsion (or excycloduction; green arrows). These secondary actions can be  
100 counteracted by the contraction of oblique muscles, for the contraction of inferior oblique  
101 (IO) muscle fibers causes elevation, abduction and excycloduction, whereas the contraction of  
102 superior oblique (SO) muscle fibers causes depression, abduction and incycloduction (Demer  
103 2019).

104         Binocular conjugate movements are made when the head rotates while a visual target  
105 is being fixated (vestibulo-ocular reflex), when the whole visual scene is moving (optokinetic  
106 reflex) and whenever a target appears or is imagined in the peripheral visual field (saccades).  
107 We shall first examine the neurophysiology of saccade generation when the head does not  
108 move. Then, we shall study the case when a rotation of the head accompanies the saccade.  
109 During these combined eye-head movements, two couplings can happen: the eyes and the  
110 head move either in the same direction or in opposite directions. Next, we shall see the  
111 neurophysiology of disconjugate movements of the eyes, which occur when gaze is shifted  
112 between targets located at different depths (vergence eye movements). Finally, we shall have  
113 an overview of the complex network that enables one to fixate and track a continuously  
114 moving target (smooth pursuit eye movements).

## 115 Binocular conjugate movements

### 116 Horizontal saccades

117 Figure 2 schematizes the current view of the premotor neurophysiology of horizontal  
118 saccades in the pontine and mesencephalic reticular formation. During leftward saccades (Fig.  
119 2A), the fast-twitch muscle fibers of the right eye's MR and of the left eye's LR contract while  
120 those of antagonist muscles (right eye's LR and left eye's MR) relax. Motor neurons in the  
121 abducens nucleus (ABD, located in the pontine reticular formation) and in the oculomotor  
122 nucleus (OMN in the midbrain tegmentum) emit bursts of action potentials that cause the  
123 phasic contraction of muscle fibers (Fuchs and Luschei 1970; Fuchs et al. 1988). The burst  
124 discharge of cells in the OMN is triggered and supported by spikes emitted by internuclear  
125 neurons (AIN) located in the contralateral abducens nucleus. The bursts of abducens motor  
126 (MN) and internuclear (AIN) neurons are driven by afferent input from excitatory burst  
127 neurons (EBN) located in the ipsilateral paramedian pontine reticular formation (PPRF,  
128 synapses a) (Keller, 1974; Luschei and Fuchs, 1972; Strassman et al., 1986a). The abducens  
129 neurons also receive excitatory input from internuclear burst-tonic neurons in the  
130 contralateral oculomotor nucleus (not shown). Discharging during saccades and increasing  
131 their firing rate during convergence, these cells are possibly involved in the motor drive for  
132 conjugate saccades because in addition to cause exophoria, lidocaine injection in the medial  
133 rectus subdivision of the oculomotor nucleus causes hypometria and slowing of abducting  
134 saccades of the contralateral eye (Clendaniel and Mays, 1994).

135 Otherwise silent, the EBN fire trains of action potentials whose interspike interval is  
136 smaller for larger saccades. Contrary to statements made in numerous articles, the  
137 instantaneous firing rate of EBN is not a replica of instantaneous eye velocity. For each  
138 saccade, the interspike interval is much more constant than expected if this claim were true  
139 (i.e, if their discharge determined instantaneous eye velocity) (Hu et al., 2007). The suggestion  
140 that the firing rate of motoneurons would "encode" the instantaneous eye velocity is also  
141 brought into question by a study in the cat (Davis-López de Carrizosa et al., 2011), which  
142 showed that a model factoring in muscle tension and its first derivative accounted for the  
143 firing rate of motor neurons better than a model factoring in eye position and its first and  
144 second derivatives (velocity and acceleration).





## 174 Vertical cardinal saccades

175 The neuronal network underlying the generation of vertical saccades is located in the  
176 midbrain tegmentum (Büttner and Büttner-Ennever, 2006). For upward saccades (Fig. 3A), the  
177 agonist muscles are the IO and the SR and the antagonist muscles the IR and the SO. As  
178 reported above, in addition to elevating the eye, the contraction of SR muscle fibers causes  
179 incycloduction, whereas contraction of IO muscle fibers causes excycloduction. Thus, the  
180 incycloduction caused by the motor commands to the SR combines with the excycloduction  
181 caused by the commands to the IO. The observation of negligible torsional component during  
182 upward saccades suggests that the two torsions cancel each other out. Such a balance of force  
183 likely involves bilateral activity in the midbrain because for each eye, the motor neurons  
184 innervating the SR muscle are located in the contralateral OMN whereas the motor neurons  
185 innervating the IO muscle are located in the ipsilateral OMN (Porter et al., 1983). The two sets  
186 of commands during upward saccades must be adjusted in a timely manner, and any  
187 asymmetry in the bilateral motor drive would engender a torsional component.

188 **< Figure 3 near here >**

189 The excitatory commands responsible for generating upward saccades are issued by  
190 burst neurons located in the left and right rostral interstitial nucleus of the medial longitudinal  
191 fasciculus (RIMLF) (Büttner et al., 1977). These commands are doubly bilateral. Indeed, on the  
192 one hand, the burst emitted by premotor neurons (uEBN) in the left RIMLF excite the  
193 motoneurons innervating the SR muscles of *both* eyes (black synapses a) and motor neurons  
194 innervating the IO muscles of *both* eyes as well (black synapses b in Fig. 3) (Moschovakis et al.,  
195 1991a). On the other hand, the burst emitted by uEBNs in the opposite RIMLF excite the same  
196 motoneuronal group (blue synapses a and b). Moreover, in addition to recruiting the motor  
197 neurons, the uEBN also excite neurons that inhibit the motor neurons that innervate the  
198 antagonist muscles (IR and SO, synapses c). Located in the interstitial nucleus of Cajal, these  
199 cells (uIBN) inhibit the motor neurons in the contralateral oculomotor nucleus, i.e., cells  
200 responsible for the contraction of the IR of the contralateral eye (synapses d) and motor  
201 neurons responsible for the contraction of the SO of the ipsilateral eye (synapses e). However,  
202 contrary to uEBN, uIBN do not send bilateral projections to the motor neurons innervating the

203 SO muscle fibers. Their projections make synaptic contacts only with motor neurons on the  
204 contralateral side (Horn et al., 2003).

205         As for the upward saccades, the discharge of neurons located in each side of the brain  
206 is capable of causing a downward movement of *both* eyes (Fig. 3B). The premotor excitatory  
207 burst neurons leading to downward saccades (dEBN) are also located in the RIMLF  
208 (Moschovakis et al., 1991b). However, unlike the uEBN, the dEBN do not send bilateral  
209 projections to the motoneurons; their projection is ipsilateral only. During downward  
210 saccades, the SO and IR muscle fibers of *both* eyes contract because the dEBN excite 1) the  
211 motor neurons in the ipsilateral OMN, which cause the contraction of IR muscle fibers of the  
212 *ipsilateral* eye (synapses a), and 2) the motor neurons which, in the ipsilateral trochlear  
213 nucleus, cause the contraction of SO muscle fibers of the *contralateral* eye (synapses b).  
214 Moreover, in addition to lowering the eyes, the contraction of SO muscle fibers causes an  
215 incyclotorsion of the eye while the contraction of IR muscle fibers causes their excyclotorsion.  
216 The commands from the ipsilateral OMN for excyclotorsion combine with commands from the  
217 contralateral trochlear nucleus for incyclotorsion. Precisely how these opposite torsional  
218 components cancel each other out during downward saccades remains unexplained. A  
219 bilateral adjustment at the level of premotor burst neurons seems inevitable. Moreover, the  
220 neural processes in charge of the relaxation of antagonist muscles during downward saccades  
221 remain to be characterized.

222         Even though the number of cells and the number of synaptic boutons likely differ  
223 between the left and right sides of the reticular formation, the connectivity patterns involved  
224 in generating leftward and rightward eye movements are symmetrical with respect to the  
225 brainstem midsagittal plane (see Fig. 2 and 5). By contrast, the networks involved in the  
226 generation of downward and upward eye movements are not symmetrical with respect to the  
227 midsagittal plane (Fig 3).

228         During vertical saccades, the EBN involved in the generation of horizontal saccades do  
229 not fire. Some IBN in the dPGRF emit action potentials whose number increases with the  
230 saccade size (Scudder et al., 1988). For vertical saccades to remain straight while their size  
231 increases, one possibility is that the motor and internuclear cells in the abducens nucleus emit  
232 additional spikes, thus reducing the contrapulsive effect of IBN spikes. This does not seem to

233 be the case because MN and AIN in the abducens nucleus do not emit action potentials during  
234 vertical saccades. A more likely possibility is that the contrapulsion exerted by IBN in the left  
235 and right dPGRF cancel each other out. If no perfect symmetry exists between the set of active  
236 neural elements (number of neurons and of synaptic boutons) located on each part of the  
237 reticular formation, then the observation of strictly vertical saccades leads us to infer that a  
238 process adjusts the bilateral activity of IBN during vertical saccades.

239         The bilateral control is not restricted to the group of IBNs, which are primarily involved  
240 in the generation of horizontal saccades. In addition to elevating both eyes, the discharge of  
241 motor neurons in the right OMN causes, as a secondary action and via the contraction of the  
242 right eye's IO and the left eye's SR, a rightward deflection of both eyes during vertical saccades  
243 while the discharge of motor neurons in the opposite side causes a leftward deflection (Fig.  
244 3A, top row). Likewise, in addition to lowering both eyes, the dEBN in the right RIMLF lead to  
245 the contraction of the left eye's SO and the right eye's IR, causing a leftward deflection of their  
246 trajectory while dEBN in the left RIMLF cause a rightward deflection during vertical saccades  
247 (Fig. 3B, top row). The observation of straight vertical saccades (with no horizontal deviation)  
248 implies then that the horizontal deflections caused by the secondary action of the muscles  
249 elevating or depressing the eyes are also canceled in the motor drives.

250         Therefore, the generation of straight vertical saccades rests upon a balance of bilateral  
251 motor activation, which itself depends upon an adjustment of premotor commands that takes  
252 into account the structural (neurons and their connectivity) and functional (firing properties,  
253 secondary and tertiary consequence of muscle contractions) asymmetries between the  
254 oculomotor territories that are distributed on either side of the brain stem. The saccade-  
255 related neurons in the left and right fastigial nuclei and in the oculomotor vermis regulate this  
256 bilateral balance. Indeed, most of them burst during vertical saccades and their asymmetrical  
257 perturbation horizontally deflects the trajectory of vertical saccades (Goffart et al., 2003;  
258 Goffart et al., 2004; Bourrelly et al. 2021). Bilateral activity in the two deep superior colliculi is  
259 also involved with their medial halves for driving upward saccades and their lateral halves  
260 driving downward saccades. The contribution of the deep superior colliculi and of the caudal  
261 fastigial nuclei differ insofar as horizontal saccades involve bursting activity of cells in only one  
262 superior colliculus, on the contralateral side (Sparks et al., 1976), whereas saccade-related  
263 neurons burst in the caudal fastigial nuclei on both sides (Fuchs et al., 1993).

## 264 Combined horizontal and vertical saccades

265           When a target appears off the cardinal visual axes, the orienting response does not  
266 consist of horizontal and vertical saccades made in sequential order. Both horizontal and  
267 vertical components are generated in such a manner that their onset and offset are relatively  
268 simultaneous. These combined horizontal-vertical saccades are conventionally called  
269 “oblique” saccades. Considering the muscle diversity (lengths, contractile properties and  
270 orbital attachments) involved in the horizontal and vertical components and the fact that their  
271 motor innervations are not located in nearby regions of the brainstem, their simultaneous  
272 onsets and the limited curvature of their spatial trajectory are empirical observations  
273 suggesting coupling mechanisms.

274           In the medial pontine reticular formation, the nucleus raphe interpositus (RIP) hosts a  
275 population of cells that exhibit a sustained firing rate during intersaccadic intervals but pauses  
276 during all saccades, regardless of their direction and amplitude (Keller 1974; Phillips et al.,  
277 1999; Strassman et al., 1987). These cells are called omnidirectional pause (or omnipause)  
278 neurons (OPN) and are thought to prevent the eyes from moving during visual fixation through  
279 their inhibitory post-synaptic influence upon the premotor burst neurons (Fig. 2). Moreover,  
280 with their pause, OPN could also be responsible for the synchronous onsets of horizontal and  
281 vertical saccades, as they project to burst neurons in both the horizontal and vertical gaze  
282 centers (Ohgaki et al., 1989). So far, however, experimental studies did not document onset  
283 asynchronies during the inactivation or the lesion of RIP. No fixation instability was reported  
284 either (Kaneko, 1996; Soetedjo et al., 2000). This absence of deficit in visual fixation may have  
285 resulted from the particular testing conditions because the consequence during delayed or  
286 memory-guided saccade tasks was not tested. The observation of irrepressible saccades to  
287 the peripheral target during the delay interval would have unambiguously confirmed the role  
288 of OPN in maintaining steady the gaze direction during visual fixation, as electrical  
289 microstimulation studies suggested (Gandhi and Sparks 2007; Keller 1974). However, these  
290 studies are not sufficiently conclusive because the interruption and delaying of saccades  
291 caused by electrical stimulation might result from the (undesired) retrograde recruitment of  
292 an inhibitory input to pause neurons. A projection from inhibitory burst neurons to the pause  
293 neurons has been reported in the cat (Takahashi et al. 2022). However, it remains to be

294 confirmed in the monkey because so far, the available data do not support it (Strassman et al.  
295 1986b).

296 Turning back to the generation of combined horizontal and vertical saccades, one  
297 study reported crucial observations signaling a process that couples their time course during  
298 oblique saccades. When the horizontal component is experimentally slowed by the local  
299 injection of a pharmacological agent in the pontine reticular formation, the vertical  
300 component is also slowed (Barton et al., 2003; Sparks et al., 2002). In some of these  
301 experiments, the duration of both components was prolonged and the accuracy of saccades  
302 was preserved, supporting further the persistence and preservation of the target-related  
303 commands. The neural connectivity underlying this “component stretching mechanism” in  
304 primates have not yet been elucidated.

## 305 Combined eye and head movements

306 Saccades are frequently associated with a head movement when the target  
307 eccentricity approaches and exceeds the limits of the oculomotor range. Moving the head  
308 enables to look at targets located more eccentrically in the visual field, and to re-center the  
309 eyes in their orbit. The deviation of the eyes in the orbit and of the head relative to the trunk  
310 add together to determine the direction of gaze.

311 Two functional modes characterize orienting gaze movements toward a static target:  
312 a mode during which both eyes and the head rotate in the same direction and a mode during  
313 which they move in opposite directions. The second mode happens sometimes when the head  
314 movement precedes the eye saccade, mostly when the target location is known or foreseeable  
315 (Bizzi et al. 1972). It happens more frequently later because the eyes move much faster than  
316 the head and because the restoration of the equilibrium of bilateral activity that determines  
317 gaze direction has been completed before the equilibrium that determines head direction.  
318 Before describing how gaze is being stabilized and ends its orienting movement, we shall  
319 examine the first mode, i.e., how despite the vestibulo-ocular reflex, the eyes and the head  
320 can move in the same direction as during horizontal gaze shifts (Figure 4).

## 321 Combining a head movement with a saccade

322 In this section, we limit our description to the horizontal eye movements that are made  
323 while the head also moves horizontally. Whether the head is moving or not, behavioral studies  
324 show that the gaze movements are equally accurate. In the monkey, around twenty muscles  
325 are involved to change the orientation of the head (Richmond et al. 2001). Among them are  
326 the muscles whose contraction changes the orientation of the head relative to the trunk, the  
327 muscles that stabilize the head during its rotation and the muscles that do not exhibit any  
328 change (Lestienne et al. 1995). The co-contraction of the left and right *rectus capitis posterior*  
329 *minor* (RCPm) stabilize the atlas while the contraction of the *rectus capitis posterior major*  
330 (RCPM) and *obliquus capitis inferior* (OCI) produce an ipsilateral horizontal rotation of the  
331 head. The observation that the contralateral muscles exhibit no electromyographic change  
332 indicates that stopping the head rotation is not caused by muscle co-contraction (Lestienne et  
333 al. 1995). For movement amplitudes greater than 20 degrees, the contraction of the *splenius*  
334 *capitis* muscle adds to that of the RCPM and OCI muscles. At the end of the orienting  
335 movement, the co-contraction of the RCPm, RCPM, OCI and *obliquus capitis superior* (OCS)  
336 muscles altogether stabilizes the head (Corneil et al., 2001; Lestienne et al. 1995).

337 Thus, orienting gaze shifts mobilize several muscles in parallel when a movement of  
338 the head accompanies the saccade. The synergy results from activities distributed within a  
339 complex set of motor and premotor neurons located in the reticular and vestibular nuclei  
340 (Cullen 2009; Sparks et al., 2001). Contrary those involved in the cat (Takahashi and Shinoda  
341 2018), the premotor processes remain incompletely characterized in the monkey.  
342 Contemporary knowledge is not sufficient to reach a synthetic understanding that is  
343 comparable to the neurophysiology of saccades.

344 The recruitment of EBN and reticulo-spinal neurons (RSN) by descending commands  
345 from bursting cells in the deep superior colliculus (grey-colored synapses a in Fig. 4) leads to  
346 the excitation of the pools of extraocular motoneurons (ABD) in the abducens nucleus and  
347 neck motoneurons (NMN) in the cervical spinal cord (green and blue synapses b), and thus, to  
348 the contraction of the agonist extraocular and neck muscle fibers, respectively. Contrary to  
349 the cat, collicular connections with EBN do not seem to be direct in the monkey (Keller et al.,  
350 2000). The EBN and RSN also excite the IBN (synapse a'), thereby suppressing the activity of

351 cells that otherwise act to facilitate the contraction of antagonist extraocular (synapses c) and  
352 neck muscles (synapse g), respectively. Finally, they also excite secondary vestibular neurons  
353 which are inhibitory (IVN-2; blue and green colored synapses d) and located in the ipsilateral  
354 medial vestibular nucleus. Within the vestibular nuclei, the discharge of IVN-2 inhibits the  
355 secondary vestibular neurons, IVN-1 and EVN-1 (purple-colored synapse e). By inhibiting IVN-  
356 1, the motor neurons innervating the agonist extraocular and neck muscles fibers (red  
357 synapses f and f') are disinhibited, and the contraction of these muscles is facilitated. By  
358 inhibiting the EVN-1, the IVN-2 prevent the primary vestibular neurons (PVN), whose firing is  
359 enhanced by the head movement, from causing a counter-rotation of the eyes in the orbits  
360 (synapse h). The contraction of antagonist neck muscles through vestibulospinal pathways is  
361 also prevented (synapse h').

362 **< Figure 4 near here >**

### 363 **Stopping gaze while the head terminates its motion**

364 The second mode of combined eye head movements is similar to the vestibulo-ocular  
365 reflex recorded when the head is passively rotated while subjects maintain their gaze directed  
366 toward a visual target. During active eye and head movements, the premotor input to motor  
367 neurons makes a transition from commands fed by target-related (visual or auditory) signals  
368 to commands fed by head movement-related signals (Cullen 2009; Cullen and Roy, 2004). The  
369 latter consist of trains of action potentials that originate in the three semicircular canals buried  
370 within the temporal bone. Each semicircular canal consists of a ring within which a fluid  
371 (endolymph) flows and mechanically deflects the stereocilia of multiple cells whenever the  
372 head rotation accelerates or decelerates. This deflection either increases or decreases the  
373 discharge of primary vestibular neurons (PVN) with a rate proportional to head velocity.

374 The two lateral canals are located in the left and right inner ears and lie roughly in a  
375 "plane" which is tilted not only relative to the Reid plane, but also to the "plane" passing  
376 through the medial and lateral rectus muscles (Cox and Jeffery, 2008; Ostriker et al., 1985).  
377 These canals are often called "horizontal" because they are primarily activated during head  
378 rotations about the Earth gravity axis. During such rotations, PVN on the side toward which  
379 the nose is rotating (ipsilateral side) increase their firing rate while those on the contralateral  
380 side decrease their firing rate. These bilateral changes modify the firing rate of post-synaptic

381 neurons (secondary vestibular neurons) located in the medial and superior vestibular nuclei  
382 (McCrea et al., 1987b). On either side of the brain's midsagittal plane, these nuclei are  
383 bilaterally organized and house two categories of neurons: type 1 and type 2 neurons. Type 1  
384 neurons increase their firing rate during head rotations toward the side (left or right)  
385 containing the nucleus in which their discharge is recorded. During contraversive head  
386 rotations, they decrease their discharge. In addition, they pause during saccades (McCrea et  
387 al. 1987). In the monkey, these neurons have been called Position Vestibular Pause (PVP)  
388 neurons. Type 2 neurons exhibit the opposite pattern, increasing their firing rate during  
389 contraversive head rotations and decreasing it during ipsiversive head rotations (Fuchs et al.  
390 2005; Roy and Cullen, 2002; 2003).

391 **< Figure 5 near here >**

392 Figure 5 schematizes the mechanism by which vestibular signals contribute to ending  
393 a leftward movement of gaze toward a visual target. The end of the orienting movement is  
394 characterized by a time interval during which the gaze direction remains stationary relative to  
395 the trunk while the head slowly terminates its motion. The saccades by both eyes give way to  
396 their rotation in the opposite direction. As the head rotates, the primary vestibular neurons  
397 (PVN) excite the type I vestibular neurons (EVN-1) in the ipsilateral medial and ventrolateral  
398 vestibular nuclei (Broussard et al. 1995). In turn, the EVN-1 initiate and drive the counter-  
399 rotation of both eyes in the orbit by exciting the motor (LRMN) and internuclear (AIN) neurons  
400 in the contralateral abducens nucleus (red-colored synapses a). Thus, the abducens neurons  
401 can resume their activity from the pause imposed by the inhibitory input from IBN in the left  
402 Med RF (see blue-colored synapses b in Fig. 2). The LR muscle fibers of the right eye can  
403 contract, as well as the MR muscle fibers of the left eye, which are activated via motoneurons  
404 located in the OMN. The latter cells (MRMN) are also excited by neurons in the ipsilateral  
405 nucleus of the ascending tract of Deiters (ATDN; green-colored synapse b). In parallel, the  
406 spikes emitted by other type 1 vestibular neurons (IVN-1) choke the activity the LRMN and  
407 AIN in the abducens nucleus (red-colored synapses c), preventing them from responding to  
408 any residual descending (target-related) commands. The recruitment of type 2 neurons (IVN-  
409 2) in the contralateral vestibular nuclei (red-colored synapse d) complements the cessation of  
410 agonist commands by inhibiting the activity of EVN-1, thereby reducing their excitatory  
411 influence upon the motor and internuclear neurons (synapses e). IVN-2 also inhibit the activity



412 of IVN-1, which in turn favors the disinhibition of cells (synapses e) in charge of the counter-  
413 rotation of the eyes under the influence of EVN-1 (synapses a) (Broussard et al., 1995; Scudder  
414 and Fuchs, 1992).

415 The functional anatomy schematized in Fig. 5 enables us to see how the disinhibition  
416 of type 1 vestibular neurons can quickly stop the eye saccade during ipsilateral orienting  
417 movements. The spikes of IVN-1 (inhibitory synapses c) choke the burst commands while the  
418 spikes of EVN-1 order the eyes to counter-rotate as the head terminates its motion (excitatory  
419 synapses a). This mechanism also helps us to understand the hypometria of contralateral eye  
420 and head movements after unilateral lesion of the caudal fastigial nucleus (for instance the  
421 right nucleus) (Quinet and Goffart, 2007). Contralateral (leftward) saccades are hypometric  
422 because the agonist drive from EBN lacks of the excitatory input from inactivated (right)  
423 fastigial cells, and because the saccade-related burst of neurons in the opposite (unaffected)  
424 fastigial nucleus excite IBN in the contralateral (right) reticular formation. These IBN inhibit  
425 IVN-2 in the opposite (left) vestibular nuclei, disinhibiting the excitatory influence of EVN-1  
426 (initiating the counter-rotation of the eyes) and the inhibitory influence of IVN-1 upon  
427 ipsilateral motor neurons (inhibiting the saccade-related drive). The latter mechanism also  
428 explains the hypometria of head movements. Their amplitude is truncated because the IVN-1  
429 inhibits the ipsilateral neck motor neurons (NMN; synapse e) while the EVN-1 facilitates the  
430 contraction of contralateral neck muscles (synapse f).

431 **< Figure 6 near here >**

432 As for the generation of upward and downward saccades (Fig. 3), the neural  
433 connectivity involved in the generation of downward and upward slow eye movements are  
434 not symmetrical (McCrea et al. 1987a). Figure 6A schematizes the network that stabilizes gaze  
435 during downward gaze movements. While the head pitches down and slowly terminates its  
436 motion, both eyes rotate upward in the orbits. The upward eye movement is the outcome of  
437 contracting SR and IO muscles fibers. Driven by the increased firing of PVN connected with the  
438 left anterior canal, excitatory vestibular neurons (EVN-U) in the left medial vestibular nucleus  
439 activate the motor neurons innervating the left eye's SR and the right eye's IO muscle fibers  
440 (synapses a).

441 In addition to elevating both eyes, the contraction of these fibers causes an  
442 incyclotorsion of the left eye and an excyclotorsion of the right eye, as if both eyes were  
443 counteracting a tilt of the head toward the left shoulder. This clockwise torsion of both eyes  
444 can be attenuated by the torsion caused by the excitatory input from EVN-U in the right MVN.  
445 Because of their excitation by the right anterior canal, PVN drive the firing rate of EVN-U,  
446 which in turn excite the motor neurons that innervate the right eye's SR and the left eye's IO  
447 muscle fibers (synapses b), causing the right eye's incyclotorsion and left eye's excyclotorsion.  
448 The absence of torsion during strictly upward slow eye movements suggests that the output  
449 of the left and right vestibulo-oculomotor channels have been adjusted so that the torsional  
450 signals balance out.

451 Regarding the antagonist muscles, their inhibition is promoted by IVN-U located in the  
452 superior vestibular nuclei. These cells inhibit the motor neurons innervating the IR of the  
453 ipsilateral eye (synapses c) and those innervating the SO muscle of the contralateral eye  
454 (synapse d). Contrary to the network involved in horizontal eye and head movements (Fig. 5),  
455 the neural mechanisms triggering the counter-rotation of the eyes when the head pitches  
456 down are not yet elucidated. However, the inputs are necessarily bilateral and balanced since  
457 the eyes move by the same amount and their torsion canceled.

458 Finally, figure 6B schematizes the neuronal network involved in stopping an upward  
459 gaze shift while the head slowly terminates its upward motion. Both eyes rotate downward in  
460 the orbits because of the contraction of IR and SO muscle fibers. This is driven by the increased  
461 firing of primary vestibular neurons (PVN) connected with the left posterior canal. Excitatory  
462 vestibular neurons (EVN-D) in the left medial vestibular and ventral lateral vestibular nuclei  
463 activate the motor neurons innervating the fibers of the right eye's IR and the left eye's SO  
464 muscles (synapses a).

465 As above, in addition to depressing both eyes, the contraction of these fibers cause an  
466 excyclotorsion of the right eye and an incyclotorsion of the left eye, as if the eyes are  
467 counteracting a tilt of the head toward the right shoulder. Once again, the binocular torsion  
468 is attenuated by a torsion made in the opposite direction and caused by excitatory input from  
469 the right posterior canal to the motor neurons innervating the left eye's IR and the right eye's  
470 SO muscle fibers (synapses b). Inhibitory vestibular neurons (IVN-D) located in the superior

471 vestibular nuclei prevent the antagonist muscles from contracting by inhibiting the motor  
472 neurons innervating the SR of the contralateral eye (synapses c) and possibly also the motor  
473 neurons innervating the IO muscle of the ipsilateral eye (synapse d). As for the neural  
474 mechanisms ending downward gaze shifts, the neural mechanisms triggering the counter-  
475 rotation of the eyes when the head pitches up are not completely identified. Nevertheless, if  
476 the eyes do not exhibit any torsional component, the motor commands are necessarily  
477 bilateral and balanced.

478         In summary, by studying the networks underlying the generation of slow eye  
479 movements, we discover a complexity that radically differs from the straightforward solutions  
480 that human engineers would have designed. One puzzling question concerns the constraints  
481 that led the torsional components caused by the contraction of elevator or depressor muscles  
482 to cancel each other out. Moreover, the connectivity that we have described is not complete,  
483 because new eye movements can be produced in response to “unusual” combinations of head  
484 rotations and visual stimulation. Experiments in the cat have shown that the visual stimulation  
485 exerts a significant influence on the functional connectivity yielding the vestibulo-oculomotor  
486 responses. Horizontal compensatory eye movements can be generated during vertical head  
487 rotations in the dark after training sessions during which the visual field moved horizontally  
488 whenever the head rotated vertically. The horizontal nystagmus persisted in the absence of  
489 any new visuo-vestibular experience (Schultheis and Robinson, 1981).

## 490 Fixating a static visual target

491         Considering the line of sight as the direction of gaze measured when a subject fixates  
492 a visual target, the binocular fixation point designates the intersection between the two lines  
493 of sight (Collewijn et al., 1997). Of course, the quantification of movements must be  
494 distinguished from their neurophysiological correspondence. Looking at a visual target  
495 obviously does not reduce to the excitation of one single photoreceptor on the fovea of each  
496 eye. We will therefore rather speak of a binocular fixation zone. On the motor side, the  
497 orientation of the eyes is maintained steady by the sustained discharge of a tonic neurons  
498 distributed in the nucleus prepositus hypoglossi (NPH), the vestibular nuclei (in the medullary  
499 reticular formation) and in the interstitial nucleus of Cajal (Fukushima et al. 1992; McFarland  
500 and Fuchs, 1992; Moschovakis, 1997). The more deviated the eyes in the orbit, the higher their

501 firing rate. In addition to connective tissues that wrap each eyeball within the orbit, two  
502 neuronal networks are involved in maintaining the rotation axes of the eyes within Listing's  
503 plane and deviating them horizontally and vertically. These networks are relatively  
504 independent from each other insofar as a lesion in the NPH primarily affects the ability to  
505 maintain gaze direction within the horizontal plane, with marginal effects on vertical gaze  
506 direction (Kaneko, 1997; 1999). After the saccades, whose amplitude is unaffected, the eyes  
507 exhibit an exponential drift toward their primary orientation (roughly straight ahead). By  
508 contrast, lesion in the NIC causes a failure to hold vertical deviations of the eyes (i.e. both  
509 upward and downward) but not horizontal deviations. A torsional drift of the eyes is also  
510 observed when the lesion is unilateral (Helmchen et al., 1998).

511           Considering now the case when the foveation changes between targets or locations  
512 situated at different depths in the three-dimensional physical space, three visuomotor  
513 processes occur: 1) vergence, 2) accommodation and 3) variation of pupil diameter.  
514 Convergence designates the symmetrical eye movements made when the MR muscle fibers  
515 of both eyes contract, diminishing the distance of the binocular fixation zone relative to the  
516 head. Divergence designates those movements made when the distance increases because of  
517 a binocular relaxation of MR muscle fibers. The contraction level of intraocular muscles also  
518 changes (McDougal and Gamlin, 2015). During convergence, the contraction of ciliary muscles  
519 (CM) reduces the tension in zonular fibers, changing the refractive power of the lens as its  
520 anterior surface bulges forward (increase in convexity). Thus, the target images are brought  
521 into focus on the foveae. This accommodation is associated with a myosis, i.e., the constriction  
522 of the iris and the reduction of the pupil diameter, thereby increasing the depth of field. The  
523 myosis itself results from the contraction of the sphincter pupillae (SP) combined with the  
524 relaxation of the dilator pupillae (DP). Altogether, these three visuomotor processes  
525 constitute the so-called the near response (or near triad).

526           Although these processes are generated jointly, clinical studies report pathological  
527 cases in which they are dissociated and the neuroanatomy helps us to understand why. Figure  
528 7 shows that the contraction of MR muscle fibers is controlled by the firing rate of motor  
529 neurons (MRMN) located in the oculomotor nucleus whereas the intrinsic musculature of each  
530 eye is controlled by motor neurons located in the ciliary ganglions (CG) and premotor neurons  
531 in the Edinger-Westphal preganglionic nucleus (EWpg). In both cases, the innervation is

532 ipsilateral (Gamlin, 1999). The binocular control and the near triad starts with their afferent  
533 input from two major regions of the midbrain tegmentum: the supraoculomotor area (SOA)  
534 and the central mesencephalic reticular formation (cMRF) (May et al., 2018; 2019).

535 **< Figure 7 near here >**

536 The SOA is primarily involved in the generation of the slow near response and its  
537 sustained maintenance. Therein, we find burst neurons and tonic neurons, with separate  
538 subgroups characterized by different discharge patterns during the generation of diverging  
539 and converging eye movements. More common just lateral to the MLF, four categories of  
540 neurons are found: convergence burst neurons, divergence burst neurons, convergence tonic  
541 neurons and divergence tonic neurons (Mays, 1984; Mays et al., 1986). Whether divergence  
542 neurons exert an inhibitory influence upon the firing rate of convergence neurons is not  
543 known yet. Neurons in SOA send projections to the medial rectus MN that are ipsilateral,  
544 whereas the projections to the EWpg are bilateral (May et al., 2018).

545 In the cMRF, we find neurons that emit a burst discharge whenever the near response  
546 accompanies a saccadic eye movement: saccade convergence burst neurons and saccade  
547 divergence burst neurons. The former fire during asymmetrical saccades associated with an  
548 increase of the vergence angle and the latter fire during asymmetrical saccades associated  
549 with a divergence (Quinet et al., 2020). Each cMRF innervates the SOA and the EWpg  
550 bilaterally. It also sends ipsilateral projections to the sites in the OMN in which the motor  
551 neurons that innervate the singly-innervated muscle fibers are located (May et al., 2018).

552 The bilateral projections from SOA to the EWpg, and from the cMRF to both EWpg and  
553 SOA are completed by bilateral afferents from caudal fastigial nuclei (CFN) (Bohlen et al. 2021;  
554 May et al. 1992) whose contribution in the near-triad has been reported (Bohlen et al., 2021;  
555 Gamlin and Zhang, 1996). In addition to send bilateral projections to the midbrain tegmentum  
556 and contralateral projections to the pontomedullary reticular formation (where EBN and IBN  
557 are located, Fig. 2), the CFN also project bilaterally to the rostral part of the deep superior  
558 colliculi, with a contralateral predominance (May et al. 1990). Therein, some cells either  
559 increase (convergence neurons) or decrease (divergence neurons) their firing rate during  
560 vergence eye movements (Bohlen et al., 2021; Gamlin 2002; Gamlin et al., 1996; Zhang and  
561 Gamlin, 1996).

562 In addition to modulations during vergence (van Horn et al., 2013), recording studies  
563 in the rostral superior colliculi also revealed the presence of cells that burst during miniature  
564 saccades (also called microsaccades), like more caudal cells discharge during larger saccades  
565 (Hafed and Krauzlis 2012). Local pharmacological inactivation confirmed their causal role in  
566 the generation of microsaccades (Hafed et al. 2009). However, it also unraveled an implication  
567 of rostral SC in specifying the direction of gaze when a target is presented (or even imagined)  
568 in the central visual field, static or moving (Hafed et al. 2008). Indeed, unbalanced activity  
569 between the two rostral SC causes a fixation offset to the extent that gaze direction is not  
570 directed anymore to the target center but toward an offset location. The same deficit happens  
571 after unilateral pharmacological perturbation of CFN, suggesting that the sustained firing rate  
572 of its neurons adjusts the balance of activity between the two rostral SC during visual fixation  
573 (Bourrelly et al., 2018b; Goffart et al., 2012; Guerrasio et al., 2010). Thus, the direction of gaze  
574 would correspond to an equilibrium of commands that counterbalance with each other,  
575 involving fastigial projections to the left and right rostral SC but also to the left and right nuclei  
576 *reticularis tegmenti pontis* (NRTP). Through their projections to NRTP, the two rostral SC and  
577 CFN have access to neurons which, in the flocculus and paraflocculus, influence the firing rate  
578 of tonic neurons that innervate the motor and internuclear neurons in the abducens nuclei  
579 (Belton and McCrea 2000; Lisberger et al. 1994; Noda and Mikami, 1986; Noda and Suzuki,  
580 1979; Noda et al., 1990).

581 In summary, the knowledge of the detailed neuronal circuitry underlying the  
582 generation of disjunctive eye movements is not advanced as much as the circuitry for  
583 conjugate saccades (Mays and Gamlin, 1995a, b) but a lot of progress has been made during  
584 the last decade (e.g., May et al., 2022). Soon it will be possible to understand the complex  
585 neurophysiology that underlies the generation of vergence eye movements and their  
586 dysfunction (Das 2016; Lennerstrand 2007).

## 587 Tracking a moving visual target

588 A target drifting in the visual field often elicits a primary saccade (called interceptive  
589 saccade) at the end of which gaze does *not* land ahead of the moving target. Interceptive  
590 saccades either accurately capture (foveate) or fall behind the target. Then, a slow eye  
591 movement follows with a velocity that rarely matches the target's. A textured background

592 (yielding visual motion in the direction opposite to the eye movement) does not seem to be  
593 responsible for the pursuit slower than target velocity because the consequences of its  
594 suppression are very weak (Keller and Khan, 1986). A subsequent correction saccade (called  
595 catch-up saccade) restores the foveation. Thus, unless the target trajectory is already known  
596 and foreseeable, gaze lags behind the target most of the time (Goffart et al., 2017a), especially  
597 when the target is small: the visual tracking is mostly composed of catch-up saccades  
598 interspersed by intervals during which the eyes drift roughly in the same direction as the target  
599 and with a lesser speed. In well-trained subjects, the catch-up saccades can be eliminated  
600 (Botschko et al. 2018; Bourrelly et al., 2016). Moreover, increasing the target size enhances  
601 the velocity of slow eye movements and reduces the size and number of catch-up saccades  
602 (Pola and Wyatt, 1985). This point is important because most experimental studies use a small  
603 spot of light as a target.

604         Contrary to a static target which yields a bounded activity, a moving spot evokes on  
605 the retina a streak of activity the tail of which corresponds to past locations of the target and  
606 the leading edge the most recent location. In the deep superior colliculus, as for saccades to  
607 a static target, the population of saccade-related burst neurons is expanded (Anderson et al.,  
608 1998; Goossens and van Opstal 2006; Sparks et al., 1976). However, it does not recruit cells  
609 that fire during saccades to future target locations. The population consists of a continuum of  
610 cells ranging from neurons issuing commands related to past locations of the target to neurons  
611 issuing commands related to its current location (Goffart et al., 2017). At the level of motor  
612 neurons, other input must therefore complement the collicular signals. This input stems, at  
613 least in part, from motion signals processed in area MT because its lesion leads to saccades  
614 landing at locations that the target crossed earlier. Thus, the ability to foveate the visual target  
615 may consist of adding a “predictive” component based on the integration of putative target-  
616 related “velocity” signals to collicular signals (Keller et al., 1996; Optican, 2009). However, an  
617 alternative explanation is possible. While considering that any target recruits an extended  
618 assembly of neurons, the generation of accurate interceptive saccades may result from the  
619 attenuation of the synaptic weight of spikes emitted by the cells that were the earliest excited  
620 by the passage of the target, combined with the promotion of the synaptic weight of spikes  
621 emitted by the latest and most recently excited cells.

622 The dorsolateral pontine nucleus (DLPN) is one of the nuclei that relays signals from  
623 motion-related areas of the cerebral cortex to the cerebellum. When a chemical lesion is  
624 placed in the DLPN, saccades toward a moving target are hypometric whereas saccades to a  
625 static target remain unchanged (May et al., 1988; Ono et al., 2003). The hypometria suggests  
626 that the saccades were directed toward the past location of the target. Neurons in DLPN  
627 project to the floccular and medio-posterior regions of the cerebellum. Ablation of the  
628 floccular region (flocculus and paraflocculus) impairs the velocity of slow eye movements,  
629 seemingly without affecting catch-up saccades (Zee et al., 1981). By contrast, unilateral  
630 inactivation of the output nucleus of the medio-posterior cerebellum, the caudal fastigial  
631 nucleus, impairs both contralesional saccadic and pursuit eye movements (Bourrelly et al.,  
632 2018a; 2018b). Because of the hypometria of saccades and the slowing of pursuit velocity,  
633 gaze direction always lags behind the target when it moves in the direction contralateral to  
634 the lesion.

635 **< Figure 8 near here >**

636 Concerning the generation of slow pursuit eye movements, the figure 8 schematizes  
637 the complex neuronal network involved in their generation when the movement direction is  
638 horizontal. The schema is not complete because it does not show how neurons in the  
639 oculomotor vermis and the rostral superior colliculi are being recruited during the generation  
640 of tracking (saccadic and slow) eye movements.

641 Some cells firing tonically in the nucleus prepositus hypoglossi (NPH) and the nearby  
642 medial vestibular nucleus (MVN) increase their firing rate during ipsilateral pursuit (McFarland  
643 and Fuchs, 1992). Although called “eye-head velocity” neurons in the monkey, we shall name  
644 them tonic neurons for simplicity and for distinguishing them from the burst neurons and EVN-  
645 1 described in the previous paragraphs. Some of the tonic neurons are believed to provide an  
646 excitatory input to the abducens neurons for contracting the agonist muscle fibers during  
647 ipsilateral pursuit. While documented in the cat, this ipsilateral excitatory tonic input (ETN)  
648 has been questioned in the monkey (Langer et al., 1986). Most NPH/MVN neurons seem to be  
649 inhibitory and to project to the contralateral side (synapses a) (McCrea and Horn, 2006). When  
650 the sustained firing rate of tonic neurons is considered, we understand that the reciprocal  
651 commissural inhibition between the NPH/MVN in the left and right sides yields a push-pull



652 organization, such that a reduced firing rate on one side enhances the firing rate on the  
653 opposite side. Thus, by suppressing the activity of the neurons that innervate the antagonist  
654 muscle fibers (red synapses a), the inhibitory tonic neurons (ITN) in the NPH/MVN contribute  
655 to the relaxation of these muscles, while disinhibiting the ipsilateral abducens and  
656 internuclear neurons (blue synapses a) and promoting an ipsiversive movement of both eyes.

657         Neurons in NPH/MVN are monosynaptically inhibited (synapse b) by Purkinje cells in  
658 the flocculus and the ventral paraflocculus (Lisberger et al. 1994), which receive excitatory  
659 input from the three major pontine nuclei (synapses c) involved in relaying visual motion  
660 signals to the cerebellum: the rostral part of nucleus reticularis tegmenti pontis (rNRTP), the  
661 dorsolateral pontine nucleus (DLPN) and the dorsomedian pontine nucleus (DMPN). These  
662 pontine nuclei contribute to the inhibition that Purkinje cells exert upon NPH/MVN neurons.  
663 After a chemical lesion in the dorsolateral pontine nucleus (DLPN) or in the rostral nucleus  
664 reticularis tegmenti pontis (rNRTP), ipsilesional pursuit eye movements are severely impaired  
665 (May et al., 1988; Ono et al. 2003; Suzuki et al., 1999). The suppression of pontine input likely  
666 reduces the floccular inhibition of ITN neurons, which in turn impede the recruitment of  
667 agonist motor and internuclear neurons. The consequences of suppressing the input from  
668 DMPN have not been tested yet. However, an impairment of ipsilesional pursuit is expected  
669 because the DMPN and the contralateral caudal fastigial nucleus exhibit strong reciprocal  
670 connections, and inactivation of the latter severely impairs the generation of contralesional  
671 pursuit eye movements (Bourrelly et al., 2018b).

672         The NPH/MVN are also the target of signals from neurons in the pretectal nucleus of  
673 the optic tract (NOT; synapse d) (Mustari et al. 1994), some of which are sensitive to the  
674 motion of a small visual target (Fuchs et al., 1992; Mustari and Fuchs, 1990). These neurons  
675 fire during ipsilateral target motions (Mustari et al., 1990) and their loss severely impairs the  
676 ability to generate ipsilesional slow pursuit eye movements (Yakushin et al., 2000). NOT  
677 receives visual signals from the retina and from the middle temporal (MT) and medial superior  
678 temporal (MST) areas of cerebral cortex (synapse f) wherein numerous cells are sensitive to  
679 target motion as well (Distler et al., 2002). Projections of the frontal eye field (FEF) to NOT and  
680 to NPH have been documented (synapses e and e'). This access of frontal cortex to premotor  
681 neurons does not indicate a voluntary control of pursuit eye movements since the presence  
682 of a target is required for initiating a smooth pursuit. The NOT contributes to the maintenance

683 of ipsilateral pursuit eye movements by its direct projections to tonic neurons in the ipsilateral  
684 NPH/MVN (synapse d), but also to the ipsilateral pontine nuclei (synapses g).

685 Through their projections to the ipsilateral rostral SC (synapse j), Gaba-ergic cells in  
686 NOT may contribute to suppression of the generation of saccades made in the direction  
687 opposite to the target motion. Simultaneously, they may depress the excitatory drive that  
688 NRTTP exerts upon the ipsilateral paraflocculus (synapse k).

689 Finally, the secondary excitatory vestibular neurons (EVN-1 or PVP cells) that are  
690 involved in moving the eyes in the direction opposite to the head movement (Fig. 5) increase  
691 their firing rate during contraversive pursuit eye movements. However, as they do not seem  
692 to be inhibited by Purkinje cells located in the floccular region, the origin of the discharge  
693 modulation during contraversive pursuit remains to be identified. Direct projections from the  
694 frontal eye fields to the NPH/MVN might support this influence.

## 695 Conclusion

696 Studying orienting movements of gaze is a convenient means for investigating how  
697 intertwined networks of neurons in the central nervous system transforms sensory signals into  
698 motor commands, but also, how it enables an entire animal to visually locate and capture an  
699 object in the physical environment and to adapt when intrinsic damage or contextual changes  
700 alter their execution.

701 During the last decades, neurophysiologists and neuroanatomists gathered in the  
702 monkey considerable knowledge that enabled identifying the core networks involved in the  
703 generation of eye movements (Büttner-Ennever, 2006; Fuchs et al., 1985; Goffart et al., 2017a;  
704 Grandin et al., 2002; Henn et al., 1984; Horn and Leigh, 2011; Krauzlis, 2004; Krauzlis et al.  
705 2017; Moschovakis et al., 1996; Raphan and Cohen, 1978; Scudder et al., 2002; Soetedjo et  
706 al., 2019; Sparks, 2002; Sparks and Mays, 1990; Ugolini et al. 2006). Technical developments  
707 offered the possibility to measure precisely the time course of these movements and to study  
708 correlations between the firing rate of neurons and kinematic parameters such as movement  
709 amplitude, velocity, acceleration and various differences (e.g., gaze error, velocity error, etc.).  
710 However, these correlation studies should not lead us to believe that a one-to-one  
711 correspondence exists between the multiple networks within which neuronal activities

712 propagate, and the extrinsic and homogeneous medium (mathematical space) with which we  
713 quantify the motion of rigid objects such as the eyeballs, the head and targets. Such a mapping  
714 is not at all obvious; it is even questionable. Contrary to the physical space, the medium of  
715 neuronal activity is neither homogeneous nor passive. Unlike most objects at which we look  
716 and that we manipulate, the corresponding brain activity is not rigid. Even the mere spot of  
717 activity that a small static object evokes on the retina yields multiple parallel flows of activity  
718 that make its correspondence in the brain spatially distributed, temporally extended and  
719 context-dependent (Goffart et al. 2018). Moreover, reducing neurons or neuronal chains to  
720 units encoding geometric or kinematic relations between gaze and target conceals the muscle  
721 forces and the multiple antagonisms that we have described between muscles (Miller et al.  
722 2002). Furthermore, the velocity profile of the movement and the time course of force  
723 development do not match (Miller and Robins, 1992). During horizontal saccades for example,  
724 the duration of the interval during which the muscle force increases is on average 60% shorter  
725 than the duration of the total change in eye orientation. A force decay happens well before  
726 the change in eye position ends and the larger the saccade, the longer its lead-time relative to  
727 saccade arrest (Lennerstrand et al., 1993). Finally, the temporal series of numerical values  
728 quantifying the changes during eye reorientation hides the antagonisms between those  
729 multiple channels that generate each movement. To our knowledge, no study has reported  
730 identical time courses between the kinematic and neurophysiological recordings that would  
731 support the assumption of an isomorphism.

732           In the majority of models proposed during the last decades, the movements of the  
733 eyes and the head were considered as driven by (intrinsic) error signals encoding displacement  
734 vectors in physical space (e.g., Lisberger et al. 1987). These models have definitely been useful  
735 to communicate concepts and to bring a comprehensive picture of the complexity underlying  
736 the generation of movements. However, embedding geometric and kinematic notions within  
737 the inner functioning of the brain (i.e., mapping intrinsic neuronal signals with extrinsic  
738 behavioral measurements) may be neurophysiologically misleading because different  
739 constraints characterize the neurophysiological and kinematic descriptions. In fact, rather  
740 than outcomes of processes reducing geometric or kinematic errors, the saccade and pursuit  
741 deceleration may resume merely to transitions from imbalance to equilibria opposing

742 populations of neurons whose activity leads to mutually antagonist movement tendencies  
743 (Goffart, 2019).

744 Further empirical investigation is still required to determine and explain several other  
745 issues such as: whether and how the networks underlying orienting movements of the eyes  
746 and head interact with those generating other types of goal-directed action like hand reaching  
747 movements or whole-body locomotion; whether and how they interact with the networks  
748 involved in the navigation and the memory of locations; whether and how they support the  
749 learning of new skills and possibly the acquisition of more abstract knowledge such as  
750 geometry or counting; etc. With the recent multiplication of cognitive studies that use eye-  
751 tracking techniques to explore with quantitative methods the so-called “inner space”  
752 (Johansson et al., 2013; Strohmaier et al. 2020), more effort is required to characterize what  
753 exactly are those covert processes that eye movements would express. Neurophysiological  
754 and neuroanatomical works must also continue to reveal the innervation of extraocular  
755 muscles compartments and unravel the multiplicity of channels and neuronal networks that  
756 enable a living organism to interact visually with its natural and social environment.

757 By studying the simple and seemingly straightforward problem of orienting the eyes  
758 toward the location of a physical object, we see how the neurophysiological and  
759 neuroanatomical studies performed with animals enables us to understand the symptoms  
760 exhibited by patients suffering from eye movement disorders (Horn and Leigh, 2011; Rucker  
761 and Lavin, 2021; Sharpe, 2008; Sharpe and Wong, 2005). They also show that evolutionary  
762 and embryological developments led to patterns that are much more complex and redundant  
763 than the straightforward strategies of human engineers. Contrary to the case where a design  
764 precedes the realization of a machine for solving a specific problem, the Physiology teaches  
765 us that any behavioral observation is the outcome of a multiple networks and parallel chains  
766 of neurons. It also teaches us how the multiplicity and the diversity of elements enable an  
767 organism to solve several problems in parallel and even take up new challenges.

768

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- 1144

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1146

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1152



## 1153 Figure captions

1154

1155 **Figure 1:** Schematic representation of the extraocular muscles (A) and pulling directions  
1156 engaged by the contraction of their fibers when the eyes are centered in the orbit (B). LR:  
1157 lateral rectus, MR: medial rectus, SR: superior rectus, IR: inferior rectus, SO: superior oblique,  
1158 IO: inferior oblique, tr: trochlea. The red arrows indicate the muscles whose contraction  
1159 abducts the eye, the black arrows the muscles whose contraction adducts the eye. The  
1160 turquoise arrows indicate the muscles whose contraction elevates the eye (supraduction), the  
1161 yellow arrows those whose contraction infraducts the eye. The blue arrows indicate the  
1162 muscles whose contraction causes an incyclotorsion (incycloduction) of the eye, the green  
1163 arrows those whose contraction causes an excyclotorsion (excycloduction).

1164

1165 **Figure 2:** Neuronal network involved during horizontal saccades toward the left (A) and the  
1166 right (B). Connecting lines ended by an arrow indicate excitatory connections; those ended by  
1167 a circle indicate inhibitory synaptic connections. Blue color indicates the agonist neuronal  
1168 elements, red color the antagonist ones. The thickness of connecting lines schematizes the  
1169 strength with which the neurons fire. OPN: omnipause neurons, EBN: excitatory burst  
1170 neurons, IBN: inhibitory burst neurons, MN: abducens motoneurons, AIN: abducens  
1171 internuclear neurons. In the bottom, the thickness of arrows attached to the eyeballs  
1172 schematizes the strength of muscle contraction. LR: lateral rectus, MR: medial rectus, SR:  
1173 superior rectus, IR: inferior rectus, SO: superior oblique, IO: inferior oblique.

1174

1175 **Figure 3:** Neuronal network involved during vertical saccades toward the top (A) and the  
1176 bottom (B). Connecting lines ended by an arrow indicate excitatory connections; those ended  
1177 by a circle indicate inhibitory synaptic connections. Blue color indicates the agonist neuronal  
1178 elements, red color the antagonist ones. The thickness of connecting lines schematizes the  
1179 strength with which the neurons fire. uEBN: upward excitatory burst neurons, dEBN:  
1180 downward excitatory burst neurons, uIBN: upward inhibitory burst neurons, MN:  
1181 motoneurons. In the top, the thickness of arrows attached to the eyeballs schematizes the  
1182 strength of muscle contraction. LR: lateral rectus, MR: medial rectus, SR: superior rectus, IR:  
1183 inferior rectus, SO: superior oblique, IO: inferior oblique.

1184

1185 **Figure 4:** Neuronal network involved during combined horizontal eye and head movements  
1186 toward the left. Connecting lines ended by an arrow indicate excitatory connections; those  
1187 ended by a circle indicate inhibitory synaptic connections. Blue color indicates the agonist  
1188 neuronal oculomotor elements, red color the antagonist ones. Green color indicates the  
1189 cephalomotor elements. The thickness of connecting lines schematizes the strength with  
1190 which the neurons fire. dSC: deep superior colliculus, RSN: reticulospinal neurons, EBN:  
1191 excitatory burst neurons, IBN: inhibitory burst neurons, ABD: abducens motor and  
1192 internuclear neurons, NMN: neck motoneurons, PVN: primary vestibular neurons, IVN:  
1193 inhibitory vestibular neurons, EVN: excitatory vestibular neurons, VIII: eight cranial nerve.

1194

1195 **Figure 5:** Neuronal network involved in ending a leftward gaze shift while the head terminates  
1196 its rotation (stabilized gaze direction). Connecting lines ended by an arrow indicate excitatory  
1197 connections; those ended by a circle indicate inhibitory synaptic connections. Blue color  
1198 indicates the agonist neuronal oculomotor elements, red color the antagonist ones. Green  
1199 color indicates the neurons of the ascending tract of Deiters (ATDN). The thickness of  
1200 connecting lines schematizes the strength with which the neurons fire. LR: lateral rectus, MR:  
1201 medial rectus, VI, abducens nerve, MRMN: motor neurons innervating the medial rectus  
1202 muscle, LRMN: motor neurons innervating the lateral rectus muscle, AIN: abducens  
1203 internuclear neurons, NMN: neck motoneurons, PVN: primary vestibular neurons, IVN:  
1204 inhibitory vestibular neurons, EVN: excitatory vestibular neurons, VIII: eight cranial nerve.

1205

1206 **Figure 6:** Neuronal network involved in ending a downward (A) and upward (B) gaze shift while  
1207 the head terminates its movement (stabilized gaze direction). Connecting lines ended by an  
1208 arrow indicate excitatory connections; those ended by a circle indicate inhibitory synaptic  
1209 connections. Blue color indicates the agonist neuronal oculomotor elements, red color the  
1210 antagonist ones. IOMN: motor neurons innervating the inferior oblique muscle, IRMN: motor  
1211 neurons innervating the inferior rectus muscle, SRMN: motor neurons innervating the  
1212 superior rectus muscle, SOMN: motor neurons innervating the superior oblique muscle, PVN:  
1213 primary vestibular neurons, IVN: inhibitory vestibular neurons, EVN: excitatory vestibular  
1214 neurons, VIII: eight cranial nerve.

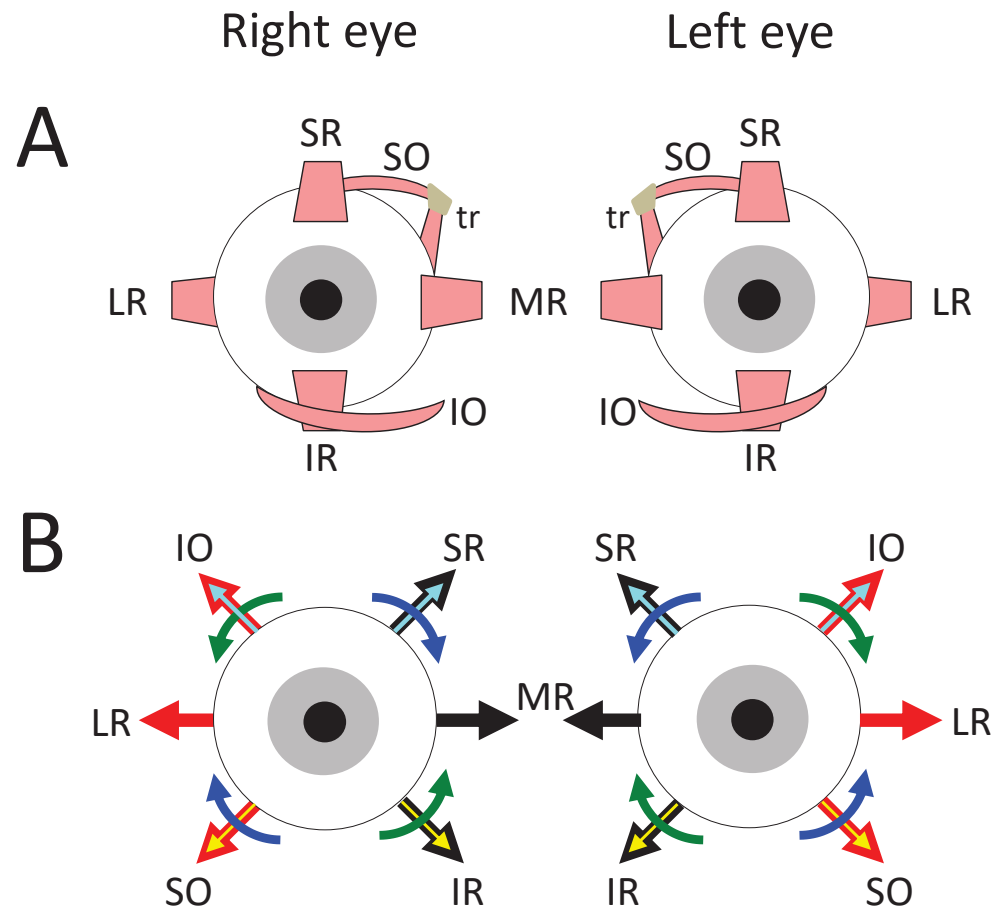
1215

1216 **Figure 7:** Neuronal network involved in the near response. LR: lateral rectus, MR: medial  
1217 rectus, SP: sphincter pupillae, DP: dilator pupillae, CM: ciliary muscle, CG: ciliary ganglion,  
1218 MRMN: motor neurons innervating the medial rectus muscle, EWpg: Edinger-Westphal  
1219 parasympathetic nucleus, cMRF: central mesencephalic reticular formation, SOA:  
1220 supraoculomotor area, cFN: caudal fastigial nucleus, SC: superior colliculus.

1221

1222 **Figure 8:** Neuronal network involved in the generation of horizontal slow pursuit eye  
1223 movements. LR: lateral rectus, MR: medial rectus, MN: motor neurons, AIN: abducens  
1224 internuclear neurons, NHP/MV: complex nucleus prepositus hypoglossi-medial vestibular  
1225 nucleus, ETN: excitatory tonic neurons, ITN: inhibitory tonic neurons, cFN: caudal fastigial  
1226 nucleus, NOT: nucleus of the optic tract, rSC: rostral superior colliculus, rNRTP: rostral part of  
1227 nucleus reticularis tegmenti pontis, DMPN: dorsomedian pontine nucleus, DLPN: dorsolateral  
1228 pontine nucleus, VPL-Th: ventroposterolateral part of thalamus, FEF: frontal eye field, MST:  
1229 medial superior temporal area of cerebral cortex.

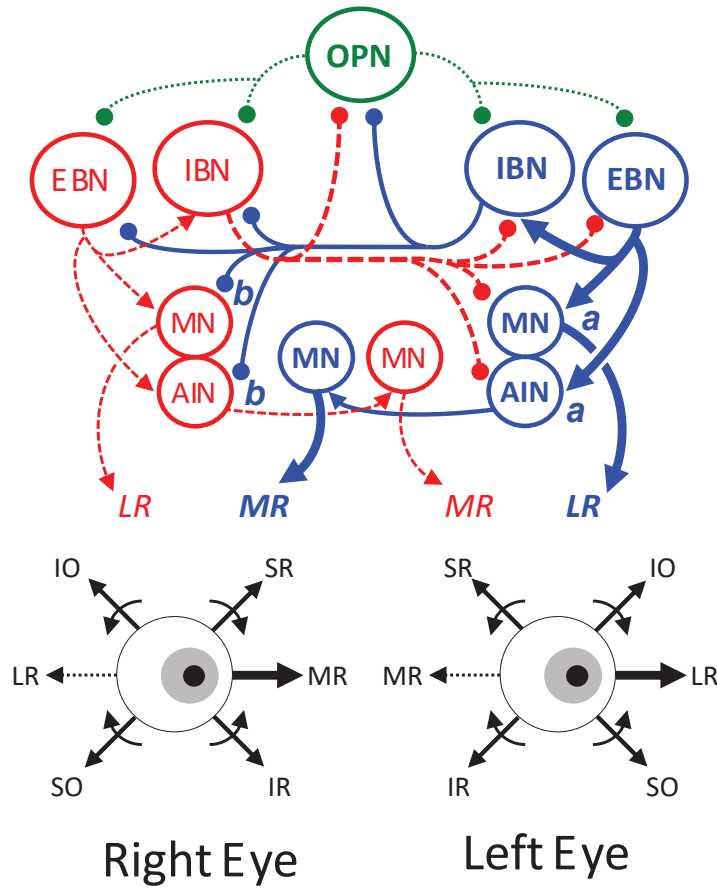
# Figure 1



# Figure 2

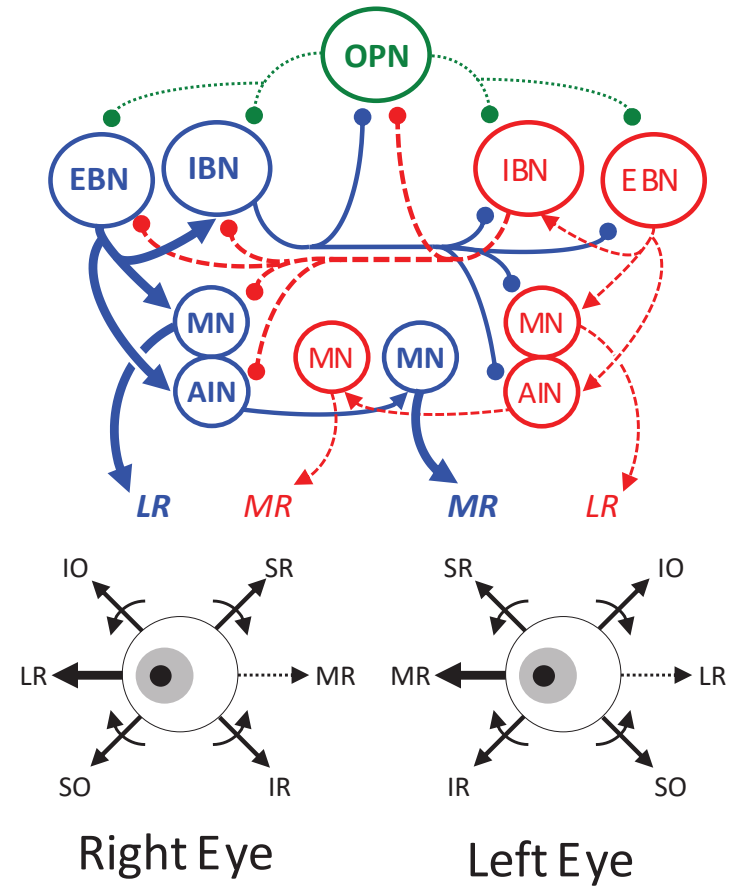
## A

### LEFTWARD

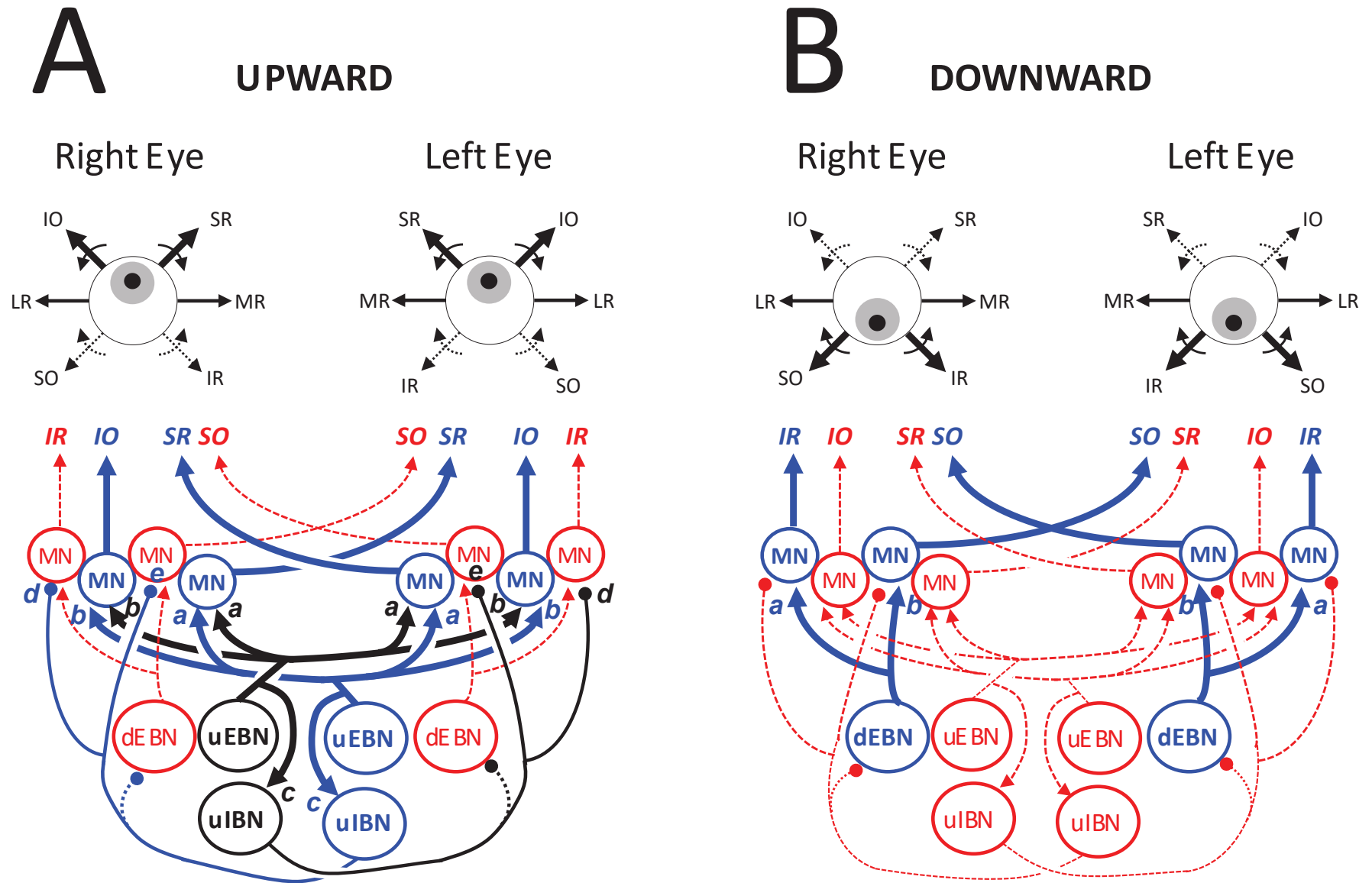


## B

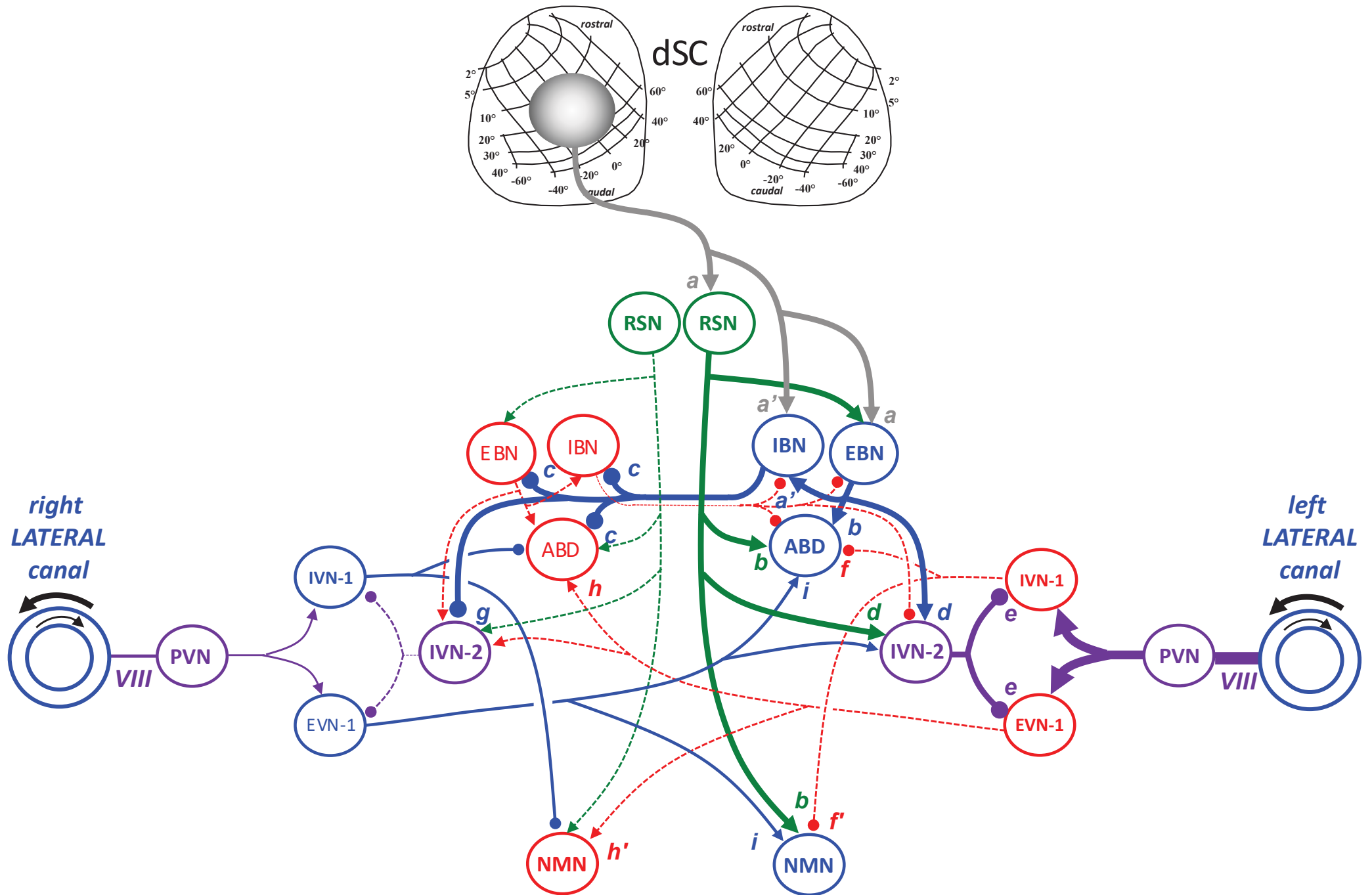
### RIGHTWARD



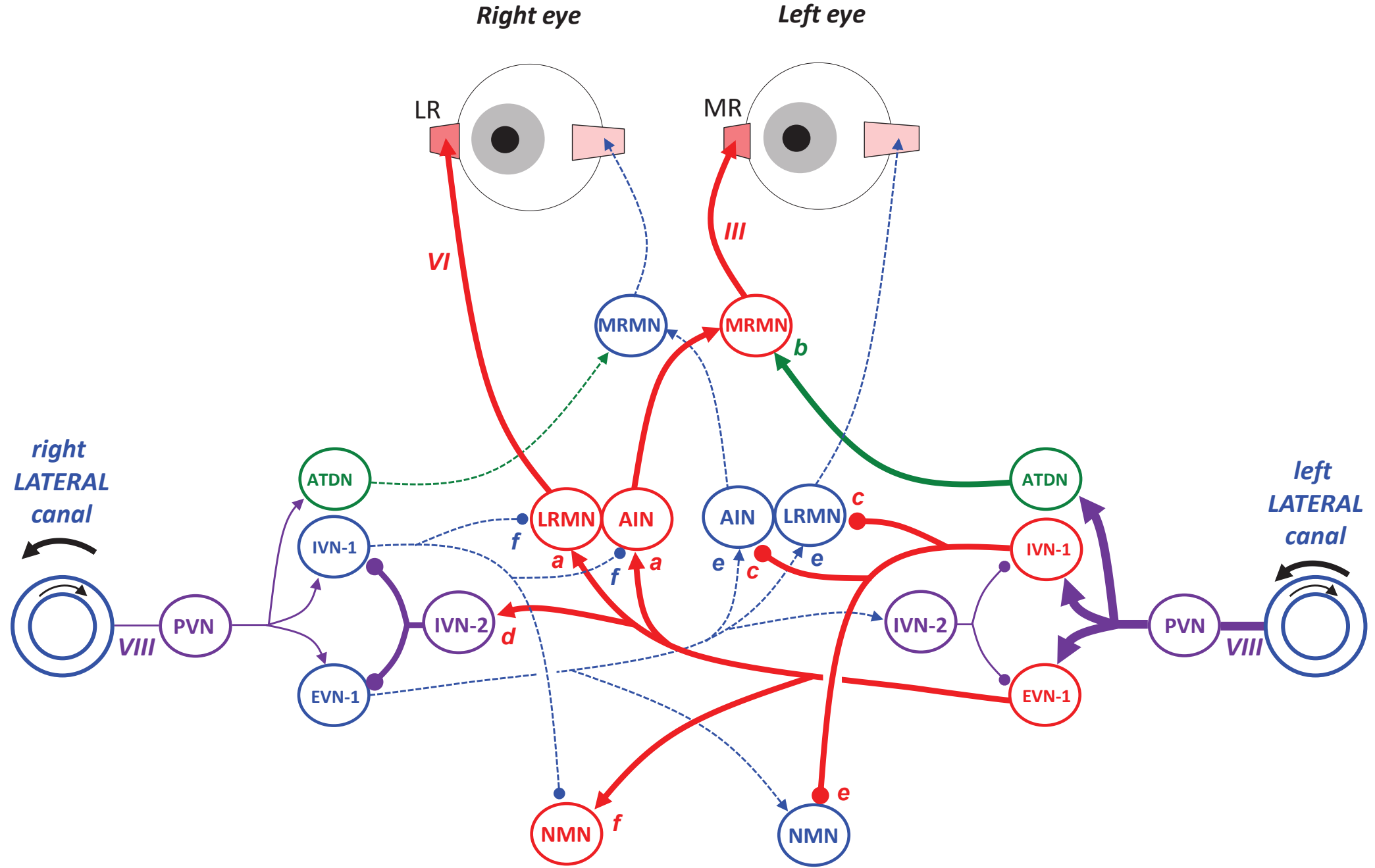
# Figure 3



# Figure 4

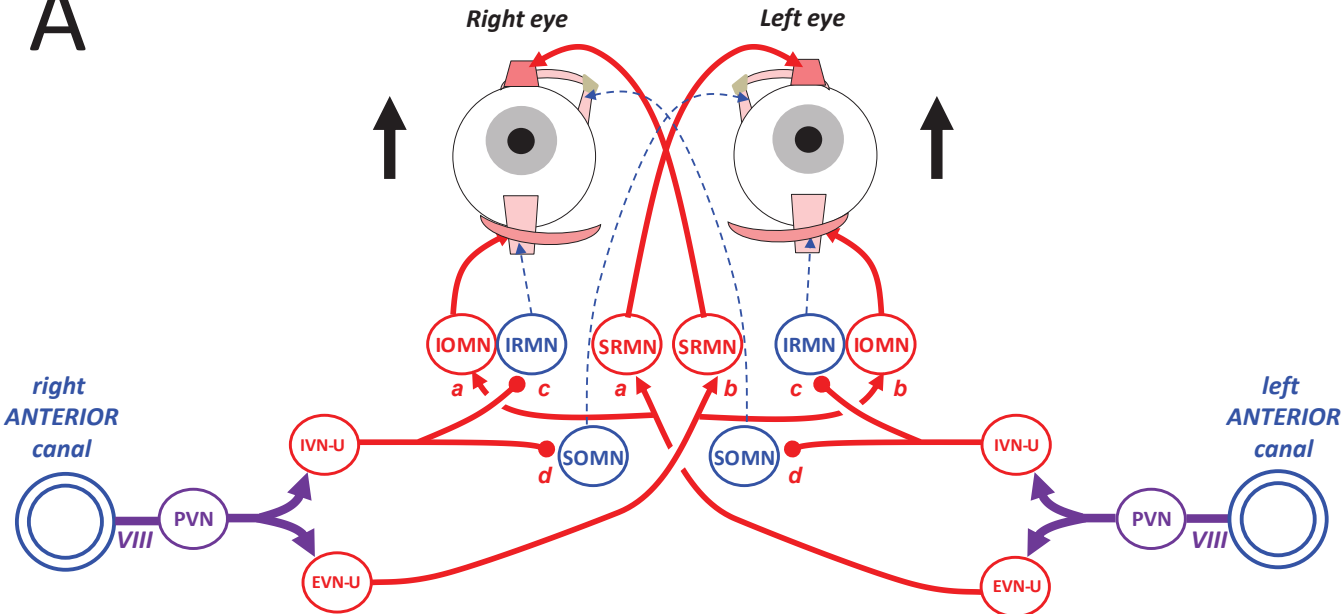


# Figure 5

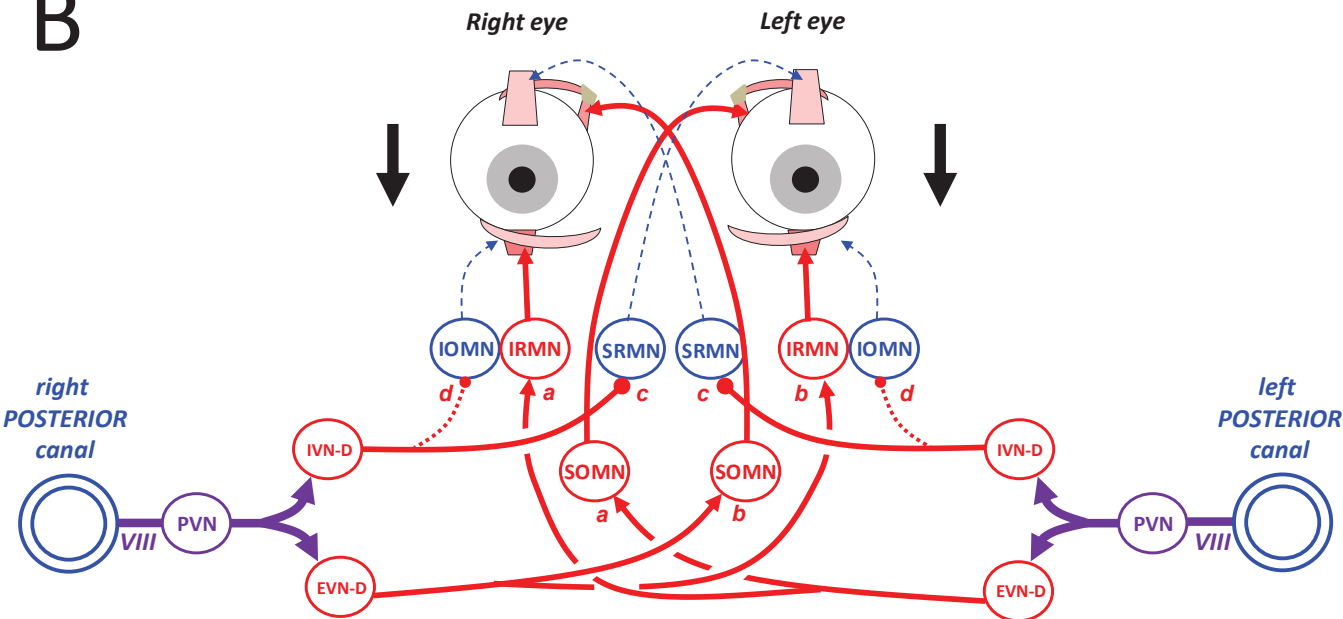


# Figure 6

## A

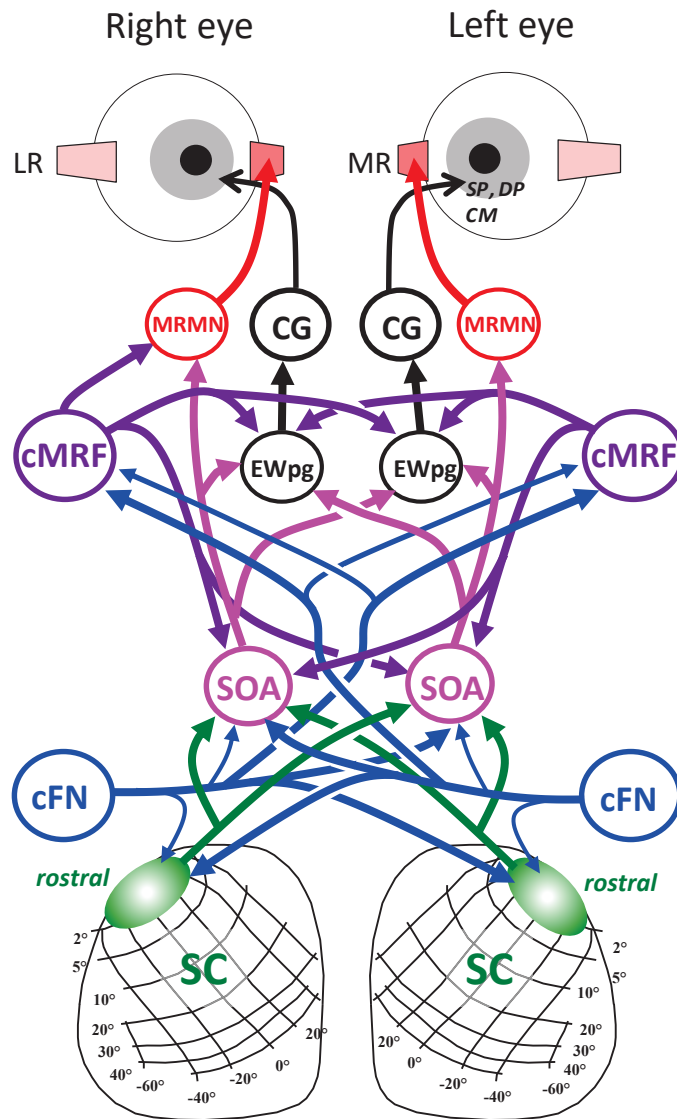


## B





# Figure 7



# Figure 8

