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# Bilateral fastigial control of interceptive saccades: evidence from the ipsipulsion of vertical saccades after caudal fastigial inactivation

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1           Bilateral fastigial control of interceptive saccades:  
2           evidence from the ipsipulsion of vertical saccades after  
3                           caudal fastigial inactivation

4  
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11           Title for running head: Neural control of interceptive saccades

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19

20

21 **Abstract (250 words <= 250 words)**

22 During the last decades, the concept was spread that saccades toward a visual target are the  
23 outcome of a process transforming the locus of retinal activity into a discharge whose duration  
24 determines saccade duration. A “gaze velocity” command would be extracted from target-  
25 related signals and sent to the motoneurons while a feedback loop would reduce the mismatch  
26 between neurally-encoded target and gaze directions. A different viewpoint has been proposed  
27 in which a saccade is the physical outcome of a process that, under cerebellar control, restores  
28 the equilibrium of bilateral activity in the brainstem. According to this hypothesis, saccade  
29 velocity is not directly encoded within the firing rate of neurons in the brainstem. We further  
30 developed this hypothesis by testing, in two head-restrained macaques, the effects of  
31 unilaterally inactivating the caudal fastigial nucleus on saccades toward a target moving  
32 vertically with a constant, increasing or decreasing speed. After local muscimol injection,  
33 vertical saccades were deviated horizontally toward the injected side. The magnitude of this  
34 ipsipulsion depended upon the tested target speed, but not its instantaneous value because it did  
35 not increase (decrease) when the target accelerated (decelerated). By subtracting the effect on  
36 contralesional horizontal saccades from the effect on ipsilesional ones, we found that the net  
37 bilateral effect on horizontal saccades was strongly correlated with the effect on vertical  
38 saccades. We explain how this correlation corroborates the bilateral hypothesis while raising  
39 numerous concerns about the putative encoding of saccade velocity within the discharge of  
40 neurons in the brainstem and oculomotor vermis.

41

42 **NEW & NOTEWORTHY (73 <= 75 words)**

43 Besides causing dysmetric horizontal saccades, unilateral inactivation of caudal fastigial  
44 nucleus causes an ipsipulsion of vertical saccades. This study is the first to quantitatively  
45 describe this ipsipulsion during saccades toward a moving target. By subtracting the effects on  
46 contralesional (hypometric) and ipsilesional (hypermetric) horizontal saccades, we find that this  
47 net bilateral effect is strongly correlated with the ipsipulsion of vertical saccades, corroborating  
48 the suggestion that a common disorder affects all saccades.

49

## 50 **Introduction**

51           Saccades are rapid changes in eye orientation whose time course is characterized by an  
52 interval during which the rotation speed increases to a maximum (acceleration) followed by an  
53 interval during which it returns to zero (deceleration). Starting with the eyes centered in the  
54 orbits, the changes in the contraction of lateral and medial recti muscles rotate the eyes  
55 horizontally whereas combined changes in the contraction of superior and inferior recti  
56 muscles, and the superior and inferior oblique muscles rotate them vertically (Robinson 1975).  
57 During vertical saccades, the tension in muscles involved in horizontal rotations exhibit a  
58 transient small reduction at the level of medial recti (Miller and Robins 1992). A burst of spikes  
59 from motoneurons causes the phasic contraction of agonist muscles while the relaxation of  
60 antagonist muscles is enabled by a pause of motoneurons which innervate them (Fuchs and  
61 Luschei 1970; Robinson 1970; Schiller 1970). Premotor commands for horizontal and vertical  
62 eye rotations originate in distinct regions of the reticular formation: burst neurons in the  
63 pontomedullary reticular formation drive horizontal saccades whereas those controlling vertical  
64 saccades are located in the rostral midbrain tegmentum (Fuchs et al. 1985; Hepp et al., 1989;  
65 Horn 2006; Moschovakis et al. 1996).

66           Robinson and Fuchs (2001) proposed that these populations of premotor neurons and  
67 the time course of saccades are under the control of neurons in the medio-posterior cerebellum:  
68 burst neurons in the contralateral caudal fastigial nucleus (cFN) would support the acceleration  
69 of saccades while those in the ipsilateral cFN would help their deceleration. This biphasic  
70 pattern was suggested by the delay between the peaks of cFN discharge during contralateral  
71 and ipsilateral saccades (Fuchs et al. 1993; Ohtsuka and Noda 1991; Kleine et al. 2003).  
72 Moreover, after unilateral cFN inactivation, contralesional saccades are hypometric and exhibit  
73 lower peak velocity whereas ipsilesional saccades are hypermetric with a longer deceleration

74 (Buzunov et al. 2013; Goffart et al. 2004). Thus, it was suggested that a shift of activity from  
75 the contralateral to the ipsilateral cFN would guide the trajectory of saccades (Optican 2005).

76 Numerous observations lead to questioning this isomorphism which was assumed  
77 between the brainstem activity and the kinematics of saccades. Firstly, Davis-Lopez de  
78 Carrizosa et al. (2011) showed that a model factoring muscle tension and its first derivative  
79 accounted for the firing rate of motoneurons better than a model factoring eye position and its  
80 first and second derivatives (velocity and acceleration). Secondly, the resemblance between the  
81 firing rate of premotor burst neurons and saccade instantaneous velocity (see for example Fig.  
82 5B of Cromer and Waitzman (2007)) disappears when the spikes are not convolved with a  
83 Gaussian kernel (see Figs. 2 and 3 in Hu et al. (2007); see also Fig. 4 in van Gisbergen et al.  
84 (1981)). Thirdly, the inspection of cFN bursts reveals that the transition between the activity of  
85 the left and right cFN is not as sharp as the separation between the acceleration and deceleration  
86 phases. In fact, the bursts in the two nuclei largely overlap around the time of saccade peak  
87 velocity (Kleine et al. 2003). Moreover, some neurons burst after saccade onset during large  
88 contralateral head unrestrained gaze shifts, casting doubt on the cFN's role in accelerating  
89 saccades (Fuchs et al. 2010). Involvement in only decelerating ipsilateral saccades is also called  
90 into question by the changes in the acceleration of saccades after cFN inactivation (Buzunov et  
91 al. 2013; Quinet and Goffart 2007). Finally, a horizontal deviation (ipsipulsion) affects the full  
92 time course of vertical saccades, including both acceleration and deceleration, following  
93 unilateral cFN inactivation (Goffart et al. 2004; Iwamoto and Yoshida 2002; Quinet and Goffart  
94 2007).

95 The hypothesis that cFN activity helps to accelerate contralateral horizontal saccades  
96 and to decelerate ipsilateral ones does not explain why vertical saccades exhibit this ipsipulsion.  
97 Robinson et al. (1993) proposed a different explanation: “during saccades to vertical targets,  
98 there is activity in the horizontal burst generator on one side that is not balanced by activity on

99 the other. Such unbalanced activity might arise because in the normal animal, caudal fastigial  
100 neurons on each side burst at about the same time during vertical saccades”. Emphasizing the  
101 bilateral organization of cFN efferences to premotor burst neurons (Sparks and Barton 1993)  
102 and the bilateral control of saccades (van Gisbergen et al. 1981), Goffart et al. (2004) went  
103 further by proposing that the unbalanced activity accounts for the dysmetria of all saccades  
104 during cFN unilateral inactivation, regardless of whether the saccade is horizontal, oblique, or  
105 vertical. According to this bilateral hypothesis, both cFN influence the premotor process, from  
106 saccade onset to saccade end. Regardless of its direction, the saccade is influenced by the  
107 discharge from both cFN. If the causes are the same, the ipsipulsion of vertical saccades should  
108 be correlated with the dysmetria of horizontal (ipsilesional and contralesional) saccades; this  
109 inference is not deducible from the scheme proposed by Robinson and Fuchs (2001). In the  
110 present study, we characterize the ipsipulsion of vertical saccades, and confirm this prediction  
111 using saccades toward a moving target as a probe. We investigated such saccades because they  
112 offer the methodological advantage of enabling to vary both target eccentricity and the saccade  
113 amplitude more easily than saccades toward static targets. Goffart et al. (2004) indeed found  
114 that the magnitude of the ipsipulsion increased when target eccentricity (see also Iwamoto and  
115 Yoshida 2002) or saccade duration increased. Which of these features (target eccentricity or  
116 saccade duration) determines the size of the horizontal error could not be determined from their  
117 data. Our results do not support a link between the ipsipulsion and saccade duration because  
118 across all our testing conditions, its magnitude was less frequently dependent upon the duration  
119 than upon the amplitude of vertical saccades.

## 120 **Materials and Methods**

121           The materials and methods used in this work are identical to those described in Burrelly  
122 et al. (2018a, b) and comply with the ARRIVE (Animal Research: Reporting of In Vivo  
123 Experiments) guidelines. We will remind them only briefly.

### 124 *Subjects and surgical procedures*

125           Two adult male rhesus monkeys (*Macaca mulatta*, 11-12 kg) participated in this study.  
126 Their eye movements were recorded with the electromagnetic induction technique. Training to  
127 the eye movement tasks started after full recovery (> 1 month after surgery). A craniotomy was  
128 made to permit the electrophysiological localization of saccade-related neurons in both fastigial  
129 nuclei. The surgical procedures and experiments were performed in accordance with the  
130 guidelines from the French Ministry of Agriculture and the European Community, after  
131 approval from the Regional Ethics Committee (authorization # A13/01/13). Care and  
132 maintenance of animals were made under the auspices of a veterinarian and the assistance of  
133 animal facilities staff.

### 134 *Eye movement recording and visual stimulation*

135           During the experimental sessions, the monkeys were seated in a chair with their head  
136 restrained, facing a LCD video monitor (Samsung SyncMaster, P227f; 1,280 × 1,024 pixels,  
137 100-Hz refresh rate, 39 × 29 cm) located at a viewing distance of 38 cm. The visual target was  
138 a Gaussian blurred white disk of 0.4° diameter displayed over a gray background. Eye  
139 movements were measured with a phase-angle detection system (CNC Engineering, 3-ft. coil  
140 frame) and voltage signals encoding the horizontal and vertical positions of one eye were  
141 sampled at 500 Hz. The triggering of stimuli, the on-line recording of the oculomotor  
142 performance and the data acquisition were controlled by a PC using the Beethoven software



143 package (Ryklin Software). Eye position signals were calibrated by having the animal fixate  
144 stationary targets presented at  $\pm 16^\circ$  along the horizontal or vertical meridians.

#### 145 *Oculomotor tests*

146 The experiments were performed more than one year after the monkeys were tested and  
147 trained to make saccades toward moving targets (Quinet and Goffart 2015; Burreilly et al.  
148 2014, 2016). Each experiment consisted of several pre-injection (control) sessions and one post-  
149 injection session. During the control sessions, the eye movements were recorded with a series  
150 of trials performed over 3-4 successive days before the injection whereas the post-injection  
151 session consisted of recordings made during trials collected approximately 30-50 minutes after  
152 the muscimol was injected in the cFN (after removing the cannula from the brain and recording  
153 saccades toward static targets). Each trial started with a brief tone followed by the appearance  
154 of a target at the center of the visual display (straight ahead). After the monkey directed its gaze  
155 toward its location within a surrounding invisible window ( $12^\circ$  centered on the target) and for  
156 a variable interval (ranging from 750 to 1500 ms by increments of 250 ms), the central target  
157 moved centrifugally along a cardinal (horizontal and vertical meridians) or oblique axis with a  
158 constant speed ( $10^\circ/\text{s}$  during 1,200 ms,  $20^\circ/\text{s}$  during 600 ms or  $40^\circ/\text{s}$  during 300 ms), or with an  
159 increasing (from 0 to  $40^\circ/\text{s}$  during 600 ms) or decreasing speed (from 40 to  $0^\circ/\text{s}$  during 600 ms).  
160 The different types of target speed were tested in separate blocks of trials. Within each block,  
161 the direction of target motion (cardinal or oblique) was pseudo-randomly selected (one out of  
162 eight possible directions) in order to prevent the generation of anticipatory eye movements. The  
163 monkeys' task was to track the target until the location where it disappeared at the end of the  
164 trial. The fixation constraints for controlling the accuracy of eye movements were relaxed with  
165 respect to requirements for obtaining their reward. Indeed, the monkeys had to direct their gaze  
166 within a large invisible window around the moving target ( $12^\circ$  centered on the moving target).  
167 Otherwise, the trial was aborted and a new trial started. Our recordings show that these relaxed

168 constraints do not incite monkeys to perform inaccurate saccades (see Figs. 3, 5, 7 and 9 in  
169 Bourrelly et al. 2018; see also Fleuriet and Goffart 2012; Quinet and Goffart 2015). Each  
170 session (lasting 1 to 2 hours) was composed of different blocks of trials whose number  
171 depended upon the monkey's motivation. Water-deprived in their home cage, the monkeys  
172 obtained the water they need during daily sessions. A session ended when they stopped fixating  
173 the central target for more than ten successive trials.

#### 174 *Muscimol injection*

175 A thin cannula (beveled tip) was connected to a Hamilton syringe with polyethylene  
176 tubing. We filled the inner volume with a saline solution of muscimol (2  $\mu\text{g}/\mu\text{l}$ ). The cannula  
177 was lowered through the same guide tube used during the electrophysiological sessions and  
178 aimed at the fastigial region where neurons emitted bursts during saccades. Small volumes (0.2–  
179 1.1  $\mu\text{l}$ ) of muscimol were injected by small pulses over a time interval of approximately 15  
180 minutes. The injected volume was checked by the displacement of a meniscus of air in the  
181 tubing (1 mm corresponding to 0.1  $\mu\text{l}$ ). Before starting the recording of eye movements toward  
182 a moving target, saccades toward static targets were recorded for approximately 15-30 minutes  
183 in order to complete a companion study (Goffart et al. 2005, 2017; Quinet and Goffart 2016).  
184 During the muscimol sessions, the blocks that tested the tracking of accelerating or decelerating  
185 targets were always the last ones.

#### 186 *Data analysis*

187 The results presented in this paper concern the data obtained before and after ten  
188 unilateral muscimol injections performed in the cFN of two monkeys (6 injections in monkey  
189 A, 4 in monkey Bi). For each experiment, the performance after muscimol injection was  
190 compared with that recorded during the 3-4 preceding control daily sessions. No noticeable  
191 difference was observed between the responses collected during the pre-injection sessions, so

192 movements were pooled together to include some day-to-day variability in our control dataset.  
193 For each monkey, we injected muscimol into the left cFN in half of the experiments and in the  
194 right cFN in the others. All data were digitized on-line and analyzed off-line using a custom-  
195 made software program that detected the onset and offset of the horizontal and vertical  
196 components of saccades on the basis of a velocity threshold ( $30^\circ/\text{s}$ ). The results of this automatic  
197 detection were checked by inspecting each trial individually, and were adjusted manually when  
198 necessary. The present study describes the effect of unilateral cFN inactivation on the  
199 interceptive saccades made in response to the target when it moved along the vertical meridian.  
200 The effects of fastigial inactivation on movements toward the horizontally moving target were  
201 thoroughly described elsewhere (Bourrelly et al. 2018a, b). The interceptive saccade  
202 corresponds to the first saccade made from a static target toward the target after the onset of its  
203 motion. To make sure that the interceptive saccade was not triggered prematurely, those with  
204 latency  $< 80$  ms were excluded from analysis (0.3% of the total number of trials). The Statistica  
205 software (Statsoft) was used for statistical analyses and figure illustrations. Statistical  
206 significance threshold was set to P-value  $< 0.05$ . Because the size of deficits could differ  
207 between different injections, the mean values of the pre- and post-injection movements were  
208 compared with the non-parametric Wilcoxon test (for paired comparison). Thus, our main  
209 conclusions are based on the systematic effects that were revealed by this overall comparison  
210 across different experiments. The correlations between different behavioral measurements were  
211 evaluated with the (parametric) Bravais-Pearson test whereas the correlation between a  
212 behavioral parameters and the target speed was evaluated with the non-parametric Spearman  
213 test.

## 214 **Results**

### 215 **Figure 1 approximately here**

216 Figure 1 illustrates with a few selected trials how a unilateral injection of muscimol in the cFN  
217 affects the eye movements made in response to a centrifugal target moving at a constant speed  
218 ( $20^\circ/\text{s}$ ) along the vertical meridian. The time course of the horizontal (top row) and vertical  
219 (bottom row) components is shown for movements produced before (gray) and after muscimol  
220 injection (black) in the left (A and B: experiments A2 and A3 in monkey A) or right cFN (C:  
221 experiment Bi9 in monkey Bi). As described elsewhere (Guerrasio et al. 2010), inactivation of  
222 cFN caused a fixation offset toward the injected side. Most starting eye positions were shifted  
223 to the right after muscimol injection in the right cFN (see black arrow in C) and to the left after  
224 muscimol injection in the left cFN (black arrow in A). The ipsilesional offset was not observed  
225 on every trial. We show examples (recorded during the experiments A2 and A3) in which the  
226 saccades were initiated from positions near the vertical meridian (horizontal position values  
227 close to zero in the upper graphs) but below the horizontal meridian (negative values of vertical  
228 position in the lower graphs). In addition to altering gaze direction during fixation, unilateral  
229 cFN inactivation also perturbed vertical saccades. Their trajectory was deviated horizontally  
230 toward the injected side, regardless of whether the target moved upward or downward. In the  
231 following paragraphs, after describing the velocity of their vertical component, we describe the  
232 ipsipulsion that alters the trajectory of vertical saccades.

### 233 **Figure 2 approximately here**

234 As for horizontal saccades (see Fig. 2 in Bourrelly et al. 2018a), muscimol injection in  
235 the cFN barely affected the vertical velocity of saccades. Figure 2 illustrates the vertical  
236 amplitude-peak velocity relationship for four different experiments (two per monkey; A and B:  
237 experiments A2 and A3 in monkey A; C and D: Bi7 and Bi8 in monkey Bi). The peak velocity

238 values are plotted for all upward and downward saccades (positive and negative amplitude  
239 values, respectively) made in response to the different target speeds. When we consider  
240 saccades of comparable vertical amplitude, we can see that the peak velocity is similar between  
241 the pre and post-injection movements.

242 **Figure 3 approximately here**

243 Figure 3 describes the landing position and time of interceptive saccades made toward  
244 a target moving with a constant speed ( $20^\circ/\text{s}$ ) along the vertical meridian (black: upward  
245 motion, gray: downward). For three different experiments (A3 and Bi7: left cFN inactivation;  
246 Bi9: right cFN inactivation), the vertical (top row) and horizontal (bottom row) landing  
247 positions are plotted as a function of their times relative to target motion onset. During the  
248 control sessions (open squares), the vertical landing position increased as the landing time  
249 increased, and the saccades were directed toward locations close to the physical target  
250 (represented by the dashed lines). After muscimol injection (filled squares), the vertical landing  
251 positions still increased as the landing time increased, regardless of the motion direction. The  
252 overlap between pre- and post-injection data points indicates that unilateral cFN inactivation  
253 did not noticeably affect the vertical component of interceptive saccades. Similar findings were  
254 found with respect to saccades toward a static target (Goffart et al. 2004). By contrast, the  
255 horizontal landing positions changed after muscimol injection. While they were scattered along  
256 the vertical meridian (position values close to zero) during the control sessions, their  
257 distribution was shifted toward the injected side after muscimol injection (to the left in  
258 experiments A3 and Bi7, to the right in experiment Bi9). This effect is rather small in  
259 experiment A3 (B: mean  $\pm$  standard deviation values changing from  $-0.1 \pm 0.3^\circ$  to  $-0.5 \pm 0.4^\circ$   
260 after muscimol injection), but the change of horizontal position was much larger in experiments  
261 Bi7 (D: from  $0.0 \pm 0.3^\circ$  to  $-3.5 \pm 1.6^\circ$ ), with Bi9 displaying intermediate values (F: from  $0.3 \pm$   
262  $0.4^\circ$  to  $2.0 \pm 0.7^\circ$ ). Regardless of whether the target moved upward (black symbols) or

263 downward (gray symbols), the horizontal landing position was always shifted toward the  
264 injected side. The size of the ipsipulsion was, in some cases, relatively constant (as in B) or  
265 increased with the landing time (as in D). It is worth noting that the hypermetria of ipsilesional  
266 horizontal saccades was relatively small during experiment A3 whereas it was larger during  
267 experiments Bi7 and Bi9 (see Figures 7 and 10 in Bourrelly et al. 2018a). In summary, an  
268 ipsilesional deviation was observed in the trajectory of vertical saccades during cFN  
269 inactivation. The magnitude of the ipsipulsion varied between experiments, but as we will show,  
270 it is correlated to the magnitude of the dysmetria that impairs the horizontal saccades.

271 To quantify the accuracy of vertical saccades, we calculated for each component the  
272 ratio of landing position to landing time. This parameter (called position/time landing)  
273 characterizes both spatial *and* temporal aspects of saccades made toward a moving target  
274 (Bourrelly et al. 2018a). When we consider saccades toward a target moving along the vertical  
275 meridian, the values of vertical position/time landing are expected to be close to the target speed  
276 if gaze lands next to the target location. A ratio larger than the target speed indicates an  
277 overshoot (too large amplitude) whereas a smaller value means an undershoot (too small  
278 amplitude). Concerning the horizontal component, if gaze lands close to the target, its value is  
279 expected to be close to zero because the target does not move horizontally. We will use the  
280 convention that a positive horizontal ratio indicates an ipsilesional deviation whereas a negative  
281 value is the signature of a contralesional deviation.

282 **Figure 4 approximately here**

283 Figure 4 shows the average vertical position/time landing relationships for each monkey  
284 and each experiment in which the target moved at constant speed. During the control sessions,  
285 the values were close to the target speed ( $11.2 \pm 1.3$ ,  $21.9 \pm 2.0$  and  $38.9 \pm 4.6$  °/s for the 10, 20  
286 and 40 °/s targets, respectively). After muscimol injection, these ratios were larger ( $12.3 \pm$

287 3.8°/s,  $24.3 \pm 4.0^\circ/\text{s}$  and  $44.2 \pm 6.3^\circ/\text{s}$  for the 10, 20 and 40 °/s targets, respectively) (Fig. 4A).  
288 This increase was small but statistically significant (Wilcoxon test, all P values < 0.05). A  
289 stronger affect was observed in the horizontal component of vertical saccades. Figure 4B shows  
290 the average horizontal position/time landings for each tested constant speed, in each experiment  
291 and both monkeys. After muscimol injection, the horizontal position/time landings increased  
292 from  $0.0 \pm 0.7^\circ/\text{s}$  (range:  $-1.1 - 1.6^\circ/\text{s}$ ) to  $5.4 \pm 3.6^\circ/\text{s}$  (range:  $0.8 - 12.1^\circ/\text{s}$ ) when the target  
293 speed was 10°/s, from  $0.0 \pm 1.1^\circ/\text{s}$  (range:  $-2.6 - 2.9^\circ/\text{s}$ ) to  $8.0 \pm 4.9^\circ/\text{s}$  (range:  $1.8 - 18.6^\circ/\text{s}$ )  
294 with the 20°/s target and from  $-0.2 \pm 1.6^\circ/\text{s}$  (range:  $-2.5 - 2.9^\circ/\text{s}$ ) to  $12.0 \pm 7.6^\circ/\text{s}$  (range:  $3.1 -$   
295  $24.2^\circ/\text{s}$ ) with the 40°/s target. The ranges of mean values and the examination of data points in  
296 Fig 4B indicate more variability after muscimol injection than before (see the scattering toward  
297 more positive values; note also the different scales for the x and y axes). During the control  
298 sessions, the average horizontal position/time landings were close to zero (grand averages =  
299 0.0, 0.0 and  $-0.2^\circ/\text{s}$  for the 10, 20 and 40°/s target, respectively; all monkeys considered). After  
300 muscimol injection, the values were larger and also increased with target speed (5.4, 8.0 and  
301  $12.0^\circ/\text{s}$  for the 10, 20 and 40°/s target, respectively). Figure 4C compares the average horizontal  
302 position/time landing between saccades toward the 20°/s target and saccades to the 10°/s (gray  
303 symbols) and 40°/s (black symbols) targets. The values with the 10°/s target were smaller than  
304 the values with the 20°/s target (gray symbols are situated below the diagonal line of equality)  
305 whereas the values with the 40°/s target were larger than those obtained with the 20°/s target  
306 (almost all black symbols above the diagonal line). Thus, within the same experiment, the size  
307 of the ipsipulsion was larger during saccades to the fastest target than during saccades to the  
308 slowest ones. Moreover, the injections which led to the larger horizontal errors with the 20°/s  
309 target were those caused the bigger changes with the other speeds. Statistically significant  
310 correlations were indeed found between the average horizontal position/time landing values  
311 calculated with the 20°/s and 10°/s targets (Bravais-Pearson correlation coefficient  $R = 0.94$ , P

312 < 0.05) as well as between the mean values obtained with the 20°/s and 40°/s targets ( $R(x,y) =$   
313 0.93,  $P < 0.05$ ).

314 **Figure 5 approximately here**

315 In our previous report, we documented the dysmetria of horizontal interceptive saccades  
316 after cFN inactivation: ipsilesional saccades are hypermetric whereas contralesional saccades  
317 are hypometric (Bourrelly et al. 2018a). Like the dysmetria that affects horizontal saccades  
318 toward a static target (Goffart et al. 2004, in preparation), the sizes of the ipsilesional and  
319 contralesional dysmetria are unrelated. However, it is known that the cFN projects to the region  
320 in the contralateral medullary reticular formation (medRF) where premotor inhibitory burst  
321 neurons (IBNs) are located (Noda et al. 1990) and that these neurons, in addition to firing a  
322 burst during horizontal saccades, also fire during vertical saccades (Scudder et al. 1988; van  
323 Gisbergen et al. 1981). Because of this involvement of IBNs in horizontal and vertical saccades,  
324 it is quite reasonable to consider that a common dysfunction causes the ipsipulsion of vertical  
325 saccades and the dysmetria of horizontal saccades (Goffart et al. 2004). Therefore, we tested  
326 the relation between these two disorders and found a significant correlation between the average  
327 horizontal position/time landings of ipsilesional horizontal saccades and vertical saccades  
328 toward the 10°/s ( $R = 0.77$ ,  $P < 0.05$ ), 20°/s ( $R = 0.62$ ,  $P < 0.05$ ) and 40°/s ( $R = 0.81$ ,  $P < 0.05$ )  
329 targets (Fig. 5A). When the correlation was instead tested between the horizontal position/time  
330 landings of contralesional horizontal saccades and vertical saccades, the coefficients were  
331 smaller and negative. Furthermore, the correlation did not reach statistical significance when  
332 the target moved at 10°/s ( $R = -0.41$ ,  $P > 0.05$ ) and 40°/s ( $R = -0.13$ ,  $P > 0.05$ ). A significant  
333 correlation was found only with the 20°/s target ( $R = -0.47$ ,  $P < 0.05$ ) (Fig. 5B). Then, for each  
334 experiment, we subtracted the average contralesional position/time landing from the  
335 ipsilesional position/time landing, the resulting difference (hereafter called net bilateral effect  
336 on horizontal saccades) characterizing the dysmetria of saccades made toward a target moving



337 horizontally (leftward or rightward). In this case, we found significant correlations between the  
338 horizontal position/time landings of vertical saccades and the net bilateral effect on horizontal  
339 saccades (Fig. 5C) that were stronger than those obtained with ipsilesional horizontal saccades  
340 ( $10^\circ/s$  target:  $R = 0.91$  versus  $0.77$ ;  $20^\circ/s$   $R = 0.81$  versus  $0.62$ ;  $40^\circ/s$ :  $R = 0.90$  versus  $0.81$ ).

341 In summary, after muscimol injection in the cFN, all vertical saccades made toward a  
342 target moving at a constant speed along the vertical meridian were deviated horizontally toward  
343 the injected side. Their vertical components were slightly affected but not as dramatically as  
344 the horizontal component. The size of the ipsipulsion differed between experiments and the  
345 average horizontal position/time landing increased with the target speed. Moreover, the  
346 ipsipulsion is correlated with the dysmetria that impaired the horizontal (ipsilesional and  
347 contralesional) saccades.

348 **Figure 6 approximately here**

349 In the figure 4C, we showed that the ipsipulsion of vertical saccades depends upon the  
350 target speed. To further explore this dependence, we tested saccades toward a target that moved  
351 with continuous acceleration or deceleration. If the ipsipulsion depends on target speed, the  
352 horizontal landing position should increase with later landing times when the target accelerates  
353 but decrease or stagnate when it decelerates. Figure 6 describes the horizontal landing position  
354 and time of saccades to a target moving with an increasing (top row) and decreasing speed  
355 (bottom row) for three experiments (A3: left column; Bi8: middle and Bi9: right). During the  
356 control sessions (open squares), the saccades landed on locations situated along the vertical  
357 meridian (open symbols are close to the line of zero horizontal position) whereas after muscimol  
358 injection (filled squares), they landed on locations which were shifted toward the injected side  
359 (see negative position values in experiments A3 and Bi8 and positive values in experiment Bi9).  
360 For these three experiments, the ipsipulsion of vertical saccades did not depend on the

361 instantaneous speed of the target. Statistically significant correlations were found in only two  
362 experiments: A6 (positive correlation  $R = 0.54$ , injection in the right cFN) and A2 (negative  
363 correlation  $R = -0.35$ , left cFN). For the other experiments, no correlation was found between  
364 the horizontal landing position and the landing time when the target accelerated ( $R$  values  
365 ranged from  $-0.25$  to  $0.19$ ,  $P$ -values  $> 0.05$ ). Concerning the saccades toward a decelerating  
366 target, no statistically significant correlation was found between the horizontal landing position  
367 and the landing time ( $R$  values ranged from  $-0.42$  to  $0.34$ ,  $P$ -values  $> 0.05$ ). In summary, we  
368 found no evidence suggesting that the ipsipulsion depends on the instantaneous target speed:  
369 the horizontal landing position neither increased with later landing times when the target  
370 accelerated nor decreased when it decelerated.

371 **Figure 7 approximately here**

372 Fig. 7 documents the mean values of vertical (A) and horizontal (B) position/time  
373 landing of saccades toward the accelerating (gray symbols) and decelerating (black symbols)  
374 targets, before and after muscimol injection, as a summary of our results. The vertical  
375 position/time landing of saccades was changed after muscimol injection, more with the  
376 decelerating target than with the accelerating one (Fig. 7A). With the accelerating target, the  
377 pre- and post-injection mean values of vertical position/time landing were not significantly  
378 different (Wilcoxon test,  $P = 0.47$ ) whereas with the decelerating target, the post-injection  
379 values were significantly different from pre-injection values (16% average increase,  $P < 0.05$ ).  
380 Regarding the horizontal position/time landing (Fig. 7B), it increased from  $0.1 \pm 0.7^\circ/s$  (range:  
381  $-0.8 - 1.9^\circ/s$ ) to  $5.0 \pm 2.9^\circ/s$  (range:  $0.8 - 9.5^\circ/s$ ) after muscimol injection with the accelerating  
382 target and from  $0.0 \pm 1.8^\circ/s$  (range:  $-3.6 - 3.4^\circ/s$ ) to  $11.6 \pm 5.9^\circ/s$  (range:  $2.6 - 20.1^\circ/s$ ) with the  
383 decelerating target. In both groups of saccades, the changes were statistically significant ( $P <$   
384  $0.05$ ). Like saccades toward a target moving with a constant speed, the mean values of  
385 horizontal landing position were also variable between the different muscimol injections (see

386 range values reported above and the scatter of post-lesion data points in Fig. 7B). Finally, the  
387 injections which led to the larger horizontal position/time landings with the 20°/s moving target  
388 were those which led to the bigger changes with the accelerating and decelerating targets (Fig.  
389 7C). Statistically significant correlations were indeed found between the horizontal  
390 position/time landings of saccades toward the 20°/s and those directed toward the accelerating  
391 (Bravais-Pearson correlation coefficient  $R(x,y) = 0.86$ ,  $P < 0.05$ ) or decelerating target ( $R(x,y)$   
392  $= 0.90$   $P < 0.05$ ). In summary, all vertical saccades toward a target moving with a changing  
393 speed were shifted horizontally after muscimol injection in the cFN. Like saccades toward a  
394 target moving at a constant speed, the amplitude of their vertical component was slightly  
395 increased after muscimol inactivation. Their horizontal component was biased toward the  
396 injected side with a magnitude which differed between experiments. The ipsipulsion was larger  
397 for saccades aimed toward a fast target than toward a slow target. It was also smaller when the  
398 target accelerated than when it decelerated.

399         As for saccades to a target moving horizontally, the larger deficit with fast targets can  
400 result from the fact that at identical landing times, a fast target is more eccentric than a slow  
401 one. The dependency of the ipsipulsion upon the target speed can result from the fact that a  
402 larger amplitude was required to intercept the target when it moves fast. Studies of vertical  
403 saccades toward a static target do indeed show that after cFN inactivation, the ipsipulsion  
404 increases with more eccentric targets (Goffart et al. 2004; Iwamoto and Yoshida 2002; Quinet  
405 and Goffart 2007). However, increasing target eccentricity enhances both the amplitude and  
406 duration of saccades for larger saccades that last longer. It is not known which of these  
407 parameters affect more the magnitude of ipsipulsion. Therefore, we tested the correlation  
408 between the horizontal landing position and saccade duration for each post-injection session.  
409 The parameters of the equations fitting the relation between the horizontal landing position and  
410 the saccade duration after muscimol injection are documented for all the experiments (upward

411 and downward movements pooled together) in table 1 (constant speeds) and table 2 (changing  
412 speeds). The correlation was statistically significant in 13 out of 44 test sessions (corresponding  
413 to 30% of cases) with coefficients of correlation ranging from 0.37 to 0.72. When we instead  
414 considered the relation between the horizontal landing position and vertical saccade amplitude,  
415 statistically significant correlations were found in 30 out of 44 experiments (corresponding to  
416 68% of the post-injection sessions), with coefficients of correlation ranging from 0.38 to 0.81.  
417 The parameters of the equations fitting the relation between the horizontal landing position and  
418 the vertical saccade amplitude after muscimol injection are documented for all the experiments  
419 (upward and downward movements pooled together) in table 1 (target moving at a constant  
420 speed) and table 2 (accelerating and decelerating targets). Altogether, these results suggest that  
421 it is more likely that the ipsipulsion increased because saccades had larger amplitudes than  
422 because they lasted longer.

423 **Figure 8 approximately here**

424 To illustrate this correlation between the vertical amplitude of saccades and the  
425 ipsipulsion, Fig. 8 plots the horizontal landing position as a function of vertical saccade  
426 amplitude before and after muscimol injection. Both upward and downward saccades were  
427 included (the amplitude of downward saccades was multiplied by -1). The relations are shown  
428 for four injections made in the left cFN of monkey A (experiments A2 and A3, top row) and Bi  
429 (experiments Bi7 and Bi8, bottom) for saccades to targets moving with a constant speed (light  
430 gray, dark gray and black symbols correspond to the 10, 20 and 40°/s target speeds,  
431 respectively). Negative values of horizontal eye position indicate that the saccades were  
432 deviated toward the left (inactivated side). Thus, we can see that while the target speed increases  
433 from 10 to 40°/s (symbols with different shades of grey), the horizontal landing position and  
434 the vertical saccade amplitude increased. During experiment A2 (Fig. 8A), as the target speed  
435 increased, the horizontal landing position changed from  $-0.3 \pm 0.3^\circ$  (10°/s) to  $-0.7 \pm 0.5^\circ$  (20°/s)

436 and  $-1.4 \pm 0.8^\circ$  ( $40^\circ/\text{s}$ ), while the vertical amplitude increased from  $2.8 \pm 0.6^\circ$  ( $10^\circ/\text{s}$ ) to  $5.1 \pm$   
437  $1.1^\circ$  ( $20^\circ/\text{s}$ ) and  $10.2 \pm 1.9^\circ$  ( $40^\circ/\text{s}$ ). Likewise, during experiment A3 (Fig. 8B), the horizontal  
438 landing position increased from  $-0.3 \pm 0.3^\circ$  to  $-0.5 \pm 0.4^\circ$  and  $-1.3 \pm 0.6^\circ$  while the vertical  
439 amplitude increased from  $2.7 \pm 0.6^\circ$  to  $5.1 \pm 1.1^\circ$  and  $10.5 \pm 1.1^\circ$  (values for the 10, 20 and  
440  $40^\circ/\text{s}$  target speed, respectively). The same relationship was found in monkey Bi. During  
441 experiment Bi7 (Fig. 8C), the horizontal landing position increased from  $-2.4 \pm 0.7^\circ$  to  $-3.4 \pm$   
442  $1.6^\circ$  and  $-4.3 \pm 1.1^\circ$  and the vertical amplitude from  $2.2 \pm 0.7^\circ$  to  $5.1 \pm 1.2^\circ$  and  $9.0 \pm 1.3^\circ$ .  
443 Finally, during experiment Bi8 (Fig. 8D), the horizontal landing position increased from  $-2.0 \pm$   
444  $0.7^\circ$  ( $10^\circ/\text{s}$ ) to  $-2.8 \pm 0.8^\circ$  ( $20^\circ/\text{s}$ ) to  $-3.7 \pm 1.0^\circ$  ( $40^\circ/\text{s}$ ), while the vertical amplitude increased  
445 from  $2.2 \pm 0.6^\circ$  to  $5.0 \pm 1.6^\circ$  and  $9.1 \pm 1.1^\circ$ . A relation was observed between the horizontal  
446 landing position and the vertical amplitude of saccades. Each inset graph plotted in the right  
447 part of the panels of Figure 8 shows an overlap of data points corresponding to saccades to a  
448 target moving at constant speed (gray symbols) and to an accelerating or decelerating target  
449 (black symbols). In summary, after cFN inactivation, the landing position of vertical saccades  
450 was deviated toward the injected side by an amount that varied between experiments and that  
451 was larger when the target moved quickly than when it moved slowly. The dependency of the  
452 ipsipulsion upon the target speed indicates that the saccade oculomotor system has access to  
453 different signals when the target moves at different speeds. However, the use of accelerating  
454 and decelerating target enabled us to exclude a dependency upon the instantaneous speed of the  
455 target. Further analyses revealed that the ipsipulsion was more frequently correlated with the  
456 vertical amplitude of saccades rather than with their duration.

## 457 **Discussion**

458           This study is the first to describe the consequences of unilateral pharmacological  
459 inactivation of cFN on the generation of vertical saccades toward a moving target. As for the  
460 saccades toward a static target, interceptive saccades exhibit a horizontal deviation of their  
461 trajectory toward the lesioned side (ipsipulsion; Figs. 3, 4B and 7B) whereas the vertical  
462 component is barely affected (Figs. 3, 4A and 7A). The magnitude of the ipsipulsion is larger  
463 for fast targets than for slowly moving targets (Fig. 4C) but the use of accelerating and  
464 decelerating targets indicates that this relation is due less to the instantaneous target speed (Fig.  
465 6) than to the saccade size. Indeed, like saccades toward a static target, the ipsipulsion increased  
466 with the vertical amplitude of saccades (Fig. 8). Statistical analyses made across all sessions  
467 indicate that the correlations between the ipsipulsion and the vertical amplitude were more  
468 frequent than the correlations between the ipsipulsion and the duration. In the following, we  
469 discuss the implications of our results after reminding the alternative viewpoint that we propose  
470 to investigate the neurophysiology of saccades.

471

### 472 *Recasting the neurophysiology of saccades*

473           Saccades are engendered by an abrupt increase in the firing rate of motor neurons which  
474 innervate the agonist muscles; a concomitant decrease happens in the neurons innervating the  
475 antagonist muscles. Due to the highly damped nature of the oculomotor plant (Robinson 1964),  
476 a braking action is not exerted upon the antagonist motor neurons to stop the saccade (Robinson  
477 1970; Schiller 1970). While the agonist burst duration increases with the duration of saccades  
478 and determines their size, a saturated firing rate leads to the firing frequency of the discharge  
479 being poorly related to saccade speed (Fuchs and Luschei 1970; Robinson 1970; Schiller 1970).  
480 For the generation of horizontal saccades, the burst causing the phasic contraction of the medial  
481 rectus (and the saccade of the contralateral eye) originates in burst-tonic (internuclear) neurons

482 in the abducens nucleus while the burst causing the phasic contraction of the lateral rectus  
483 (saccade of the ipsilateral eye) originates in abducens motoneurons. These bursts are caused by  
484 excitatory burst neurons in the paramedian pontine reticular formation (Keller 1974; Luschei  
485 and Fuchs 1972; Strassman et al. 1986a). It has been suggested that the discharge profile of  
486 these neurons is a “replica of eye velocity” (Scudder et al. 2002). Their instantaneous firing rate  
487 would be closely related with instantaneous eye velocity (Leigh and Zee 2006, page 126). Thus,  
488 kinematic notions have been used to interpret the neuronal activity and to model the generation  
489 of saccades. Beyond pragmatic reasons related to its simplicity, such a way of investigating the  
490 neurophysiology of eye movements led to assume a correspondence between the discontinuous  
491 emission of action potentials and the continuous changes in the orientation of the eyes. Yet, one  
492 of the major founders of oculomotor physiology warned that “the models [...] do not contribute  
493 much to the neurophysiology (or neurology) of eye movements and incur the danger of  
494 suggesting that there actually are segregated portions of the nervous system which perform the  
495 differentiation” (Robinson 1971, see also Becker 1995). Moreover, when we see that the firing  
496 rate of premotor neurons does not exhibit the same time course as instantaneous eye velocity  
497 (see Figs. 2 and 3 in Hu et al. 2007 and Fig. 5 in van Gisbergen et al. 1981), the  
498 “neuronalization” of saccade velocity becomes quite questionable.

499 Each saccade is caused by changes in the firing rate of neurons distributed in many brain  
500 regions. Its normal execution is altered when a perturbation affects the functioning of neurons  
501 in the frontal cortex (Dias and Segraves 1999), mesencephalon (Aizawa and Wurtz 1998;  
502 Sparks et al. 1990), pons (Kaneko and Fuchs 2006), cerebellum (Goffart et al. 2004; Kojima et  
503 al. 2010) and reticular formation (Barton et al. 2003). Several studies reported on a relationship  
504 between saccade velocity and the burst discharge of motoneurons (Sylvestre and Cullen 1999)  
505 and premotor neurons (Cromer and Waitzman 2007; Cullen and Guitton 1997; King and Fuchs  
506 1979). The correlation was recently extended to more central neurons in the superior colliculus

507 (SC) and the oculomotor vermis (Herzfeld et al. 2015; Smalianchuk et al. 2018). Consistent  
508 with the crucial role of these two regions in continuously driving the saccades (Goffart et al.  
509 2003; Goossens and van Opstal 2006), they proposed that the discharge of their neurons  
510 “encodes” the instantaneous velocity. Beyond the fundamental concerns raised above and  
511 elsewhere (Goffart et al. 2018; Goffart 2019), three major observations must be considered.  
512 Firstly, the instantaneous firing rate of motoneurons is better fitted by a model factoring muscle  
513 tension and its first derivative than by a model that uses eye position, velocity and acceleration  
514 (Davis-Lopez de Carrizosa et al., 2011). Secondly, the instantaneous discharge of burst neurons  
515 is clock-like and quasi-regular (Hu et al. 2007). Its time course is radically different from the  
516 bell-shaped profile reported by studies which convolve each spike with a Gaussian kernel.  
517 Thirdly, interposed between the saccade-related bursts of collicular and Purkinje cells on the  
518 one hand, and the premotor bursts on the other hand, a population of neurons in the caudal  
519 fastigial nuclei (cFN) emit spikes which have a strong impact on the trajectory of saccades  
520 toward their landing position. Indeed, changes in cFN activity alter not only the endpoint of  
521 saccades (Goffart et al. 2003; Noda et al. 1991) but also their trajectory (see Figs. 1 and 7 in  
522 Goffart et al. 2004; Fig. 1 in Iwamoto and Yoshida 2002). The absence of relation between their  
523 firing rate and saccade velocity (Fuchs et al. 1993; Helmchen et al. 1994; Ohtsuka and Noda  
524 1991) draws into question the suggestion that the population discharge of Purkinje cells  
525 “encodes” instantaneous saccade velocity (Herzfeld et al. 2015). When a correlation is found,  
526 caution must be taken that it does not result from idiosyncrasy (all monkeys do not make the  
527 same saccade amplitude with the same speed) or from unspecific factors like different levels of  
528 motivation or arousal (Fuchs et al. 1993) as shown also in the deep superior colliculus (Ikeda  
529 and Hikosaka 2007; Soetedjo et al. 2000). Finally, it is worth considering that if muscle tension  
530 had been recorded (Davis-Lopez de Carrizosa et al., 2011; Gamlin and Miller; 2012;



531 Lennerstrand et al. 1993; Miller and Robins 1992) instead of eye position, different  
532 neurophysiological processes would have been proposed.

533 **Figure 9 approximately here**

534 *How does bilateral fastigial activity influence the online steering of saccades?*

535 Numerous works show that the activity of cFN neurons plays a crucial role in the  
536 brainstem control of saccade generation. Overlooking them runs the risk to make statements  
537 which remain epiphenomenal; the causal relations between changes in firing rate and changes  
538 in eye movements must be explained explicitly. Two major reasons led us to investigate this  
539 influence on the steering of saccades made toward a target moving along the vertical meridian:  
540 1) vertical saccades are deviated horizontally after unilateral cFN inactivation and 2) the same  
541 etiology can account for this ipsipulsion and the dysmetria observed in horizontal saccades. In  
542 the framework of negative feedback control in which internal estimate of current eye position  
543 (or displacement) is compared to a desired eye position (or displacement) command (Robinson  
544 1975; Sparks 1989; Becker 1995; Pola 2002), the horizontal bias could impair vertical saccades  
545 in a cumulative manner as long as motor error is not zeroed and omnipause neurons do not  
546 resume their activity (Goffart et al. 2004). Our results do not support this link between the  
547 horizontal targeting error and the duration of vertical saccades because the magnitude of the  
548 ipsipulsion was less frequently dependent upon duration than amplitude. An independence  
549 between the dysmetria and duration of gaze shifts was already noticed in the head unrestrained  
550 cat (see Figs. 5 and 6 in Goffart et al. 1998). Finally, because Soetedjo et al. (2000) reported no  
551 change in the accuracy of saccades after muscimol injection in the nucleus raphe interpositus,  
552 we are inclined to think that the dysmetria of saccades after cFN inactivation is not due to the  
553 pause of OPNs (under the influence of the vertical burst generator). It seems more reasonable  
554 to think that the ipsipulsion is actually caused by action potentials that abducens neurons emit  
555 under the influence of unbalanced input from excitatory and inhibitory burst neurons.

556           The known physiology of the gaze circuitry indeed explains the ipsipulsion of vertical  
557 saccades: if the activity of neurons in the left and right abducens nuclei is not balanced during  
558 vertical saccades, there will be horizontal deviation of the eyes. The elevated speed and the  
559 large magnitude of the ipsipulsion during head-unrestrained gaze shifts (Quinet and Goffart  
560 2007) indicate that this imbalance is not caused by a reduced inhibition that IBNs in the  
561 contralateral medullary reticular formation exert upon neurons in the abducens nucleus  
562 ipsilateral to the inactivated cFN (synapses a and b in Fig. 9). An excitatory drive is required  
563 and we hypothesize that it is conveyed by neurons in the opposite (unaffected) cFN (synapse  
564 f). Transmitted by crossed projections (Noda et al. 1990), their spikes excite premotor burst  
565 neurons in the pontomedullary reticular formation ipsilateral to the inactivated cFN, which in  
566 turn activate motor and internuclear neurons in the ipsilateral abducens nucleus (synapses g and  
567 h). This crossed excitatory influence upon premotor burst neurons is supported by the fact that  
568 fastigial electrical stimulation evokes contralateral saccades (Cogdell et al. 1977; Noda et al.  
569 1988; Quinet and Goffart 2015). It is also consistent with the contrapulsion of vertical saccades  
570 when the oculomotor vermis is asymmetrically lesioned (Takagi et al. 1998) or inactivated with  
571 muscimol (Nitta et al. 2007). This crossed fastigioreticular projection does not concern the  
572 reticulospinal neurons that Takahashi et al. (2014) identified in the cat. Indeed, if it also exists  
573 in the macaque, this fastigio-reticulospinal connection is likely involved in the postural tone of  
574 the head because the head barely moves when the cFN is electrically stimulated (Quinet and  
575 Goffart 2009). Also, during cFN inactivation in both the cat and monkey, the head exhibits an  
576 ipsilesional deviation (Goffart and Pélisson 1998; Quinet and Goffart 2005). Furthermore, the  
577 increase of ipsipulsion with saccade amplitude indicates that abducens neurons and excitatory  
578 burst neurons (EBNs) fire more as the vertical amplitude increases. Although EBNs do not  
579 normally fire during vertical saccades (Strassman et al. 1986a; Sparks et al. 2002) and unilateral  
580 inactivation of their territory yields no ipsipulsion (Barton et al. 2003), it is possible that after

581 cFN inactivation, ipsilateral MNs, INs and EBNs abnormally fire during vertical saccades  
582 because they are released from the inhibition exerted by burst neurons (IBNs) in the  
583 contralateral reticular formation (synapses a, b and d; Cullen and Guitton 1997; Scudder et al.  
584 1988; Strassman et al. 1986b). Those IBNs are silenced because of the suppression of their  
585 fastigial drive (synapse i) by the muscimol injection, because also of the inhibition exerted by  
586 IBNs located in the opposite side (synapse j) and recruited by neurons in the unaffected cFN  
587 (synapse e). Scudder et al. (1988) indeed showed that IBNs fire more spikes as the size of  
588 vertical saccades increases (see also van Gisbergen et al. 1981). Thus, when released from the  
589 inhibitory influence of contralateral IBNs (synapses a and b), MNs and INs emit spikes that  
590 deviate vertical saccades with a magnitude that increases with saccade size. The burst would be  
591 triggered by excitatory input from EBNs or from other neurons innervating the abducens  
592 nucleus (Langer et al. 1986; Ugolini et al. 2006).

593         According to the bilateral hypothesis, the activity of saccade-related fastigial neurons  
594 influences the horizontal component of all saccades (vertical and/or horizontal). Ipsilesional  
595 saccades overshoot horizontally their target because following cFN inactivation, the agonist  
596 motor neurons receive a drive from excitatory burst neurons that exceeds the pre-lesional drive,  
597 as it is no longer attenuated by spikes emitted by IBNs in the contralateral side. Indeed, these  
598 IBNs not only lack their fastigial excitatory input but they are also inhibited by IBNs driven by  
599 neurons in the unaffected cFN. Likewise, contralesional saccades prematurely stop for two  
600 reasons: because the agonist motor neurons lack the drive they usually receive from EBNs (as  
601 a result of suppressing their fastigial input) and because the opposite (unaffected) cFN excites  
602 IBNs which in turn inhibit the agonist motor neurons. Thus, regardless of saccade direction, the  
603 same bilateral mechanism (altered balance of excitatory and inhibitory input to the motor  
604 neurons) explains the effects on the horizontal component of all saccades. This conclusion is  
605 further supported when the results from the present study are synthesized with those reported

606 in Bourrelly et al. (2018a). Indeed, the net bilateral effect of inactivation on horizontal saccades  
607 (calculated by subtracting the average contralesional position/time landing ratio from the  
608 ipsilesional ratio) is strongly correlated with the horizontal position/time landing of vertical  
609 saccades.

610

### 611 ***Conclusion***

612         Instead of reflecting the reduction of an internal signal encoding the horizontal distance  
613 between gaze and target positions (or displacements), the horizontal component of saccades can  
614 be viewed as the outcome of a process which restores, under bilateral fastigial control, an  
615 equilibrium (symmetry) that has been broken by asymmetric descending input from cortical eye  
616 fields and deep superior colliculus to the horizontal saccade generators. According to this  
617 alternative theory, speed is not encoded in the discharge of neurons in the brainstem. Calculated  
618 from eye position measurements, speed is the physical expression of an intrinsic process that  
619 opposes mutually antagonist motor processes (Goffart et al. 2018; Goffart 2019). In the future,  
620 more studies will have to clarify the cerebellar control of the vertical component of saccades  
621 (see page 3333 in Quinet and Goffart 2015; Robinson 2000) and its coupling with the processes  
622 controlling their horizontal component (Goffart et al. 2005).

623

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837

838 **Legends of figures**

839 Fig. 1. Effect of unilateral muscimol injection in the caudal fastigial nucleus on tracking a visual  
840 target moving along the vertical meridian. The time course of eye movements produced before  
841 (gray) and after (black) unilateral muscimol injection in the cFN is shown for six different trials.  
842 The eye position (horizontal: upper row; vertical: bottom row) is plotted as a function of time  
843 after target motion onset. The target moved at the constant speed of 20°/s. The selected trials  
844 were recorded during the experiments A2 (A, injection in left cFN) and A3 (B, left cFN) in  
845 monkey A and the experiment Bi9 (C, injection in the right cFN) in monkey Bi.

846

847 Fig. 2. Amplitude-peak velocity relationship of the vertical component of interceptive saccades  
848 toward a target moving along the vertical meridian. This relationship is shown for two  
849 experiments made in each monkey (upper row: A2 and A3 in monkey A; lower row: Bi7 and  
850 Bi8 in monkey Bi), before (gray symbols) and after muscimol injection in the left cFN (black  
851 symbols). The different symbols indicate the different target speeds (●: 10°/s, ■: 20°/s, \*: 40°/s,  
852 ▲: accelerating target, ◆: decelerating target). The number of observations are reported in the  
853 tables 1 and 2.

854

855 Fig. 3. Landing position and time of saccades toward a target moving at constant speed along  
856 the vertical meridian. The vertical (top row) and horizontal (bottom row) landing positions are  
857 plotted as a function of the time after target motion onset when the target moved vertically at  
858 20°/s. Data from before (open symbols) and after (solid symbols) muscimol injection is plotted.  
859 Black and gray symbols correspond to the upward and downward moving target, respectively.  
860 For each monkey, the effects of muscimol injection in the left or right cFN are documented (left  
861 cFN: experiments A3 and Bi7: A-D, right cFN: experiment Bi9: E-F). The dashed line  
862 corresponds to the target position.

863

864 Fig. 4. Position/time landing of saccades toward a target moving at constant speed along the  
865 vertical meridian. The average values of the vertical (panel A) and horizontal (panel B)  
866 components are plotted for the pre- and post-injection sessions of each experiment (square  
867 symbols: monkey A; circle symbols: monkey Bi). The light gray, dark gray and black symbols

868 correspond to the 10, 20 and 40°/s target speeds, respectively. Open and filled symbols  
869 correspond to the upward and downward moving target, respectively. To illustrate the influence  
870 of target speed, the post-injection horizontal average position/time landing of saccades to the  
871 10°/s and 40°/s targets is plotted as a function of the average values obtained with the 20°/s  
872 target (panel C). Diagonal gray lines correspond to equality between abscissae and ordinate  
873 values.

874

875 Fig. 5. Comparing the effects on horizontal and vertical saccades. The post-injection average  
876 values of horizontal position/time landing of vertical saccades are plotted as a function of the  
877 ipsilesional (panel A) and contralesional (panel B) position/time landing of horizontal saccades  
878 (previously described in Burrelly et al. 2018a) for each experiment and each monkey (square  
879 symbols: monkey A; circle symbols: monkey Bi). The panel C shows the horizontal  
880 position/time landing of vertical saccades after muscimol injection as a function of the net  
881 bilateral effect on horizontal saccades (difference of ipsilesional and contralesional horizontal  
882 position/ time landing ratios). The light gray, dark gray and black symbols correspond to the  
883 10, 20 and 40°/s target speeds, respectively. Open and filled symbols correspond to the upward  
884 and downward moving target, respectively.

885

886 Fig. 6. Landing position and time of saccades toward a target moving with a non-constant speed  
887 along the vertical meridian. The horizontal landing positions are plotted as a function of the  
888 landing times for saccades made toward an accelerating (A, B and C) or decelerating (D, E and  
889 F) target, before (open symbols) and after (filled symbols) muscimol injection. Black and gray  
890 symbols correspond to the upward and downward moving target, respectively. The dashed lines  
891 show the horizontal target position.

892

893 Fig. 7. Position/time landing of saccades toward a target moving along the vertical meridian  
894 with a non-constant speed. The average values of the vertical (panel A) and horizontal (panel  
895 B) component were calculated for the pre- and post-injection sessions of each experiment and  
896 plotted for each monkey (square symbols: monkey A; circle symbols: monkey Bi). The gray  
897 and black symbols correspond to the accelerating and decelerating target, respectively. Open  
898 and filled symbols correspond to the upward and downward moving target, respectively. To

899 illustrate the effect of target speed, the post-injection horizontal average position/time landing  
900 of saccades to the accelerating and decelerating targets is plotted as a function of the values  
901 obtained with the 20°/s target (constant speed) (panel C). Diagonal gray lines correspond to  
902 unity lines.

903

904 Fig. 8. Horizontal landing position of saccades toward a target moving along the vertical  
905 meridian. The horizontal landing positions are plotted as a function of the vertical amplitude  
906 after muscimol injection in the left cFN in monkey A (A and B: experiments A2 and A3) and  
907 monkey Bi (C and D: experiments Bi7 and Bi8). The light gray, dark gray and black symbols  
908 correspond to the 10, 20 and 40°/s target speed, respectively. Open and filled symbols  
909 correspond to the upward and downward moving target, respectively. The relation obtained  
910 with saccades toward a target moving with changing speeds are shown in the insets (gray  
911 symbols: constant speeds, black symbols: changing speeds).

912 Fig. 9. Pathophysiology of the ipsipulsion of vertical saccades after muscimol injection in the  
913 right caudal fastigial nucleus. The arrows correspond to excitatory connections whereas the  
914 connecting lines ended by a circle depict inhibitory connections. The gray stain illustrates the  
915 muscimol spread. MR: medial rectus; LR: lateral rectus; MNs: motoneurons; INs: internuclear  
916 neurons; EBns and IBns: excitatory and inhibitory burst neurons; SFNs: saccade-related  
917 fastigial neurons. See text for detailed explanation.

918

919 **Legends of tables**

920 Table 1. Relation between horizontal landing position and both vertical saccade duration and  
921 amplitude after cFN inactivation (target moving at constant speed). Values are the slope, y  
922 intercepts and coefficient of determination of the regression lines that fit the relationship  
923 between the horizontal landing position and the vertical amplitude or duration of saccades  
924 toward a target moving at constant speed (upward and downward movement pooled together).  
925 Injections are labeled as defined in the text. The side and volume of injection are also indicated.  
926 Bold numerical values correspond to statistically significant correlations ( $P < 0.05$ ).

927

928 Table 2. Relation between horizontal landing position and both vertical saccade duration and  
929 amplitude after cFN inactivation (accelerating and decelerating target). Values are the slope, y  
930 intercepts, and coefficient of determination of the regression lines that fit the relationships  
931 between horizontal landing position and the vertical amplitude and duration of saccades toward  
932 a target moving with an increasing speed (from 0 to 40°/s, accelerating target) or decreasing  
933 speed (from 40 to 0°/s, decelerating target). Upward and downward movement are pooled  
934 together. Injections are labeled as defined in the text. The side and volume of injection are also  
935 indicated. Bold numerical values correspond to statistically significant correlations ( $P < 0.05$ ).

936

937



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Fig. 1

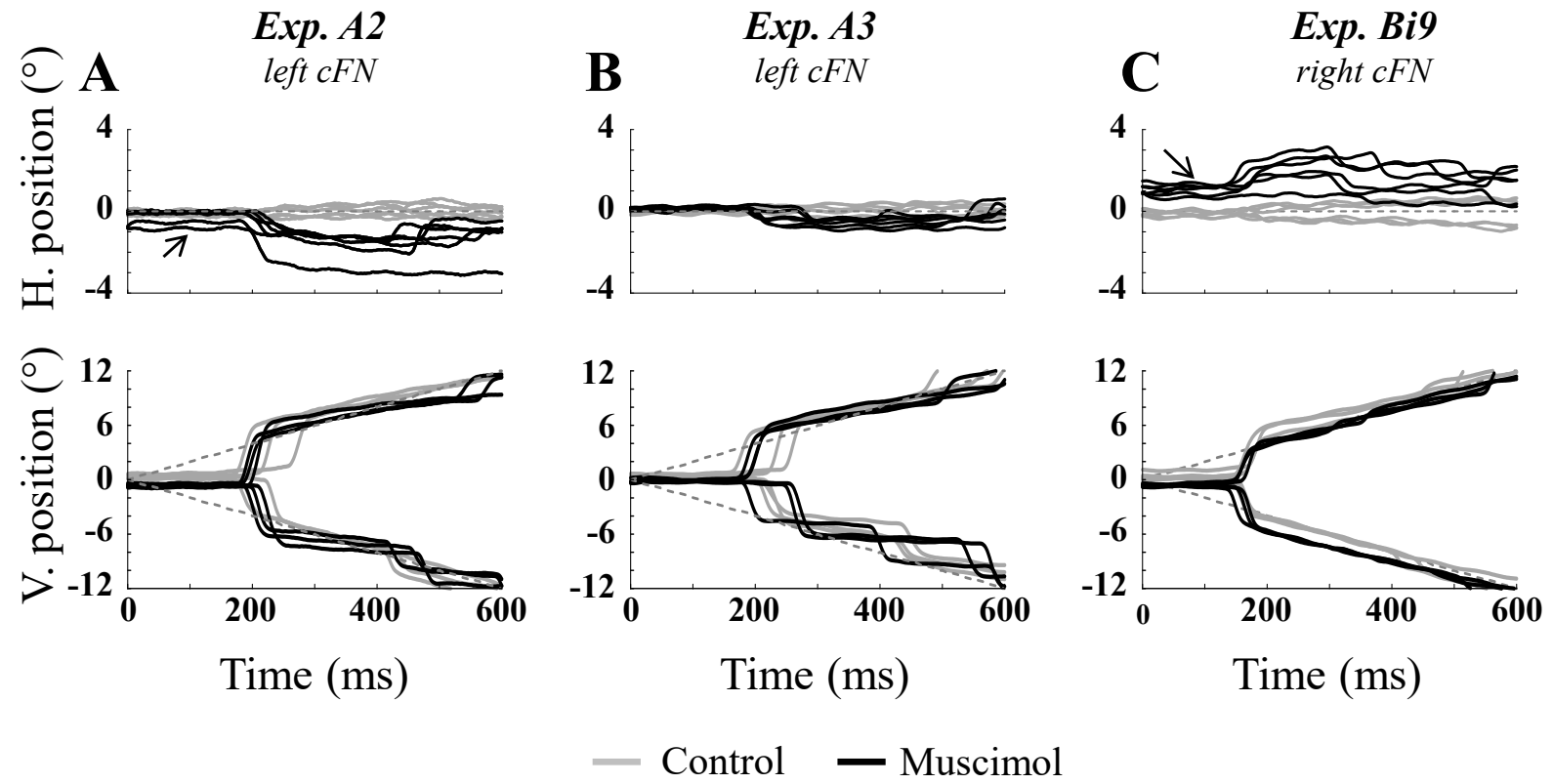


Fig. 2

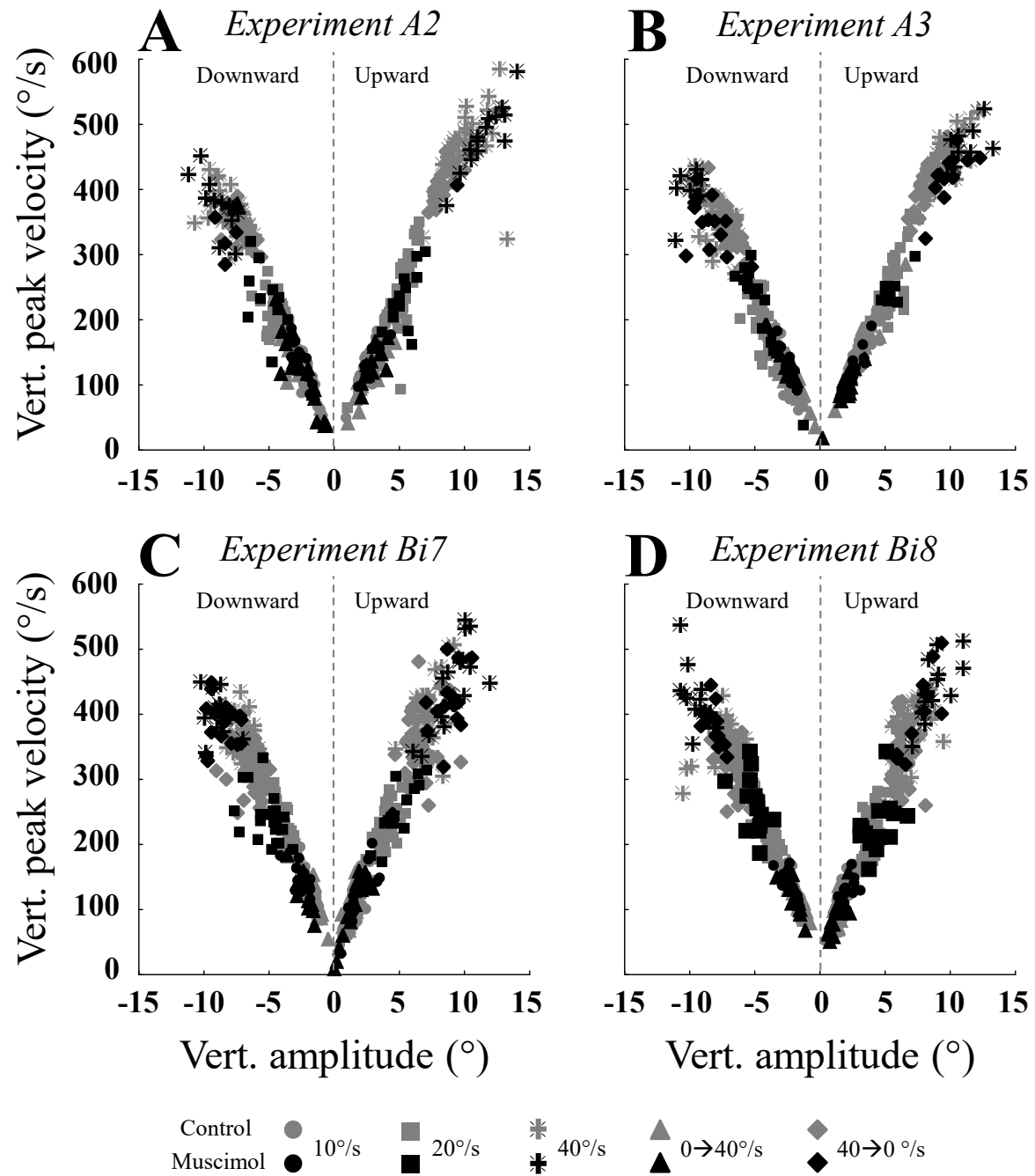


Fig. 3

# Constant target speed

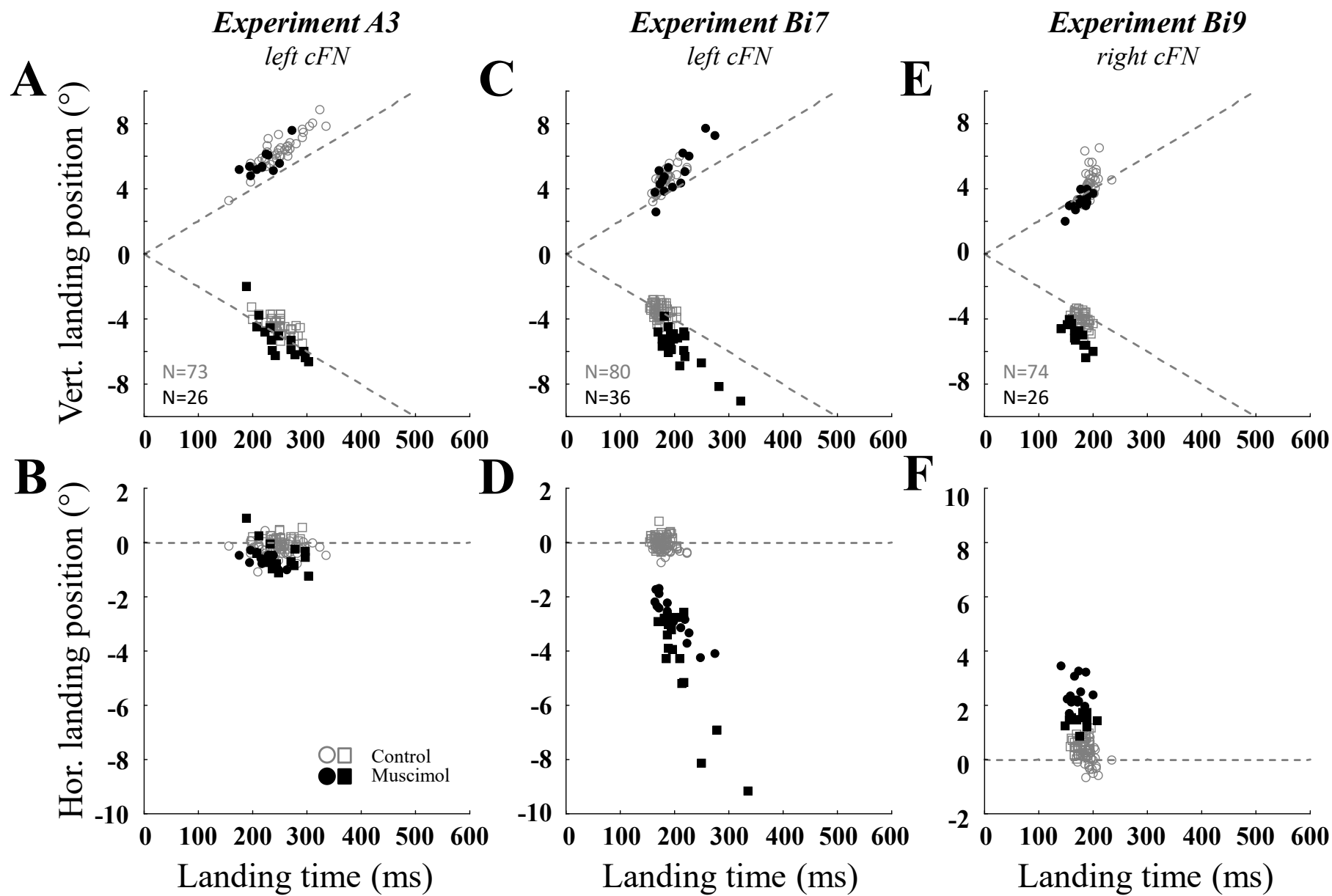




Fig. 5

## Constant target speed

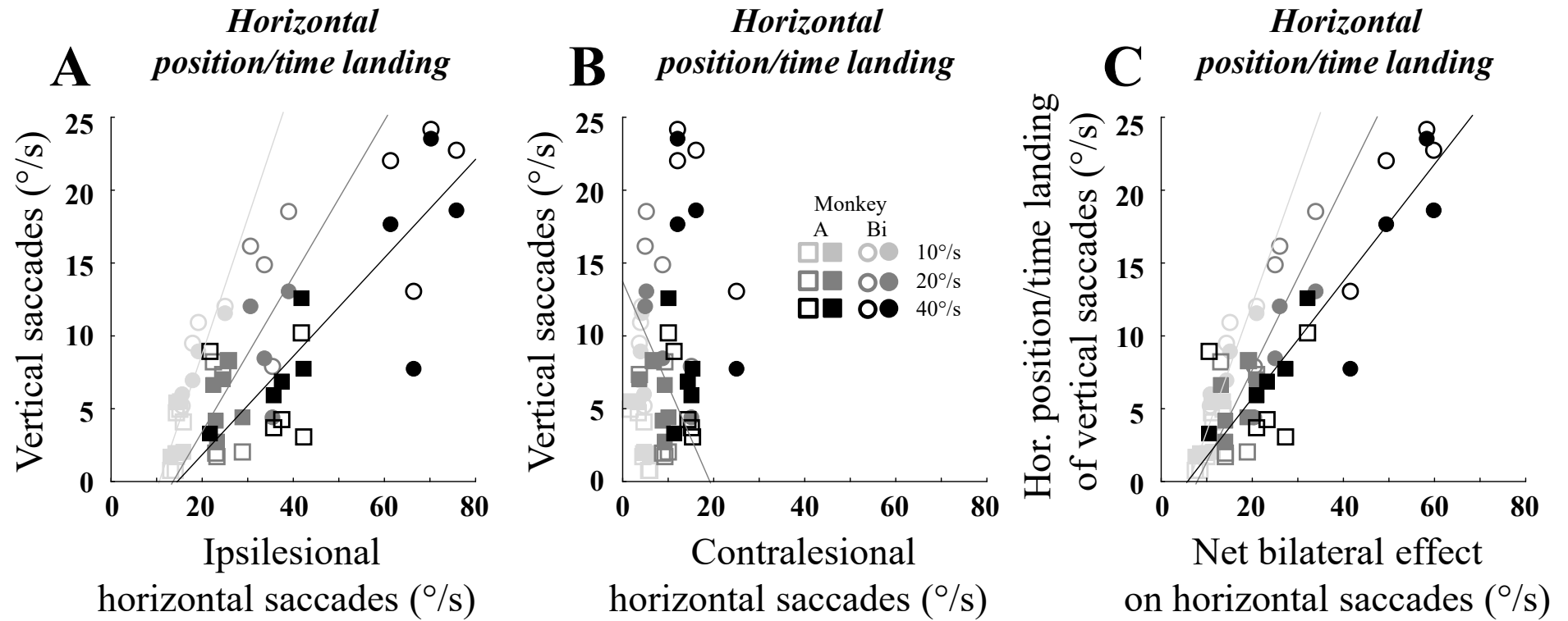


Fig. 6

## Changing target speed

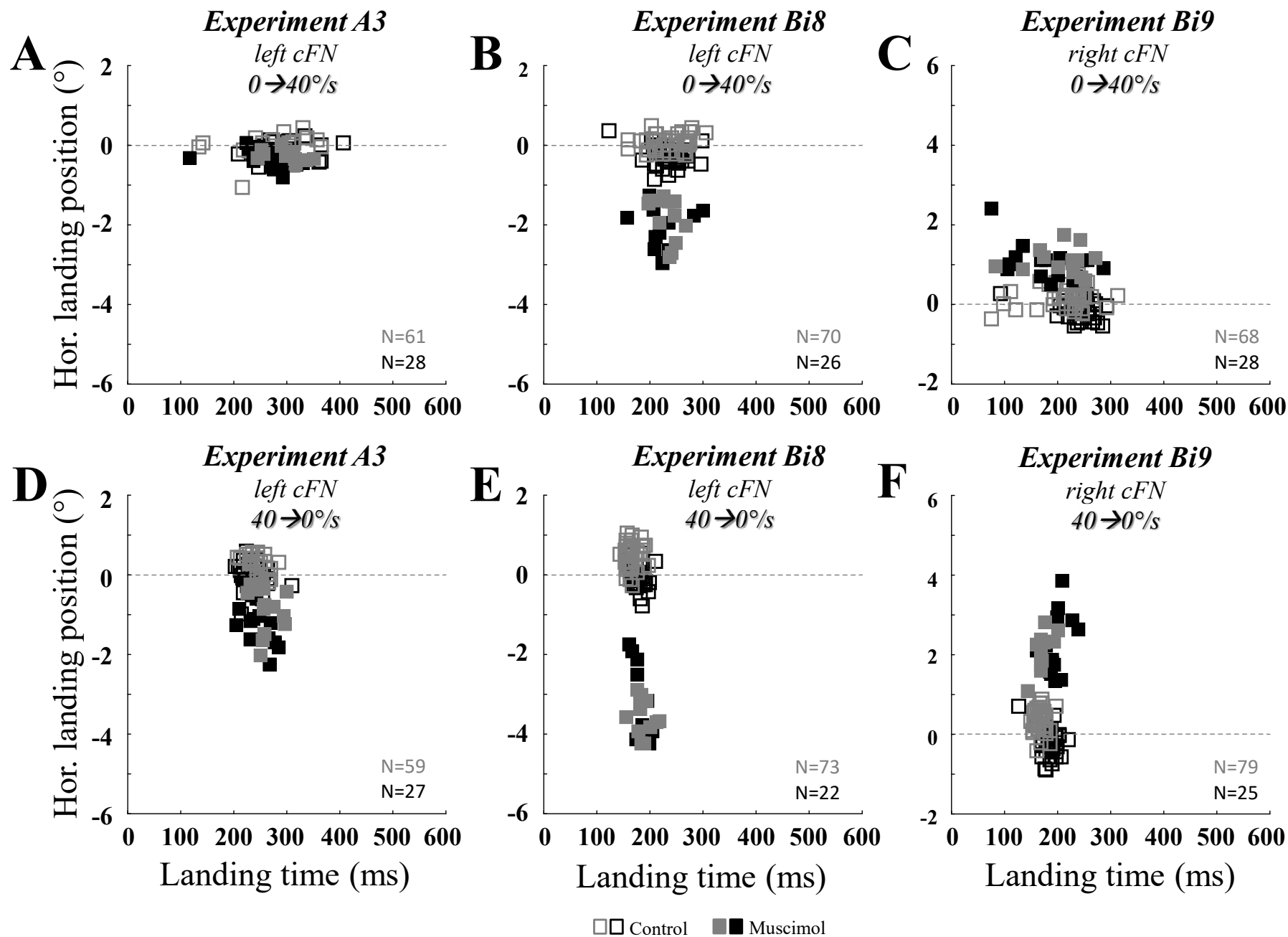


Fig. 7

## Changing target speed

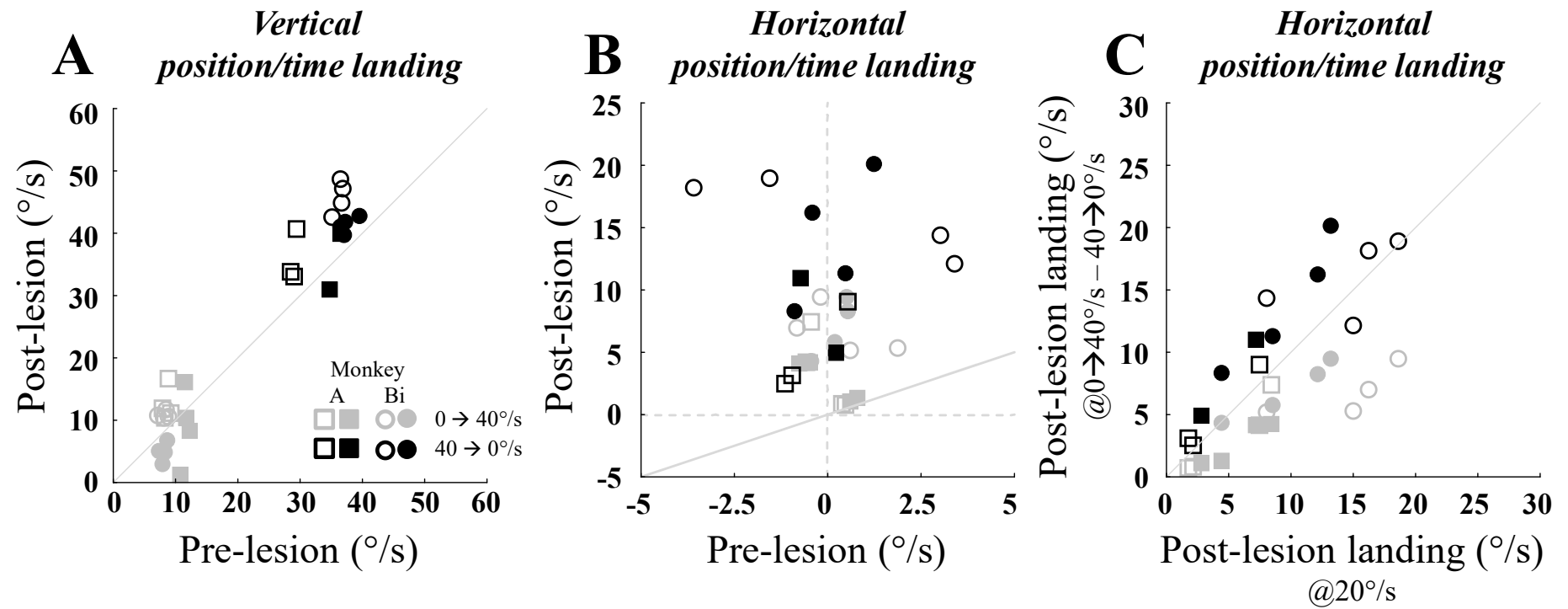




Fig. 8

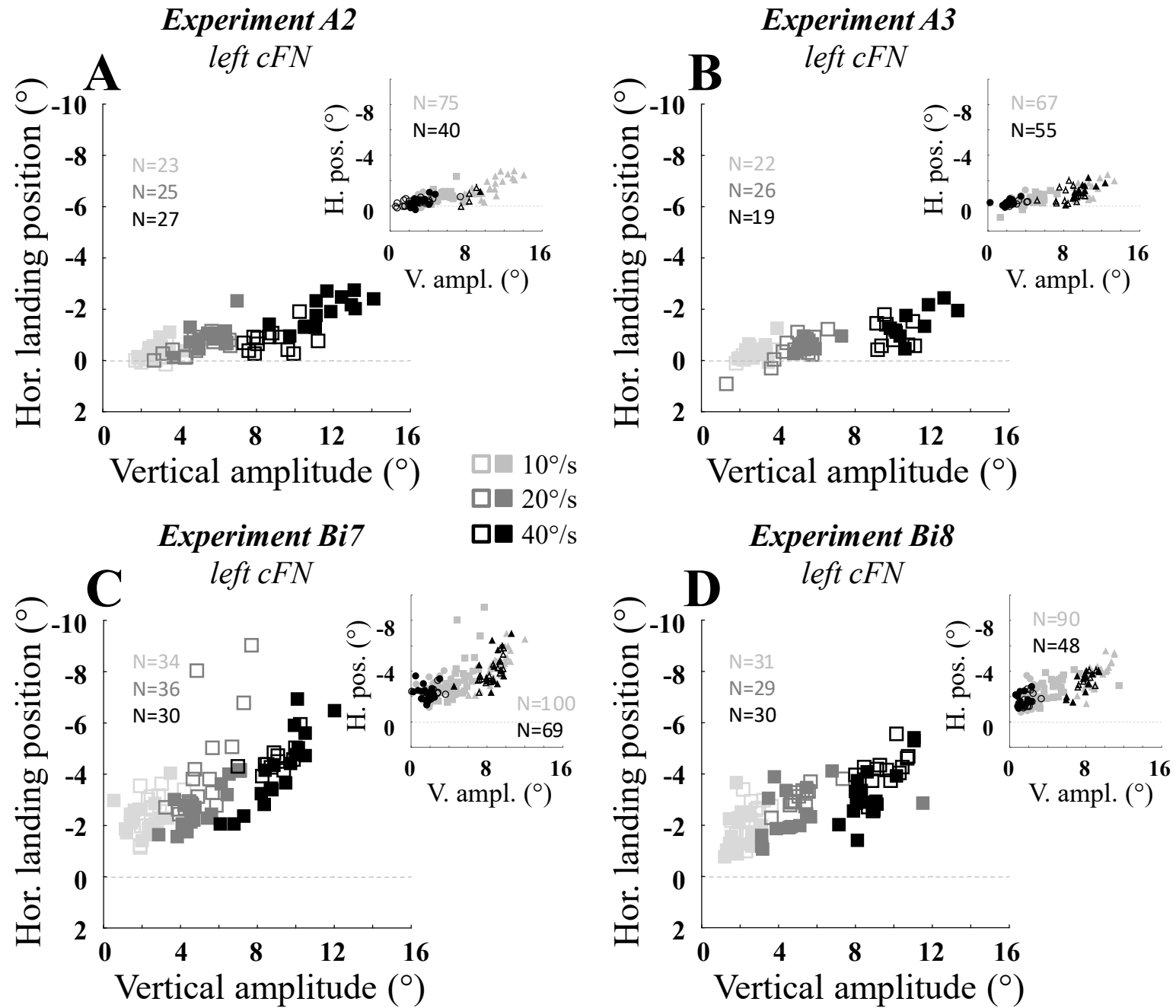
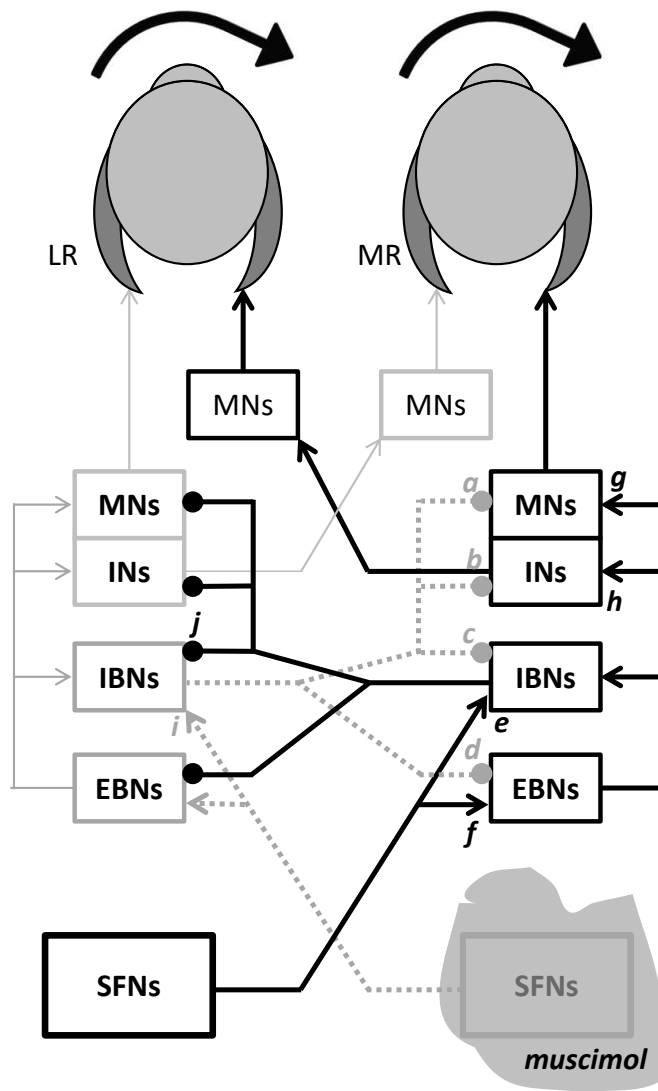


Figure 9



# Table 1

Exp	injection		10°/s				20°/s				40°/s			
			N	Y-int	slope	R <sup>2</sup>	N	Y-int	slope	R <sup>2</sup>	N	Y-int	slope	R <sup>2</sup>
A1	Left cFN 1.0 µl	Amplitude	18	-0.2	-0.108	0.09 NS	<b>38</b>	<b>-0.0</b>	<b>-0.132</b>	<b>0.26*</b>	<b>20</b>	<b>1.1</b>	<b>-0.239</b>	<b>0.48*</b>
		Duration	18	-0.5	-0.001	0.001 NS	<b>38</b>	<b>0.3</b>	<b>-0.028</b>	<b>0.14*</b>	<b>20</b>	<b>1.6</b>	<b>-0.067</b>	<b>0.52*</b>
A2	Left cFN 0.5 µl	Amplitude	23	0.2	-0.185	0.15 NS	<b>25</b>	<b>0.7</b>	<b>-0.281</b>	<b>0.42*</b>	<b>27</b>	<b>1.9</b>	<b>-0.327</b>	<b>0.65*</b>
		Duration	23	-0.1	-0.009	0.01 NS	25	-0.2	-0.014	0.07 NS	<b>27</b>	<b>1.5</b>	<b>-0.065</b>	<b>0.17*</b>
A3	Left cFN 0.3 µl	Amplitude	<b>22</b>	<b>0.4</b>	<b>-0.278</b>	<b>0.33*</b>	<b>26</b>	<b>1.1</b>	<b>-0.328</b>	<b>0.66*</b>	<b>19</b>	<b>1.7</b>	<b>-0.284</b>	<b>0.29*</b>
		Duration	22	0.4	-0.024	0.10 NS	26	0.6	-0.031	0.06 NS	19	-1.0	-0.005	0.003 NS
A4	Right cFN 1.1 µl	Amplitude	30	1.3	0.055	0.001 NS	26	2.4	-0.062	0.003 NS	-	-	-	-
		Duration	30	-0.9	0.070	0.08 NS	26	0.7	0.034	0.03 NS	-	-	-	-
A5	Right cFN 1.0 µl	Amplitude	<b>15</b>	<b>2.5</b>	<b>-0.411</b>	<b>0.29*</b>	28	1.5	0.044	0.00 NS	<b>18</b>	<b>5.7</b>	<b>-0.413</b>	<b>0.31*</b>
		Duration	15	3.1	-0.069	0.10 NS	28	1.5	0.005	0.00 NS	18	1.9	-0.007	0.002 NS
A6	Right cFN 0.5 µl	Amplitude	<b>26</b>	<b>0.6</b>	<b>0.252</b>	<b>0.18*</b>	<b>24</b>	<b>0.5</b>	<b>0.207</b>	<b>0.26*</b>	<b>26</b>	<b>-0.1</b>	<b>0.312</b>	<b>0.53*</b>
		Duration	26	0.5	0.026	0.13 NS	24	0.8	0.019	0.11 NS	<b>26</b>	<b>-0.1</b>	<b>0.066</b>	<b>0.36*</b>
Bi7	Left cFN 0.2 µl	Amplitude	<b>34</b>	<b>-1.6</b>	<b>-0.355</b>	<b>0.15*</b>	<b>36</b>	<b>1.0</b>	<b>-0.889</b>	<b>0.41*</b>	<b>30</b>	<b>2.6</b>	<b>-0.772</b>	<b>0.67*</b>
		Duration	<b>34</b>	<b>-0.5</b>	<b>-0.078</b>	<b>0.28*</b>	<b>36</b>	<b>3.2</b>	<b>-0.198</b>	<b>0.37*</b>	30	-1.8	-0.066	0.09 NS
Bi8	Left cFN 0.2 µl	Amplitude	<b>31</b>	<b>-0.9</b>	<b>-0.522</b>	<b>0.18*</b>	<b>29</b>	<b>-1.7</b>	<b>-0.209</b>	<b>0.18*</b>	<b>30</b>	<b>2.7</b>	<b>-0.701</b>	<b>0.56*</b>
		Duration	<b>31</b>	<b>0.1</b>	<b>-0.088</b>	<b>0.30*</b>	<b>29</b>	<b>-0.5</b>	<b>-0.073</b>	<b>0.28*</b>	<b>30</b>	<b>-0.6</b>	<b>-0.078</b>	<b>0.14*</b>
Bi9	Right cFN 0.5 µl	Amplitude	<b>24</b>	<b>0.8</b>	<b>0.338</b>	<b>0.22*</b>	<b>26</b>	<b>-0.2</b>	<b>0.576</b>	<b>0.34*</b>	24	3.1	0.061	0.00 NS
		Duration	24	1.0	0.021	0.07 NS	26	-0.3	0.081	0.11 NS	24	3.4	0.006	0.00 NS
Bi10	Right cFN 0.2 µl	Amplitude	28	1.3	-0.130	0.02 NS	<b>28</b>	<b>-0.3</b>	<b>0.351</b>	<b>0.23*</b>	26	0.8	0.120	0.02 NS
		Duration	28	0.5	0.023	0.06 NS	28	0.7	0.013	0.01 NS	26	2.0	-0.005	0.00 NS

## Table 2

Exp	injection		Accelerating target				Decelerating target			
			N	Y-int	slope	R <sup>2</sup>	N	Y-int	slope	R <sup>2</sup>
A2	Left cFN 0.5 µl	Amplitude	<b>35</b>	<b>0.0</b>	<b>-0.131</b>	<b>0.34*</b>	5	4.9	-0.663	0.74 NS
		Duration	35	0.0	-0.012	0.06 NS	5	-0.8	0.001	0.00 NS
A3	Left cFN 0.3 µl	Amplitude	<b>28</b>	<b>-0.0</b>	<b>-0.104</b>	<b>0.18*</b>	<b>27</b>	<b>1.1</b>	<b>-0.233</b>	<b>0.31*</b>
		Duration	<b>28</b>	<b>0.2</b>	<b>-0.016</b>	<b>0.15*</b>	27	-0.5	-0.012	0.04 NS
A4	Right cFN 1.1 µl	Amplitude	15	2.7	-0.196	0.10 NS	-	-	-	-
		Duration	15	3.1	-0.034	0.06 NS	-	-	-	-
A6	Right cFN 0.5 µl	Amplitude	<b>24</b>	<b>0.7</b>	<b>0.215</b>	<b>0.29*</b>	<b>27</b>	<b>0.4</b>	<b>0.231</b>	<b>0.39*</b>
		Duration	24	0.4	0.026	0.14 NS	27	1.1	0.027	0.14 NS
Bi7	Left cFN 0.2 µl	Amplitude	35	-2.3	0.016	0.00 NS	<b>34</b>	<b>0.9</b>	<b>-0.581</b>	<b>0.34*</b>
		Duration	35	-1.8	-0.019	0.04 NS	<b>34</b>	<b>-0.7</b>	<b>-0.088</b>	<b>0.25*</b>
Bi8	Left cFN 0.2 µl	Amplitude	26	-1.4	-0.205	0.06 NS	<b>22</b>	<b>1.5</b>	<b>-0.594</b>	<b>0.55*</b>
		Duration	<b>26</b>	<b>-0.4</b>	<b>-0.063</b>	<b>0.32*</b>	22	-1.3	-0.052	0.10 NS
Bi9	Right cFN 0.5 µl	Amplitude	28	1.0	0.013	0.00 NS	<b>25</b>	<b>-0.3</b>	<b>0.310</b>	<b>0.33*</b>
		Duration	28	1.0	0.002	0.00 NS	<b>25</b>	<b>0.7</b>	<b>0.039</b>	<b>0.17*</b>
Bi10	Right cFN 0.2 µl	Amplitude	29	0.9	0.115	0.04 NS	<b>22</b>	<b>-2.2</b>	<b>0.537</b>	<b>0.12*</b>
		Duration	29	0.7	0.016	0.04 NS	22	3.7	-0.04	0.05 NS