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Clara Bourrelly*, Julie Quinet and Laurent Goffart*

Aix Marseille Université, Centre National de la Recherche Scientifique,

Institut de Neurosciences de la Timone, Marseille, France.

Laurent Goffart : https://orcid.org/0000-0001-8767-1867

Julie Quinet : https://orcid.org/0000-0003-3043-3424

Title for running head: Neural control of interceptive saccades

*: C. Bourrelly and L. Goffart contributed equally to this work.

Address for correspondence:

Laurent Goffart, PhD,

E-mail: laurent.goffart@univ-amu.fr

Institut de Neurosciences de la Timone, Campus de Sante, 27 Bd Jean Moulin, 13385 Marseille cedex 5, France.

Abstract (219 words <= 250 words)

The caudal fastigial nuclei (cFN) are the output nuclei by which the medio-posterior cerebellum influences the production of saccades toward a visual target. On the basis of the organization of their efferences to the premotor burst neurons and the bilateral control of saccades, the hypothesis was proposed that the same unbalanced activity accounts for the dysmetria of all saccades during cFN unilateral inactivation, regardless of whether the saccade is horizontal, oblique, or vertical. We further tested this hypothesis by studying, in two head-restrained macaques, the effects of unilaterally inactivating the caudal fastigial nucleus on saccades toward a target moving vertically with a constant, increasing or decreasing speed. After local muscimol injection, vertical saccades were deviated horizontally toward the injected side with a magnitude that increased with saccade size. The ipsipulsion indeed depended upon the tested target speed, but not its instantaneous value because it did not increase (decrease) when the target accelerated (decelerated). By subtracting the effect on contralesional horizontal saccades from the effect on ipsilesional ones, we found that the net bilateral effect on horizontal saccades was strongly correlated with the effect on vertical saccades. We explain how this correlation corroborates the bilateral hypothesis and provide arguments against the suggestion that the instantaneous saccade velocity would somehow be "encoded" by the discharge of Purkinje cells in the oculomotor vermis.

NEW & NOTEWORTHY (73 <= 75 words)

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

Introduction

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

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

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

Numerous observations lead to questioning this isomorphism which was assumed between the brainstem activity and the kinematics of saccades. Firstly, Davis-Lopez de Carrizosa et al. (2011) showed that a model factoring muscle tension and its first derivative accounted for the firing rate of motoneurons better than a model factoring eye position and its first and second derivatives (velocity and acceleration). Secondly, the resemblance between the firing rate of premotor burst neurons and saccade instantaneous velocity (see for example Fig. 5B of Cromer and Waitzman (2007)) disappears when the spikes are not convolved with a Gaussian kernel (see Figs. 2 and 3 in Hu et al. (2007); Fig. 3C in Sparks & Hu (2006) and Fig. 4 in van Gisbergen et al. (1981)). Thirdly, the inspection of cFN bursts reveals that the transition between the activity of the left and right cFN is not as sharp as the separation between the acceleration and deceleration phases. In fact, the bursts in the two nuclei largely overlap around the time of saccade peak velocity (Kleine et al. 2003). Moreover, some neurons burst after saccade onset during large contralateral head unrestrained gaze shifts, casting doubt on the cFN's role in accelerating saccades (Fuchs et al. 2010). Involvement in only decelerating ipsilateral saccades is also called into question by the changes in the acceleration of saccades after cFN inactivation (Buzunov et al. 2013; Quinet and Goffart 2007). Finally, a horizontal deviation (ipsipulsion) affects the full time course of vertical saccades, including both acceleration and deceleration, following unilateral cFN inactivation (Goffart et al. 2004; Iwamoto and Yoshida 2002; Quinet and Goffart 2007).

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

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

Materials and Methods

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

Subjects and surgical procedures

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

Eye movement recording and visual stimulation

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

package (Ryklin Software). Eye position signals were calibrated by having the animal fixate stationary targets presented at ±16° along the horizontal or vertical meridians.

Oculomotor tests

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

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

Muscimol injection

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

Data analysis

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

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

Results

Figure 1 approximately here

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

Figure 2 approximately here

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

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

Figure 3 approximately here

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

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

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

Figure 4 approximately here

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

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

310 < 0.05) as well as between the mean values obtained with the 20°/s and 40°/s targets (R(x,y) =
311 0.93, P < 0.05).

312 **Figure 5 approximately here**

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

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

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

Figure 6 approximately here

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

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

369 **Figure 7 approximately here**

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

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

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

409 and downward movements pooled together) in table 1 (constant speeds) and table 2 (changing
410 speeds). The correlation was statistically significant in 13 out of 44 test sessions (corresponding
411 to 30% of cases) with coefficients of correlation ranging from 0.37 to 0.72. When we instead
412 considered the relation between the horizontal landing position and vertical saccade amplitude,
413 statistically significant correlations were found in 30 out of 44 sessions (corresponding to 68%
414 of the post-injection sessions), with coefficients of correlation ranging from 0.38 to 0.81. The
415 parameters of the equations fitting the relation between the horizontal landing position and the
416 vertical saccade amplitude after muscimol injection are documented for all the experiments
417 (upward and downward movements pooled together) in table 1 (target moving at a constant
418 speed) and table 2 (accelerating and decelerating targets). In several instances, the correlation
419 between the saccade duration and the horizontal landing position (R(Dur,HorP)) did not reach
420 statistical significance whereas the correlation between the saccade amplitude and the
421 horizontal landing position (R(Amp,HorP)) was statistically significant (see Table 1:
422 experiments A3, A5, A6 and Bi9 for the 10°/s target; A2, A3, A6, Bi9 and Bi10 for the 20°/s
423 target; in A3, A5 and Bi7 for the 40°/s target). Likewise, when we consider the saccades toward
424 an accelerating target (leftmost columns in Table 2), R(Dur,HorP) was not statistically
425 significant although R(Amp,HorP) was during the experiments A2 and A6. Finally, when the
426 target was decelerating (rightmost columns in Table 2), R(Dur,HorP) was not statistically
427 significant but R(Amp,HorP) was significant during the experiments A3, A6, Bi8 and Bi10.
428 Considering all 44 sessions, a significant correlation R(Dur,HorP) without significant
429 correlation R(Amp,HorP) was observed in one single experiment (Bi8, accelerating target).
430 Altogether, these results strongly suggest that the ipsipulsion increased mostly because
431 saccades had larger amplitudes than because they lasted longer.

432 **Figure 8 approximately here**

To illustrate this correlation between the vertical amplitude of saccades and the ipsipulsion, Fig. 8 plots the horizontal landing position as a function of vertical saccade amplitude before and after muscimol injection. Both upward and downward saccades were included (the amplitude of downward saccades was multiplied by -1). The relations are shown for four injections made in the left cFN of monkey A (experiments A2 and A3, top row) and Bi (experiments Bi7 and Bi8, bottom) for saccades to targets moving with a constant speed (light gray, dark gray and black symbols correspond to the 10, 20 and 40°/s target speeds, respectively). Negative values of horizontal eye position indicate that the saccades were deviated toward the left (inactivated side). Thus, we can see that while the target speed increases from 10 to 40°/s (symbols with different shades of grey), the horizontal landing position and the vertical saccade amplitude increased. During experiment A2 (Fig. 8A), as the target speed increased, the horizontal landing position changed from -0.3 ± 0.3° (10°/s) to -0.7 ± 0.5° (20°/s) and -1.4 ± 0.8° (40°/s), while the vertical amplitude increased from 2.8 ± 0.6° (10°/s) to 5.1 ± 1.1° (20°/s) and 10.2 ± 1.9° (40°/s). Likewise, during experiment A3 (Fig. 8B), the horizontal landing position increased from -0.3 ± 0.3° to -0.5 ± 0.4° and -1.3 ± 0.6° while the vertical amplitude increased from 2.7 ± 0.6° to 5.1 ± 1.1° and 10.5 ± 1.1° (values for the 10, 20 and 40°/s target speed, respectively). The same relationship was found in monkey Bi. During experiment Bi7 (Fig. 8C), the horizontal landing position increased from -2.4 ± 0.7° to -3.4 ± 1.6° and -4.3 ± 1.1° and the vertical amplitude from 2.2 ± 0.7° to 5.1 ± 1.2° and 9.0 ± 1.3°. Finally, during experiment Bi8 (Fig. 8D), the horizontal landing position increased from -2.0 ± 0.7° (10°/s) to -2.8 ± 0.8° (20°/s) to -3.7 ± 1.0° (40°/s), while the vertical amplitude increased from 2.2 ± 0.6° to 5.0 ± 1.6°and 9.1 ± 1.1°. A relation was observed between the horizontal landing position and the vertical amplitude of saccades. Each inset graph plotted in the right part of the panels of Figure 8 shows an overlap of data points corresponding to saccades to a target moving at constant speed (gray symbols) and to an accelerating or decelerating target

458 (black symbols). In summary, after cFN inactivation, the landing position of vertical saccades
459 was deviated toward the injected side by an amount that varied between experiments and that
460 was larger when the target moved quickly than when it moved slowly. The dependency of the
461 ipsipulsion upon the target speed indicates that the saccade oculomotor system has access to
462 different signals when the target moves at different speeds. However, the use of accelerating
463 and decelerating target enabled us to exclude a dependency upon the instantaneous speed of the
464 target. Further analyses revealed that the ipsipulsion was more frequently correlated with the
465 vertical amplitude of saccades rather than with their duration.

Discussion

This study is the first to describe the consequences of unilateral pharmacological inactivation of cFN on the generation of vertical saccades toward a moving target. As for the saccades toward a static target, interceptive saccades exhibit a horizontal deviation of their trajectory toward the lesioned side (ipsipulsion; Figs. 3, 4B and 7B) whereas the vertical component is barely affected (Figs. 2, 3, 4A and 7A). The magnitude of the ipsipulsion is larger for fast targets than for slowly moving targets (Fig. 4C) but the use of accelerating and decelerating targets indicates that this relation is due less to the instantaneous target speed (Fig. 6) than to the saccade size. Indeed, like saccades toward a static target, the ipsipulsion increased with the vertical amplitude of saccades (Fig. 8). Statistical analyses made across all sessions indicate that the correlations between the ipsipulsion and the vertical amplitude were more frequent than the correlations between the ipsipulsion and the duration. Moreover, in several sessions, the correlation between the ipsipulsion and the duration of saccades did not reach statistical significance whereas the correlation with the vertical amplitude was significant (Tables 1 and 2). Below, we explain the neurophysiological mechanisms leading to the ipsipulsion of vertical saccades and further develop facts which call for an alternative approach to investigate the neurophysiology of visually-guided eye movements and their cerebellar control.

Figure 9 approximately here

How does bilateral fastigial activity influence the trajectory of saccades?

Numerous works show that the activity of cFN neurons plays a crucial role in the cerebellar control of saccade generation. Two major reasons led us to investigate their influence on the trajectory of saccades toward a target moving along the vertical meridian: 1) vertical saccades are deviated horizontally after unilateral cFN inactivation and 2) the same etiology can account for this ipsipulsion and the dysmetria of horizontal saccades. In the framework of

491 negative feedback control in which an internal estimate of current eye position (or
492 displacement) is compared to a desired eye position (or displacement) command (Robinson
493 1975; Sparks 1989; Becker 1995; Pola 2002), a horizontal bias could impair vertical saccades
494 in a cumulative manner as long as motor error is not zeroed and omnipause neurons do not
495 resume their activity. Our results do not support this link between the horizontal targeting error
496 and the duration of vertical saccades because the magnitude of the ipsipulsion was less
497 frequently dependent upon the duration than the amplitude, and because in many cases, the
498 correlation between the ipsipulsion and the duration did not reach statistical significance
499 whereas the correlation between the ipsipulsion and the amplitude was statistically significant.
500 An independence between the dysmetria and duration of gaze shifts was already noticed in the
501 head unrestrained cat after cFN inactivation (see Figs. 5 and 6 in Goffart et al. 1998). Finally,
502 it is worth reminding that neither Kaneko (1996) nor Soetedjo et al. (2000) reported changes in
503 the accuracy of saccades when the nucleus raphe interpositus is lesioned or inactivated. The
504 dysmetria of saccades after cFN inactivation is therefore not caused (but permitted) by the pause
505 of OPNs (under the influence of the vertical burst generator). We propose that the ipsipulsion
506 is driven by action potentials that abducens neurons emit under the influence of unbalanced
507 input from excitatory and inhibitory burst neurons.

508 The known physiology of the saccade-related circuitry indeed explains the ipsipulsion
509 of vertical saccades: if the activity of neurons in the left and right abducens nuclei is not
510 balanced during vertical saccades, there will be horizontal deviation of the eyes. The elevated
511 speed and the large magnitude of the ipsipulsion during head-unrestrained gaze shifts (Quinet
512 and Goffart 2007) indicate that this imbalance is not caused by a reduced inhibition that IBNs
513 in the contralateral medullary reticular formation exert upon neurons in the abducens nucleus
514 ipsilateral to the inactivated cFN (synapses a and b in Fig. 9). An excitatory drive is required
515 and we hypothesize that it is conveyed by neurons in the opposite (unaffected) cFN (synapse

516 f). Transmitted by crossed projections (Noda et al. 1990), their spikes excite premotor burst
517 neurons in the pontomedullary reticular formation ipsilateral to the inactivated cFN, which in
518 turn activate motor and internuclear neurons in the ipsilateral abducens nucleus (synapses g and
519 h). This crossed excitatory influence upon premotor burst neurons is supported by the fact that
520 fastigial electrical stimulation evokes contralateral saccades (Cogdell et al. 1977; Noda et al.
521 1988; Quinet and Goffart 2015). It is also consistent with the contrapulsion of vertical saccades
522 when the oculomotor vermis is asymmetrically lesioned (Takagi et al. 1998) or inactivated with
523 muscimol (Nitta et al. 2007). This crossed fastigioreticular projection does not concern the
524 reticulospinal neurons that Takahashi et al. (2014) identified in the cat. Indeed, if it also exists
525 in the macaque, this fastigio-reticulospinal connection is likely involved in the postural tone of
526 the head because the head barely moves when the cFN is electrically stimulated (Quinet and
527 Goffart 2009). Also, during cFN inactivation in both the cat and monkey, the head exhibits an
528 ipsilesional deviation (Goffart and Pélisson 1998; Quinet and Goffart 2005). Furthermore, the
529 increase of ipsipulsion with saccade amplitude indicates that abducens neurons and excitatory
530 burst neurons (EBNs) fire more as the vertical amplitude increases. Although EBNs do not
531 normally fire during vertical saccades (Strassman et al. 1986a; Sparks et al. 2002) and unilateral
532 inactivation of their territory yields no ipsipulsion (Barton et al. 2003), it is possible that after
533 cFN inactivation, ipsilateral MNs, INs and EBNs abnormally fire during vertical saccades
534 because they are released from the inhibition exerted by burst neurons (IBNs) in the
535 contralateral reticular formation (synapses a, b and d; Cullen and Guitton 1997; Scudder et al.
536 1988; Strassman et al. 1986b). Those IBNs are silenced because of the suppression of their
537 fastigial drive (synapse i) by the muscimol injection, because also of the inhibition exerted by
538 IBNs located in the opposite side (synapse j) and recruited by neurons in the unaffected cFN
539 (synapse e). Scudder et al. (1988) indeed showed that IBNs fire more spikes as the size of
540 vertical saccades increases (see also van Gisbergen et al. 1981). Thus, released from the

inhibitory influence of contralateral IBNs (synapses a and b), MNs and INs emit spikes that deviate vertical saccades with a magnitude that increases with saccade size. The burst would be triggered by excitatory input from EBNs or from other neurons innervating the abducens nucleus (Langer et al. 1986; Ugolini et al. 2006).

According to the bilateral hypothesis, the activity of saccade-related fastigial neurons influences the horizontal component of all saccades (vertical and/or horizontal). Ipsilesional saccades overshoot horizontally their target because following cFN inactivation, the agonist motor neurons receive a drive from excitatory burst neurons (synapses g and h in Fig. 9) that exceeds the pre-lesional drive, as it is no longer attenuated by spikes emitted by IBNs in the contralateral side (synapses a, b and d). Indeed, these IBNs not only lack their fastigial excitatory input (synapse i) but they are also inhibited by IBNs driven by neurons in the unaffected cFN (synapse e). Likewise, contralesional saccades prematurely stop for two reasons: because the agonist motor neurons lack the drive they usually receive from EBNs (as a result of suppressing their fastigial input; synapse k) and because the opposite (unaffected) cFN excites IBNs which in turn inhibit the agonist motor neurons (synapses l and m). Thus, regardless of saccade direction, the same bilateral mechanism (i.e., an altered balance of excitatory and inhibitory input to the motor neurons) explains the effects on the horizontal component of all saccades. This conclusion is further supported when the results from the present study are synthesized with those reported in Bourrelly et al. (2018a). Indeed, the net bilateral effect of inactivation on horizontal saccades (calculated by subtracting the average contralesional position/time landing ratio from the ipsilesional ratio) is strongly correlated with the horizontal position/time landing of vertical saccades.

Recasting the neurophysiology of saccades

In the preceding section as well as in our previous reports (Bourrelly et al. 2018a,b; Goffart et al. 2004; Guerrasio et al. 2010; Quinet & Goffart 2007), the oculomotor disorders observed after cFN inactivation were explained without assuming perturbations of some internal (and putative) estimate of the eye kinematics, as one might expect for example, if their input from Purkinje cells in the oculomotor vermis were to encode the instantaneous velocity of saccades (Herzfeld et al. 2015). In this section, we want to further develop additional concerns which support our alternative viewpoint and call for recasting the neurophysiology of eye movements (Goffart et al. 2018; Goffart 2019).

First of all, it is important to realize that if the recording of eye muscle tension had been used more frequently (Davis-Lopez de Carrizosa et al., 2011; Gamlin and Miller; 2012; Lennerstrand et al. 1993; Miller and Robins 1992) than the recording the orientation of the eyes during neurophysiological experiments, different processes and models might have been proposed. Then, it is also important to consider the fact that the time course of saccades is not exclusively determined by the discharge of premotor and motor neurons. It involves changes in the firing rate of neurons distributed in many brain regions such as the frontal cortex (Dias and Segraves 1999), the mesencephalon (Aizawa and Wurtz 1998; Sparks et al. 1990), the pons (Kaneko and Fuchs 2006), the medio-posterior cerebellum (Goffart et al. 2003; Kojima et al. 2010) and the reticular formation (Barton et al. 2003; Soetedjo et al. 2000). Right upstream from the extraocular muscle fibers, saccades are engendered by an abrupt increase in the firing rate of motor neurons which innervate the agonist muscles and a concomitant decrease in the discharge of neurons innervating the antagonist muscles. Due to the highly damped nature of the oculomotor plant (Robinson 1964), a braking action is not exerted upon antagonist motor neurons to stop the saccade (Robinson 1970; Schiller 1970). Thus, the agonist burst duration increases with the duration of saccades and determines their size and the saturated firing rate leads to a discharge frequency which is poorly related to saccade speed (Fuchs and Luschei

590 1970; Robinson 1970; Schiller 1970; Sparks and Hu 2006). Synchronous presynaptic spikes
591 converging upon the motor neurons could be one way to overcome the limitations of interspike
592 intervals (Schiller 1970; Goffart et al. 2017a). For the generation of horizontal saccades, the
593 burst causing the phasic contraction of the medial rectus (and the saccade of the contralateral
594 eye) originates in burst-tonic (internuclear) neurons in the abducens nucleus while the burst
595 causing the phasic contraction of the lateral rectus (saccade of the ipsilateral eye) originates in
596 abducens motoneurons. These bursts are caused by excitatory burst neurons in the paramedian
597 pontine reticular formation (Keller 1974; Luschei and Fuchs 1972; Strassman et al. 1986a).
598 In several synthesis articles, we can read that the discharge profile of burst neurons is a
599 "replica of eye velocity" (Scudder et al. 2002) and that pontine and midbrain EBNs encode
600 saccade velocity by the frequency of spikes (Sparks 2002). Their instantaneous firing rate would
601 be closely related with instantaneous eye velocity (Leigh and Zee 2006, page 126), as supported
602 by several recording studies in the premotor and motor neurons (e.g., Cromer and Waitzman
603 2007; Cullen and Guitton 1997; King and Fuchs 1979; Sylvestre and Cullen 1999). For several
604 years, kinematic notions were used to interpret the spiking activity of neurons and to model the
605 generation of saccades. Yet, when we examine the firing rate of premotor neurons, we discover
606 that they do not exhibit the same time course as instantaneous eye velocity (see Figs. 2 and 3 in
607 Hu et al. 2007, Fig. 3C in Sparks and Hu 2006 and Fig. 5 in van Gisbergen et al. 1981). In fact,
608 the meticulous inspection reveals that the instantaneous discharge of burst neurons is almost
609 clock-like and quasi-regular (Hu et al. 2007), radically different from the bell-shaped profile
610 shown by studies which convolve each spike with a Gaussian kernel.
611 The relation between the firing rate and the instantaneous saccade velocity was recently
612 extended to more central neurons in the superior colliculus (Smalianchuk et al. 2018) and the
613 oculomotor vermis (Herzfeld et al. 2015). In agreement with the crucial role of these two
614 regions in continuously driving the saccades (Goffart et al. 2003; Goossens and van Opstal

615 2006), these studies proposed that the discharge of their neurons encodes the instantaneous
616 velocity. Two major observations must, nevertheless, be considered. Firstly, a model factoring
617 muscle tension and its first derivative fits better the instantaneous firing rate of motoneurons
618 than a model that uses eye position, velocity and acceleration (Davis-Lopez de Carrizosa et al.,
619 2011). The putative velocity commands must therefore be translated into force-related
620 commands somewhere before reaching the motor neurons. Interposed between the saccade-
621 related bursts of Purkinje cells and the premotor burst neurons, the caudal fastigial nuclei host
622 a population of neurons which emit spikes that have a strong impact on the time course of
623 saccades toward their landing position. Changes in cFN activity alter not only the endpoint of
624 saccades (Goffart et al. 2003; Noda et al. 1991) but also their trajectory (see Figs. 1 and 7 in
625 Goffart et al. 2004; Fig. 1 in Iwamoto and Yoshida 2002). However, the absence of relation
626 between their firing rate and saccade velocity (Fuchs et al. 1993; Helmchen et al. 1994; Ohtsuka
627 and Noda 1991) draws into question the suggestion that the population discharge of Purkinje
628 cells "encodes" instantaneous saccade velocity (Herzfeld et al. 2015). When correlations are
629 found between the population firing rate and saccade velocity, caution must be taken that they
630 do not result from idiosyncratic (all monkeys do not make the same saccade amplitude with the
631 same speed) or unspecific factors like different levels of motivation or arousal (Fuchs et al.
632 1993) as shown also in the deep superior colliculus (Ikeda and Hikosaka 2007; Soetedjo et al.
633 2000).
634
635 ***Conclusion***
636 Instead of reflecting the reduction of an internal signal encoding the horizontal distance
637 between gaze and target positions (or displacements), we propose that the horizontal component
638 of saccades is the outcome of a process which restores, under bilateral fastigial control, an
639 equilibrium (symmetry) that has been broken by asymmetric descending input (from cortical

640 eye fields and deep superior colliculus) to the horizontal saccade generators (Goffart et al. 2018;
641 Goffart 2019). In the future, more studies will have to clarify the cerebellar control of the
642 vertical component of saccades (Quinet and Goffart 2015; Robinson 2000) and its coupling
643 with the processes controlling their horizontal component (Goffart et al. 2005).
644

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Legends of figures

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

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

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

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

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

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

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

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

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

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

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

Legends of tables

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

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

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Fig. 1

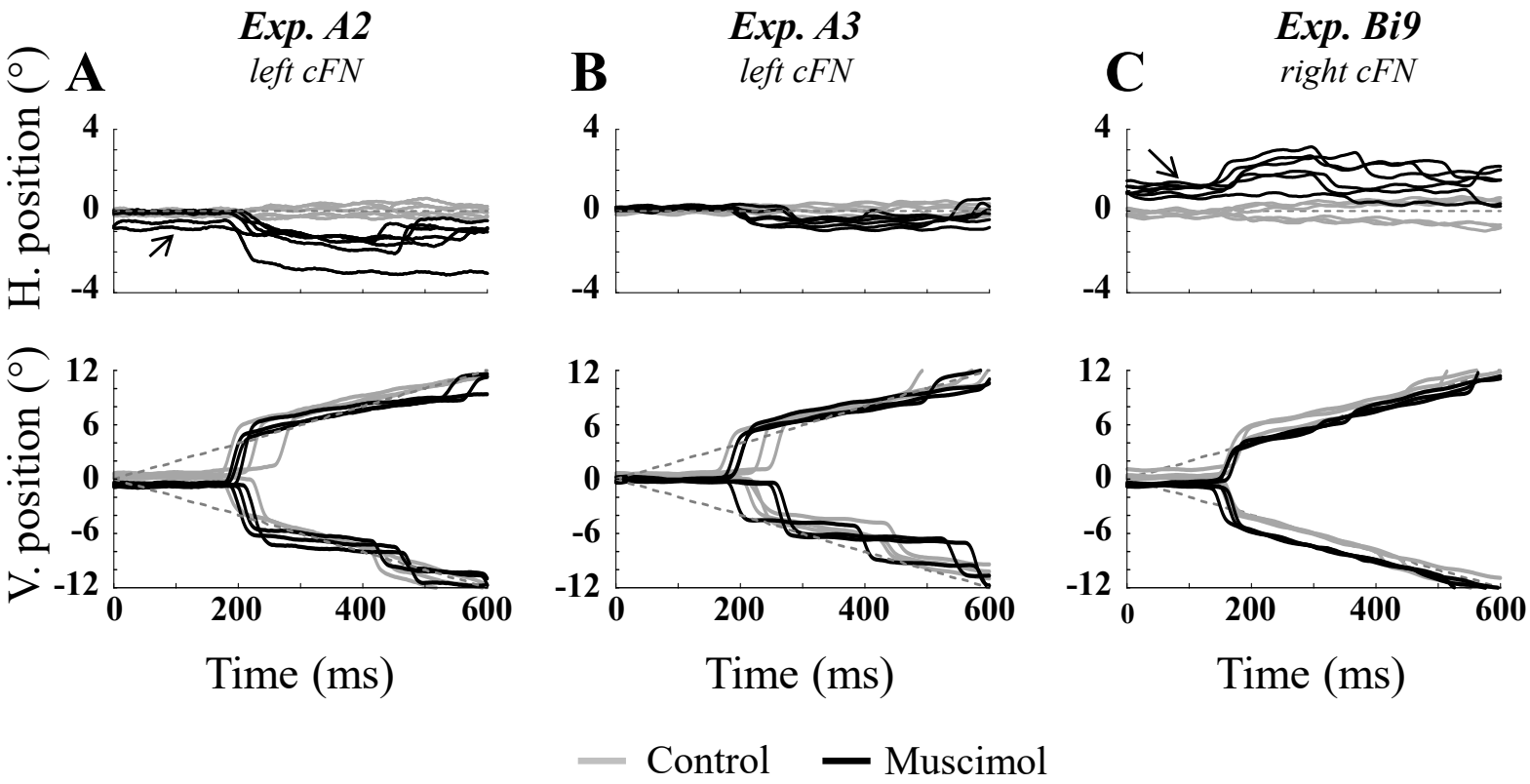
Exp. A2
left cFN
A
Exp. A3
left cFN
B
Exp. Bi9
right cFN
C
H. position (°)
V. position (°)
4
0
-4
12
6
0
-6
-12
0
200
400
600
Time (ms)
Control
Muscimol

Fig. 2

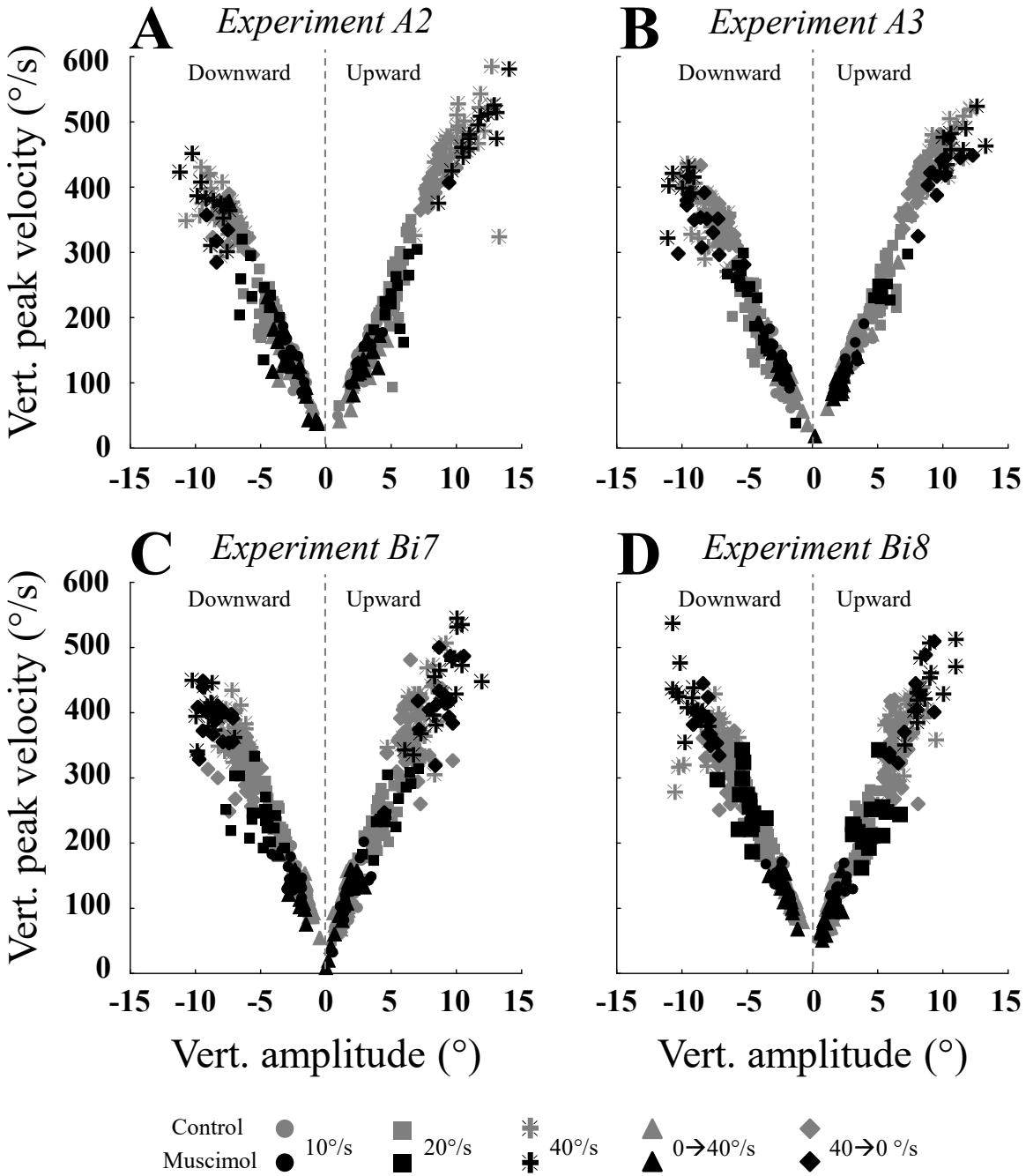
A
Experiment A2
B
Experiment A3
C
Experiment Bi7
D
Experiment Bi8
Downward
Upward
Vert. peak velocity (°/s)
Vert. amplitude (°)
600
500
400
300
200
100
0
-15
-10
-5
0
5
10
15
Control
Muscimol
10°/s
20°/s
40°/s
0→40°/s
40→0 °/s

Fig. 3

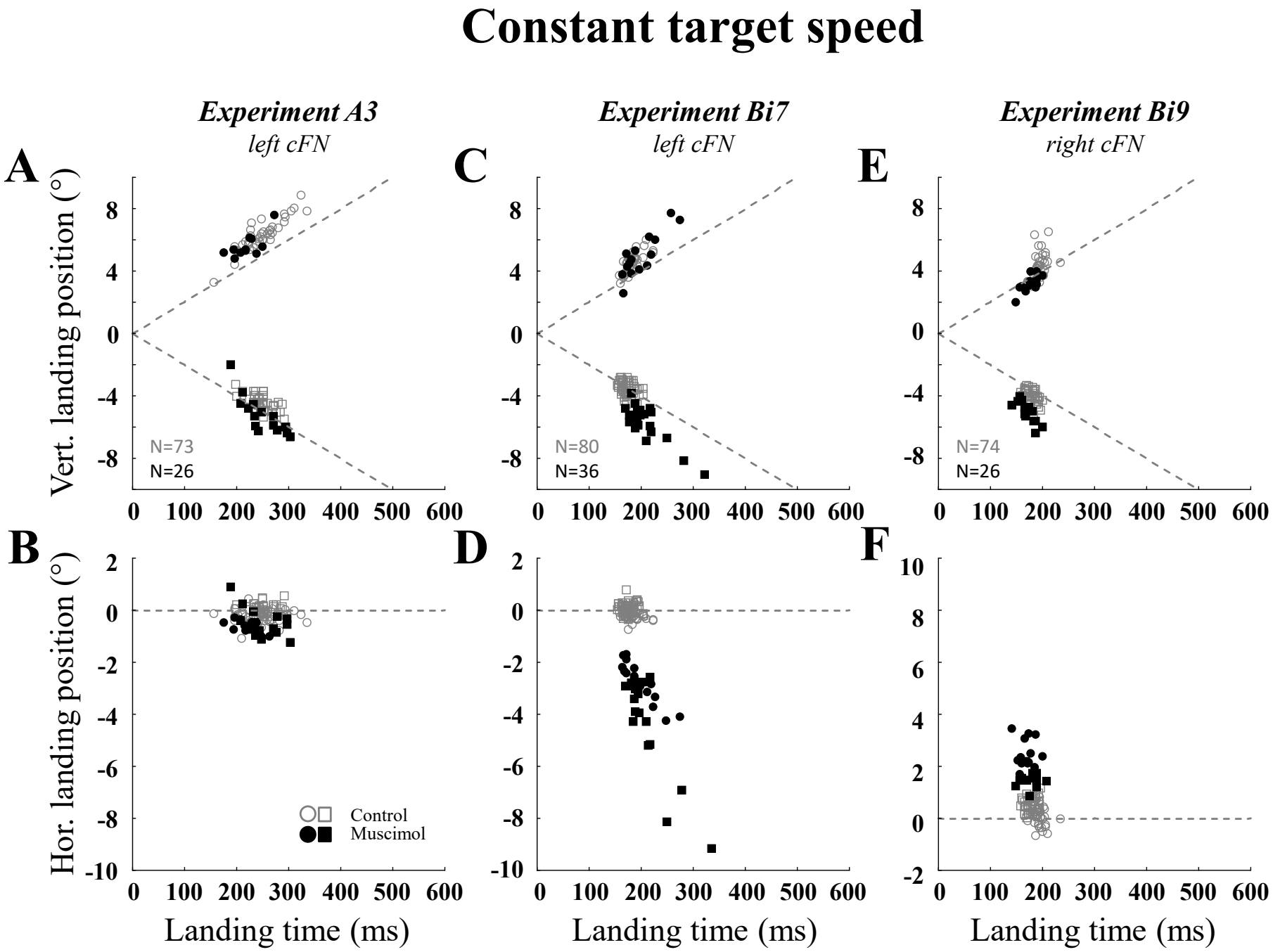
Constant target speed
Experiment A3
left cFN
Experiment Bi7
left cFN
Experiment Bi9
right cFN
A
B
C
D
E
F
Vert. landing position (°)
Hor. landing position (°)
N=73
N=26
N=80
N=36
N=74
N=26
Control
Muscimol
Landing time (ms)
Landing time (ms)
Landing time (ms)

Fig. 4

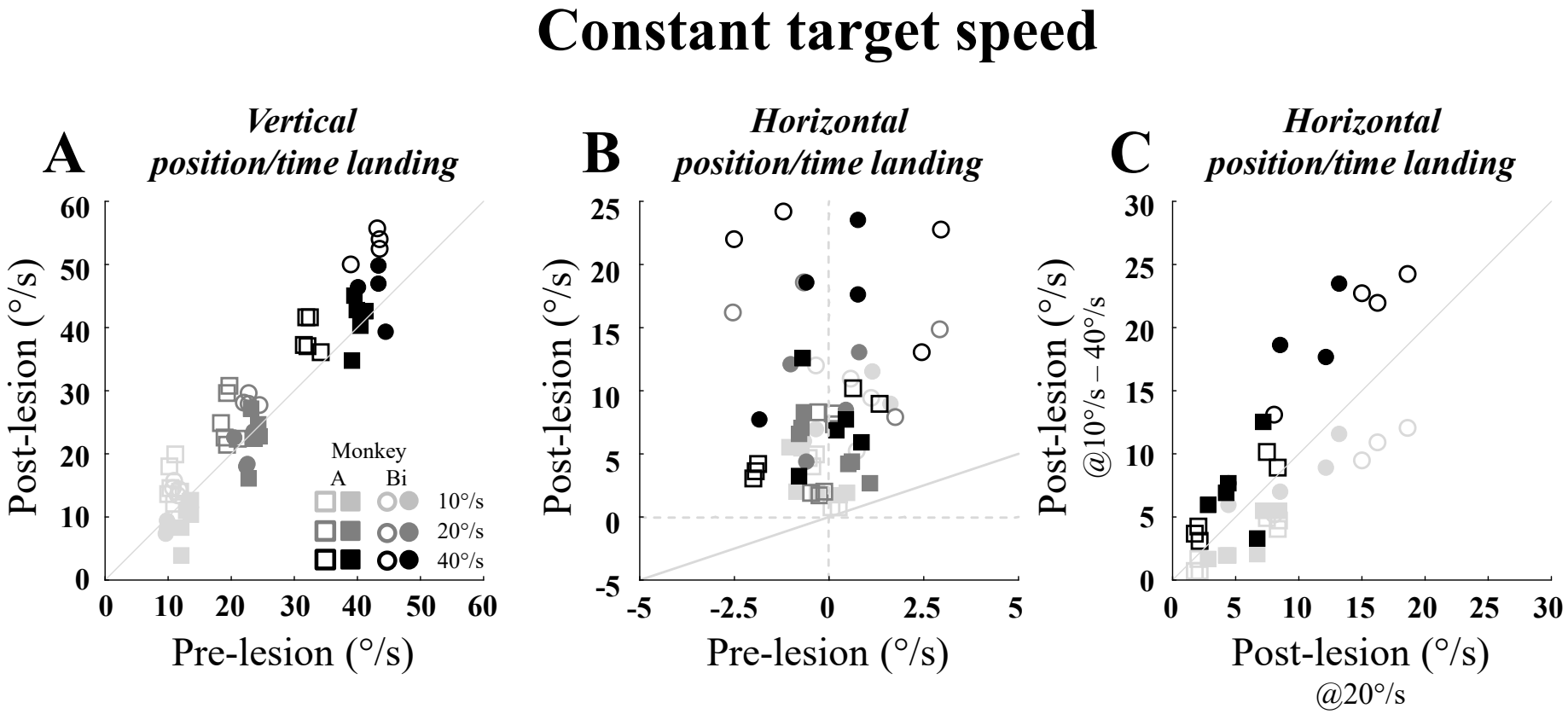
Constant target speed
A
Vertical
position/time landing
Post-lesion (°/s)
Pre-lesion (°/s)
Monkey
A
Bi
10°/s
20°/s
40°/s
B
Horizontal
position/time landing
Post-lesion (°/s)
Pre-lesion (°/s)
C
Horizontal
position/time landing
Post-lesion (°/s)
@10°/s – 40°/s
Post-lesion (°/s)
@20°/s

Fig. 5

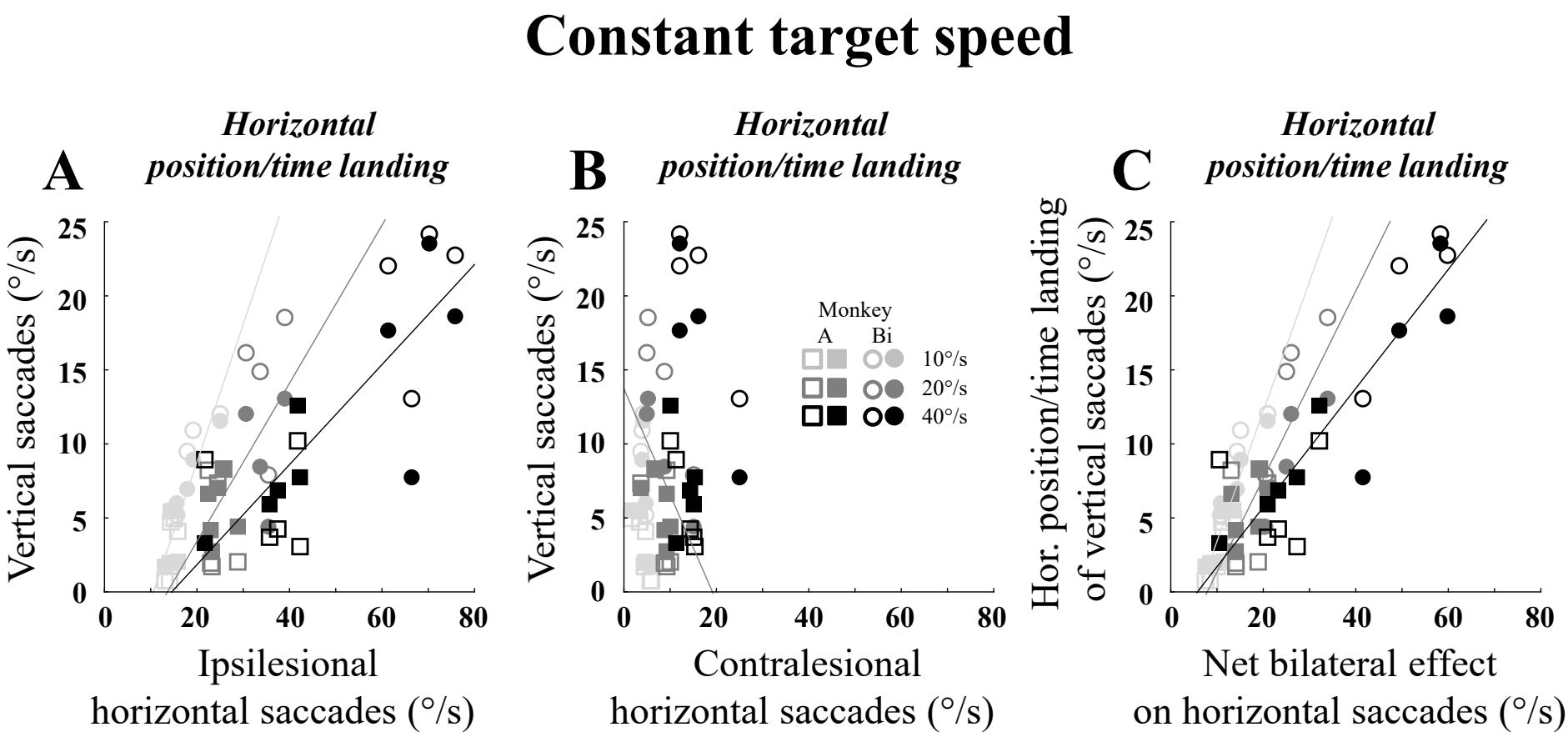
Constant target speed
A
Horizontal position/time landing
Vertical saccades (°/s)
Ipsilesional horizontal saccades (°/s)
B
Horizontal position/time landing
Vertical saccades (°/s)
Contralesional horizontal saccades (°/s)
Monkey
A
Bi
10°/s
20°/s
40°/s
C
Horizontal position/time landing
Hor. position/time landing of vertical saccades (°/s)
Net bilateral effect on horizontal saccades (°/s)
0
5
10
15
20
25
0
20
40
60
80

Fig. 6

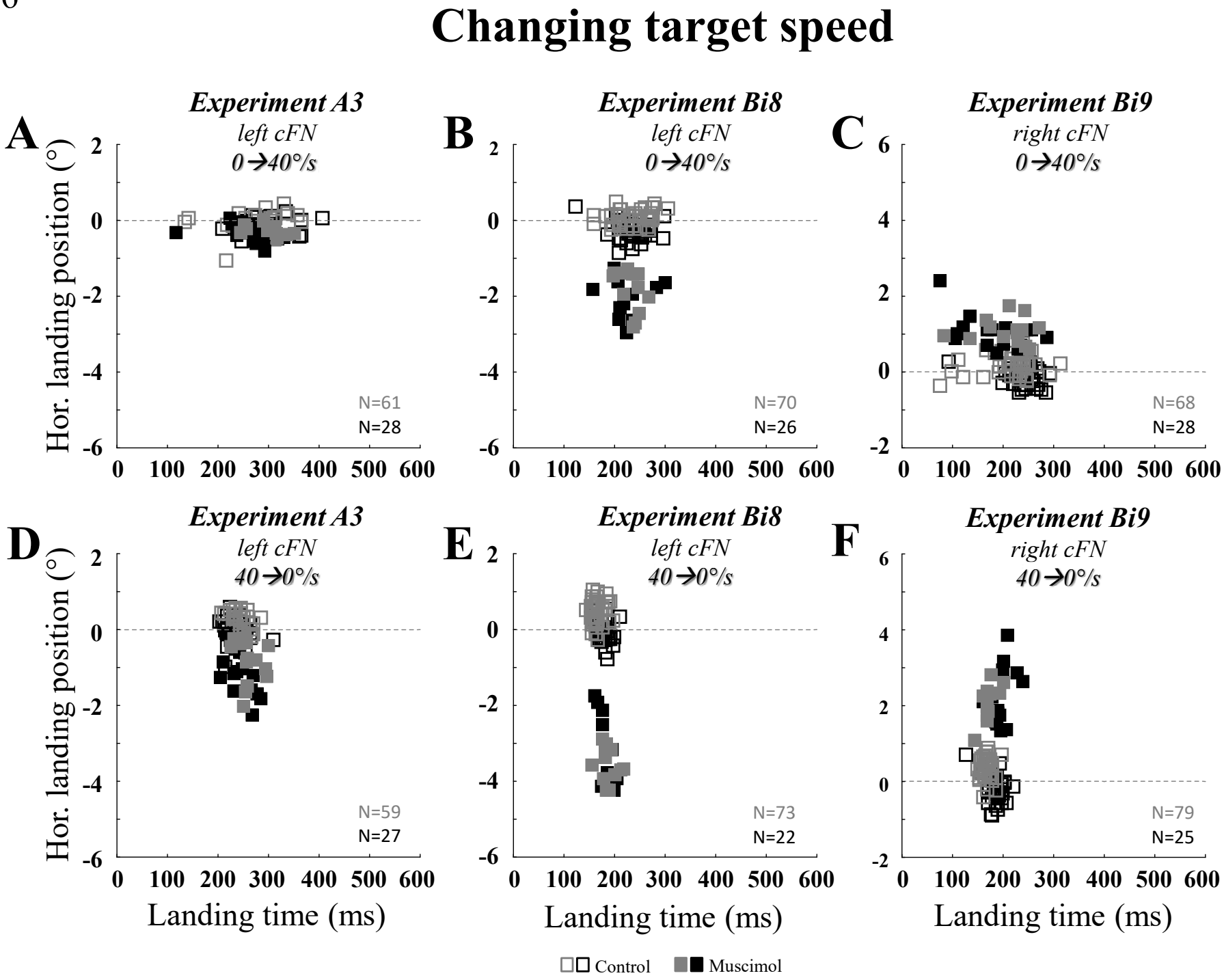
Changing target speed
A
Experiment A3
left cFN
0→40°/s
N=61
N=28
B
Experiment Bi8
left cFN
0→40°/s
N=70
N=26
C
Experiment Bi9
right cFN
0→40°/s
N=68
N=28
D
Experiment A3
left cFN
40→0°/s
N=59
N=27
E
Experiment Bi8
left cFN
40→0°/s
N=73
N=22
F
Experiment Bi9
right cFN
40→0°/s
N=79
N=25
Hor. landing position (°)
Landing time (ms)
Control
Muscimol

Fig. 7

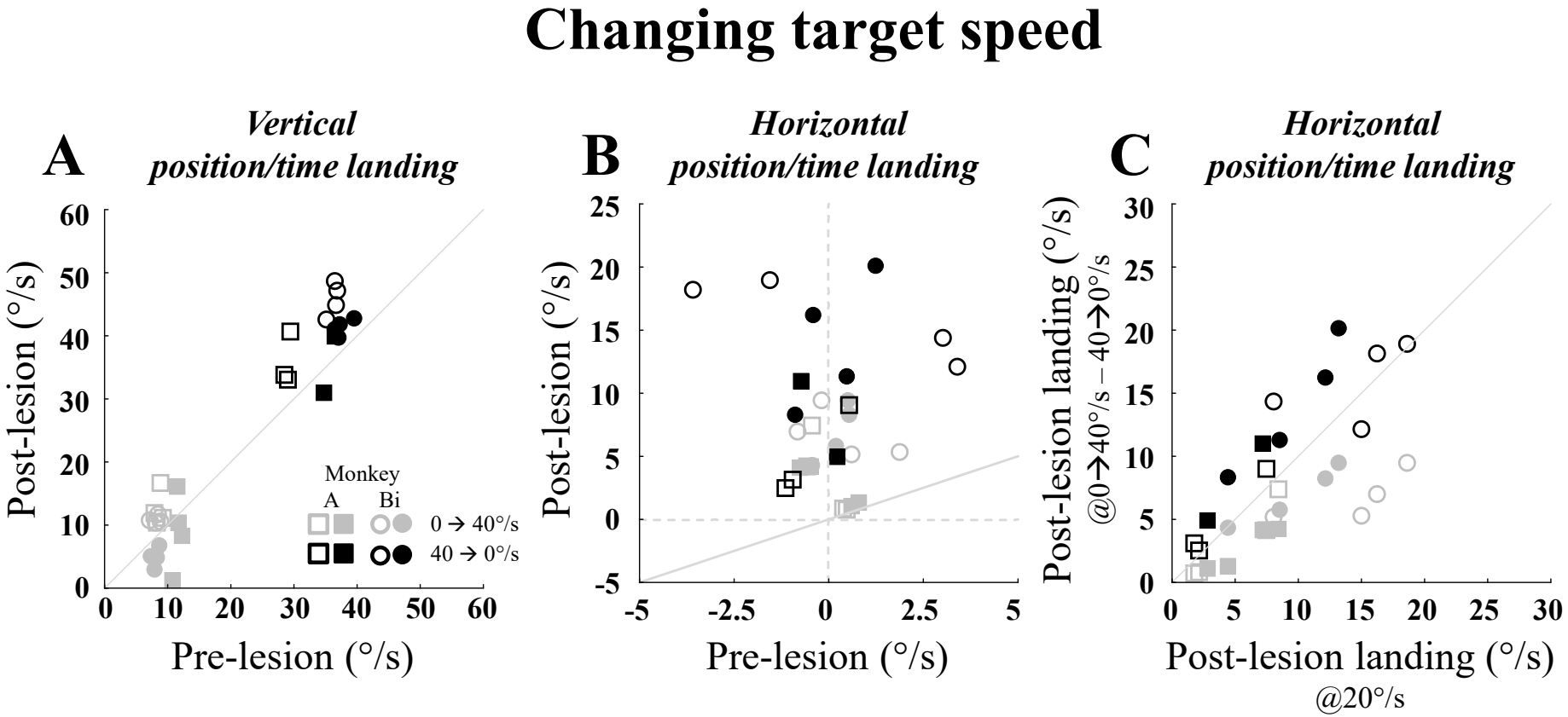
Changing target speed
A
Vertical
position/time landing
Post-lesion (°/s)
Pre-lesion (°/s)
Monkey
A
Bi
0 → 40°/s
40 → 0°/s
B
Horizontal
position/time landing
Post-lesion (°/s)
Pre-lesion (°/s)
C
Horizontal
position/time landing
Post-lesion landing (°/s)
@0→40°/s – 40→0°/s
Post-lesion landing (°/s)
@20°/s

Fig. 8

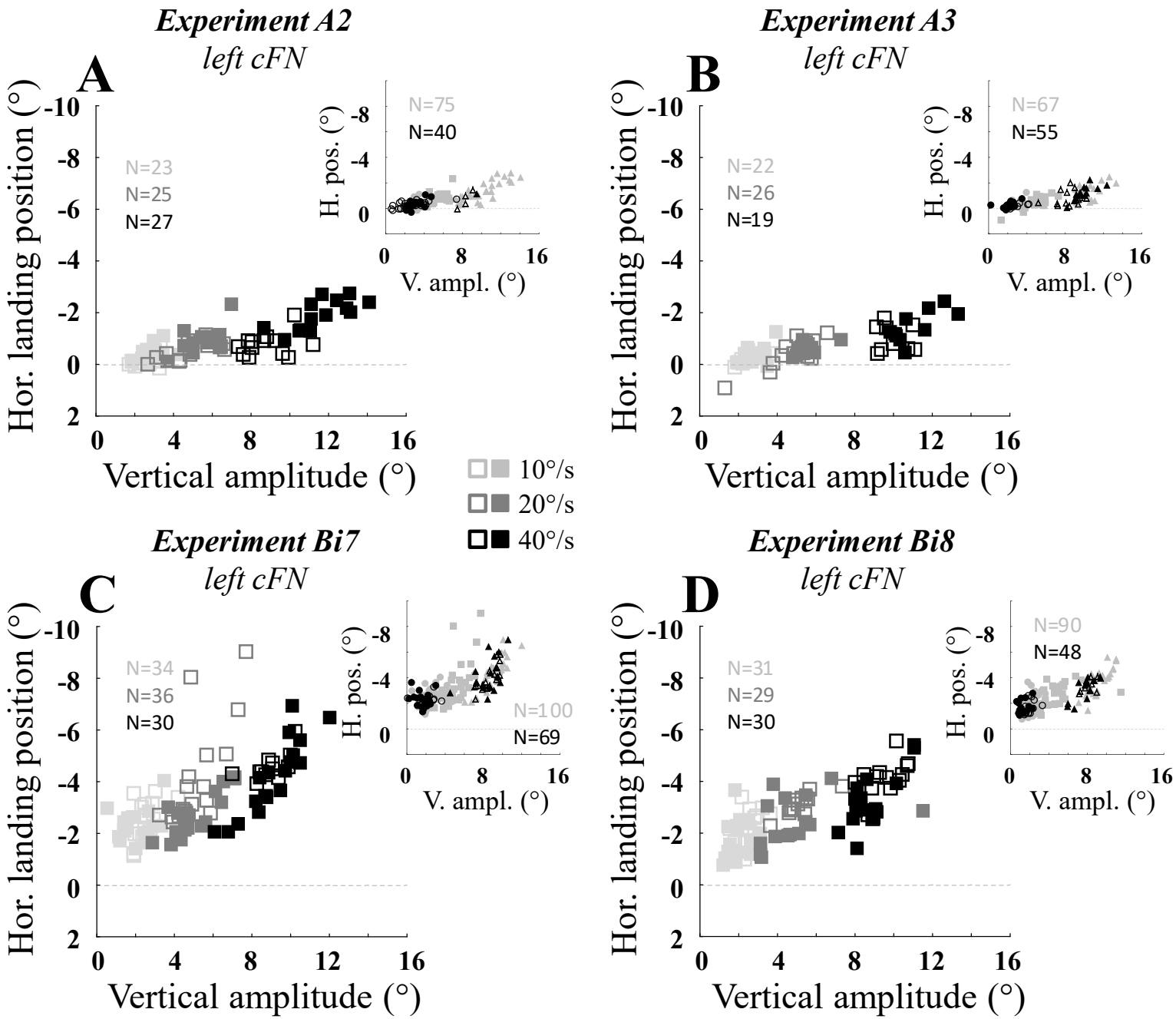
Experiment A2
left cFN
A
Experiment A3
left cFN
B
Experiment Bi7
left cFN
C
Experiment Bi8
left cFN
D
Hor. landing position (°)
Vertical amplitude (°)
H. pos. (°)
V. ampl. (°)
N=23
N=25
N=27
N=75
N=40
N=22
N=26
N=19
N=67
N=55
N=34
N=36
N=30
N=100
N=69
N=31
N=29
N=30
N=90
N=48
10°/s
20°/s
40°/s

Figure 9

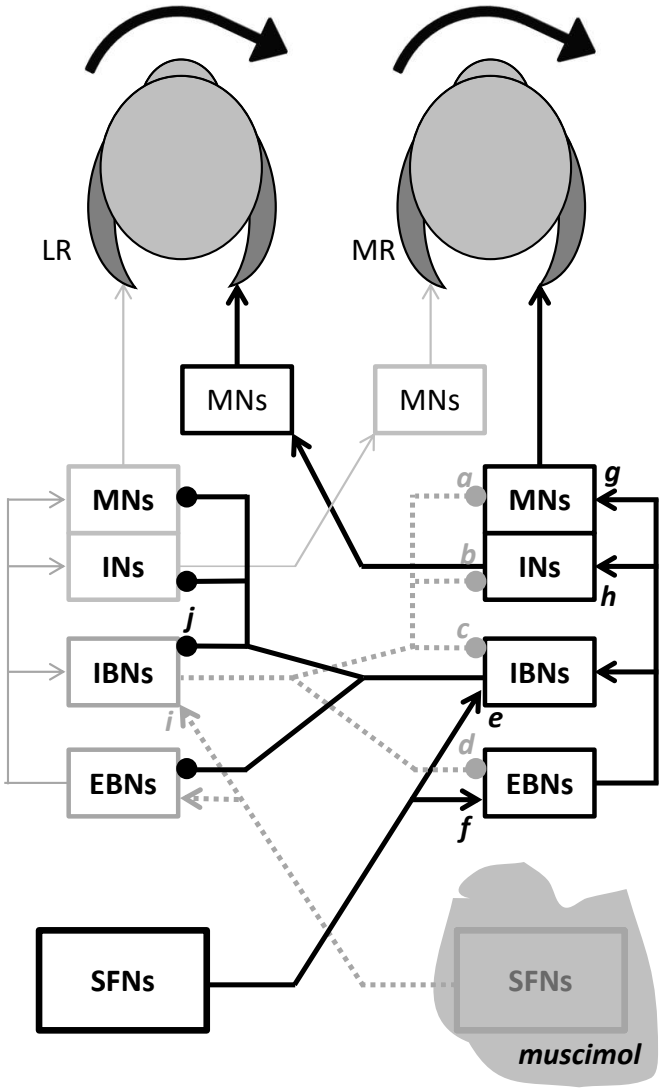
LR
MR
MNs
MNs
MNs
INs
IBNs
EBNs
MNs
INs
IBNs
EBNs
a
b
c
d
e
f
g
h
i
j
SFNs
SFNs
muscimol

Table 1

			10°/s				20°/s				40°/s			
Exp	injection		N	Y-int	slope	R^2	N	Y-int	slope	R^2	N	Y-int	slope	R^2
A1	Left cFN 1.0 µl	Amplitude	18	-0.2	-0.108	0.09 NS	**38**	**-0.0**	**-0.132**	**0.26***	**20**	**1.1**	**-0.239**	**0.48***
		Duration	18	-0.5	-0.001	0.001 NS	**38**	**0.3**	**-0.028**	**0.14***	**20**	**1.6**	**-0.067**	**0.52***
A2	Left cFN 0.5 µl	Amplitude	23	0.2	-0.185	0.15 NS	**25**	**0.7**	**-0.281**	**0.42***	**27**	**1.9**	**-0.327**	**0.65***
		Duration	23	-0.1	-0.009	0.01 NS	25	-0.2	-0.014	0.07 NS	**27**	**1.5**	**-0.065**	**0.17***
A3	Left cFN 0.3 µl	Amplitude	**22**	**0.4**	**-0.278**	**0.33***	**26**	**1.1**	**-0.328**	**0.66***	**19**	**1.7**	**-0.284**	**0.29***
		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	**15**	**2.5**	**-0.411**	**0.29***	28	1.5	0.044	0.00 NS	**18**	**5.7**	**-0.413**	**0.31***
		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	**26**	**0.6**	**0.252**	**0.18***	**24**	**0.5**	**0.207**	**0.26***	**26**	**-0.1**	**0.312**	**0.53***
		Duration	26	0.5	0.026	0.13 NS	24	0.8	0.019	0.11 NS	**26**	**-0.1**	**0.066**	**0.36***
Bi7	Left cFN 0.2 µl	Amplitude	**34**	**-1.6**	**-0.355**	**0.15***	**36**	**1.0**	**-0.889**	**0.41***	**30**	**2.6**	**-0.772**	**0.67***
		Duration	**34**	**-0.5**	**-0.078**	**0.28***	**36**	**3.2**	**-0.198**	**0.37***	30	-1.8	-0.066	0.09 NS
Bi8	Left cFN 0.2 µl	Amplitude	**31**	**-0.9**	**-0.522**	**0.18***	**29**	**-1.7**	**-0.209**	**0.18***	**30**	**2.7**	**-0.701**	**0.56***
		Duration	**31**	**0.1**	**-0.088**	**0.30***	**29**	**-0.5**	**-0.073**	**0.28***	**30**	**-0.6**	**-0.078**	**0.14***
Bi9	Right cFN 0.5 µl	Amplitude	**24**	**0.8**	**0.338**	**0.22***	**26**	**-0.2**	**0.576**	**0.34***	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	**28**	**-0.3**	**0.351**	**0.23***	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

			Accelerating target				Decelerating target			
Exp	injection		N	Y-int	slope	R^2	N	Y-int	slope	R^2
A2	Left cFN 0.5 µl	Amplitude	**35**	**0.0**	**-0.131**	**0.34***	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	**28**	**-0.0**	**-0.104**	**0.18***	**27**	**1.1**	**-0.233**	**0.31***
		Duration	**28**	**0.2**	**-0.016**	**0.15***	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	**24**	**0.7**	**0.215**	**0.29***	**27**	**0.4**	**0.231**	**0.39***
		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	**34**	**0.9**	**-0.581**	**0.34***
		Duration	35	-1.8	-0.019	0.04 NS	**34**	**-0.7**	**-0.088**	**0.25***
Bi8	Left cFN 0.2 µl	Amplitude	26	-1.4	-0.205	0.06 NS	**22**	**1.5**	**-0.594**	**0.55***
		Duration	**26**	**-0.4**	**-0.063**	**0.32***	22	-1.3	-0.052	0.10 NS
Bi9	Right cFN 0.5 µl	Amplitude	28	1.0	0.013	0.00 NS	**25**	**-0.3**	**0.310**	**0.33***
		Duration	28	1.0	0.002	0.00 NS	**25**	**0.7**	**0.039**	**0.17***
Bi10	Right cFN 0.2 µl	Amplitude	29	0.9	0.115	0.04 NS	**22**	**-2.2**	**0.537**	**0.12***
		Duration	29	0.7	0.016	0.04 NS	22	3.7	-0.04	0.05 NS