Head-Unrestrained Gaze Shifts After Muscimol Injection in the Caudal Fastigial Nuclei of the Monkey

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Quinet J, Goffart L. Head-unrestrained gaze shifts after muscimol injection in the caudal fastigial nucleus of the monkey. J Neurophysiol 98: 3269–3283, 2007. First published October 10, 2007; doi:10.1152/jn.00741.2007. The effects of unilateral cFN inactivation on horizontal and vertical gaze shifts generated from a central target toward peripheral ones were tested in two head unrestrained monkeys. After muscimol injection, the eye component was hypermetric during ipsilesional gaze shifts, hypometric during contralesional ones and deviated toward the injected side during vertical gaze shifts. The ipsilesional gaze hypermetria increased with target eccentricity until ~24° after which it diminished and became smaller than the hypermetria of the eye component. Contrary to eye saccades, the amplitude and peak velocity of which were enhanced, the amplitude and peak velocity of head movements were reduced during ipsilesional gaze shifts. These changes in head movement were not correlated with those affecting the eye saccades. Head movements were also delayed relative to the onset of eye saccades. The alterations in head movement and the faster eye saccades likely explained the reduced head contribution to the amplitude of ipsilesional gaze shifts. The contralesional gaze hypometria increased with target eccentricity and was associated with uncorrelated reductions in eye and head peak velocities. When compared with control movements of similar amplitude, contralesional eye saccades had lower peak velocity and longer duration. This slowing likely accounted for the increase in head contribution to the amplitude of contralesional gaze shifts. These data suggest different pathways for the fastigial control of eye and head components during gaze shifts. Saccade dysmetria was not compensated by appropriate changes in head contribution, raising the issue of the feedback control of movement accuracy during combined eye-head gaze shifts.

INTRODUCTION

Orienting the line of sight toward a visual target involves a saccadic movement of the eyes that can be accompanied by a movement of the head. Despite the fact that movements of the eyes and the head can be generated with relatively variable latencies and amplitudes and show different patterns of coordination (Freedman and Sparks 1997, 2000; Guitton and Volle 1987; Phillips et al. 1995; Zangemeister and Stark 1982), gaze shifts are astonishingly rapid and accurate.

The medioposterior cerebellum (MPC) is an important structure for controlling the accuracy of gaze shifts (for reviews, see Noda 1991; Pélisson et al. 2003). It consists of the vermal lobules VIc and VII (also called oculomotor vermis) and the caudal part of the two fastigial nuclei. The caudal fastigial nuclei (cFN) are major output nuclei by which the MPC can influence saccade generation. They receive inhibitory afferents from Purkinje cells in the oculomotor vermis (Yamada and Noda 1987) and mossy fiber input from the pontine and reticular medial nuclei (Gonzalo-Ruiz and Leichnetz 1990; Noda et al. 1990). On the efferent side, the cFN project to pontomedullary territories implicated in the generation of saccadic eye movements (Noda et al. 1990). In spite of the numerous studies in the head-restrained monkey that describe the discharge of saccade-related neurons in the caudal fastigial nuclei, the functional role of this activity is still enigmatic (Kleine et al. 2003; see also Fuchs et al. 1993; Ohtsuka and Noda 1991). Their inactivation by local injection of muscimol severely impairs the horizontal component of saccades aimed at visual targets: it is hypermetric (too large) for ipsilesional saccades and hypometric (too short) for contralesional ones, and vertical saccades are deviated toward the injected side with a magnitude that increases with saccade amplitude/duration (Goffart et al. 2004; see also Iwamoto and Yoshida 2002; Robinson et al. 1993).

Very few studies have examined the consequences of a cerebellar disorder on head-unrestrained gaze shifts. In experiments testing subjects suffering from cerebellar ataxia, Shimizu et al. (1981) observed that the hypermetria of gaze shifts was the same regardless of whether the head was restrained or unrestrained. Similarly, after an extensive lesion involving the fastigial nuclei and the posterior vermis in the monkey, Ritchie (1976) reported that the postlesional error of visually triggered gaze shifts was the same whether the head was immobilized or not. More recently, it has been shown that cFN inactivation in the head-unrestrained monkey rendered gaze shifts dysmetric and that the dysmetria was primarily and consistently due to dysmetric movements of the eyes (Quinet and Goffart 2005). This observation suggests that in primates, the cFN output essentially influences an oculomotor stage for the control of gaze accuracy, i.e., a functional stage which is situated after that gaze-related commands are decomposed into premotor commands for moving the eyes in the orbit and premotor commands for moving the head. This hypothesis is consistent with an anatomical study showing that fastigial neurons projecting to the peri-abducens region are located more caudally than those projecting to the neck motoneurons pool in the upper cervical C2 (Robinson et al. 1994). Thus the fastigial control of gaze shifts would involve different path-
ways for controlling the eye and head components of gaze shifts. This conclusion contrasts with an alternative hypothesis that was proposed based on observations made in head-unrestrained cat after muscimol injection in cFN. Here, gaze inaccuracy was due to dysmetric movements of the eyes in the orbits and of the head (Goffart et al. 1998). The lack of noticeable change in the coupling between the eye and head components suggested that the cat cFN affects gaze-related premotor commands before being decomposed into separate commands for moving the eyes in the orbit and the head. Moreover, in the head-unrestrained cat, it was shown that the error of ipsilesional horizontal gaze shifts was constant, irrespective of the target eccentricity, whereas the hypometria of contralesional gaze shifts was larger with more eccentric targets (Goffart and Pélisson 1994, 1997, 1998).

In our previous report (Quinet and Goffart 2005), the analysis was mostly restricted to the amplitudes of movements toward the most eccentric target (40°). No information was given about how the eccentricity influenced the dysmetria of gaze shifts or whether cFN inactivation also affected the dynamics of eye and head components or their coordination. In the present study, we complement this preliminary report by providing an extensive description of the effects of cFN inactivation on the accuracy, the velocity and the latency of horizontal and vertical gaze shifts aimed at different target eccentricities as well as on the coupling between their eye and head components.

**Methods**

Subjects and surgical procedures

Two adult rhesus monkeys (E and B, female and male weighing 5.7 and 8.8 kg, respectively) were used for this experiment. Two surgical procedures under isoflurane anesthesia and aseptic conditions were performed. First, a light titanium head post for immobilizing the head was secured with stainless steel screws and bone cement on the top front center of the skull. For the monitoring of eye movements, a three-turn magnetic search coil (Cooner Wire, AS 632) was sutured with silk (6–0 Ethicon) to the sclera under the conjunctiva of one eye. Leads were passed under the skin to a connector located on the top of the skull. For the monitoring of head movements, a similar coil was glued to a piece of plastic and fixed to the skull with bone cement (Palacos, Smith and Nephew). Training was initiated after full recovery. In a second surgical procedure, a craniotomy was made in the skull, and a recording chamber was stereotaxically implanted for inactivating the caudal part of the fastigial nucleus. The chamber was placed in the frontal plane, centered stereotaxically on the midline between the two fastigial nuclei (9 mm posterior and 7 mm above the interaural line), and tilted 20° to the right with respect to the sagittal plane (Goffart et al. 2004). The materials (head post, screws, chamber, and cement) that were added on the top of the head weighted ~60 g. All surgical procedures and experiments were in accordance with the guidelines from the French Ministry of Agriculture (87/848) and from the European Community (86/609/EEC).

Behavioral tasks

Animals were seated in a primate chair that prevented movements of the body without restraining movements of the head. The primate chair was fitted with foam cushions (front and back) that gently but firmly positioned the animal’s trunk in front of the target display. Gaze and head positions were measured with a phase angle detection system (CNC Engineering, 3-ft coil frame). Two phase detectors were used to independently record gaze and head angular deviations (hereafter called positions). Gaze position signals were calibrated by having the head-unrestrained animal fixate stationary targets that were placed ±20° horizontally or vertically. The head coil was first calibrated before placement on the top of the animal’s head using a gimbal and rotating the coil ±30° horizontally and vertically. This calibration was verified after the head coil was embedded in the bone cement by rotating the restrained head with the same angles.

Experiments were conducted in a dimly illuminated room (luminance = 0.05cd/m²) where the monkey faced a spherical array of light-emitting diodes (LEDs; 0.16° visual angle, luminance = 10.7cd/m²) that were all located at a distance of 110 cm from the midpoint between both eyes in the center of the magnetic fields. Each animal was trained to perform a saccade task that shifted gaze from a central (located straight ahead) LED toward a peripheral one. We only tested centrifugal eye-head gaze shifts from the straight ahead direction to compare ipsi- and contralesional eye-head gaze shifts starting from the same origin before and after pharmacological inactivation. The straight ahead direction was defined as the intersection between the mid-sagittal plane of the animal (vertical meridian) and the orthogonal horizontal plane passing through both eyes and the interaural line when the head was restrained (horizontal meridian). For each trial, a warning tone preceded the onset of the central LED. The monkey’s task was to maintain gaze within a spatial window around this central LED (3° radius) for a variable interval (1,000–2,000 ms varied in increments of 500 ms). After this interval, the central LED was extinguished, and after a gap interval of 200 ms, the peripheral LED was flashed for 100 ms (80% of the trials) or remained on for the duration of the trial (maintained LED). Reward was delivered after a fixation interval (>300 ms) within a spatial window around the peripheral LED (4–8° radius). The location of peripheral LEDs was pseudorandomly selected among several predefined positions along the horizontal meridian (8, 16, 24, 32, and 40° to the left or to the right of the central LED) or along the vertical meridian (8, 16, 24, and 32° above or below). In the head-unrestrained condition, the water reward was delivered via a lightweight (50 g) tubing system that neither obstructed the monkey’s vision nor impeded its head movements. This system was made of two lateral thin tubes that were attached to the head post and went down in front of each cheek before joining at a small Y-shaped plastic tubing piece in front of the mouth.

Because of the muscimol-induced dysmetria, several saccades were required to acquire the central LED and saccades toward the peripheral LED frequently terminated outside the acceptance window around it. Therefore the radius of the windows was increased after the injection (10–20 and 12–30° around the central and peripheral LEDs, respectively). Moreover, to increase the number of gaze movements aimed at the flashed peripheral LEDs, the percentage of trials with a maintained peripheral LED was reduced to <10% after muscimol injection. These latter trials provided the experimenters with a convenient visual feedback of the amount of dysmetria that impaired gaze shifts during the running of the experiment (because of the correction saccades that followed the primary gaze shift). The use of flashed targets was preferred to minimize the influence of visual feedback on the generation of gaze movements (see example in Goffart et al. 1998). In this article, the analysis was restricted to movements toward the flashed LEDs.

Muscimol injections

Before the injection of muscimol, the location of the saccade-related region of the fastigial nucleus was identified after several experimental sessions using electrophysiological recording and electrocorticography in the head-restrained and -unrestrained conditions. The caudal fastigial nuclei were located using the following criteria: presence of saccade-related neurons that discharged bursts of activity during omni directional saccades (Fuchs et al. 1993; Ohtsuka...
Localization of inactivation sites

After termination of all experiments (unit recording studies, microstimulation and pharmacological local injections), one animal (monkey B) was killed by an overdose of pentobarbital sodium and perfused transcardially with saline, followed by 10% formalin. Standard techniques were used to prepare 60-µm slices on a freezing microtome. Standard cresyl violet coloration was used to locate nuclei and guide-tube locations. The observation of electrode tracks in coronal sections (see arrows in Fig. 1) confirmed that our electrode penetrations were all made in the deep medial cerebellum. Some traces may appear more laterally; they are due to our preliminary mapping studies (see preceding text) and do not concern the present study. Muscimol injections in sites lateral to the cFN would not lead to a horizontal deviation of vertical saccades that would change in a symmetrical manner, e.g., from a leftward deviation to a rightward deviation when the injection site is located ~5 mm to the right. Indeed, the distance along the medio-lateral axis that separated the most eccentric injections toward the left and the right fastigial nucleus was 4.9 and 4.8 mm for monkeys B and E, respectively. In the other monkey (monkey E), histological reconstruction could not be made. Concerning the depth, the injections were made at the same depth as the depth of saccade-related responses. It is worth mentioning that one injection performed in monkey B led to a sudden fall in motivation (oculomotor behavior characterized by a strong reduction in the frequency of saccades and a preponderance of slow eye movements, very slow head movements in the head unrestrained condition) that rapidly turned into vertigo-like symptoms (pale face, nausea, and vomiting after the monkey returned inside its cage). Because the same observations were also made 2–3 h after some of the other injections, such symptoms were presumably due to a diffusion of muscimol toward the vestibulo-cerebellum (nodulus or uvula) situated ventrally relative to the saccade related fastigial region (see also Goffart et al. 1998 for similar observations made in the cat).
injection in the cFN (black, experiment E3). Before the injection and for both movement directions (Fig. 2: ipsilateral to the injected side, Fig. 3: contralateral), the amplitude of gaze shifts, eye saccades, and head displacements increased with target eccentricity. After muscimol injection, the amplitude of ipsilesional gaze and eye displacements was larger than during the control session (Fig. 2). The average change in gaze amplitude ($\Delta g$) gradually increased with target eccentricities ranging from 8 to 24° (increase from 0.7 to 3.2° and 3.8° for the 8, 16, and 24° targets, respectively) and then slightly declined with the most eccentric targets (2.8° for the 32 and 40° targets). The average change in eye amplitude ($\Delta e$) also increased with target eccentricity up to a maximum value of 5.7° for the 40° eccentric target. Contrary to eye saccades, the amplitude of ipsilesional head displacements did not increase but decreased after muscimol injection. Note that the decrease in head amplitude also happened during gaze shifts toward the 16 and 24° targets, i.e., targets that could be foveated with a single saccade.

For contralesional movements (Fig. 3), gaze shifts were hypometric after muscimol injection (negative values of $\Delta g$). The average amount of gaze hypometria increased with target eccentricity, from $-3.6^\circ$ for the 8° target to $-17.4^\circ$ for the 40° target. Similarly, the amplitude of eye saccades was reduced with a magnitude of hypometria that also increased with target eccentricity. The amplitude of contralesional head displacements was larger after muscimol injection, but this observation was not consistently made after each injection (see following text).

Figure 4 describes for each target the average changes in gaze ($F$) and eye ($E$) horizontal amplitude after six muscimol injections (monkey B: experiments B1, B3, and B5, monkey E: experiments E3, E1, and E5). These experiments were selected because they provided the largest datasets. Positive values of changes in amplitude indicate hypermetria, negative values hypometria. For targets ipsilateral to the injection side, (positive values of target eccentricity) and for each experiment, the hypermetria of gaze shifts and eye saccades increased with target eccentricity up to the 24° target. Then the changes in gaze amplitude declined with the most eccentric targets (32 and 40°). Interestingly, the hypermetria of eye saccades exceeded that of gaze shifts for these two targets (significant differences were found in B1, B3, E3, E1, and E5 for the 40° target and in B1, B3, B5, and E5 for the 32° target), indicating that the amplitude of the head contribution was diminished during these gaze shifts. The comparison between the top (monkey B) and bottom graphs (monkey E) in Fig. 4 also shows idiosyncratic differences in the amount of gaze hypermetria induced...
by cFN inactivation: the magnitude of gaze hypermetria was larger in monkey B than in monkey E. For contralateral targets (negative values of target eccentricity), Fig. 4 shows that the amount of eye and gaze hypometria increased with target eccentricity: larger amounts of hypometria were observed with more eccentric targets. The changes in gaze amplitude matched the changes in eye amplitude for nearly every target. For the most eccentric target (40°), there was a tendency for gaze hypometria to exceed the reduction in eye amplitude (see B3, B5, E1, and E5). And the paired comparison between the changes in gaze amplitude and the changes in eye amplitude confirmed this small but statistically significant difference (average difference $\pm$ SD).

Muscimol injection in the cFN also affected the amplitude of head movements. For movements generated toward the 40° target. Indeed, graph C in Fig. 5 shows that the reduction in head amplitude increased with target eccentricity for ipsilateral targets (positive values of target eccentricity). These reductions in head amplitude contrast with the increases in gaze and eye amplitude illustrated in Fig. 4. For contralesional movements (B), significant changes in head amplitude were observed in 6 of 10 experiments. But the changes were not consistent: the amplitude was increased in three experiments (e.g., E1, E3, and E4), decreased in three experiments (B3, B4, and B5), and unchanged in the others. The paired comparison between the changes in head amplitude and the changes in gaze amplitude confirmed this small but statistically significant difference (average difference $\pm$ SD).

To test whether the changes in head movements influenced the gaze dysmetria, we tested for each experiment, the correlation between the horizontal dysmetria of gaze shifts (difference between horizontal final gaze position and horizontal target position) and the head contribution to the horizontal amplitude of these gaze shifts. For ipsilesional gaze shifts, statistically significant correlations were only found in two experiments where the correlation coefficients were 0.94 (B2) and 0.74 (E4). For contralesional gaze shifts, the amount of

FIG. 3. Time course of the mean ± SE contralesional gaze (top), eye (middle), and head (bottom) displacements aimed at the different horizontal targets (8, 16, 24, 32, and 40°), before (gray) and after (black) muscimol injection in the left cFN of monkey E (experiment E3). The average changes in gaze ($\Delta_g$), eye ($\Delta_e$), and head ($\Delta_h$) amplitude are indicated on the figure. Number of averaged movements: 21, 26, 26, 23, and 27 (control), 11, 14, 11, 10, and 9 (muscimol) for the 8, 16, 24, 32, and 40° target, respectively. Tic marks indicate the ends of gaze shifts and head movements. The apparent slowing of gaze displacements (after the tic marks) toward the 32 and 40° targets was due to variable onset times of secondary (correction) saccades.
hypometria was correlated with the amplitude of the head contribution in only three experiments (E1, E3, and E4, \( r = 0.70, 0.74, \) and \( 0.64, \) respectively). The correlations were positive, indicating that gaze dysmetria increased when the head contribution increased.

**Changes in the dynamics of horizontal gaze shifts**

The postlesional changes in amplitude described in the preceding text were associated with modifications in movement kinematics. Figure 6A illustrates the effects of muscimol injection in the left cFN (experiment B1) on the velocity profiles of gaze (left), eye (middle), and head (right) movements for five individual ipsilesional gaze shifts aimed at the 40° and 32° LED targets. During the control session (---), gaze shifts toward the 40° eccentric target were extremely rapid with rather short durations [103 ± 14 (SD) ms] and high values of maximum velocities (706 ± 44, 646 ± 44, and 94 ± 12°/s for gaze shifts, eye saccades, and head movements, respectively). Maximum velocities of movements toward the 32° target were also very high: 697 ± 81, 633 ± 68, and 87 ± 24°/s. After muscimol injection (—), the peak velocities of ipsilesional gaze shifts were significantly increased for both target eccentricities (14 and 17% increase for the 40 and 32° target, respectively). Similar increases were observed in eye velocity (19 and 23% increases). Like their amplitude (which was diminished), the peak velocity of ipsilesional head movements was reduced after muscimol injection, decreasing from 94 ± 12 to 58 ± 18°/s (38% change) for the 40° target and from 87 ± 24 to 47 ± 22°/s (46% change) for the 32° target.

Concerning contralesional movements recorded during the same experiment (Fig. 6B), reductions in the horizontal peak velocity were observed in gaze shifts (20 and 21% decrease for...
the 40 and 32° target, respectively) and eye saccades (21% decrease for both targets), whereas the head peak velocity was increased (14 and 32% increase) after muscimol injection.

The consistency of these changes in eye and head velocity was tested across all experiments. Figure 7 plots the average postinjection eye (A) and head (B) peak velocities against the preinjection values for ipsilesional (left) and contralesional (right) movements toward the 40° targets. After muscimol injection, the eye peak velocity of ipsilesional gaze shifts was significantly changed in 6 of 10 experiments (increase in B1, B2, B3, E1, E3, and E4), whereas the head peak velocity was reduced in nearly every experiment (reduction did not reach statistical significance in E3). Note that reductions in head peak velocity also happened even when the eye peak velocity did not significantly change (e.g., B4, B5, E2, and E5). The paired comparison between the control and postinjection average values revealed a significant increase in eye peak velocity (difference = 72 ± 51°/s, 12% increase) and decrease in head peak velocity (difference = −40 ± 15°/s, 47% decrease) after muscimol injection in the cFN. There was no correlation between the changes in eye peak velocity and the changes in head peak velocity (r = 0.38, P value = 0.27). For contralesional movements, significant decreases in eye peak velocity were observed in all experiments (average reduction = −247 ± 94°/s, 40% decrease), whereas significant reductions in head peak velocity were observed in only four experiments (E2, B3, B4, and B5). Nevertheless, the paired comparison between the control and postinjection average values revealed a significant decrease in the head peak velocity (difference = −16 ± 17°/s, 20% decrease) after muscimol injection. Again, there was no correlation between the changes in eye peak velocity and those in head peak velocity that affected contralesional movements.

![FIG. 6. Velocity profiles (n = 5 per target) of the horizontal gaze shifts (left), eye saccades (middle), and head movements (right) produced before (- - -) and after (—) a muscimol injection in the left cFN (experiment B1). A: ipsilesional movements. B: contralesional movements. The peripheral light-emitting diode (LED) was located 40° (top) or 32° (bottom) horizontally. Data are aligned on gaze shift onset.](http://jn.physiology.org/Downloadedfrom)
sional movements ($r = -0.01$, $P$ value = 0.98). Reductions in eye peak velocity happened even when the head peak velocity did not change significantly ($B1$, $B2$, $E1$, $E3$, $E4$, and $E5$).

The increases in eye peak velocity observed in ipsilesional saccades (Fig. 7A, left) suggest that cFN inactivation changed their acceleration phase (acceleration phase defined as the period unfolding from saccade onset to peak velocity time). Indeed, the hypermetria of ipsilesional saccades toward the $40^\circ$ target was associated with a significant increase in the amplitude of the eye displacement during the acceleration phase (difference $= 1.6 \pm 2.0^\circ$, 20% increase) as well as during the deceleration phase (average difference $= 5.2 \pm 4.3^\circ$, 25% increase, not shown), whereas the duration of acceleration and deceleration phases did not significantly change (acceleration: $P$ value $= 0.57$, deceleration: $P$ = 0.24). This change during the acceleration phase was not observed by Goffart et al. (2004): the hypermetria of ipsilesional saccades was primarily due to an increase in eye amplitude during the deceleration phase (no significant change in amplitude during the acceleration phase).

To test whether this new observation was due to the different sizes of tested saccades ($12^\circ$ in Goffart et al. 2004 vs. $40^\circ$ here), the same analysis was performed on gaze shifts aimed at the $16^\circ$ target. For those smaller movements, the horizontal amplitude of ipsilesional eye saccades was consistently increased in all experiments (average change $= 7.1^\circ$, 51% increase). The amplitude of eye displacement during the acceleration phase was significantly increased in 6 of 10 experiments (average change $= 1.7^\circ$, 28% increase), whereas the amplitude during the deceleration phase was increased in 9 experiments (average change $= 5.6^\circ$, 70% increase). Again, the eye peak velocity was significantly increased after cFN inactivation in 7 of 10 experiments (average change $= 68^\circ/s$, 10% increase). Finally, this increase in eye peak velocity was not due to the fact that the head was unrestrained (contrary to the study by Goffart et al. 2004) because an enhanced eye peak velocity (average difference $= 60 \pm 96^\circ/s$, 10% increase) was also observed in ipsilesional saccades generated toward the $16^\circ$ target with the head restrained. Thus after cFN inactivation, changes in eye amplitude can occur during both the acceleration and the deceleration phases of ipsilesional gaze shifts.

In the preceding paragraphs, comparisons were made between pre- and postinjection movements directed toward the same target. Ipsilesional saccadic eye movements were shown to be hypermetric and faster (increased peak velocity) and contralesional saccades hypometric and slower (reduced peak velocity). In normal conditions (prelesional), it is well known that the peak velocity and the duration increase with the size of saccades/gaze shifts (e.g., Fuchs 1967; Tomlinson and Bahra 1986). The question that we address now is whether the postinjection movements followed the same relationship (also called main sequence relationship) (Bahill et al. 1975) as the one describing control movements or whether they were generated with different kinematics.

Figure 8 shows the relationships between the amplitude and peak velocity of gaze shifts (A), eye saccades (B), and head movements (C) for two experiments ($B1$ and $E3$: muscimol injection in the left cFN). These experiments were selected because they provided the largest number of responses ($B1$: 77 ipsilesional and 75 contralesional movements; $E3$: 58 ipsilesional and 55 contralesional movements). Similar observations were made in the other experiments. For ipsilesional movements (positive values of amplitude), the comparison between the control (○) and postinjection (●) movements with matched amplitudes shows that the peak velocity of gaze shifts and eye saccades were slightly faster after muscimol injection, whereas the peak velocity of head movements matched relatively well with those observed during the control sessions. When eye saccades with matched amplitude were compared ($monkey B$: $28.4 \pm 0.9^\circ$, $n = 21$ control saccades vs. $28.9 \pm 0.8^\circ$, $n = 10$ postinjection saccades; $monkey E$: $21.9 \pm 0.9^\circ$, $n = 28$ vs. $22.5 \pm 1.2^\circ$, $n = 17$; nonstatistically significant differences in amplitude), the postlesional peak eye velocities were significantly larger than the control values ($monkey B$: $784 \pm 64$ vs. $624 \pm 69^\circ/s$; $monkey E$: $547 \pm 51$ vs. $443 \pm 51^\circ/s$, corresponding to 25 and 23% increases in peak velocity). In contrast, for contralesional movements (negative values of amplitude), a marked reduction in peak velocity was observed for gaze shifts and eye saccades of matched amplitude while the relationship between amplitude and velocity for head movements (main sequence) did not show such a clear-cut difference after muscimol injection.

These changes in the amplitude/peak velocity relationships of gaze shifts and eye saccades were paralleled by changes in the amplitude/duration relationships. In Fig. 9, the duration of gaze shifts (A), eye saccades (B), and complete head movements (C) was plotted against their amplitude for movements recorded before (○) and after (●) muscimol injection (same experiments as in Fig. 8). Large ipsilesional eye saccades were slightly shorter in duration than prelesional ones (B): when ipsilesional eye saccades with matched amplitude were compared (same set of saccades as in the preceding text), the postinjection durations were significantly shorter than the con-
In addition to altering their amplitude and velocity, muscimol injection in the cFN also affected the coupling between the eye and the head during horizontal gaze shifts. In a previous report (Quinet and Goffart 2005), we showed that after muscimol injection in the cFN, the amplitude of eye saccades generated during ipsilesional gaze shifts was consistently increased while the amplitude of the head contribution was consistently reduced. Such opposite effects on the amplitude of eye and head movements suggest changes in the relative amount that these two components contribute to the amplitude of ipsilesional gaze shifts. For contralesional gaze shifts, the parallel changes in the amplitude of the eye saccades and in the head contribution would also lead to modifications in the eye-head coupling if the ratios of changes affecting the eye and head components were different. Figure 10 shows the effect of muscimol injection on the head contribution to the amplitude of gaze shifts in four experiments (B1, B3, E1, and E3). During both control (○) and muscimol (●) sessions, the control values (monkey B: 79 ± 9 vs. 93 ± 19 ms; monkey E: 75 ± 16 vs. 89 ± 9 ms, both corresponding to 15% decreases in duration). For contralesional movements, a marked increase in duration was observed in gaze shifts and eye saccades but not in head movements. The same observations were made in the other experiments.

In summary, when compared with control movements of similar amplitude, contralesional gaze shifts were slower, i.e., they had a lower peak velocity and a longer duration. The reduction in gaze peak velocity was due to a diminished eye velocity since the head peak velocity was relatively unchanged. Ipsilesional gaze shifts did not show changes in peak velocity as apparent as those affecting contralesional movements, presumably because they had already reached high velocity values. Significant changes in peak velocity and in duration were observed in ipsilesional saccadic eye movements while the amplitude/peak velocity and amplitude/duration relationships were relatively unaffected for head movements.
The comparison between control and postinjection movements of matched amplitudes shows that for gaze shifts >20°, the head contribution after muscimol injection was smaller for ipsilesional gaze shifts (positive values of gaze amplitude) and larger for contralateral ones (negative values of gaze amplitude) than that observed during the control sessions. It is noteworthy that the reduction in head contribution during ipsilesional gaze shifts is consistent with the reductions in head peak velocity and amplitude described in the preceding text (Figs. 5 and 7).

Another important aspect of the coordination between the eye and head components concerns the delay between their respective onsets. Indeed, changes in the head contribution to the amplitude of gaze shifts could be due to changes in the onset of head movements relative to the onset of eye saccades (which also corresponds to the onset of gaze shifts). Specifically, a later onset of the head movement relative to the saccade onset could also account for the reduced head contribution to the amplitude of ipsilesional gaze shifts. Similarly, an earlier onset of the head movement relative to the saccade onset could account for the increased head contribution during contralateral gaze shifts. The latency of eye saccades and head movements (relative to the target appearance) and the eye-head delay were then calculated for each experiment. Figure 11 plots the postlesional average values against the prelesional values for ipsilesional (A) and contralateral (B) gaze shifts aimed at the 40° targets. During the control sessions, the average latencies were similar between ipsi- and contralateral eye saccades (146 ± 15 vs. 149 ± 29 ms) and between ipsi- and contralateral head movements (121 ± 15 vs. 125 ± 19 ms). The fact that the head onset preceded eye onset was observed in both monkeys. In monkey B, the average eye saccade latency was 148 ± 14 ms, whereas the average head latency was 128 ± 19 ms (average values for both directions). In monkey E, the latencies were 135 ± 19 ms (eye) and 118 ± 15 ms (head). After muscimol injection, the latency of ipsilesional eye saccades was significantly changed in 5 of 10 experiments (increase in B3, decrease in B1, E3, E4, and E5), whereas that of contralateral eye saccades was changed in only 3 experiments (increase in B2 and E4, decrease in E3). For head movements (middle), their latency was significantly changed in three experiments (increase in B2—B4) for ipsilesional movements and in five experiments for contralateral movements (increase in B1, B2, B5, and E4, decrease in E3).

Because of these inconsistent changes, we did not find significant changes in the latency of eye saccades (differences = 3 ± 28 and 14 ± 27 ms for ipsi- and contralateral movements, respectively) or head movements (differences = 24 ± 32 ms) when comparing pairwise the control and postinjection average latencies. For the eye-head delay (difference between the onset of the eye saccade and the onset of the head movement), positive values indicating that the head started moving before the eye saccade, the head moved on average 26 ± 15 ms before the eye during the control session. After muscimol injection, significant changes in eye-head delay of ipsilesional movements were observed in seven experiments. For six of those experiments (B1—B4, E4, and E5), the delay was significantly reduced, whereas in the last one (E1), it was increased. The paired comparison between the average pre- and postlesional values revealed a significant change in eye-head delay (difference = −23 ± 24 ms). Thus the onset of head movements became significantly delayed relative to the onset of eye saccades, a result that is consistent with the reduced contribution of the head during ipsilesional gaze shifts. Note that this change in eye-head delay does not fully account for the reduced head contribution to the amplitude of ipsilesional gaze shifts. Indeed, a reduction in head contribution was observed in E3 and E1 (see Fig. 10, bottom), whereas the eye-head delay either did not show any significant change (E3) or even increased (E1). For contralateral gaze shifts, significant changes in eye-head delay were observed in four experiments (E2—E5), but the paired comparison between the pre- and postlesional values failed to reveal a consistent change after muscimol injection (difference = −8 ± 15 ms).

**Vertical gaze shifts**

Figure 12 shows the time course of typical gaze (A and B and E and F) and head (C and D and G and H) movements recorded in response to a target appearing 32° up- and downward before (---) and after muscimol injection (——) in the cFN (experiments B6 and E1). First the vertical amplitude of upward gaze shifts was smaller after muscimol injection than during the...
control session (average difference in amplitude = $-10^\circ$ for B6 and $-2.9^\circ$ for E1). The same decrease in amplitude was observed in a third experiment where vertical targets were used (E5, data not shown, average decrease = $-2.9^\circ$). The vertical amplitude of downward gaze shifts was increased in B6 (average difference in amplitude = $1.7^\circ$) and E1 ($2.4^\circ$) but not in E5 ($-0.8^\circ$). Second, the trajectory of postinjection vertical gaze shifts was deviated toward the injected side. Interestingly, this ipsilesional deviation of gaze shifts only affected the eye saccades and not the accompanying head movements. There was no sign that the head would deviate toward the contralateral side to compensate for the ipsipulsion of vertical eye trajectory. Note the lack of change in horizontal head position after muscimol injection in graphs D and H. Finally, analysis of the vertical and horizontal amplitudes of head movements did not show any significant change for upward and downward movements.

The ipsilesional deviation of eye saccade increased with target eccentricity, like in the head-restrained condition (Goffart et al. 2004; Iwamoto and Yoshida 2002). Figure 13 shows the horizontal final error (mean ± SD) of gaze shifts directed toward targets located at different eccentricities along the vertical meridian (positive values correspond to upward targets, negative values to downward ones) before (○) and after (●) muscimol injection in the cFN (A: experiment B6, B: experiment E1). Before the injection, the horizontal final error
(horizontal distance between the final gaze position and target position) was close to zero (average value = 0.4 ± 1.7° and 1.0 ± 1.5° for experiments B6 and E1, respectively). After muscimol injection, vertical gaze shifts were deviated toward the injected side and missed the target with a horizontal final error that increased with target eccentricity. In experiment B6 (injection in the left cFN), the horizontal error was leftward (negative value), whereas in the experiment E1 (injection in the right cFN), it was rightward (positive value). Significant correlations were found between the magnitude of the horizontal final error and the vertical target eccentricity (upward targets: r = −0.83 and 0.68, downward targets: r = 0.76 and −0.82 for experiments B6 and E1, respectively).

**Discussion**

To complement our previous report (Quinet and Goffart 2005), the present study further describes the effects in the monkey of inactivating the cFN on the accuracy, velocity, and latency of eye and head components during head-unrestrained gaze shifts. It is shown that after local injection of muscimol, the hypermetria of ipsilesional saccades increased with target eccentricity until ~24° after which it diminished and became smaller than the hypermetria of the eye component (Figs. 2 and 4). Contrary to eye saccades the amplitude and peak velocity of which were enhanced, the amplitude and peak velocity of head movements were reduced after cFN inactivation (Figs. 5 and 7). These changes in head amplitude and peak velocity were not correlated with those affecting the eye saccades. Head movements were also delayed relative to the onset of eye saccades (Fig. 11). These alterations in head movement and the faster eye saccades likely accounted for the reduced contribution of the head to the amplitude of ipsilesional gaze shifts (Fig. 10). Contralesional gaze shifts undershot the target with a hypometria that increased with the eccentricity of the target (Figs. 3 and 4). Within the range of targets used, most of the gaze hypometria was due to hypometric saccadic movements of the eyes (Fig. 4) (see also Quinet and Goffart 2005). Contralesional movements were characterized by reductions in eye and head peak velocities that were not correlated either (Fig. 7). When compared with control movements of similar amplitude, contralesional eye saccades were much slower (lower peak velocity and longer duration, Figs. 8 and 9). This saccade slowing probably accounted for the observed increase in head contribution to the amplitude of contralesional gaze shifts (Fig. 10). Finally, vertical gaze shifts were deviated toward the injected side (without change in head trajectory, Fig. 12) and missed their target with an error that increased with the eccentricity of the target (Fig. 13).

**Comparison with studies in the head-restrained monkey**

Previous experiments in the head restrained monkey have shown that muscimol injection in the cFN impaired the horizontal component of saccades: the horizontal component becomes hypermetric for ipsilesional saccades and hypometric for contralesional ones (Goffart et al. 2004; see also Iwamoto and Yoshida 2002; Ohtsuka et al. 1994; Robinson et al. 1993). In the study of Goffart et al. (2004), it was shown that ipsilesional saccades were associated with an increase in the amount that the eyes moved during the deceleration phase without consistent change in the amplitude during the acceleration phase. There was neither consistent change in eye peak velocity nor in eye amplitude during the acceleration phase. In another study, Robinson et al. (1993) found a significant increase in the velocity of ipsilesional saccades, suggesting changes in eye amplitude also during the acceleration phase. Unfortunately, this velocity increase is difficult to interpret because of the admixture of centripetal and centrifugal saccades in their summary data. Indeed, several studies report that centripetal saccades are faster than centrifugal ones (Collereijn et al. 1988; Koene and Erkelens 2002; Pélisson and Prablanc 1988; Rottach et al. 1998). The increase in peak velocity reported by Robinson and colleagues could be due to a larger proportion of centripetal saccades than of centrifugal ones. In the present study, when pre- and postinjection centrifugal saccades toward the same target were compared, we find that the peak velocity and amplitude of the acceleration displacement were also increased for ipsilesional eye saccades, whether the head was restrained or not. These observations indicate that the ipsilesional hypermetria can result from a perturbation occurring during both acceleration and deceleration phases. A perturbation affecting the acceleration of ipsilesional saccades questions the “push-pull” hypothesis according to which the saccade-related burst from neurons in the contralateral cFN helps accelerate saccades whereas the burst from neurons in the
ipsilateral cFN helps decelerate or stop them (Fuchs et al. 1993; Ohtsuka and Noda 1991). The increases in eye peak velocity and in acceleration amplitude imply that the burst emitted by saccade-related neurons in the ipsilateral cFN does not only influence the deceleration of saccades but also their acceleration. Interestingly, a unit recording study (Kleine et al. 2003) based on a large number of neurons (n = 75) did not show such a clear difference in timing between the burst generated by saccade-related neurons in the cFN ipsilateral to the direction of the impending saccade and the burst emitted by neurons in the contralateral cFN. Examination of the latency of the onset and peak discharges showed not only considerable overlap between the ipsi- and contralateral bursts but also ipsilateral bursts that occurred relatively early relative to saccade onset (see their Fig. 8). These discharge properties and the changes in the acceleration of ipsilesional saccades reported in the present study are compatible with the hypothesis of a “bilateral” (rather than “push-pull”) mechanism by which the activity from saccade related neurons in both cFN regulates the balance between the inhibitory and excitatory input to the ocular motoneurons pool (see Fig. 10 in Goffart et al. 2004; see also Goffart 2007; Sparks and Barton 1993). In this hypothesis, the increase in eye peak velocity would be due to the removal by cFN inactivation of an inhibition that contralateral inhibitory burst neurons (off-direction burst) exert on motoneurons innervating the agonist muscles. For contralesional movements, Goffart and colleagues (2004) showed that the contralesional hypometria was mostly due to a reduction of eye amplitude during the acceleration phase (no consistent change in the amplitude during the deceleration phase). The present study extends these findings to the head unrestrained condition: the peak velocity of eye saccades and the duration of their acceleration phase (not shown) were also reduced after unilateral inactivation. These reductions could result from two mechanisms: the suppression of a driving influence exerted by saccade-related fastigial neurons on excitatory (EBN) and inhibitory burst neurons (IBN) located in the contralateral ponto-medullary reticular formation and the burst generated by saccade-related neurons in the unaffected cFN. The latter would lead to an inhibition of the agonist MNs and to an excitation of antagonist MNs, respectively, through their projections to EBN and IBN located in the ponto-medullary reticular formation contralateral to the saccade direction.

Fastigial control of head-unrestrained gaze shifts

Some experiments in monkeys (Ritchie 1976), humans (Shimizu et al. 1981), and cats (Goffart and Pélisson 1998; Goffart et al. 1998; Pélisson et al. 1998) have tested head-unrestrained gaze shifts during cerebellar dysfunction. In the study of Ritchie (1976), gaze shifts were measured in both head-restrained and -unrestrained conditions after an extensive lesion involving the cFN and the oculomotor vermis. The postlesional error was the same whether or not the head was immobilized. Similarly, in experiments testing subjects suffering from cerebellar ataxia, Shimizu et al. (1981) observed that the hypometria of gaze shifts was the same between the head-restrained and -unrestrained conditions. In experiments conducted in the head-unrestrained cat, no comparison was made between head-restrained and -unrestrained gaze shifts after cFN inactivation. However, the constant horizontal error of ipsilesional gaze shifts and the minor, if any, changes in the contribution of the head to the amplitude of gaze shifts (Goffart et al. 1998) suggested a similar hypometria regardless of the amount of head contribution. Our results in the head-unrestrained monkey are also compatible with the results of those experiments. Indeed, in most experiments, we did not find any correlation between the amount of gaze hypometria and the amplitude of the head contribution. In only two experiments (B2 and E4), the correlation was positive: the amount of gaze hypometria increased when the amplitude of the head contribution increased.

During ipsilesional gaze shifts, a decrease in head contribution was observed together with an increase in eye amplitude (Figs. 2 and 4) (see also Quinet and Goffart 2005). Such opposite effects might suggest that the head motor system tried to compensate for the increase in eye amplitude to limit the amount of gaze hypometria. Two arguments lead us to consider that this was not the case and that instead, the perturbations that affected the eye saccades and the head movements were functionally independent. First there was no correlation between the postlesional changes in gaze amplitude and those in head contribution (Quinet and Goffart 2005). Second, during each control session, negative correlations were found between the head contribution and the eye amplitude of gaze shifts toward the 32 and 40° targets (head contribution decreased when eye amplitude increased). After cFN inactivation, this relationship disappeared (not shown). For ipsilesional gaze shifts, the amplitude of eye saccades was increased without a proportional change in the amount of head contribution (loss of correlation between the 2 components). Ipsilesional gaze shifts were hypometric because and only because the amplitude of saccadic eye movements was increased. Rather than attempt to compensate for the hypometria of the eye saccades, the reduction in head contribution corresponded to a deficit in generating head movements that was independent of the eye dysmetria and also responsible for the reduction in the amplitude of complete head movements. Thus depending on the changes that affected the amplitude of eye saccades and head contributions, ipsilesional gaze shifts were hypometric (most frequent observation), normometric or even hypometric (see examples in Quinet and Goffart 2005).

For contralesional movements, there was no correlation between the amount of gaze hypometria and the amplitude of the head contribution. After cFN inactivation, the amplitude of contralesional eye saccades was decreased without significant change of the head contribution. Like the deficit affecting ipsilesional gaze shifts, contralesional were hypometric because of hypometric eye saccades, a hypometria that was not compensated by increases in the amplitude of the head contribution. In contrast, when the most eccentric target (40°) was used, the gaze hypometria tended to exceed that of the eye, suggesting a reduction (instead of an increase) in head contribution (Fig. 4). The magnitude of this reduction was small (~1°), and future studies might reveal a more pronounced decrease in head contribution during gaze shifts larger than those we tested here. Similarly, during vertical gaze shifts, the ipsilesional deviation of the eyes in the orbit was not compensated for by a movement of the head toward the contralateral side (Fig. 12). These absences of compensation during ipsilesional, contralesional, and vertical gaze shifts raise the issue of the feedback control of gaze shifts accuracy (Guitton 1992;
Sparks 1999). They indicate that cFN inactivation impaired neural elements that are part of the feedback paths or located downstream from them. Interestingly, the analysis of how the vertical component reacted to the changes in the horizontal component during head-restrained oblique saccades suggests that both cases might happen (Goffart et al. 2005). Indeed, during ipsilesional oblique saccades, the duration of the vertical component was increased in correlation with the increase in horizontal duration, indicating that the vertical saccade generator was “informed” of the changes that affected the horizontal component. Whereas during contrallesional oblique saccades, such correlated changes were not observed, suggesting a perturbation downstream from the feedback loop controlling the eye displacement (see also Noda et al. 1991). Thus during any saccade, activity in the ipsilateral cFN would influence the gain of the feedback path estimating the horizontal eye displacement, whereas activity in the contralateral cFN would influence elements located downstream from the feedback loop. The fact that the head did not compensate for the eye dysmetria during ipsilesional or vertical gaze shifts indicates either that muscimol injection disrupted the head compensatory mechanism or that the feedback control does not involve a single gaze controller.

Finally, our study provides several lines of evidence indicating that the control of eye and head movements involves separate population of neurons in the fastigial nucleus. Indeed muscimol injection in the cFN affected the eye and head movements in different manners. For example, during ipsilesional movements, the amplitude of eye saccades was increased, whereas that of head movements was reduced. For both ipsi- and contrallesional movements, the changes that affected the amplitude and peak velocity of eye saccades were not correlated with the changes altering head movements. Moreover, no change was found in the main sequence of head movements, but this relation was severely altered for contrallesional eye saccades. This independent control of eye and head movements by the fastigial nucleus is also corroborated by results from two other studies. First, an anatomic study showed that fastigial neurons projecting to the peri-abducens region are located more caudally than those projecting to the neck motoneurons pool in the upper cervical C2 (Robinson et al. 1994). Second, during electrical microstimulation of the fastigial oculomotor region, saccadic eye movements were mostly evoked and rarely accompanied with head movements (Quinet and Goffart 2007). Presumably, the changes in head movements reported in our inactivation study result from a diffusion of muscimol toward a head related region rostral to the saccade-related region.

To date, only one group has examined in the monkey the discharge of saccade-related fastigial neurons during head-unrestrained gaze shifts (Brettler et al. 2003). Preliminary results showed that for gaze shifts of 20°, some neurons exhibited a presaccadic burst for contralateral gaze shifts and a burst near the onset of ipsilateral movements. For larger movements (60°), their discharge occurred later during both ipsi- and contralateral movements, suggesting a participation in terminating ipsi- and contralateral gaze shifts. During these large gaze shifts, the peak velocity was followed either by a velocity plateau or by a second reacceleration (Freedman and Sparks 1997). Brettler and colleagues suggested that this late burst emitted during contralateral movements helped to stabilize gaze velocity or contributed to the generation of a second peak velocity (however, see Gandhi 2007 for blinks as a possible origin of 2nd peaks). According to Brettler and colleagues, and assuming that most neurons in the cFN behave similarly, the burst would help to prolong the eye component of gaze shifts, and its suppression by local injection of muscimol should affect the late part of contrallesional gaze shifts and cause their hypometria. Yet, an alternative explanation is possible. The hypometria of the eye saccade after cFN inactivation may not be due to the suppression of neural activity but instead to the remaining activity, and more particularly to the burst generated by the unaffected cFN, as proposed during saccades generated in the head restrained condition (Goffart et al. 2004). Finally, it is worth noting that although gaze shifts tested in our study were smaller in amplitude (~40° amplitude gaze shifts before the injection of muscimol) than those described by Brettler et al., the changes in the peak velocity and in the duration of the acceleration phase can hardly be explained by removing bursts controlling the termination of saccades.

**Conclusion**

In the primate orienting its gaze toward small visual targets, inactivation of the cFN by local injection of muscimol differentially affects the eye and head components of gaze shifts leading to severe changes in their coupling. The observed deficits corroborate the hypothesis that the fastigial control of gaze shifts involves different pathways for controlling their eye and head components. Unit recording studies are required to verify that the fastigial nuclei house separate eye- and head-related neurons and examine whether they contain gaze (i.e., eye+head)-related neurons that our inactivation study could not reveal.

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