Deficits in Saccades and Fixation During Muscimol Inactivation of the Caudal Fastigial Nucleus in the Rhesus Monkey

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Goffart, Laurent, Longtang L. Chen, and David L. Sparks. Deficits in saccades and fixation during muscimol inactivation of the caudal fastigial nucleus in the rhesus monkey. J Neurophysiol 92: 3351–3367, 2004. First published June 30, 2004; doi:10.1152/jn.01199.2003. The caudal fastigial nucleus (cFN) is a major nucleus by which the cerebellum influences the accuracy of saccades. In head-restrained monkeys generating saccades from a fixation light-emitting diode (LED) toward a flashed target LED, we analyzed the effects of unilateral pharmacological inactivation of cFN on horizontal, vertical, and oblique saccades. When animals were viewing the fixation LED, usually after one or more correction saccades, the positions of the eyes were slightly offset in comparison with the positions maintained before the injection (average offset = 1.1°). The offset was ipsilateral to the injected side and did not depend on the target location. The horizontal component of all ipsilesional saccades was hypermetric and associated with a 32–42% increase in the amplitude of the deceleration displacement without significant change in the amplitude of the acceleration displacement. The horizontal component of all contralesional saccades was hypometric and associated with a decrease in the peak velocity and in the acceleration component of all contralesional saccades. The horizontal offset was deviated toward the injected side. They missed the target with an error that depended on saccade duration or amplitude. If any, the effects of muscimol injections on the vertical component of oblique saccades were very small. The changes in fixation and the dysmetria are both viewed as consequences of an impairment in the cFN bilateral influence on the burst neurons located in the left and right brain stem.

INTRODUCTION

Orienting the line of sight toward a visual target requires a transformation of target-related retinal signals into commands to move the eyes and sometimes also the head. The medioposterior cerebellum, consisting of the lobules VIc–VII in the vermis and the two caudal fastigial nuclei, is an important brain region for this visuomotor behavior. Lesion of this region severely impairs the accuracy of orienting gaze shifts (for review, see Pelisson et al. 2003; Robinson and Fuchs 2001). In the head-restrained monkey, the unilateral disinhibition of neuronal activity in the caudal fastigial nucleus (cFN) by local injection of bicuculline (Sato and Noda 1992) renders saccades toward the disinhibited side hypometric and saccades toward the opposite side hypermetric. Conversely, the inactivation of cFN activity by local injection of muscimol leads to hypermetria of ipsilesional saccades and hypometria of contralesional saccades (Ohtsuka et al. 1994; Robinson et al. 1993). In the head-unrestrained cat, after unilateral injection of muscimol in the cFN, ipsilesional eye-head gaze shifts become hypermetric and contralesional ones become hypometric without significant change in the contribution of the head to the overall gaze displacement (Goffart and Pelisson 1994, 1998; Goffart et al. 1998b).

Neurons in the lobules VIc and VII (Helmchen and Büttner 1995; Kase et al. 1980; Llinas and Wolfe 1977; Ohtsuka and Noda 1995; Thier et al. 2000) and in the cFN (cat: Gruart and Delgado-Garcia 1994; monkey: Fuchs et al. 1993; Helmchen et al. 1994; Hepp et al. 1982; Kleine et al. 2003; Ohtsuka and Noda 1991) display saccade-related bursts of activity. Although most of these neurons also show a steady firing rate during intersaccadic intervals (Fuchs et al. 1993; Helmchen et al. 1994; Kleine et al. 2003; Ohtsuka and Noda 1991), the dysmetria observed during muscimol injection in the cFN is interpreted as resulting from the suppression of the saccade-related bursts. The hypermetria observed after muscimol injection in the cFN would be due to the suppression of the burst that lags the onset of ipsilesional saccades, whereas the hypometria would be due to the suppression of the burst that precedes the onset of contraversive saccades (Fuchs et al. 1993; Ohtsuka and Noda 1991). According to this view, the cFN would control the acceleration of contraversive saccades and the deceleration of ipsiversive ones.

An alternative hypothesis holds that the dysmetria is due to an impaired specification of the movement metrics prior to movement onset. This proposal is briefly considered by Robinson et al. (1993) and suggested by several observations made in the head-unrestrained cat after unilateral muscimol injection into the cFN. First, irrespective of the starting gaze position, ipsilesional gaze shifts overshoot the target by a constant horizontal error and terminate at a location that is shifted with respect to the actual target position (Goffart and Pelisson 1994, 1998; Goffart et al. 1998a). Similar observations were made in one head-restrained monkey after muscimol injection in the cFN (Fig. 2H of Ohtsuka et al. 1994); saccades initiated from various eccentric eye positions are directed to a final position that is horizontally shifted relative to the target. Second, the lack of systematic modifications in the dynamics of the eye, head, and gaze displacements or in the eye-head coupling is

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more compatible with the hypothesis of a deficit unfolding prior to movement onset rather than a disorder in movement execution (Goffart et al. 1998b; see also Goffart and Pélisson 1997).

This paper reports results of additional studies, in head-restrained monkeys, of the effects of unilateral inactivation of the saccade-related area in the cFN on saccades to visual targets. A major goal was to pursue the suggestion that the dysmetria is associated with a selective impairment in the acceleration for contralesional saccades and in the deceleration for ipsilesional saccades. This hypothesis is based primarily on data from two injections (Robinson et al. 1993; see their Fig. 7), and information about the magnitude of the dysmetria that can be attributed to the acceleration and deceleration phases is not directly available. A second goal was to determine the effect of cFN inactivation on the generation of oblique saccades. Finally, we reexamined the question whether ipsilesional saccades initiated from different starting positions overshoot the target by a constant horizontal error. Some of the results reported here have been presented previously in an abstract form (Goffart and Sparks 1997; Goffart et al. 2003a).

METHODS

Subjects and surgical procedures

Three adult rhesus monkeys (Macaca mulatta, 5.6–8.8 kg) were used for this study. Two surgical procedures were performed on each under isoflurane anesthesia. For the monitoring of eye movements, a three-turn magnetic search coil (Cooner Wire, AS 632) was sutured to the sclera under the conjunctiva of the left eye (Fuchs and Robinson 1966; Judge et al. 1980). Lead wires were passed under the skin to a connector located on the top of the skull. During the same procedure, a head-restraint fixture was positioned on the top front center of the skull and secured with bone cement (Palacos, Smith, and Nephew) layered about stainless screws attached to the skull. Training was initiated after full recovery. In a second surgical procedure, a 15-mm-diam craniotomy was performed to permit the electrophysiological recording of fastigial neuronal activity. A stainless steel cylinder was attached to the skull just above the opening with bone cement and stainless steel screws. The cylinder 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. All surgical and experimental procedures were approved by the University of Pennsylvania or the Baylor College of Medicine Animal Care and Use Committee and were in accordance with the National Institutes of Health Guide for Care and Use of Animals. Care and maintenance of the animals was under the auspices of full-time veterinarians.

Behavioral training and experimental apparatus

Experiments were conducted in a dimly illuminated room. The animals were seated in a primate chair with the head restrained inside two 23-kHz sinusoidally oscillating magnetic fields arranged in spatial and phase quadrature. The voltage induced in the scleral search coil by the magnetic fields was phase detected to provide measures of horizontal and vertical eye angular deviation with an accuracy of <0.25°. Eye position signals were calibrated by having the animal fixate stationary targets that were placed ± 18° on the horizontal and vertical meridians. The horizontal and vertical meridians are defined as the intersection of the tangent board with the horizontal plane passing through both eyes and the animal’s sagittal plane, respectively. Small green light-emitting diodes (LEDs) subtending a visual angle of 0.25° embedded in a tangent board at 1-in intervals served as visual targets. The board, made of 49 columns and 41 rows of LEDs, was placed 57 in (<145 cm) in front of the monkey’s eyes.

The monkeys were trained to perform a saccade task that shifted gaze from a fixation LED to a target LED. For each trial, a warning tone (duration = 200 ms) preceded the onset of a fixation LED. If the fixation LED was acquired within 1,000 ms and if gaze was maintained within a spatial window around it (2° radius) for a variable fixation interval (400–800 ms varied in increments of 100 ms), the fixation LED was extinguished, and, simultaneously, the target LED was illuminated. The duration of the fixation interval was variable so that the animal could not anticipate the onset of the target LED. Reward was contingent on directing gaze within 500 ms to a spatial window around the target LED (5° radius) and maintaining fixation for ≥300 ms. The locations of the fixation and target LEDs were pseudorandomly selected from several predefined locations. The location of fixation LEDs was restricted either to the horizontal meridian (0, 4, 8, and 12° leftward or rightward) or to the vertical meridian (0, 6, 8, 12, and 16° upward or downward). The target LEDs were located on the same meridians except when the fixation LED was at the center of the display. In this case, the target LED could also be 12° down (or up) and 12° left (or right) with respect to the horizontal and vertical meridians (only monkeys Q and S were tested with these target conditions). For 70–90% of the trials in the data collection, the target LED was flashed (durations = 50, 100, or 150 ms) and was extinguished before saccade onset. For the remaining trials, the target LED stayed illuminated until the reward was delivered, i.e., after the line of sight was in the target window for 300–500 ms. During these trials, the correction saccades that followed the primary saccades allowed the experimenter to have a visual feedback of the amount of dysmetria during the running of the experiments.

Because of the muscimol-induced dysmetria, several saccades were required to acquire the fixation LED and the saccades toward the target LED frequently terminated outside the acceptance window around it. Therefore the radius of the windows was increased after the injection (≤10 and 20° around the fixation and target LEDs, respectively).

Injection

The location of each caudal fastigial nucleus was determined during several experimental sessions involving electrophysiological recording and electrical microstimulation conducted a few days before the pharmacological inactivation experiments. Both cFNs were located by using the following criteria: recording of neurons generating omnidirectional saccade-related bursts of activity (see Fuchs et al. 1993; Heladena et al. 1994; Kleine et al. 2003; Ohnaka et al. 1991), low current thresholds for electrically evoking saccades (thresholds ranging from 6 to 30 μA) (see Noda et al. 1988), and ipsilateral direction of electrically evoked saccades. Indeed, electrical microstimulation (60–ms train of 0.2–ms pulses at 600 Hz) of the saccade-related region in the cFN evokes an ipsiversive saccade most of the time (see also Noda et al. 1988). This ipsiversive saccade can be followed by a rebound contraversive saccade (Goffart et al. 1998c). If the direction of the first evoked saccade was rightward and if saccade-related units were recorded at the same depth, then we postulated that the right cFN was located. Then the electrode tracks were shifted 3–4 mm to the left: if saccade-related units could be recorded and if a low current was sufficient to electrically evoke a leftward saccade at their site, then we concluded that the two saccade-related fastigial regions were located. In monkeys Q and S, muscimol injections were made into these sites with a stainless-steel cannula (OD: 230 μm, tip beveled) that was connected with a Hamilton syringe (1 μl) by a transparent flexible tubing. In monkey I, one single injection was made with a stainless-steel cannula fitted with a microelectrode in its lumen (Chen et al. 2001) to compare within the same experiment the effects of muscimol injection to those of low-frequency electrical microstimulation (Goffart et al. 2003a). The injection of a saline solution of
muscimol (1 µg/µl, total 0.4–1.2 µl; see details in Table 1) was performed unilaterally by small pulses of 0.1 µl during a total period of 10–15 min. A small air bubble (meniscus) inside the tubing was monitored to verify that the muscimol was going out the cannula. The volume of the injection was checked by measuring the displacement of the meniscus (1 mm/0.1 µl).

Histological control has been performed in all monkeys. Electrolytical marks as well as traces of electrode tracks confirmed that the caudal fastigial nuclei were the cerebellar region that was recorded, electrically stimulated, and inactivated by the injection of muscimol.

Data analysis

The findings presented in this paper were based on the data obtained from all injections (except 1) performed in the cFN of three monkeys. One injection was excluded because the monkey (monkey S) suddenly stopped working very soon after the injection. In that case, the monkey was brought back to its cage where it appeared nauseous and vomited. This sickness was possibly due to the diffusion of the muscimol toward the nearby vestibulocerebellum (nodulus or uvula).

The data analysis reported in the following text was restricted to sacades toward the flashed target LED that were collected before (control session) and after the injection (muscimol session). All sacades were initiated after the target was extinguished and thus were guided by retinal signals generated before sacade onset. This point is important because Robinson et al. (1993; their Fig. 8) showed that muscimol injection in the cFN could dramatically increase the duration of sacades, leaving the possibility that retinal signals generated by a continuously lit target influence the late part of saccade trajectory. Except for the analysis of oblique sacades, the control data used for comparison with data collected after the muscimol injection were recorded just before lowering the cannula to the cerebellum. For the analysis of oblique sacades, control data for one of the monkeys (monkey S) also included data from sessions during the week preceding the first injection (S1, 3 control sessions) as well as three days after injection S2 (1 control session). This procedure was used because this monkey did not work as long as the other animals. Collecting data from a large number of trials with horizontal, vertical, and oblique sacades was associated with the risk that the monkey would stop performing the behavioral task shortly after the muscimol injection. The effects of muscimol injection were recorded after the injection cannula was removed from the brain (~5–10 min after the last injection pulse). The recording typically lasted for 30–150 min. Because there was no discernable difference in saccade dysmetria or in fixation during this recording period, data obtained throughout this interval were pooled.

The data were first measured and collated using a software program developed in the laboratory. This program displayed for each trial the velocity profiles of the horizontal, vertical, and tangential displacements as well as the trajectory of the eye relative to the fixation and target LEDs. Because the LED board was flat, a “tangent correction” was applied to better determine the angular displacement performed by the eyes (see Barton and Sparks 2001 for further details). The saccade onset and offset times were determined on the basis of a velocity threshold (30°/s). The results of this automatic detection were checked by inspecting each trial and corrected when required. It is noteworthy that this velocity threshold did not lead us to miss any sacade with an amplitude <1°. Indeed the analysis of these small sacades (when aimed at the fixation LED) had a peak velocity that ranged between 40 (minimal value) and 110°/s (maximum value). Several parameters such as the amplitude, the duration and the peak velocity of each displacement (horizontal, vertical, and tangential) were extracted automatically from detected sacades.

Most of the analyses reported in the following text are based on sacades initiated from the central fixation LED and aimed at targets with horizontal/vertical eccentricity of 12°. This target eccentricity was selected because it corresponds to an eccentricity for which hypermetric sacades generated after the muscimol injection remained within the oculomotor range and the conditions where the most numerous data were collected after each injection.

For each experiment, the behavioral performance during the control session was compared with the performance after muscimol injection. The nonparametric Mann Whitney U test was used because in a few cases the number of measurements was <10. To take into account differences in the behavioral effects of injections on different days, a paired comparison (nonparametric Wilcoxon test) was performed.

### Table 1. Comparison of the horizontal and vertical position of the eye prior to the saccade toward the target LED before and after muscimol injection in the cFN

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Injection</th>
<th>Session</th>
<th>n</th>
<th>Horizontal Eye Position</th>
<th>Vertical Eye Position</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>Q1</td>
<td>Left cFN (0.4 µl)</td>
<td>Control</td>
<td>378</td>
<td>−0.5 ± 0.6</td>
<td>[−1.9; 1.3]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscimol</td>
<td>614</td>
<td>−1.7 ± 1.0</td>
<td>[−6.9; 2.4]</td>
</tr>
<tr>
<td>Q2</td>
<td>Left cFN (0.4 µl)</td>
<td>Control</td>
<td>605</td>
<td>0.6 ± 0.6</td>
<td>[−1.1; 2.4]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscimol</td>
<td>502</td>
<td>−1.8 ± 1.6</td>
<td>[−6.6; 4.0]</td>
</tr>
<tr>
<td>Q3</td>
<td>Left cFN (0.8 µl)</td>
<td>Control</td>
<td>782</td>
<td>0.0 ± 0.7</td>
<td>[−1.9; 2.3]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscimol</td>
<td>1071</td>
<td>−1.2 ± 1.2</td>
<td>[−7.2; 2.7]</td>
</tr>
<tr>
<td>Q4</td>
<td>Right cFN (0.6 µl)</td>
<td>Control</td>
<td>690</td>
<td>−0.2 ± 1.0</td>
<td>[−3.5; 2.3]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscimol</td>
<td>962</td>
<td>1.8 ± 1.3</td>
<td>[−3.5; 6.4]</td>
</tr>
<tr>
<td>S1</td>
<td>Left cFN (1.0 µl)</td>
<td>Control</td>
<td>335</td>
<td>0.0 ± 0.6</td>
<td>[−1.3; 2.3]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscimol</td>
<td>341</td>
<td>−1.4 ± 1.1</td>
<td>[−6.4; 1.4]</td>
</tr>
<tr>
<td>S2</td>
<td>Left cFN (0.6 µl)</td>
<td>Control</td>
<td>199</td>
<td>0.1 ± 0.7</td>
<td>[−1.1; 1.9]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscimol</td>
<td>378</td>
<td>−1.2 ± 0.8</td>
<td>[−3.4; 3.6]</td>
</tr>
<tr>
<td>S3</td>
<td>Right cFN (0.6 µl)</td>
<td>Control</td>
<td>488</td>
<td>0.0 ± 0.8</td>
<td>[−2.3; 2.0]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscimol</td>
<td>470</td>
<td>0.4 ± 0.7</td>
<td>[−2.8; 2.8]</td>
</tr>
<tr>
<td>S4</td>
<td>Right cFN (0.8 µl)</td>
<td>Control</td>
<td>396</td>
<td>0.1 ± 0.6</td>
<td>[−2.4; 1.7]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscimol</td>
<td>422</td>
<td>0.9 ± 0.7</td>
<td>[−2.3; 5.2]</td>
</tr>
<tr>
<td>S5</td>
<td>Left cFN (0.8 µl)</td>
<td>Control</td>
<td>471</td>
<td>0.0 ± 0.8</td>
<td>[−2.8; 2.2]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscimol</td>
<td>609</td>
<td>−0.3 ± 0.8</td>
<td>[−3.2; 2.2]</td>
</tr>
<tr>
<td>S1</td>
<td>Right cFN (1.2 µl)</td>
<td>Control</td>
<td>88</td>
<td>0.3 ± 0.8</td>
<td>[−2.0; 2.5]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscimol</td>
<td>154</td>
<td>0.6 ± 1.0</td>
<td>[−1.6; 3.8]</td>
</tr>
</tbody>
</table>

Difference was tested with a Student’s t-test for independent samples: NS; no statistically significant difference; *P < 0.05. LED, light-emitting diode; CFN, caudal fastigial nucleus.
between the mean values of the pre- and postinjection performance collected in all experiments. Our main conclusions about the effect of muscimol injection were based on the systematic effects that were revealed by this overall comparison. The Statistica software (Statsoft) was used for statistical analyses and figure illustrations. Statistical significance threshold was set to \(P < 0.05\).

**RESULTS**

We first describe the effects of unilateral muscimol injections in the cFN on horizontal, vertical, and oblique saccades initiated from a fixation LED located straight ahead. Then a description of the effects on saccades initiated from various starting eye positions and aimed at a same visual target follows.

**Qualitative description**

Figure 1 illustrates the major effects of unilateral injection of muscimol in the cFN on fixation and saccade trajectory. The trajectories of representative saccades produced before (B, control) and after injections in the left (A) or in the right (C) cFN are shown. The saccades were initiated from the centrally located fixation LED (the zero-crossing of the horizontal and vertical axes) and aimed at eight different eccentric target LEDs (E). Horizontal coordinates of the target LEDs were 0, 12, or \(-12^\circ\); vertical target coordinates were also 0, 12, or \(-12^\circ\). First, note that during the control session, the vertical component was too large for upward saccades, too small for downward saccades, and horizontal saccades had an upward bias. This observation is typical of saccades generated by rhesus monkeys in a dim visual background (Goffart et al. 2003b; see also Fig. 7 in White et al. 1994). Second, note the injection-induced offset in starting eye position when the animal was viewing the central fixation LED. The initial eye positions were offset to the left after the injection in the left cFN (A) and to the right after the injection in the right cFN (C). Third, the horizontal component of saccades was hypermetric for ipsilesional saccades and hypometric for contralesional saccades. Fourth, the amplitude of the vertical component of saccades did not dramatically change. Fifth, muscimol-induced perturbations in saccade trajectory could be observed relatively early (compare the initial direction of upward oblique saccades in A and C to the control saccades) as well as later during the course of the saccade (note the curved tails of the movements). Finally, the end points of saccades toward targets located on the vertical meridian were also offset horizontally toward the injected side.

Figure 2 illustrates the effect of muscimol injection in the cFN on the velocity profile of saccades to LEDs flashed 12° to the left or right and/or 12° above or below a central fixation LED. The average velocity profiles of the horizontal and vertical components are shown before (---) and after (—) a muscimol injection in the left cFN. For ipsilesional saccades (A–C), the rise and the peak of the horizontal velocity profiles were similar in the control and muscimol conditions. However, beginning \(-10\) ms after the time of peak velocity, the decline in horizontal velocity was slower for movements produced after the injection. During oblique saccades, the increase in the duration of the horizontal component (average difference for upward saccades = 33 ms corresponding to a 56% average increase; 41 ms or 68% average increase for downward saccades) was associated with an increase in the duration of the vertical component (average difference for upward saccades = 36 ms corresponding to a 66% average increase; 34 ms i.e., 60% average increase for downward saccades). For contralesional saccades (D–F), the peak velocity of the horizontal and vertical components of postinjection saccades was reduced, compared with control movements, and a small increase in movement duration was also observed. Finally, muscimol injection had little effect on the velocity of saccades to vertical targets (G and H).

**FIG. 1.** Trajectories of saccades (\(n = 4\) per target) produced before (B) and after injections in the left caudal fastigial nucleus (cFN; A, experiment Q3) or in the right cFN (C, experiment Q4). The intersection of the horizontal and vertical axes in each panel indicates the location of the fixation light-emitting diode (LED). ○, the location of the brief targets. Note that the vertical bias observed in control saccades is typical of saccades generated by rhesus monkeys in a dim visual background (see text for more details).
Horizontal saccades initiated from straight ahead

Based on the timing of the burst of cFN neurons, Robinson and colleagues (1993) hypothesized that the dysmetria of saccades after unilateral cFN muscimol injections was due to changes in the acceleration of contralesional saccades and the deceleration of ipsilesional saccades. They presented data collected from two injections of muscimol that corroborated this hypothesis. A small increase in the peak velocity of ipsilesional saccades and a decrease in the peak velocity of contralesional saccades were described. The data presented in the following text provide information about the consistency and variability of muscimol-induced effects on saccades. More importantly, a more direct test of the Robinson et al. (1993) hypothesis is provided by computing the actual magnitude of the error that can be attributed to the acceleration and deceleration component of saccades. Figure 3 shows the average amplitude (error bar = 1 SD) of the overall saccadic displacement (top), and of the displacements during the acceleration (middle), and the deceleration (bottom) phases, before (C) and after (D) nine muscimol injections in the cFN (■). The data were obtained from ipsilesional (A) and contralesional (B) saccades initiated from a straight ahead fixation LED and aimed at 12° eccentric target LED. The amplitude of ipsilesional saccades was significantly increased in seven of the nine experiments for which these conditions were tested. In the two other experiments, the increase did not reach statistical significance for one experiment (Q2), and there was no change in average value for the other experiment (S2). The paired comparison of the control and postinjection average amplitude values revealed a statistically significant increase in the total amplitude of ipsilesional saccades (difference = 2.8 ± 2.5° corresponding to a 24% average increase). The amplitude of contralesional saccades was significantly reduced in seven experiments. In the two other experiments (Q2 and Q4), the reduction did not reach statistical significance. The paired comparison of the control and postinjection average amplitude values showed a statistically significant reduction in the total amplitude of contralesional saccades (difference = −1.6 ± 1.0° corresponding to a 13% average decrease). The lack of a statistically significant change in amplitude for both ipsilesional and contralesional saccades in experiment Q2 might suggest that the muscimol injection had no effect, but it is shown in the following text that saccades were altered in other ways.

FIG. 2. Average velocity profiles of the horizontal (top graphs) and vertical (bottom graphs) components of saccades directed toward brief targets presented 12° to the left or right and/or 12° above or below a central fixation target before (– - -) and after (—) a muscimol injection in the left cFN (experiment Q3). Insets: the location of the target LED (●) relative to the fixation LED (center cross). The number of saccades that were averaged is also indicated for the control and the muscimol data.
The hypermetria of ipsilesional saccades was consistently associated with an increase in the amplitude during the deceleration phase (note the significant increase in amplitude during deceleration in experiment Q2 too). In one experiment (Q4), an increase in the amplitude of the displacement during the acceleration phase was also observed. The paired comparison of the control and postinjection average values revealed a statistically significant increase in the amplitude of the deceleration phase (difference $\pm 1.4 \pm 0.4^\circ$, 30% increase) without statistically significant change in the amplitude of the acceleration phase (difference $\pm 0.1 \pm 0.8^\circ$). The fact that the average increase in total amplitude ($2.8 \pm 2.5^\circ$) was similar to the average increase in the amplitude during the deceleration phase ($3.0 \pm 2.0^\circ$) indicates that the change in saccade size was mostly occurring during the deceleration phase. This similarity was confirmed by the fact that there was no significant difference between the increase in total saccade amplitude and the increase in amplitude during the deceleration phase (Wilcoxon test).

The hypometria of contralesional saccades was consistently associated with a reduction in the amplitude of the acceleration displacement, whereas the amplitude of the displacement during the deceleration phase could be either increased (see experiments Q3 and S2) or decreased (S3–S5). The paired comparison of the control and postinjection average values revealed, for contralesional saccades, a statistically significant decrease in the amplitude of the acceleration phase (difference $\pm 1.4 \pm 0.4^\circ$, 30% reduction) but no statistically significant change in the amplitude of the deceleration phase (difference $\pm 0.1 \pm 0.8^\circ$). The fact that the average decrease in total amplitude ($\pm 1.6 \pm 1.0^\circ$) was similar to the average decrease in the amplitude during the acceleration phase ($\pm 1.4 \pm 0.4^\circ$) indicates that the change in saccade size was mostly occurring during the acceleration phase. This similarity was confirmed by the fact that there was no significant difference between the increase in total saccade amplitude and the increase in amplitude during the acceleration phase (Wilcoxon test).
For ipsilesional saccades, the increased horizontal amplitude during the deceleration phase was associated with an increased deceleration duration, whereas for contralesional saccades, the reduced horizontal amplitude during the acceleration phase was associated with a decreased peak velocity rather than a shorter acceleration duration. Figure 4 illustrates for the same set of saccades as in Fig. 3 the average maximum velocity (top), the average duration of the acceleration phase (middle), and of the deceleration phase (bottom), before and after muscimol injections. For ipsilesional saccades (A), a significant increase in saccade duration was observed in eight of nine tested experiments (not shown), mostly in the absence of any significant change in maximum velocity (a significant difference in peak velocity was only observed in experiment S2). The paired comparison of the control and postinjection average values showed a statistically significant increase in saccade duration (difference = 17 ± 9 ms, 50% increase) and no statistically significant change in the acceleration duration (difference = 0 ± 2 ms). The average increase in deceleration duration (17 ± 9 ms) was equal to the increase in total saccade duration (17 ± 10 ms), indicating that the latter was occurring during the deceleration phase.

For contralesional saccades (Fig. 4B), the maximum velocity was significantly reduced in all experiments and the duration increased after muscimol injection in seven of nine experiments (not shown). The paired comparison of the control and postinjection average values showed statistically significant reduction in maximum velocity (difference = −107 ± 53°/s, 26% decrease) and increase in duration (difference = 12 ± 9 ms, 23% increase). The acceleration duration was significantly reduced in five experiments, and the deceleration duration significantly increased in eight of nine experiments. The paired comparison of the control and postinjection average values

**FIG. 4.** Dynamics of horizontal ipsilesional (A) and contralesional (B) saccades before (○) and after (■) muscimol injection in the cFN. Top: the average maximum velocity; middle: the average duration of the acceleration phase; and bottom: the average duration of the deceleration phase. Saccades were initiated from the central fixation LED and aimed at a 12° eccentric target LED. The error bars represent the SDs. *P < 0.05 (Mann Whitney U test).
revealed a statistically significant increase in the deceleration duration (difference $= 13 \pm 8$ ms, 38% increase) and no statistically significant change in the acceleration duration (difference $= 1 \pm 2$ ms). Here again, the average increase in deceleration duration ($13 \pm 8$ ms) was similar to the increase in total saccade duration ($12 \pm 9$ ms), indicating that the latter was occurring during the deceleration phase.

To summarize, the increased size of ipsilesional saccades was largely due to an increase in the amplitude of the displacement during the deceleration phase without significant change in the maximum velocity or in the amplitude of the displacement during the acceleration phase. The decreased size of contralesional saccades was largely due to a decrease in the amplitude of the displacement during the acceleration phase without significant change in the amplitude of the displacement during the deceleration phase. An increase in saccade duration also characterized ipsilesional and contralesional saccades and for both directions, this increase in duration was occurring during the deceleration phase.

Vertical saccades initiated from straight ahead

Qualitative Figs. 1 and 2 showed that purely vertical saccades were relatively unaffected. This result is now examined for each experiment. Figure 5 shows the average amplitude (top), maximum velocity (middle), and duration (bottom) of saccades initiated from the central fixation LED and aimed at a 12° eccentric target LED. The error bars represent the SDs. *$P < 0.05$ (Mann Whitney U test).

FIG. 5. Effect of muscimol injection in the cFN on vertical upward (A) and downward (B) saccades. □ and ■ saccades recorded before and after muscimol injection in the cFN, respectively. Top: the mean amplitude of saccades; middle: maximum velocity; and bottom: saccade duration. Saccades were initiated from the central fixation LED and aimed at a 12° eccentric target LED. The error bars represent the SDs. *$P < 0.05$ (Mann Whitney U test).
The paired comparison of the control and postinjection average values revealed a significant although weak difference in velocity for downward saccades only (difference $=-24 \pm 19$°/s, 5% decrease). A small but significant increase in duration was observed for both upward and downward saccades in three experiments for upward saccades and in four experiments for downward saccades. The paired comparison of the control and postinjection average values indicated a significant difference for downward saccades only (differences $= 6 \pm 4$ ms, 15% increase). In summary, muscimol injection in the cFN did not impair vertical saccades in a systematic way. The failure to observe a strong slowing in vertical saccades indicates that the slowing of contralesional saccades cannot be accounted for by reduced alertness.

Oblique saccades initiated from straight ahead

We now describe for the first time the effects of unilateral muscimol injections on oblique saccades initiated from the central fixation LED and directed to a target LED located 12° to the left or to the right and 12° above or below the horizontal meridian.

The duration of the horizontal component was significantly longer than the duration of the vertical component for oblique upward saccades (average differences $= 8 \pm 5$ and $8 \pm 3$ ms for ipsilesional and contralesional saccades, respectively) but not for oblique downward saccades (average differences $= 3 \pm 3$ and $0 \pm 1$ ms for ipsilesional and contralesional saccades, respectively).

Ipsilesional oblique saccades

HORIZONTAL COMPONENT. When compared with control upward saccades, the total amplitude of the horizontal component of oblique saccades was significantly increased after muscimol injection (average increase $= 2.3 \pm 2.6$°, 19% increase). An increase was also observed in the horizontal amplitude of downward oblique saccades but did not reach statistical significance (average increase $= 2.1 \pm 2.6$°). Figure 6 shows that the horizontal amplitude during the deceleration phase was significantly increased in five of six experiments for upward oblique saccades (A, bottom left) and in four experiments for downward oblique saccades (B, bottom left). The paired comparison of the control and postinjection amplitude values revealed a significant increase in the horizontal amplitude during the deceleration phase for both upward (average difference $= 2.6 \pm 2.0$°, 37% increase) and downward oblique saccades ($2.2 \pm 2.1$°, 32% increase) without significant change in the horizontal amplitude during the acceleration phase (see A and B, top left, for details related to each experiment). The average increase in total horizontal amplitude (2.3 and 2.1° for upward and downward saccades, respectively) was similar to the average increase in the horizontal amplitude during the deceleration phase (2.6 and 2.1°), indicating that for ipsilesional oblique saccades, the change in saccade size was mostly occurring during the deceleration phase. The paired comparison of the control and postinjection average values also revealed a significant increase in the duration of the horizontal component for both upward (average difference $= 15 \pm 12$ ms, 26% increase) and downward (average difference $= 18 \pm 19$ ms, 32% increase) oblique saccades. A significant reduction in horizontal peak velocity was also observed in oblique downward saccades (average difference $= -46 \pm 31$°/s, 11% decrease) but not in oblique upward saccades (average change $= 9 \pm 37$°/s).

VERTICAL COMPONENT. When compared with control oblique saccades, the paired comparison of the control and postinjection average values revealed a small but significant increase in the amplitude (average difference $= 0.8 \pm 0.6$°, 8% increase) and duration (average difference $= 11 \pm 17$ ms, 27% increase) of the vertical component for downward oblique saccades only.

To summarize, after muscimol injection in the cFN, the horizontal component of oblique ipsilesional saccades was changed like purely horizontal saccades: the deceleration phase was affected (increase in duration and amplitude), whereas the acceleration phase was relatively unaffected.

Contralesional oblique saccades

HORIZONTAL COMPONENT. When compared with control saccades, the total amplitude of the horizontal component of oblique saccades with either upward or downward vertical components was significantly reduced after muscimol injections (average differences $= -2.7 \pm 1.4$ and $-2.6 \pm 1.6$° for upward and downward saccades, respectively, 22% decreases). Figure 6 shows that for both upward (A, top right) and downward (B, top right) oblique saccades, the decrease in horizontal amplitude was associated with a significant decrease in the horizontal amplitude during the acceleration phase in five of six experiments for upward saccades (the 1 exception is experiment S1) and in all experiments for downward saccades. Significant reductions in the horizontal amplitude during the deceleration phase were also observed in three of six experiments for upward and downward saccades (the 1 exception is experiment Q3). But the paired comparison of the control and the postinjection amplitude values failed to reveal any significant change in the horizontal amplitude during the deceleration phase, whereas the changes in the amplitude during the acceleration phase were statistically significant (average differences $= -1.5 \pm 0.5$ and $-1.6 \pm 0.6$° for upward and downward saccades, respectively, 35% decreases). The average changes in total horizontal amplitude ($-2.7$ and $-2.6$° for upward and downward saccades, respectively) were bigger than the average changes in the horizontal amplitude during the deceleration phase ($-1.5$ and $-1.6$°), suggesting that some changes in saccade size also occurred during the deceleration phase. An increase in the duration of the horizontal component of oblique saccades was also observed although the difference reached statistical significance for upward saccades (average difference $= 11 \pm 8$ ms, 19% increase) but not for downward ones (average increase $= 8 \pm 9$ ms).

VERTICAL COMPONENT. When compared with control oblique saccades, the amplitude of the vertical component of oblique contralesional saccades was not significantly changed after muscimol injection (paired comparison of the control and postinjection average values). These saccades were characterized with a significant decrease in the vertical peak velocity ($-82 \pm 46$ and $-45 \pm 37$°/s for upward and downward saccades, respectively, 15% decreases) and an increase in the duration of the vertical component that reached statistical significance for upward saccades only ($5 \pm 2$ ms, 9% increase).
To summarize, after muscimol injection in the cFN, the horizontal amplitude of oblique contralesional saccades was significantly reduced during the acceleration phase. Some reduction was also observed during the deceleration phase, but it did not always reach statistical significance.

**Effects of varying initial eye position**

Figure 7 illustrates the dysmetria of saccades initiated from various starting eye positions and aimed at a same visual target. Variations in the horizontal starting position of the eyes were obtained by using seven different fixation LEDs (∅): ±12°, ±8, ±4, and 0° along the horizontal meridian. Target LEDs (∅) were located 16° to the left (or to the right) and 12° above (or below) the horizontal meridian. A: oblique upward saccades. B: oblique downward saccades. For each panel, the mean amplitude of the horizontal displacements during the acceleration (top) and the deceleration (bottom) phase is shown. The error bars represent the SDs. *P < 0.05 (Mann Whitney U test).

FIG. 6. Amplitude of the horizontal component of oblique ipsilesional (left) and contralesional (right) saccades before (□) and after (■) muscimol injection in the cFN. Saccades were initiated from the central fixation LED and aimed at a target LED that was located 12° to the left (or to the right) and 12° above (or below) the horizontal meridian. A: oblique upward saccades. B: oblique downward saccades. For each panel, the mean amplitude of the horizontal displacements during the acceleration (top) and the deceleration (bottom) phase is shown. The error bars represent the SDs. *P < 0.05 (Mann Whitney U test).
The horizontal component was hypometric. The initial direction of saccades starting from fixation LEDs located to the right had more of a leftward component than that required to look to the target LED. The horizontal component was hypermetric with an overshoot that increased with more eccentric starting horizontal position (compare the end point of saccade a to the end point of saccade b). Similar effects were apparent for saccades directed to the 12° target (C). However, when the vertical eccentricity of the target was reduced, the horizontal error at the end of the saccades was also reduced. The end points of saccades starting from the straight ahead fixation LED were offset relative to the target LED with a magnitude that increased with the vertical eccentricity (values given in the figure, see also Fig. 9). Moreover, when examining the contralesional saccades initiated from the most eccentric fixation LEDs to the left (−8 or −12°), the amplitudes of the horizontal component were larger when the vertical target position decreased from 16° to 6° upward (compare saccades labeled c among A–C).

In summary, saccades initiated from different starting positions did not end at a final eye position that was shifted relative to the target location by a constant horizontal error. Rather, ipsilesional saccades missed the target with a horizontal error that increased with more eccentric starting eye positions (and concomitantly, as horizontal target eccentricity and saccade duration increased). Contralesional saccades also missed the target with a horizontal error that increased with target eccentricity.

Figure 8 provides a detailed report of the results described in the preceding text for all experiments in which the same target conditions were used. The horizontal error of saccades is plotted as a function of starting position along the horizontal meridian. Horizontal error is defined as the difference between the horizontal target position and the horizontal final eye position. The target LED was located on the vertical meridian with an upward eccentricity of 6, 12, or 16°. The relationships are illustrated for each monkey with the experiment that provided the largest dataset. Positive values of horizontal eye
position correspond to deviations of the eye toward the injected side. Because the target LED was located on the vertical meridian, saccades initiated from positive horizontal eye position were contralesional saccades, whereas those initiated from negative horizontal eye position were ipsilesional saccades. Note that ipsilesional saccades were hypermetric (positive values of error) and contralesional saccades were hypometric (negative values of error). For each experiment, the magnitude of the error increased with increasing initial deviation of the eyes. It also increased with increasing vertical eccentricity of the target (compare the error for target 16° to the dysmetria for target 6° in A and the error for target 16° to the error for target 12° in B). The same pattern characterized contralesional saccades.

In summary, in contrast to previous reports on cat gaze movements (Goffart and Pélisson 1994, 1998), saccades initiated from various starting positions in monkey did not miss the target by a constant horizontal error. Instead, for monkey saccades, the magnitude of the hypometria of contralesional saccades and the hypermetria of ipsilesional saccades depended on both the starting position of the eyes and the vertical position of the target.

As illustrated in Figs. 1 and 7, the trajectory of vertical saccades was biased horizontally toward the injected side. Figure 7 also showed that the amount of deviation increased with more eccentric vertical targets. This increase in the horizontal bias of vertical saccades with larger vertical target eccentricity was further tested in eight experiments by comparing the horizontal targeting error remaining after each saccade for saccades starting from a fixation LED located at the center of the display and aimed at two different targets along the vertical meridian (Fig. 9A). The horizontal targeting error was defined as the difference between the absolute value of the final horizontal eye position and the absolute value of horizontal target position. The absolute value of the horizontal targeting error was significantly larger for the most eccentric targets in five of the eight experiments. The paired comparison of the error between the 12 and 16° target positions revealed a statistically significant increase in the horizontal targeting error for saccades toward the most eccentric target (average difference = 0.8 ± 0.3° corresponding to a 80% average increase).

The larger horizontal targeting error with more eccentric vertical target after muscimol injection may not be due to the vertical target eccentricity per se. Instead, the changes could be related to the duration of the movement because saccade duration increases with target eccentricity. This possibility was examined by analyzing the relationship between the horizontal targeting error and the duration of vertical saccades. The horizontal targeting error remaining after each saccade is plotted as a function of vertical eccentricity of the target (Fig. 9B, top) and saccade duration (bottom). The saccades were recorded in monkeys Q (left) and S (right) before (+) and after muscimol injection in the left cFN (●) or right cFN (●). During the control session, the horizontal targeting error did not vary with vertical target eccentricity or saccade duration, but after muscimol injection, it significantly increased with increasing vertical target eccentricity or saccade duration. The horizontal targeting error was leftward (negative values) when muscimol was injected in the left cFN and rightward (positive values) after injections in the right cFN. When all saccades toward a target located along the vertical meridian (upward and downward saccades) are considered, the horizontal targeting error was significantly correlated with the absolute value of vertical target eccentricity in 8 of the 10 muscimol experiments (Pearson correlation coefficients $R = 0.25–0.84$) and to saccade duration in 9 experiments ($R = 0.47–0.82$).

**Fixation**

Previous studies reported a deficit in fixation when the cFN was inactivated (Goffart and Pélisson 1998; Robinson et al.)
1993). Indeed, when animals were viewing the fixation LED, usually after one or more correction saccades during the fixation interval (see METHODS), the position of the eye was on average offset after injection of muscimol in comparison with the position maintained before the injection. The mean (± SD) and the range (in brackets) of the horizontal and vertical offsets are presented for each experiment in Table 1. The average horizontal offset was toward the injected side in 9 of the 10 experiments and downward in 5 of the 10 experiments. The average horizontal offset for all experiments was $1.1 \pm 0.7^\circ$ toward the injected side ($P < 0.05$) and $-0.1 \pm 0.3^\circ$ downward ($P > 0.05$). As indicated by the ranges, the magnitude of the offset could reach relatively large values (e.g., $7.2^\circ$ toward the injected side in experiment Q3). Such large values correspond to cases where the fixation interval was too short for correction saccades to reach the fixation LED. Besides, it is noteworthy that monkeys were able in a substantial number of cases to look at the fixation LED. Graphical plots comparing the scatters of starting eye positions before and after muscimol injection showed several trials without fixation offset (not shown). To test whether the offset depended on the positions of the eyes in the orbit, the horizontal and vertical offsets when the monkeys were viewing a fixation LED located 12° in the ipsilesional side were compared with the offsets when they were viewing a fixation LED situated 12° in the contralesional side (Wilcoxon test). Neither horizontal nor vertical offsets were significantly different (8 tested experiments, average differences $= 0.6 \pm 1.7$ and $0.5 \pm 0.6^\circ$ for the horizontal and vertical offsets, respectively). Similarly, neither horizontal nor vertical offsets were significantly different for trials with fix-
ation LEDs located 12° below or above the straight ahead position (7 tested experiments, average differences = 0.0 ± 1.2° and −0.6 ± 1.0° for the horizontal and vertical offsets, respectively).

DISCUSSION

Deficits in saccade

After unilateral injection of muscimol in the cFN, the accuracy of all saccades was impaired. The injections mainly affected the amplitude of the horizontal component of saccades. When the saccade direction was ipsilateral to the injected side, the horizontal amplitude was larger than before the injection. When the saccade was contralesional, the horizontal amplitude was smaller. The amplitude of the vertical component of oblique saccades was slightly altered but mostly during oblique downward saccades. Vertical saccades were also impaired because their trajectory was biased horizontally toward the injected side, but the vertical amplitude was not significantly altered.

The hypermetria of ipsilesional saccades was mostly due to an increase in the distance the eye moved during the deceleration phase, whereas the hypometria of contralesional saccades was mostly due to a reduction in the distance the eye moved during the acceleration phase. The increase in the deceleration amplitude of ipsilesional saccades was associated with an increase only in the duration of the deceleration phase. In contrast to Robinson et al. (1993), we did not find any significant change in the saccade peak velocity for ipsilesional saccades. The increase in peak velocity reported by these authors may have been due to the admixture of centripetal and centrifugal saccades in their summary data. Indeed, for ipsilesional saccades, the maximum velocity of centripetal saccades was significantly larger than that of centrifugal ones (data not shown). The reduced acceleration amplitude of contralesional saccades was not associated with a shorter acceleration duration (in comparison with the increased deceleration duration of ipsilesional saccades) but with a strongly reduced peak velocity. Contralesional saccades were also associated with an increase in the duration of the deceleration phase.

The selective change in the acceleration amplitude for contralesional saccades and in the deceleration amplitude for ipsilesional saccades is compatible with the hypothesis that the cFN is involved in accelerating contraversive saccades and in decelerating ipsiversive ones (Fuchs et al. 1993; Ohtsuka and Noda 1991). The results presented here extend this hypothesis to the control of the horizontal component of oblique saccades. However, the hypothesis that cFN activity helps to accelerate contralateral saccades and to decelerate ipsilateral ones does not explain why saccades become inaccurate. This hypothesis is not satisfactory either when one considers the contribution of the cFN to the control of vertical saccades. In the following text, we propose an alternative view for understanding all the deficits that are induced by cFN inactivation. This view emphasizes the bilateral organization of cFN influence on the brain stem control of saccades (Sparks and Barton 1993). The period when the saccade-related neurons in both left and right cFN are simultaneously bursting is very important for understanding the dysmetria of saccades during cFN inactivation, whether the saccade is horizontal, oblique, or vertical.

The hypothesis of an involvement of cFN in accelerating/decelerating saccades is based on the timing of the burst generated by some neurons in the cFN during saccades. Saccade-related neurons in the cFN were shown to emit a burst of action potentials during all saccades, irrespective of their direction and amplitude (Fuchs et al. 1993; Ohtsuka and Noda 1991). On average, the burst precedes the onset of contraversive saccades and lags the onset of ipsiversive ones (see also Kleine et al. 2003). Anatomical studies indicate that the cFN projects primarily to regions of the medial brain stem reticular formation that have direct projections to the extraocular motor nuclei (Noda et al. 1990; Sugita and Noda 1991). In particular, the cFN projects contralaterally toward the pontine and the medullary reticular formations. These two target regions are known to be the sites where excitatory and inhibitory burst neurons (EBNs and IBNs) are located, respectively (Strassman et al. 1986a,b).

The connection among saccade-related fastigial neurons (SRFNs), EBNs, IBNs and the motoneurons innervating the medial and lateral recti are schematically shown in Fig. 10. Cells in the cFN have axons that project to contralateral EBN and IBN regions (illustrated by bold lines). In turn, the EBNs provide monosynaptic excitatory input to ipsilateral IBNs and to the motoneurons (MNs) and internuclear neurons (INs) found in the ipsilateral abducens nucleus. IBNs provide monosynaptic input to contralateral IBNs and to MNs and INs in the contralateral abducens nucleus (Moschovakis et al. 1996). Thus during contraversive saccades (e.g., rightward saccades), SRFNs contribute to the activation of both EBNs and IBNs (path a1), allowing the excitation of MNs innervating the agonist muscles (path a2) and the inhibition of MNs innervating the antagonist muscles (path a3). Then SRFNs in the opposite cFN start bursting and activate EBNs and IBNs (path...
b1), which excite MNs innervating antagonist muscles (path b3) and inhibit MNs innervating the agonist muscles (path b2), respectively. Paths a1 and b1 are antagonizing each other for the generation of horizontal saccades. During muscimol inactivation of the left cFN, presumably the deficits in contralateral saccades occur because activity in path a1 is reduced without a corresponding decrease in activity in path b1. Thus contralateral saccades are hypometric because the early cFN activation of EBNs producing excitation in agonist MNs (conveyed by paths a1 and a2) and the early activation of IBNs inhibiting antagonist MNs (conveyed by paths a1 and a3) are missing. The later burst of SRFNs located in the unaffected cFN also contributes (via path b1) to the hypometria by producing an inhibition of the agonist MNs and an excitation of antagonist MNs that both are unopposed by the effects produced by the inactivated cFN neurons. EBNs and IBNs are mostly silent during contralateral saccades (see however Cullen and Guitton 1997), but they may be active when the fastigial input to IBNs is removed by unilateral muscimol injections. The possibility that the burst of SRFNs in the unaffected cFN is responsible for stopping contralateral saccades is supported by the hypermetria of saccades during bilateral inactivation of cFN (Robinson et al. 1993; L. Goffart and J. Quinet, unpublished observations). In the context of a control of saccade accuracy by a local negative feedback loop (Barton et al. 2003; Jürgens et al. 1981; Robinson 1975), there would be no compensation for this alteration in neural activity if the output of IBNs is not part of the feedback signal. Concerning ipsilesional saccades, an increase in the amplitude of the deceleration phase would occur because the late activation of antagonist EBNs and IBNs and the associated (late) inhibition of agonist EBNs are missing. Concerning vertical saccades, unit recording studies show that SRFNs in both cFN are active during these saccades (Fuchs et al. 1993; Ohotsuka and Noda 1991). After unilateral cFN injections, the burst of SRFNs in the unaffected cFN provides excitation to the contralateral EBNs that is unopposed by an inhibition normally mediated by the inactivated cFN, leading to the horizontal deviation of vertical saccades. The presumed decreases in discharge rate of IBNs driven by the inactivated cFN would be responsible for the horizontal deviation of saccades to vertical targets. Three critical assumptions are made in the scheme we propose. First, activity of unaffected SRFNs is sufficient to produce a burst of activity in contralateral EBNs and IBNs in the absence of inhibition of the ipsilateral IBNs. Second, actions of IBNs exerted at MN and IN level are not included in the local feedback loop (Barton et al. 2003; Jürgens et al. 1981; Robinson 1975). Third, the same command for a saccade is being issued (e.g., from deep superior colliculus) after the muscimol injection in the cFN. These assumptions need to be tested experimentally.

The magnitude of the horizontal bias during vertical saccades increased when target eccentricity (see also Iwamoto and Yoshiida 2002) or saccade duration increased. Which of these features (target eccentricity or saccade duration) determines the size of the horizontal error cannot be determined from our data. The comparison of the horizontal deviation of vertical saccades during normal saccades and experimentally slowed saccades (e.g., see Gandhi and Keller 1999) during cFN inactivation should help to exactly determine which parameter is critical. However, according to the neurophysiological view proposed in the preceding text for understanding the deficits induced by cFN inactivation, saccade duration is the more plausible parameter because it corresponds to the period when omnipause neurons are silent and, consequently, the period when the cFN impairment can affect the burst neurons. Purely vertical saccades could still be generated after muscimol inactivation of the cFN as long as they were launched from an initial eye position that was slightly deviated toward the ipsilateral side. This deviated initial eye position called for a saccade with a contralateral horizontal component that would cancel with the ipsilesional horizontal bias, leading thus to purely vertical saccades. The starting eye position from which the saccade toward a vertical target had to be launched had to be more deviated toward the contralateral side as the vertical target eccentricity increased to be purely vertical. These purely vertical saccades presumably corresponded to conditions where the activity between the left and the right saccade generators were balanced and cancelled each other.

Finally, unilateral inactivation of the cFN in the head-restrained monkey did not lead to the same deficits as those observed in the head-unrestrained cat (Goffart and Pélisson 1998; Goffart et al. 1998b). The difference could result from species differences. Both the visual and oculomotor systems are different between cats and monkeys. The different deficits could also be due either to the fact that the head was also moving in the cat experiments or to the nature of the target that was used. Data showing the effects of cFN inactivation in the head-unrestrained monkey or in the head-restrained cat are not yet available to solve the issue raised by the influence of restraining (or unrestraining) the head. Moreover, in the cat experiments, the food target was triggering an orienting gaze shift but also an orienting movement of the mouth (and thus of the head). In the monkey experiments, target acquisition required only a shift of the line of sight. Part of the dysmetria observed in cat’s gaze shifts could be due to deficits in orienting movements of the mouth.

**Deficit in fixation**

After muscimol injection in one cFN, when the animals were viewing the fixation LED, usually after one or more correction saccades, the positions of the eyes were slightly offset toward the injected side in comparison with the positions maintained before the injection. An ipsilesional offset has also been observed in previous studies in the head-restrained monkey (Ohotsuka et al. 1994; Robinson et al. 1993) and in the head-unrestrained cat (Goffart and Pélisson 1998) during muscimol injection in the cFN. The offset was toward the contralateral side after bicuculline was injected in the cFN (Sato and Noda 1992). To our knowledge, no valuable hypothesis has been proposed to explain why a small offset consistently occurs and why it is ipsilesional after muscimol injections and contralateral after bicuculline injections. During bilateral injection of muscimol in the cFN, the offset appears toward the side where the hypermetria is the most pronounced (Robinson et al. 1993; L. Goffart and J. Quinet unpublished observations). One possibility is that the offset is merely a residual effect of the pharmacologically induced dysmetria. Assume the fixation LED appears to the right of the current eye position after a muscimol injection in left cFN. The initial saccade to the fixation LED (contralional) will be hypometric and subse-
quent correction saccades (in the same direction) will also be hypometric. Each successive correction saccade is a little smaller, and the interval between successive corrections is longer (Robinson et al. 1993). If the fixation LED appears to the left of current gaze position, the initial saccade (ipsilateral) will be hypermetropic; subsequent correction saccades will be in the opposite direction and hypometric. Thus if the fixation LED appears to the right or left of current eye position, after the first saccade to it, the direction of gaze will be deviated ipsilaterally.

The mislocalization of the target produced by the dysmetria is not ignored by the visual/oculomotor system. Correction saccades occur. The amplitude of the offset is usually measured at the time of the primary saccade to an eccentric target LED. In the current experiment, the target LED appeared after a 400- to 800-ms fixation interval, and this could have limited the number of correction saccades possible. However, an offset of comparable size was reported by Robinson and colleagues (Robinson et al. 1993) when a fixation interval of ~2 s was used. But it should be noted that neither the LEDs used in the current experiment nor the laser spot used by Robinson and colleagues were small, sharply focused stimuli. Moreover, in both experiments, there was no incentive for more accurate fixation and no penalty for a small fixation offset. It would be informative to determine if the offset persists when animals are performing a task that requires more accurate fixation. In the absence of such information, we assume that the offset is a consequence of the dysmetria produced by the pharmacological perturbation of the cFN.

Conclusion

The present study provides data suggesting that the timing of activity in the left and right cFN regulates the balance of activity between the EBNs and IBNs located in the left and right pontine and medullary reticular formation (Sparks 2002; Sparks and Barton 1993; van Gisbergen et al. 1981). According to this hypothesis, dysmetria occurs because modulations in the activity between the EBNs and IBNs located in the left and right pontine and medullary reticular formation (Sparks and Barton 1993; van Gisbergen et al. 1981). According to this hypothesis, dysmetria occurs because modulations in the speed and amplitude of saccades mediated by the IBNs are not included in the feedback signals controlling saccade amplitude.

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References


