

3-DIMENSIONAL EYE-HEAD COORDINATION IN GAZE SHIFTS EVOKED DURING STIMULATION OF THE LATERAL INTRAPARIETAL CORTEX

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Abstract—Coordinated eye-head gaze shifts have been evoked during electrical stimulation of the frontal cortex (supplementary eye field (SEF) and frontal eye field (FEF)) and superior colliculus (SC), but less is known about the role of lateral intraparietal cortex (LIP) in head-unrestrained gaze shifts. To explore this, two monkeys (M1 and M2) were implanted with recording chambers and 3-D eye+ head search coils. Tungsten electrodes delivered trains of electrical pulses (usually 200 ms duration) to and around area LIP during head-unrestrained gaze fixations. A current of 200 μ A consistently evoked small, short-latency contralateral gaze shifts from 152 sites in M1 and 243 sites in M2 (Constantin et al., 2007). Gaze kinematics were independent of stimulus amplitude and duration, except that subsequent saccades were suppressed. The average amplitude of the evoked gaze shifts was 8.46° for M1 and 8.25° for M2, with average head components of only 0.36 and 0.62° respectively. The head's amplitude contribution to these movements was significantly smaller than in normal gaze shifts, and did not increase with behavioral adaptation. Stimulation-evoked gaze, eye and head movements qualitatively obeyed normal 3-D constraints (Donders' law and Listing's law), but with less precision. As in normal behavior, when the head was restrained LIP stimulation evoked eye-only saccades in Listing's plane, whereas when the head was not restrained, stimulation evoked saccades with position-dependent torsional components (driving the eye out of Listing's plane). In behavioral gaze-shifts, the vestibuloocular reflex (VOR) then drives torsion back into Listing's plane, but in the absence of subsequent head movement the stimulation-induced torsion was "left hanging". This suggests that the position-dependent torsional saccade components are preprogrammed, and that the oculomotor system was expecting a head movement command to follow

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Abbreviations: 1-d, one-dimensional; 2-d, two-dimensional; 3-d, three-dimensional; CCW, counterclockwise; CV, characteristic vector; CW, clockwise; FEF, frontal eye field; IPS, intraparietal sulcus; LED, light emitting diode; LIP, lateral intraparietal; SC, superior colliculus; SEF, supplementary eye field; VOR, vestibuloocular reflex.

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the saccade. These data show that, unlike SEF, FEF, and SC stimulation in nearly identical conditions, LIP stimulation fails to produce normally-coordinated eye-head gaze shifts. © 2009 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: electrical stimulation, lateral intraparietal cortex, eye-head coordination, saccades, head movement, torsion.

Numerous neurophysiological studies have implicated lateral intraparietal cortex (LIP) in saccade planning (Andersen and Buneo, 2002; Astafiev et al., 2003; Colby and Duhamel, 1996; Colby et al., 1996; Duhamel et al., 1992; Goldberg et al., 2002) and execution (Andersen et al., 1992; Barash et al., 1991a,b; Constantin et al., 2007; Gaymard et al., 2003; Grekes and Fink, 2005; Thier and Andersen, 1996, 1998). Neurons in LIP exhibit delay activity related to saccade execution (Andersen et al., 1990, 1998; Colby et al., 1996; Snyder et al., 2000) and also show remapped activity that is retained after an intervening saccade (Duhamel et al., 1992; Gottlieb et al., 2005). LIP also has visual receptive fields which have been said to be organized in eye-centered (Andersen and Buneo, 2002; Andersen et al., 1998; Colby et al., 1995; Colby and Duhamel, 1996; Constantin et al., 2007) or head-centered (O'dhanial et al., 2005) coordinates. One characteristic of LIP neuronal activity associated with eye saccades is a modulation of this activity with eye position (Boussaoud and Bremmer, 1999; O'dhanial et al., 2005), and head (O'dhanial et al., 2005) or body/space (Platt and Glimcher, 1997) orientation. However, it is not clear what role LIP plays in the control of coordinated eye-head gaze shifts as opposed to head-fixed saccades.

Microstimulation studies of head-restrained monkeys showed the presence of a "parietal eye field" (Andersen et al., 1992; Mushiaki et al., 1999; Shibusaki et al., 1984; Thier and Andersen, 1996, 1998) located in the posterior parietal cortex, and identified as area LIP. In these studies, small saccades were evoked by stimulating area LIP using a variety of microstimulation parameters (Kurylo and Skavenski, 1991; Shibusaki et al., 1984). The most comprehensive microstimulation studies in LIP were effected by Thier and Andersen (1996, 1998); using high stimulation frequencies of 500 Hz and mostly 200 ms. They obtained mostly small saccades (up to 15°), which seemed to be slightly influenced by initial eye position. When they increased the length of the stimulation train to 500 ms, they reported stair-case saccades—which is a notable result, presenting some similarities with multi-step saccades evoked from superior colliculus (SC) or frontal eye field (FEF). Moreover, area LIP was stimulated in monkeys with

partially-restrained heads, where the head was allowed only horizontal movements (Brotchie et al., 1995; Thier and Andersen, 1998). The resulting stimulation-evoked gaze shifts showed only small head movement components depending on the stimulation site.

In contrast to these findings, microstimulation studies of other brain areas implicated in gaze control (i.e. SC and SEF) have shown significant head amplitude contributions to the amplitude of head-unrestrained gaze-shifts (Freedman and Sparks, 1997; Martinez-Trujillo et al., 2003a; Roucoux et al., 1980). Moreover, SC, supplementary eye field (SEF), and FEF stimulation (Chen, 2006; Chen and Walton, 2005; Freedman et al., 1996; Elsley et al., 2007; Martinez-Trujillo et al., 2003b; Tu and Keating, 2000) produced a range of gaze-shift amplitudes having behaviorally-normal 1-D, 2-D and 3-D patterns of eye-head coordination (Martinez-Trujillo et al., 2003a; Roucoux et al., 1980; Russo and Bruce, 2000; Tu and Keating, 2000). However, since LIP stimulation has never been performed in head-unrestrained animals using 3-D eye and head movement recordings; the same could not yet be said for LIP. In our previous paper (Constantin et al., 2007) we described the frame of reference that best characterized the goals of the stimulation-evoked gaze shifts of the same dataset that has been reported here, concluding that an eye-centered frame provided the best fit across all of our stimulation sites. In the current study, we investigated the role of LIP in head-free gaze control, by using three-dimensional recordings, by performing a thorough examination of the lateral intraparietal area, analyzing in depth the patterns of eye-head coordination observed during stimulation-evoked gaze shifts and by answering the following questions: (1) what are the kinematics of the LIP stimulation-evoked movements? and, (2) are they accompanied by, and coordinated with, normal head movements?

To answer these questions we used a method used by Martinez-Trujillo et al. (2003a), and compared stimulation-evoked gaze-shifts against naturally-coordinated eye+head gaze-shifts. For this comparison we took into account the detailed analysis of the amplitude and velocity of the stimulation-evoked gaze, eye and head movements—in particular head amplitude as a function of gaze amplitude and the “main sequence” (peak velocity vs. amplitude) of the eye, head, and gaze movements. If the kinematics relationships observed in normal gaze shifts are preserved in the stimulus-evoked movements, one might conclude that LIP activation can trigger a gaze control command involving the normal eye and head movement circuits.

We also tested whether varying LIP microstimulation parameters (train duration and pulse amplitude) changed the amplitude and velocity of the stimulation-evoked gaze, eye and head movements. Stimulation of the SC (Freedman et al., 1996; Roucoux et al., 1980), SEF (Chen and Walton, 2005) or FEF (Chen, 2006; Elsley et al., 2007), in head-free monkeys showed that varying the amplitude, duration and/or frequency of the stimulation changes the amplitude, duration and velocity of the stimulation-evoked gaze shifts. Previous LIP microstimulation studies (Thier

and Andersen, 1996, 1998) varied both the amplitude of the electrical stimuli (from 100 μ A up to 400 μ A) and the length of the electrical stimuli (up to 500 ms) and obtained staircase saccades. However, these studies did not include a quantitative analysis of these effects.

Furthermore, we examined the role of area LIP in adaptive eye-head coordination during gaze-shifts by varying the subject's eye-head coordination strategy using the “pinhole goggle paradigm” (Ceylan et al., 2000; Constantin et al., 2004; Crawford and Guitton, 1997). In this, subjects are trained to switch rapidly between a “normal” eye-head coordination strategy and a “head-mover” strategy by donning a pair of opaque goggles that reduce the visual field to a smaller, head-fixed pin hole. Electrophysiological studies in SC (Constantin et al., 2004; Crawford and Guitton, 1997) showed that, when SC was stimulated using this paradigm, the evoked gaze shifts included adjustments in eye-head coordination strategies, but not in head movements seen during ordinary behavior. The latter study suggested that the adjustments in head amplitudes were likely made through a parallel channel from cortex to the brainstem. According to this, one might expect that head movement adjustments to be preserved when the cortex is stimulated with the goggle paradigm.

Finally, it is useful to analyze the 3-D components of each movement, because the brain orients itself in a 3-D space with the torsional position component for gaze, head and eye following certain constraints during behavior gaze-shifts (e.g. Donders' and Listing's law). Stimulation-evoked gaze-shifts from SC (Klier et al., 2003, 2001; Martinez-Trujillo et al., 2003b), and SEF (Martinez-Trujillo et al., 2003b) closely follow these constraints, including the complex saccade-vestibuloocular reflex (VOR) coordination strategies required to control eye torsion (Crawford et al., 1999; Tweed, 1997). It is unknown whether movements evoked during LIP stimulation share these characteristics.

EXPERIMENTAL PROCEDURES

Animal preparation

The surgical and experimental procedures used in this study were in compliance with the Canadian Council on Animal Care policy on the use of laboratory animals, and were approved by York University Animal Care Committee. Two female *Macaca mulatta* underwent surgical procedures under general anesthesia using 1.5% isoflurane and Ketamine 10 mg/kg. During the procedures, each monkey was implanted with one head post for restraining the head, one recording chamber (Narishige, Japan), and sockets for a cable connection. Implants were attached to the skull using a dental acrylic cap. A 20 mm diameter plastic recording chamber was placed on the skull at 5 mm posterior and 12 mm lateral to the right in stereotaxic coordinates, above the right lateral intraparietal sulcus. The head post, positioned over the frontal bone and on the midline, consisted of a stainless steel cylinder with a rapid release mechanism (described by Crawford et al., 1999). We also implanted two custom-built scleral search coils (copper wire) of 5 mm diameter, subconjunctivally (in the nasal half on one eye). These coils were later used to measure three-dimensional (3-D) eye orientations during training and experimental procedures (for details see, Crawford et al., 2003). After the surgery, the monkeys were allowed to recover for 2 weeks before experiments commenced.

During the training and experimental procedures, each animal wore a primate jacket and was sitting upright in a modified Crist primate chair (Crist Instruments, Hagerstown, MD, USA). The primate chair modifications constrained the torso movements of the animals, therefore allowing for a larger range of head movements (for details see Constantin et al., 2004). The monkeys were able to accomplish natural and unrestricted movements of the eyes and head, except for gaze directions larger than 50° downward. The primate chair was placed near the center (± 15 cm) of three orthogonal magnetic fields (Tweed et al., 1990). While in the chair, the acrylic skull caps were fitted with two orthogonal coils, of 1 cm diameter, which allowed measurements of 3-D head orientations. The eyes and head coil signals were recorded at a sampling frequency of 1000 Hz.

During the experiments, we used a small hydraulic microdrive (Narishige model MO-95S, Tokyo, Japan), custom-fitted onto a stage with a radial placement system to lower electrodes into the lateral bank of the intraparietal sulcus (IPS). The total weight of the system was of 48 g, which remained constant throughout experimentation.

Training and experimental procedures

Animals were trained to fixate light emitting diodes (LEDs) using head-free (head unrestrained) gaze shifts in the dark. A spherical LED screen was positioned at 80 cm in front of the monkey, with the lights located at center and at $\pm 20^\circ$ and $\pm 40^\circ$, on the vertical, horizontal and oblique meridians respectively, totaling 17 different LED's. Individual LEDs were illuminated for 500 ms, accompanied by a brief burst of white noise at the same location, as an orienting aid to the animal. The speakers responsible for the white noise burst were situated 3 to 5 mm below the LED's. Animals were required to fixate the LED within a spatial window of 5 to 10°, and then were required to maintain fixation for an additional 500–800 ms after the LED was extinguished (in complete darkness) in order to receive a juice reward. Animals were trained in this way so that during experiments electrical stimulation could be provided over a wide range of stable initial gaze and head positions in complete darkness.

Experiments began after a training period of 3 weeks, for both monkeys. Tungsten microelectrodes (0.15–2.5 m Ω impedance at 1 kHz, FHC) were lowered through a guide tube, which stopped 3 mm beyond the dura. During each experiment we made penetrations at one or two locations (tracks) with a maximum vertical excursion of the electrode of 10 to 20 mm. Initially, the head was restrained while we searched for a site that showed saccade- or visually-related activity, and then stimulation-evoked eye movements. The electrode was slowly lowered and 10–20 cathodal trains were applied each 0.5 mm (100–300 Hz, 80–100 μ A, and 200 ms). For the first monkey (M1), we recorded the head-fixed stimulation-evoked movements from 187 sites; subsequent comparison analysis (head-free vs. head-fixed) was performed for 48 sites. Then we stimulated each site using trains of 300 Hz frequency, 200 μ A intensity and 200 ms duration. Stimulation was applied several times, randomly interleaved with no-stimulation trials for each gaze fixation LED (two-thirds stimulation trials vs. one-third non-stimulation trials), at a random time within the 400 to 600 ms after the LED was extinguished see the line plot in Fig. 1E. Monkeys received a juice reward 100 to 200 ms after the stimulation, independent of their gaze behavior. After characterizing each stimulation site we moved the electrode by 0.5 mm vertically and repeated the process. In this way we investigated 152 sites (in 47 electrode tracks) in M1 and 243 sites (in 47 electrode tracks) in M2. Our subsequent data selection criteria (described below) reduced the number of sites used in this study to 100 sites in M1 and 226 sites in M2.

Thirteen sites from M1 and 8 sites from M2 that consistently evoked gaze movements larger than 10° (when stimulated) were selected for a second experimental procedure in which we varied

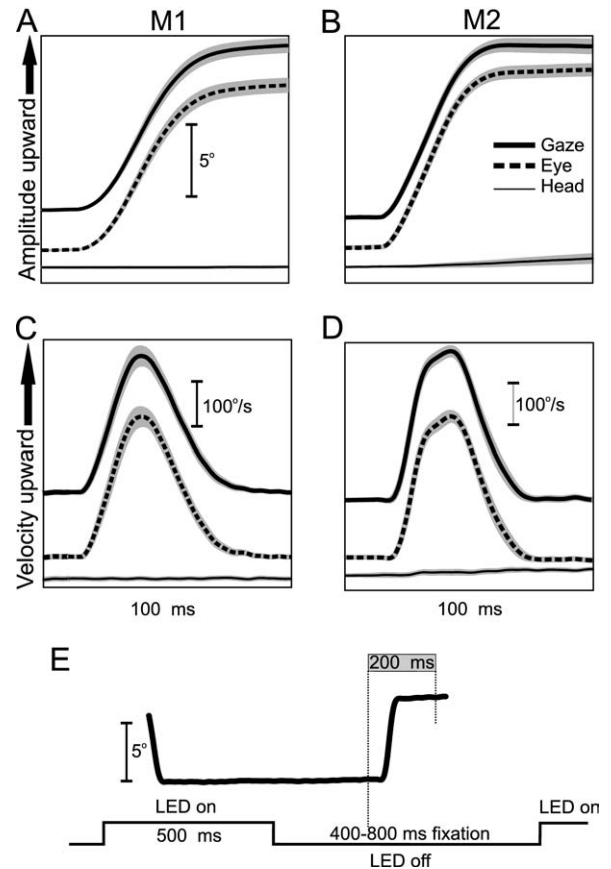


Fig. 1. Average stimulation-evoked gaze shifts. Vertical position (A and B) and corresponding velocity traces (C and D) as a function of time for typical stimulation-evoked gaze (dark-solid traces), head (dark-thin traces) and eye (dark-dashed traces) movements. The plots represent averaged traces \pm standard errors (gray shadows) for one typical site from M1 (A and C) and a similar gaze amplitude site from M2 (B and D). The traces are aligned with the beginning of stimulation; the traces are also plotted separately for display purposes. The averaged stimulation-evoked gaze shifts with relatively small amplitudes (12.23° for M1 and 13.1° for M2), in both monkeys (A and B), were mainly accomplished through eye movements; the head movement contribution was negligible. The corresponding averaged velocity traces (C and D) seem to have similar peak values ($289.2^\circ/\text{s}$ for M1 and $311.23^\circ/\text{s}$ for M2); the gaze and eye averaged velocity traces seem comparable within each site and between sites. E. Experimental paradigm. Grey bar represents a microstimulation train; it was applied at random, while the monkey was fixating in the darkness, 400–800 ms after the LED was turned off.

the microstimulation trains parameters. We applied series of 10–30 stimulations for each experimental condition such that the stimulation duration was varied from 100 to 200, 300, 400 and in some cases 1000 ms. Moreover, for some sites, the cathodal train amplitude was varied from 200 to 400 μ A and the subsequent stimulation-evoked movements were recorded from six sites in M1.

M1 was also trained with the goggle paradigm (for details see Crawford and Guitton, 1997; Constantin et al., 2004). The animal was fitted with a pair of opaque plastic goggles, shaped to the contour of its face, with a single round aperture located at the center of the mechanical range of the eye. This aperture gave the eye a useful visual range of only 10° through which the animal was trained to fixate the LED's. After training, we stimulated 35 sites while the animal was wearing the goggles, and we recorded the

corresponding stimulation-evoked gaze movements to explore whether this training procedure and the subsequent LIP stimulation changed the eye-head coordination pattern.

Data analysis

We used a computer program to convert the coil signal into quaternions for the eye-in-space (gaze) and head-in-space (head) 3-D orientations. From these we calculated the eye-in-head orientation quaternions (eye) (Crawford et al., 1999; Tweed et al., 1990). Quaternions represent orientations as fixed-axis rotations from a reference position (Westheimer, 1957), that is, when the animal is looking straight ahead (Tweed et al., 1990). From these quaternions we computed the gaze trajectories, angles of rotation and angular velocities. Gaze shifts to visual targets were used as control data in some of our analyses. The beginning and the end of the visually-evoked and stimulation-evoked gaze, eye and head movements were manually selected during visual inspection of the movement trajectories plotted on a computer screen. This ensured that both gaze and head position were stable at the beginning and the end each movement. Note that the complete head movement was selected, starting about the same time as beginning of the gaze shift, but generally continuing for 100–200 ms after the gaze shift was complete (when the head moved). We use the term “head movement amplitude” to distinguish the full movement from “head contribution,” which is the head movement up until the end of the gaze shift (Freedman and Sparks, 1997). Stimulation-evoked movements were included for analysis if the peak gaze velocity was larger than 50°/s and the latency from stimulation onset to peak velocity was less than 200 ms (the duration of the electrical stimulus). We also eliminated movements with maximum values higher than two SD from the average. We did not analyze sites in which stimulation evoked eyelid, ear or paw movements. As described in our previous paper (Constantin et al., 2007), LIP stimulation did not always evoke gaze shifts on every trial, and the probability of evoking gaze shifts depended on initial eye position. Here we only examine the kinematics of eye movements that were evoked.

In order to characterize the typical results obtained by stimulating each site we applied the method used by Klier et al. (2001) and Martinez-Trujillo et al. (2003a, 2004), and calculated the “characteristic vector” (CV) for gaze, head, and eye-in-head, to express the stimulation-evoked trajectory expected if the eyes and head were pointing straight ahead at the beginning of the stimulation. The CV’s were calculated using a multiple linear regression of the vector components of movements as a function of their initial position vectors (scaled as a function of angle, computed from quaternions). The CV is the zero vertical-horizontal position intercept of this regression (Klier et al., 2001; Martinez-Trujillo et al., 2004). The goodness of fit for the regression model is given by the corresponding r^2 -values. For the CV analysis we included data only from sites at which we evoked at least seven movements from different initial gaze positions, which were evenly dispersed around the center, and that covered at least three of the four spatial quadrants. The average number of stimulation-evoked gaze shifts included in the calculation of the CV was 36.7 ± 10.3 (with a maximum number of 84 gaze shifts) for M1 and 25.8 ± 10.9 (with a maximum number of 55 gaze shifts from one site) for M2.

We also quantified the 3-D range of eye, head and gaze orientations as described in previous studies (Crawford et al., 1999, 2003; Tweed, 1997). We did this during periods of fixation in normal-behavior gaze/head movements (defined as when the gaze velocity was less than 20°/s and head velocity was less than 10°/s), and at the end of the stimulation-evoked gaze/head movement (which were manually selected). It was ensured that (1) gaze and head position were stable at the start of stimulation, (2) the eye, head and gaze quaternions for the corresponding conditions were selected and the second-order surfaces of best fit to these quaternions calculated (Constantin et al., 2007; Tweed et al.,

1990). This best fit is similar to a linear regression model in a 2-D space and is represented by a twisted plane described by the equation:

$$q_1 = a_1 + a_2 q_2 + a_3 q_3 + a_4 (q_2)^2 + a_5 q_2 q_3 + a_6 (q_3)^2$$

where q_1 represents torsional orientation, q_2 represents vertical, and q_3 represents horizontal orientation. This fitted surface represents the 2-D range given by the best polynomial fit through the data. For both conditions behavior (control) and stimulation we calculated the torsional SD (expressing how close the eye, head and gaze quaternions were to the fitted plane).

Anatomical location of recording sites. Histological verification confirmed that the stimulation sites reported in this study for animal M1 were situated on the lateral bank of the intraparietal sulcus (IPS); M2 is still being used in other experiments. A detailed stereotaxic reconstruction of the stimulation sites was provided in our previous paper (Constantin et al., 2007), which did reveal a slight topographic organization. CV’s evoked from more posterior sites have a larger vertical component; those evoked from more medial sites had a larger horizontal component. Furthermore, deeper sites evoke more downward movements and more superficial sites evoke more upward movements.

RESULTS

General observations

Fig. 1. plots vertical position, and corresponding velocity, traces as a function of time for typical stimulation-evoked gaze (thick-solid lines), head (thin-solid lines) and eye in head (dashed lines) movements. The data represent averaged traces \pm standard error (SE) for one typical site from M1 (A, C) and one typical site from M2 (B, D) (average over 37 and 56 trials respectively). Stimulation of both sites evoked relatively small gaze-shifts (thick-solid lines) that were mainly accomplished through eye movement (dashed lines). The average latency for these stimulation-evoked gaze-shifts was 53.23 ms (± 22.1 ms) for M1 and 55.64 ms (± 11.7 ms) for M2. The head amplitude contribution was negligible (thin-solid lines). Similar observations results were observed for all stimulation sites in both animals. In contrast to long-train stimulation of the SC, our 200 ms stimulation trains never evoked more than one eye movement. Moreover, in our data, gaze position appeared to be “clamped” at the final position of the first saccade until the stimulation train ended. This phenomenon will be quantified in the next section.

Fig. 2 plots 2-D movement trajectories evoked by stimulation of one putative LIP site, during head-unrestrained (head-free—left column) and head-restrained (head-fixed—right column) conditions. Each line represents one stimulation-evoked movement trajectory and the circle (○) indicates its final position. The stimulation-evoked gaze movements (A) were similar in amplitude and direction among all trials within each site, irrespective of the initial gaze position. The eye component traces (C) had similar amplitudes and directions as the gaze traces (in the head-free condition) but showed a decrease in the range of initial eye positions. The reason for this decrease is that the natural range of initial head positions (E) increased the initial range of gaze orientations when the head is free to move. However, the corresponding head movement traces

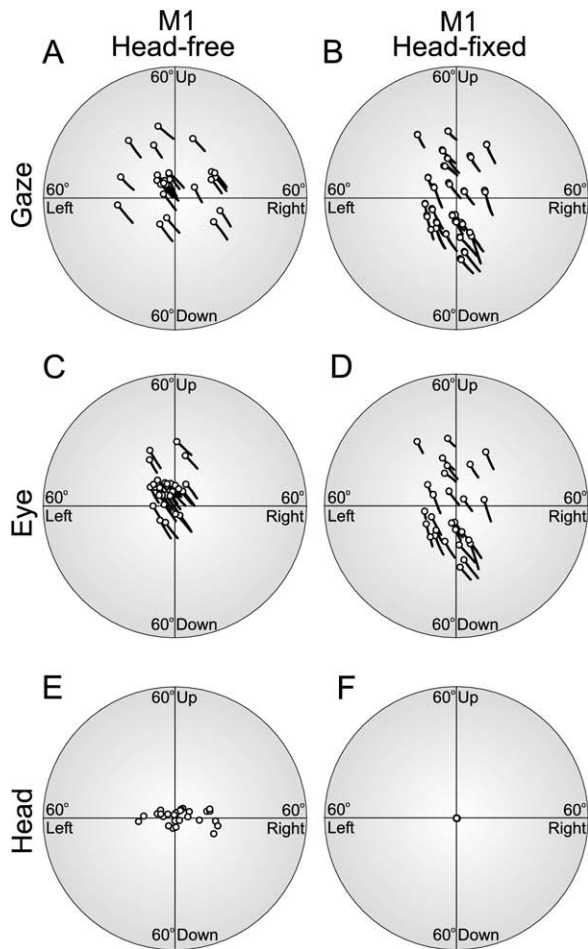


Fig. 2. Behind view of the 2-D trajectories of gaze (A and B), eye (C and D) and head (E and F) evoked by stimulating one putative LIP site during head-free (left column) and head-fixed (right column) conditions. Each point corresponds with the tip of the unit-vector (computed from quaternions, see Experimental procedures) and represents the position for gaze, eye and head, with the horizontal and vertical components projected from behind, plotted on a linear scale. Small circles (○) indicate the end of the movement. The stimulation-evoked gaze (A) and eye (C) movements were similar in amplitude and direction among all trials, irrespective of the initial gaze/eye position. The eye trajectories showed a decrease in the range of initial positions explained by the fact that the natural range of initial head positions (E) increased the initial range of gaze orientations. The head movement trajectories bring a very small head contribution to the gaze trajectories. For the head-restrained condition, the amplitude and direction of the stimulation-evoked gaze (B) and eye (D) trajectories are similar between trials because the head orientation did not vary.

(E) show very small head amplitude contribution to the gaze trajectories.

The right column of Fig. 2 plots 2-D movement traces evoked by *head-fixed* stimulation of the same M1 site shown in the left column. The amplitude and direction of the stimulation-evoked gaze (B) and eye (D) movements are identical between trials and between conditions (*head-fixed* vs. *head-free*); for obvious reasons (the head was immobilized), the head orientation does not vary for the head-fixed condition. Compared to the head-free condition (left column) the only differences appear to be a small

increase in the initial eye position range with the head-fixed (D) relative to the head-free data (C). This is probably due to the fact that with the head fixed, the head cannot assume various initial positions and larger eye-in-head movements were required to compensate for the lack of head motility (E vs. F) as opposed to the head-free condition in which different initial gaze positions were associated with an increased variability of head orientation, simply due to the natural behavior of the animal. During stimulation the head was not moving, therefore the only head contribution to these data analysis was the increased range of initial head, that is gaze orientations.

Each stimulation site evoked specific gaze, eye and head movement components, which varied in direction and amplitude. We used stimulation-evoked movements that met the criteria described in the Experimental procedures in order to calculate the CV for gaze, head and eye for each site.

Fig. 3. plots CVs for gaze, eye and head stimulation-evoked movements, calculated for all sites in M1 (A, C and E) and M2 (B, D and F). For gaze and eye, stimulation always evoked movements contralateral to the stimulated hemisphere (right) with a preferential upward range of movements for M1 and a more varied upward and downward range of movements for M2 (the CV's are spread out more evenly between upward and downward quadrants). In M2 we were able to explore a larger portion of LIP, which allowed for a larger sample of movement orientations. The purpose of this plot and the following analysis is to consider the amplitude and direction of the stimulation-evoked movements as a population. The orientation of the CV_{head} varied, covering the entire 360° range of directions. However, when we compared the CV_{gaze} direction as a function of CV_{head} direction, the correlations were quite small (with values of 0.25 for M1 and 0.137 for M2, calculated for all sites), but statistically different from zero (with a P -value of .009 for M1 and .02 for M2, using a paired Student's t -test, with Bonferroni correction).

The inserts show the amplitude distribution of the CV's for each plot. The large majority of the CV_{head} amplitudes were distributed between 0 and 2°. For M1 the amplitude of CV_{gaze} varied between 2.65° and 14.59° with an average of $8.36 \pm 0.28^\circ$; the amplitude of CV_{eye} varied between 2.42 and 16.7 with an average of $8.61 \pm 0.30^\circ$ and the amplitude of CV_{head} varied between 0.03 and 3.2 with an average of $0.36 \pm 0.03^\circ$.

For M2 the amplitude of CV_{gaze} varied between 2.01° and 15.5° with an average of $7.68 \pm 2.38^\circ$; the amplitude of CV_{eye} varied between 1.71° and 15.27° with an average of $7.55 \pm 2.41^\circ$ and the amplitude of CV_{head} varied between 0.02° and 5.37° with an average of $0.62 \pm 0.83^\circ$. A Student's t -test shows that there was a small but statistically significant difference between the amplitude gaze and eye CV's in both monkeys; for CV amplitude $P=0.016$ for M1 and $P=0.000071$ for M2. For M1 the direction of the gaze and eye CVs was mainly distributed through the upper left quadrant, with very few downward movements. CV_{gaze} direction varied between 87.8° and 194.8° with an average of $129.8 \pm 1.8^\circ$ in polar coordinates and a median

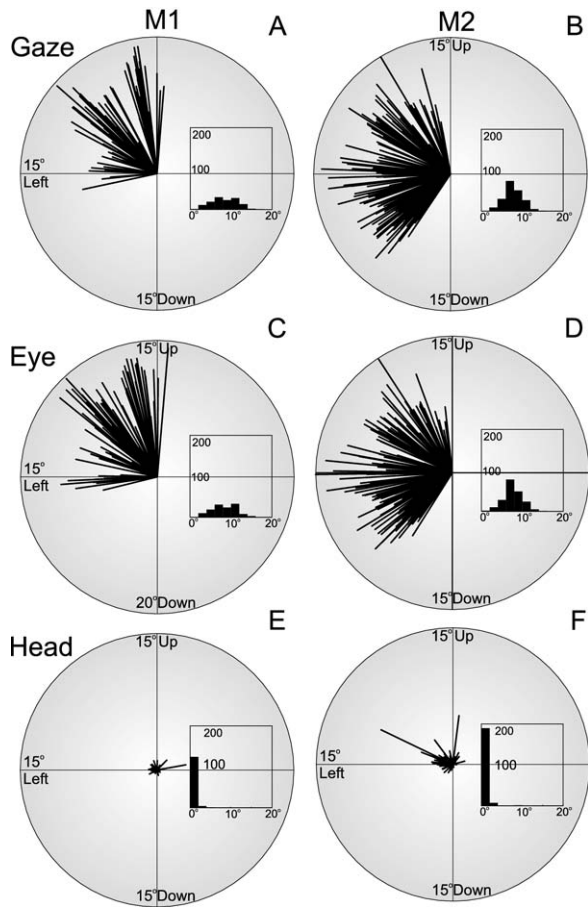


Fig. 3. Characteristic vectors (CV) for gaze (A and B), eye (C and D) and head (E and F), calculated for all sites in M1 (left column) and M2 (right column). Each line represents the CV computed for one particular site. The gaze and eye CV's are leftward oriented, with a preferred upward range for M1. The LIP area for M2 was more thoroughly investigated with the CV's spread out evenly between upward and downward quadrants. The head CV's orientation varied, covering the entire 360° range of directions. The embedded histograms show the distribution of the CV amplitudes for each CV plot. The gaze and eye amplitude distributions were comparable (with each other and in between animals); the large majority of head CV's amplitudes were distributed in a range between 0° and 2°. Note that the CV's for head were calculated from total head movements—marked till the end of the head movement not end of gaze movement.

value of 132.52° ; its direction was similar with CV_{eye} direction which varied between 87.1° and 193.1° with an angular average value of $130.717^\circ \pm 2.02^\circ$ in polar coordinates and a median value of 131.17° . For M2 the direction of the calculated CV's for gaze and eye were spread out between upper left and lower left quadrants. CV_{gaze} direction varied between 99.93° and 236.27° with an average of $190.71 \pm 2.50^\circ$ (in polar coordinates) and a median value of 207.23° ; the CV_{eye} direction seemed similar with gaze, with values that varied between 96.22° and 237.72° , and with an angular average value of $189.73^\circ \pm 2.46^\circ$ (in polar coordinates) and a median value of 205.46° . The direction of the stimulation evoked head movements varied wildly, covering all four quadrants, but note again that the amplitudes were very small.

We also investigated how well the calculated CV's direction fit the actual data (i.e. the direction of the stimulation evoked movements) by calculating the goodness of fit for each site, for gaze, head and eye CV's. The mean values were $.823 \pm 0.023$ for gaze and $.872 \pm 0.024$ for eye (in M1) and $.806 \pm 0.013$ for gaze and $.893 \pm 0.013$ for eye (in M2). The averaged correlation between the head movements and the calculated CVs were weaker, with some sites having strong correlations; but the majority of sites were having very weak correlations (with average values of 0.233 ± 0.158 for M1 and 0.323 ± 0.149 for M2).

The CV's plotted in Fig. 3 provide the overall trends of movement direction and amplitude from our stimulation sites. Henceforth, all statistical analyses that accompanied the figures were based on individual trajectories rather than calculated CV values.

Effects of varying stimulation parameters

Previous SC stimulation studies have shown that: (a) increasing the intensity/amplitude of the stimulation evokes larger gaze shifts (Guillaume and Pelisson, 2001) and (b) increasing the stimulation duration increases head movement duration and therefore the total gaze movement amplitude (e.g. Freedman et al., 1996). We repeated a similar procedure for our LIP stimulation sites. For six stimulation sites in M1 we retested the site with stimulation current amplitudes of $400 \mu A$. For 13 sites in M1 and eight sites in M2 we used four different train durations: 100, 200, 300 and 400 ms with the standard current amplitude, and for three sites in M1 we also applied a stimulation duration of 1000 ms.

Doubling LIP stimulation amplitude from $200 \mu A$ to $400 \mu A$ (with other parameters constant) had no significant effect on the amplitudes and peak velocities of the stimulation-evoked gaze, eye and head movements. This is documented in Table 1. Similarly, increasing the duration of stimulation up to 400 ms had no significant effect on the amplitude of the gaze, eye, or head movements (see Table 1 for *P*-values). The correlations between train duration

Table 1. Effects of varying stimulation parameters

Changed stimulation parameters		P_{GAZE}	P_{EYE}	P_{HEAD}
Train duration	Amplitude M1	0.4082	0.4045	0.7511
Train duration	Amplitude M2	0.1501	0.4461	0.252
Train duration	Velocity M1	0.3515	0.328	0.1958
Train duration	Velocity M2	0.7514	0.5756	0.4669
Train amplitude	Amplitude M1	0.1265	0.1351	0.0531
Train amplitude	Velocity M1	0.8091	0.4295	0.3283

Amplitude and peak velocity *P*-values for gaze, eye and head movements evoked by varying the stimulation parameters: using five different stimulation durations (first four rows), and using two different stimulation amplitudes (last two rows). Using ANOVA as an analysis tool, we investigated the effect (or lack thereof) of increasing the duration of the train stimulation of the amplitude and velocity of the resulting movements. We calculated the average amplitude and velocity (for gaze, head and eye), per site and per different condition (train direction or train amplitude used) and compared those values, for each monkey. The multiple comparisons showed no statistical significance in between conditions.

and amplitude of stimulation evoked movements were very weak, with $R^2=0.102$ for M1 and $R^2=0.230$ for M2. Moreover, there were even weaker correlations between train duration and velocities of stimulation evoked movements, with $R^2=0.0005$ for M1 and $R^2=0.032$ for M2. Furthermore, the amplitude and velocity of stimulation evoked movements did not increase with train duration, such that the slopes of the lines fitted to the data were very close to 0, in both monkeys. In summary, stimulation-evoked movements from LIP appear to be “all or nothing” for gaze and eye movements and close to “nothing” for the head movements, independent of stimulation parameters once threshold had been reached.

However, stimulation duration was correlated with another parameter that we did not anticipate. As mentioned above, we noticed in general that during stimulation after the initial stimulation-evoked saccade, subsequent gaze shifts appeared to be suppressed (i.e. there was a prolonged period resembling fixation). This contrasts, for example, with prolonged stimulation of the SC, which often produces multiple “staircases” of saccades (Bergeron and Guitton, 2002; Paul and Gnadt, 2006). Thier and Andersen, using high frequency and duration electrical stimuli (500 ms, 500 Hz) qualitatively reported and documented staircase saccades being evoked from LIP. Fig. 4 documents this effect by plotting the duration of this suppression effect as a function of stimulus duration. Fig. 4A plots several stimulation-evoked gaze-shifts from a site that produced mainly vertical saccades, plotting the vertical component of gaze position as a function of time; the movements were evoked from one site using five train durations (100, 200, 300, 400 and 1000 ms—the long, vertical dotted line denotes the beginning of stimulation, the short vertical thin black lines denote the end of stimulation). Consistent with our previous analysis, the amplitude of the stimulation-evoked movements was relatively constant between conditions (varying between 6.45 and 7.27° for Fig. 4A). However the absence of further saccades continued up to and beyond the end of stimulation.

To quantify this effect we calculated the average latency between stimulation onset and the start of the 2nd saccade (after the initial stimulation-evoked saccade). We then plotted this “fixation period” as a function of stimulus duration (100–400 ms) for animals M1 (Fig. 4B) and M2 (Fig. 4C). The regression fits to these data confirmed a strong correlation ($R^2=0.989$ for M1 and $R^2=0.972$ for M2) corroborating that stimulation produced a prolonged “fixation” period after the initial evoked saccade. For stimulus durations of up to 400 ms, the “fixation” period (●) always outlasted stimulation (○). This was true even for the first few trials of a given stimulus duration, so there does not appear to be any alternative way that the animals were somehow waiting for the trial to end. The 1000 ms duration trials (tested on just 3 sites in M1) are plotted separately. In these cases the animal usually “broke free” from fixation before stimulation ended, but only after an interval that would normally correspond to 2–3 saccades.

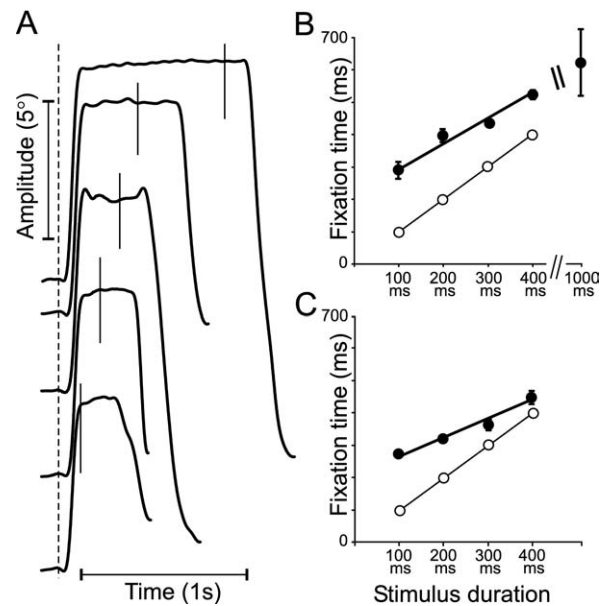


Fig. 4. Effects of varying stimulation train duration on post-saccadic suppression. (A) Typical vertical stimulation-evoked gaze shifts trajectories plotted as a function of time for a representative LIP site, using five train durations (100, 200, 300, 400 and 1000 ms); the beginning of the stimulation is shown by the vertical dotted line; the small vertical filled line that intersects each trajectory shows the end of the stimulation train. The amplitude of the stimulation-evoked trajectories was nearly constant between conditions, but the fixation period that followed each movement increased in duration as a function of stimulation duration. In the right column, this saccade suppression effect is quantified for M1 (B) and for M2 (C), by plotting—●— the average latency between the stimulation start and the beginning of the post-fixation saccade as a function of stimulation train duration, \pm SE. The end point of stimulation is also plotted (○) as a visual reference. Regression lines were fit to the data in the 100–400 ms stimulation duration ranges, showing a strong correlations and positive slope (see text). The 1000 ms data were not included in the regression because we obtained only 19 trials from M1. The suppression period continued to increase for 1000 ms stimulation durations tested in M1, but for these very long intervals monkeys were sometimes able to break fixation before the end of stimulation.

Comparison of normal behavior and stimulation-evoked movements

In contrast to our previous studies in the SC and SEF (Constantin et al., 2004; Martinez-Trujillo et al., 2003a), when we stimulated LIP sites, we obtained small gaze shifts carried mainly by the eye component, with very small head components. This suggests that movements triggered by LIP stimulation may not share the same characteristics as movements evoked by stimulation of the aforementioned structures. It may also suggest that their kinematics are different from normal head free gaze shifts. In order to test the latter hypothesis we compared the evoked gaze shifts with gaze shifts made by the animals during normal visuomotor behavior. The subsequent figures and analysis were done using all our stimulation evoked movements, not taking into account the initial position of gaze and eye. An analysis that accounted for eye and head position gave similar statistical significance, but at the price of losing two-thirds of our data.

Fig. 5. Typical behavioral vs. stimulation-evoked gaze-shifts. Vertical position as a function of time for behavioral-evoked (A) and stimulation-evoked (B) gaze (thick dark line), eye (dotted line) and head (thin dark line) trajectories corresponding to gaze-shifts of similar amplitudes. The behavioral-evoked gaze shift (A) has a small but significant head component and a corresponding eye-saccade component. For comparison, the stimulation-evoked gaze-shift (B) was accomplished mainly by an eye-saccade component and an almost negligible head component. The manually selected movements required a stable gaze position and the beginning of each behavioral or stimulation-evoked movement. The corresponding velocity trajectories for behavioral (C) and stimulation (D) evoked movements support the amplitude trajectories, such that gaze (thick dark lines) and eye (dotted lines) peak velocities have comparable amplitudes between conditions (behavior vs. stimulation); the obvious difference rests with head (thin dark lines) velocities with a value of $34^\circ/\text{s}$ for behavioral-evoked head component and close to $0^\circ/\text{s}$ for stimulation-evoked head component.

Fig. 5 plots vertical position components as a function of time for a typical visually-evoked gaze shift (A) and stimulation-evoked (B) gaze shift, chosen because they had similar amplitudes and starting positions. The corresponding velocities look similar for gaze (thick line) and eye saccade (dotted line) for the behavioral (C) and stimulation-evoked (D) movements. This figure illustrates that stimulation-evoked gaze shift of about 9.5° (B) was accomplished by a 9.3° eye-saccade and an almost negligible head movement component (close to 0°). For comparison, a behavioral gaze shift of about 9.7° (A) that was accompanied by a slightly smaller eye-saccade component accompanied by a small but significant (3.2°) head component.

The velocity traces (C and D) for gaze (thick line), head (thin line) and eye (dashed line) support the amplitude traces such that gaze velocities had similar values between conditions (behavior peak velocity of $253^\circ/\text{s}$ versus stimulation peak velocity of $238^\circ/\text{s}$) and also similar with the saccade velocities. The obvious difference rests in the head velocity values—with a value of $43^\circ/\text{s}$ for the behavioral evoked movement and close to $0^\circ/\text{s}$ for the stimulation-evoked movement. These are just typical examples;

for a more comprehensive analysis we pooled all the stimulation-evoked gaze-shifts and their corresponding eye and head components and compared them against behavioral gaze-shifts of similar amplitude (up to 25°).

Eye and head contributions to the gaze shift

Fig. 6 shows the relative contribution of eye (A and B) and head (C and D) to gaze, for behavior (\circ) versus stimulation-evoked (\bullet) gaze-shifts, in both monkeys. The amplitude of the behavioral eye component increased steadily as a function of gaze, in both monkeys. For the stimulation-evoked gaze movements, the eye-saccade contribution to gaze increased with gaze amplitude, in a fashion similar to the behavioral data. The visually-evoked and stimulation-evoked movements were interleaved within the same recording sessions. The contribution of eye amplitude to gaze was statistically similar between conditions (behavioral versus stimulation) in both monkeys ($P=0.334$ for M1 and $P=0.485$ for M2, paired Student's *t*-test with Bonferroni correction). The head amplitudes during behaviour condition increased with larger gaze amplitudes (gaze movements larger than 5°). However, in contrast to behavior condition, the stimulation head amplitudes were

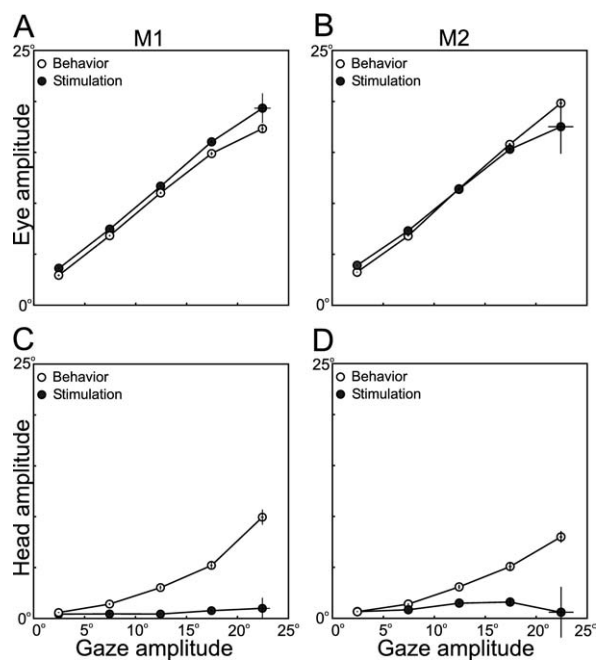


Fig. 6. Relative contributions of eye and head to gaze. We plotted the eye amplitude (A and B) and head amplitude (C and D) as a function of gaze amplitude after averaging the eye and head movements corresponding to each 5° bin of gaze movement. We plotted the behavior data (\circ)—averaged for a total of 1135 movements for M1 and 1661 movements for M2) versus stimulation data (\bullet)—averaged for a total of 1156 movements for M1 and 2857 movements for M2). The amplitude of the behavioral and stimulation-evoked eye component increased as a function of gaze in both monkeys. The head amplitudes increased with gaze amplitude for the behavioral data (\circ); in contrast the head amplitudes were small and did not vary with gaze amplitude for stimulation data (\bullet). Left panel: M1 (A and C). Right panel: M2 (B and D). Note that we measured head amplitude to the end of head movement, not the end of gaze-shift.

very small (less than 3°) and it did not vary with gaze amplitude (Fig. 6, lower panels analyze the head relative contribution to gaze). The slopes of regression lines fit to these data had very small values (slope=0.034 for M1 and slope=0.009 for M2). Moreover, there was a statistical difference between behavioral and stimulation-evoked head movements ($P=4.1 \times 10^{-113}$ for M1 and $P=5.8 \times 10^{-126}$ for M2, paired Student's *t*-test, with Bonferroni correction).

It is possible that our stimulation data and behavioral data did not follow the same directional distributions. Since the relative contributions of the eye and head are different for horizontal and vertical gaze-shifts (Tweed et al., 1995) we also repeated our analysis separately for the vertical and horizontal amplitudes of gaze, eye and head movements. The statistical tests calculated using one dimensional components of gaze, head and eye movements showed similar results to those reported above. For the horizontal movement components, the contribution of eye amplitude to gaze was not significantly different between behavioral and stimulation data, in either monkey ($P=0.231$ for M1 and $P=0.152$ for M2; paired Student's *t*-test). The vertical component analysis showed similar results with $P=0.534$ for M1 and $P=0.674$ for M2 (paired Student's *t*-test). The relative contribution of head amplitude to gaze did not vary with gaze amplitude in either dimension; both vertical and horizontal datasets had a statistical difference between behavioral and stimulation conditions, with $P=6 \times 10^{-4}$ for $M1_{\text{horizontal}}$; $P=23 \times 10^{-5}$ for $M2_{\text{horizontal}}$; also $P=0.003$ for $M1_{\text{vertical}}$ and $P=45 \times 10^{-3}$ for $M2_{\text{vertical}}$ (paired Student's *t*-test). Thus, the difference between the behavioral and stimulation data cannot be accounted for by directional differences.

Previous behavior studies have shown that contribution of head amplitude to gaze can be increase by training the monkey to make gaze shifts while wearing pin-hole goggles, which restricts their useful eye-in-head range to a diameter of 10° (Crawford and Guitton, 1997). However, this increased trend in head amplitude was not preserved during the stimulation of the SC (Constantin et al., 2004). We initially hypothesized that this might be more likely to occur with LIP stimulation, because LIP is fairly early in the gaze control system where one would not expect eye and head signals to have been separated yet. Conversely we expected the eye-head coordination gate to be located somewhere downstream where it could be accessed by a signal arising from LIP. Therefore, we hypothesized that the trained "goggle" strategy would be preserved during LIP stimulation. To test this, we trained M1 with the goggle paradigm for 3 weeks until it was able to switch between goggles/no goggles strategy just by donning/removing the goggles.

Fig. 7. plots the head amplitude as a function of gaze amplitude, binned every 5° , for the behaviour and stimulation evoked movements in the "no goggles" condition (\circ and \bullet) versus the goggles conditions (\square and \blacksquare). After training, the contribution of head amplitude to behavioural gaze-shifts increased with the goggles (\square) compared to the "no goggles" condition (\circ) ($P=7 \times 10^{-7}$, ANOVA). How-

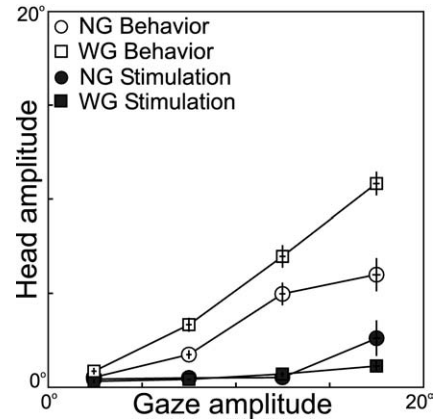


Fig. 7. With goggle (WG) versus no goggles (NG). We plotted the head relative contribution to gaze, by averaging the head movement amplitudes corresponding to each 5° bin of gaze movement, in four different conditions—NG (\circ) versus WG (\square), and stimulation (black symbols— \bullet) versus behavior (white symbols— \circ). In behavioral condition the head amplitudes increase with larger gaze movements; the goggle condition boosts the head amplitude contribution even more. In the stimulation condition, head amplitude contribution was almost negligible in the no goggle condition and did not increase with the goggles.

ever, in gaze-shifts evoked during LIP stimulation, the head amplitude did not significantly increase when the monkey donned the goggles ($P=0.535$, in paired Student's *t*-test).

Main sequence

The peak velocity amplitude relationship for gaze, eye and head movements during normal behavior follows a well-known trend in which the maximum gaze and eye peak velocities increase almost linearly as a function of the corresponding gaze and eye amplitudes, for movements less than 20° (Freedman and Sparks, 1997, 2000; Freedman et al., 1996). Fig. 8 compares the main-sequence relationships for gaze, eye and head between behavioral and stimulation-evoked movements. As expected, for gaze shifts with larger amplitudes, the maximum velocities of the movement increased, in both monkeys (A and B), for both behavior (\circ) and stimulation-evoked movements (\bullet). The peak eye velocity followed the same trend (C and D).

Based on inspection of Fig. 8C, D, it appears that the stimulation data and behavioral data diverge slightly above 15° . However, this part of the range makes up only $\sim 1\%$ of the data, and the trends are opposite for M1 and M2. When one considers the entire data range, there was no statistical difference between behavioral and stimulation-evoked movements ($P=0.08$ for M1 and $P=0.43$ for M2, paired Student's *t*-test). The head peak velocity follows a steady increase as a function of head amplitude in the behavioral condition, for both monkeys (E and F). This increase is not observed in the stimulation-evoked head movements, most of which are less than 5° , with very few movements between 5 and 15° . To clarify this, we increased the scale of the head data points and plotted them above the original panel (E and F, grey area). We fitted regression lines to the "blown up" data, and then compared the slopes of the two

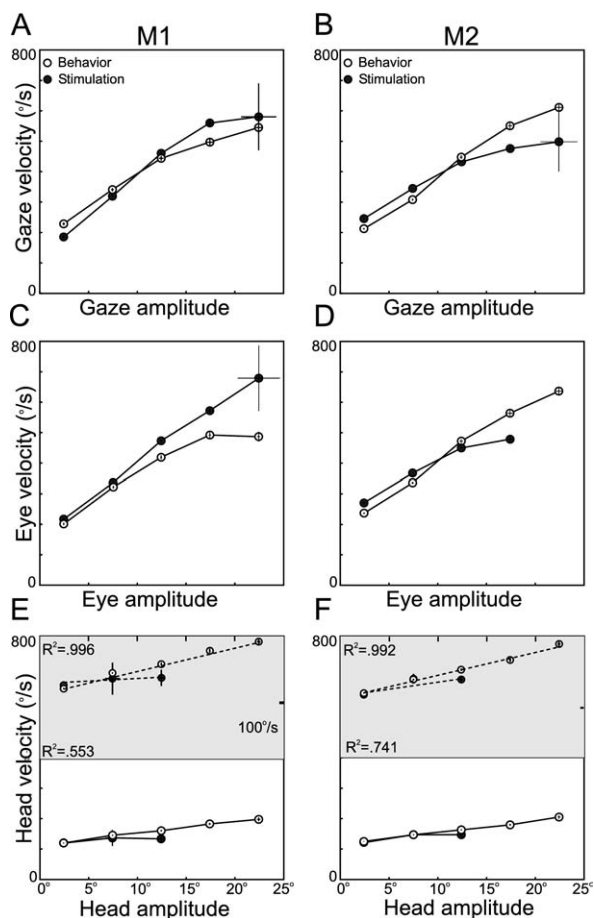


Fig. 8. Amplitude-velocity relationships. Average peak velocity as a function of average amplitude, for Gaze (A and B), Eye (C and D), and Head (E and F) for M1 (left column) and M2 (right column), contrasted behavior (○) and stimulation (●) data binned into 5°. Panels (E) and (F) plot a double graph; the points plotted in the grey area are just the “blown-up” version of the averaged head values plotted in the white area, to clarify the difference, between the stimulation and the behavioural data. Moreover, we fitted the “blown up” points with linear regression lines which show very high correlations, especially for the behavioural data.

lines. The results showed no statistical difference between stimulation and behavioural conditions, with $P=0.793$ for M1 and $P=0.824$ for M2 (two-tailed t -test). Thus, although the amplitudes of the movements were small, overall they followed normal velocity-amplitude relationships.

An analysis that accounted for initial eye and head positions gave similar statistical significance, but at the price of losing two-thirds of our data. In this analysis we matched the initial eye and head position for behavioural and stimulation evoked gaze shifts and calculated the eye and head contributions to gaze. In both monkeys, the eye-saccade amplitude increased with gaze amplitude, in both stimulation and behavioural conditions, with $P=0.87$ for M1 and $P=0.56$ for M2 (paired Student's t -test with Bonferroni correction); the stimulation head amplitude did not vary with gaze (with amplitude values up to 1.8°). We also compared the main sequence for the matched data with the following results: the peak gaze velocities showed

a steady increase with amplitude, with no statistical significance between the behavioural and stimulation conditions, with $P=0.32$ for M1 and $P=0.45$ for M2. The peak eye velocities followed the same trend, with $P=0.38$ for M1 and $P=0.48$ for M2. The trend for behavioural head movements was not followed in the stimulation condition—with average head amplitudes of $0.88^\circ \pm 0.1^\circ$ for M1 and $0.56^\circ \pm 0.01^\circ$ for M2.

3-D kinematics

During natural fixations, the eyes and head follow Donders' law (Crawford et al., 1999; Crawford and Vilis, 1991), which states that for any 2-D gaze pointing direction (defined by a horizontal and vertical component), there is a unique amount of eye and head torsion respectively. Here we assessed whether the restrictions from the behavioural movements are also obeyed by the stimulation-evoked movements.

Fig. 9. (left column) shows data from one site from M2, the horizontal component (ordinate) being plotted as a function of the torsional component (abscissa), in right-hand rule coordinates, for quaternions representing the gaze (A), eye (D) and head (G). We fitted second-order surfaces to the 3-D datasets for gaze, eye and head during natural fixations (defined when the gaze velocity was less than 20°/s and head velocity was less than 10°/s). These planes of best fit are called Donders' surfaces and represent a 2-D range given by a polynomial best fit through the data. The front edge of the fitted planes is emphasized by the thick line. For gaze and head positions, the plane fits highlight those positions with larger oblique components, also have a larger torsional component in space-fixed Cartesian coordinates. It has been shown that this is because these ranges follow a zero-torsion rule in Fick coordinates (Glenn and Vilis, 1992; Radau et al., 1994).

The fit of the eye component results in a flatter plane, suggesting that the eye-saccade component might follow Listing's law—a version of Donders' law in which the torsional component for any gaze direction comes close to an ideal zero torsion in a head-fixed, orthogonal coordinate system named “Listing's coordinates” (Tweed et al., 1995).

The middle column in Fig. 9. displays the same fixation points as the left column, but this time plotted in Donders' coordinates: where the vertical and horizontal axis are aligned with the fitted surfaces of the left column, and the orthogonal axis plots torsion relative to the Donders surface (Klier et al., 2003; Martinez-Trujillo et al., 2003a). Here, any torsional deviations from zero represent deviations from Donders' law. The right column displays quaternions for gaze, eye and head corresponding to the stimulation-evoked movement end-points from the same animal and recorded in the same day as the behavioural data, plotted in Donders' coordinates. Note that these values were always taken at the end of both the gaze movement and any head movement.

For both behavioural and stimulation data, the fixation points are situated quite close to the y-axis, showing that Donders' law is obeyed. For both behavioural and stimulation data, the fixation points show a larger spread for the

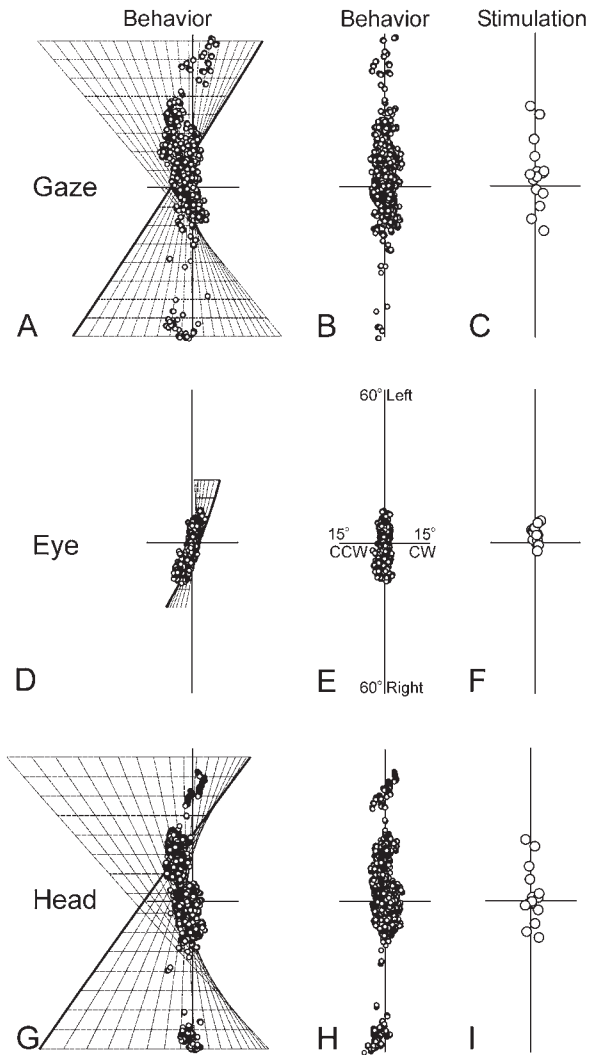


Fig. 9. 3-D analysis of behavior versus stimulation for one site. Scatter plots of the torsional (abscissa) and horizontal (ordinate) components of gaze (A, B and C), eye (D, E and F), and head (G, H and I) position quaternions converted to angles of rotation in right-hand rule coordinates see Experimental procedures. Left and middle column: behavior fixation points from a M2 site; right column: stimulation fixation points. Left column: 2nd-order best-fit surfaces were computed to the behavior data points; the front vertical edges of the surfaces was emphasized (black thick line) to ease visual interpretation of these 3-dimensional plots. The gaze and head fitted surfaces look like flat planes twisted about the center; the eye surface seems to be more flat. Determining how well Listing's and Donders' laws are obeyed is measured by how well the points adhere to their best-fit surfaces (see text for values). Middle and right columns: Behavior and stimulation end points in Donders' coordinates. Scatter plots of the behavioral fixation points (B, E and H) and stimulation fixation points (C, F and I) quaternions torsional components (abscissa) against the horizontal components (ordinate) in Donders' coordinates. For both behavioral and stimulation data, the data show a larger spread for the torsional component of gaze (B and C) and head (H and I) than for the eye (E and F).

torsional component of gaze (B and C), and head (H and I) than for the eye (E and F). This suggests a tighter control of the torsional component for the eye. It appears that the stimulation-evoked gaze shift end points and their corre-

sponding eye and head components might fall within a similar 3-D range as the behavioral evoked movements, but this is difficult to judge visually.

For a more quantitative approach we calculated the torsional standard deviation (SD), separately for gaze, head and eye fixation points in both conditions: visual and stimulation-evoked movements, for each site (Klier and Crawford, 2003; Martinez-Trujillo et al., 2003a) in both monkeys. In the 48 sites where we recorded head-fixed data, the torsional SD of the stimulation-evoked eye movements (average=0.57°) was not significantly greater than the torsional standard deviation (average=0.47°) of normal head-fixed saccades ($P=0.75$, paired Student's *t*-test). The head-free data were more complex. On average, the torsional SDs for visually-evoked gaze, head, and eye movements were 3.67°, 3.38° and 1.62° respectively. In comparison, the average torsional SDs of stimulation-evoked gaze, head and eye movements were 4.83°, 4.68°, and 2.00° respectively. These values were significantly larger than the behavioral data end-points: for gaze ($P=0.009$, paired Student's *t*-test), eye ($P=0.05$, paired Student's *t*-test) and head ($P=0.007$, paired Student's *t*-test). Thus, visually and stimulation-evoked movements followed similar 3-D rules, but the latter were less precise.

What might explain the increased torsional range of stimulation-evoked gaze and eye movements? One possibility is that the pattern of torsional eye-head coordination observed in normal behavior (Crawford et al., 1999) is disrupted in gaze shifts evoked during LIP stimulation. Fig. 10 shows examples of normal eye movement behavior, with eye torsion plotted in Listing's coordinates. For the movements plotted in Fig. 10 panels A through F, we matched the kinematics (positions, gaze metrics) of the behavioral and stimulation-evoked movements as well as possible, given the differences in head movement. The stimulation-evoked movements were collected from a site that was stimulated during both head-fixed and head-free conditions. The question here is whether the torsional aspects of these movements matched, as we observed for the SC and SEF (Klier et al., 2003; Martinez-Trujillo et al., 2003a, b).

Fig. 10A. plots torsional eye position as function of time for a typical head-free saccade (solid line) and a typical head-fixed saccade (dotted line). (The horizontal and vertical components of the saccade are not shown.) The head-fixed saccade essentially remained in Listing's plane, whereas the head-free saccade had a fast torsional component that was followed by a slower torsional VOR phase in the opposite direction. The same pattern can be seen in the 2-D trajectories in a series of head-fixed saccades (Fig. 10B) and head-free saccades+VOR (Fig. 10C). These observations have been reported previously in numerous studies (Crawford et al., 2003; Klier et al., 2003; Misslisch et al., 1994a; Tweed et al., 1994).

What would happen in head-free gaze shifts evoked during stimulation of LIP, which we have already shown do not include normal head movement components? We have proposed that the torsional components observed in head-free saccades are pre-programmed to compensate

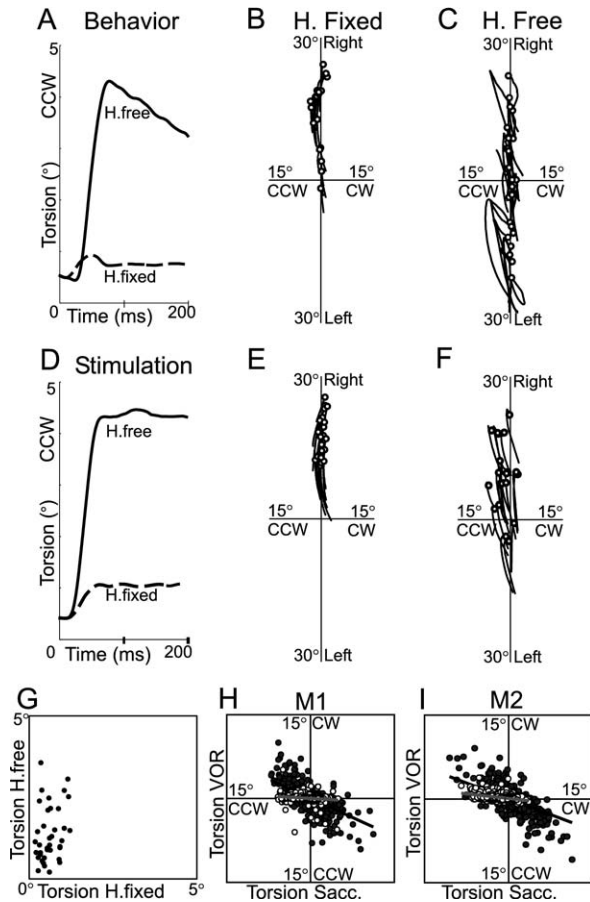


Fig. 10. (A) and (D): Eye torsion trajectories during head-fixed (dashed lines) vs. head-free (filled line) movements, are plotted as a function of time in Listing's coordinates; the movement traces are aligned on initial position and beginning of stimulation. 2-D plot of the torsional (abscissa) and horizontal (ordinate) components of eye position quaternions converted to angles of rotation in right-hand rule coordinates, plotted in Listing's plane. (B) and (E): with the head fixed, torsion remains in Listing's plane (i.e. parallel to the plane of 0 torsion) throughout behavior (B) and stimulation-evoked (E) movements. (C) and (F): in contrast, with the head free, torsion is driven out of and then back into Listing's plane during behavior (C); during stimulation (F), the eye is driven out of Listing's plane and there is no VOR (no head movement) to bring it back. shows the end of the movement. These effects are quantified in the lower panel (G, H and I). (G): mean absolute torsion for head-free saccade as a function of head-fix saccade. (H) and (I) plots torsional VOR component as a function of the torsional saccade component for M1 (H) and M2 (I) (○). stimulation-evoked versus (●) behavioral eye movements. In both monkeys, the behavioural data (●) shows a normal negative relationship between torsional saccade and torsional VOR. In contrast, stimulation data (○) shows the torsional saccade spread over a similar distribution but a very small torsional VOR.

for the expected torsional VOR components associated with head movement (Crawford and Vilis, 1991; Crawford et al., 1999), or they could be triggered by low-latency vestibular feedback, since normally the head is starting to move at about the same time. During stimulation, the head does not move, so if these components are vestibular-triggered (or if the brain "knows" that the head is not going to move) they should no longer appear. But if the brain pre-programs these movements and "expects" a head

movement, it should continue producing torsional saccades.

During head-fixed LIP stimulation (Fig. 10D; dashed line and Fig. 10E), saccades remained in Listing's plane. In the head-free condition (Fig. 10D; solid line and Fig. 10F), LIP stimulation produced saccades with larger torsional components even though they were not followed by VOR. Fig. 10F plots stimulation-evoked movements from a typical LIP site, the same site that evoked the head-fixed movements plotted in Fig. 10E. Torsional eye position traces held their final position, presumably sustained by tonic motoneuron signals originating from the torsional neural integrator (Crawford et al., 2003). This explains why eye-in-head torsion was higher—at the end of gaze shifts—during LIP stimulation. Moreover, this suggests that torsional components in head-free saccades are pre-programmed to anticipate the VOR, and that the system responsible for this was "expecting" a head movement during LIP stimulation.

These results are quantified and documented in the lower row of Fig. 10. Fig. 10G plots the absolute value of torsion for head-free saccades versus head-fixed saccades, averaged for each site, for the 48 stimulation sites in which obtained both sets of data. The head-free torsional saccade amplitudes were significantly larger (Mann-Whitney $U=10.5$, $n_1=n_2=48$, $P<0.05$) than head-fixed torsional amplitudes. This shows that this behavior was context-dependent, and that torsion is not just generally sloppy during LIP stimulation. In Fig. 10, panels H and I plotted the torsional components of the VOR as a function of the torsional component of head-free saccades for M1 and M2, respectively. Every stimulation-evoked data movement is shown (○), along with a similar population size-matched behavioral data (●). In the behavioral data, the amplitude of the saccades and VOR torsion showed a clear negative correlation with $R^2=0.571$ for M1 and $R^2=0.489$ for M2. In the stimulation-evoked data (○) the amplitude of the eye-VOR torsional component did not vary with the eye-saccade torsion; it remains close to 0, with $R^2=0.044$ for M1 and $R^2=0.124$ for M2. The regression slopes fitted to the behavioral data points and stimulation-evoked data were statistically different from each other in both monkeys (two-tailed t -test with $P=0.001$ for M1 and M2). Thus, the increase in eye (and gaze) torsion was due to the continued presence of torsional saccade components and the absence of subsequent VOR slow phases (which normally cancel out).

In the previous analysis we implicitly assumed that the torsional saccade components were still being programmed in the normal way: to anticipate VOR movements related to head movement. Another possibility is that these movements were simply random. One way to test between these possibilities is to plot the torsional saccade component as a function of the initial vertical eye position. Here is the logic behind this test. Approximately 98% of our evoked gaze movements were directed to the left. If we further refine this to just the sites that gave CVs within 30° of horizontal, the associated head movements (had they occurred) should have been even closer to pure

horizontal (because the eye moves more vertically than the head in our preparation, e.g., Crawford et al., 1999). Given this expectation, the laws of rotational kinematics predict that the associated VOR movements would have CCW components for eye positions above primary position, and CW components for downward eye positions (Crawford and Vilis, 1991; Smith and Crawford, 1998). Conversely if the system were expecting these movements and produced anticipatory torsional components in saccades, the saccade data should show the opposite correlations: clockwise torsion for upward eye positions and CCW for downward eye positions (Crawford and Vilis, 1991; Tweed, 1997; Crawford et al., 1999).

The results of this test are shown for both monkeys in Fig. 11. As one can see, the relationship between vertical eye position and saccade torsion during leftward gaze shifts is not random, but rather follows the prediction of a system that is producing anticipatory torsional saccade components for head movements that do not come. The slopes of the regression lines fitted to the data were 0.095 (M1) and 0.109 (M2). The r -values showed a solid correlation between torsional eye saccade and initial vertical eye position with $r=0.750$ for M1 and $r=0.788$ for M2, with $P=0.001$ for both monkeys. This not only confirms that saccade torsion is anticipatory, as in normal head-free gaze shifts, it also tends to confirm that the system was expecting a head movement.

DISCUSSION

The goal of the present study was to analyze the 3-D eye-head coordination patterns of gaze shifts evoked dur-

ing stimulation of LIP in head-unrestrained monkeys, and compare these to normal behavior. Note that extra-physiological electrical stimulation might change the dynamics of a system so much so that it is hard to assign the results to any one point in the brain: all we know is the source of the perturbation, not the extent of its effects. Nevertheless, our result show that LIP stimulation evoked small, “all or nothing” contralateral gaze-shifts, accomplished mainly by eye-saccades with negligible (close to 0) head components. For small gaze shifts it is hard to qualitatively predict how much the head should be moving, therefore we quantitatively compared these movements with visually-evoked gaze-shifts. The amplitude-velocity relationships of the stimulation-evoked gaze and eye movements were comparable with the behavioral movements. However the stimulation-evoked head movements are close to 0 and obviously they do not follow the pattern of the behavioral head movements. Moreover, although some aspects of the normal 3-D eye-head coordination strategy were followed, eye saccades had torsional components that were not followed by equal and opposite VOR components (as during normal behavior). The latter was related to the paucity of head movements.

Thus, probably the most important message derived from our data are that during LIP stimulation-evoked gaze shifts the eye saccade component behaves in a way appropriate for head-free gaze shifts, but the head movement component is somehow absent. This was unexpected, given our very different results in similar stimulation experiments with the SEF, FEF, and SC, especially since LIP is placed even further upstream in the gaze control system,

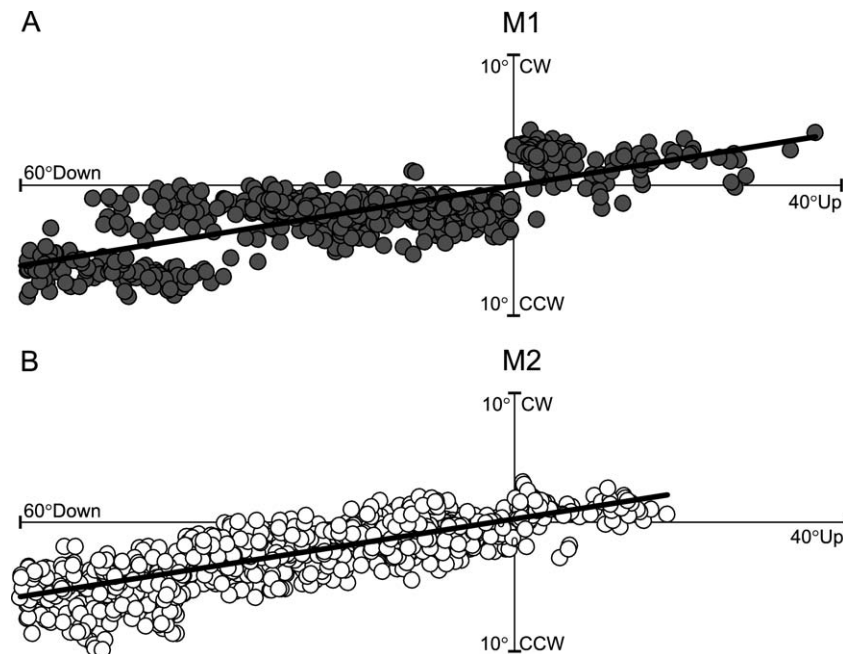


Fig. 11. (A) and (B) Torsional eye saccade component plotted as a function of initial vertical eye position, for all the leftward stimulation evoked eye movements (● – M1; ○ – M2). For these plots we only used the movements evoked from sites with CV's within 30° from the horizontal direction. These data suggest that the saccades possess the normal torsional kinematics that would have been present if a normal horizontal head movement accompanied the gaze shift (which was not the case in these stimulation-evoked movements).

well before one would expect any separation of the gaze signal into eye and head components. However, one clue to this phenomenon might be another unexpected observation: after the initial short-latency stimulation-evoked saccade, other saccades were suppressed for the duration of stimulation. We will consider these findings in the context of the literature below.

Comparison with previous LIP stimulation studies

The results of our head-free study extend a picture sketched by previous head-restrained microstimulation studies (Mushiaki et al., 1999; Shibutani et al., 1984; Thier and Andersen, 1996, 1998) in LIP which evoked contralateral saccades with relatively small amplitudes (mostly between 0 and 20°) and a large variety of vertical components, as a function of site. Our data showed a very similar range of amplitudes. The directional range of our movements were also very similar to those reported by Thier and Andersen (1996, 1998) in one monkey (which seemed to also favour more upwards movements). The second monkey showed an increase and movements range, with a larger downward component, but this might simply be due to the fact that we explored many more sites than they did. Moreover, in both of our studies, the movements evoked from a given LIP site had similar direction and amplitude, irrespective of the initial position, and eye movements were essentially similar to the gaze movements, with the accompanying head movements being absent or very small (although they did not document this to the extent provided here: only one head-free site was quantified, and they could not do a 3-D analysis). Thus, the general 2-D observations made by those authors for LIP were essentially the same as those reported here.

However, there were some differences between the results reported in our studies. First, Thier and Andersen reported gaze shifts evoked from an “intercalated zone” (a small strip of cortex located at the floor of the intraparietal sulcus) which showed goal-directed characteristics and slightly larger head movements. We attempted to explore this region as well, but were unable to evoke such gaze shifts, either because of some difference in the stimulation parameters, the behavioral state of the animal, or perhaps we simply missed this small area. We did not deem this to be a failure in our study because our goal was to characterize LIP. Second, they reported “staircase saccades” (a series of saccades evoked during prolonged stimulation) for at least one LIP site. We never observed in hundreds of sites tested, even with 1 s stimulation. Our study found that once threshold was reached, neither amplitude nor duration increases had any effect on the evoked gaze shift. And once threshold was reached we never observed a second gaze movement even during stimulation trains of up to 1000 ms, the eye tending to continue fixation until the end of stimulation: Thier and Andersen did not report this, although a similar pattern can be observed in some of their data (Thier and Andersen, 1996—Fig. 3).

There are several methodological differences between our studies that might account for these minor differences. First, our monkeys were always in a head-free state,

whereas theirs were only in a semi-free state on some trials. Second, they used of a higher stimulation frequency (500 Hz), whereas we only used frequencies up to 300 Hz. Ultimately our parameters arose from our original SC studies (Constantin et al., 2004; Klier et al., 2001) which were derived from Freedman et al. (1996) and from our own preliminary work. Finally, it is possible that our animals had been trained differently: behavioral state is known to influence the results of stimulation (Ascencio-Monteon et al., 2007; Constantin et al., 2007; Tehovnik et al., 2003).

Comparison with normal behavior

At a first glance, the velocity and position trajectories of stimulation-evoked gaze and eye movements seemed to be quite similar with amplitude-matched behavioral movements. Indeed, it is tempting to conclude, erroneously, that the lack of head movements in these gaze shifts is simply because the gaze shifts were small. However, our behavioral results confirm that in monkeys allowed to freely move both the eye and head, even small gaze shifts are accomplished by a combination of eye and head components (Constantin et al., 2004; Freedman and Sparks, 2000). Our quantitative comparison of these data with the stimulation-evoked data showed that, even for size matched gaze shifts, the accompanying head movement components were too small to be considered normal. On the other hand, the individual eye-in-head saccade and head movement components had essentially normal velocity-amplitude relationships (Freedman and Sparks, 1997, 2000), suggesting that these were normal movement components, just not coordinated with each other in a normal fashion. This seemed to be similar with the results qualitatively presented by Thier and Anderson study, that evoked very small head movements, when the head was allowed horizontal rotations.

The current study also confirms the observation, now shown many times for both the human and monkey, that normal gaze, head, and eye movements obey various forms of Donders’ law (Crawford et al., 1999, 2003; Klier and Crawford, 2003; Tweed, 1997), including the Fick strategy for head movements associated with gaze shifts (Crawford and Vilis, 1991; Misslisch et al., 1994b; Tweed et al., 1995) and Listing’s for eye movements (Crawford and Vilis, 1991; Misslisch et al., 1994b; Tweed et al., 1995). Our observations confirm that in general these rules are also followed in gaze shifts evoked during LIP stimulation. This is not a trivial result, because brainstem stimulation can produce quite dramatic torsional violations in all of these forms of Donders’ laws (Crawford and Guitton, 1997; Klier and Crawford, 2003). However, the stimulation-evoked movements obeyed these rules with less precision, and differed from the visually-evoked movements in one qualitatively important respect.

As confirmed here, during normal head-free gaze shifts the saccade portion of the eye-in head gaze shift consistently include torsional components (Crawford et al., 1999; Crawford and Vilis, 1991; Tweed, 1997), depending on the overall kinematics of the gaze shifts. The apparent reason for this is to predictively cancel out torsional VOR compo-

nents associated with the post-gaze shift head movement, so that torsion always ends up at zero (Radau et al., 1994; Solomon et al., 2003; Straumann and Zee, 1995). These large torsional “blips” all but disappear in head-fixed movements (Cohen et al., 1992; Fetter et al., 1994; Henn et al., 1992; Lee et al., 2000; Misslisch et al., 1994a; Moore et al., 2001; Raphan and Cohen, 2002; Schmid-Priscoveanu et al., 1999; Solomon et al., 2003; Straumann et al., 1991; Straumann and Zee, 1995; Straumann et al., 1996; Tweed, 1997), either because the system “knows” that the head will not move or from a lack of vestibular feedback. The saccade-related torsion was still present in our head-free stimulation-evoked gaze shifts, but of course they were not followed by significant torsional VOR components, resulting in an overall increase in the torsional width of Listing’s plane. This cannot be explained as a general sloppiness in torsional control, because torsional saccade components remained small when the head was fixed. This provides the first direct evidence for the supposition that these saccade-related torsional blips are pre-programmed in an anticipatory fashion, and are not triggered by vestibular feedback (Crawford et al., 1999; Crawford and Vilis, 1991).

Moreover, the persistence of these eye-in-head torsional components in our stimulation data suggest that the oculomotor system was “expecting” a normally-coordinated head movement. This in turn suggests that LIP usually is involved in the generation of normally coordinated eye-head gaze shifts, but in these stimulation-evoked movements the head component is lacking, either because it is implemented through a parallel channel or because it is damped at a fairly low level. We prefer the latter explanation, because (1) LIP is at a fairly early stage in the visuomotor transformations for gaze, and (2) an efference copy of the head movement plan is probably required to compute the necessary torsional component of the saccade, a process that likely occurs downstream from the cortex (Klier et al., 2003; Martinez-Trujillo, 2003b). Some sort of unnatural breaking of the head might also explain the otherwise strangely increased torsional standard deviation of head orientation, despite the absence of head movement.

Comparison with other gaze control structures

This study produced a number of unique results, even relative to our very similar studies of head-free stimulation of the SC, SEF, and FEF which used almost identical methodologies (except for stimulation amplitude). Prolonged stimulation to these structures produced “staircase” repetitions of gaze shifts (McIlwain, 1988; Stanford et al., 1996) and/or (when the head is free to move) prolonged head movement (Chen and Walton, 2005; Corneil et al., 2002; Freedman et al., 1996). Again, we did not observe this here: stimulation duration did not affect head movement and with prolonged stimulation gaze appeared to be “locked in place” until the stimulation train was

turned off. This is unusual because this has been seldom reported previously for other structures in the gaze control system, such as the most anterior parts of the SC which encode either fixation or microsaccades (Bergeron and Guitton, 2000; Gandhi and Keller, 1999b; Hafed et al., 2009; Munoz and Wurtz, 1992, 1993a,b; Pare and Guitton, 1994). Stimulation of the fastigial oculomotor region does not produce head movements (Quinet and Goffart, 2009). Conversely, lesion or inactivation of FEF and SC seems to only compromise eye movements, while head movements are spared (van der Steen et al., 1986; Walton et al., 2008).

Moreover, gaze movements evoked during LIP stimulation show quite different kinematics from those produced by stimulation of the SC (Freedman et al., 1996; Klier et al., 2001; Roucoux et al., 1980), the FEF (Ascencio-Monteon et al., 2005; Chen, 2006; Knight and Fuchs, 2007; Tu and Keating, 2000), and the SEF (Chen, 2006; Chen and Walton, 2005; Martinez-Trujillo et al., 2003b). First, the amplitudes of gaze shifts evoked from LIP are always very small. This absence of large gaze shifts could indicate that LIP is not concerned with the encoding of targets beyond a central visual range, and that these targets are handled by the other structures. But it could also result from the notorious lack of topography in LIP (Gottlieb et al., 2005; Thier and Andersen, 1998). This lack of topography might lead to a “vector averaging” effect where the co-activation of different movement vectors in the same vicinity would weigh the overall vector toward the more common small amplitude vectors (Gottlieb et al., 2005; Groh, 2001; Thier and Andersen, 1996, 1998). In contrast, stimulation of the SC, which shows a very clear-cut topography, can evoke gaze shifts in excess of 100°, but only along a very narrow fringe of sites at the posterior edge of its retinotopic map (Freedman et al., 1996).

Second, LIP stimulation does not evoke the normal eye-head coordination pattern observed (at least most of the time) with the SC, FEF, and SEF. This cannot be explained away as differences in paradigms and behavioral sets between laboratories, because we have tested the SC, FEF, and SEF in our laboratory using essentially identical experimental conditions to those employed here (except lower stimulus amplitudes) and found completely different results. Electrical stimulation of LIP did not activate the normal pattern of motoneuron activity required for a gaze shift. This remained the case when we adapted animals using the “Goggle Paradigm.” We previously hypothesized that stimulation of a cortical gaze control system, by virtue of its early placement in the system, would produce context-dependent patterns of eye-head coordination (Constantin et al., 2004; Crawford and Guitton, 1997). The current results appear to conflict with the hypothesis that LIP is upstream from the context-dependent eye-head gating mechanisms. However, the expected context-dependent effect may have been obscured by an overall general absence of head movement, so we do not think that this hypothesis can be rejected.

Why is LIP different?

Some of the differences between stimulation of LIP and other structures—for example stimulation threshold—can be explained in terms of the “chain of command” for gaze control: LIP is anatomically upstream from the SC and FEF (Andersen et al., 1992; Astafiev et al., 2003; Blatt et al., 1990; Fang et al., 2005; Ferraina et al., 2002; Gattass et al., 2005; Gaymard et al., 2003), whereas the latter structures have direct access to the brainstem reticular formation centers for gaze control (Ferraina et al., 2002; Gattass et al., 2005; Gaymard et al., 1998; Munoz, 2002; Sparks et al., 2001). However, this does not explain (1) the almost complete absence of head movements in our data, (2) why the 3-D oculomotor system behaved as if it were expecting a head movement, nor (3) the lasting suppression of gaze shifts that followed the initial evoked gaze shift.

Clearly LIP stimulation did not produce a normal pattern neural activity produced by a visual stimulus, because it did not result in normally coordinated behavior. The question is, why? It is tempting to conclude that that LIP only controls eye movements, not head movements. We think this is unlikely because LIP is functionally upstream from other gaze control centers (SEF, FEF, and SC) that produced coordinated eye-head gaze shifts when stimulated in nearly identical experimental conditions (Ascencio-Monteon et al., 2006; Klier et al., 2003; Martinez Trujillo et al., 2003a). Moreover, this hypothesis does not explain the longer-term suppression in eye movement that we observed, nor the reason why LIP stimulation produced eye movements that obey Listing’s law when the head was fixed and not when the head was free. Our analysis of saccade torsion (Figs. 10, 11) especially suggests that the system was expecting a head movement.

One hypothesis—purely speculative—that fits all three of these observations, is that LIP output normally does encode eye-head gaze shifts in physiology, but during LIP stimulation, a brief excitatory signal to the gaze control system is followed by a longer lasting inhibitory effect. This explains the absence of further saccades, the suppression of head movement (which normally lasts much longer than the saccade and requires a longer-term drive signal), and why the initial 3-D saccade had torsional components—as though it “expected” a head movement that did not come. This suppression could happen through excitatory activation of physiological pathways to the fixation systems for gaze (Anderson et al., 1998; Bergeron and Guitton, 2000, 2002; Everling et al., 1998; Gandhi and Keller, 1999a,b; Munoz and Wurtz, 1992, 1993a,b; Pare and Guitton, 1998) and head control. Or it could happen as a result of synaptic inhibition of the normal excitatory pathways. For example, stimulation of visual cortex is thought to produce mainly widespread inhibition, leading to the delays in eye movement initiation (Tehovnik and Slocum, 2007; Tehovnik et al., 2003, 2004, 2005). If the latter is also the case for LIP, then its uniqueness (relative to SC, SEF, and FEF) could be either in its intrinsic excitatory-inhibitory circuitry (being somehow more like V1) or in the much higher currents

required to reach motor threshold, or an interaction of between both of these factors.

In any case, our data demonstrate that although stimulation of LIP can evoke gaze shifts, their kinematics are not normal and therefore LIP does not seem to have the same direct access to gaze motor circuitry as these other structures. These findings are generally consistent with the idea that LIP is not a motor structure, but rather is involved in specifying high-level goals for action (Andersen et al., 1992; Cohen and Andersen, 2002; Colby et al., 1996; Culham et al., 2006; Fernandez-Ruiz et al., 2007; Gaymard et al., 2003; Gottlieb, 2007; Ipata et al., 2006; Thomas and Pare, 2007).

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APPENDIX

Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.neuroscience.2009.08.066](https://doi.org/10.1016/j.neuroscience.2009.08.066).

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