

Electrical Microstimulation of the Superior Colliculus in Strabismic Monkeys

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PURPOSE. Visually guided saccades are disconjugate in human and nonhuman strabismic primates. The superior colliculus (SC) is a region of the brain topographically organized in visual and motor maps where the saccade goal is spatially coded. The present study was designed to investigate if a site of stimulation on the topographic motor map was evoking similar or different saccade vectors for each eye.

METHODS. We used microelectrical stimulation (MS) of the SC in two strabismic (one esotrope and one exotrope) and two control macaques under binocular and monocular viewing conditions. We compared the saccade amplitudes and directions for each SC site and each condition independently of the fixating eye and then between each fixating eye. A comparison with disconjugacies of visually guided saccades was also performed.

RESULTS. We observed different saccade vectors for the two eyes in strabismic monkeys, but conjugate saccades in normal monkeys. Evoked saccade vectors for the left eye when that eye was fixating the target were different from those of the right eye when it was fixating. The disconjugacies evoked by the MS were not identical but similar to those observed for visually guided saccades especially for the dominant eye.

CONCLUSIONS. Our results suggest that, in strabismus, the saccade generator does not interpret activation of a single location of the SC as the same desired displacement for each eye. This finding is important for advancing understanding of the development of neural circuits in strabismus.

Keywords: superior colliculus, strabismus, disconjugacy, saccades

OBJECTIF. Les saccades visuellement guid es de chaque  il sont asym triques chez le primate humain et non humain strabique. Le colliculus sup rieur (CS) est une r gion sous-corticale topographiquement organis e en cartes visuelles et motrices o  le but de la saccade est spatialement cod . La pr sente  tude a  t  con ue afin de tester si la stimulation  lectrique de la carte topographique motrice du CS  voquait des vecteurs saccadiques similaires pour chaque  il.

M THODES. Nous avons utilis  des micro-stimulations  lectriques (MS) du CS chez deux singes strabiques (un  sotrope et un exotrope) et deux macaques t moins en vision binoculaire et monoculaire. Nous avons compar  les amplitudes et directions des saccades pour chaque site et condition ind pendamment de l' il utilis  lors de la fixation puis, entre chaque  il utilis  lors de la fixation. Une comparaison avec les asym tries observ es au niveau des saccades visuellement guid es a  galement  t  r alis e.

R SULTATS. Nous avons observ  diff rents vecteurs saccadiques pour chaque  il chez les singes strabiques, mais des saccades identiques chez les singes sains. Les vecteurs des saccades  voqu es pour l' il gauche lorsque cet  il fixait la cible  taient diff rents de ceux de l' il droit lorsque celui-ci fixait. Les asym tries  voqu es par la MS n' taient pas identiques mais similaires   celles observ es lors de saccades visuellement guid es et particuli rement pour l' il dominant.

CONCLUSIONS. Nos r sultats sugg rent que, dans le cas d'un strabisme, le g n rateur saccadique n'interpr te pas la stimulation d'un site du CS comme le m me d placement d sir  pour chaque  il. Ce r sultat est important pour la compr hension du d veloppement des circuits neuronaux lors d'un strabisme.



Everyday actions require orienting our gaze toward a spatial region of interest. An approaching object, a pedestrian crossing the street or keeping an eye on progeny activates brain circuits to generate quick saccadic gaze shifts. The saccade goal, where we need to look, is shaped from the retinotopic location of the target's image. Once the saccade goal is identified, an oculomotor command can then be generated in the brainstem saccade generator.¹ Visually guided saccades will then be directed toward the visual target conjugately, providing the new target and the initial fixating point are equidistant. In contrast, strabismic human and nonhuman primates produce disconjugate saccades toward targets presented on a tangent screen²⁻⁵ possibly related to functional abnormalities in saccadic structures as the paramedian pontine reticular formation (PPRF).^{6,7}

In recent years, numerous studies have used a nonhuman primate model of infantile strabismus to investigate possible neural correlates of oculomotor symptoms. Compelling evidence has emerged to show that, regardless of the method used to induce strabismus, the loss of binocular vision during a sensitive period early in postnatal life leads to abnormalities of brainstem oculomotor structures.⁶⁻¹²

The superior colliculus (SC) constitutes the last visuomotor relay in the brainstem carrying a spatial representation of the saccade goal.^{13,14} Neurons in the superficial and intermediate layers (iSC) are topographically organized and have, respectively, visual and motor maps that are aligned.^{15,16} Single unit recordings in the motor map of the iSC show neurons evincing a burst of action potentials 20 to 30 ms preceding a saccade.^{17,18} Electrical microstimulation (MS) at a specific iSC recording site evokes a saccade of short latency (~30 ms) with amplitude and direction matching the location of the electrode on the topographic map.^{15,16,19,20} According to many models of the saccadic system, a desired displacement command from the SC serves as the input to a local feedback loop, which controls saccade dynamics.^{1,21,22} During the saccade, the current displacement is constantly compared with this command. When the difference between these two signals reaches zero, the movement ends. Because human and nonhuman primates with strabismus are able to perform accurate saccades with either eye fixating, and even perform accurate "crossover" saccades,^{23,24} the desired eye displacement and the control loop processes described above must be achieved accurately.

It is currently unknown if the iSC specifies a common saccade goal for each eye on its topographic map or if one site is specifying two different saccade goals according to which eye is used. To address this gap in knowledge, we electrically evoked saccades from the iSC in strabismic and normal monkeys in binocular and monocular viewing conditions. We then compared the evoked saccades with visually guided saccades. This methodology has several goals: (1) testing if disconjugate saccades can be evoked from the iSC in strabismic monkeys, (2) testing if the saccade vectors are dependent on which eye is used and therefore if the common topography for each eye is broken, and (3) testing if the pattern of disconjugacies is similar to those reported for visually guided saccades.

MATERIALS AND METHODS

Monkey Preparation

Four monkeys (*Macaca mulatta*) were used as subjects. We performed electrical microstimulation at 48 sites in the intermediate layers of the SC of one female exotropia (XT1; 7 years of age, 6.5 kg) and one female esotropia (ET1; 5 years of age, 7 kg), and 24 sites in one normal female (N1; 7 years of

age, 6.6 kg) and one normal male (N2; 5 years of age, 9.1 kg). Strabismus was created early in life by two different approaches. Monkey ET1 wore prism goggles for the first 3 months of life, resulting in incomitant esotropia (typically ~15° but could range from ~25° esotropia to 2° of exotropia). Monkey XT1 underwent a bilateral medial rectus tenotomy during the first week of life, which resulted in a strong "A" pattern exotropia (25° when fixating with the right eye and 35°-40° when fixating with the left eye). To prepare for neurophysiological experiments, the monkeys were equipped with a scleral search coil on each eye for measurement of eye movements (CNC Engineering, Seattle, WA, USA) and recording chambers. Detailed descriptions of our surgical procedures can be found in previous reports.^{25,26} All procedures complied with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. Experimental protocols were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Washington (Seattle, WA, USA).

Eye Movement Recordings

The eye position data were sampled at 1 kHz. Calibration of each eye was performed under monocular viewing conditions by requiring the animal to fixate the target as it was stepped systematically from -20° to 20°, in 5° increments, horizontally and vertically. Eye position signals and target position feedback signals were passed through an antialiasing, 6-pole Bessel filter (200 Hz). These signals then were digitized at 1 kHz with 16-bit precision using CED-Power1401 hardware (Cambridge Electronic Designs, Cambridge, England).

Electrical Microstimulation

Electrical microstimulation was performed using glass-coated tungsten microelectrodes (Alpha-Omega, Alpharetta, GA, USA) with impedances ranging from 1 to 5 megaohms (MΩ). Monophasic current pulses (0.1 ms, 7-40 μA, 400 Hz, 200-ms train duration) were delivered during fixation of static targets. Stimulation was applied only at sites where visuomotor neurons were identified, approximately 1.2 to 2 mm below the surface of the superior colliculus. For a given site, the intensity of the delivered current was adjusted to the lowest value needed to consistently evoke a staircase of saccades. The train duration of 200 ms evoked a staircase of at least two saccades per trial.

Data Analysis

Spike 2 was used for data acquisition and preliminary offline analyses. Data were then imported into MATLAB (Mathworks, Natick, MA, USA) and analyzed further using custom software. To avoid contamination by postsaccadic drifts, saccade onsets and offsets were measured using a combination of velocity and acceleration criteria. Saccade offset was defined as the first point in time at which either of two conditions was met: (1) the eye velocity dropped below 50°/s, or (2) eye velocity dipped below 100°/s and the absolute value of acceleration dropped below 10,000°/s/s. This algorithm successfully detected the occasional large postsaccadic drift in strabismic monkeys that reaccelerated the eye before the velocity dipped below the 50°/s threshold. For each eye, saccade onsets and offsets were measured separately for the horizontal and vertical components. The amplitudes and durations of each component were defined with respect to these time points. The conjugacy of the horizontal and vertical components was quantified using the following equation:

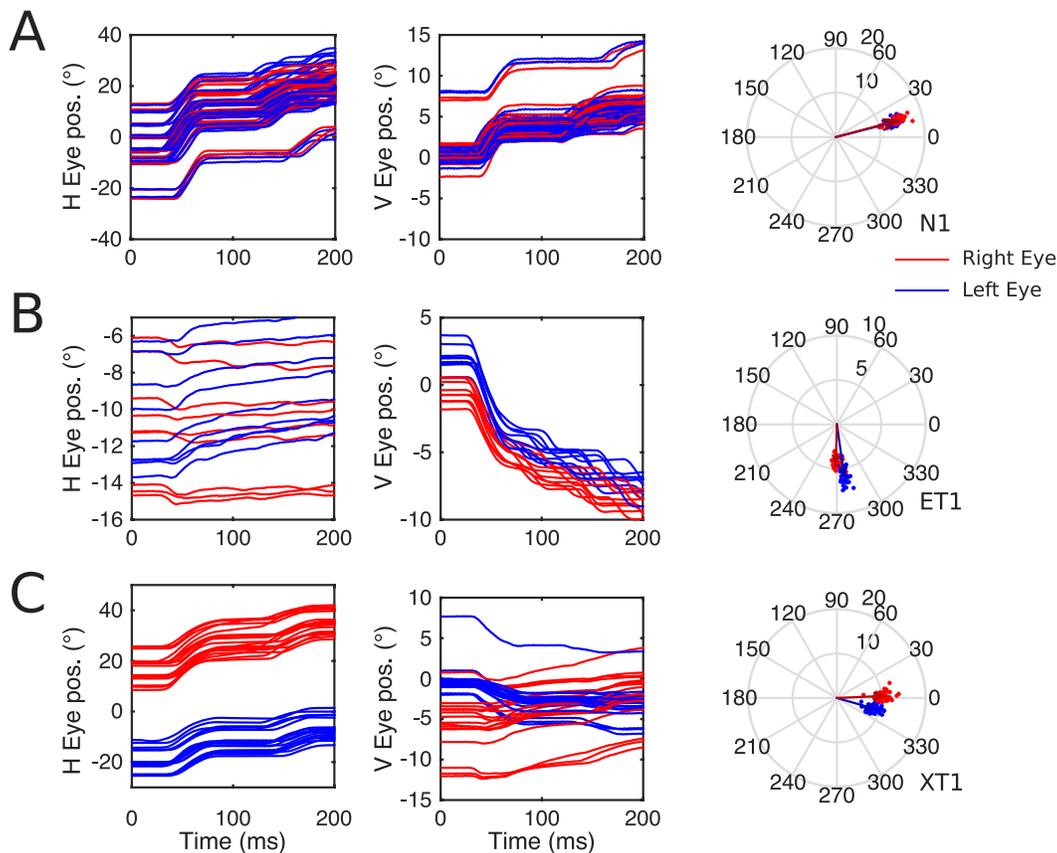


FIGURE 1. Example sites of the SC after MS in binocular viewing condition. Three example stimulation sites, including one site in a normal monkey N1 (A) and two sites in strabismic monkeys ET1 and XT1 (B and C, respectively) under binocular viewing. The stimulation onset starts at 0 ms and ends at 200 ms (see Methods). Horizontal and vertical components of the evoked saccades are represented in the first and second columns, respectively. The arrows on the third column represent the mean saccade vector in polar coordinates for each eye with each trial represented by a dot. Red color represents the right eye and blue color the left eye. Note that for more visibility only 9/38 trials are represented for the site of monkey ET1, 10/50 trials for monkey XT1, and 49/49 for monkey N1.

$$\text{Amplitude ratio} = \text{RA}_{\text{LeftEye}} / \text{RA}_{\text{RightEye}} \quad (1)$$

Where RA represents the radial amplitude of the saccade. The differences in saccade direction were computed as:

$$\text{Direction Difference} = \text{Polar direction}_{\text{LeftEye}} - \text{Polar direction}_{\text{RightEye}} \quad (2)$$

For saccade directions falling between 270° and 90°, there was a risk of finding very large differences in saccade direction. For example, if saccade directions were 20° and 330° for the left and right eyes respectively, the direction difference would be -310°. In order to avoid this error, if one evoked saccade was slightly down, its direction was transformed by subtracting 360 from its direction. For our given example, the directions were then 20° and -30° resulting in a direction difference of 50°.

Due to large variability in eye positions and evoked saccade amplitudes, four sites were excluded for monkey XT1. The final number of sites was 32 sites for this monkey and 44 sites for the strabismic monkeys.

In binocular conditions, we first computed the two conjugacy parameters without taking into account which eye was fixating the target. Then we calculated the same parameters but between the left eye fixating and the right eye fixating in binocular and monocular conditions as defined by the following equations:

$$\text{Amplitude ratio} = \text{geomean}(\text{RA}_{\text{LeftEyeFixating}})$$

$$/ \text{geomean}(\text{RA}_{\text{RightEyeFixating}}) \quad (3)$$

and

$$\text{DirectionDifference}$$

$$= \text{mean}(\text{PolarDirection}_{\text{LeftEyeFixating}})$$

$$- \text{mean}(\text{PolarDirection}_{\text{RightEyeFixating}}) \quad (4)$$

In the binocular condition, our algorithm first checked if at least one eye was within 3° of the target. Then the fixating eye was defined as the closest to the target. In this analysis, eight sites were included for monkey ET1 and 22 sites for monkey XT1 in binocular viewing condition. In monkeys XT1 and ET1, eight and seven sites, respectively, were tested in monocular viewing condition. In monkeys N1 and N2, six and seven sites were tested, respectively.

During free binocular viewing, we noticed that monkeys XT1 and ET1 each had a preferred eye that we defined as the dominant eye (left eye for XT1 and right eye for ET1). The influence of the fixation on the dominant eye or the nondominant eye was analyzed by computing the amplitude ratios and saccade direction differences when each eye was fixating versus not fixating during binocular and monocular viewing. The following equations defined our quantification for the dominant eye but the same procedure was used for the nondominant eye:

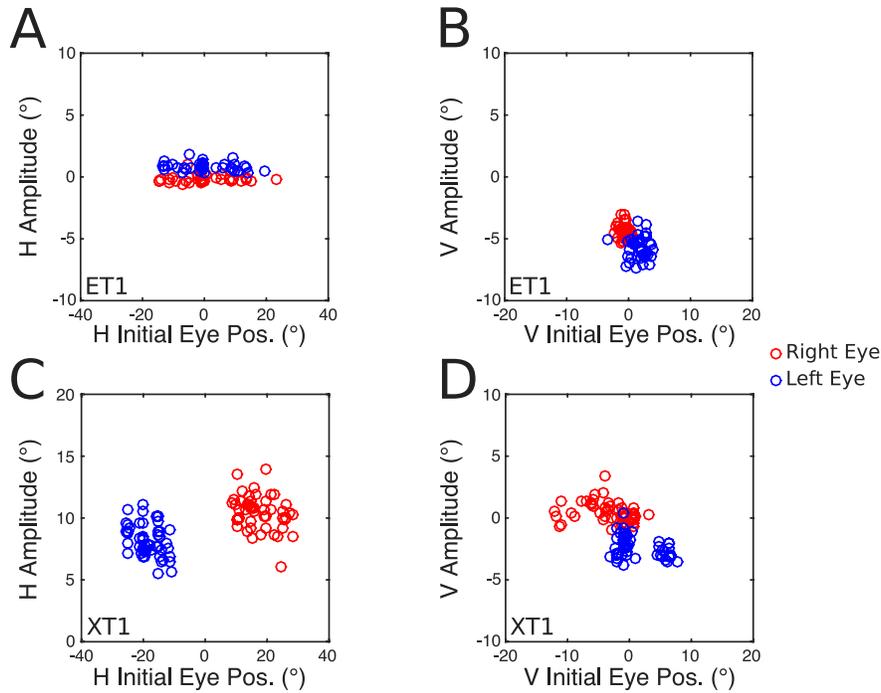


FIGURE 2. Relationship between initial eye positions and evoked saccade amplitudes. For the two example stimulation sites shown in Figure 2 for monkey ET1 and XT1, the saccade amplitudes of the evoked saccades are plotted against the initial eye positions for each monkey (ET1: [A], [B]; XT1: [C], [D]) and each saccade component (horizontal component in [A], [C]; vertical component in [B], [D]). Blue circles represent the left eye, red circles the right one. All the trials for each site are represented (38 trials for monkey ET1 and 50 trials for monkey XT1).

$$\begin{aligned}
 & \text{AmplituderatioDomEye} \\
 &= \text{geomean}(\text{RADomEyeFixating}) \\
 & \quad / \text{geomean}(\text{RADomEyeNotFixating}) \quad (5)
 \end{aligned}$$

and

$$\begin{aligned}
 & \text{Direction DifferenceDomEye} \\
 &= \text{mean}(\text{Polar directionDomEyeFixating}) \\
 & \quad - \text{mean}(\text{Polar directionDomEyeNotFixating}) \quad (6)
 \end{aligned}$$

To compare the evoked saccade amplitudes to the visually guided saccade amplitudes, we proceeded in two steps. The first step was to create a pool of visually guided saccade amplitudes matching the evoked ones. The criteria for selection were defined by drawing an ellipse around the dispersion of the evoked saccade amplitudes of the fixating eye for each site. The positions of the center of this ellipse was defined as:

$$\begin{aligned}
 x0 = & \frac{\left(\left(Qb3 + 1.5 * Iqr(bor.ampl.) \right) - \left(Qb1 - 1.5 * Iqr(bor.ampl.) \right) \right)}{2} \\
 & + \left(Qb1 - 1.5 * Iqr(bor.ampl.) \right) \quad (7)
 \end{aligned}$$

and

$$\begin{aligned}
 y0 = & \frac{\left(\left(Qv3 + 1.5 * Iqr(vert.ampl.) \right) - \left(Qv1 - 1.5 * Iqr(vert.ampl.) \right) \right)}{2} \\
 & + \left(Qv1 - 1.5 * Iqr(vert.ampl.) \right) \quad (8)
 \end{aligned}$$

Where Qh1 and Qv1 are the first quartiles of the horizontal and vertical evoked amplitudes, respectively, and Qh3 and Qv3 the third quartiles. Iqr is the interquartile range. The ellipse border was then determined by:

$$\begin{aligned}
 xs = x0 & + \left(\frac{\left(\left(Qb3 + 1.5 * Iqr(bor.ampl.) \right) - \left(Qb1 - 1.5 * Iqr(bor.ampl.) \right) \right)}{2} \right) \\
 & * \cosinus(\theta) \quad (9)
 \end{aligned}$$

and

$$\begin{aligned}
 ys = y0 & + \left(\frac{\left(\left(Qv3 + 1.5 * Iqr(vert.ampl.) \right) - \left(Qv1 - 1.5 * Iqr(vert.ampl.) \right) \right)}{2} \right) \\
 & * \sinus(\theta) \quad (10)
 \end{aligned}$$

where θ is an independent parameter increasing from 0 to 2π .

By using the MATLAB function `inpolygon()`, we then searched for matching visually guided saccades for the same eye taken from a dataset of visually guided saccades used for a previous study.⁴ The distribution of selected visually guided saccades was controlled manually to verify any accumulation of points close to an edge of the ellipse. For only three sites (two in monkey XT1 and one for monkey ET1) the radius of the ellipse was reduced to one SD. For rostral sites, an additional criterion was used to exclude amplitudes of visually guided saccades less than 0.5° .

Once the visually guided saccade population was selected, the second step consisted of drawing a second ellipse based on the dispersion of the evoked saccade amplitudes of the fellow eye (nonfixating eye). This second hull was drawn following

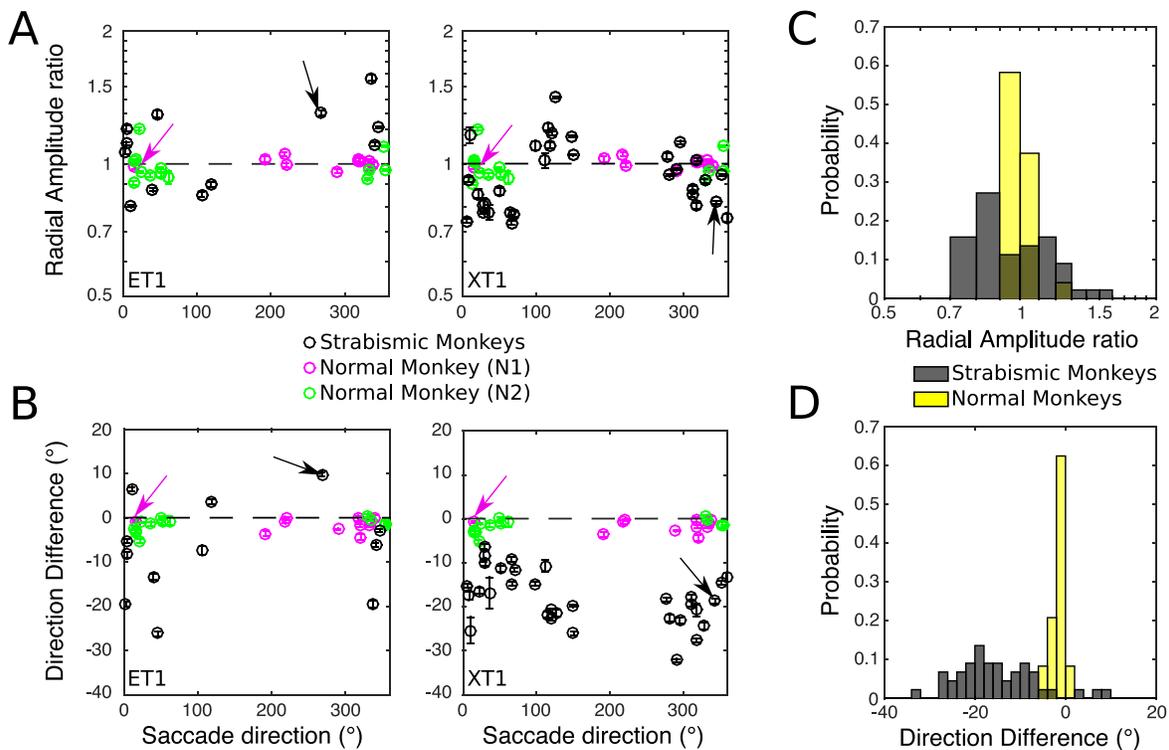


FIGURE 3. Saccade disconjugacies after electrical microstimulation of the SC in binocular viewing condition. Radial amplitude ratios (A) and direction differences (B) for each site are represented as a function of saccade direction for each strabismic animal (ET1 first column and XT1 second column, *black circles*; $N = 12$ and 32 , respectively). Saccade direction is the direction of the evoked saccade for the dominant eye (right eye for ET1 and left eye for monkey XT1). Sites from the two normal monkeys are represented with *magenta* (N1) and *green* (N2) circles ($N = 11$ and 13 , respectively). *Error bars* represent the standard error. *Black arrows* indicate the sites represented in Figure 2 for monkeys ET1 and XT1. *Magenta arrows* indicate the corresponding site represented in Figure 2 for monkey N1. (C) Distributions of the radial amplitude ratios, and (D) direction differences in normal (*yellow bars*, $N = 24$) and strabismic (*black bars*, $N = 44$) monkeys. A third color appears by the superposition of *black and yellow bars*. For amplitude ratios the bin size is 0.1 . Bin size is 2° for the direction differences. Log scale was used for the axis representing amplitude ratios.

the same equations above. Finally, we counted the number of visually guided saccades for which the fellow eye fell inside this second ellipse, using the MATLAB function `inpolygon()`.

A matching percentage (MP) was then calculated by the following equation:

$$MP = \frac{n2}{n1} * 100 \quad (11)$$

where $n1$ is the number of saccades selected with our first step procedure and $n2$ the number of saccades for which the fellow eye fell inside the second hull.

From these two populations (evoked versus visually guided saccades), we also calculated the mean deviations in terms of amplitude ratios and saccade direction differences of each eye between the two conditions with these two equations:

$$\text{Amplituderatio} = \frac{\text{geomean}(\text{RAVisuallyGuidedSaccades})}{\text{geomean}(\text{RAEvokedSaccades})} \quad (12)$$

and

Direction Difference

$$= \text{mean}(\text{Polar directionVisualGuidedSaccades}) - \text{mean}(\text{Polar directionEvokedSaccades}) \quad (13)$$

All statistical analyses and confidence intervals (CI) were computed with freeware R (in the public domain, www.r-project.org). Confidence intervals were calculated through a

bootstrap method. Direction differences have been represented by negative and positive values. The means, CI, and statistical tests were computed on absolute values. All CIs are 95% CI.

RESULTS

Figure 1 illustrates eye movement data from example sites for one normal (N1, Fig. 1A) and two strabismic macaques (ET1 and XT1, Figs. 1B, 1C, respectively) under binocular viewing. For these three cases, we found a standard pattern of staircase-like saccadic eye movements evoked by left iSC stimulation. The first evoked saccades of each staircase in normal monkeys display a quasiperfect conjugacy between the two eyes (left eye, blue; right eye, red). As we can see in the polar representations of the first evoked saccades, the two vectors were similar in amplitude (mean \pm SD: $13.76 \pm 0.8^\circ$ and $14.09 \pm 1.6^\circ$ for left and right eye, respectively) and direction (mean \pm SD: $14.27 \pm 2.82^\circ$ and $14.97 \pm 2.22^\circ$ for left and right eye, respectively). In contrast, MS in strabismic monkeys evoked saccades with both amplitude and direction differences, as reported for visually guided saccades in human^{2,5} and nonhuman primates.^{3,4} In monkey ET1 (Fig. 1B), the evoked saccades for the two eyes differed in both amplitude (mean \pm SD: $5.79 \pm 0.91^\circ$ and $4.42 \pm 0.56^\circ$ for left and right eye, respectively) and direction (mean \pm SD: $278.1 \pm 2.7^\circ$ and $268.25 \pm 4.1^\circ$ for left and right eye, respectively). Some disconjugacies are also illustrated for monkey XT1 in Figure 1C with differences in radial amplitudes (mean \pm SD: $8.6 \pm 1.26^\circ$;

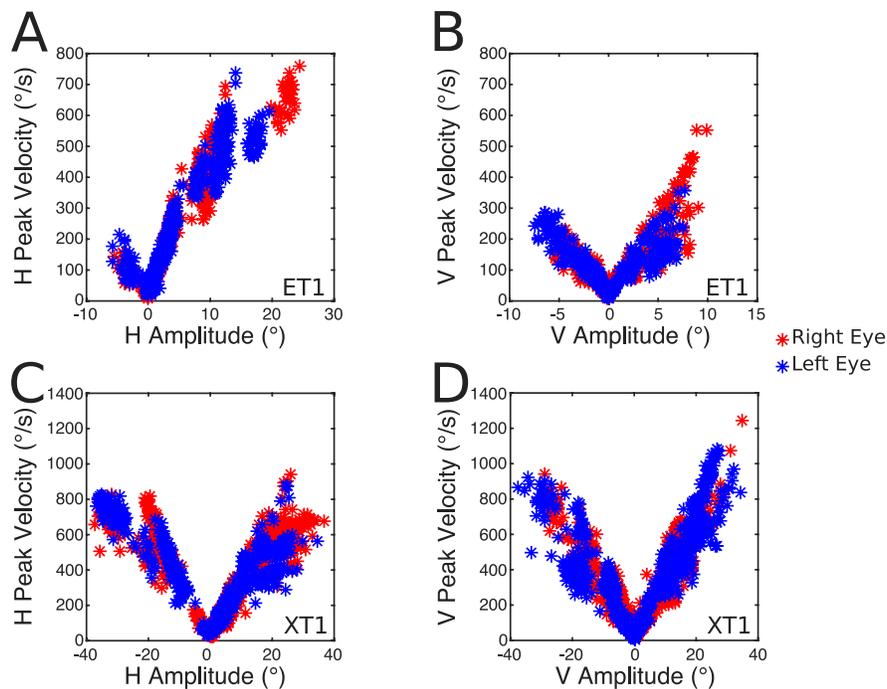


FIGURE 4. Main sequences of evoked saccade amplitudes for each component and each eye. (A, C) Horizontal peak velocity as a function of horizontal amplitude for the monkey ET1 and XT1, respectively. (B, D) Vertical peak velocity as a function of vertical amplitude for the monkey ET1 and XT1, respectively. *Blue stars* represent the left eye and *red stars* the right eye. All the evoked saccades acquired through the electrical microstimulation sites in the SC are represented here for a total of 925 evoked saccades in monkey XT1 and 530 evoked saccades in monkey ET1.

$10.5 \pm 1.38^\circ$ for left and right eye, respectively) and directions (mean \pm SD: $343.71 \pm 5.94^\circ$; $2.43 \pm 4.19^\circ$ for left and right eye, respectively).

Figure 2 represents the relation between the initial eye positions and the evoked saccade amplitudes for horizontal and vertical components at the same sites illustrated in Figure 1 for monkeys ET1 (Figs. 2A, 2B) and XT1 (Figs. 2C, 2D) under binocular viewing. In monkey ET1, we checked if nonmatching initial orbital positions were associated with changing the evoked saccade in amplitude. This control was made for each site. For monkey XT1 though, this control was not possible due to large exotropia. However, the possible effect of initial eye positions on evoked saccades was unlikely to be a factor because each eye was not limited by initial eye position based on what has been observed in behavior previously⁴ and by using high frequency MS (>300 Hz).²⁷ The left eye position limits in monkey XT1 for goal-directed saccades ranged between -30 and $+5^\circ$ whereas it was between 0 and $+35^\circ$ for the right eye.

To quantify the disconjugacies across stimulation sites, the amplitude ratios and the direction differences between the two eyes were calculated (see Methods) and plotted. This allowed us to illustrate, for the first time, saccade disconjugacies evoked by microstimulation of SC in strabismic monkeys. The mean amplitude ratios and direction differences were calculated subsequently between the fixating eyes. We analyzed the possible influence of fixation on the evoked saccades for each eye (dominant and nondominant eye). Finally, comparison with matching visual saccades was made in the two different fixation conditions.

Comparison of Evoked Saccade Conjugacies Between Normal and Strabismic Monkeys Under Binocular Viewing

If the evoked saccades are conjugate for each stimulation site, then the amplitude ratios and direction differences should be

near the conjugacy values (1 for the amplitude ratios and 0° for the direction differences). In Figures 3A and 3B, we show a wider dispersion of these two indicators around the conjugacy values for the two strabismic monkeys confirming preliminary results (Fleuriot, et al., *IOVS* 2013;54:ARVO E-Abstract 1930). Sites from monkey ET1 had large saccade direction differences (10.71° , CI: 7.25° - 15.36° , $N = 12$) and likewise for monkey XT1 (17.93° , CI: 15.78° - 20.03° , $N = 32$). The geometric means of the amplitude ratios were not far from 1 on average for these two monkeys (ET1: 1.09, CI: 0.97-1.21, $N = 12$; XT1: 0.93, CI: 0.88-0.99, $N = 32$) but only a small percentage fell within the range of 0.9-1.1 (ET1: 8% [1/12]; XT1: 31% [10/32]).

Microelectrical stimulation of the iSC in normal monkeys did not evoke disconjugate saccades. Sites from monkey N1 were associated with small saccade direction differences (1.53° , CI: 0.82° - 2.48° , $N = 11$) similar to the sites from monkey N2 (1.7° , CI: 1.1° - 2.69° , $N = 13$). Amplitude ratios are very close to 1 on average (N1: 1, CI: 0.99-1.02, $N = 11$; N2: 0.99, CI: 0.95-1.03, $N = 13$) and almost exclusively concentrated within the range of 0.9 to 1.1 (N1: 100% [11/11]; N2: 92% [12/13]).

Altogether, the mean of the absolute direction deviations for strabismic monkeys was 15.96° (CI: 13.64° - 17.92° , $N = 44$), in contrast with the normal monkeys (mean: 1.62° ; CI: 1.17° - 2.3° , $N = 24$) as illustrated in Figure 3D. These saccade direction differences between normal and strabismic monkeys were significantly different ($P < 0.001$, Kolmogorov-Smirnov test). The mean amplitude ratios were similar for normal and strabismic monkeys (geometric mean: 0.99 and 0.97; CI: 0.97-1.02 and 0.92-1.03 for normal versus strabismic monkeys, respectively), but were distributed differently (Fig. 3C). Indeed, while 96% (23/24) of sites in normal monkeys showed an amplitude ratio between 0.9 and 1.1, only 25% (11/44) of sites were in this range in strabismic monkeys. A significant difference was found between the two amplitude ratio populations ($P < 0.01$, Kolmogorov-Smirnov test).

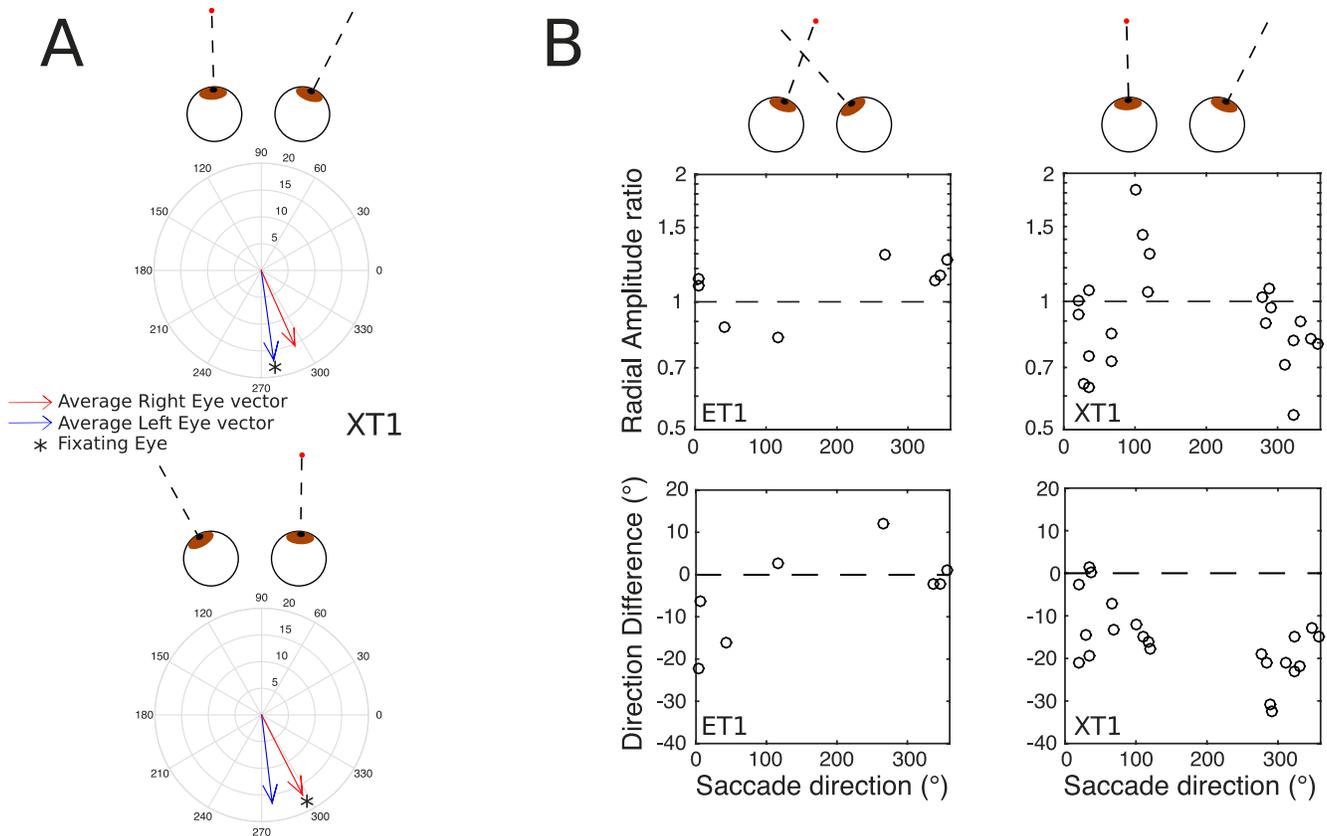


FIGURE 5. Comparison of mean saccade vectors for each fixating eye in binocular viewing condition. (A) Mean saccade vectors (left eye in *blue*, right eye in *red*) in polar coordinates for one site in monkey XT1 during binocular viewing condition. The polar plots represent the saccade vectors when the monkey is fixating with the left eye (first line) and when the monkey is fixating with the right eye (second line). Fixating eye is indicated by an *asterisk*. (B) Contrary to Figure 2, the disconjugacies depicted here were based on a comparison of the saccade vectors for each eye, when that eye was fixating. Consequently, the disconjugacies here (amplitude ratios and direction differences) are for the differences between the mean saccade vector evoked for the left eye when that eye is fixating the target and the mean saccade vector evoked for the right eye when it is fixating the target. The *circles* represent radial amplitude ratios and direction differences for each site in ET1 ($N = 8$, first column) and in XT1 ($N = 22$, second column). Log scale was used for the axis representing amplitude ratios.

Figure 4 shows the main sequences of all the evoked saccades for the two strabismic monkeys on each component (horizontal and vertical) and each eye. It is clear that the two eyes move at a similar speed for similar amplitude in the range of amplitudes tested. This indicates that the disconjugacies described above could not be fully explained by a change in the muscles or motor plant.

Comparison of Saccade Vectors for Each Fixating Eye Under Binocular Viewing

We then compared amplitude and saccade direction associated with each attending eye. For example, we compared evoked saccades for the left eye when the left eye was fixating with evoked saccades for the right eye when the right eye was fixating (see Methods).

In Figure 5A, we illustrate our analysis for one example site in monkey XT1. In this example, we separated the trials where XT1 fixated with the right eye versus the left eye during binocular viewing. By comparing the two eyes in the two fixation conditions (same comparison as in Fig. 3), we found the evoked movements were similar. When the left eye was fixating, the amplitude ratio was 1.1 and the direction difference 16.2° . When the right eye was fixating, the amplitude ratio was 0.98 and the direction difference 20.3° . When we compared only the vectors obtained for each fixating eye (represented by an asterisk in Fig. 5A), the amplitude ratio

was 1 and the direction difference 14.3° . This observation shows that, for a given site in SC, MS will evoke different vectors regardless of which eye is fixating.

Across all of the sites we tested in this condition (Fig. 5B), the two evoked vectors for each fixating eye were displaced far from the expected conjugacy values in terms of both amplitude ratios and directions for each strabismic monkey. During the binocular viewing condition, only 13% (1/8) and 36% (8/22) of sites were in the amplitude ratio range of 0.9 to 1.1 for monkeys ET1 and XT1, respectively. Saccade direction differences were consistently found between the two fixating eyes, with a mean absolute deviation of 8.12° for monkey ET1 (CI: 3.28° - 13.71° , $N = 8$) and 16.07° for XT1 (CI: 12.84° - 19.62° , $N = 22$).

No significant difference was found between the amplitude ratios and direction differences for the same sites represented in Figures 3A and 3B for both strabismic monkeys ($P > 0.05$, Kolmogorov-Smirnov test) indicating that fixation has no significant effect on these values.

Comparison of Saccade Vectors for Each Fixating Eye Under Monocular Viewing

To ensure that these differences were not due to visual influences coming from the nonfixating eye, we explicitly suppressed the visual sensory influence of this eye by placing an opaque occluder in front of that eye. The same example site

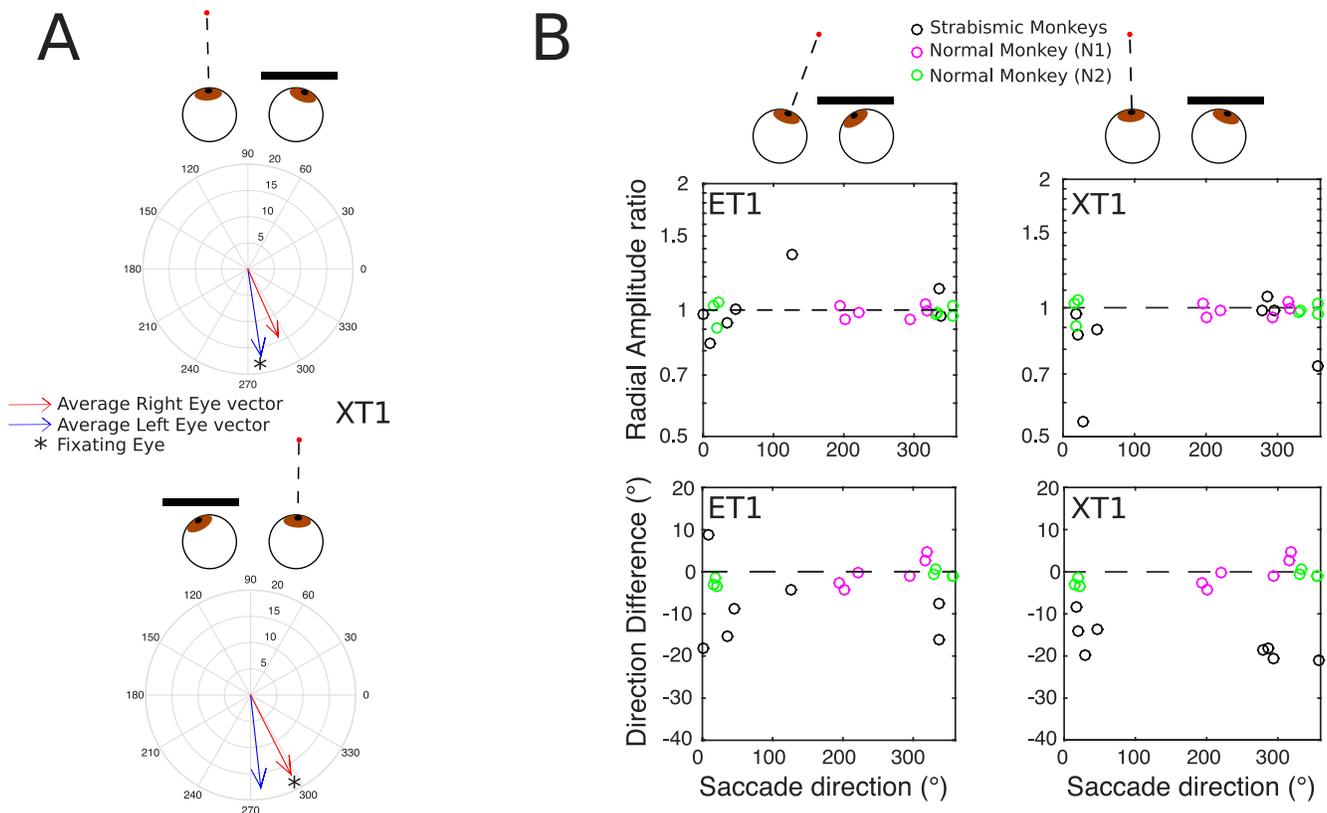


FIGURE 6. Comparison of mean saccade vectors for each fixating eye in monocular viewing condition. **(A)** Mean saccade vectors (left eye in blue, right eye in red) in polar coordinates for the same site illustrated in Figure 5A in monkey XT1 during monocular viewing condition. The polar plots represent the saccade vectors when the monkey is fixating with the left eye (first line, right eye occluded) and when the monkey is fixating with the right eye (second line, left eye occluded). Fixating eye is indicated by an asterisk. **(B)** The disconjugacies here (amplitude ratios and direction differences) are for the differences between the mean saccade vector evoked for the left eye when that eye is fixating the target and the mean saccade vector evoked for the right eye when it is fixating the target. The circles represent radial amplitude ratios and direction differences for each site in ET1 ($N = 7$, first column) and in XT1 ($N = 8$, second column). Magenta color represents the sites collected in monkey N1 ($N = 6$) and green color the sites collected in monkey N2 ($N = 7$). Log scale was used for the axis representing amplitude ratios.

described in Figure 5A for monkey XT1 is illustrated in Figure 6A under this monocular viewing configuration. The direction difference is 21° and the amplitude ratio 1.02 between the fixating eyes (represented by asterisks). This shows that the same differences exist between the fixating eyes but with a larger direction difference when vision was prevented for one eye.

Across the sites tested under this monocular viewing condition in strabismic monkeys, the saccade direction differences we found were large, averaging 11.33° (CI: 7.76° – 14.86° , $N = 7$) for monkey ET1 and 16.8° (CI: 13.3° – 19.6° , $N = 8$) for monkey XT1. The amplitude ratios also showed some differences in conjugacy values. On average, this ratio was of 1.02 (CI: 0.92–1.14, $N = 7$) for monkey ET1 and 0.86 (CI: 0.74–0.98, $N = 8$) for monkey XT1. Only 57% (4/7) and 50% (4/8) of these amplitude ratios were within the range of 0.9 to 1.1 in monkeys ET1 and XT1, respectively.

In normal monkeys N1 and N2 though, both direction differences and amplitude ratios were close to the conjugacy values as indicated by the colored circles on each graph (Fig. 6B). The saccade direction differences were, on average, 2.56° (CI: 1.32° – 3.82° , $N = 6$) for monkey N1 and 1.54° (CI: 0.82° – 2.37° , $N = 7$) for monkey N2. Amplitude ratios were 0.99 (CI: 0.96–1.02, $N = 6$) and 0.99 (CI: 0.95–1.02, $N = 7$) for monkeys N1 and N2, respectively.

Altogether, the amplitude ratios for the two normal monkeys were inside the range of 0.9 to 1.1 in 100% of cases (13/13). In contrast, only 53% (8/15) of the amplitude ratios

were inside this range in strabismic monkeys. However, no significant difference was found between the two amplitude ratio populations ($P > 0.05$, Kolmogorov-Smirnov test). Saccade direction differences were small in normal monkeys because 77% (10/13) of sites had a difference of less than 3° , and the maximum difference found was only 4.5° . In strabismic monkeys, 67% (10/15) of sites produced direction differences greater than 10° . These saccade direction differences were significantly different between normal and strabismic monkeys ($P < 0.001$, Kolmogorov-Smirnov test).

No significant differences were found between the amplitude ratios and direction differences for the same sites represented in Figures 3A and 3B for both strabismic monkeys ($P > 0.05$, Kolmogorov-Smirnov test).

Comparison of Saccade Vectors for Each Eye in Different Fixation Conditions

We then analyzed the influence of fixation on the saccade vector evoked for each eye (when that eye was fixating versus when it was not) in monocular and binocular conditions, as summarized in Figure 7. In the binocular condition (solid lines), the evoked saccades of the dominant (in black) or the nondominant (in gray) eye were only slightly affected by fixation. For monkey ET1, the amplitude ratios (Fig. 7A) were very close to 1 for the dominant eye (mean: 1.01, CI: 0.99–1.04, $N = 8$) and for the nondominant eye (mean: 0.99, CI:

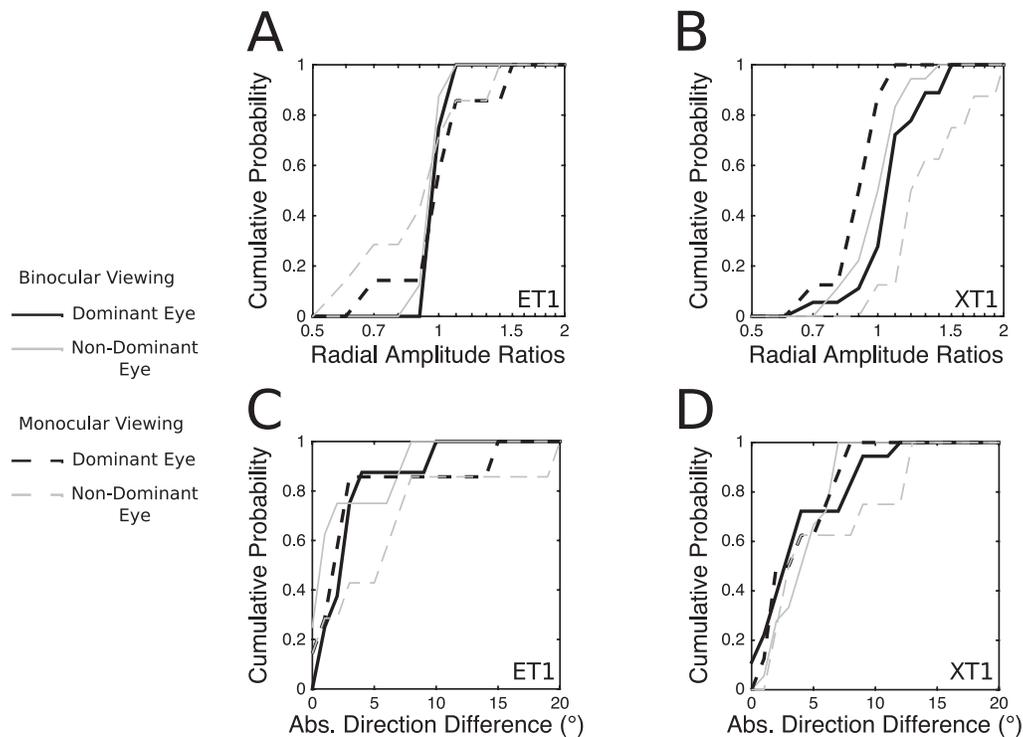


FIGURE 7. Comparison of mean saccade vectors for the dominant or nondominant eye when fixating versus not fixating the target in binocular and monocular viewing conditions. The disjugacies here (amplitude ratios and direction differences) are for the comparison between the mean saccade vector evoked for the dominant eye (black) or nondominant eye (gray) when that eye is fixating the target and the mean saccade vector evoked for this same eye when it is not fixating the target, in binocular (solid lines) and monocular (dashed lines) conditions. The cumulative distributions of radial amplitude ratios are plotted for monkey ET1 in (A) and for monkey XT1 in (B). The cumulative distributions of the absolute direction differences are plotted for monkey ET1 in (C) and for monkey XT1 in (D). In this analysis, 18 sites were included for monkey XT1 during binocular viewing, eight sites for monkey ET1. During monocular viewing, eight and seven sites were included for monkey XT1 and ET1, respectively. Log scale was used for the axis representing amplitude ratios.

0.96–1.01, $N = 8$). The amplitude ratios for the dominant eye and nondominant eye of monkey XT1 (Fig. 7B) were also very close to 1 even though the dominant eye showed a little more variability (dominant eye: 1.11, CI: 1.03–1.19, $N = 18$; nondominant eye: 1.03, CI: 0.96–1.02, $N = 18$). The saccade direction deviations (Figs. 7C, 7D) were mostly less than 5° for monkeys ET1 (dominant eye: 88% [7/8]; nondominant eye: 75% [6/8], Fig. 7C) and XT1 (dominant eye: 72% [13/18]; nondominant eye: 56% [10/18], Fig. 7D). In this binocular viewing condition (solid lines), the two eyes (dominant versus nondominant eye in black and gray, respectively) had similar sensitivities to the fixation because we did not find any significant difference between their amplitude ratios and direction differences in monkey ET1 ($P > 0.05$, Kolmogorov-Smirnov test, $N = 8$). In monkey XT1, only the amplitude ratios were significantly different between the dominant and nondominant eyes ($P < 0.05$, Kolmogorov-Smirnov test, $N = 18$).

In the monocular viewing condition, the dominant eyes (black dashed lines) for each monkey still showed small changes in their amplitudes. The amplitude ratios were close to 1 for ET1 (mean: 1.05, CI: 0.9–1.21, $N = 7$, Fig. 7A) and XT1 (mean: 0.95, CI: 0.86–1.04, $N = 8$, Fig. 7B). The saccade direction deviations were again mostly less than 5° (ET1: 86% [6/7]; XT1: 63% [5/8]). It was however the nondominant eye (dashed lines in gray) of each monkey that seemed to be the most sensitive in this condition. For monkey ET1, 57% (4/7) of saccade direction deviations were greater than 5° and, for monkey XT1, the amplitudes ratios were mostly greater than 1 (mean: 1.35, CI: 1.15–1.5, $N = 8$). As for the binocular viewing

condition, the two eyes (dominant versus nondominant eye in black and gray, respectively) had similar sensitivities to the fixation because only the amplitude ratios were significantly different between the dominant and nondominant eyes in monkey XT1 in this monocular viewing condition ($P < 0.01$, Kolmogorov-Smirnov test).

Comparison of Evoked Versus Visually Guided Saccades in Different Fixation Conditions

To compare evoked with visually guided saccades, we first selected visually guided saccades from one eye matching evoked saccades when this same eye was fixating, using a first hull (ellipse). Then we calculated for how many visually guided saccades from this group, the other eye was inside the second hull (see Methods).

Figure 8 shows one example site from monkey XT1 (Fig. 8A, 8B). In Figure 8A, we have drawn ellipses around the evoked saccades of each eye. The black hull is the one drawn for the fixating eye (dominant eye, in black) and was used to select the visually guided saccades. The group of visually guided saccades selected by this method is represented in Figure 8B in black. From the nondominant eye evoked saccades dispersion on the two amplitude components (horizontal and vertical), a second hull was drawn. We then calculated the percentage of visually guided saccades for which the nondominant eye fell inside the gray hull. In this example, we can see that a majority of visually guided saccades (69%, 53/77) are inside this ellipse (Fig. 8B) even though a greater

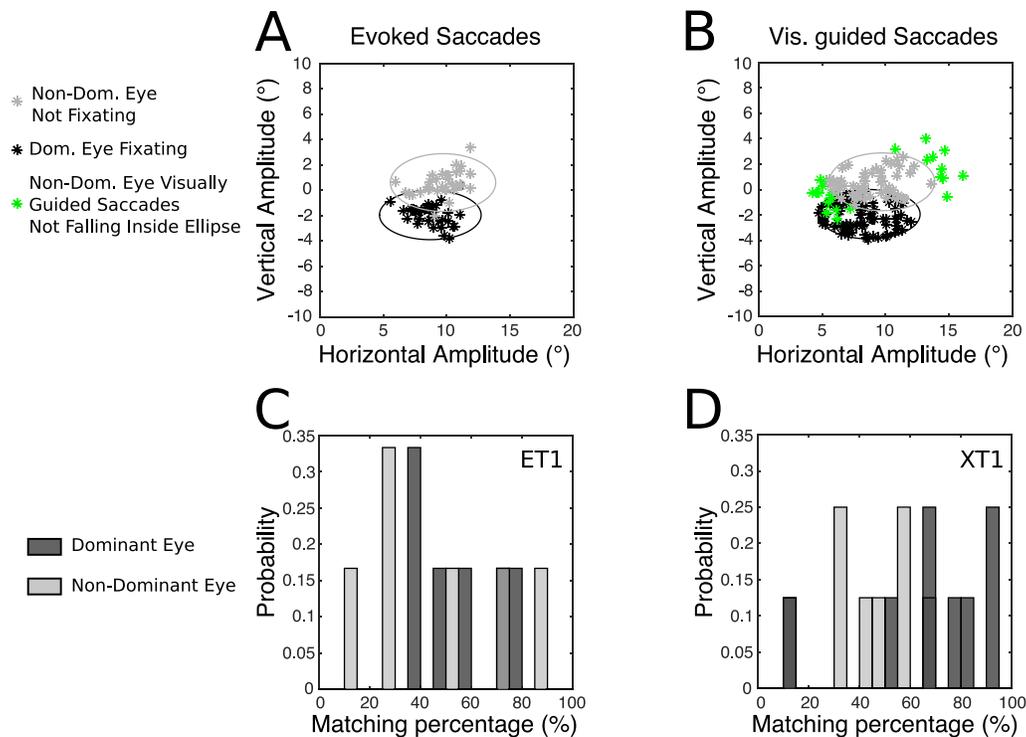


FIGURE 8. Comparison of evoked versus visually guided saccades during different fixation conditions. (A, B) In this example site, monkey XT1 is fixating the target with the dominant eye (left eye). (A) Represented evoked saccades of the dominant eye in *black* and of the nondominant eye (right eye) in *gray*. The *black and gray ellipses* are the windows used in this example to select the visually saccades (*black ellipse*) and to calculate the matching percentage (*gray ellipse*). (B) Plotted the selected visually guided saccades with the same color code. The same ellipses are plotted. The *green stars* represent the visually guided saccades for the nondominant eye not matching inside the *gray ellipse*. (C, D) Histograms of the matching percentage (MP, see methods) for each eye (*black and gray bars* for dominant and nondominant eyes, respectively) in monkey ET1 (C, $N = 6$) and XT1 (D, $N = 8$).

dispersion can also be observed (see green stars representing visually guided saccades outside the gray ellipse).

When we applied this method for our tested sites (8 in XT1 and 6 in ET1), a tendency emerged with a higher matching percentage (MP, see methods) when the dominant eye was used for fixation during MS or to foveate a peripheral target during visually guided saccades (Figs. 8C, 8D). In monkey XT1 (Fig. 8D) this tendency was clear and significant ($P < 0.05$, Fisher's exact test), with a majority of sites (6/8) having a MP higher than 60% when the dominant eye (in black) was used. When the nondominant eye was used though, only one site (1/8) showed a MP superior to 60% (in gray). In monkey ET1 (Fig. 8C), the MPs were in general lower than for monkey XT1. When the dominant eye (in black) was used, 67% (4/6) presented a MP greater than 45% and no case with a percentage inferior to 35%. For the nondominant eye (in gray), 50% (3/6) presented a percentage greater than 45% and the other half presented a low percentage of matching (<30%). However, this trend was less obvious than for monkey XT1 and no significant difference was found between the two populations (dominant versus non dominant eyes; $P > 0.05$, Kolmogorov-Smirnov test) and no higher probability to get a better matching percentage was found for the dominant eye ($P > 0.05$, Fisher's exact test).

Finally, in Figures 9 and 10 we show the mean deviations in terms of amplitude ratios and direction difference for each eye between the evoked and the selected visually guided saccades. Due to the methods we used to select the visually guided saccades, the eye serving as a reference for the saccade selection showed small differences, supporting our selection methods (dominant eye in Figs. 9A and 9C and nondominant

eye in 9B and 9D). In both animals this eye serving as a reference presented no deviation in direction greater than 10° with the selected visually guided saccades. In monkey XT1 (Fig. 9) no sites (0/8) presented an amplitude ratio outside the range 0.9 to 1.1. In monkey ET1 (Fig. 10) only one site (1/6) was outside this range for the dominant eye.

The fellow eyes (the eye not fixating the target) in monkey XT1 (Fig. 9) showed significantly different deviations in amplitude ratios for both eyes ($P < 0.05$, Kolmogorov-Smirnov test) but only for the dominant eye in direction ($P < 0.05$, Kolmogorov-Smirnov test) in comparison with the values obtained when the same eye was fixating (and then used as a reference). In monkey ET1 though (Fig. 10), only the amplitude ratios when the dominant eye was not fixating eye showed a significant difference ($P < 0.05$, Kolmogorov-Smirnov test). Besides, we observed some values close to a ratio of one and a direction deviation of 0° in both monkeys, showing some similarities to the visually guided saccades. In monkey XT1 (Fig. 9), for example, only 25% (2/8) showed a saccade direction differences with visually guided saccades greater than 10° , regardless of which eye was fixating/targeting the visual target. For monkey ET1 (Fig. 10), these differences were greater than 10° for only 17% (1/6) when the dominant eye was used as the reference, and 50% (3/6) when it was the nondominant eye. Finally, some more marked differences were observed in the amplitude ratios. When the dominant eye was used as a reference in monkey XT1 (Fig. 9A), 25% (2/8) were inside the range of 0.9 and 1.1 and 38% (3/8) in case of the nondominant eye (Fig. 9B). In ET1 (Fig. 10A), 33% (2/6) were in this range when the dominant eye was used, 17% (1/6) when it was the nondominant eye (Fig. 10B).

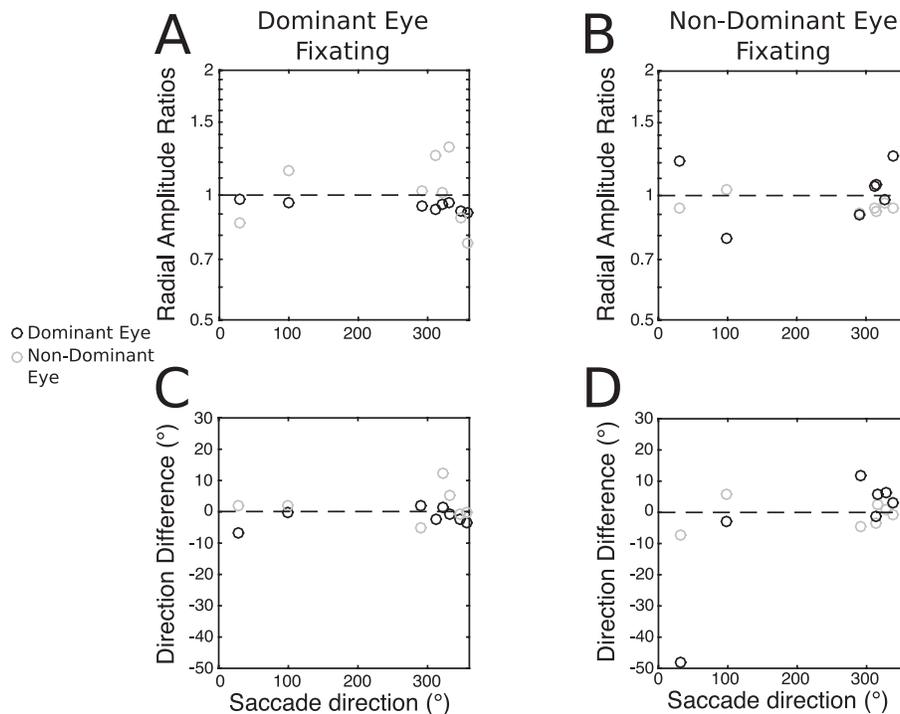


FIGURE 9. Deviation of visually guided saccades from the evoked saccades in monkey XT1. (A, C) Monkey XT1 is fixating the target with the dominant eye (left eye) in the MS condition and targeting the target with the same eye in the visually guided saccade condition. (A) Represented the radial amplitude ratios between the same eyes in the two different conditions and (C) their direction differences. (B, D) Monkey XT1 is fixating the target with the nondominant eye (right eye) in the MS condition and targeting the target with the same eye in the visually guided saccade condition. (B) Represented the radial amplitude ratios and (D) their direction differences. *Black circles* represent the dominant eye and *gray circles*, the nondominant eye. Log scale was used for the axis representing amplitude ratios. $N = 8$.

DISCUSSION

Electrical MS of iSC has been extensively used in normal monkeys to map and understand the topographic organization and the integration mechanisms of the iSC.^{15,16,19,20,28,29} In the present study, we provide the first evidence of large and significant differences in the conjugacy of evoked saccades (amplitude ratios and direction differences) between strabismic and normal monkeys (Figs. 1 and 3). These results do not seem to be due to abnormalities in the motor plant because the main sequences of both eyes were overlapping (Fig. 4). Similar disconjugacies were reported previously for visually guided saccades.²⁻⁵ In our study, we wanted to test if a same locus of activity in the iSC was coding for a common desired displacement for both eyes. Because some functional abnormalities have been found at the level of the PPRF,^{6,7} the disconjugacies could be due to unbalanced drives for the two eyes but, depending on which eye was used, the evoked vector from the iSC could still be the same. To test this possibility, we compared the evoked saccade vectors of each eye when that eye was fixating. The vectors observed for each fixating eye were different (Fig. 5) and even when vision was prevented for one eye (Fig. 6). Comparison of the disconjugacy values (amplitude ratios and direction differences) for the same sites (sites in Fig. 3 versus in Fig. 5 and sites in Fig. 3 versus in Fig. 6) did not show significant differences suggesting that the fixating eye in both viewing condition has few influence on these values. Also, a monocular analysis showed that evoked saccade vectors were nearly identical regardless of the fixation condition (Fig. 7).

These observations are particularly interesting because human and nonhuman primates with strabismus are able to perform accurate saccades with either eye fixating, and even

perform accurate “crossover” saccades.^{23,24} Because either eye can be used to perform accurate saccades (even though a preference could be given to the dominant eye), the desired eye displacement and the control loop processes must be achieved accurately. If we consider that the SC is still providing the desired displacement in strabismic monkeys, different populations of neurons in the SC have to be recruited to accurately bring the chosen eye to the target according to our results. The SC is indeed a key structure along with the frontal eye field (FEF) in saccade generation in normal monkeys.³⁰⁻³² This FEF-SC pathway also informs the brain of where the eye is going after a saccade. Perturbation studies have indeed shown that saccades evoked from MS of the SC^{33,34} or the FEF³⁵ before an interceptive saccade (the intended saccade) are compensated. This compensation mechanism has not been found when the evoked saccade was triggered from the caudal fastigial nucleus (cFN),³⁶ the only output nucleus of the cerebellum projecting to the saccade generator. The FEF-SC pathway plays an essential role in the construction of the saccade plan. The hypothesis of two desired displacements implemented in the iSC would presuppose the development of two different topographic maps in strabismic monkey, as studies in other mammals have already shown that normal visual experience is crucial to the development of normal motor maps in the SC.^{37,38} The FEF and perhaps other brain regions could activate these populations according to which eye was used for foveation of the visual target.

However, the way to control which eye was used in our experiments was by determining the fixating eye in binocular condition, and the nonoccluded eye in monocular condition. There is a possibility that, in strabismus, the SC could function as a switch to evoke saccades for only one eye. In normal monkeys, in some very specific experimental conditions, the

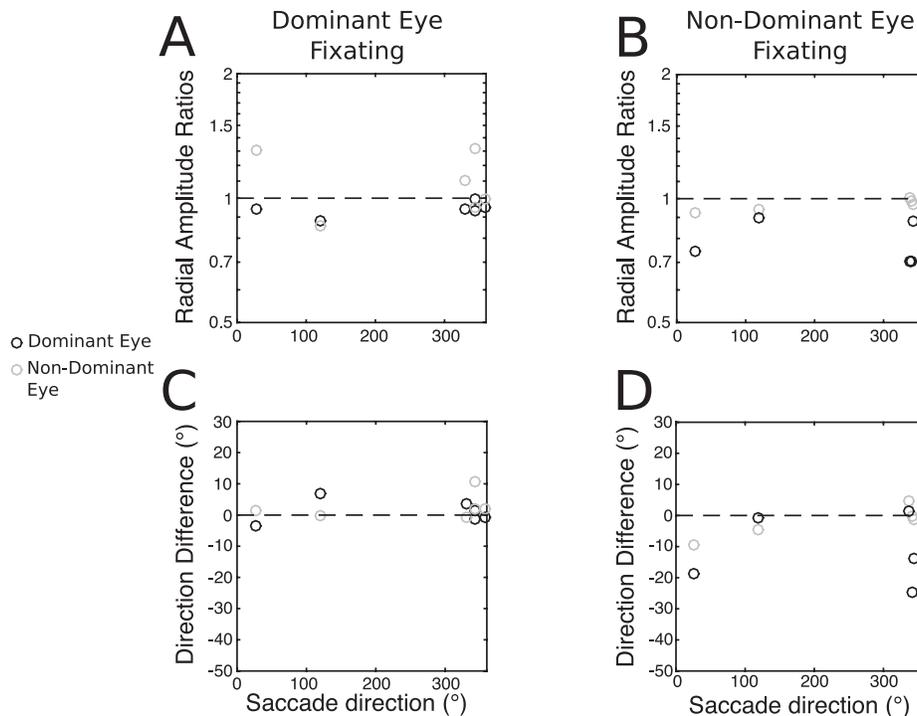


FIGURE 10. Deviation of visually guided saccades from the evoked saccades in monkey ET1. (A, C) Monkey ET1 is fixating the target with the dominant eye (right eye) in the MS condition and targeting the target with the same eye in the visually guided saccade condition. (A) Represented the radial amplitude ratios between the same eyes in the two different conditions and (C) their direction differences. (B, D) Monkey ET1 is fixating the target with the nondominant eye (left eye) in the MS condition and targeting the target with the same eye in the visually guided saccade condition. (B) Represented the radial amplitude ratios and (D) their direction differences. *Black circles* represent the dominant eye and *gray circles*, the nondominant eye. Log scale was used for the axis representing amplitude ratios. $N = 6$.

site of activity on the topographic map of the SC could be momentarily dissociated from the actual saccade after adaptation,³⁹ suggesting that the locus of activity from the SC is read out differently by distal structures including nucleus reticularis tegmenti pontis (NRTP), cerebellum, and PPRE. If a similar mechanism is at play during development of strabismus in early life then, for any given saccade, the SC might be uninformed of the desired displacement for one of the two eyes. From our results, the evoked saccades of the dominant eye were more predictive of the disconjugacies observed in visually guided saccades (Figs. 8–10). The probability to get a better matching percentage with the dominant eye was significant for monkey XT1 but not for monkey ET1 though. In this case, the locus of activity for a defined saccade amplitude and direction could be the same for both eyes in the iSC but read out differently by other structures for the nondominant eye. The cerebellum, via the cFN, could steer saccades differently, according to which eye is used to accomplish the desired displacement. This hypothesis is plausible, as the cerebellum seems to influence saccade velocity and duration in normal monkeys.^{40,41} If this alternative is supported by future experiments, it will invalidate the hypothesis of two different topographic maps in the iSC. However, the final result would be that the neural circuits, as a whole, are indirectly using two different functional maps through different structures.

Elucidating the neural pathways that code the saccade goal for each eye presents an important and interesting challenge that will answer questions about how the visuo-oculomotor system develops and adapts to eye misalignment in early life. Determining if the separate maps are implemented in the SC could be answered using single-unit recordings of neurons at specific sites in the iSC. Different firing rates for the same

saccade vector should emerge for each eye. Perturbation studies evoking a saccade before a target interception, as described above, could also help to determine if only one or both eyes compensate and then inform us if the saccade plan for each eye was built from the same neural pathway.

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References

1. Sparks DL. The brainstem control of saccadic eye movements. *Nat Rev Neurosci.* 2002;3:952–964.
2. Kapoula Z, Bucci MP, Eggert T, Garraud L. Impairment of the binocular coordination of saccades in strabismus. *Vis Res.* 1997;37:2757–2766.
3. Fu L, Tusa RJ, Mustari MJ, Das VE. Horizontal saccade disconjugacy in strabismic monkeys. *Invest Ophthalmol Vis Sci.* 2007;48:3107–3114.
4. Walton MM, Ono S, Mustari M. Vertical and oblique saccade disconjugacy in strabismus. *Invest Ophthalmol Vis Sci.* 2014; 55:275–290.

5. Ghasia FF, Shaikh AG, Jacobs J, Walker MF. Cross-coupled eye movement supports neural origin of pattern strabismus. *Invest Ophthalmol Vis Sci.* 2015;56:2855-2866.
6. Walton MM, Ono S, Mustari MJ. Stimulation of pontine reticular formation in monkeys with strabismus. *Invest Ophthalmol Vis Sci.* 2013;54:7125-7136.
7. Walton MM, Mustari MJ. Abnormal tuning of saccade-related cells in pontine reticular formation of strabismic monkeys. *J Neurophysiol.* 2015;114:857-868.
8. Das VE. Cells in the supraoculomotor area in monkeys with strabismus show activity related to the strabismus angle. *Ann N Y Acad Sci.* 2011;1233:85-90.
9. Das VE. Responses of cells in the midbrain near-response area in monkeys with strabismus. *Invest Ophthalmol Vis Sci.* 2012;53:3858-3864.
10. Das VE, Mustari MJ. Correlation of cross-axis eye movements and motoneuron activity in non-human primates with "A" pattern strabismus. *Invest Ophthalmol Vis Sci.* 2007;48:665-674.
11. Joshi AC, Das VE. Responses of medial rectus motoneurons in monkeys with strabismus. *Invest Ophthalmol Vis Sci.* 2011;52:6697-6705.
12. Walton MM, Mustari MJ, Willoughby CL, McLoon LK. Abnormal activity of neurons in abducens nucleus of strabismic monkeys. *Invest Ophthalmol Vis Sci.* 2014;56:10-19.
13. May PJ. The mammalian superior colliculus: laminar structure and connections. *Prog Brain Res.* 2006;151:321-378.
14. Gandhi NJ, Katnani HA. Motor functions of the superior colliculus. *Annu Rev Neurosci.* 2011;34:205-231.
15. Robinson DA. Eye movements evoked by collicular stimulation in the alert monkey. *Vision Res.* 1972;12:1795-1808.
16. Schiller PH, Stryker M. Single-unit recording and stimulation in superior colliculus of the alert rhesus monkey. *J Neurophysiol.* 1972;35:915-924.
17. Wurtz RH, Goldberg ME. Activity of superior colliculus in behaving monkey. III. Cells discharging before eye movements. *J Neurophysiol.* 1972;35:575-586.
18. Sparks DL. Functional properties of neurons in the monkey superior colliculus: coupling of neuronal activity and saccade onset. *Brain Res.* 1978;156:1-16.
19. Van Opstal AJ, Van Gisbergen JA, Smit AC. Comparison of saccades evoked by visual stimulation and collicular electrical stimulation in the alert monkey. *Exp Brain Res.* 1990;79:299-312.
20. Stanford TR, Freedman EG, Sparks DL. Site and parameters of microstimulation: evidence for independent effects on the properties of saccades evoked from the primate superior colliculus. *J Neurophysiol.* 1996;76:3360-3381.
21. Robinson DA. Implications of neural networks for how we think about brain function. *Behav Brain Sci.* 1992;15:644-655.
22. Goffart L. Saccadic eye movements. In: Squire LR, ed. *Encyclopedia of neuroscience.* Oxford, UK: Oxford Academic; 2009:437-444.
23. Das VE. Alternating fixation and saccade behavior in nonhuman primates with alternating occlusion-induced exotropia. *Invest Ophthalmol Vis Sci.* 2009;50:3703-3710.
24. Economides JR, Adams DL, Horton JC. Eye choice for acquisition of targets in alternating strabismus. *J Neurosci.* 2014;34:14578-14588.
25. Mustari MJ, Tusa RJ, Burrows AF, Fuchs AF, Livingston CA. Gaze-stabilizing deficits and latent nystagmus in monkeys with early-onset visual deprivation: role of the pretectal not. *J Neurophysiol.* 2001;86:662-675.
26. Ono S, Mustari MJ. Horizontal smooth pursuit adaptation in macaques after muscimol inactivation of the dorsolateral pontine nucleus (DLPN). *J Neurophysiol.* 2007;98:2918-2932.
27. Groh JM. Effects of initial eye position on saccades evoked by microstimulation in the primate superior colliculus: implications for models of the SC read-out process. *Front Integr Neurosci.* 2011;4:130.
28. Katnani HA, Gandhi NJ. The relative impact of microstimulation parameters on movement generation. *J Neurophysiol.* 2012;108:528-538.
29. Katnani HA, Van Opstal AJ, Gandhi NJ. A test of spatial temporal decoding mechanisms in the superior colliculus. *J Neurophysiol.* 2012;107:2442-2452.
30. Schiller PH, True SD, Conway JL. Deficits in eye movements following frontal eye-field and superior colliculus ablations. *J Neurophysiol.* 1980;44:1175-1189.
31. Sommer MA, Wurtz RH. Composition and topographic organization of signals sent from the frontal eye field to the superior colliculus. *J Neurophysiol.* 2000;83:1979-2001.
32. Hanes DP, Wurtz RH. Interaction of the frontal eye field and superior colliculus for saccade generation. *J Neurophysiol.* 2001;85:804-815.
33. Sparks DL, Mays LE. Spatial localization of saccade targets. I. Compensation for stimulation-induced perturbations in eye position. *J Neurophysiol.* 1983;49:45-63.
34. Fleuriet J, Goffart L. Saccadic interception of a moving visual target after a spatiotemporal perturbation. *J Neurosci.* 2012;32:452-461.
35. Schiller PH, Sandell JH. Interactions between visually and electrically elicited saccades before and after superior colliculus and frontal eye field ablations in the rhesus monkey. *Exp Brain Res.* 1983;49:381-392.
36. Noda H, Murakami S, Warabi T. Effects of fastigial stimulation upon visually-directed saccades in macaque monkeys. *Neurosci Res.* 1991;10:188-199.
37. du Lac S, Knudsen EI. Early visual deprivation results in a degraded motor map in the optic tectum of barn owls. *Proc Natl Acad Sci U S A.* 1991;88:3426-3430.
38. Wang L, Liu M, Segraves MA, Cang J. Visual experience is required for the development of eye movement maps in the mouse superior colliculus. *J Neurosci.* 2015;35:12281-12286.
39. Quessy S, Quinet J, Freedman EG. The locus of motor activity in the superior colliculus of the rhesus monkey is unaltered during saccadic adaptation. *J Neurosci.* 2010;30:14235-14244.
40. Keller EL, Slakey DP, Crandall WF. Microstimulation of the primate cerebellar vermis during saccadic eye movements. *Brain Res.* 1983;288:131-143.
41. Quinet J, Goffart L. Cerebellar control of saccade dynamics: contribution of the fastigial oculomotor region. *J Neurophysiol.* 2015;113:3323-3336.