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RESEARCH ARTICLE

Saccades evoked in response to electrical stimulation of the posterior bank of the arcuate sulcus

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Abstract To test the hypothesis that the premotor cortex in and behind the caudal bank of the arcuate sulcus can generate saccades, we stimulated electrically the periarcuate region of alert rhesus monkeys. We were able to produce saccades from sites of the premotor cortex that were contiguous with the frontal eye fields and extended up to 2 mm behind the smooth pursuit area. However, premotor sites often elicited saccades with ipsiversive characteristic vectors, lower peak velocities, and flatter velocity profiles when compared to saccades evoked from the frontal eye field.

Keywords Intracortical microstimulation · Frontal eye field · Premotor eye field · PMv · Mirror neurons

Introduction

The posterior bank of the arcuate sulcus (AS) is part of the premotor cortex (Brodmann's area 6). Dorsally, in the superior limb of the AS, it belongs to area F2 which has been implicated in forelimb movements (Gregoriou and Savaki 2003; Raos et al. 2003). Similarly, area F5 of the ventral premotor cortex (PMv), in the posterior bank of the inferior limb of the AS, is thought to participate in the visual guidance of reaching (Gregoriou and Savaki 2003) and the control of hand movements (Raos et al. 2004, 2006;

Rizzolatti et al. 1988). It also participates in the generation of rapid eye movements (saccades) as shown with the help of imaging, tract tracing, and extracellular recording techniques. ^{14}C-deoxyglucose experiments demonstrated that saccades activate both the posterior bank of the AS, as well as the low threshold FEF in its rostral bank and nearby pre-arcuate convexity (Moschovakis et al. 2004; Savaki et al. 2015). Functional magnetic resonance imaging studies led to similar conclusions (Baker et al. 2006; Koyama et al. 2004). Moreover, the caudal bank of the AS, particularly in and near its spur, contains cells oligosynaptically connected to the lateral rectus muscle, as shown after retrograde trans-synaptic transport of rabies virus (Moschovakis et al. 2004). Finally, the posterior bank of the AS has been shown to contain cells that discharge for saccades (Fujii et al. 1998; Neromyliotis and Moschovakis 2017; Tanaka and Fukushima 1998). Because it is part of the premotor cortex, the term premotor eye field (PEF) has been coined to refer to this region (Amiez and Petrides 2009).

It has been argued that rather than generate saccades, the saccade-related discharges of premotor cortical cells provide spatial information to their targets (Pesaran et al. 2010). To test the hypothesis that the premotor cortex evokes saccades, we stimulated electrically the region in and behind the caudal bank of the AS in alert behaving monkeys. The present study demonstrates that saccades evoked from the premotor cortex differ in several respects from those evoked from the FEF. A brief account of some of our data has appeared in an abstract (Neromyliotis and Moschovakis 2016).

Methods

We obtained data from three hemispheres of two adult female rhesus monkeys (*macaca mulatta*), weighing

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5.2 and 6 kg, respectively. They were purpose-bred by authorized suppliers within the European Union (Deutsches Primatenzentrum, Gottingen, Germany). Experimental protocols were approved by the Ethics Committee of FORTH and the Veterinary authorities of the Region of Crete and complied with European (directive 2010/63/EU and its amendments) and National (Presidential Decree 56/2013) laws on the protection of animals used for scientific purposes. Both animals had extensive experience in directing hand and eye movements towards visual targets.

Animal preparation

Subjects were surgically prepared for painless head immobilization, eye position monitoring, and intracortical microstimulation under anesthesia and aseptic conditions. For head immobilization, we cemented a metal bolt onto mandibular plates secured on the cranium with titanium screws (Synthes, Bettlach, Switzerland). Following craniotomy, a metal chamber (Crist Instr., Damascus, MD), 1 cm in radius, was cemented onto the bone at stereotaxic coordinates appropriate for lowering electrodes in the AS [17 mm anterior to the interaural line and 19 mm lateral to the midline in subject L, and 22 (21) mm anterior to the interaural line and 15.5 (14.5) mm lateral to the midline for the left (right) chamber of subject (R)]. In between stimulation sessions, the chamber was filled with a gel containing antibiotic (Tobramycin 0.3%) and capped. To monitor eye movements (Robinson 1963), a scleral search coil (AS633 Cooner wire, Chatsworth, CA) was sutured on the sclera [modified from (Judge et al. 1980)].

Subjects sat in a primate chair in the dark, facing a 21″ 120 Hz monitor (MicroTouch 3 M, St. Paul, MN) positioned 27 cm in front of their head. It was centered within two orthogonal magnetic fields generated by currents alternating at 50 and 75 kHz, respectively (Robinson 1963). The current induced in the eye coil was demodulated (Remmel labs, Ashland, MA) to obtain the vertical and horizontal components of instantaneous eye position (Remmel 1984). We sampled eye position at a rate of 1000 Hz through the A/D converter (Cambridge Electronics Design-CED-micro1401-3, Cambridge, UK) of a microcomputer running the Spike2 software (CED, Cambridge, UK) and stored on disk for offline analysis. The system resolution was 0.1° and the noise level 0.3° peak to peak. Its gain was calibrated frequently, by averaging at least ten movements in each direction after asking the animal to execute a series of vertical and horizontal movements of 10° amplitude centered on straight ahead.

Data recording

During microstimulation sessions, animals faced a computer screen that was usually blank. We chose to stimulate between spontaneous movements and not while the subject fixated a visual target, because fixation raises the stimulation threshold for evoked saccades and affects the metrics of the evoked movements (Goldberg et al. 1986). When needed, a slowly moving picture of a monkey was, at infrequent intervals, presented on the screen to direct the subject's gaze towards desired parts of the oculomotor field. Otherwise, the animals were free to move their eyes as they wished. Periods of reduced alertness were identified by drifts of eye position and were excluded from analysis.

We used glass-coated tungsten electrodes (impedance: 1 MΩ; AlphaOmega, Nazareth, Israel). They were slowly lowered through the dura and the cortical gray matter, at steep medial (30°, relative to the sagittal plane) and caudal (15°, relative to the frontal plane) angles with the help of a hydraulic micromanipulator (Trent-Wells, Coulterville, CA) that was firmly secured on the recording chamber. Stimuli used to activate the cortex were trains of monopolar pulses (0.25 ms pulse duration) produced by a WPI stimulator and driven by the spike2 version 5 sequencer (CED, Cambridge, UK). Because the metrics of the evoked saccades depend on the stimulation parameters, these were held constant (rate: 300 Hz; number of pulses: 45; train duration: 150 ms). The current intensity was set to 80 μA, but other intensities (10–100 μA) were also used to determine thresholds or verify that no movement could be evoked from a site. Electrical stimuli such as these have been repeatedly used in the past to study movements generated from the periarcuate cortex (Bruce et al. 1985; Chen 2006; Fujii et al. 2000; Knight and Fuchs 2007; Monteon et al. 2010; Russo and Bruce 1993).

Analysis

We used the Spike2 version 5 software (CED, Cambridge, UK) to analyze saccades. Eye velocity (in deg/s) was obtained by numerical differentiation and smoothing of the instantaneous eye position trace. Saccade onset was defined automatically as the moment when velocity exceeded 20 deg/s (Moschovakis et al. 1998). Onsets were visually checked and corrected when necessary. Saccades with latencies >80 ms were considered spontaneous and were excluded from further

analysis. For each stimulation site, we obtained the rate of successful stimulations for the whole oculomotor field and for each quadrant of the oculomotor field, separately. We used linear regression to examine how much evoked saccade size depended on the initial position of the eyes (fitlm function, MATLAB statistical toolbox). To compare the main sequence plots of different samples of saccades (spontaneous and evoked from different sites), a power law was first fit to the data. After log-linearizing the power law equations, we performed ANCOVA using MATLAB's aoctool.

Track reconstruction and neuron location

After collecting samples of evoked eye movements, we made small injections of biotinylated dextran amine (10 kDa) and placed a series of small electrolytic lesions at widely spaced coordinates within the recording chamber by passing 20–150 µA cathodal DC current for 15–68 s (corresponding to 1.5–2.8 mCb of total electric charge) of one of the monkeys we studied shortly before its perfusion. The subject was killed with an overdose of pentobarbital and perfused transcardially with 1 l of saline followed by a buffered solution of 4% paraformaldehyde, 0.05% glutaraldehyde, and 15% (v/v) saturated picric acid (pH 7.4). After the end of the perfusion, the brain was photographed in situ at a plane parallel to that of the recording chamber. It was then blocked and cut frontally, in 100 micron sections, with a vibratome. Selected sections were processed with DAB (Lanciego et al. 1998). To reconstruct tracks, we employed a Zeiss microscope equipped with a drawing tube. Tracing of section outer contours and of the outlines of selected regions and nuclei was done using a 2.53 objective. Subsequently, entire sections were systematically scanned to detect and plot the location of lesions and electrode tracks.

Results

A total of 232 sites from subject R and 89 sites from subject L were stimulated. Figure 1 provides examples of typical saccades evoked in response to identical electrical stimuli applied to a site (marked with an arrow in Fig. 6) in the right post-arcuate cortex of subject R. Ninety-five per cent of the stimuli delivered at this site were followed by saccades. The examples shown in Fig. 1 have been arranged from left to right in order of initial horizontal eye position. As shown here, the size of their horizontal component decreased as the eyes started from progressively more rightward positions and they reversed direction when the starting position exceeded a certain eccentricity, roughly equal to 20° to the right of straight ahead. Figure 2a shows an XY plot of the trajectories of saccades elicited from another site (marked with a triangle
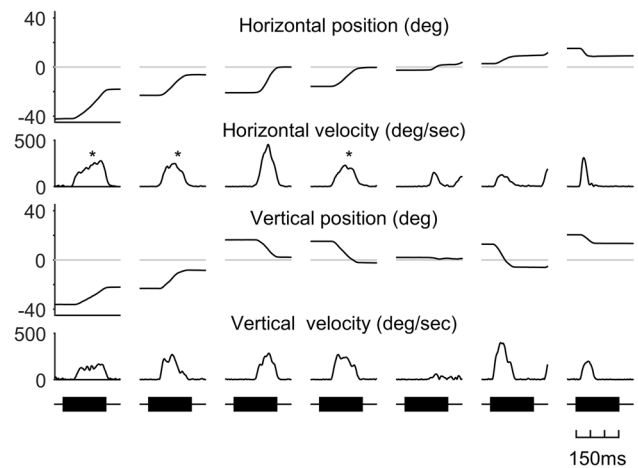

Fig. 1 Stimulation of the premotor cortex. Examples of eye movements evoked in response to identical electrical stimuli (45 pulses of 80 µA) delivered at a single site of the right hemisphere of subject R. *Gray lines* indicate zero *horizontal* (*top*) and *vertical* (*bottom*) position. *Boxes* underneath the *vertical* instantaneous velocity *traces* indicate the duration of the stimulus trains. Flattened velocity profiles are indicated with *asterisks*

in Fig. 6) within 80 ms of the onset of the stimulation (their latencies are displayed in Fig. 2b). Again, saccades evoked from a single site in response to identical stimuli differed by a lot. Most of them were directed down and to the right (ipsiversive), but there were some almost purely rightward or purely downward and even some upward and leftward (contraversive). The amplitude and direction of evoked movements depended on initial eye position and they seemed to converge towards a "goal area", down and to the right relative to straight ahead.

To obtain a quantitative estimate of the strength of the position sensitivity of evoked saccades, in Fig. 3a, we plotted the size of their vertical component (ΔV) as a function of initial vertical eye position (V_1). The solid line is the linear regression line through the data and obeys the expression displayed in the plot. It explains much of the variance of the dependent variable ($R^2 = 0.77$, $p < 0.001$) and its slope ($k_V = -0.51$) was in this case moderately steep. The intercept (S_V) is the characteristic vector of saccades evoked from this site (McIlwain 1988). The value of S_V ($-13.7°$) indicates that had the eyes started from straight ahead they would have moved down by almost 14°. The horizontal components of the same saccades (ΔH) were less sensitive to the initial horizontal eye position (H_1) as indicated by the shallower slope ($k_H = -0.29$; $R^2 = 0.85$, $p < 0.001$) of the relationship between the two variables (Fig. 3b). The size of the horizontal component of the characteristic vector (S_H) was also smaller (6.3°) than the vertical. More importantly, it was rightward, i.e., ipsiversive.

In contrast, saccades evoked from the frontal eye field (FEF) were mainly contraversive. An example is shown in

Fig. 2 Stimulation of the premotor cortex. **a** *XY* plot of the saccades evoked in response to the electrical stimulation of a PMv site of subject R. Each *arrow* starts from the initial position of the eyes (H_1) and its *arrowhead* points to the position reached after the end of the saccade. The ipsilateral hemifield is rendered in *gray*. **b** Distribution of the latencies of evoked saccades
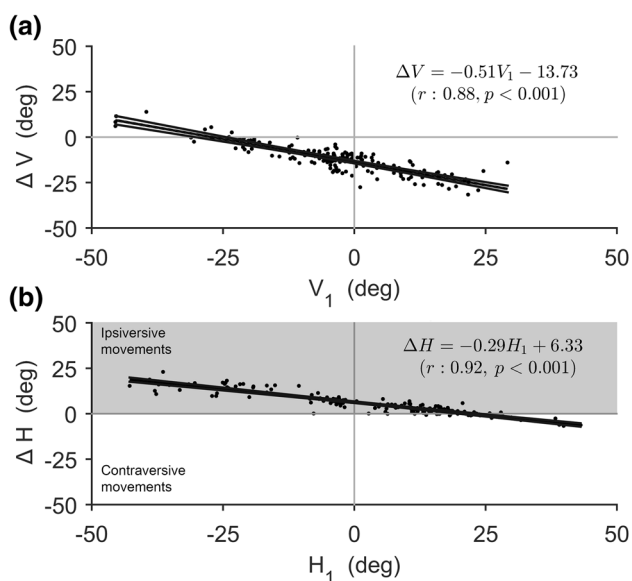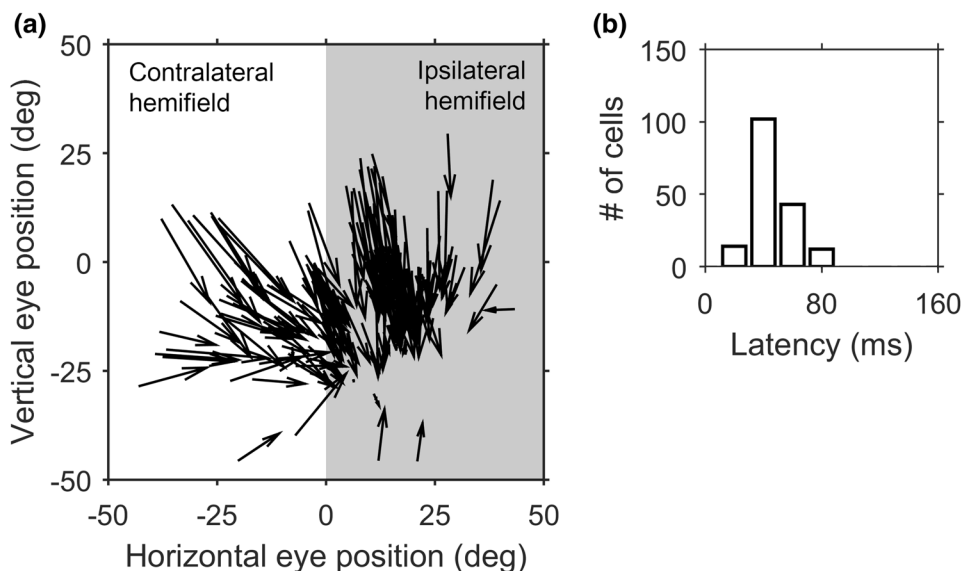

Fig. 3 Stimulation of the premotor cortex. *Plot* of the initial *vertical* (V_1; **a**) and *horizontal* (H_1; **b**) position of the eyes (abscissa) versus the *vertical* (ΔV; **a**) and *horizontal* (ΔH; **b**) displacement of saccades (ordinate) evoked in response to the electrical stimulation of the same PMv site that generated the saccades of Fig. 2. The *solid straight lines* are the *least-squares* regression lines through the data and obey the expressions displayed. The *curved lines* are the 95% confidence intervals. The part of the position-displacement *plot* occupied by ipsiversive movements is shown in *gray*

Fig. 4a, which is the *XY* plot of the trajectories of saccades elicited from a site (marked with an asterisk in Fig. 6) of the right FEF of the same subject that generated the movements shown in Figs. 1, 2, and 3. Here again, identical stimuli applied to a single site evoked a large variety of leftward (contraversive) saccade vectors that collectively converged

towards a "goal area" which in the case of Fig. 4b was down and to the left of straight ahead. Because their horizontal ($k_H = -0.44$, $R^2 = 0.54$) and vertical ($k_V = -0.58$, $R^2 = 0.84$) components were again sensitive to the initial position of the eyes, the characteristic vector of evoked saccades was obtained from the linear regression lines, as illustrated in Figs. 4b, c, respectively. The S_H ($-12.9°$) and S_V ($-2.2°$) values we obtained indicate that they were indeed leftward (contraversive) and downward.

As shown in Fig. 1 (asterisks), the velocity profiles of post-arcuate evoked saccades could be relatively shallow and display multiple peaks. Figure 5 compares the main sequence relationship of saccades evoked from the post-arcuate cortex to that of saccades evoked from the FEF. To this end, we first obtained the main sequence curve of this subject (green line) after fitting the expression $V_{max} = \alpha \Delta E^\beta$ to a sample of 5426 spontaneous and visually guided saccades executed by this animal. A value of 103 s^{-1} for α and 0.62 for β gave a reasonable fit to the data in that it accounted for 70% of the variance of the dependent variable (radial peak velocity). Very similar values (β: 0.62, α: 100, and 105 s^{-1}) provided excellent fit to the 279 ipsiversive (blue) and 1493 contraversive (red) saccades, respectively, electrically evoked from 22 FEF sites ($R^2 = 0.84$ and 0.87, respectively). Saccades evoked from the 35 post-arcuate sites were slower. Here, significantly smaller α values ($p < 10^{-8}$; post hoc ANCOVA) equal to 84 and 76 s^{-1}, respectively, had to be used, while keeping β equal to 0.62, to fit the 2267 contraversive (red) and 943 ipsiversive (blue) saccades evoked from them ($R^2 = 0.83$ and 0.76, respectively). The α value used to fit the visually guided and spontaneous saccades of a second monkey had to be similarly reduced, by about 25%, to fit the maximal velocities of ipsiversive and contraversive saccades evoked
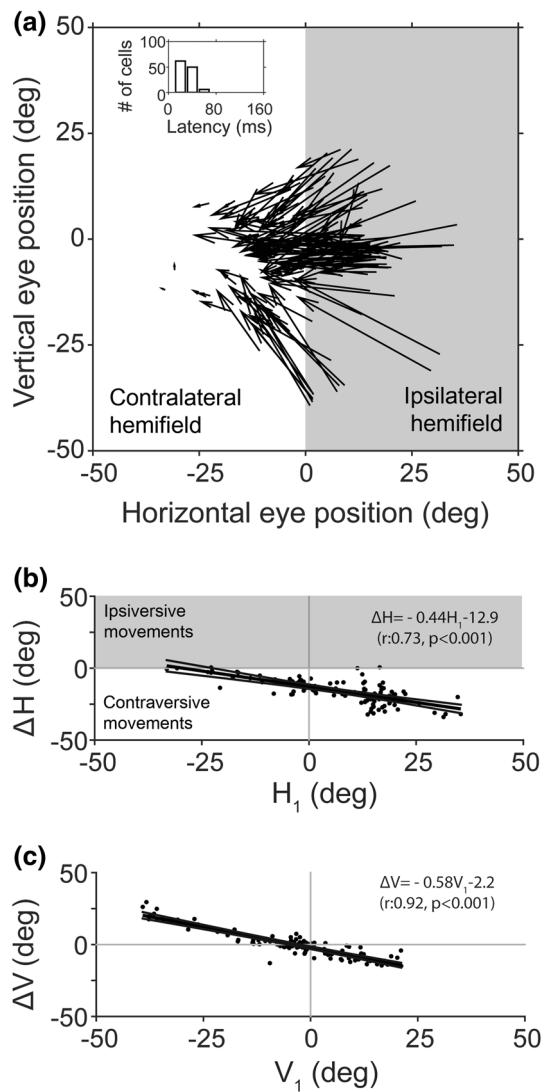
(a)

(b)

(c)

Fig. 4 Stimulation of the FEF. **a** *XY plot* of saccades elicited by electrical stimulation of an FEF site. Conventions as in Fig. 2. The *inset* is the frequency histogram of the latencies of evoked saccades. **b, c** *Plot* of initial *horizontal* (H_1; **b**) and *vertical* (V_1; **c**) position of the eyes (abscissa) versus the *vertical* (ΔV; **c**) and *horizontal* (ΔH; **b**) displacement of saccades (ordinate) evoked in response to the electrical stimulation of the same FEF site. Conventions as in Fig. 3

in response to the electrical stimulation of the premotor cortex in this second subject.

Figure 6 shows a plot of the efficacy of periarcuate cortical sites in generating saccades. All penetrations ($N = 103$) are from one of the hemispheres of one of the subjects we studied (subject R). They are arranged in a 1 mm square grid extending from 5 mm in front of the center of the recording chamber to 8 mm behind it and from 6 mm medially to 6 mm lateral to it. Fifty seven of these penetrations evoked saccades with thresholds as low as 20 μA. They included 22 sites that were found in the FEF and 35 in the caudal bank of the AS and the arcuate spur following

histological verification of their location (see below). Finally, in agreement with previous observations (Fujii et al. 2000), we found two saccade evoking sites in the rostral and dorsal premotor cortexes that were relatively isolated. Saccades evoked from them were contraversive and their velocity profiles resembled those of FEF evoked saccades. Unfortunately, chamber placement did not allow us access to additional such sites to study their properties.

We did not wish to use the proportion of effective stimuli (incidence ratio) to quantify each site's efficacy in evoking saccades, because it depends on the frequency of spontaneous saccades executed by different subjects in different days and at different times within the same session. It varied between 1.1 and 2.7 spontaneous saccades per second in one animal and between 1.9 and 3.6 saccades per second in the other. The more frequent the spontaneous saccades generated by an animal the more likely it is that a number of them will fall accidentally within the first 80 ms of the stimulation interval and be falsely considered evoked. To correct for this, we employed a Monte Carlo simulation of our data. To this end, in each stimulation session, we removed the stimulation periods and repositioned them randomly ($N = 500$) within the session's record. This reshuffling decouples the stimulation events from the evoked movements and generates sessions, where saccades are no longer causally linked to the stimulation. In each reshuffled record, we counted the number of stimuli accompanied by saccades. The first moment of their distribution is the number of spontaneous saccades expected to fall accidentally within the stimulation periods we employed. The second moment is indicative of the speed with which this drops to zero. Each recording site (1) was assigned a standard score (in multiples of SD), σ_i, indicative of the likelihood that its electrical stimulation evokes saccades. Sites that evoked saccades robustly in response to electrical stimulation display large values of σ_i, while sites that evoked saccades less frequently display small values of σ_i. A value of σ_i equal to 2 corresponds to a probability smaller than 0.05 that the null hypothesis (i.e., that the movements produced during a stimulation session are spontaneous rather than evoked) is true, while a value equal to 5 corresponds to a probability $<5 \times 10^{-7}$. In Fig. 6, values of σ_i are plotted as solid circles, whose radius is proportional to σ_i. They were all obtained with the same current intensity (80 μA), train duration (150 ms), and pulse frequency (300 Hz).

Most of the sites that evoked saccades occupied an area that was contiguous and covered the rostral and lateral quarter of our recording chamber. Sites that evoked saccades with high certainty ($\sigma_i = 14$) were next to sites with much smaller values of σ_i (as small as 2). The caudal ones occupied a region that corresponds well to a part of the PMv, where we encountered cells discharging for saccades (Fig. 6, inset) in single cell recording experiments
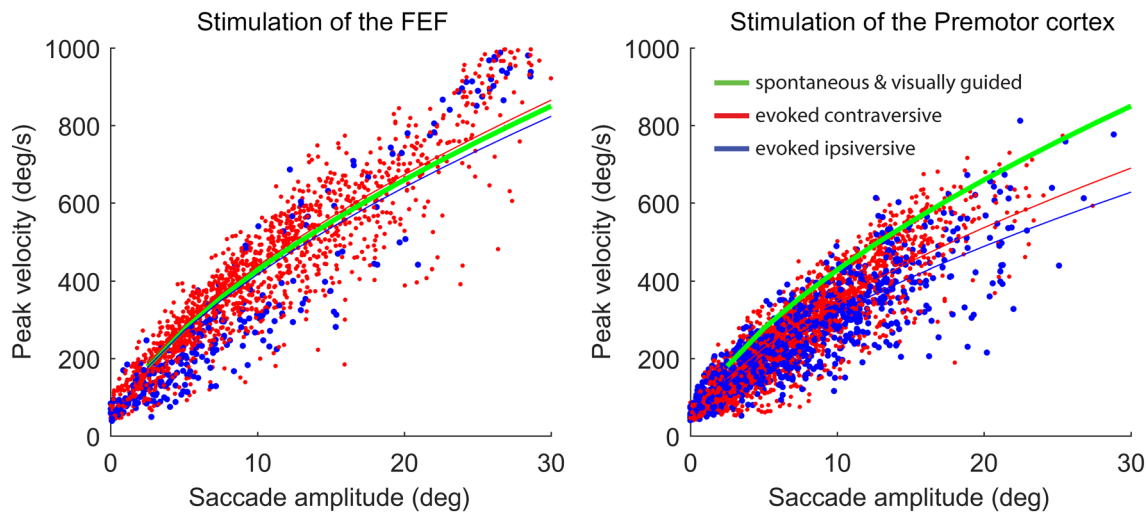
Stimulation of the FEF

Stimulation of the Premotor cortex

Fig. 5 *Plot* of peak radial velocity (ordinate) versus saccade amplitude (abscissa) for contraversive (*red*) and ipsiversive (*blue*) saccades evoked in response to electrical stimulation of the FEF and the premotor cortex of subject R. The *green*, *red* and *blue lines* are the power

law fits to spontaneous/visually guided, contraversive electrically evoked and ipsiversive electrically evoked, respectively, saccades executed by this subject
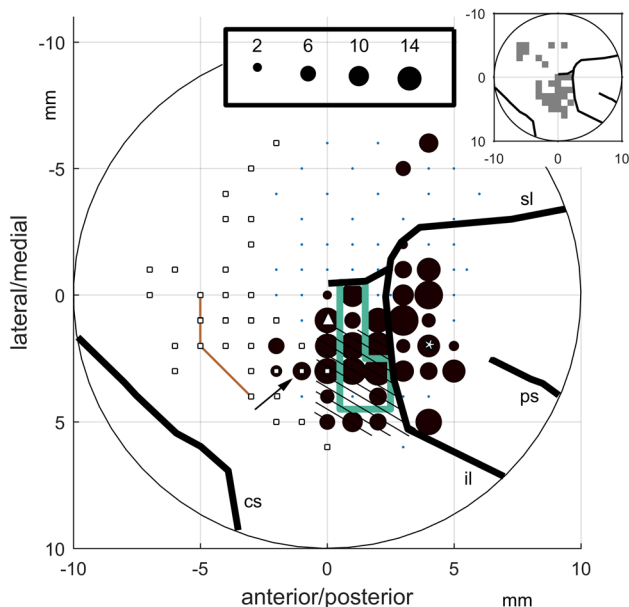
Fig. 6 Map of stimulation sites through the right hemisphere of one monkey. They are marked depending on whether they evoked saccades (*solid circles*), skeletomotor movements (*open squares*) or were not effective (*dots*). The radius of the *solid circles* is proportional to the likelihood that electrical stimulation of a site would evoke saccades (in terms of a standard score σ_i, see text for a description). An *arrow* points to the site that generated the saccades illustrated in Fig. 1. Other *symbols* mark sites that generated the data for Figs. 2, 3 (*triangle*), and 4 (*star*). The rostral border of M1 (*orange lines*), the smooth pursuit region (*green lines*) and area F5 (*hatches*) are also indicated. The *inset* shows the location of premotor cortical sites containing saccade-related cells encountered in single cell recording studies from our laboratory. The location of the spur has been moved slightly to avoid clutter. Cs central sulcus, *il* inferior limb of the AS, *ps* principal sulcus, *sl* superior limb of the AS

(Neromyliotis and Moschovakis 2017). Much of this region also contained mirror neurons (hatched) found in the context of a different experiment in which this subject also participated. Caudally and medially to this area, we were generally unable to evoke saccades (dots). Instead, it became progressively easier to evoke skeletomotor movements, usually of the upper limb and face/jaw (open squares). Note that three sites could evoke both saccades and skeletomotor movements (open squares inside the solid circles). Further caudally, we could evoke muscle twitches (primarily of the thumb and wrist muscles) with current intensities as low as 10 µA from sites presumably corresponding to the rostral edge of the primary motor cortex (orange). Finally, 2 mm in front of the caudal edge of our saccade generating area we found a smaller contiguous region of sites that evoked smooth pursuit eye movements (enclosed in green lines). These continued until the end of the stimulation, occasionally interrupted by small saccades. Sites evoking smooth pursuit were on average deeper (5 mm) than those evoking ipsiversive saccades (4.5 mm) and these in turn were deeper than sites evoking contraversive saccade (3.5 mm, on average). However, the range of depths of all three kinds of sites was considerable (1–8 mm) and their overlap so extensive that differences in average depth were not statistically significant.

Examples of the slow, ramp-like eye movements evoked from the smooth pursuit part of the left post-arcuate cortex of another animal (subject L) are shown in Fig. 7a. Evoked eye movements were ipsiversive, started soon (within 28.8 ± 8.4 ms) after the onset of the stimulation and their velocity remained roughly constant (<20 deg/s)
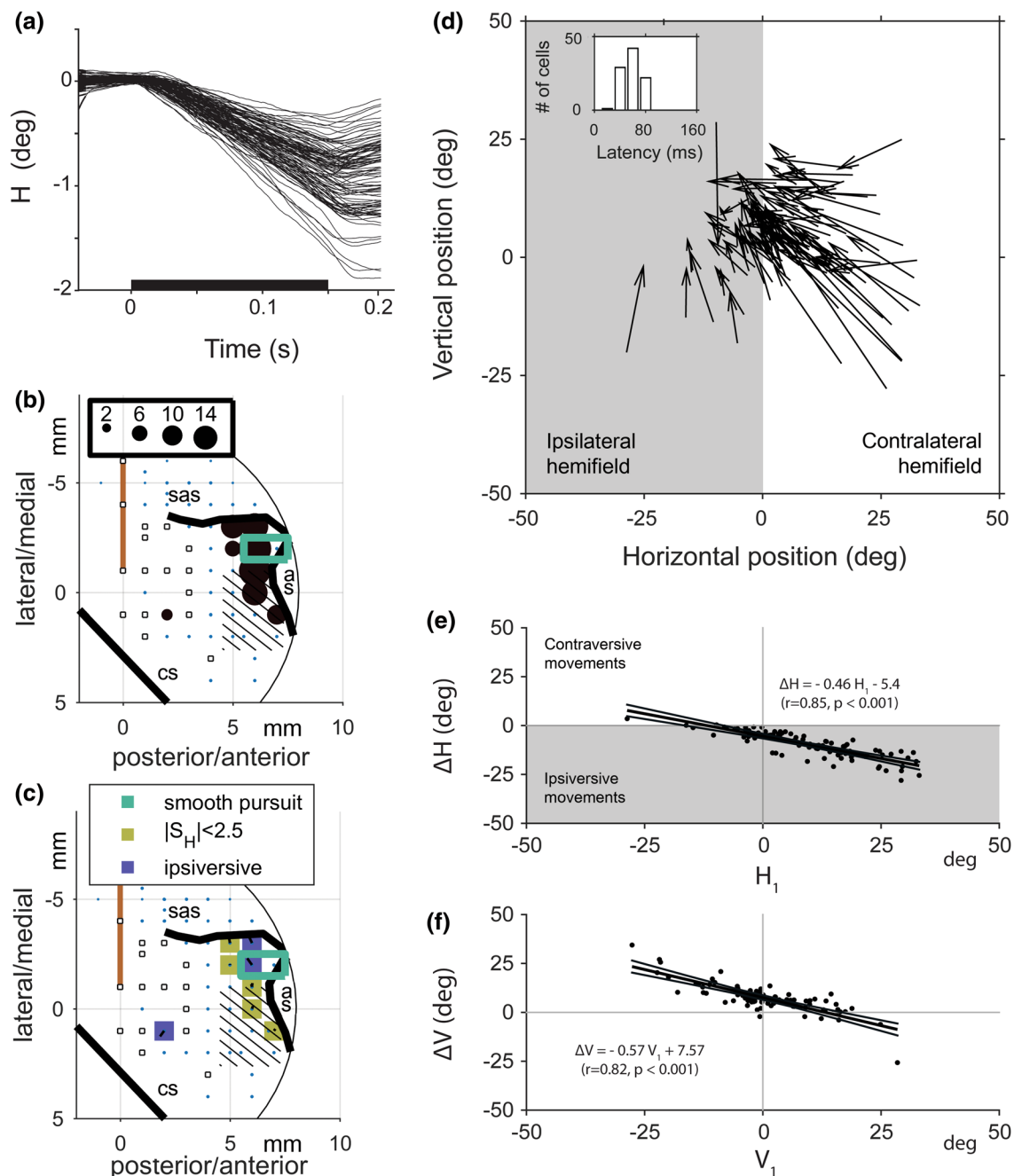
Fig. 7 Stimulation of the premotor cortex of subject L. **a** Superposition of the *horizontal* component of slow eye movements generated in response to the same electrical stimulation (again 45 pulses of 80 μA) of a site in the *left* hemisphere. All records were *vertically* aligned around the straight ahead *horizontal* position. *Black bar* indicates the duration of the stimulation. **b**, **c** *Maps* of the efficacy (**b**) and of the characteristic vectors (**c**) of saccades evoked from post-arcuate sites of the left hemisphere of subject L; conventions as in Figs. 6 and 8, respectively. **d** *XY* plot of saccades elicited by electrical stimulation of another site of the same hemisphere of subject L. Their latencies are shown in the inset. Conventions as in Fig. 2. **e**, **f** *Plot* of initial *horizontal* (H_1; **e**) and *vertical* (V_1; **f**) position of the eyes (abscissa) versus the *horizontal* (ΔH; **e**) and *vertical* (ΔV; **f**) displacement of saccades (ordinate) evoked in response to the electrical stimulation of the same site. Conventions as in Fig. 3

for the duration of the stimulation. Saccades evoked from nearby sites were also ipsiversive. An example is shown in Fig. 7d, e, f which displays data obtained in response to the electrical stimulation of the same site. Figure 7d shows an

XY plot of the saccade vectors elicited from this site within 80 ms of the onset of the stimulation (their latencies are shown in the inset). Here again, identical stimuli applied to a single site evoked a large variety of mostly leftward

(ipsiversive) saccade vectors that collectively converge towards a "goal area" which in the case of Fig. 7d is up and to the left of straight ahead. Their horizontal ($k_H = -0.46$, $R^2 = 0.72$) and vertical ($k_V = -0.57$, $R^2 = 0.68$) components were again sensitive to the initial position of the eyes. Accordingly, the characteristic vector of evoked saccades was again obtained from the linear regression lines, as illustrated in Fig. 7e and Fig. 7f, respectively. The S_V (7.6°) and S_H (−5.4°) values we obtained indicate that they were indeed upward and, more importantly, leftward, i.e., ipsiversive. Figure 7b shows a plot of the efficacy (σ_i) of periarcuate cortical sites in generating saccades in subject L. As in subject R (Fig. 6), they are arranged in a 1 mm square grid which in this case extends up to 7 mm in front of the center of the recording chamber and 5–6 mm lateral to the spur of the AS. Chamber placement did not allow us access to FEF sites or to more ventral and lateral PMv sites in this animal. Sites evoking saccades in subject L were again found in the caudal bank of the AS in or near regions that evoked smooth pursuit eye movements (green lines) or contained mirror neurons (hatched).

To summarize, comparison of Fig. 7d to Figs. 2a and 4a indicates that the characteristic vectors of saccades evoked in response to stimulation of FEF sites were contraversive, while those of post-arcuate sites were ipsiversive. Figure 8 uses a color code to plot the direction of the characteristic vectors of saccades evoked from the sites shown in Fig. 6. Characteristic vectors of evoked saccades were drawn to scale (proportional to their size) and are arranged in the 1 mm square grid used in Fig. 6. In addition, Fig. 8 retains the symbols and landmarks of Fig. 6, i.e., the borders of the smooth pursuit area (green), the rostral borders of M1 (orange), the location of sites giving rise to musculoskeletal movements (open squares), and the location of sites that proved ineffective (blue dots). Sites within 0.5 mm of the rostrocaudal and mediolateral coordinates of a grid point are shown as distinct vectors. Sites evoking saccades with appreciable (>2.5°) contraversive $|S_H|$ are marked with a red square and occupy the relatively rostral part of our plot. In turn, sites that could evoke saccades with appreciable (again >2.5°) ipsiversive $|S_H|$ are marked with a blue square and occupy the relatively caudal part of the saccade generating region of our plot. Between these two regions, we found sites (marked with a green square) giving rise to characteristic vectors with very small horizontal components ($|S_H| < 2.5$). Their vertical components were often large, and thus, the region housing them could correspond to the representation of the vertical meridian, shown in a previous study to run along the fundus of the AS between area 6 and the FEF (Savaki et al. 2015). Using the same color code, Fig. 7c shows that post-arcuate sites evoked ipsiversive (blue) saccades or saccades with very small horizontal components (green) in subject L as well.
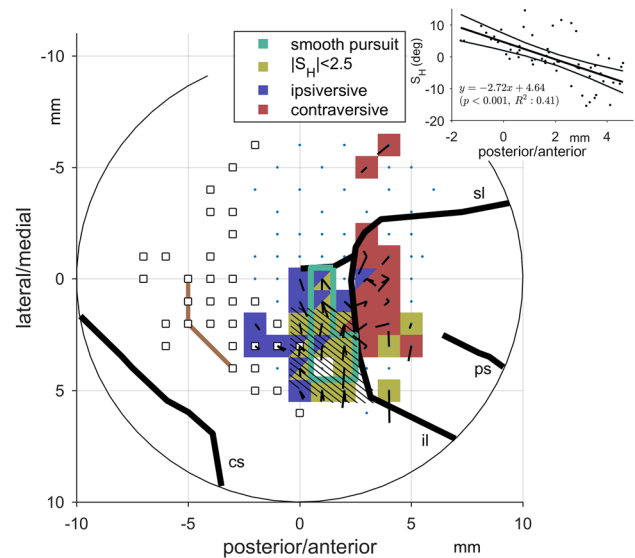

Fig. 8 *Map* of the characteristic vectors of saccades evoked after stimulation of the same hemisphere as in Fig. 6. They are marked depending on whether their direction is contraversive (*red*), ipsiversive (*blue*) or whether $S_H < 2.5°$ (*green*). *Black lines* originating from grid points correspond to different characteristic vectors, evoked from different sites within 0.5 mm of the rostrocaudal and mediolateral coordinates of the grid point. Grid points containing sites that gave rise to different kinds of saccades (ipsiversive, contraversive or small) are marked with triangles of the appropriate color instead. Other conventions and abbreviations as in Fig. 6. The *inset* is a plot of S_H versus rostrocaudal distance of the stimulation site from the center of the recording chamber. Each data point is from a different site. The *solid straight line* is the *least-squares* regression line through the data and obeys the expressions displayed. The *curved lines* are the 95% confidence intervals

To further examine if the characteristic vectors of saccades evoked from post-arcuate sites differ from those of pre-arcuate sites, we plotted S_H as a function of the actual rostrocaudal distance of stimulation sites from the center of our chamber in subject R (Fig. 8, inset). Despite considerable noise, the two variables were fairly well correlated ($R^2 = 0.41$, $p < 0.001$). S_H values were positive (i.e., rightward, ipsiversive) for sites caudal to the center of the chamber and their size increased progressively as the electrode moved caudally away from the AS. They reversed sign ($S_H < 0$), i.e., they became leftward, contraversive, for values of $x > 1.7$ mm (=4.64/2.72) rostral to it, a point that roughly corresponds to the distance of the AS from the center of the chamber, and their size also increased progressively as the electrode moved further rostrally in the prefrontal cortex. Figure 9a illustrates the direction (θ) of the characteristic vectors of saccades evoked from periarcuate sites of both subjects (R and L), pooled together. Assuming that 0° corresponds to horizontal contraversive saccades, those evoked from pre-arcuate sites (red) were mostly contraversive while those evoked from post-arcuate sites (blue) were mostly
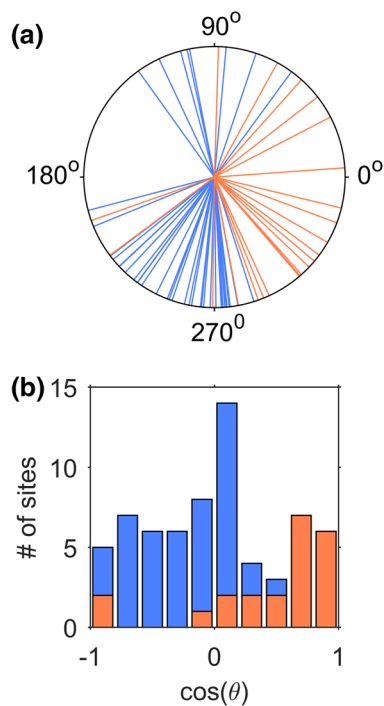
(a)

(b)

Fig. 10 *Plot* of the *horizontal* position sensitivity (k_H; abscissa) against the *vertical* position sensitivity (k_V; ordinate) of saccades evoked from FEF (*dots*) or post-arcuate (*open circles*) sites

Fig. 9 **a** Distribution of the direction (θ) of the characteristic vectors of saccades evoked from pre-arcuate (*red*) and post-arcuate (*blue*) sites of both subjects (R and L), pooled together. 0° corresponds to *horizontal* contraversive saccades. **b** Frequency histogram of cosθ

ipsiversive. It is instructive to examine the frequency histogram of cosθ (Fig. 9b), which obtains values <0 for ipsiversive directions $\left[\frac{\pi}{2}, \frac{3\pi}{2} \right]$ and values >0 for contraversive directions $\left[-\frac{\pi}{2}, \frac{\pi}{2} \right]$, respectively. Although there was some overlap, the values of cosθ for the characteristic vectors of post-arcuate sites (blue) differed significantly ($p < 10^{-6}$, Wilcoxon) from those of pre-arcuate sites (red).

It has been argued that saccades evoked from the premotor cortex are also more sensitive to initial eye position (Fujii et al. 1998) relative to those evoked from the FEF and thus give the impression that they are more convergent and goal directed. Indeed, some of the FEF sites we studied generated saccades with little position sensitivity. To further explore this issue, Fig. 10 shows the distribution of the k_H versus k_V values for saccades generated in response to stimulation of 22 FEF and 35 post-arcuate sites of subject R. It does not include data from the two sites of the rostral dorsal premotor cortex that were far from the PMv and were seen to evoke contraversive saccades. In agreement with Fig. 3a of Fujii et al. (1998), horizontal and vertical position sensitivities were correlated obeying the expression $k_V = 0.94\ k_H - 0.13$ ($R^2 = 0.61$, $p < 0.001$). Similar expressions were obeyed when the data from the FEF and the post-arcuate sites were considered in isolation (slopes: 0.9 for the FEF and 1.13 for the post-arcuate
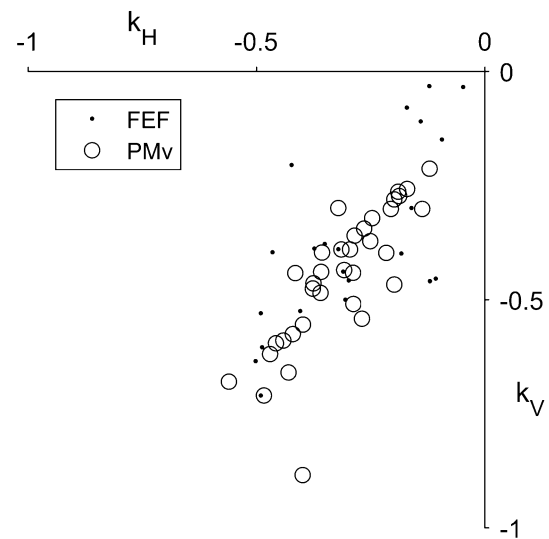
cortex, respectively). In addition, consistent with previous reports (Russo and Bruce 1993), the horizontal position sensitivity depended on the size of the horizontal component of the characteristic vectors of evoked saccades ($k_H = -0.01 |S_H| - 0.27$; $R^2 = 0.08$, $p < 0.05$). The average position sensitivity of the horizontal components of evoked saccades was -0.29 (SD: 0.15) for the FEF and -0.31 (SD: 0.11) for the post-arcuate cortex, while the average position sensitivity of the vertical components of evoked saccades was -0.37 (SD: 0.19) for the FEF and -0.45 (SD: 0.15) for the post-arcuate cortex. Although the position sensitivity of post-arcuate evoked saccades was higher than that of FEF evoked ones, the difference did not reach statistical significance ($p = 0.2$, MANOVA).

Cortical stimulation sites were verified histologically in one of the hemispheres of one of the animals (subject R, which provided the data for Figs. 6 and 8). Figure 11a provides an example of sites located within 0.5 mm of a frontal section through the caudal bank of the AS along with the electrode tracks leading to them. The deeper half of the tracks (below the breaks) belong to a row of tracks entering the brain 2 mm in front of the center of the chamber, while the top half (above the breaks) belongs to a more caudal row (by 1 mm). One of the tracks passed through two electrolytic lesions (asterisks) shown in the photomicrograph of Fig. 11b. The second animal is still used in experiments and histological evaluation of the material is not yet possible. Site localization was in this subject based on the borders of the smooth pursuit region, the rostral edge of the primary motor cortex, and the borders of area F5 as judged from the location of mirror neurons.
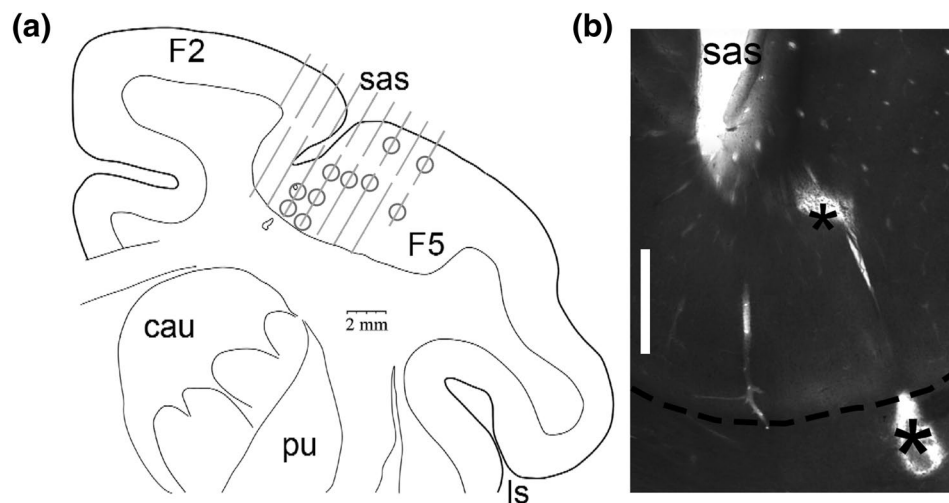
Fig. 11 a Camera lucida drawing of a coronal section passing through the lesion illustrated in B, together with the electrode tracks located within 0.5 mm of it. Electrode track segments below the break belong to penetrations 2 mm anterior to the center of the recording chamber, while segments above the break belong to penetrations 1 mm in front of the center of the chamber. *Open circles* indicate the location of sites evoking saccades. **b** Photomicrograph of electrolytic lesions (*asterisks*). The *dashed line* emphasizes the border between *white* and *gray* mater. Calibration bar is 1 mm. *Cau* caudate, *pu* putamen, *sas* spur of the AS, *ls* lateral sulcus

Discussion

The present study demonstrates that electrical stimulation of the premotor cortex in and behind the caudal bank of the AS and its spur evokes saccades. Our findings are consistent with the activation of the posterior bank of the AS for saccades (Moschovakis et al. 2004; Savaki et al. 2015), its oligosynaptic connection to lateral rectus motoneurons (Moschovakis et al. 2004), its projection to the superior colliculus (Borra et al. 2014; Distler and Hoffmann 2015; Fries 1984, 1985; Leichnetz et al. 1981; Segraves and Goldberg 1987) and the FEF (Huerta et al. 1987; Jacobson and Trojanowski 1977; Stanton et al. 2005) as well as with the phasic, saccade-related discharges of the neurons it contains (Neromyliotis and Moschovakis 2016, 2017) and thus support the use of the term premotor eye field (PEF) to refer to it.

The post-arcuate region from which we consistently evoked saccades with current intensities <80 µA was largely confined to the spur of the AS and the caudal bank of its inferior limb. It overlapped extensively a region found to contain mirror neurons in the same subjects (Papadourakis and Raos 2015). Accordingly, we do not think that this region of the premotor cortex is exclusively devoted to the representation of oculomotor processes. In fact, cells in the caudal bank of the AS have been shown to discharge phasically before and during grasping movements of the hand (Raos et al. 2004, 2006; Rizzolatti et al. 1988) or for voluntary movements of the arm, the mouth, and the head (Graziano et al. 1997). Moreover, its electrical stimulation has been shown to evoke forelimb movements, both distal and proximal (Dum and Strick 2002; Godschalk et al. 1995), or

even complex sequences of movements of several effectors, such as closure of the hand into a grip and its movement to an opening mouth (Graziano et al. 2002). Finally, the two major deficits arising from lesions of the posterior bank of the AS also lend support to such a cautious interpretation of the evidence in hand. Although they include contralateral hemi-neglect typical of insults to saccade-related regions such as the superior colliculus, the substantia nigra, the lateral intraparietal area, the FEF, etc. (reviewed in Mesulam 1981), they also include musculoskeletal deficits such as clumsy use of the fingers and difficulty in grasping food with the mouth (Rizzolatti et al. 1983).

Rostrally, the PEF overlapped the smooth pursuit and the mirror neuron area. This agrees well with previous work showing that the smooth pursuit region occupies part of the posterior bank of the AS (Gottlieb et al. 1993), and the same is true of mirror neurons (Murata et al. 1997; Raos et al. 2006). Further caudally, the region we studied extended into the post-arcuate convexity for about 2 mm behind the caudal borders of the smooth pursuit area. It differs from the small region of the ventral post-arcuate convexity shown by Fujii et al. (1998) to evoke saccades when stimulated electrically. The medial-rostral limits of the region studied in this earlier work were 5 mm ventro-lateral to the spur and at least 3 mm behind the AS from which it is separated by an area representing the arm (Fujii et al. 1998). In contrast, we studied a region that lies within and close to the spur. The placement of our chamber was optimal for an exploration of this part of the AS and did not allow us to explore more lateral and caudal sites likely to correspond to those studied by Fujii and his colleagues.

The characteristic vectors of the saccades we evoked from the PEF clearly differ from FEF evoked ones. The latter were contraversive, whereas the characteristic vectors of saccades evoked from the PMv were ipsiversive. The post-arcuate region from which we could evoke saccades overlaps extensively a region of the premotor cortex that contains neurons active before and during visually guided saccades (Neromyliotis and Moschovakis 2016, 2017). In contrast to FEF presaccadic sells that generally prefer contraversive saccades, the on-directions of PMv presaccadic cells are not lateralized. There are as many PMv cells with ipsiversive on-directions as there are cells with contraversive on-directions. This could account for the fact that the percentage of FEF evoked ipsiversive saccades is only 10% of the total number of evoked saccades, a percentage that more than triples (it becomes 34%) in post-arcuate sites. In addition, in agreement with previous observations (Fujii et al. 1998), post-arcuate evoked saccades were found to be modestly sensitive to the initial position of the eyes, a phenomenon that has been observed after electrical stimulation of several brain regions of both cats and monkeys (reviewed in Kardamakis et al. 2010; Moschovakis et al. 1998).

The main sequence relationship between the amplitude (ΔE) and peak velocity (V_{max}) of saccades evoked from the FEF obeyed a power law ($V_{max} = \alpha \Delta E^{\beta}$), whose parameters ($\alpha$, β) were statistically indistinguishable from those of spontaneous and visually guided ones. The fact that the curve fits for evoked saccades, both contraversive (red) and ipsiversive (blue), lie above that to spontaneous and visually guided ones (green) has been documented before (Fuchs 1967). Both ipsiversive and contraversive saccades evoked from caudal sites were slower; intercepts (α) had to be lowered by about 25% to fit the data ($p < 10^{-8}$; post hoc ANCOVA) while keeping the exponent (β) equal to 0.62. Similar conclusions were reached when the relationship $V_{max} = A(1 - e^{-\Delta E/B})$ was used to allow comparisons with the data of Cromer and Waitzman (2006). Values of 753 deg/s (for A) and 11 deg^{-1} (for B) provided roughly as good a fit ($R^2 = 0.68$) to visually guided and spontaneous saccades as $\alpha \Delta E^{\beta}$. Keeping B constant (at 11 deg^{-1}) the value of A had to be lowered to 609 and 559 deg/s to fit ($R^2 = 0.81$ and 0.73, respectively) the contraversive (red) and ipsiversive (blue) saccades, respectively, evoked from post-arcuate sites. These numbers are a little smaller than those employed by Cromer and Waitzman (2006) to fit their sample of visually guided saccades ($A = 614$ deg/s, $B = 11$ deg^{-1}) but quite higher than the value they used to fit the peak velocities of memory guided saccades ($A = 393$ deg/s, $B = 10$ deg^{-1}).

Any one of several mechanisms could account for the reduced velocity of post-arcuate evoked saccades.

Besides saccades, smooth pursuit, eye-hand coordination and grasping movements, the posterior bank of the AS has been implicated in the generation of blinks (Amiez and Petrides 2009). In turn, blinks have been shown to interrupt the discharge of omnipause neurons (OPNs; Schultz et al. 2010). Inhibition of OPN discharges is expected to slow down saccades, because it intervenes in the normal build-up of activity of the resettable integrator (Moschovakis 1994). Consistent with this, OPN lesions in monkeys have been shown to reduce saccadic eye velocity (Kaneko 1996) and the same is true of blinks (Goossens and van Opstal 2000; Rottach et al. 1998). Alternatively, the generation of slower saccades with multi-peak velocity profiles could be due to the engagement of head movers as expected from models that hypothesize the existence of a cross-talk from the head moving to the saccadic part of the gaze displacement circuitry (Freedman 2001; Kardamakis et al. 2010). Consistent with these expectations, slower saccades with multi-peak velocity profiles, such as those evoked from the PEF (Fig. 1, asterisks), have been shown to participate in large eye-head gaze shifts (Freedman and Sparks 1997). Similarly, there are several anatomical pathways that could account for the fact that both ipsiversive and contraversive saccades are evoked in response to electrical stimulation of the PMv. First, the projection of the PMv to the paramedian pontine reticular formation (PPRF) is bilateral (Leichnetz et al. 1984) as is its projection to the superior colliculus (Borra et al. 2010). Moreover, the PMv projects to the ipsilateral mesencephalic reticular formation (Borra et al. 2010) which in turn projects to the ipsilateral PPRF (Wang et al. 2017), a structure responsible for ipsiversive saccades (Scudder et al. 1996; Strassman et al. 1986a, b).

To summarize, the present study demonstrates that electrical stimulation of the PEF in the caudal bank of the AS and its spur evokes saccades with ipsiversive characteristic vectors. In addition, the saccades evoked from it are slower than visually guided saccades and saccades evoked from the FEF.

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